Clinical differences between eosinophilic and non-eosinophilic acute exacerbation of chronic obstructive pulmonary disease (AECOPD), a multicenter cross-sectional study

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Research

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Abstract

Background AECOPD is highly heterogeneous with respect to etiology and inflammation. COPD with higher blood eosinophils is associated with increased readmission rates and better corticosteroid response. However, the clinical features of eosinophilic AECOPD aren't well explored. Then, the aim of this study was to investigate the clinical differences between eosinophilic and non-eosinophilic AECOPD.

Methods A total of 643 AECOPD patients were enrolled in this multicenter cross-sectional study. Finally, 455 were included, 214 in normal eosinophils AECOPD (NEOS-AECOPD) group, 63 in mild increased eosinophils AECOPD (MEOS-AECOPD) group, and 138 in severe increased eosinophils AECOPD (SEOS-AECOPD) group. Then, demographic data, underlying diseases, symptoms, and laboratory findings were collected. Multiple logistic regression was performed to identify the independent factors associated with blood EOS. Correlations between blood EOS and its associated independent factors were evaluated.

Results The significant differences in 19 factors, including underlying disease, clinical symptom, and laboratory parameters, were identified by univariate analysis. Subsequently, multiple logistic regression revealed that lymphocytes%, neutrophils% (NS%), procalcitonin (PCT), and anion gap (AG) were associated with blood EOS in AECOPD. Both blood EOS counts and EOS% significantly correlated with lymphocytes%, NS%, PCT, and AG.

Conclusions The blood EOS was independently associated with lymphocytes%, NS%, PCT, and AG in AECOPD patients. Lymphocytes% was lower, and, NS%, PCT, and AG were higher in eosinophilic AECOPD. Our results indicate that viral dominant infections probably were the major etiology of eosinophilic AECOPD. Non-eosinophilic AECOPD was more likely associated with bacterial dominant infections. The systemic inflammation in non-eosinophilic AECOPD was more severe.

1. Background

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 C *et al*/ showed that the prevalence of COPD was 8.6%, about 99.9 million patients, in mainland China [2]. It is estimated that about 3.2 million people died from COPD worldwide in 2015 [1]. Globally, COPD is going to be the third leading cause of death by diseases in recent years [3, 4]. Meanwhile, COPD is also a highly heterogeneous disease [5, 6]. In clinical practice, the response and outcome of the treatments were different individually. Most clinicians realized the importance and needs of individual and target therapies in COPD.

Although amount of potential biomarkers [7], from inflammatory mediators/proteins[8] to miRNAs[9, 10], DNA methylation CpG sites [11, 12], single nucleotide polymorphisms (SNPs) [13, 14], and metabolites [15, 16], were found, blood eosinophil (EOS) is considered to be a stable, available and acceptable marker in clinical practice [17, 18]. Classically, COPD is considered as a Th1 dependent chronic airway inflammation. Neutrophils (NS), macrophages, and Th1 cells were the major immunological cells in COPD, whereas eosinophils (EOS), B cells, and Th2 cells were essential for asthma [3, 19, 20]. However, mounting evidence reported that sputum and blood eosinophils also increased in a subset of COPD patients [17, 21, 22]. Several studies showed that higher blood eosinophil counts were associated with an increased risk of readmission, severe lung function impairment, and longer length hospital stay (LHS) in COPD [23-26]. Some studies identified that inhaled corticosteroid (ICS) plus long-acting β_2 -agonist (LABA) and ICS plus LABA plus long-acting muscarinic antagonist (LAMA) brought more benefits in eosinophilic (EOS) COPD than in non-eosinophilic COPD [27, 28]. Therefore, increased blood EOS was considered to be a "treatable trait" of COPD [18, 24]. Nevertheless, the clinical features of eosinophilic hospitalized AECOPD are still not well studied. Thus, the aim of this study was to investigate the clinical differences between eosinophilic and non-eosinophilic AECOPD.

Additionally, the best cut-off value of blood EOS is still not determined. With the cut-off of EOS% $\geq 2\%$ and/or EOS counts ≥ 200 cells/ μL , Couillard S *et al*/ showed that the risk of 12-month COPD-related readmission in eosinophilic AECOPD was

increased and LHS was not different, compared with non-eosinophilic AECOPD [21]. With the cut-off value of 300 cells/ μ L, Qi YJ *et al*/found that sputum microbiome richness and plasma IL-6 level in eosinophilic AECOPD decreased more significantly than in non-eosinophilic AECOPD, after 7 days treatments [29]. Cheng SL *et al*/demonstrated that the ICS response in COPD with EOS% > 3% was better than non-eosinophilic COPD [30]. Therefore, in our study, based on both blood EOS counts and EOS%, the patients with AECOPD were divided into 3 subgroups (Figure 1).

2. Methods

2.1 Study design and population

This multicenter cross-sectional study was performed at respiratory departments of two tertiary hospitals in China between January 2017 and January 2020. This study was approved by the Research Ethics Committees of our hospital (No. 2019-23) in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients by the responsible physician or an appropriately trained staff member. Standard care and treatments were provided in our study according to current clinical guidelines [3, 5].

2.2 Sample size determinations

As for 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 $\alpha = 0.05$ and allocation ratio = 1:1:1. Furthermore, 20% more (64 in each group) patients were recruited.

2.3 Inclusion and exclusion criteria

The inclusion criterion was COPD exacerbation requiring hospitalization. Exclusion criteria were as follows: age < 40 years, non-respiratory failure patients without lung function test, active pulmonary tuberculosis (TB), asthma, bronchiectasis, pneumoconiosis, interstitial lung diseases (ILDs), other chronic lung diseases, dysphagia and aspiration, dementia, hospital-acquired pneumonia (HAP), immunocompromised status (organ transplant, system steroid use within the last 2 weeks, immunosuppressive agents use within the last 4 weeks, and HIV infection), history of malignant diseases, renal failure, and liver failure. A total of 643 patients with hospitalized AECOPD were enrolled. Finally, 455 were included, 214 in normal eosinophils AECOPD (NEOS-AECOPD) group, 63 in mild increased eosinophils AECOPD (MEOS-AECOPD) group, and 138 in severe increased eosinophils AECOPD (SEOS-AECOPD) group (Figure 1).

2.4 Definitions

According to the COPD guidelines [3, 5], the diagnosis of COPD was confirmed by the pulmonologists, based on noxious stimuli exposure history, risk factors, clinical symptoms, and spirometry ($FEV_1/FVC\% < 0.7$ after bronchodilator inhalation). 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 [3, 5]. Both blood EOS counts and EOS% were considered to set the cut-off values of EOS. In this study, normal eosinophils AECOPD (NEOS-AECOPD) was defined as AECOPD with EOS% < 2% and EOS counts < 200 cells/ μ L. Mild increased eosinophils AECOPD (MEOS-AECOPD) was defined as AECOPD with EOS% 2%-2.99% and/or EOS counts 200-299 cells/ μ L. Severe increased eosinophils AECOPD (SEOS-AECOPD) was defined as AECOPD with EOS% $\geq 3\%$ and/or EOS counts ≥ 300 cells/ μ L. The ex-smoker was defined as abstaining from smoking ≥ 6 months. Neutrophils-to-lymphocytes 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 length of hospital stay (LHS) were recorded and collected. The blood samples for laboratory tests and lung function tests were all collected and

performed within 24h after admission. However, for safety reason and cooperation concerns, the spirometer test wasn't performed in patients with respiratory failure. All patients underwent CT scans within 48 hours of hospitalization and the results were reviewed by one independent radiologist and one pulmonologist in each hospital.

2.6 Statistical analysis

Data were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the Mean $\pm$ Standard Deviation (SD), and categorical data were expressed as frequencies. The data distribution was analyzed by 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 by Kruskal-Wallis H test. Chi square test or Fisher's exact test was used to analyze categorical variables. Multiple logistic regression analysis was performed to investigate the independent risk factors associated with blood eosinophils in AECOPD patients. 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 enrolled, and 188 patients were excluded (Figure 1). At last, 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 was shown in Table 1. The rate of CTD was significantly higher in SEOS-AECOPD.

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%, lymphocytes%, NLR, procalcitonin (PCT), C-reaction protein (CRP), erythrocyte sedimentation rate (ESR), anion gap (AG), serum sodium (Na), serum potassium (K), serum calcium (Ca), serum magnesium (Mg), blood urea nitrogen (BUN), direct bilirubin (DBIL), and LHS were significantly different among 3 groups.

3.3 Multiple logistic regression analysis in AECOPD patients.

To explore independent factors associated with blood eosinophils in AECOPD patients, multiple logistic regression analysis was performed. In multiple logistic regression model, 19 factors significantly association with blood eosinophils in univariate analysis, including the rates of CTD, fever, and MV, WBC, NS, NS%, lymphocytes%, NLR, PCT, CRP, ESR, AG, serum Na, serum K, serum Ca, serum Mg, BUN, DBIL, and LHS, were included. Multiple logistic regression analysis revealed that lymphocytes%, NS%, PCT, and AG were independently associated with blood eosinophils in AECOPD patients (Table 3).

3.4 Correlations between blood EOS counts/EOS% and lymphocytes%, NS%, PCT, AG in AECOPD patients.

Since lymphocytes%, NS%, PCT, and AG were independently associated with blood eosinophils in AECOPD patients. Then, their correlations with blood EOS counts and EOS% were explored. The significant correlations were found between blood EOS counts and lymphocytes%, NS%, PCT, AG, and, between blood EOS% and lymphocytes%, NS%, PCT, AG in patients with AECOPD (Table 4). Among them, lymphocytes% was positively, and, NS%, PCT, and AG were negatively correlated with blood EOS counts and EOS%.

4. Discussion

In this multicenter cross-sectional study, the clinical features of patients with eosinophilic AECOPD were explored. Based on the two cut-off values of blood EOS, the patients were divided into 3 subgroups, normal eosinophils AECOPD (NEOS-AECOPD) was defined as EOS% < 2% and EOS counts < 200 cells/ μ L, mild increased eosinophils AECOPD (MEOS-AECOPD) was defined as EOS% 2%-2.99% and/or EOS counts 200-299 cells/ μ L, and severe increased eosinophils AECOPD (SEOS-AECOPD) was defined as EOS% $\geq$ 3% and/or EOS counts $\geq$ 300 cells/ μ L. Our results showed that lymphocytes%, NS%, PCT, and AG were the independent factors associated with blood EOS in AECOPD patients. Then, these results indicate that viral dominant infection probably was related to eosinophilic AECOPD. And, non-eosinophilic AECOPD was more likely associated with bacterial dominant infections.

As the most common lung disorder, the prevalence of COPD is still increasing in recent years [2, 3, 5]. It was estimated that the prevalence of COPD was 11.7% (8.4%-15.0%) and the COPD case number was about 384 million globally in 2010 [3, 4]. Wang, C *et al* showed that the overall prevalence of COPD in mainland China was 8.6% (95% CI 7.5-9.9) in $\geq$ 40 years-old population, namely about 99.9 (95% CI 76.3-135.7) million cases [2, 3]. Simultaneously, COPD is a chronic disease with high mortality and disability. It was reported that about 3 million people dead from COPD every year [3, 31]. Patel JG *et al* showed that COPD caused average of 5 more days of work absence and \$641 short-term disability associated extra costs each year in the USA [32]. It was estimated that the global years lived with disability (YLDs) of COPD was about 29.4 million in 2010 [33].

Nevertheless, COPD is a highly heterogeneous disease, with significantly differences in treatment response and outcomes in patients. Mounting evidence suggested that individual therapy and target therapy are the major trends of COPD in the future. Then, to explore and differentiate the phenotypes of COPD is valuable in clinical practice. In recent years, amount of studies showed that blood eosinophil is an effective, stable, and available biomarker in COPD, which can be used to define the phenotypes of COPD [17, 25, 34, 35]. However, the cut-off value of blood EOS is still in debate, ranging from 150 to 400 cells/ μ L and/or 2% to 4% in different studies [17, 18, 22, 24, 25, 34-36]. Then, in this study, both 200 cells/ μ L and 300 cells/ μ L, and, 2% and 3% were considered as the cut-off values of blood EOS counts and EOS% in AECOPD patients (Figure 1). According to demographic data, no differences in sex, age, BMI, smoking status, lung functions (GOLD stages), and most of comorbidities and complications were found among 3 groups (Table 1). Only connective tissue disease (CTD) was found significant differently among 3 groups. The rate of CTD in SEOS-AECOPD was higher than NEOS- and MEOS-AECOPD group (Table 1). These results indicate that sex, BMI, smoking, and lung function were not associated with blood EOS in AECOPD patients.

The correlations between blood EOS and EOS in the lungs (induced sputum, BAL, and tissues) were still in controversy. Many studies showed that blood EOS was considered to be a reasonably good predictor of EOS in airways in COPD patients [22, 37, 38]. Eltboli O *et al* showed that the strong correlations between blood EOS% and the submucosal eosinophil counts ($r = 0.57$) and reticular basement membrane (RBM) thickness ($r = 0.59$) were found in COPD [37]. Kolsum U *et al* reported that compared with COPD with blood EOS < 150 cells/ μ L, EOS% in induced sputum, BALF, and submucosa were all significantly increased in COPD with blood EOS > 300 cells/ μ L [38]. Nevertheless, several studies found that the correlation between lung tissue and blood EOS was not very well [36, 39]. Turato G *et al* explored the correlations between blood eosinophils and central airways, peripheral airways, and lung parenchyma, from COPD patients underwent lung resection for solitary pulmonary nodules without additional complications [36]. Initially, no difference in the eosinophil number in central airways, peripheral airways, and lung parenchyma was observed in COPD, and, pulmonary eosinophil counts weren't associated with disease severity. Subsequently, they revealed that the correlations between blood eosinophils and any of the three lung compartments were not significant. Meanwhile, in a randomized, double-blind, placebo-controlled trial (RCT), EOS counts and EOS% in induced sputum were markedly reduced after 16 weeks of roflumilast (a PDE4 inhibitor) treatment in COPD [39]. However, blood eosinophil counts were not changed by roflumilast. Whatever, the significant differences in some aspects of clinical characteristics and outcomes were identified between eosinophilic and non-eosinophilic AECOPD patients by many studies [17, 20, 23-25, 30, 35, 40]. Mounting evidence showed

that increased blood EOS was associated with higher risk readmission, severe lung function impairment, longer LHS and survival time, and better ICS response in COPD patients [23-25]. Nevertheless, the clinical features, particularly laboratory parameters, of eosinophilic AECOPD were still not well studied. In this study, commonly used laboratory parameters and tests, including blood routine, PCT, ESR, CRP, ABG, serum electrolytes, liver function test, and renal function test, were included. Our data showed that the rates of fever and MV, WBC, NS, NS%, lymphocytes%, NLR, PCT, CRP, ESR, AG, serum Na, serum K, serum Ca, serum Mg, BUN, DBIL, and LHS were significantly different among 3 groups (Table 2). Subsequently, 19 variables with significant differences in univariate analysis were included in multiple logistic regression model. We found that lymphocytes%, NS%, PCT, and AG were independently associated with blood EOS in AECOPD patients.

Meanwhile, as shown in Table 4, lymphocytes% was positively, and, NS%, PCT, and AG were negatively correlated with both blood EOS counts and EOS% in AECOPD. In this study, according to the criteria, asthma was strictly excluded, which was considered to be the most commonly confounder of the COPD study [18, 23, 40]. Meanwhile, patients with recent system steroid use and immunosuppressive agents use were also excluded. These data indicate that inflammatory types were significantly different between eosinophilic and non-eosinophilic AECOPD patients. Namely, eosinophils and lymphocytes were the major inflammatory cells in eosinophilic AECOPD, and, neutrophils were the dominant inflammatory cells in non-eosinophilic AECOPD. Meanwhile, it is well known that respiratory tract infection is the leading etiology of acute exacerbation in COPD [3, 35, 41-43]. Among them, bacteria and viruses are the most common pathogens. In a prospective observational study, Bafadhel M *et al* showed that 55% and 29% of acute exacerbation were related to bacterial and viral infection in COPD [43]. Meanwhile, Papi A *et al* demonstrated that bacterial and/or viral infection was found in 78.1% (29.7% bacterial, 23.4% viral, 25% viral/bacterial coinfection) of AECOPD patients [41]. Simultaneously, several studies showed that airway eosinophilic inflammation was related to viral infection in AECOPD [35, 41]. Additionally, it is confirmed that blood neutrophils and PCT are the biomarkers of bacterial infection in COPD [44]. In a meta-analysis, Ni W *et al* showed that the sensitivity and specificity of PCT in diagnosing bacterial infections were 0.60 and 0.76, and AUC of ROC curve was 0.77 [44]. Ergun B *et al* found that compared with culture-negative patients, PCT was markedly increased in culture-positive patients in AECOPD [45]. Their data also showed that 0.25 ng/ml was the optimal cut-off value, with 63% sensitivity, 67% specificity, and 0.73 AUC, to predict bacterial infection in AECOPD. Collectively, our results suggested that viral and virus dominant infections probably were the major etiology of eosinophilic acute exacerbation in COPD. Then, non-eosinophilic acute exacerbation in COPD was more likely associated with bacterial and bacterial dominant infection.

Additionally, NS%, PCT, and AG were negatively correlated with blood EOS in AECOPD (Table 4). And, AG, PCT, and NS% in SEOS-AECOPD were significantly lower than NEOS-AECOPD and MESO-AECOPD (Table 2). No difference in metabolic acidosis was observed in three groups (Table 1). Circulation and tissue hypoperfusion are associated with severe infection in clinical practice. Generally, hypoperfusion-induced hyperlactacidemia is the major reason for increased AG in infection diseases patients without renal failure and ketoacidosis. Durmuş U *et al* revealed that lactate clearance in AEOPD patients with hospitalization (severe patients) was significantly lower than in AECOPD patients without hospitalization (non-severe patients) [46]. Taken together, these results indicate that bacterial infection and systemic inflammation in non-eosinophilic AECOPD were more severe than in eosinophilic AECOPD.

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, the direct correlations between pathogen types and blood eosinophils were not evaluated. The main strength of our study is that relatively comprehensive laboratory data were collected, which accurately evaluated the severity and complications of the underlying diseases. Particularly, chest HRCT scan was performed in each patient, which effectively promoted the diagnosis accuracy and excluded most other lung diseases. Furthermore, the different cut-off values of blood EOS were considered, making our data more convincing.

5. Conclusions

Collectively, our results indicated that lymphocytes%, NS%, PCT, and AG were the independent factors associated with blood EOS in AECOPD patients. Viral and viral dominant infections probably were the major etiology of eosinophilic AECOPD. Then, non-eosinophilic AECOPD was more likely associated with bacterial and bacterial dominant infections. The systemic inflammation in non-eosinophilic AECOPD was more severe than in eosinophilic AECOPD. Nevertheless, further study with high sensitivity and specificity in pathogen tests, such as bronchoscope, should be carried out to validate this result.

Abbreviations

AECOPD: chronic obstructive pulmonary disease); AB: Actual base; ABG: Air blood gas; AG: anion gap; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; Ca: Calcium; Cr: Creatinine; CRP: C-reaction protein; CTD: Connective tissue disease; DBIL: Direct bilirubin; EOS: eosinophil; ESR: Erythrocyte sedimentation rate; FEV1: Forced expiratory volume at 1 second; FVC: forced vital capacity; HAP: hospital-acquired pneumonia; Hb: Hemoglobin; IBIL: Indirect bilirubin; K: Potassium; ICS: inhaled corticosteroid; ILDs: interstitial lung diseases; IPPV: Invasive positive pressure ventilation; LHS: longer length hospital stay; MEOS-AECOPD: mild increased eosinophils AECOPD; Mg: Magnesium; MV: Mechanical Ventilation; Na: Sodium; NEOS-AECOPD: normal eosinophils AECOPD; NIPPV: Non-invasive positive pressure ventilation; NLR: Neutrophils-to-lymphocytes ratio; NS: neutrophils; OI: Oxygen index; PCT: procalcitonin; PE: Pleural effusion; PLTs: Platelets; RBCs: Red blood cells; RBG: Random blood glucose; SB: Standard base; SEOS-AECOPD: severe increased eosinophils AECOPD; SNPs: single nucleotide polymorphisms; TB: tuberculosis; WBCs: White blood cells

Declarations

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Authors' Contributions

All authors read and approved the final manuscript. Tao Zhu conceived the study design. Guangming Dai, Jiajia Wang, Yajuan Ran, Xingru Chen, Junnan Peng, and Xinglong Li collected the data. Guangming Dai, Yajuan Ran, Jiajia Wang, Huojin 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.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committees of our hospital (No. 2019-23) in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients by the responsible physician or an

appropriately trained staff member.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Tables

Table 1. Demographic data of the patients with AECOPD (n=455)

	NEOS-AECOPD (n= 214)	MEOS-AECOPD (n= 63)	SEOS-AECOPD (n=178)	Statistical values	P
Sex (Male, %)	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
Non-smoking	74	24	71		
Ex-smoking	56	11	36		
current-smoking	84	28	71		
GOLD Stages				5.875	0.053
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

Table 2. Clinical features and laboratory data of the patients with AECOPD (n=455)

	NEOS-AECOPD (n= 214)	MEOS-AECOPD (n= 63)	SEOS-AECOPD (n=178)	Statistical values	P
Fever (n)	29	0	7	18.622	0.000
WBCs ($\times 10^9/L$)	9.127710 $\pm$ 4.0336889	6.900000 $\pm$ 3.3279302	7.207528 $\pm$ 2.5874116	19.396	0.000
NS ($\times 10^9/L$)	7.495327 $\pm$ 6.4450553	4.818889 $\pm$ 3.1813231	4.869382 $\pm$ 2.1464153	17.341	0.000
Lymphocytes ($\times 10^9/L$)	1.365327 $\pm$ 0.9051292	1.470476 $\pm$ 0.6305692	1.479326 $\pm$ 0.5649365	1.253	0.287
EOS ($\times 10^9/L$)	0.059393 $\pm$ 0.0508252	0.156032 $\pm$ 0.0493683	0.502022 $\pm$ 0.5874828	71.795	0.000
NS%	78.291729 $\pm$ 37.4499608	67.818413 $\pm$ 9.5222841	66.115618 $\pm$ 10.2687442	11.008	0.000
Lymphocytes%	16.887710 $\pm$ 9.9761204	23.018254 $\pm$ 7.9939971	21.994551 $\pm$ 8.6718274	19.520	0.000
EOS%	0.747570 $\pm$ 0.6408311	2.359206 $\pm$ 0.3470767	6.685562 $\pm$ 5.0527810	170.959	0.000
NLR	7.945654 $\pm$ 9.5498819	4.191587 $\pm$ 5.7973724	3.699944 $\pm$ 2.0624385	19.620	0.000
RBCs ($\times 10^{12}/L$)	4.416748 $\pm$ 0.7819829	4.535873 $\pm$ 0.5766411	4.525337 $\pm$ 0.6074892	1.474	0.230
Hb (g/L)	132.35514 $\pm$ 17.8379520	135.31746 $\pm$ 14.2464771	134.23118 $\pm$ 18.3276071	0.944	0.390
Hct (%)	40.175467 $\pm$ 5.3567446	40.890476 $\pm$ 3.9642643	40.921348 $\pm$ 4.3530357	1.337	0.264
PLTs ($\times 10^9/L$)	203.242991 $\pm$ 76.3426106	186.555556 $\pm$ 60.5199988	201.404494 $\pm$ 73.6012649	1.301	0.273
PCT (ng/ml)	0.218766 $\pm$ 0.7493592	0.139349 $\pm$ 0.6293068	0.065798 $\pm$ 0.0805874	3.545	0.030
CRP (mg/ml)	27.364953 $\pm$ 40.8671745	16.965079 $\pm$ 28.8966242	17.563483 $\pm$ 29.1130111	4.563	0.011
ESR (mm/first hour)	24.635514 $\pm$ 20.9070793	19.714286 $\pm$ 20.5578872	19.932584 $\pm$ 19.6588404	3.095	0.046
ABG					
PH	7.412682 $\pm$ 0.2815835	7.431905 $\pm$ 0.0361385	7.429663 $\pm$ 0.0477150	0.458	0.633
PaCO2 (mmHg)	43.564486 $\pm$ 13.6961751	40.746032 $\pm$ 6.5302479	42.502247 $\pm$ 9.1182623	1.600	0.203
PaO2 (mmHg)	82.598131 $\pm$ 28.5118738	79.777778 $\pm$ 19.4492262	78.938202 $\pm$ 21.5099925	1.115	0.329
OI (mmHg)	343.990654 $\pm$ 97.8380856	347.984127 $\pm$ 72.4307215	346.898876 $\pm$ 85.3106050	0.075	0.928
AB (mmol/L)	28.489252 $\pm$ 6.1881931	26.898413 $\pm$ 3.8558080	27.778090 $\pm$ 4.0188008	2.582	0.077
SB (mmol/L)	27.662150 $\pm$ 3.4513272	26.823810 $\pm$ 2.7911562	27.159551 $\pm$ 2.3971602	2.505	0.083
AG (mmol/L)	12.104299 $\pm$ 4.3290494	12.295238 $\pm$ 4.0810905	9.645506 $\pm$ 5.4451873	14.966	0.000
Serum Na (mmol/L)	137.636916 $\pm$ 5.0665516	139.073016 $\pm$ 4.0107198	138.876966 $\pm$ 4.4745202	4.308	0.014
Serum K (mmol/L)	3.896262 $\pm$ 0.4741605	3.965556 $\pm$ 0.3839051	4.016742 $\pm$ 0.0303221	3.737	0.025
Serum Ca (mmol/L)	2.223738 $\pm$ 0.1488486	2.242222 $\pm$ 0.1972917	2.268483 $\pm$ 0.1781526	3.452	0.033
Serum Mg (mmol/L)	0.839720 $\pm$ 0.0951594	0.886032 $\pm$ 0.1219669	0.870730 $\pm$ 0.1146699	6.539	0.002
ALB (g/L)	37.813551 $\pm$ 4.3179452	37.894127 $\pm$ 3.9404780	38.765169 $\pm$ 4.1056968	2.703	0.068
BUN (mmol/L)	6.562897 $\pm$ 2.5492516	6.708571 $\pm$ 2.3177268	5.946236 $\pm$ 1.8600346	4.539	0.011
Cr (μ mol/L)	72.299533 $\pm$ 27.8074238	73.471587 $\pm$ 23.2868408	73.812865 $\pm$ 20.2982227	0.196	0.822
ALT (U/L)	24.677570 $\pm$ 38.0325258	26.728571 $\pm$ 43.6346209	21.196629 $\pm$ 22.0215762	0.836	0.434
AST (U/L)	27.925234 $\pm$ 43.1549672	28.396825 $\pm$ 45.6301894	23.117978 $\pm$ 16.9972617	1.030	0.358
IBIL (μ mol/L)	6.397243 $\pm$ 3.3865077	6.846032 $\pm$ 3.6854914	5.984831 $\pm$ 2.8904372	1.826	0.162
DBIL (μ mol/L)	5.060234 $\pm$ 3.0660336	4.557143 $\pm$ 2.8291521	4.007865 $\pm$ 1.7511723	8.000	0.000
RBG (mmol/L)	6.878692 $\pm$ 2.8710151	6.809048 $\pm$ 2.3441855	6.508539 $\pm$ 1.9257216	1.136	0.322
LHS (day)	9.9112 $\pm$ 4.90727	9.2381 $\pm$ 4.02698	8.6180 $\pm$ 3.80605	4.233	0.015
Mechanical Ventilation (MV)				8.671	0.013
Non- ventilation(n)	187	59	170		
NIPPV(n)	26	4	8		
IPPV(n)	1	0	0		

Abbreviations: WBCs: White blood cells; NS: Neutrophils; NLR: Neutrophils-to-lymphocytes ratio; EOS: Eosinophils; RBCs: Red blood cells; PLTs: Platelets; Hb: Hemoglobin; CRP: C-reaction protein; ESR: Erythrocyte sedimentation rate; ABG: Air blood gas; OI: Oxygen index; AB: Actual base; SB: Standard base; AG: Anion gap; Na⁺: Sodium; K⁺: Potassium; Ca²⁺: Calcium; Mg²⁺: Magnesium; Cr: Creatinine; BUN: Blood urea nitrogen; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IBIL: Indirect bilirubin; DBIL: Direct bilirubin; PCT: Procalcitonin; RBG: Random blood glucose; LHS: Length of hospital stay; MV: Mechanical Ventilation; NIPPV: Non-invasive positive pressure ventilation; IPPV: Invasive positive pressure ventilation.

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

	Estimate	S.E	Wals	df	Sig.	95% C.I.
Lymphocytes%	-0.238	0.037	41.127	1	0.000	-0.311~-0.165
NS%	-0.254	0.041	38.431	1	0.000	-0.334~-0.174
PCT (ng/ml)	-1.494	0.355	17.739	1	0.000	-2.189~-0.799
AG (mmol/L)	-0.099	0.022	19.587	1	0.000	-0.142~-0.055

Table 4. The correlations between EOS counts/EOS % in blood and lymphocytes%, NS%, PCT, AG in AECOPD patients

		Lymphocytes%	NS%	PCT	AG
EOS counts ($\times 10^9/L$)	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

Figures

Figure 1

The flow diagram of the study.