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Relationship of Blood Eosinophils with Fractional Exhaled Nitric Oxide and Pulmonary Function Parameters in Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The 2018 Global Initiative for Chronic Obstructive Lung Disease Report reveals that the blood eosinophil count could forecast the risk of flare-ups. This study explored the correlations of blood eosinophils with fractional exhaled nitric oxide (FeNO) and pulmonary function parameters in acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

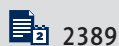
Material/Methods: The data of patients with AECOPD at our hospital admitted between July 2018 and June 2019 were retrospectively analyzed. All patients were stratified into an eosinophilic group ($\geq 2\%$) or a noneosinophilic group ($< 2\%$) based on the peripheral eosinophil count per centum. Cross-sectional analysis was performed to compare clinical characteristics, percentage of eosinophils, FeNO, and pulmonary function between the 2 groups.

Results: After applying the inclusion/exclusion criteria, 247 patients were included. FeNO values were higher in eosinophilic group ($n=97$) than in noneosinophilic group ($n=150$) ($P=0.005$). The forced expiratory volume in 1 second% predicted (FEV1% predicted), FEV1, and forced vital capacity (FVC) were higher in the eosinophilic group than in the noneosinophilic group ($P=0.043$; $P=0.040$; and $P=0.011$, respectively). Blood eosinophilia showed positive correlations with FeNO ($P=0.004$) and spirometry variables (FEV₁ [% predicted], $P=0.003$; FEV₁, $P<0.001$; and FVC, $P<0.001$). An FeNO level of 22.5 ppb was the best cutoff value to predict blood eosinophilia ($P=0.000$).

Conclusions: Blood eosinophil count is a likely biomarker that can predict positive relationship with FeNO values and pulmonary function parameters.

MeSH Keywords: **Disease Progression • Eosinophils • Nitric Oxide • Pulmonary Disease, Chronic Obstructive • Respiratory Function Tests**

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Background

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, and to has been predicted to rise to the third leading cause of death by 2020 [1]. It is a heterogeneous disease, characterized by incomplete reversible progressive airflow limitation, which is consistent with chronic inflammation-induced permanent structural changes to airways and pulmonary blood vessels [1,2]. Acute exacerbation of COPD (AECOPD) is characterized by rapid aggravation of clinical manifestations, flare-up of airway inflammation, rapid decrease in pulmonary function, and increased risk of death; thus, it also increases socio-economic pressure and reduces the life quality of patients [1,3].

The 2018 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report suggests that the sputum or blood acidophilic leukocytes per centum could forecast the risk of flare-ups [1]. Based on former research, 28% of AECOPD patients present with hypereosinophilia in the sputum, which could forecast flare-up risk and the effects of glucocorticoid treatment [4]. Despite its simplicity and reliability in evaluating respiratory tract inflammatory reactions, the sputum specimen collection also has some disadvantages in clinical use. For instance, 1) testing can become complicated and cannot be applied at the bedside; 2) specific requirements for patients' physical conditions; 3) high professional and technical ability of the operator required; and 4) it may pose other complications.

Therefore, simple, easy methods of clinical examination, including blood peripheral eosinophilic evaluation and fractional exhaled nitric oxide (FeNO), have attracted increasing attention [5,6]. The FeNO, a noninvasive detection technique, could safely, quickly, and simply determine the eosinophilic respiratory tract inflammatory response [7]. Previous studies have shown that the FeNO aids in the distinction of eosinophilic and noneosinophilic airway inflammation, and may play potential roles in COPD, asthma, and interstitial lung diseases [8–10]. Chou et al. [11] showed that FeNO is positively associated with sputum eosinophils in patients with COPD. However, whether a relationship exists between FeNO and blood eosinophils in patients with AECOPD is unknown.

Accordingly, peripheral blood eosinophil counts/ratio have also been gaining increasing research attention as a potential diagnostic alternative, given their ease of evaluation in clinical practice. Several studies have investigated the influence of eosinophils on airway inflammation in COPD [11–14]. A cut-off point of 2% was used as the defined threshold for blood eosinophilia stratification, which is a very sensitive approach to predict eosinophil-related airway inflammation and eosinophil-related flare-up [4,15]. The study of Choi et al. [16] revealed that the level of forced expiratory volume in 1 second (FEV₁) in

an eosinophilic group (% of blood eosinophils $\geq 2\%$) was markedly higher than that in a noneosinophilic group (% of blood eosinophils $< 2\%$) of AECOPD patients. Nevertheless, the aim of their research was to explore the association of blood eosinophil per centum and bacterial infection, but not pulmonary function [16].

Consequently, based on the foregoing information, this cross-sectional project was designed to assess the association of blood eosinophil per centum with FeNO values in with AECOPD patients. We also investigated the correlation between the percentage of blood eosinophils and pulmonary function parameters (i.e., FEV_{1%} predicted, FEV₁ and forced vital capacity [FVC]).

Material and Methods

Protocol design

The present project was a cross-sectional research (Figure 1). The included patients with AECOPD were stratified into an eosinophilic group ($\geq 2\%$) and a noneosinophilic group ($< 2\%$), based on their peripheral eosinophil cell counts. The data, which linked real-world clinical and medical administrative records, were derived from routine clinical practice and medical procedures, respectively.

Data sources and patients

We made the data extraction of the study based on the electronic medical database at Jiangxi Provincial People's Hospital. We retrospectively reviewed and analyzed the medical demographic features and baseline clinical records of subjects involved in the study. We also collected the following postbronchodilator values of the pulmonary function test (PFT): % predicted FEV₁, FEV₁, FVC, and FEV₁/FVC (%). Tests for FeNO, other laboratory tests, and spirometry measurements were conducted within 24 hours of admission, all on the same day.

Study patients

Inclusion and exclusion criteria

All patients hospitalized for AECOPD (diagnosed according to the 2018 GOLD guidelines [1]) from July 2018 to June 2019 were included. Patients were no younger than 40 years. Patients were excluded if: 1) valid data on demographic and/or clinical characteristics or outcome records (including FeNO levels, PFT results, and peripheral blood cell counts/ratios) were absent; 2) they had one or more of the following diseases, e.g., acute pulmonary edema, pulmonary tuberculosis, interstitial lung disease, pneumothorax, lung cancer, asthma-COPD, acute cardiac dysfunction, or amnesia; 3) they had a comorbidity that could

affect the blood eosinophilic granulocyte per centum, such as allergic diseases, parasitic infections/diseases, cancer, or any dermatological, hematological, infectious, or autoimmune disease; or 4) they had undergone any steroid or antibiotic treatments 4 weeks prior to hospitalization.

Assessments and study outcomes

Blood collection and analysis: peripheral venous blood eosinophilic count/ratio analysis was performed using an Automated Hematology Blood Analyzer (Abbott Cell-Dyn3700; Abbott, USA) and its imported high-quality matching reagents.

FeNO

Measurements of FeNO levels were performed before the PFT, using an exhaled nitric oxide determination system (NIOX MINO, sensor model TK300/500, Aerocrine AB, Solna, Sweden), in accordance with the instruction for standardized FeNO procedures [17]. Participants were required no eating, drinking, or smoking for 1 hour or longer, before the FeNO tests. Briefly, patients were required to breathe in exogenous nitric oxide-free air to the maximum lung capacity, after which they had to breathe out with a velocity of 50 mL/s, which lasted for 6–10 seconds. The expiratory pressure was controlled at 10–20 cmH₂O, and the nitric oxide analyzer automatically calculated the required values.

Spirometry

Airflow limitation was calculated using spirometry (MasterScreen Pneumo PC spirometer; JAEGER; Germany) to measure post-bronchodilator FEV₁, FVC, and FEV₁/FVC, according to the manufacturer's instructions [18]. In addition, based on the reported reference equations, we computed the prediction percentage values (% predicted) [19]. All patients were required to undergo PFT in a reproducible manner, to obtain optimal results.

Ethics approval

We performed the present protocol in compliance with the tenets of the Helsinki Declaration, and got endorsement from our hospital's ethics committee. Considering the retrospective design of the study, the hospital's ethics committee exempted the need for informed consent; however, all identifying patient data were anonymized.

Statistical analysis

Data analysis was conducted by SPSS 25. We described the normally distributed data of continuous variables as mean±standard deviation (SD) and conducted *t*-tests for comparisons. We expressed nonparametric data in median

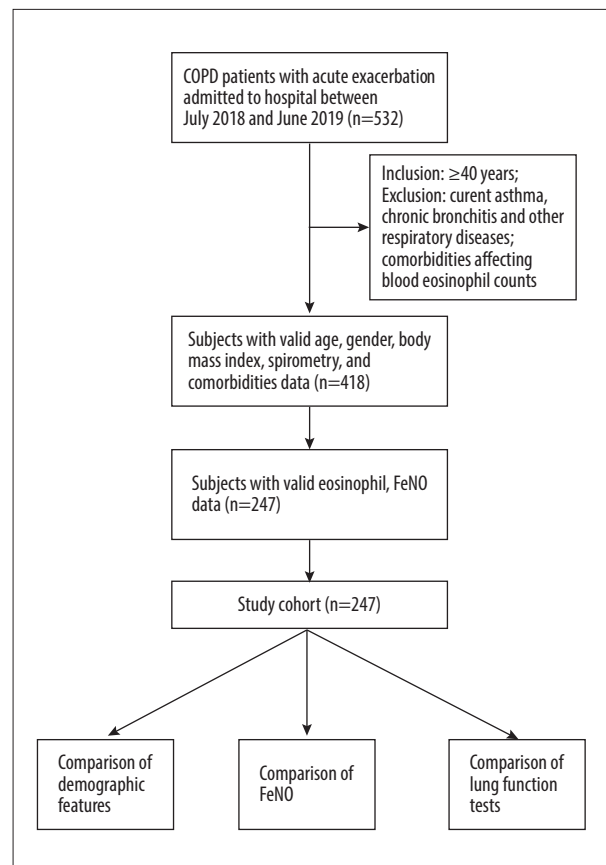


Figure 1. Flow chart showing the screening procedure for the participants.

(interquartile range) and employed Mann-Whitney U test for comparisons. The comparisons between classification variables using chi-squared test. The relationship of blood eosinophilic cell per centum with FeNO and lung function was calculated by means of the Spearman's rank correlation coefficient. The correlation of FeNO and blood eosinophil per centum was determined by performing receiver operating characteristic (ROC) curve calculation. The optimum cutoff point was identified by the maximum sum of the sensitivity and specificity. For all analyses, statistical difference was defined at $P < 0.05$.

Results

Clinical features of participants

This present study flowchart is shown in Figure 1. The demographic and clinical characteristic data of all participants enrolled in this project are shown in Table 1. In our retrospective cross-sectional study, 247 eligible participants with AECOPD were included. The median age was 72.0 years (67.0–79.0 years). Approximately 78.1% (193 patients) were male, and almost all participants were either a current-smoker or an

Table 1. Demographic features and baseline characteristics of present research population.

Variable	Total (n=247)	Noneosinophilic* (n=150)	Eosinophilic** (n=97)	P-value#
Age (years)	72.0 (67.0, 79.0)	72.0 (67.0, 79.0)	72.0 (65.0, 80.0)	0.814
Males, n (%)	193 (78.1)	119 (79.3)	74 (76.3)	0.572
Body mass index, kg/m ² , Mean (SD)	21.5 (3.7)	22.4 (3.4)	22.3 (4.0)	0.860
Smokers, n (%)	173 (70.0)	108 (72.0)	65 (67.0)	0.403
Pack years	30.0 (0.0, 40.0)	23.0 (0.0, 40.0)	30.0 (0.0, 40.0)	0.115
FeNO, levels, ppb, mean (SD)	27.2 (20.7)	23.9 (15.2)	32.3 (26.3)	0.005
Postbronchodilator FEV ₁ (% predicted)	37.0 (27.0, 49.0)	34.5 (26.0, 48.3)	40.0 (30.0, 49.0)	0.012
Postbronchodilator FEV ₁ (L)	0.74 (0.57, 0.98)	0.72 (0.56, 0.97)	0.82 (0.63, 1.04)	0.010
Postbronchodilator FVC (L)	1.39 (1.07, 1.76)	1.30 (1.06, 1.69)	1.52 (1.19, 1.82)	0.011
Postbronchodilator FEV ₁ /FVC (%)	53.0 (49.0, 65.0)	53.0 (48.0, 65.0)	53.0 (50.0, 66.0)	0.563
Comorbidities				
Coronary artery disease, n (%)	39 (15.8)	21 (14.0)	18 (18.6)	0.338
Hypertension, n (%)	79 (32.0)	52 (34.7)	27 (27.8)	0.261
Diabetes, n (%)	16 (6.5)	9 (6.0)	7 (7.2)	0.704

* Refers to blood eosinophil count <2%; ** Refers to blood eosinophil count ≥2%. # P-value is for eosinophilic group vs. noneosinophilic group. SD – standard deviation; FeNO – fractional exhaled nitric oxide; ppb – parts per billion; FEV₁ – forced expiratory volume in one second; FVC – forced vital capacity.

ex-smoker (78 out of 169 patients) with a median pack-years of 30.0 (range: 0.0–40.0 pack-years). As expected, patients had several comorbidities such as coronary artery disease (15.8%), high blood pressure (32.0%), and diabetes (6.5%).

Spirometry measurements are presented in Table 1. All patients had severe lung impairment, and the median postbronchodilator FEV₁ (% predicted), FEV₁ (L), FVC (L), and FEV₁/FVC (%) values were 37.0 (range: 27.0–49.0); 0.74 (range: 0.57–0.98); 1.39 (range: 1.07–1.76); and 53.0 (range: 49.0–65.0), respectively. The patient population had mean ± SD FeNO levels of 27.2 ± 20.7 parts per billion (ppb).

Considering a threshold value of ≥2% for the per centum of eosinophilic granulocytes in blood, 97 patients (39.2%) were classified as having peripheral blood eosinophilia, and the remaining 150 patients (60.8%) with peripheral blood noneosinophilia.

FeNO and lung function parameters

We compared the primary parameters using 2% as peripheral blood eosinophil percentage. The eosinophilic group showed significantly higher FeNO values than the noneosinophilic group (mean [SD] was 32.3 [26.3] ppb versus 23.9 [15.2] ppb, $P=0.005$) (Table 1, Figure 2A).

The postbronchodilator% predicted FEV₁ levels in eosinophilic patients were markedly higher in comparison with those in noneosinophilic patients (40.0% [range: 30.0–49.0%] versus 34.5% [range: 26.0–48.3%], $P=0.043$) (Table 1, Figure 2B). Furthermore, eosinophilic patients had significantly higher levels of FEV₁ and FVC than noneosinophilic patients (0.82 L (range: 0.63–1.04 L) versus 0.72 L (range: 0.56–0.97 L), $P=0.040$; 1.52 L (range: 1.19–1.82 L) versus 1.30 L (range: 1.06–1.69 L), $P=0.011$, respectively) (Table 1, Figure 2C, 2D). However, no significant differences were noted in FEV₁/FVC ($P=0.563$) between the 2 groups (Table 1).

Correlations among blood eosinophilic granulocyte numbers, FeNO levels, and pulmonary function parameters

A markedly positive correlation was observed between the number of eosinophilic granulocytes in blood and FeNO values ($P=0.383$; $P=0.004$) (Figure 3A). We also observed a significant correlation of blood eosinophilia and FEV₁ (% predicted) in AECOPD ($P=0.387$; $P=0.003$) (Figure 3B). Similarly, blood eosinophilic counts were associated with both FEV₁ ($P=0.413$; $P<0.001$) (Figure 3C) and FVC ($P=0.444$; $P<0.001$) (Figure 3D).

However, no significant correlation was observed between the blood eosinophilic granulocyte count and the FEV₁/FVC ($P=0.092$;

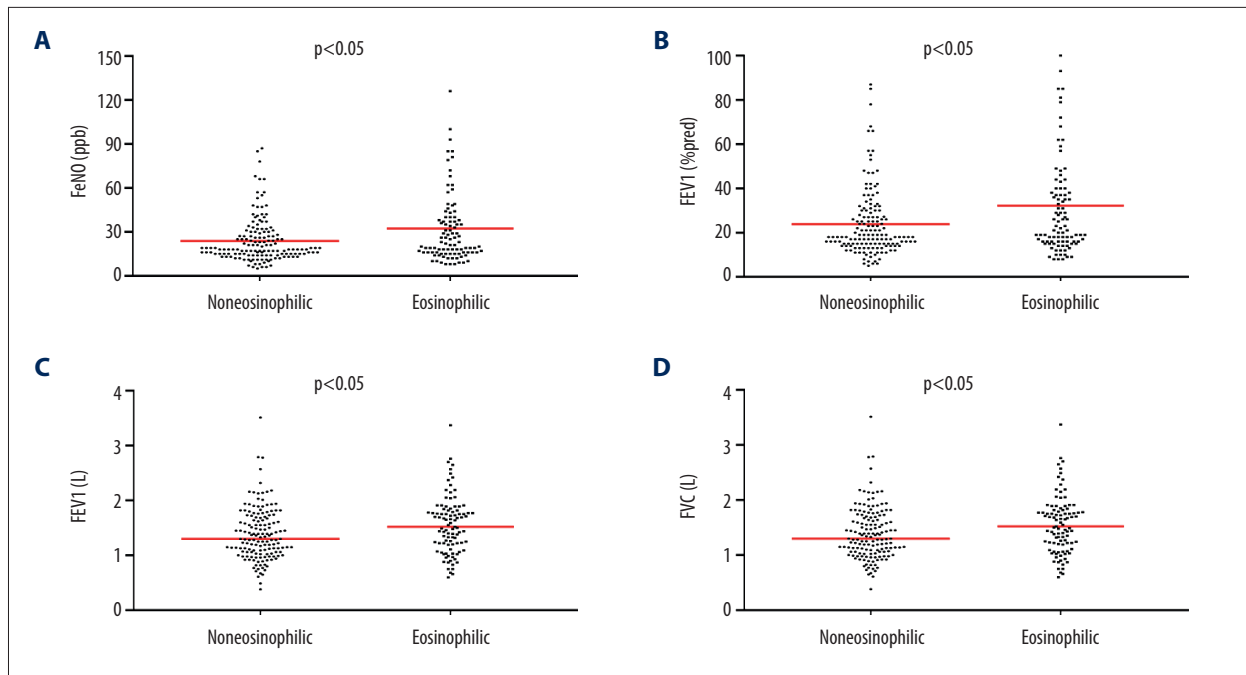


Figure 2. Scatter plots for comparison between the noneosinophilic group (<2% blood eosinophils) and eosinophilic group (≥2% blood eosinophils). **(A)** Comparison of FeNO levels. **(B)** Comparison of FEV₁ (% predicted) levels. **(C)** Comparison of FEV₁ levels. **(D)** Comparison of FVC levels. FeNO – fractional exhaled nitric oxide; FEV₁ – forced expiratory volume in one second; FVC – forced vital capacity.

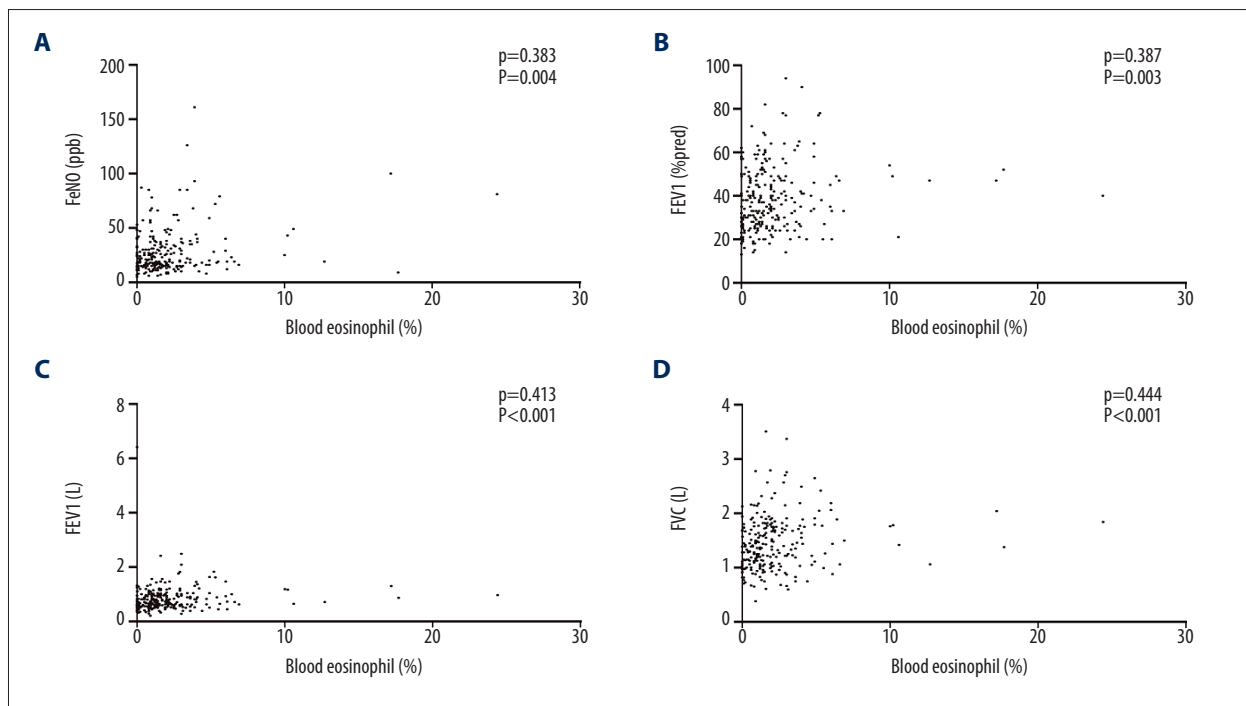


Figure 3. Scatter plots for correlations among blood eosinophil count (%), FeNO levels, and pulmonary function parameters. **(A)** Correlation of blood eosinophil per centum and FeNO values (ppb). **(B)** Correlation of blood eosinophil per centum and FEV₁ (% predicted). **(C)** Correlation of blood eosinophil per centum and FEV₁ (L). **(D)** Correlation of blood eosinophil per centum and FVC (L). FeNO – fractional exhaled nitric oxide; ppb – parts per billion. FEV₁ – forced expiratory volume in one second; FVC – forced vital capacity.

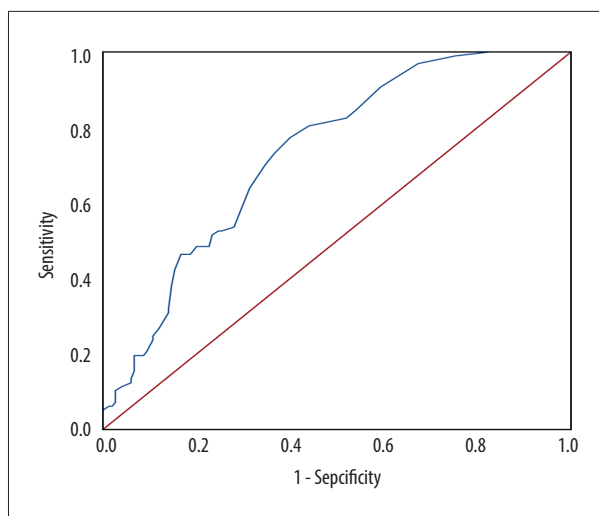


Figure 4. Receiver operating characteristic curve to predict blood eosinophilia ($\geq 2\%$ blood eosinophils) using FeNO values. FeNO – fractional exhaled nitric oxide.

$P=0.148$). The ROC curve analysis showed that an FeNO level of 22.5 ppb was the best cutoff value to predict blood eosinophilia, the area under the curve (AUC) = 0.73; 95% confidence interval=0.67–0.79, $P=0.000$). The sensitivity and specificity for predicting blood eosinophilia at an FeNO level of 22.5 ppb were 77.3% and 60.0%, respectively (Figure 4).

Discussion

The current study was conducted using a real-world electronic medical database and retrospectively analyzed the relationship among peripheral blood eosinophils, lung function parameters, and FeNO values ($n=247$). We analyzed detailed information regarding patients with AECOPD. The following are the 3 main findings of the study: first, 97 patients (39.2%) had a peripheral blood eosinophilic percentage $\geq 2\%$. This may provide important information for future large-scale surveys of blood eosinophil levels. Second, the results revealed that FeNO levels were significantly higher among eosinophilic patients than non-eosinophilic patients. This indicates that FeNO may be a good marker to identify eosinophilic inflammation in patients with AECOPD. Third, patients in the eosinophilic group showed better pulmonary function (FEV_1 [% predicted], FEV_1 [L], FVC [L]), which suggests that different levels of blood eosinophils may independently influence the PFT results.

Previous studies on peripheral blood eosinophils have been mainly focused on stable COPD [20–23]. Hence, studies evaluating the latent role of blood eosinophilic granulocytes in patients with AECOPD are scarce. Several studies have reported that up to 40% of patients with AECOPD show $\geq 2\%$ blood eosinophils at admission [24–27]. Bélanger et al. [28] reported

that 36% of AECOPD patients have confirmed blood eosinophilia, which is consistent with our present findings.

In contrast, DiSantostefano et al. [29], in their cross-sectional study based on an American COPD population survey cohort ($n=948$), showed that up to 70% of adults with COPD in the United States have $>2\%$ blood eosinophil levels. The disparity in these results may be related to differences in the inclusion/exclusion criteria employed by the studies. For instance, unlike the National Health and Nutrition Examination Survey 2007–2010, DiSantostefano et al. [29] based their findings on a study population comprising patients with spirometry-defined COPD, including patients with asthma. However, our study participants did not show the asthma-COPD overlap syndrome.

The ECLIPSE study [30] reported that an eosinophilic group tends to have higher FEV_1 , which is consistent with our findings. Furthermore, our study evaluated a greater number of pulmonary function parameters. However, the observation of elevated FEV_1 in eosinophilia is not consistent with the findings of the Copenhagen General Population Study, which reported no differences in FEV_1 among individuals with different blood eosinophil counts [31]. Considering the Copenhagen General Population Study used 3.3% (340 cells/ μ L) as the blood eosinophil cutoff point for patient stratification, it is likely that different cutoff points could affect the correlations observed with PFT parameters.

According to the 2015 recommendation, the FeNO level is significantly increased if its value is ≥ 32 ppb [32]. The mean FeNO level of the eosinophilic group in the present study was 32.3 ppb. This suggests a considerably high level of FeNO in patients with eosinophilia, and a positive correlation between blood eosinophilic granulocyte count and FeNO values.

Furthermore, the present results also provide evidence of a positive correlation between peripheral blood eosinophilic percentage and FeNO in AECOPD. However, Gao et al. [33] reported that blood eosinophil percentage has no significant correlation with FeNO in patients with AECOPD. The disparity in these results might be related to different eosinophil thresholds. In the Gao et al. study, eosinophilia was defined as the percentage of eosinophils in the blood $\geq 1\%$, while the threshold for eosinophilia in the present study was $\geq 2\%$ [33].

This study has several limitations. First, strict inclusion and exclusion criteria were applied before finalizing the study design, to ensure reliable results. Only patients with AECOPD and complete available data were included, leading to a relatively small sample size. In addition, our findings should be cautiously extrapolated to patients with AECOPD worldwide, considering that all our patients were Chinese. Finally, considering the single-center, retrospective nature of the study,

there were no consecutive measurements of any study variable. However, this limitation may have had only a negligible effect on the results.

Larger, more appropriate multicenter prospective surveys should be undertaken in the future to more reliably and comprehensively evaluate the clinical significance of peripheral blood eosinophils in the AECOPD phenotype. These studies should be specifically designed to evaluate the clinical relevance of peripheral blood eosinophils to lung function and FeNO levels.

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Conclusions

This study using real-world medical data provides useful and comprehensive evidence that blood eosinophil count may be a biomarker to predict a positive relationship with FeNO values and lung function variables (i.e., FEV₁% predicted, FEV₁, and FVC) in patients with AECOPD. The findings are clinically significant and will likely aid in the advancement of future therapy and management of AECOPD. Larger, long-term trials are warranted in the future.

Conflicts of interest

None.