Blood eosinophil levels and prognosis of hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease

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Abstract

**Background:** Studies about the clinical significance of high eosinophil levels in chronic obstructive pulmonary disease (COPD) are conflicting, and it has been less studied in hospitalized patients with acute exacerbation of COPD (AECOPD). This study was to examine blood eosinophil levels in relation to the prognosis of hospitalized patients with AECOPD.

**Methods:** This was a retrospective cohort study of patients with AECOPD as their primary diagnosis and admitted to Beijing Shijitan Hospital, Capital Medical University, from January 2010 to December 2016. The patients were assigned according to the proportion and count of eosinophil in peripheral blood at their first hospitalization. Patients were grouped as ≤100, 100-300, and ≥300 eosinophils/µL of peripheral blood. The use of glucocorticoids, duration of hospitalization, in-hospital mortality, and re-hospitalization were examined.

**Results:** Compared with the 100-300 eosinophils/µL group, the ≤100 eosinophils/µL group showed higher frequencies of fever, respiratory failure, and the use of systemic glucocorticoids. Eosinophil counts were not associated with in-hospital mortality and duration of hospitalization. The multivariable analysis showed that GOLD3/4 (odds ratio (OR)=2.04, 95%CI: 1.20-3.44, P=0.008), neutrophil count (OR=1.21, 95%CI: 1.03-1.41, P=0.019), systemic glucocorticoids (OR=1.84, 95%CI: 1.41-2.98, P=0.012), mechanical ventilation (OR=2.66, 95%CI: 1.36-5.18, P=0.004), and acute exacerbation in the past year before hospitalization (OR=2.03, 95%CI: 1.27-3.23, P=0.003) were independently associated with acute exacerbation within 1 year after discharge. Eosinophil count was not associated with acute exacerbation within 1 year after discharge.

**Conclusion:** Peripheral blood eosinophil counts are not associated with the 1-year AECOPD prognosis.
**Background**

Chronic obstructive pulmonary disease (COPD) is characterized by significant airflow limitation associated with a chronic inflammatory response in the airways and lungs, resulting in the destruction of lung tissue [1]. It commonly affects adults >40 years old who smoke, with an estimated worldwide prevalence of 4%-10% [1, 2]. The disease course is usually progressive, with a long-term decline in lung function [3]. It is a preventable and treatable disease commonly associated with co-morbidities (such as cardiovascular disease) and significant systemic consequences (such as skeletal muscle dysfunction) [1]. COPD has several complications, including acute exacerbation, respiratory failure, and pulmonary hypertension. The 4-year mortality rates range from 28% for mild-to-moderate COPD to 62% for moderate-to-severe COPD [4, 5].

Acute exacerbation of COPD (AECOPD) is characterized by an acute worsening in baseline symptoms such as cough, dyspnea, and/or sputum production beyond normal daily variations to the extent where it requires a change in therapy [1, 6]. AECOPD is commonly caused by viral or bacterial infections, including pneumonia and air pollution [1, 6, 7]. In-hospital mortality for patients with AECOPD is around 2.5% in general and 10% with hypercarbia [1, 8]. All-cause mortality within 3 years of hospitalization may be as high as 49% [1, 6].

The pathogenesis of COPD involves inflammation-induced structural changes that result in small airway remodeling and narrowing and parenchymal destruction, decreased elastic recoil, and reduction in the ability of the airways to remain open [1]. COPD progression is associated with the accumulation of inflammatory mucous exudate and inflammatory exudate in the airway wall [9]. COPD is a heterogeneous disease among patients. Eosinophil infiltration was previously thought to be limited to asthma, but it is now known that eosinophil infiltration constitutes a subset of COPD [10-13], with about 37% of
patients with persistently elevated eosinophil counts [14]. Among all patients with COPD, the patients with eosinophil infiltration show the greatest response to corticosteroid therapy [10-13]. Eosinophil numbers are increased in the sputum and peripheral blood during exacerbation episodes [15, 16].

Nevertheless, the exact role of eosinophil counts in the management of patients with COPD remains controversial. The Copenhagen City Lung study showed that high peripheral eosinophil counts (>340 cells/µL) were associated with increased risk of AECOPD [17], as supported by other studies [15, 16], but such association was not observed when using a threshold of 2% [14, 17, 18]. Further contributing to the controversy, elevated blood eosinophil counts are associated with better lung function, quality of life, and mortality rates [14, 19, 20]. Eosinopenia is associated with sepsis, pneumonia, and worse prognosis of AECOPD [21-23].

Studies are lacking about the clinical significance of high eosinophil levels in hospitalized patients with AECOPD. Therefore, the aim of the present study was to examine blood eosinophil levels in relation to the prognosis of hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease.

Methods

**Study design and patients**

This was a retrospective cohort study of patients with AECOPD as their primary diagnosis and admitted to Beijing Shijitan Hospital, Capital Medical University, from January 2010 to December 2016. This study was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (#2018-10-66). The informed consent was waived because of the retrospective study.

The inclusion criteria were: 1) the diagnosis and hospitalization indications of AECOPD were consistent with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1];
and 2) complete clinical data, including one-year follow-up data. The exclusion criteria were: 1) bronchiectasis, pulmonary interstitial fibrosis, active tuberculosis, lung cancer, or other diseases; 2) diseases of the blood and endocrine system that affect blood eosinophil count; or 3) confirmed history of bronchial asthma.

**Grouping and definitions**

All patients matching the criteria during the study period were included. The patients were assigned according to the proportion and count of eosinophil in peripheral blood at their first hospitalization: \( \leq 100 \) cells/µL, \( 100 < EO < 300 \) cells/µL, and \( \geq 300 \) cells/µL. COPD was staged as GOLD1 (FEV1 >80% of predicted value), GOLD2 (50% ≤ FEV1 < 80% of predicted value), GOLD3 (30% ≤ FEV1 < 50% of predicted value), and GOLD4 (FEV1 < 30% of predicted value).

**Data collection**

Basic data and clinical manifestations included sex, age, history of disease (hypertension, type II diabetes, ischemic heart disease, asthma, tuberculosis, and osteoporosis), history of smoking, course of COPD, COPD stage, use of inhaled corticosteroids in a stable period, and acute exacerbation in the past year before hospitalization were collected. The main clinical symptoms of acute exacerbation included wheezing, coughing, and expectoration with/without purulent sputum were also collected.

Results of the first examination after admission were collected, including white blood cell count, neutrophil percentage and count, eosinophil percentage and count, arterial blood gas analysis, sputum culture, chest imaging examination, and lung function (FEV1/FVC, FEV1%, bronchodilatation test).

Treatment and outcome included patients' use of glucocorticoids during hospitalization, including duration of use and total use, duration of hospitalization, and hospital mortality.

**Follow-up**
All patients were followed at 30 days and 1 year after discharge by telephone. Follow-up was censored on 2017.12.31. Whether the patient was hospitalized again due to acute exacerbation within 30 days and 1 year after discharge was recorded (acute exacerbation of re-hospitalization refers to coughing, sputum expectoration, or wheezing).

**Statistical analysis**

SPSS 20.0 (IBM, Armonk, NY, USA) was used to analyze the data. Categorical data are expressed as n (%) and were analyzed using the chi-square test. Continuous data are presented as means ± standard deviation (SD) and were tested using ANOVA with the LSD post hoc test. Multivariable logistic regression analysis was used to analyze the association of eosinophil counts and percentage with patient outcomes. The regression method was Backward and the included variables had to be significant in the univariable analyses. The results are shown as odds ratio (OR) and 95% confidence interval (95%CI). Two-sided P-values <0.05 were considered statistically significant.

**Results**

**Characteristics of the patients**

A total of 1287 patients with AECOPD were first identified, and 132 were excluded because of concomitant asthma and 647 because they were readmissions. Among the 508 evaluable patients, 328, 142, and 38 were in the <100, 100-300, and >300 eosinophils/µL groups, respectively (Figure 1). Table 1 presents the characteristics of the patients. There were no differences among the three groups, except that the ≤100 eosinophils/µL group, compared with the 100-300 eosinophils/µL group, showed higher frequencies of fever (50.6% vs. 35.2%, P=0.002) and respiratory failure (30.5% vs. 20.4%, P=0.025).

**Blood test results**

Table 2 presents the results of the blood tests. There were no differences among the three groups regarding white blood cells (P=0.10), pH (P=0.31), PCO2 (P=0.89), and FEV1
(P=0.59). Compared with the 100-300 eosinophils/µL group, the ≤100 eosinophils/µL group showed higher neutrophil percentage (74.85±11.5% vs. 67.8±9.0%, P<0.05) and higher neutrophil count (6.33±3.97 vs. 5.01±2.08, P<0.05). Compared with the ≥300 eosinophils/µL group, the 100-300 eosinophils/µL groups showed higher neutrophil percentage (67.8±9.0 vs. 62.4±13.0%, P<0.05), lower neutrophil count (5.01±2.08 vs. 5.20±2.28, P<0.05), and higher PO2 (71.9±27.7 vs. 66.6±30.3, P<0.05).

**Clinical outcomes**

Table 3 presents the clinical outcomes. There were no differences among the three groups regarding the admission rate to the ICU (P=0.06), mechanical ventilation (P=0.24), the use of ICS (P=0.95), in-hospital mortality (P=0.98), duration of hospitalization (P=0.77), acute exacerbation within 30 days after discharge (P=0.45), and acute exacerbation within 1 year after discharge (P=0.46). Compared with the 100-300 eosinophils/µL group, the ≤100 eosinophils/µL group showed a higher use of systemic glucocorticoids (27.4% vs. 14.8%, P=0.003). Eosinophil counts were not associated with in-hospital mortality and duration of hospitalization.

**Factors associated with acute exacerbation within 1 year after discharge**

Table 4 shows the univariable and multivariable analyses of the factors associated with acute exacerbation within 1 year after discharge. GOLD3/4 (OR=2.04, 95%CI: 1.20-3.44, P=0.008), neutrophil count (OR=1.21, 95%CI: 1.03-1.41, P=0.019), systemic glucocorticoids (OR=1.84, 95%CI: 1.41-2.98, P=0.012), mechanical ventilation (OR=2.66, 95%CI: 1.36-5.18, P=0.004), and acute exacerbation in the past year before hospitalization (OR=2.03, 95%CI: 1.27-3.23, P=0.003) were independently associated with acute exacerbation within 1 year after discharge. Eosinophil count was not associated with acute exacerbation within 1 year after discharge.

**Discussion**
Studies about the clinical significance of high eosinophil levels in COPD are conflicting, and it has been even less studied in hospitalized patients with AECOPD. Therefore, the aim of the present study was to examine blood eosinophil levels in relation to the prognosis of hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease. The results suggest that peripheral blood eosinophil counts are not associated with the 1-year prognosis of AECOPD.

Eosinophils play important roles in inflammatory diseases, especially the initiation and modulation of inflammation [24]. Their role in diseases like asthma has been known for a long time, but they are now known to play roles in diseases like COPD, inflammatory bowel diseases, autoimmune myocarditis, and primary biliary cirrhosis, among others [10-13, 24, 25]. The mechanisms for their association with autoimmune diseases include degranulation of their granule content, autoantibody-dependent cell-mediated cytotoxicity, degradation of the extracellular matrix, cytokine secretion, antigen presentation, induction of fibrosis; and role in thrombosis [24, 25]. Patients with underlying eosinophil-associated diseases might be at higher risk of autoimmune diseases [24-27].

COPD is a heterogeneous disease that differs in etiology, progression, and prognosis from one patient to the other [28, 29]. About 37% of patients with COPD display a persistently elevated eosinophil count [14]. Despite the association of eosinophils with inflammatory and autoimmune diseases, the exact clinical implications of those elevated counts in COPD remain controversial [24, 25]. On the one hand, the Copenhagen City Lung study showed that eosinophil count >340 cells/µL were associated with a higher risk of AECOPD, but that the threshold of 2% was not [17], as supported by Singh et al. [14] and Zysman et al. [18]. In addition, eosinophil counts are increased in the sputum and peripheral blood during exacerbation episodes [15, 16]. Surprisingly when we consider their role in inflammation
and autoimmune diseases, elevated peripheral blood eosinophils have been associated with better lung function, improved quality of life, and lower mortality rates in patients with COPD [14, 19, 20], but this could be due to the fact that patients with COPD and high eosinophil counts respond better to corticosteroids than patients with lower eosinophil counts [10-13, 19, 30, 31]. Low eosinophil counts have also been associated with a higher occurrence of complications of AECOPD, including sepsis, pneumonia, longer hospitalization, and mortality [21-23, 32].

In the present study, the patients were grouped according to eosinophil counts of ≤100, 100-300, and ≥300 cells/µL, and no association was observed between eosinophil count and acute exacerbation within 1 year after discharge. A recent study suggested that eosinophil counts could predict exacerbation events in patients with COPD, but only in ex-smokers [33]. Brusselle et al. [34] showed that eosinophil counts could predict the recurrence of AECOPD in patients who already had a history of AECOPD episodes. Therefore, because COPD is a complex disease, it is possible that eosinophil counts are associated with the prognosis of AECOPD only in subgroups of patients. In addition, future studies should account for the environmental factors associated with the development of COPD and AECOPD [35]. On the other hand, stratification of the patients of the SPIROMICS study according to eosinophil counts showed no association between blood eosinophil counts and AECOPD, while sputum eosinophil counts were associated with AECOPD [36], therefore supporting the present study.

This study has limitations. The sample size was relatively small and from a single center. In addition, environmental factors like air pollution were not controlled for, and it is known that air pollution is elevated in Chinese cities [37], limiting the generalizability of the study. Finally, due to the retrospective nature of the study, only the data that were included in the patient charts could be analyzed.
Conclusion

Peripheral blood eosinophil counts are not associated with the 1-year AECOPD prognosis.

Abbreviations

COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD;
GOLD: Global Initiative for Chronic Obstructive Lung Disease; SD: standard deviation; OR: odds ratio; 95%CI: 95% confidence interval.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (#2018-10-66). The informed consent was waived because of the retrospective study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

ZHT have made contributions to the conception; QHF and SSY have made contributions to
design of the work; SSY and JZ have made contributions to the collection, acquisition, analysis; SSY have drafted the work or substantively revised it. All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of the patients

| Variables                  | ≤100 cells/µL (N=328) | 100-300 cells/µL (N=142) | ≥300 cells/µL (N=38) | P     |
|----------------------------|-----------------------|--------------------------|----------------------|-------|
| Age (years)                | 76.5±8.8              | 76.4±8.9                 | 75.7±8.6             | 0     |
| Sex (male)                 | 229 (69.8%)           | 107 (75.4%)              | 30 (78.9%)           | 0     |
| Course of COPD (months)    | 16.3±13.6             | 15.2±12.8                | 17.1±12.0            | 0     |
| History of smoking         | 244 (74.4%)           | 111 (78.2%)              | 33 (86.8%)           | 0     |
| GOLD3/4                    | 219 (66.8%)           | 90 (63.4%)               | 25 (65.8%)           | 0     |
| Fever                      | 166 (50.6%)           | 50 (35.2%)              | 14 (36.8%)           | 0     |
## Symptoms

| Condition                  | Group 1 | Group 2 | Group 3 |
|---------------------------|---------|---------|---------|
| Cough, expectoration      | 43 (13.1%) | 17 (12.0%) | 6 (15.8%) | < 0.001 |
| Wheezing                  | 46 (14.0%) | 19 (13.4%) | 5 (13.2%) | 0.976   |
| Both                      | 239 (72.9%) | 106 (74.6%) | 27 (71.1%) | 0.902   |
| Respiratory failure       | 100 (30.5%) | 29 (20.4%) \(^a\) | 6 (15.8%) \(^a\) | 0.022   |
| Hypertension              | 188 (57.3%) | 76 (53.5%) | 21 (55.3%) | 0.744   |
| Type 2 diabetes           | 65 (19.8%) | 36 (25.4%) | 11 (28.9%) | 0.234   |
| Ischemic cardiomyopathy   | 148 (45.1%) | 61 (43.0%) | 17 (44.7%) | 0.910   |
| Osteoporosis              | 20 (6.1%) | 8 (5.6%) | 1 (2.6%) | 0.683   |
| Previous tuberculosis     | 74 (22.6%) | 37 (26.1%) | 7 (18.4%) | 0.546   |

## Imaging manifestations

| Condition                        | Group 1 | Group 2 | Group 3 |
|----------------------------------|---------|---------|---------|
| Chronic bronchitis               | 209 (63.7%) | 95 (66.9%) | 25 (65.8%) | 0.795   |
| Pneumonia                        | 90 (27.4%) | 31 (21.8%) | 8 (21.1%) | 0.358   |
| ICS in a stable period           | 38 (11.6%) | 13 (9.2%) | 1 (2.6%) | 0.200   |

EO: eosinophils; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for
Chronic Obstructive Lung Disease; ICS: inhaled corticosteroids; ICU: intensive care unit.

\(^a\) P < 0.05 vs. the ≤100 eosinophils/μL group.

**Table 2.** Blood and pulmonary test results of patients hospitalized for AECOPD and according to eosinophil levels at admission

| Variables          | EO ≤100/μl (N=328) | 100 < EO < 300/μl (N=142) |
|--------------------|--------------------|---------------------------|
| WBC (×10^9/L)      | 7.83±3.97          | 7.20±2.34                 |
| NE%                | 74.84±11.53        | 67.78±9.02 \(^a\)         |
| Parameter                        | Value 1       | Value 2       |
|---------------------------------|---------------|---------------|
| NE count (x10^9/L)             | 6.33±3.97     | 5.01±2.08 a   |
| EO%                            | 0.500 (0.200-1.100) | 2.550 (1.800-3.30) |
| EO count (/µl)                  | 39.55±31.97   | 177.02±51.38 a |
| pH                             | 7.09±1.50     | 6.84±1.99     |
|                  | Value 1 | Value 2 |
|------------------|---------|---------|
| **PO$_2$ (mmHg)** | 73.69±25.40 | 71.87±27.67 |
| **PCO$_2$ (mmHg)** | 43.13±16.08 | 38.68±15.33 |
| **FEV1% predicted** | 52.05±19.20 | 53.84±17.69 |

EO: eosinophils; WBC: white blood cells; NE: neutrophils; PO$_2$: partial pressure of oxygen; PCO$_2$: partial pressure of carbon dioxide; FEV1: forced expiratory volume in 1
second.

^\text{a}P<0.05 \text{ vs. the } \leq 100 \text{ eosinophils/µL group}; ^\text{b}P<0.05 \text{ vs. the } 100-300 \text{ eosinophils/µL group.}

**Table 3. Clinical outcomes of patients with AECOPD after hospitalization and according to the blood eosinophil levels**

| variables                        | EO \(\leq 100/\mu l\) (N=328) | 100<EO<300/µl (N=142) | EO \(\geq 300/\mu l\) (N=38) |
|----------------------------------|--------------------------------|------------------------|-----------------------------|
| Admission to ICU                 | 41 (12.5%)                     | 10 (7.0%)              | 1 (2.6%)                    |
| ICS                              | 264 (80.5%)                    | 113 (79.6%)            | 31 (81.6%)                  |
| Mechanical ventilation           | 32 (9.8%)                      | 14 (9.9%)              | 1 (2.6%)                    |
| Systemic glucocorticoids         | 90 (27.4%)                     | 21 (14.8%)^a           | 9 (23.7%)                   |
| In-hospital mortality            | 10 (3.0%)                      | 4 (2.8%)               | 1 (2.6%)                    |
| Duration of hospitalization (days)| 10.8\pm9.9                     | 11.4\pm13.4            | 10.0\pm4.8                  |
| Acute exacerbation within 30 days after discharge | 14 (4.4%)                     | 3 (2.2%)               | 1 (2.7%)                    |
| Acute exacerbation within 1 year after discharge | 99 (31.1%)                    | 35 (25.4%)             | 13 (35.1%)                  |

EO: eosinophils; ICU: intensive care unit; ICS: inhaled corticosteroids.
Table 4. Univariable and multivariable analyses of factors associated with acute exacerbation within 1 year after discharge

| Variables                        | Univariable |              | Multivariable |              |
|----------------------------------|-------------|--------------|---------------|--------------|
|                                  | OR          | 95% CI       | P             | OR           | 95% CI       |
| Age                              | 1.011       | 0.989-1.034  | 0.338         |              |              |
| Sex                              | 1.606       | 1.057-2.440  | 0.026         |              |              |
| History of smoking               | 0.994       | 0.632-1.564  | 0.979         |              |              |
| GOLD 3/4                         | 3.397       | 2.114-5.459  | <0.001        | 2.035        | 1.203-3.4    |
| Fever                            | 1.265       | 0.725-1.575  | 0.736         |              |              |
| Admission to ICU                 | 3.527       | 1.875-6.633  | <0.001        |              |              |
| Respiratory failure              | 2.418       | 1.575-3.711  | <0.001        |              |              |
| Hypertension                     | 1.045       | 0.708-1.542  | 0.826         |              |              |
| Type 2 diabetes                  | 1.504       | 0.956-2.365  | 0.078         |              |              |
| Previous tuberculosis            | 1.374       | 0.884-2.136  | 0.158         |              |              |

aP<0.05 vs. the ≤100 eosinophils/µL group
| Condition                                | Odds Ratio | 95% CI          | p-value |
|------------------------------------------|------------|-----------------|---------|
| Ischemic cardiomyopathy                 | 1.496      | 1.015-2.206     | 0.042   |
| Osteoporosis                            | 1.256      | 0.569-2.772     | 0.572   |
| Chronic bronchitis on CT                | 0.734      | 0.492-1.096     | 0.131   |
| Pneumonia on CT                         | 1.017      | 0.652-1.587     | 0.941   |
| pH                                      | 1.066      | 0.945-1.203     | 0.300   |
| PaO₂                                     | 1.003      | 0.995-1.010     | 0.464   |
| PaCO₂                                    | 1.030      | 1.017-1.043     | <0.001  |
| Count of WBC                            | 1.015      | 0.964-1.069     | 0.566   |
| Count of NE                             | 1.049      | 0.994-1.108     | 0.082   | 1.206 | 1.031-1.4 |
| Count of EO                             |            |                 |         |
| EO ≤ 100/µl                             | Reference  |                 |         |
| 100 < EO < 300/µl                       | 0.812      | 0.548-1.205     | 0.302   |
| EO ≥ 300/µl                             | 1.198      | 0.586-2.451     | 0.620   |
| ICS in a stable period                  | 0.979      | 0.518-1.848     | 0.947   |
### Systemic glucocorticoids
- Value: 2.663
- Confidence Interval: 1.716-4.131
- p-value: <0.001
- Odds Ratio: 1.843
- Confidence Interval: 1.414-2.9

### Mechanical ventilation
- Value: 4.327
- Confidence Interval: 2.269-8.252
- p-value: <0.001
- Odds Ratio: 2.656
- Confidence Interval: 1.363-5.1

### Acute exacerbation in the past year before hospitalization
- Value: 2.900
- Confidence Interval: 1.902-4.422
- p-value: <0.001
- Odds Ratio: 2.025
- Confidence Interval: 1.269-3.2

**ICU**: intensive care unit; **ICS**: inhaled corticosteroids; **CT**: computed tomography; **PaO$_2$**: partial pressure of oxygen; **PaCO$_2$**: partial pressure of carbon dioxide; **WBC**: white blood cells; **NE**: neutrophils; **EO**: eosinophils; **AE**: acute exacerbation.

**Figures**

![Flowchart](image)

**Figure 1**
Patient flowchart and selection process

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