

# High Blood Eosinophil and YKL-40 Levels, as Well as Low CXCL9 Levels, are Associated with Increased Readmission in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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**Background:** Readmission after hospital discharge is common among patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Predictive biomarkers of readmission would facilitate stratification strategies and individualized prognosis. Therefore, this study aimed to investigate the utility of type 2 biomarkers (eosinophils, periostin, and YKL-40) and a type 1 biomarker (CXCL9) in predicting readmission events in patients with AECOPD.

**Methods:** This is a prospective observational study design. Blood levels of eosinophils, periostin, YKL-40, and CXCL9 were measured at admission. The clinical outcomes were 12-month COPD-related readmission, time to COPD-related readmission, and number of 12-month COPD-related readmissions. These outcomes were analyzed using logistic and Cox regression models and Spearman's rank test.

**Results:** A total of 123 patients were included, of whom 51 had experienced at least one readmission for AECOPD. High levels of eosinophils ( $\geq 200$  cells/ $\mu$ L or 2% of the total white blood cell count, adjusted odds ratio [aOR] = 3.138,  $P=0.009$ ) and YKL-40 ( $\geq 14.5$  ng/mL, aOR = 2.840,  $P=0.015$ ), as well as low CXCL9 levels ( $\leq 30.1$  ng/mL, aOR = 2.551,  $P=0.028$ ), were associated with an increased COPD-related readmission. The highest relative readmission rate was observed in patients with both high eosinophil and YKL-40 levels. Moreover, high eosinophil and YKL-40 levels were associated with a shorter time to first COPD-related readmission and an increased number of 12-month COPD-related readmissions.

**Conclusion:** High blood eosinophil and YKL-40 levels, as well as low CXCL9 levels, have predictive utility for the 12-month COPD-related readmission rate. Using eosinophils and YKL-40 together allows more precise identification of patients at high risk of COPD-related readmission.

**Keywords:** COPD, exacerbation, readmission, biomarker, prospective observational

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## Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with subsequent readmission is considered to be a catastrophic event during the clinical course of COPD.<sup>1</sup> In the United States, the COPD readmission rate are 22.6% within 30 days<sup>2</sup> and 64.2% within 12 months of discharge,<sup>3</sup> while in Europe, approximately 35.1% are

readmitted within 90 days,<sup>4</sup> and up to 50.0% within 12 months in China.<sup>5</sup> This indicates that it is important to identify patients at high risk of readmission after AECOPD.

Airway inflammation is a consistent feature in the pathogenesis and progression of COPD.<sup>6</sup> Neutrophilic-associated T helper type 1 (Th1) inflammation is regarded as the predominant characteristic of COPD. However, approximately 30% of patients demonstrate an eosinophilic phenotype with increased T helper type 2 (Th2) immunity,<sup>6,7</sup> which is more likely to present with unstable clinical conditions and experience repeated readmissions.<sup>7,8</sup> Thus, the biomarker-based strategy for identifying a COPD eosinophilic phenotype and stratifying readmission rates is valuable to improve clinical outcomes of patients with COPD.<sup>9</sup>

Recent studies have shown a significant association between blood and lung eosinophil counts.<sup>7,10</sup> The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has reported blood eosinophils as a potential candidate for Th2-oriented therapies.<sup>11</sup> However, there have been inconsistent findings regarding the association of blood eosinophils with clinical outcomes of COPD patients, especially the future risk of readmissions.<sup>12–19</sup> Therefore, this association warrants further research.

Given different inflammatory phenotypes of COPD are caused by an imbalance of Th1/Th2 immune response,<sup>6</sup> we hypothesized that Th1- and Th2-related biomarkers may be useful predictors of readmission. Periostin is an extracellular matrix protein crucially involved in Th2-associated eosinophilic inflammation,<sup>20</sup> and serum concentrations of periostin is reported to parallel with airway eosinophils.<sup>21</sup> YKL-40, originally known as an upstream cytokine inducing Th2-type inflammation,<sup>22,23</sup> is now thought to be associated with bronchial inflammation and tissue remodeling in COPD.<sup>24</sup> CXCL9 is a well-characterized Th1-type chemokine that is primarily induced by IFN- $\gamma$ ,<sup>25</sup> and positively correlated with airway neutrophils in COPD.<sup>26</sup>

Therefore, the primary objective of this study was to investigate the association between these four biomarkers and adverse clinical outcomes following hospitalization for AECOPD. Furthermore, we determined whether any combination of two biomarkers could improve the ability to risk-stratify patients.

## Materials and Methods

### Study Design and Population

This prospective observational study enrolled patients hospitalized due to AECOPD at the Department of

Respiratory Medicine, the 2nd Affiliated Hospital of Chongqing Medical University, between November 2017 and March 2019. The inclusion criteria were being aged above 40 years and having a previous confirmed COPD diagnosis according to the GOLD 2017 classification criteria<sup>11</sup> based on smoking history (>10 packs/year) or biomass exposure history (wood, charcoal or grass for cooking and/or heating, exposure  $\geq$ 100 h/year), typical clinical symptoms, and lung function tests (a post-bronchodilator fixed ratio of FEV1/FVC <0.7). AECOPD was defined as an event in the natural disease course characterized by acute changes in clinical symptoms beyond normal day-to-day variation.<sup>11</sup> The exclusion criteria were: 1) having an exacerbation history within the previous 1 year; 2) having radiographic evidence of pneumonia at the time of admission; 3) having coexisting chronic respiratory diseases, including asthma, bronchiectasis, tuberculosis, lung cancer, and interstitial lung disease, as well as immune system diseases such as rheumatoid arthritis, gout, and osteoarthritis; 4) having been treated with systemic corticosteroids before the blood sample collection; 5) having cognitive disorders, liver dysfunction, renal failure, or other severe organ dysfunctions; 6) dying during hospitalization; and 7) refusing to provide voluntary informed consent. During the study period, a total of 419 candidate patients were included. Of these patients, 293 were excluded according to the exclusion criteria and 3 were lost to follow-up. Finally, 123 eligible patients were recruited for this study ([Supplementary Figure 1](#)).

Baseline characteristics, including age, sex, body mass index (BMI), smoking status, underlying disease, and exacerbation history, were collected upon hospital admission. Subsequently, the responsible physician assessed each patient to obtain functional data, including lung function measurements; the 6-minute walk distance (6MWD) test; and scores of quality of life tests, including the modified Medical Research Council dyspnea scale and the COPD Assessment Test. According to the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines,<sup>27</sup> spirometry was measured using a computerized spirometer (MasterScreen, Leibnizstrasse, Hochberg, Germany) where parameters, including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), their percent predicted values (%FVC, %FEV1), and FEV1/FVC were recorded. The spirometry was performed just before discharge, at which time the patients had no symptoms of wheezing, and each patient

inhaled 400 µg salbutamol at 20 minutes before the test. Chest computed tomography (CT) was conducted within 24 hours after hospital admission to rule out a pneumonia diagnosis. CT images were reconstructed using a standard algorithm (Philips Systems, Netherlands) into a 512 × 512 matrix size with a trans-axial slice thickness of 1.0 mm. Two well-trained radiologists independently read the images with discrepancies being resolved by a third radiologist. Blood samples were collected on the day of admission. At discharge, inpatient laboratory findings, the administration of systemic corticosteroids during hospitalization, home oxygen use, and inhalation therapy were recorded. All patients were followed up at 1, 3, 6, and 12 months (face-to-face visits or telephone calls if unavailable) and assessed for COPD-related readmissions. The study protocol was approved by the Second Affiliated Hospital of Chongqing Medical University (no 2017–08). Written informed consent was obtained from all patients.

## Measurements

Blood samples were collected followed by routine analysis of peripheral blood cell counts and C-reactive protein (CRP) at the Department of Clinical Laboratory in our hospital. Cells were classified as neutrophils, lymphocytes, monocytes, eosinophils, and basophils; moreover, the absolute number of each cell type was calculated. The minimum detectable CRP level was 24.9 pg/mL. Additionally, serum samples were collected after centrifugation at 4500 rpm for 15 min and then stored at –80 °C until subsequent analysis. Serum periostin, YKL-40, and CXCL9 levels were determined using commercially available enzyme-linked immunosorbent assay kits (Cloud-Clone, Wuhan, China), according to the manufacturer's instructions, with their minimum detectable levels being 31.0 pg/mL, 13.5 pg/mL, and 12.2 pg/mL, respectively.

## Study Variables and Clinical Outcomes

Regarding blood eosinophil count, the cutoffs for a high and low eosinophil count were ( $\geq 200$  cells/ $\mu\text{L}$  and/or  $\geq 2\%$  of the total white blood cell [WBC] count) and ( $< 200$  cells/ $\mu\text{L}$  and  $< 2\%$  of the total WBC count), respectively. We selected this threshold since patients with values above this cutoff are more likely to have sputum eosinophilia and are considered to be “eosinophilic patients with AECOPD”.<sup>10,16</sup> Most of the observational studies previously done used these cutoff values.<sup>16,18</sup> However, there is still controversy regarding the optimum eosinophil cutoff levels and whether to use absolute or

relative counts. Therefore, we also reported the results with different cutoff values of eosinophils. Regarding periostin, YKL-40, and CXCL9 levels, cutoffs were arbitrarily defined as high and low levels using the median instead of the mean values, due to their skewed distributions.

The primary outcome was 12-month COPD-related readmission (yes/no). The secondary outcomes were time to first COPD-related readmission and the number of 12-month COPD-related readmissions.

## Statistical Analyses

Data were analyzed for normality and descriptive statistics were presented as the numbers (percentages) for categorical variables and mean  $\pm$  standard deviation (SD) or median (interquartile range; IQR) for continuous variables, as appropriate. Between-group comparisons of normally and non-normally distributed continuous variables were performed using Student's *t*-test and Mann–Whitney U-test, respectively. Categorical data were compared using the chi-squared test or Fisher's exact test when appropriate.

Regarding primary outcome, we used a univariate logistic regression to evaluate the association of the four biomarkers (eosinophils, periostin, YKL-40, and CXCL9) with 12-month COPD-related readmission (yes/no); next, we built a multivariable logistic regression model forcing variables with a  $P < 0.1$  in univariate analysis and other potentially related variables, including age, sex, BMI, D'Hoore et al<sup>28</sup> version of the Charlson comorbidity index (CCI), smoking status, COPD severity and CRP. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Further, the primary outcome distribution was presented as the cumulative probability for 12-month COPD-related readmission stratified by any pair of the four biomarkers.

Regarding secondary outcomes, Kaplan–Meier survival curves, the Log rank test, and the Cox proportional hazard regression model were used to evaluate the time to first COPD-related readmission. Deaths during the follow-up period were considered censored. Correlations between biomarkers and the number of 12-month COPD-related readmissions were explored using Spearman's rank test with the results being presented using scatter plots.

Statistical analysis was performed using IBM SPSS 22.0 software (SPSS, Chicago, IL, USA); further, figures were created using GraphPad Prism 8.0 software (San Diego, CA, USA). All tests were two-tailed. A  $P$ -value  $< 0.05$  was considered significant.

**Table 1** Characteristic Features and Laboratory Findings of the Patients

Variables	Total (n=123)
Age, years	71.1±9.6
Male, n	90 (73.2)
Body mass index, kg/m <sup>2</sup>	22.4±3.7
Comorbidities	
Cardiovascular disease	48 (39.0)
Diabetes	20 (16.3)
Charlson comorbidity index	1.0 (0.0, 1.0)
Smoking status	
Current smoker	43 (35.0)
Ex-smoker	39 (31.7)
Non-smoker	41 (33.3)
Dyspnea (mMRC≥2)	55 (44.7)
CAT score	24.0 (20.0–30.0)
Spirometry parameter (post)	
FEV1, L	1.1 (0.7–1.4)
FVC, L	2.0 (1.6–2.7)
FEV1% predicted	49.8 (33.6–66.8)
FVC % predicted	75.1±21.6
FEV1/FVC, %	49.8 (33.6–66.8)
COPD severity, GOLD	
Mild (I) - Moderate (II)	59 (48.0)
Severe (III) - Very Severe (IV)	64 (52.0)
6-minute walk distance, m	230.0 (170.0–289.0)
Systemic corticosteroids during hospitalization	37 (30.1)
Home oxygen use	41 (33.3)
Inhalation therapy	
None or SABA prn	13 (10.6)
LAMA	27 (22.0)
ICS+LABA	35 (28.4)
ICS+LABA+LAMA	48 (39.0)
Laboratory findings	
White blood cell count, cells/μL	6960.0 (5260.0–9020.0)
Neutrophil count, cells/μL	4700.0 (3500.0–6690.0)
Neutrophil percent, % of WBC	70.2±9.5
Eosinophil count, cells/μL	120.0 (60.0–240.0)
Eosinophil percent, % of WBC	1.8 (0.7–3.5)
C-reactive protein (mg/L)	5.0 (5.0–18.1)
Serum periostin (ng/mL)	50.6 (41.9–61.2)
Serum YKL-40 (ng/mL)	14.5 (11.1–17.7)

(Continued)

**Table 1** (Continued).

Variables	Total (n=123)
Serum CXCL9 (ng/mL)	30.1 (23.6–40.7)
Length of hospital stay, days	8.0 (7.0–10.0)

**Note:** Data were presented as mean±standard deviation or median (interquartile range) or numbers (percentages).

**Abbreviations:** COPD, chronic obstructive pulmonary disease; CAT, COPD Assessment Test; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council dyspnea scale; SABA, short-acting Beta2 agonist.

## Results

### Characteristics of the Patients

Table 1 presents the baseline characteristics of the 123 patients with COPD. There were 90 (73.2%) men and 33 (26.8%) women, with a mean age of 71.1 (SD, 9.6) years. The mean BMI was 22.4 (SD, 3.7) kg/m<sup>2</sup>. The most common comorbidity was cardiovascular disease (39.0%), followed by diabetes (16.3%); further, the median CCI was 1.0 (IQR, 0.0–1.0). Most patients (66.7%) had a history of smoking with the remaining patients (33.3%) having a history of biomass exposure. Based on the GOLD criteria, 64 (52.0%) patients had severe or very severe airflow obstruction (GOLD grades III–IV). At the time of index admission, the laboratory findings were as follows: median blood eosinophil count: 120.0 cells/μL (IQR, 60.0–240.0 cells/μL); median serum periostin level: 50.6 ng/mL (IQR, 41.9–61.2 ng/mL); median serum YKL-40 level: 14.5 ng/mL (IQR, 11.1–17.7 ng/mL); median serum CXCL9 level: 30.1 ng/mL (IQR, 23.6–40.7 ng/mL).

### Comparison Between the Readmission and Non-Readmission Groups

As shown in Table 2, readmission was more likely to have a higher proportion of severe or very severe airflow obstruction (GOLD grades III–IV) ( $P=0.018$ ), shorter 6-MWD ( $P=0.042$ ), and longer length of hospital stay ( $P=0.022$ ). There were no significant between-group differences in any other clinical variables (all  $P>0.05$ ). The proportion of patients with high blood eosinophil levels ( $\geq 200$  cells/μL or 2% of the WBC count, 58.8% vs 36.1%,  $P=0.013$ ; Figure 1A) and high serum YKL-40 levels ( $\geq 14.5$  ng/mL, 64.7% vs 40.3%,  $P=0.008$ ; Figure 1C) were significantly higher in the readmission group than in the non-readmitted group. Further, there was no significant between-group difference in the proportion of patients

**Table 2** Comparison Between the Readmission and Non-Readmission Groups

Variables	12-Month COPD-Related Readmission		P-value
	Yes (n=51)	No (n=72)	
Age, years	70.7±9.1	71.5±10.0	0.653
Male, n	40 (78.4)	50 (69.4)	0.268
Body mass index, kg/m <sup>2</sup>	21.9±3.9	22.8±3.6	0.227
Comorbidities			
Cardiovascular disease	22 (43.1)	26 (36.1)	0.431
Diabetes	8 (15.7)	12 (16.7)	0.885
Charlson comorbidity index	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.258
Smoking status			
Current smoker	20 (39.2)	23 (31.9)	0.149
Ex-smoker	19 (37.3)	20 (27.8)	
Non-smoker	12 (23.5)	29 (40.3)	
Dyspnea (mMRC≥2)	27 (52.9)	28 (38.9)	0.139
CAT score	24.0 (20.0–30.0)	25.0 (21.3–30.0)	0.618
COPD severity, GOLD grade			
Mild (I) - Moderate (II)	18 (35.3)	41 (56.9)	0.018
Severe (III)-Very Severe (IV)	33 (64.7)	31 (43.1)	
6-minute walk distance, m	205.0 (145.0–281.0)	247.0 (171.3–295.0)	0.042
Systemic corticosteroids during hospitalization	17 (33.3)	20 (27.8)	0.508
Home oxygen use	18 (35.3)	23 (31.9)	0.698
Inhalation therapy			
None or SABA prn	7 (13.7)	6 (8.3)	0.473
LAMA	8 (15.7)	19 (26.4)	
ICS+LABA	15 (29.4)	20 (27.8)	
ICS+LABA+LAMA	21 (41.2)	27 (37.5)	
C-reactive protein (mg/L)	8.8 (5.0–25.9)	5.0 (5.0–15.1)	0.271
Length of hospital stay, days	9.0 (7.0 11.0)	8.00 (6.0, 10.0)	0.022

**Notes:** Data were presented as mean±standard deviation or median (interquartile range) or numbers (percentages). Between-group comparisons of normally and non-normally distributed continuous variables were performed using Student's *t*-test and Mann-Whitney U-test, respectively. Categorical data were compared using the chi-squared test or Fisher's exact test.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; CAT, COPD Assessment Test; ICS, inhaled corticosteroids; LABA, long-acting  $\beta$ -agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council dyspnea scale; SABA, short-acting Beta2 agonist.

with high serum periostin levels ( $\geq 50.6$  ng/mL, 56.9% vs 45.8%,  $P=0.228$ ; **Figure 1B**) and low serum CXCL9 levels ( $\leq 30.1$  ng/mL, 60.8% vs 43.1%,  $P=0.053$ ; **Figure 1D**).

## Association Between Biomarkers and 12-Month COPD-Related Readmission

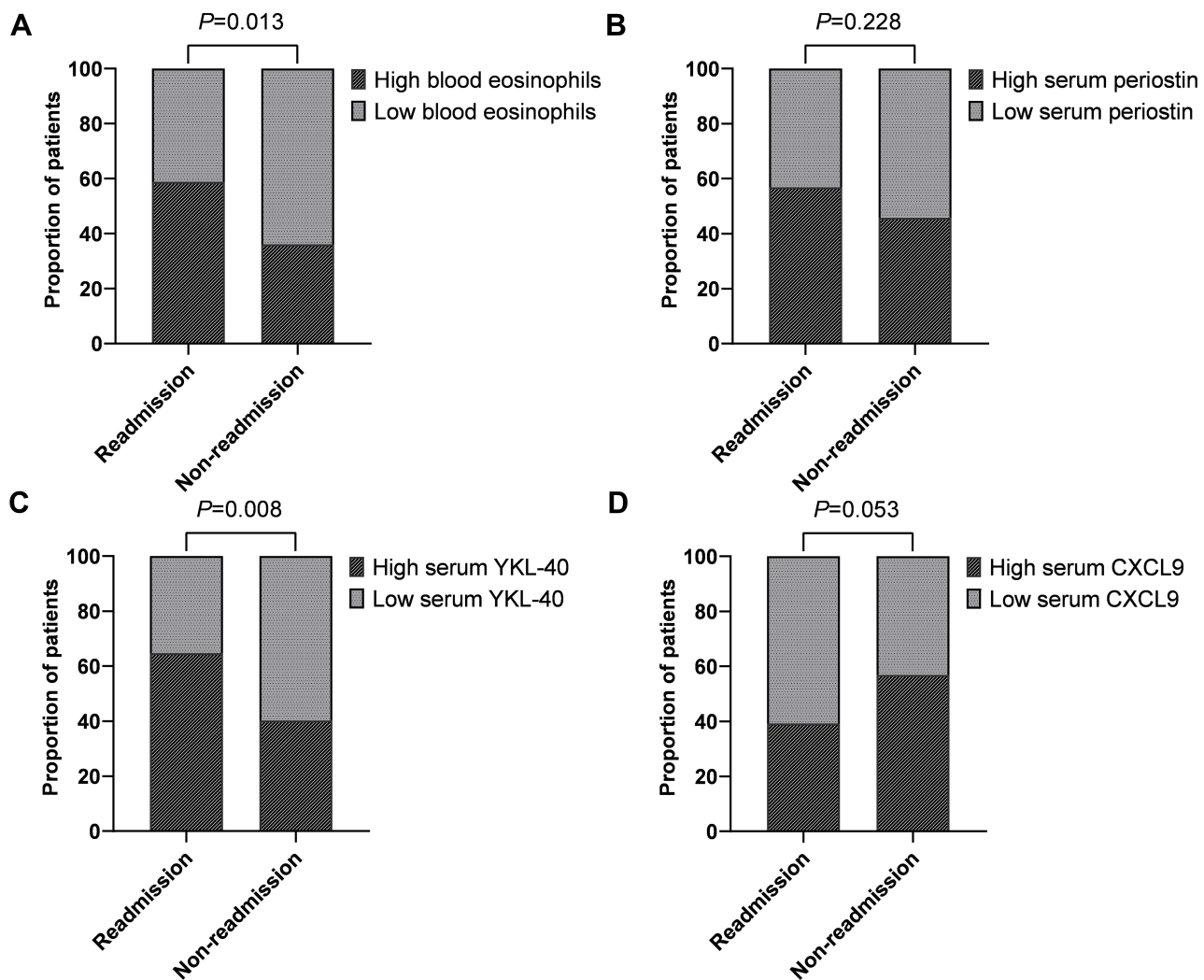
During the 12-month follow-up period, 51 (41.5%) patients experienced hospital readmission due to COPD exacerbation. Univariate analysis revealed a significant difference in the primary outcome (12-month COPD-related readmission) between the groups stratified according to the blood eosinophil count (high vs low eosinophil count: OR =2.527, 95% CI =1.210–5.278,  $P=0.014$ ) and serum YKL-40 levels (high vs low YKL-40 levels: OR =2.718, 95% CI =1.293–5.713,  $P=0.008$ ). Further, multiple logistic regression analysis revealed that a blood eosinophil count  $\geq 200$  cells/ $\mu$ L or 2% of the WBC count (aOR =3.138; 95% CI =1.325–7.439;  $P=0.009$ ), serum YKL-40 levels  $\geq 14.5$  ng/mL (aOR =2.840; 95% CI =1.228–6.568;  $P=0.015$ ), and serum CXCL9  $\leq 30.1$  ng/mL (aOR =2.551; 95% CI =1.108–5.847;  $P=0.028$ ) were associated with an increased risk of COPD-related hospital readmission. Additionally, the association between higher eosinophils and 12-month COPD-related readmission remained essentially using the different cutoff values of eosinophils. See **Table 3** for details.

## Combined Assessment of Any Pair of the Four Biomarkers

Upon stratification of event rates by any pair of the four biomarkers, there was an increase in the frequency of 12-month COPD-related readmission events with increased eosinophil, periostin, and YKL-40 levels, as well as decreased CXCL9 levels. The highest relative readmission rate (64.3% group readmission) was observed among patients with high blood eosinophil and serum YKL-40 levels. Further, the lowest relative readmission rate (18.2% group readmission) was observed in patients with low eosinophil and YKL-40 levels (**Figure 2**).

## Secondary Outcome

The Kaplan–Meier curve revealed a significant difference in the first COPD-related readmission rate among patients stratified according to the blood eosinophils, serum YKL-40, and CXCL9 levels ( $P=0.004$ , 0.006, and 0.031, respectively; **Figure 3A, C and D**, respectively). However, when



**Figure 1** (A) Comparison of the proportion of patients with high levels of blood eosinophils ( $\geq 200$  cells/ $\mu$ L or 2% of the WBC count) between the readmission and non-readmission groups. (B) Comparison of the proportion of patients with high levels of periostin ( $\geq 50.6$  ng/mL) between the readmission and non-readmission groups. (C) Comparison of the proportion of patients with high levels of YKL-40 ( $\geq 14.5$  ng/mL) between the readmission and non-readmission groups. (D) Comparison of the proportion of patients with low levels of CXCL9 ( $\leq 30.1$  ng/mL) between the readmission and non-readmission groups.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; WBC, white blood cell.

we stratified patients according to the periostin levels, no significant difference was found ( $P=0.249$ , Figure 3B). Cox regression analysis revealed that high levels of blood eosinophil ( $\geq 200$  cells/ $\mu$ L or 2% of the WBC count) and serum YKL-40 ( $\geq 14.5$  ng/mL), as well as low levels of serum CXCL9 ( $\leq 30.1$  ng/mL) remained associated with shorter time to first COPD-related readmission ( $P=0.001$ , 0.012, and 0.018, respectively). Moreover, there was a significant correlation of the number of COPD-related readmissions with eosinophil ( $r=0.206$ ,  $P=0.022$ ; Figure 4A), YKL-40 ( $r=0.375$ ,  $P<0.001$ ; Figure 4C), and periostin levels ( $r=0.213$ ,  $P=0.018$ ; Figure 4B), but no significant correlation between the number of COPD-related readmissions and CXCL9 levels was observed ( $r=-0.048$ ,  $P=0.596$ ; Figure 4D).

Figure 4 shows the scatter plots of biomarkers exhibiting correlations.

## Discussion

Our study found that levels of blood eosinophil, YKL-40, and CXCL9 were associated with COPD-related readmission during the 12-month follow-up period in patients with AECOPD. Patients with both high serum YKL-40 ( $\geq 14.5$  ng/mL) and blood eosinophil levels ( $\geq 200$  cells/ $\mu$ L or 2% of the WBC count) had the highest relative readmission rate. Furthermore, high eosinophil and YKL-40 levels were associated with a shorter time to first COPD-related readmission and an increased number of 12-month COPD-related readmissions.

**Table 3** Association Between Biomarkers and 12-Month COPD-Related Readmission

Variables	Total (n=123)	COPD-Related Readmission (n=51)	No COPD-Related Readmission (n=72)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Eosinophils					
Main cutoff values					
<200 cells/ $\mu$ L and 2%	67 (54.5)	21 (41.2)	46 (63.9)	1.0	1.0
$\geq$ 200 cells/ $\mu$ L or 2%	56 (45.5)	30 (58.8)	26 (36.1)	2.527 (1.210–5.278)*	3.138 (1.325–7.439)**
Other cutoff values					
<300 cells/ $\mu$ L and 3%	82 (66.7)	29 (56.9)	53 (73.6)	1.0	1.0
$\geq$ 300 cells/ $\mu$ L or 3%	41 (33.3)	22 (43.1)	19 (26.4)	2.116 (0.987–4.537)	2.672 (1.122–6.361)*
<400 cells/ $\mu$ L and 4%	95 (77.2)	35 (68.6)	60 (83.3)	1.0	1.0
$\geq$ 400 cells/ $\mu$ L or 4%	28 (22.8)	16 (31.4)	12 (16.7)	2.286 (0.970–5.384)	2.889 (1.067–7.817)*
<300 cells/ $\mu$ L and 4%	93 (75.6)	34 (66.7)	59 (81.9)	1.0	1.0
$\geq$ 300 cells/ $\mu$ L or 4%	30 (24.4)	17 (33.3)	13 (18.1)	2.269 (0.983–5.237)	2.910 (1.092–7.755)*
Periostin					
<50.6 ng/mL	61 (49.6)	22 (43.1)	39 (54.2)	1.0	1.0
$\geq$ 50.6 ng/mL	62 (50.4)	29 (56.9)	33 (45.8)	1.558 (0.756–3.208)	1.430 (0.641–3.191)
YKL-40					
< 14.5 ng/mL	61 (49.6)	18 (35.3)	43 (59.7)	1.0	1.0
$\geq$ 14.5 ng/mL	62 (50.4)	33 (64.7)	29 (40.3)	2.718 (1.293–5.713)**	2.840 (1.228–6.568)*
CXCL9					
>30.1 ng/mL	61 (49.6)	20 (39.2)	41 (56.9)	1.0	1.0
$\leq$ 30.1 ng/mL	62 (50.4)	31 (60.8)	31 (43.1)	2.050 (0.987–4.255)	2.551 (1.108–5.847)*

**Notes:** Data were presented as numbers (percentages). \* $P < 0.05$ , \*\* $P < 0.01$ .

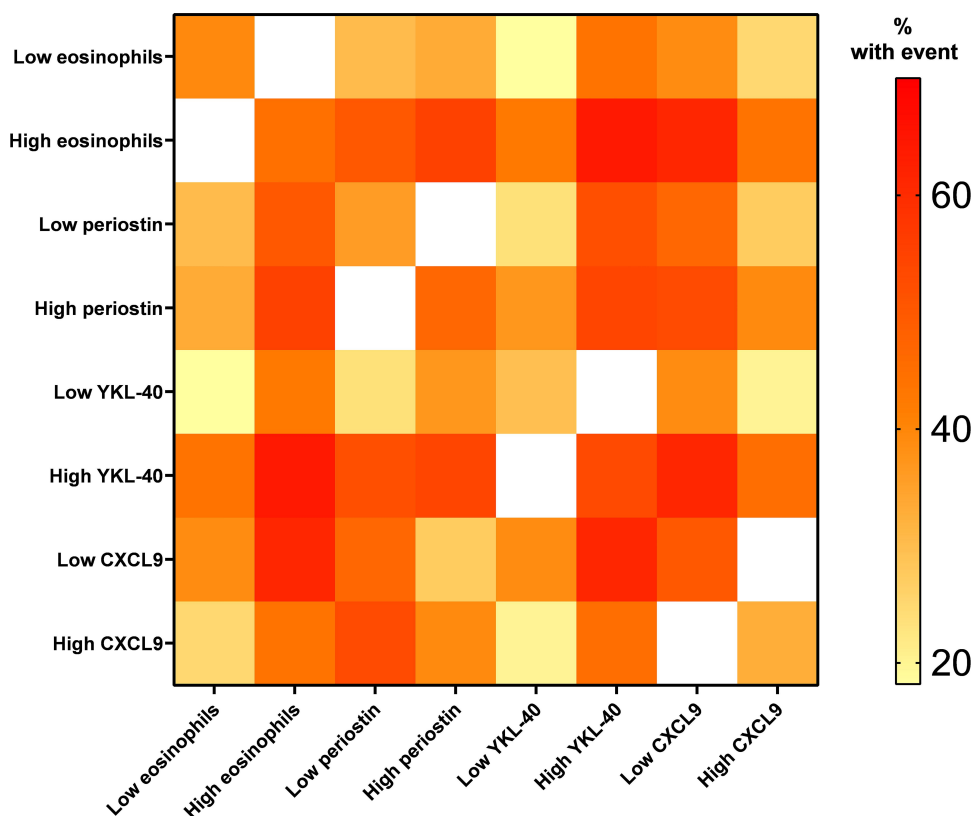
**Abbreviations:** COPD, chronic obstructive pulmonary disease; CI, confidence interval; OR, odds ratio.

Hospital readmissions for COPD impart serious burdens on society and patients.<sup>1,11</sup> Although the causes of readmission vary widely, respiratory diseases remain the leading cause.<sup>29,30</sup> Early recognition of high-risk patients and appropriate interventions can significantly reduce COPD-related readmissions.<sup>9</sup> Therefore, we sought to identify useful biomarkers to distinguish patients with high-risk for COPD-related readmission.

A subgroup of patients with COPD presents eosinophilic inflammatory profiles during clinical stability and exacerbation.<sup>6</sup> Blood eosinophils is demonstrated to be correspond to eosinophilic airway inflammation of COPD.<sup>10</sup> In our study, a high blood eosinophil count ( $\geq 200$  cells/ $\mu$ L or 2% of the WBC count) could predict a more than two-fold increase in the incidence of 12-month readmission for COPD, a shorter time to first COPD-related readmission, and an increased number of 12-month COPD-related readmissions. Consistent findings have been reported in the COPDGene and ECLIPSE cohorts<sup>13</sup> as well as the Copenhagen General Population cohort<sup>12</sup> of clinically stable COPD, while opposite evidences were reported in the BODE, CHAIN<sup>15</sup> and

SPIROMICS<sup>14</sup> cohorts; moreover, several retrospective and post hoc studies on AECOPD also reported conflicting results.<sup>16–19</sup> Couillard et al analyzed these inconsistent findings and found that the relative timing of systemic corticosteroid administration may be a confounding factor.<sup>16</sup> Blood eosinophil count is known to decrease by over 50% within the first four hours of corticosteroid administration with a subsequent gradual return to baseline within 24 hours.<sup>31</sup> The present study excluded patients who did receive systemic corticosteroid treatment before blood sample collection. Moreover, our results confirmed that COPD patients with higher blood eosinophil counts were more likely to experience repeated readmissions and have a shorter time to rehospitalization. Therefore, future studies should consider systemic corticosteroid use as an important confounding factor for its eosinopenic effect.

YKL-40, also known as Chitinase-3-like protein 1 (CHI3L1), is a crucial regulator in Th2-type inflammation and tissue remodeling.<sup>22</sup> Kang et al demonstrated that CHI3L1 contributes to the genesis of Th2 inflammation and pulmonary fibrosis, as well as inhibits Th1 inflammation in mouse models.<sup>32</sup> Our present study found that the



**Figure 2** Heatmap of 12-month COPD-related readmission events stratified by any pair of the four biomarkers. Colors in the figure represent the percentage of patients with an event.

**Abbreviation:** COPD, chronic obstructive pulmonary disease.

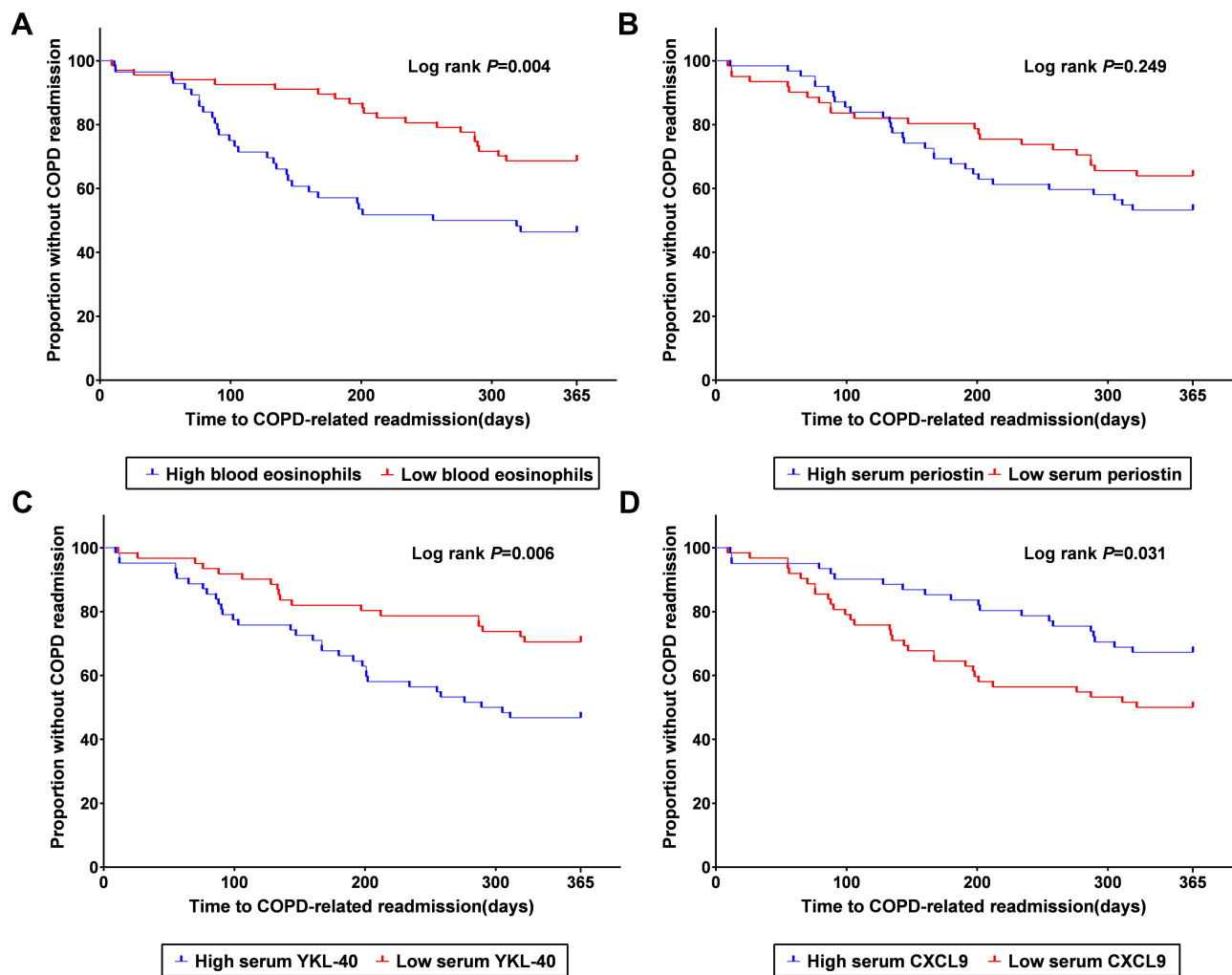
proportion of patients with high serum YKL-40 levels ( $\geq 14.5$  ng/mL) was significantly higher in the readmission group than in the non-readmission group. Both univariate and multivariate analyses revealed a high correlation of serum YKL-40 levels with the readmission risk; moreover, YKL-40 levels were negatively correlated with pulmonary function test parameters in our study (data not shown). These findings are similar to those of previous studies,<sup>23,24,33</sup> and further support that YKL-40 is useful for predicting COPD-related readmission due to its associations with Th2-type inflammation and critical pathophysiology in COPD. Additionally, the highest and lowest relative readmission rates were observed in patients with high and low levels, respectively, of both eosinophils and YKL-40. This indicates that concurrent measurement of both biomarkers could improve the accuracy of risk stratification in patients with COPD.

CXCL9 is an IFN- $\gamma$ -inducible chemokine that is released by neutrophils,<sup>25,34</sup> and serve as Th1-type inflammatory markers in respiratory diseases.<sup>35,36</sup> When compared to healthy controls, CXCL9 concentrations were increased in COPD patients and positively correlated

with markers of neutrophilic airway inflammation.<sup>26</sup> Fulkerson et al demonstrated that CXCL9 inhibits eosinophil migration to the lungs of allergen-induced mice.<sup>37</sup> Collectively, these findings suggest that CXCL9 is associated with suppressed Th2-type inflammation and increased Th1-type inflammation, respectively. In this study, we found that patients with COPD who were readmitted manifested numerically, but not significantly, lower CXCL9 levels than the non-readmitted patients. However, multivariate analysis revealed that low CXCL9 levels were markedly associated with an increased risk of readmission due to AECOPD. In addition, CXCL9 expression was related to the time to the first readmission for exacerbation of COPD, but not to the frequency of hospitalized AECOPD. These findings could be attributed to our sample size being too small to achieve statistical significance in analysis. Therefore, further studies with more participants are needed to clarify the relationship between serum CXCL9 and readmission risk in patients with COPD.

Periostin is an extracellular matrix protein in response to type 2 cytokines IL-4 and IL-13.<sup>20,21</sup> Serum periostin is known as an imperfect, surrogate





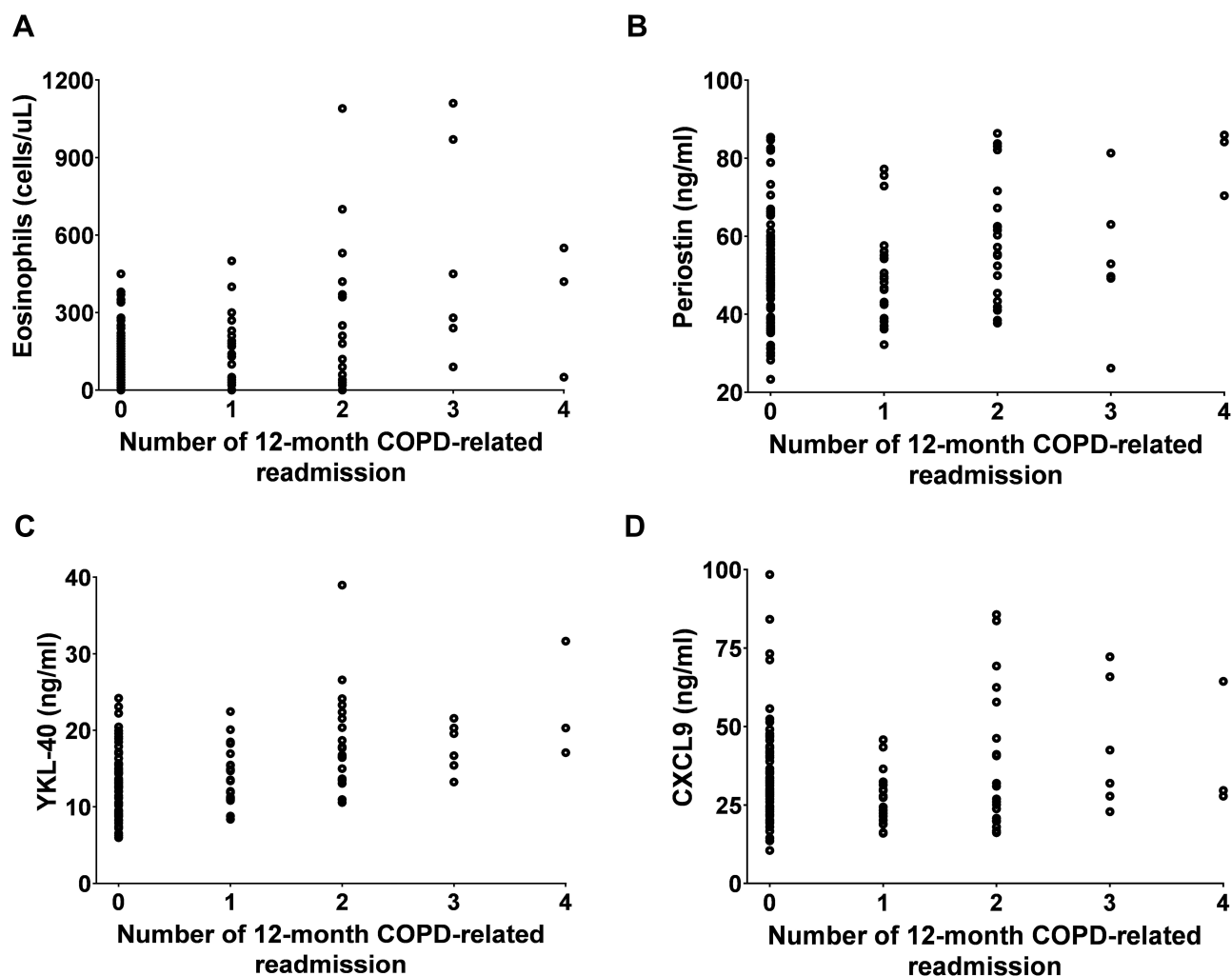
**Figure 3** (A) Kaplan–Meier curves for time until first COPD-related readmission in patients with high blood eosinophils ( $\geq 200$  cells/ $\mu$ L or 2% of the WBC count, blue line) vs low blood eosinophils ( $< 200$  cells/ $\mu$ L and 2% of the WBC count, red line). (B) Kaplan–Meier curves for time until first COPD-related readmission in patients with high serum periostin ( $\geq 50.6$  ng/mL, blue line) vs low serum periostin ( $< 50.6$  ng/mL, red line). (C) Kaplan–Meier curves for time until first COPD-related readmission in patients with high serum YKL-40 ( $\geq 14.5$  ng/mL, blue line) vs low serum YKL-40 ( $< 14.5$  ng/mL, red line). (D) Kaplan–Meier curves for time until first COPD-related readmission in patients with high serum CXCL9 ( $> 30.1$  ng/mL, blue line) vs low serum CXCL9 ( $\leq 30.1$  ng/mL, red line).

**Abbreviations:** COPD, chronic obstructive pulmonary disease; WBC, white blood cell.

marker of Th2 inflammatory response in patients with asthma.<sup>38,39</sup> Although most studies have investigated the role of periostin in asthma, data regarding COPD are scarce.<sup>20</sup> In this study, there were no significant differences in serum periostin levels between the readmission and non-readmission groups. Moreover, increased periostin levels were not associated with long-term disease outcomes, including the time to next AECOPD hospitalization and number of COPD-related readmissions. These results are consistent with those of Konstantelou et al, who found that high serum periostin levels could not predict the time of next exacerbation or hospitalization, or the time to death in patients hospitalized for

AECOPD.<sup>40</sup> Similarly, Carpaij et al reported that serum periostin was not associated with eosinophilic inflammation measured in blood, sputum, and biopsies in clinically stable patients with COPD.<sup>41</sup> Collectively, the aforementioned evidence suggests that serum periostin plays a limited role in COPD. Moreover, as the principal risk factor for COPD, cigarette smoke exposure is reported to suppress periostin expression,<sup>42,43</sup> which might attenuate the predictive ability of periostin in COPD-related readmission.

This study has several limitations. First, this was a single-center study with a relatively small sample size, which limits extensive subgroup analyses. Second, all analyses were based



**Figure 4** Scatterplot graph of blood eosinophils (A), periostin (B), YKL-40 (C), and CXCL9 (D) levels with number of 12-month COPD-related readmissions. **Abbreviation:** COPD, chronic obstructive pulmonary disease.

on a single measurement and we did not assess longitudinal changes. Third, although we adjusted for some confounding factors, there may be residual confounding factors. Therefore, there is a need for large-scale, multicenter, and well-designed studies to validate the findings.

## Conclusions

High eosinophil and YKL-40 levels, as well as low CXCL9 levels, which are assessed in a corticosteroid-free time frame, are associated with an increased risk of 12-month COPD-related readmission rate in hospitalized patients with AECOPD. Higher eosinophil and YKL-40 levels are associated with a shorter time to first COPD-related readmission and an increased number of 12-month COPD-related readmissions. Additionally, concurrent assessment of eosinophil and YKL-40 levels could provide more precise identification of patients at high risk of COPD-related readmission.

## Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; CHI3L1, chitinase-3-like protein 1; COPD, chronic obstructive pulmonary disease; CI, confidence interval; CAT, COPD Assessment Test; CRP, C-reactive protein; CT, computed tomography; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range; LABA: long-acting  $\beta$ -agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council dyspnea scale; OR, odds ratio; SABA, short-acting Beta2 agonist; SD, standard deviation; Th1, T helper type 1; Th2, T helper type 2; WBC, white blood cell; 6MWD, 6-minute walk distance.

## Data Sharing Statement

Data available on request.

## Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committees of the Second Affiliated Hospital of Chongqing Medical University (no 2017-08) in accordance with the Declaration of Helsinki.

## Consent for Publication

Not applicable.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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