

Clinical Predictors of High Blood Eosinophils in Chronic Obstructive Pulmonary Disease

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Purpose: Elevated blood eosinophils have been implicated in chronic obstructive pulmonary disease (COPD) progression and exacerbation. We aim to investigate clinical predictors of high blood eosinophils in a Chinese COPD cohort.

Patients and Methods: We conducted a retrospective cohort study in Sichuan province, a Southwest province with high prevalence of COPD in China. All patients in this cohort were extracted from the Chinese Pulmonary Health study, a large cross-sectional study on COPD epidemiology in China. Demographics, personal and family history, living condition, spirometry and blood eosinophil counts were obtained. Univariate and multiple linear regression analyses were performed to determine predictors of high blood eosinophils.

Results: A total of 375 COPD patients were included in this cohort. The median absolute blood eosinophil count was 138.8 cells/ μ L, and the prevalence of COPD with high blood eosinophils was 66.7% and 14.7% when using the thresholds of 100 cells/ μ L and 300 cells/ μ L, respectively. Univariate analyses indicated that male gender, lower body mass index, high-density lipoprotein (HDL), lower family income, raising pets and biomass use were significantly associated with high blood eosinophils ($p < 0.05$). Multiple linear regression model further revealed male gender (unstandardized coefficient (B)=66.125, 95% confidence intervals (CI) 16.350 to 115.900, $p=0.009$), age (B=2.819, 95% CI 0.639 to 5.000, $p=0.012$) predicted high blood eosinophil level, whereas HDL (B=-64.682, 95% CI -123.451 to -5.914, $p=0.031$) was a negative predictor for high blood eosinophils.

Conclusion: This retrospective cohort study suggests male gender, oldness and lower HDL could be clinical predictors of high blood eosinophils in Chinese COPD patients.

Keywords: chronic obstructive pulmonary disease, blood eosinophil count, high-density lipoprotein, predictor, retrospective study

Introduction

Chronic obstructive pulmonary disease (COPD), one of the primary health and economic burdens worldwide, has been widely accepted as a heterogeneous condition in terms of etiology, airway inflammation, exacerbation and response to inhaled corticosteroids (ICSs), etc.¹⁻⁴ As blood eosinophil count has been extensively applied to describe COPD with eosinophilic inflammation, increased blood eosinophils have been reported to play important roles in COPD progression or exacerbation.⁵⁻⁷

A growing body of evidence demonstrated that COPD patients with elevated blood eosinophil count appeared to have a higher risk of acute exacerbation and favorable response to ICS therapy,⁸⁻¹⁴ which was documented in the 2021 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy.¹⁵ The Copenhagen General Population study collected blood eosinophils at baseline, recorded future COPD

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exacerbations longitudinally, and observed a 1.76-fold increased risk of severe exacerbations in patients with high blood eosinophil level during a median of 3.3-year follow-up.⁸ Two other large longitudinal studies also demonstrated similar findings.^{9,10} A biologic clusters analysis further implied that there existed an eosinophilic-predominant exacerbation accounting for 28% of all COPD exacerbations, different from bacterial- or viral-predominant exacerbation.¹¹ Additionally, the IMPACT trial observed an increased ICS benefit on moderate and severe COPD exacerbation, Transition Dyspnoea Index, St. George's Respiratory Questionnaire (SGRQ) total score, and forced expiratory volume in 1 second (FEV1), with elevated blood eosinophil counts.¹²

It is worth noting that the mechanisms of high blood eosinophils in COPD are still undetermined. Th2 Signature score, an asthma-related gene expression metric, was reported to be increased in COPD,¹⁶ and correlated with production of interleukin-5 (IL-5),^{16,17} which was involved in activation, migration and effector functions of peripheral blood eosinophils.^{17–19} Recent studies revealed a prevalence of up to 45% of increased blood eosinophils in COPD without current asthma, and the potential features of this subgroup comprised higher body mass index (BMI), older age, male gender, former smoking, better quality of life and lung function.^{20–26} However, these results were mostly identified by univariate analyses, which needed further confirmation. Moreover, whether other factors associated with COPD, such as biomass use and history of respiratory disease, contribute to eosinophilic COPD remains unclear.

Therefore, in order to investigate the potential predictors for high blood eosinophils in COPD, we conducted a retrospective cohort study in Sichuan province, a Southwest province with high prevalence of COPD in China. All patients in this cohort were extracted from the Chinese Pulmonary Health (CPH) study, a large cross-sectional study on COPD epidemiology in China.²⁷

Materials and Methods

Study Design

This retrospective cohort study was conducted in Sichuan province, which is located in Southwest China with a high COPD prevalence. All patients in this cohort were extracted from the CPH study, a large cross-sectional study on COPD epidemiology in China.²⁷ The CPH study applied a multistage stratified cluster

sampling procedure to enroll a nationally representative sample of adults aged 20 years or older between June, 2012 and May, 2015. The clinical information associated with COPD was picked up, including demographics, personal history, family history, living condition, oral hygiene status, respiratory symptoms, COPD assessment test (CAT), drug therapy, spirometry and data on routine blood test, etc. Based on the recommendation in 2021 GOLD guideline,¹⁵ all patients were divided into three groups (<100, 100–300 and ≥ 300 cells/ μ L) by blood eosinophil thresholds of 100 cells/ μ L and 300 cells/ μ L, followed by comparisons among the three groups. Then, univariate and multiple linear regression analyses were performed to identify predictors for blood eosinophil level. The reporting of this work was compliant with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist.²⁸

Patients

Full inclusion and exclusion criteria for COPD patients have been described previously.²⁷ According to the criteria, we included COPD patients aged ≥ 40 years in Sichuan province, who provided available blood eosinophil counts. Patients with asthma, allergic rhinitis, or active tuberculosis were excluded.

Ethical Statement

Since this study was based on the data of previously published CPH study,²⁷ the patient consents for publication were obtained, and the study protocol was approved by the Institutional Review Board of West China Hospital of Sichuan University, and the present study was conducted in accordance with the Declaration of Helsinki. Moreover, all authors confirmed that the data were anonymized or maintained with confidentiality, and were accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Statistical Analysis

For test of variable normality, we combined the histogram, Q-Q diagram and the Shapiro–Wilk test. Quantitative variables were expressed as mean $\pm$ SD (standard deviation) when normally distributed, or median (interquartile range, IQR) when non-normally distributed. Qualitative variables were expressed as frequencies. Statistically significant difference was assessed by Chi-squared test or Fisher's exact test for qualitative variables, and for quantitative variables,

the analysis of variance (ANOVA) or Kruskal–Wallis *H*-test was used. *P* value <0.05 was considered statistically significant. Univariate and multiple linear regression analyses were conducted to determine factors predicting high blood eosinophil count. Considering implications between blood eosinophils and some variables associated with COPD might be concealed by potential confounding factors in univariate analyses, we applied a higher threshold of statistical significance ($p=0.2$) for entering variables in the multivariable model.^{29,30} As a result, variables with p value ≤ 0.2 in univariate analyses were regarded as potential predictors, which were chosen to enter simultaneously into the forced entry multivariable linear regression model. A multivariable regression model was constructed with the outcome in question as the dependent variable and potential predictors as the independent variables. It was presented with the constant (Y-intercept), the standardized regression coefficients (B), unstandardized B and their 95% confidence intervals (CIs). *P* value <0.05 was used to define the statistical significance of the final model. The amount of variance accounted for by the final model was expressed as R^2 and the model was checked for collinearity through the variance inflation factor. The statistical tool used was SPSS (version 19 for Windows, IBM SPSS Statistics, IBM Corporation).

Results

Baseline Characteristics of Study Population

In the CPH study, there were 548 COPD patients aged ≥ 40 years in Sichuan province, among which 402 COPD patients provided blood eosinophil counts. However, 27 patients were once diagnosed with asthma or allergic rhinitis by doctors and were excluded in the present study. Therefore, according to the eligibility criteria, 375 COPD patients were finally included in this study, with a mean age of 63.2 (SD 10.8) years, 61.9% males, 46.7% smokers, and a mean FEV1% predicted of 89.4 (SD 21.5) %. Median absolute blood eosinophil count was 138.8 cells/ μ L (IQR 82.3–226.6) in all COPD patients, with 156.0 cells/ μ L (IQR 97.9–246.0) in males and 113.4 cells/ μ L (IQR 69.4–197.5) in females. There were 125 (<100 cells/ μ L), 195 (100–300 cells/ μ L) and 55 (≥ 300 cells/ μ L) patients in the three groups stratified by absolute blood eosinophil counts, which indicated a prevalence of COPD with high blood eosinophils in this cohort was 66.7% and 14.7% when using the

thresholds of 100 cells/ μ L and 300 cells/ μ L, respectively. More characteristics of the study population are shown in Table 1. However, the medical information was missed because of incomplete records in the CPH study.

Factors Associated with Blood Eosinophil Count in COPD

Comparisons among the three groups demonstrated that male gender ($p < 0.001$), lower BMI ($p=0.001$) and family income ($p=0.012$), raising pets ($p=0.043$), biomass use ($p=0.003$), higher blood leukocytes ($p < 0.001$) and lower blood neutrophils ($p < 0.001$) were significantly different, indicative of some potential correlators for increased blood eosinophils (Table 1). However, no statistical significance regarding smoking status, pulmonary function, and duration of biomass exposure was revealed (Table 1). Furthermore, in the univariate linear regression analysis, male gender ($p=0.022$), raising pets ($p=0.038$), biomass use ($p=0.002$), lower high-density lipoprotein (HDL, $p=0.037$) and BMI ($p=0.016$) were significantly correlated with high blood eosinophils (Table 2).

Clinical Predictors of High Blood Eosinophils in COPD

Based on the univariate analyses, in addition to age, nine potential predictors with p value ≤ 0.2 , comprising male gender, raising pets, biomass use, former smoking, family income, BMI, total cholesterol (TC), HDL and low-density lipoprotein (LDL) were included in the multiple linear regression model (Table 3). As a result, determined predictors for high blood eosinophils were male gender ($B=66.125$, 95% CI 16.350 to 115.900, $p=0.009$), age ($B=2.819$, 95% CI 0.639 to 5.000, $p=0.012$) and lower HDL ($B=-64.682$, 95% CI -123.451 to -5.914, $p=0.031$). The final model explained 11.4% ($R^2=0.114$, adjusted $R^2=0.067$) of the variance in blood eosinophil count ($F=2.431$, $p=0.010$).

Discussion

The present study retrospectively investigated potential predictors of high blood eosinophils in COPD, indicating two important findings: 1) in this cohort, the median absolute blood eosinophil count was 138.8 cells/ μ L and the prevalence of COPD with high blood eosinophils was 66.7% and 14.7% when using the thresholds of 100 cells/ μ L and 300 cells/ μ L, respectively; 2) after being adjusted by raising pets, biomass use, former smoking, family income, BMI, LDL and TC, factors including male gender,

Table 1 Comparison of Clinical Characteristics in COPD Patients with Different Blood Eosinophil Levels

	<100 (125) Cells/ μ L	100–300 (195) cells/ μ L	$\geq$ 300 (55) cells/ μ L	P
Male	60 (48.0)	134 (68.7)	38 (69.1)	<0.001*
Female	65 (52.0)	61 (31.3)	17 (30.9)	<0.001*
Age ($\geq$ 40 years)	62.4 $\pm$ 11.5	63.1 $\pm$ 10.4	65.5 $\pm$ 10.1	0.195
BMI	24.5 $\pm$ 3.4	24.1 $\pm$ 2.9	22.7 $\pm$ 2.5	0.001*
Family income (10 ⁴ yuan/year)	2.0 (1.0, 3.0)	2.0 (1.0, 4.0)	1.0 (0.5,3.0)	0.012*
Raising pets	55 (44.4)	98 (51.0)	35 (64.8)	0.043*
Biomass use ^a	53 (42.7)	97 (50.8)	38 (70.4)	0.003*
Duration of biomass exposure ^b	40.4 $\pm$ 17.0	38.3 $\pm$ 18.6	42.1 $\pm$ 17.2	0.511
Smoking status				
Current smoker	33 (26.4)	73 (37.4)	19 (34.5)	0.089
Former smoker	13 (10.4)	27 (13.9)	10 (18.2)	–
Never smoking	79 (63.2)	95 (48.7)	26 (47.3)	–
Bromopnea	13 (10.7)	22 (11.6)	5 (9.6)	0.913
Teeth problem ^c	88 (71.5)	125 (65.1)	36 (66.7)	0.488
Periodontitis ^d	19 (15.3)	22 (11.5)	7 (13.2)	0.608
CAT	7.5 (3.0, 14.0)	6.0 (2.0, 11.25)	5.0 (2.0, 11.0)	0.262
NEU%	62.2 (57.1,68.9)	60.1 (54.9, 66.5)	57.0 (53.0, 62.0)	<0.001*
WBC (10 ⁹ /L)	5.4 (4.6, 6.4)	6.0 (5.1, 7.3)	6.4 (5.7, 7.2)	<0.001*
TG (mmol/L)	1.4 (1.1, 1.8)	1.3 (1.1, 1.8)	1.6 (1.2, 1.7)	0.474
TC (mmol/L)	4.9 (4.5, 5.7)	4.8 (4.2, 5.5)	5.4 (4.1, 6.1)	0.169
HDL (mmol/L)	1.5 (1.3, 1.9)	1.5 (1.3, 1.7)	1.5 (1.2, 1.8)	0.642
LDL (mmol/L)	2.7 $\pm$ 0.8	2.6 $\pm$ 0.7	2.9 $\pm$ 0.9	0.175
FEV1% predicted (%)	90.8 $\pm$ 22.6	89.0 $\pm$ 20.7	88.0 $\pm$ 22.0	0.712
Pre-bronchodilator				
PEF (L/s)	4.7 (3.0, 6.2)	4.6 (3.5, 6.1)	4.4 (3.3, 6.0)	0.710
FEV1: FVC (%)	63.3 (57.7, 67.8)	63.1 (56.7, 63.6)	60.0 (51.6, 66.1)	0.107
Post-bronchodilator				
PEF (L/s)	4.8 (3.4, 6.5)	5.0 (3.9, 6.3)	4.6 (3.3, 6.6)	0.423
FEV1: FVC (%)	65.5 (59.3, 68.0)	64.1 (57.3, 67.9)	63.1 (51.9, 67.3)	0.143
GOLD stage $\leq$ I	93 (74.4)	140 (71.8)	40 (72.7)	0.878

Notes: Data are presented as n (%), mean $\pm$ SD or median (interquartile range). * $p < 0.05$. ^aDefined as using woody fuels or animal waste for cooking or heating during the past 6 months or longer. ^bDefined as consecutive years of biomass exposure. ^cDefined as having at least one of the following conditions in the past one year, including swollen gums, gingival bleeding, toothache, tooth losing and damaging. ^dDefined as being diagnosed with periodontitis by dentists.

Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; CAT, COPD assessment test; NEU%, percentage of neutrophils; WBC, leukocyte count; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; FVC, forced vital capacity.

Table 2 Factors Associated with Blood Eosinophil Count in COPD Patients According to Univariate Linear Regression Analysis

Factors	Unstandardized Coefficients		Standardized Coefficients	P value	Adjusted R ²
	Beta	95% CI	Beta		
Age (≥ 40 years)	0.934	−0.944 to 2.813	0.051	0.329	0.000
Male	44.312	6.556 to 82.067	0.119	0.022*	0.011
BMI	−7.716	−13.989 to −1.443	−0.124	0.016*	0.013
Family income	−4.552	−11.663 to 2.559	−0.067	0.209	0.002
Raising pets	43.130	2.423 to 83.838	0.108	0.038*	0.009
Biomass use	64.788	24.307 to 105.268	0.162	0.002*	0.024
Duration of biomass exposure	0.484	−1.445 to 2.413	0.037	0.62	−0.004
Former smoking	45.279	−5.307 to 95.865	0.091	0.079	0.006
Bromopnea	15.726	−50.507 to 81.959	0.025	0.641	−0.002
Teeth problem	13.815	−29.885 to 57.516	0.032	0.535	−0.002
Periodontitis	37.972	−31.547 to 107.490	0.056	0.283	0.056
TG	4.318	−28.002 to 36.638	0.018	0.793	−0.004
TC	−10.048	−36.020 to 15.924	−0.053	0.447	−0.002
HDL	−58.688	−113.664 to −3.713	−0.144	0.037*	0.016
LDL	−3.744	−38.924 to 31.435	−0.014	0.834	−0.005

Note: *p<0.05.

Table 3 Factors Associated with Blood Eosinophil Count in COPD Patients According to Multivariable Linear Regression Analysis

Independent Variables	Unstandardized Coefficients		Standardized Coefficients	P value
	Beta	95% CI	Beta	
Constant	98.729	−180.317 to 377.775	—	0.486
Age (≥ 40 years)	2.819	0.639 to 5.000	0.183	0.012*
Male	66.125	16.350 to 115.900	0.191	0.009*
BMI	−4.888	−12.186 to 2.409	−0.093	0.188
Family income	−1.383	−9.204 to 6.438	−0.027	0.728
Raising pets	41.957	3.964 to 79.951	0.137	0.478
Biomass use	27.373	−25.966 to 80.712	0.083	0.313
Former smoking	10.545	−60.298 to 81.388	0.021	0.769
TC	3.267	−27.088 to 33.622	0.025	0.832
HDL	−64.682	−123.451 to −5.914	−0.179	0.031*
LDL	13.928	−30.342 to 58.199	0.069	0.536

Notes: R² = 0.114, adjusted R² = 0.067. Adjusted for age, male gender, BMI, family income, raising pets, biomass use, former smoking, TC, HDL and LDL. *p<0.05.

age and lower HDL were determined as predictors for higher blood eosinophils in COPD patients from the Chinese cohort. However, the correlation between higher BMI and increased blood eosinophils implied by other studies was not validated in this study.^{20,26}

Epidemiological evidence demonstrated that eosinophilic COPD could be a specific phenotype. However, the prevalence of eosinophilic inflammation in COPD varied with different thresholds. In post-hoc analyses of clinical trials, the prevalence of high blood eosinophils in COPD was more than 45% according to the threshold of

2%,^{20,22,24} whereas it was less than 20% when using the cut-off of 300 cells/μL,^{31,32} similar to the results in this cohort study.

Current evidence concerning COPD with eosinophilic inflammation was mostly based on clinical phenotypic studies.⁴ The positive association between male gender and blood eosinophils in COPD has been well established in considerable reports,^{20,25,26} even though these results were almost identified by univariate analyses. Our study further confirmed the relationship by multivariable analyses, emphasizing an existed gender-related difference

regarding blood eosinophil level. Old age is a vital factor associated with the development and progression of COPD and its exacerbation.¹⁵ In this cohort study, we found oldness was a predictor for high blood eosinophils, similar to two other cross-sectional studies that indicated COPD patients with higher blood eosinophil counts were apparently older.^{20,33} However, two other reports did not suggest the same relationship between age and blood eosinophils.^{22,24} Consequently, the underlying reasons for the different results on the link between age and blood eosinophils in COPD need further verification.

An inverse association between HDL cholesterol and blood eosinophil counts has been reported in other cross-sectional studies.^{34,35} Our results further provided confirmatory evidence in a Chinese cohort. Mechanistic studies have demonstrated HDL could regulate proliferation and differentiation of hematopoietic stem cells through a cholesterol efflux-dependent manner involving ABCA1, ABCG1 and liver X receptors.^{36,37} HDL deficiency resulted in peripheral leukocytosis, including blood eosinophilia,³⁸ and a 1 mmol/L HDL cholesterol lowering was reported to be correlated with 14.8% higher eosinophils.³⁴ Given the imbalance in lipid profile in COPD implied by previous studies,^{39–41} it is imperative to explore whether the change in HDL level plays a role in eosinophilic COPD, and whether treatment for lower HDL in COPD is beneficial to reduce eosinophil-predominant exacerbation.

A real-world research demonstrated higher BMI was correlated with pulmonary function, lower inflammation levels and acute exacerbations, drawing attention to the impact of BMI on COPD management.⁴² However, in our study, the relationship between lower BMI and higher blood eosinophils was unexpectedly revealed in the initial univariate analysis, and after adjusting potential confounding factors, statistical significance of BMI was not observed, and it was inconsistent with other relevant reports,^{20,25,26} in which COPD with increased blood eosinophils was characterized by higher BMI. Different ethnic populations might account for this controversial result, and more studies in different populations are needed to verify the relationship between BMI and blood eosinophils.

Several limitations should be noticed in this study. First, the baseline information for all patients was not fully provided. For example, the medical information was missed because of incomplete records in the CPH study. Second, there could exist some possibility that the patients with asthma were not fully excluded from the analyses because

of the lack of some related information. To avoid the potential impact, we excluded younger patients aged <40 years, a high-risk subgroup of asthma.⁴³ Third, the diagnosis of COPD in this study was based only on spirometry tests. There could exist some overdiagnosis of COPD in this study. Fourth, potential recall biases were inevitable in a retrospective study.

In summary, this retrospective cohort study suggested and identified male gender, oldness and lower HDL could be clinical predictors of increased blood eosinophils in Chinese COPD patients. However, large prospective cohort studies are warranted to validate the present findings.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding authors on reasonable requests.

Consent for Publication Statement

Details of any images, videos, recordings, etc. can be published, and all authors have been shown the article contents to be published. Authors are prepared to provide copies of signed consent forms to the journal editorial office if requested.

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Author Contributions

All authors contributed to the conception, study design, execution, acquisition of data, data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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