

# Association between blood eosinophil count and bacterial infection and clinical outcomes in patients with severe exacerbations of chronic obstructive pulmonary disease

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Appropriate management of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is very important because such exacerbation negatively impacts patients' health status, disease progression, and mortality. Exacerbation episodes are mainly triggered by viral and bacterial infections, and one study showed that 55% of hospitalized patients with AECOPD had a bacterial infection.<sup>[1]</sup> Some analyses have suggested that antibiotic therapy can reduce the risk of short-term mortality and improve the prognosis. However, not all patients with AECOPD benefit from antibiotic therapy. The blood eosinophil count has been used as a biomarker for eosinophil-associated airway inflammation and sepsis. However, the association between the peripheral blood eosinophil count and bacterial pathogens has not been reported. Our aim was to analyze the associations among the eosinophil count, bacterial pathogens, clinical treatments, and prognosis of patients and provide useful and comprehensive references for AECOPD management.

Patients aged >40 years with AECOPD who were admitted to the Department of Respiratory and Critical Care Medicine of Peking University Third Hospital from January 2013 to June 2018 were identified via an electronic database. Chronic obstructive pulmonary disease (COPD) and AECOPD were diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease criteria. Patients with the following conditions were excluded: (1) bronchial asthma; (2) allergic rhinitis, eczema, urticaria, or other allergic diseases; (3) other respiratory diseases such as bronchiectasis, interstitial lung disease, or tuberculosis; and (4) pre-admission treatment with an oral corticosteroid. This study was approved by the Ethics Committee of Peking University Third Hospital, Beijing, China (No. IRB00006761-M2020067). The

eosinophil count from the first blood cell count obtained in the hospital was used to divide the patients into a low and high eosinophil group. In accordance with previous studies,<sup>[2]</sup> we defined the low eosinophil group (eosinopenia) as <2% and the high eosinophil group (eosinophilia) as ≥2%. The patients' demographic data, comorbidities, and lung function were recorded, and their laboratory test results including blood cell counts, C-reactive protein (CRP), procalcitonin (PCT), and D-dimers were collected. The following outcome parameters were compared between the two groups: the duration of hospitalization and intensive care unit (ICU) stay, mechanical ventilation, mortality during hospitalization, readmission rate at 7 and 14 days after discharge, systemic corticosteroid use (including oral and intravenous corticosteroids), and antibiotic use.

A CRP concentration of ≥20 mg/L was used as a validated surrogate measure reflecting bacterial infection.<sup>[3]</sup> Patients who had purulent sputum with an increase in dyspnea and/or an increased sputum volume were considered to have a bacterial infection. Exacerbations were identified as being associated with bacterial infection when the CRP concentration was ≥20 mg/L or when the above-mentioned symptoms were present. Exacerbations were considered unrelated to bacterial infection when both the CRP concentration was <20 mg/L and the above-mentioned symptoms were absent. Sputum (white blood cell [WBC] count >25/high power field [HPF], epithelial cell count <10/HPF) was collected for bacterial culture and analyzed.

Data were analyzed using SPSS software version 21.0 (IBM Corp., Armonk, NY, USA). Demographic characteristics and clinical outcomes were summarized using basic descriptive statistics for parametric (mean ± standard deviation) or non-parametric (median [Q<sub>1</sub>, Q<sub>3</sub>]) data

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and analyzed by the *t* test or Mann-Whitney *U* test. Chi-square test or Fishers's exact test was used for categorical data. Time-to-event survival analyses were conducted using Kaplan-Meier methods and log-rank tests. Statistical significance was denoted by  $P < 0.05$ .

The electronic review of 1282 cases identified 630 patients with AECOPD. After excluding patients with allergic rhinitis, eczema, urticaria, and other allergic diseases ( $n=11$ ) and with prehospital oral corticosteroid use ( $n=23$ ), 596 patients were eligible for analysis. The proportion of exacerbations with a high eosinophil count (eosinophilia) was 34.9% ( $n=208$ ), and that with a low eosinophil count (eosinopenia) was 65.1% ( $n=388$ ). There was no significant difference in age or sex between the two groups ( $P > 0.05$ ). The eosinopenia group had less smokers (78.6% vs. 87.0%,  $\chi^2 = 5.819$ ,  $P = 0.012$ ) and more patients with diabetes and hypertension (26.3% vs. 15.4%,  $\chi^2 = 8.623$ ,  $P = 0.002$ ; 54.6% vs. 42.8%,  $\chi^2 = 7.141$ ,  $P = 0.006$ , respectively); patients in this group were also more likely to present with cough (88.9% vs. 82.2%,  $\chi^2 = 4.679$ ,  $P = 0.022$ ) and had worse lung function (percentage of predicted forced expiratory volume in 1 s [FEV<sub>1</sub>% pred]: (49.9 ± 24.4)% vs. (60.7 ± 28.2)%,  $t = -2.664$ ,  $P = 0.008$ ) [Supplementary Table 1, <http://links.lww.com/CM9/A720>].

A CRP concentration of  $\geq 20$  mg/L was detected in 24.5% ( $n = 51$ ) of patients in the eosinophilia group and in 42.3% ( $n = 164$ ) of patients in the eosinopenia group ( $\chi^2 = 17.736$ ,  $P = 0.004$ ). According to our criteria, bacterial infection was detected in 36.1% ( $n = 75$ ) of patients in the eosinophilia group and in 47.7% ( $n = 185$ ) of patients in the eosinopenia group ( $\chi^2 = 7.004$ ,  $P = 0.008$ ). The eosinophil percentage was significantly lower in patients with than without bacterial infection (1.3% vs. 2.4%,  $t = 2.734$ ,  $P = 0.006$ ). The WBC ( $[8.55 \pm 3.49] \times 10^9/L$  vs.  $[7.07 \pm 2.43] \times 10^9/L$ ,  $t = 5.447$ ,  $P < 0.001$ ) and neutrophil counts ( $[77.17 \pm 14.02] \times 10^9/L$  vs.  $[64.98 \pm 13.99] \times 10^9/L$ ,  $t = 10.127$ ,  $P < 0.001$ ) and the CRP (25.70 [9.11, 64.14] mg/L vs. 14.95 [6.74, 23.76] mg/L,  $U = -2.737$ ,  $P = 0.006$ ) and PCT (0.13 [0.05, 0.27]  $\mu\text{g/L}$  vs. 0.07 [0.05, 0.22]  $\mu\text{g/L}$ ,  $U = -2.558$ ,  $P = 0.010$ ) concentrations were all significantly higher in the eosinopenia than in the eosinophilia group [Supplementary Table 1, <http://links.lww.com/CM9/A720>].

In total, 233 sputum isolates with identified pathogens were included in the final analysis: 57 (24.5%) in the eosinophilia group and 176 (75.5%) in the eosinopenia group. The overall bacterial isolation rate was higher in the eosinopenia than eosinophilia group (45.4% vs. 27.4%, respectively). Gram-negative bacilli were dominant in both groups: 37 (17.8%) in the eosinophilia group and 98 (25.3%) in the eosinopenia group. The percentages of *Coagulase Negative Staphylococcus* (11.9% vs. 5.3%,  $\chi^2 = 6.014$ ,  $P = 0.006$ ) and *Enterococcus* (2.6% vs. 0,  $P = 0.013$ ) were significantly higher in the eosinopenia group than in the eosinophilia group [Supplementary Table 1, <http://links.lww.com/CM9/A720>]. In addition, the rankings of *Staphylococcus Aureus* and *Enterococcus* in all the isolated strains were higher in the eosinopenia group than in the eosinophilia group. Some sputum cultures showed only unclassified negative bacilli, and

because of the small amount of these strains, further identification was difficult.

There were significant differences in clinical outcomes. Longer hospital or ICU stay (15 [12, 21] days vs. 14 [9, 19] days,  $U = -2.715$ ,  $P = 0.007$ ; 0 [0, 0] vs. 0 [0, 0] days,  $U = -4.557$ ,  $P < 0.001$ ) and duration of antibiotic use ( $11.41 \pm 4.50$  days vs.  $10.23 \pm 4.62$  days,  $t = -2.964$ ,  $P < 0.001$ ), more need for invasive ventilation (3.4% vs. 1.0%,  $\chi^2 = 2.251$ ,  $P = 0.033$ ) were found in the eosinopenia group. Kaplan-Meier analyses showed that the hospital stay was longer in the eosinopenia than eosinophilia group ( $P = 0.027$ ). There were no significant differences in mortality during hospitalization, readmission rate at 7 and 14 days after discharge and systemic corticosteroid use between the two groups ( $P > 0.05$ ).

Determining whether AECOPD is caused by bacterial infection and ensuring more rational use of antibiotics are important issues in the clinical setting. We used the peripheral blood eosinophil count as a biomarker for auxiliary determination of the probable AECOPD-associated pathogen sub-types; these have not been previously reported and will hopefully provide some reference for AECOPD treatment. We found that when using a CRP concentration of  $\geq 20$  mg/L combined with the symptoms as criteria, the bacterial infection rate was significantly higher in the eosinopenia than in the eosinophilia group; this is consistent with the previous study.<sup>[4]</sup> Based on our data, nearly half of patients with AECOPD who have a low eosinophil count may have bacterial infection. The CRP concentration, PCT concentration, and WBC count of patients with AECOPD were significantly higher in the eosinopenia than eosinophilia group, indicating more severe infection and systemic inflammation. Moreover, a low eosinophil count was associated with a poor clinical prognosis of COPD. Accordingly, empirical use of antibiotics in patients with AECOPD who have a low eosinophil count is of value. In patients with eosinophilia, acute exacerbations may be more likely to have other causes, such as eosinophilic airway inflammation, viral infection, or other environmental factors.<sup>[5]</sup>

Bacterial pathogen analysis would help to expand our understanding of the relationship between the eosinophil count and specific infection sub-types. The overall bacterial isolations were higher in the eosinopenia than eosinophilia group (45.4% vs. 27.4%, respectively); in particular, the Gram-positive cocci load was higher in the eosinopenia group. The differences in *Coagulase Negative Staphylococcus* and *Enterococcus* between the two groups were significant. The microbiome profile analysis of AECOPD suggested that the presence of *Staphylococcus* in sputum samples was associated with a prolonged hospital stay and a 7.3-times higher mortality rate compared with patients who did not have this genus in their sputum.<sup>[6]</sup> Thus, an increased amount of Gram-positive cocci, especially *Staphylococcus*, may partly explain the poor clinical prognosis in patients with eosinopenia. The positive sputum culture rate was reduced because of the prehospital use of antibiotics in this study. However, because the patients in both groups were treated with antibiotics, the results of the comparison of the two groups should not have been affected.

These data may be helpful when choosing an empirical antibacterial medicine for patients with AECOPD who have a low eosinophil count in clinical practice, and clinicians should note that the presence of Gram-positive cocci merits more concern. For patients with high eosinophils, a short course of relatively narrow-spectrum antibiotics may be enough.

In summary, our data indicate that peripheral blood eosinophils can be used as an effective biomarker to guide antibiotic use in hospitalized patients with AECOPD. However, this study was a clinical observation with limited numbers of positive sputum cultures, and the results should be further investigated in large-scale prospective clinical trials. Eosinophils and other inflammatory indicators such as CRP and clinical symptoms could be integrated into the clinical treatment strategy of AECOPD, which is conducive to achieving personalized and precise treatment.

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### Conflicts of interest

None.

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