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Association of blood eosinophils with corticosteroid treatment failure stratified by smoking status among inpatients with AECOPD

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ABSTRACT

Background Recent studies have suggested elevated blood eosinophils are independent predictors of response to corticosteroid therapy in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Smoking status has been shown to affect corticosteroid response. Whether the association between high blood eosinophils and corticosteroid treatment failure is modified by smoking has not been fully investigated so far.

Objectives This study aimed to assess whether the association between high blood eosinophils and corticosteroid treatment failure is modified by smoking.

Methods We included 3402 inpatients with AECOPD treated with corticosteroids at Beijing Chao-Yang Hospital from July 2013 to June 2021. Blood eosinophil counts were measured within 24 hours of admission. An eosinophil percentage ≥2% was considered as high eosinophilic. Smokers in this study were defined as current or former smokers. Treatment failure was defined as a worsening of AECOPD that led to adverse clinical outcomes or required further treatment or an extended hospital stay or hospitalisation following the exacerbation. Multivariate-adjusted logistic models were used to estimate the OR and 95% CI associated with treatment failure.

Results There were 958 (28.2%) treatment failure events occurring. Patients with high eosinophils had a lower risk of treatment failure (OR 0.74, 95% CI 0.63 to 0.87) than patients with low eosinophils. Compared with never smoking and low eosinophilic group, the ORs for treatment failure were 0.70 (95% CI 0.52 to 0.96) for never smoking and high eosinophilic group, 0.82 (95% CI 0.64 to 1.05) for smoking and low eosinophilic group and 0.62 (95% CI 0.47 to 0.81) for smoking and high eosinophilic group. Furthermore, there was no significant interaction between eosinophils and smoking status in relation to treatment failure (p for interaction=0.73). Similar results were obtained from multiple secondary outcomes and subgroup analyses.

Conclusion Elevated blood eosinophils are associated with a lower rate of corticosteroid treatment failure, regardless of smoking status. Smoking does not modify the association between blood eosinophil level and corticosteroid treatment failure among inpatients with AECOPD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Elevated blood eosinophils are independent predictors of response to corticosteroid therapy in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

⇒ Whether the association between high blood eosinophils and corticosteroid treatment failure is modified by smoking has not been fully investigated so far.

WHAT THIS STUDY ADDS

⇒ Smoking does not modify the association between blood eosinophil level and corticosteroid treatment failure among inpatients with AECOPD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on these findings, inpatients with eosinophilic AECOPD may benefit from corticosteroid treatment regardless of whether they smoke.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disorder which is characterised by progressive airflow limitation due to noxious particles.[1] According to WHO estimates, COPD is currently the third leading cause of death worldwide.[2] Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is an inevitable trend in the progression of the disease. It is estimated that every year 22%–40% of all patients with COPD experience at least one acute exacerbation.[3 4] Acute exacerbations of COPD are associated with health and economic burdens as well as increased risk of future mortality.[5 6]

Corticosteroid therapy has been a mainstay of AECOPD treatment, which can reduce exacerbation rates and possibly reduce the decline in lung function.[7] However, not all patients with AECOPD benefit from their use, let alone the vast array of adverse effects that long-term use of these medicines

cause.[8] Blood eosinophils is considered to be a potential biomarker to predict response to corticosteroid treatment.[9] Several post hoc analyses of clinical trials have shown that patients with AECOPD with higher blood eosinophils had a better responsiveness to corticosteroid therapy.[10–12] A small randomised controlled trial (RCT) reported that corticosteroid use in patients with blood eosinophil counts >2% was safe, whereas treatment in low eosinophil group was associated with more treatment failures.[13] Other study found no associations between blood eosinophils at admission and moderate-to-severe relapses.[14]

Recently, it has been postulated that smoking may cause resistance to some drug treatments among patients with AECOPD, most notably corticosteroids treatment.[15–17] According to animal models, cigarette exposure may lead to loss of histone deacetylase-2 corticosteroids, resulting in steroid resistance.[18] The mechanism for this resistance has yet to be fully established. It is not yet clear if smoking status may modify the effect of blood eosinophils' response to corticosteroids in patients with AECOPD. It is currently unknown whether blood eosinophils and smoking are jointly associated with the failure of corticosteroid treatment. One substudy showed that smoking status did not influence the role of eosinophils as a biomarker in guiding corticosteroid treatment.[19] However, the small sample size (n=318) may have been insufficient to power the statistical analysis. Other cohort study has shown the increased exacerbation rate with elevated eosinophil count with stable COPD was restricted to ex-smokers.[20] Not all participants with COPD used corticosteroid, and it is not possible to truly reflect the effect of blood eosinophils' response to corticosteroids in patients with AECOPD. The real-world studies with large populations are lacking.

Therefore, our aim was to assess the association of blood eosinophils with corticosteroid treatment failure among inpatients with AECOPD based on a retrospective study design with real-world data. We also investigated whether such associations varied significantly by smoking status.

METHODS

Study design and participants

This was a retrospective cohort study that was conducted at Beijing Chao-Yang Hospital in Beijing, China. The hospital was chosen for this study because it is a leading institution for respiratory medicine in China. The subjects in this study were patients with AECOPD who were admitted to Beijing Chao-Yang Hospital from July 2013 to June 2021. The criteria for AECOPD admission in our study were based on the expert consensus on AECOPD treatment in China: (1) severe COPD with significant exacerbation of symptoms, such as dyspnoea, cough and sputum; (2) new or worsening signs, including cyanosis, changes in mental status, peripheral oedema, uncorrected hypoxaemia and pH <7.30; (3) presence of severe comorbidities, such as heart failure, arrhythmia and renal dysfunction; (4) failure of outpatient medical therapy for AECOPD; (5) lack of medical equipment and technology necessary to treat AECOPD at primary healthcare institutions (secondary and lower medical institutions). Deprivatised inpatient electronic medical records (EMR) of these patients were extracted.

All study subjects were 40 years or older with a primary discharge diagnosis of AECOPD. The AECOPD was defined as an event characterised by dyspnoea and/or cough and sputum, which was diagnosed based on the International Classification of Diseases 10th Revision code of J44.0–J44.9. For patients who had multiple AECOPD admissions during the study period, only the first admission was included. Of these subjects, we excluded patients who had missing data in blood routine tests, and inpatient prescriptions; had comorbid asthma, pneumothorax, pulmonary embolism, acute coronary syndrome, lung cancer, systemic fungal infection, severe mental illness and pneumonia at entry; received invasive mechanical ventilation within 48 hours after admission; had no blood eosinophil measured within 24 hours after admission; had extreme values in eosinophil level (count >2000 cells/μL or percentage >20%); had a length of stay (LOS) >50 days. Ultimately, a total of 3402 participants who had corticosteroids treatment during the hospitalisation were included in the current analysis (figure 1).

Exposure and covariates

Blood eosinophils measured within 24 hours after admission was obtained from the Laboratory Information System (LIS). We used a cut-off value of 2% in eosinophil percentage to define high eosinophil count and low eosinophil count according to previous studies.[21 22] Participants were categorised into current or former smokers (smokers) and never smokers (non-smokers) based on self-reported smoking history, extracted from the unstructured texts in EMR using natural language processing. Smoking status was asked and recorded by the physician during the inquiry of medical history. Former smokers referred to patients who had ever smoked in their lifetime but had quit smoking before admission, regardless of how long they had quit.

Age, sex and comorbidities were collected from the front page of discharge records. Corticosteroid treatment during hospitalisation included only inhaled corticosteroids and systemic corticosteroids (including inhaled corticosteroids plus systemic corticosteroids). Comorbidity was quantified according to the Charlson Comorbidity Index (CCI).[23] Number of AECOPD hospitalisations in the previous year was obtained from a database operated by the Beijing Public Health Information Centre that covered all AECOPD hospital admissions in Beijing.[24] Information on laboratory tests (blood routine test, biochemistry) and medication use during hospitalisation was extracted from the LIS or electronic prescription system.

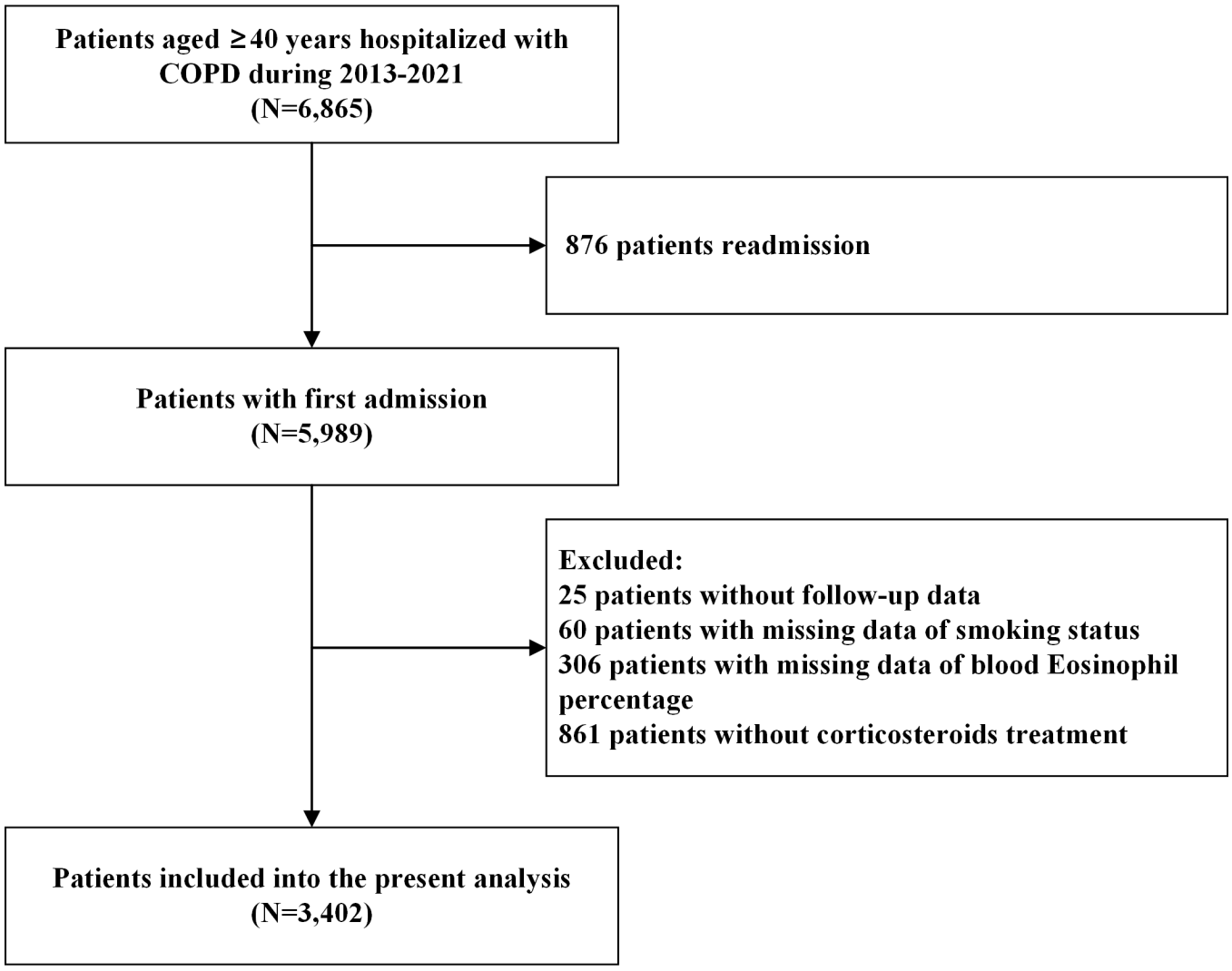

Figure 1 Flow chart of study. COPD, chronic obstructive pulmonary disease.

Study outcomes

Treatment failure was defined as a worsening of AECOPD that led to adverse clinical outcomes or required further treatment or an extended hospital stay or rehospitalisation following the exacerbation of COPD. In this study, treatment failure was a composite outcome of several events: LOS >14 days, death during hospitalisation or within 30 days after discharge, incident pneumonia during hospitalisation, receiving invasive mechanical ventilation, transferring to intensive care unit (ICU) and AECOPD readmission within 30 days of discharge.

LOS and in-hospital events were collected from EMR. AECOPD readmissions were tracked within 3 months of discharge for patients who were discharged alive. The follow-up ended at the first AECOPD readmission, death or 30 June 2021, whichever occurred first. The follow-up was conducted by electronic linkage to a citywide hospitalisation database maintained by Beijing Municipal Health Commission Information Center.[24] Readmission date and discharge diagnosis were obtained. Approximately 1% (n=20) could not be linked to the hospitalisation database and thus had no follow-up information.

Statistical analysis

All data are presented as medians and IQRs or as numbers and percentages. Continuous variables are compared using the Kruskal-Wallis test, and categorical variables are compared using the χ^2 test.

The subjects were further divided into four groups, according to their eosinophil count and smoking status: (1) non-smoker and low eosinophil count; (2) non-smoker and high eosinophil count; (3) smoker (including former or current smokers) and low eosinophil count; (4) smoker and high eosinophil count. Logistic regression models were used to investigate the association between the four groups and treatment failure. ORs with 95% CIs were calculated, with the non-smoker and low eosinophil count group as the reference group. Two models were constructed in a step-by-step manner. Model 1 was unadjusted; model 2 was adjusted for age, gender, CCI, number of AECOPD hospitalisations in the previous year, white blood cell count and antibiotic use.

To assess whether smoking status modifies the association between eosinophil count and treatment failure, we separated subjects into two subgroups based on the

Table 1 Characteristics of patients with AECOPD by blood eosinophil percentage

Variables	Overall	Eosinophil percentage		P value
		<2% (n=1896)	≥2% (n=1506)	
Age, years	71.0 (63.0–78.0)	72.0 (64.0–79.0)	70.0 (63.0–77.0)	<0.001
Male, n (%)	2524 (74.2)	1353 (71.4)	1171 (77.8)	<0.001
Smoking status, n (%)				
Non-smoker	889 (26.1)	518 (27.3)	371 (24.6)	0.08
Former smoker	1749 (51.4)	943 (49.7)	806 (53.5)	
Current smoker	764 (22.5)	435 (22.9)	329 (21.8)	
Charlson Comorbidity Index, n (%)				
0	1442 (42.4)	742 (39.1)	700 (46.5)	<0.001
1	1230 (36.2)	708 (37.3)	522 (34.7)	
2	354 (10.4)	203 (10.7)	151 (10.0)	
≥3	376 (11.0)	243 (12.8)	133 (8.8)	
Hypertension, n (%)	1504 (44.2)	832 (43.9)	672 (44.6)	0.67
Diabetes, n (%)	525 (15.4)	315 (16.6)	210 (14.0)	0.03
Congestive heart failure, n (%)	74 (2.0)	47 (2.3)	27 (1.6)	0.16
Hospitalised for AECOPD in previous year, n (%)				
0	2902 (85.3)	1582 (83.4)	1320 (87.6)	0.001
1	331 (9.7)	202 (10.6)	129 (8.6)	
≥2	169 (5.0)	112 (5.9)	57 (3.8)	
White blood cell count, 10^9/L	6.8 (5.5–8.8)	7.6 (5.8–10.0)	6.2 (5.2–7.6)	<0.001
Corticosteroid use during hospitalisation, n (%)				
Only inhaled corticosteroid	2124 (62.4)	954 (50.3)	1170 (77.7)	<0.001
Systemic corticosteroid	1278 (37.6)	942 (49.7)	336 (22.3)	
Antibiotics use during hospitalisation, n (%)	3178 (93.4)	1825 (96.3)	1353 (89.8)	<0.001

AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

status of smoking. We conducted logistic regression models in each subgroup to investigate the association between eosinophil count and treatment failure. We also performed subgroup analyses by systemic versus non-systemic corticosteroid use during hospitalisation. Additionally, considering that former smokers may differ from current smokers, we further divided smokers into current smokers and former smokers.

All analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). The significant level was 0.05 for a two-tailed test.

RESULTS

Among the 3402 patients in the analysis, the median age was 71.0 (63.0–78.0) years, and 2524 (74.2%) were male. The median percentage of eosinophil was 1.6% (0.3%–3.3%). Less than half of patients with AECOPD had an eosinophil percentage <2% (44.6%).

Table 1 shows the baseline characteristics of the study patients according to low and high blood eosinophil percentage. Patients with higher levels of eosinophils were slightly younger, more likely to be male, more frequently former smokers and less likely to have AECOPD hospitalisation in the previous year. They also had a lower white blood cell count. They also had a lower prevalence of diabetes and comorbidities. Most of the patients with AECOPD were treated with only inhaled corticosteroids during hospitalisation (n=2124, 62.4%).

There were 958 (28.2%) treatment failure events occurring, including 718 (21.1%) LOS >14 days, 128 (3.8%) ICU transfer cases, 45 (1.3%) invasive mechanical ventilation cases, 108 (3.2%) incident pneumonia cases, 69 (2.0%) deaths during hospitalisation or within 30 days after discharge and 153 (4.5%) 30-day AECOPD readmissions. The rates of treatment failure were 32.9% and 22.2% for the low eosinophilic group and high eosinophilic group, respectively. After adjustment for all covariates, including age, gender, CCI, number of AECOPD hospitalisations in the previous year, white blood cell count and antibiotic use, the high eosinophilic group had a lower risk of treatment failure than the less eosinophilic group (OR 0.74, 95% CI 0.63 to 0.87). As compared with the low eosinophilic group, the high eosinophilic group had 29.0% lower risk (95% CI 0.60 to 0.86) of LOS >14

Table 2 The relationship between blood eosinophil percentage and corticosteroid treatment failure among inpatients with AECOPD

	Case, n (%)	Unadjusted OR (95% CI)	Multiadjusted OR (95% CI)
Treatment failure			
EOS <2%	623 (32.9)	Reference	Reference
EOS ≥2%	335 (22.2)	0.58 (0.50 to 0.68)	0.74 (0.63 to 0.87)
Length of stay ≥14 days			
EOS <2%	474 (25.0)	Reference	Reference
EOS ≥2%	244 (16.2)	0.58 (0.49 to 0.69)	0.71 (0.60 to 0.86)
Transfer to ICU			
EOS <2%	110 (5.8)	Reference	Reference
EOS ≥2%	18 (1.2)	0.20 (0.12 to 0.32)	0.31 (0.18 to 0.52)
Invasive mechanical ventilation			
EOS <2%	38 (2.0)	Reference	Reference
EOS ≥2%	7 (0.5)	0.23 (0.10 to 0.51)	0.40 (0.71 to 0.93)
Incident pneumonia during hospitalisation			
EOS <2%	59 (3.1)	Reference	Reference
EOS ≥2%	49 (3.2)	1.05 (0.71 to 1.54)	1.08 (0.72 to 1.61)
Death during hospitalisation or within 30 days after discharge			
EOS <2%	57 (3.0)	Reference	Reference
EOS ≥2%	12 (0.8)	0.26 (0.14 to 0.48)	0.42 (0.22 to 0.81)
AECOPD readmission within 30 days after discharge			
EOS <2%	96 (5.0)	Reference	Reference
EOS ≥2%	58 (3.8)	0.76 (0.54 to 1.06)	0.99 (0.69 to 1.41)

Adjusted for age, gender, Charlson Comorbidity Index, smoking status, number of AECOPD hospitalisations in the previous year, white blood cell count and antibiotics use.
AECOPD, acute exacerbations of chronic obstructive pulmonary disease; EOS, eosinophil percentage; ICU, intensive care unit.

days, 69.0% lower risk (95% CI 0.18 to 0.52) of being transferred to the ICU, 60% lower risk (95% CI 0.71 to 0.93) of invasive mechanical ventilation and 58% lower risk (95% CI 0.22 to 0.81) of deaths during hospitalisation or within 30 days after discharge, respectively. There was no statistical difference in incident pneumonia during hospitalisation and 30-day AECOPD readmissions between the two eosinophilic groups (table 2).

The treatment failure rates were 29.4% for the non-smoker group and 27.0% for the smoker group, respectively. After adjusting all covariates, the association between smoking and the risk of treatment failure was not significant for smoker group; the OR was 0.85 (95% CI 0.69 to 1.04), compared with non-smoker group (online supplemental table 1).

Without adjustment for confounders, the rate of treatment failure was the highest in the non-smoker and low eosinophilic group and lowest in the smoker and high eosinophilic group (table 3). After multivariable adjustment, the ORs for treatment failure were 0.70 (95% CI 0.52 to 0.96) for non-smoker and high eosinophilic group, 0.82 (95% CI 0.64 to 1.05) for smoker and low eosinophilic group, 0.62 (95% CI 0.47 to 0.81) for smoker and high eosinophilic group, compared with non-smoker and low eosinophilic group (table 3). The secondary outcomes are also presented in table 3, with results being approximately consistent with the primary outcome, except for incident pneumonia during hospitalisation, death during hospitalisation or within 30 days after discharge and AECOPD readmission within 30 days of discharge. In the multivariable model, the ORs for AECOPD readmission within 30 days after discharge were 0.42 (95% CI 0.20 to 0.88) for the non-smoker and high eosinophilic group, 0.50 (95% CI 0.31 to 0.81) for the smoker and low eosinophilic group and 0.67 (95% CI 0.40 to 1.12) for the smoker and high eosinophilic group (table 3).

A further analysis of whether former smokers and current smokers have different effects on treatment failure can be found in online supplemental table 2. After multivariable adjustment, the ORs for treatment failure were 0.70 (95% CI 0.52 to 0.96) for the non-smoker and high eosinophilic group, 0.62 (95% CI 0.47 to 0.82) for the former smoker and high eosinophilic group and 0.62 (95% CI 0.44 to 0.90) for the current smoker and high eosinophilic group, compared with the non-smoker and low eosinophilic group (online supplemental table 2). No matter whether the patient had quit smoking or

Table 3 Risk of corticosteroid treatment failure across blood eosinophil percentage and smoking status

	Case, n (%)	Unadjusted OR (95% CI)	Multiadjusted OR (95% CI)
Treatment failure			
Non-smoker			
EOS <2%	184 (35.5)	Reference	Reference
EOS ≥2%	92 (24.8)	0.60 (0.44 to 0.80)	0.70 (0.52 to 0.96)
Smoker			
EOS <2%	439 (31.9)	0.85 (0.69 to 1.05)	0.82 (0.64 to 1.05)
EOS ≥2%	243 (21.4)	0.50 (0.39 to 0.62)	0.62 (0.47 to 0.81)
Length of stay ≥14 days			
Non-smoker			
EOS <2%	135 (26.1)	Reference	Reference
EOS ≥2%	67 (18.1)	0.62 (0.45 to 0.87)	0.72 (0.51 to 1.01)
Smoker			
EOS <2%	339 (24.6)	0.92 (0.73 to 1.17)	0.94 (0.72 to 1.22)
EOS ≥2%	177 (15.6)	0.52 (0.41 to 0.68)	0.67 (0.50 to 0.89)
Transfer to ICU			
Non-smoker			
EOS <2%	38 (7.3)	Reference	Reference
EOS ≥2%	5 (1.4)	0.17 (0.07 to 0.44)	0.23 (0.09 to 0.61)
Smoker			
EOS <2%	72 (5.2)	0.70 (0.46 to 1.05)	0.83 (0.51 to 1.35)
EOS ≥2%	13 (1.2)	0.15 (0.08 to 0.28)	0.29 (0.14 to 0.59)
Invasive mechanical ventilation			
Non-smoker			
EOS <2%	13 (2.5)	Reference	Reference
EOS ≥2%	2 (0.5)	0.21 (0.05 to 0.94)	0.33 (0.07 to 1.50)
Smoker			
EOS <2%	25 (1.8)	0.72 (0.36 to 1.41)	0.86 (0.39 to 1.88)
EOS ≥2%	5 (0.4)	0.17 (0.06 to 0.48)	0.38 (0.12 to 1.18)
Incident pneumonia during hospitalisation			
Non-smoker			
EOS <2%	16 (3.1)	Reference	Reference
EOS ≥2%	18 (4.8)	1.60 (0.80 to 3.18)	1.57 (0.78 to 3.15)
Smoker			
EOS <2%	43 (3.1)	1.01 (0.56 to 1.81)	0.76 (0.40 to 1.42)
EOS ≥2%	31 (2.7)	0.88 (0.48 to 1.62)	0.68 (0.35 to 1.34)
Death during hospitalisation or within 30 days after discharge			
Non-smoker			
EOS <2%	19 (3.7)	Reference	Reference
EOS ≥2%	3 (0.8)	0.21 (0.06 to 0.73)	0.25 (0.07 to 0.90)
Smoker			
EOS <2%	38 (2.8)	0.74 (0.42 to 1.30)	0.97 (0.50 to 1.87)
EOS ≥2%	9 (0.8)	0.21 (0.09 to 0.47)	0.51 (0.21 to 1.24)
AECOPD readmission within 30 days after discharge			
Non-smoker			

Continued

Table 3 Continued

	Case, n (%)	Unadjusted OR (95% CI)	Multiadjusted OR (95% CI)
EOS <2%	36 (7.0)	Reference	Reference
EOS ≥2%	9 (2.4)	0.33 (0.16 to 0.70)	0.42 (0.20 to 0.88)
Smoker			
EOS <2%	59 (4.3)	0.60 (0.39 to 0.92)	0.50 (0.31 to 0.81)
EOS ≥2%	49 (4.3)	0.60 (0.39 to 0.94)	0.67 (0.40 to 1.12)

Adjusted for age, gender, Charlson Comorbidity Index, number of AECOPD hospitalisations in the previous year, white blood cell count and antibiotics use.
AECOPD, acute exacerbations of chronic obstructive pulmonary disease; EOS, eosinophil percentage; ICU, intensive unit.

not, those patients with high levels of eosinophils had lower treatment failure rates than those with low levels of eosinophils.

Figure 2 illustrates interaction analyses conducted to determine whether eosinophilia and smoking contributed to treatment failure. After adjustment for potential confounders, compared with low eosinophilic group, high eosinophilic group was significantly associated with lower risk of treatment failure in non-smoker group, the OR was 0.73 (95% CI 0.54 to 0.98) and the association was also significant for smoker subjects, the OR was 0.74 (95% CI 0.61 to 0.89). Furthermore, there was no significant interactions between eosinophil percentages and smoking status in relation to treatment failure (p for interaction=0.73) (figure 2).

A subgroup analysis of patients receiving systemic corticosteroids showed a lower rate of treatment failure (20.5% vs 40.8%) than those receiving non-systemic corticosteroids. Based on the stratification of systemic corticosteroid use, the OR for treatment failure was 0.69 (95% CI 0.47 to 0.99) for the smoker and high eosinophilic group, compared with the non-smoker and low eosinophilic group. While in non-systemic corticosteroid use stratification, there were no significant differences in treatment failure rates among the four different smoking and eosinophilic groups (online supplemental table 3).

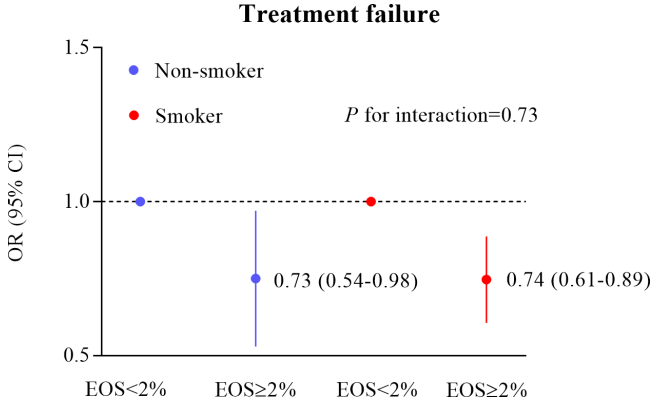

Figure 2 Association of blood eosinophil percentage with corticosteroid treatment failure across smoking status. AECOPD, acute exacerbations of chronic obstructive pulmonary disease; EOS, eosinophil percentage. Adjusted for age, gender, Charlson Comorbidity Index, number of AECOPD hospitalisations in the previous year, white blood cell count and antibiotics use.

DISCUSSION

Our EMR-based observational study of inpatients with AECODP receiving corticosteroids treatment demonstrated that higher levels of blood eosinophils were significantly associated with a lower risk of corticosteroid treatment failure, and these associations persisted even after adjustment for other conventional risk factors. Moreover, eosinophils were associated with treatment failure among patients with different smoking status, indicating that smoking status did not modify the association between eosinophils and corticosteroid treatment failure.

Recently, level of blood eosinophils has emerged as a potential biomarker in patients with COPD, based on the observation that levels of blood eosinophils appear to be associated with subsequent risk for exacerbation and to predict the response to corticosteroids treatment in clinical trials.[10 11 25] In some previous studies of patients with COPD, a cut-off value of 2% for blood eosinophils has been widely used to predict COPD exacerbations.[13 26] We used the threshold of 2% and found that >44% of patients with higher eosinophils in AECOPD were hospitalised. Several studies have reported that elevated absolute blood eosinophil counts at stable COPD may be associated with a higher risk of exacerbation.[11 27] In contrast, others also found higher levels of blood eosinophils have been associated with fewer infections and perhaps a better survival.[28–31] Recently, there has been an increasing interest in investigating the association between blood eosinophils and response to corticosteroids treatment in patients with AECOPD,[13 32 33] and some studies also have used blood eosinophils to guide corticosteroids treatment.[13 32 34] A randomised clinical trial on antibiotic prescription based on C reactive protein levels versus the Global Initiative for Chronic Obstructive Lung Disease (GOLD)-guided strategy with 207 exacerbations in patients with AECOPD showed that higher blood eosinophils were associated with higher short-term

treatment success rates.[9] Another post hoc analysis found that patients with blood eosinophil counts >200 cells/µL had a lower reduction in exacerbation rate.[35] In this study using a relatively large sample of Chinese population, it was confirmed that elevated levels of blood eosinophils were significantly associated with 26% reductions in the risk of treatment failure.

In healthy smokers, antioxidant defences would be activated to protect against oxidative stress caused by smoke. Patients with COPD are unable to resist oxidative stress and, as a result, develop a resistance to corticosteroids.[36] This theory might imply that quitting smoking would restore steroid responsiveness, however, studies have shown that even patients with COPD who stop smoking fail to respond to corticosteroids.[16] This may be due to persistent oxidative stress from irreversible airway inflammation.[37] A clinical meta-analysis of seven studies found that former smokers with COPD who were treated with inhaled corticosteroids showed greater improvements in lung function and fewer exacerbations than current smokers with COPD.[17] There is a possibility that this is the result of corticosteroid resistance caused by smoking. However, a post hoc analysis of the Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease (GLUCOLD) study, which included persistent smokers and former smokers, reported former smokers had less decline in lung function at 30 months.[38] The results of this study indicated that cigarette smokers were more responsive to corticosteroids compared with former smokers. According to our study, there was no significant difference between smokers and non-smokers when it came to the association with treatment failure. Besides, a lower rate of treatment failure in current smokers was compared with former smokers and never smokers (23.3% vs 31.0%, 28.8%). This phenomenon might be explained by the 'smoker's paradox'.[39] In one sense, the paradox is related to the sick-quitter effect, which is mainly caused by former smokers being in a sick and unhealthy physical state and having to give up smoking. Smoking patients, on the other hand, may be in better physical condition and may not passively choose to quit smoking due to their illness (online supplemental table 4). Furthermore, this study included hospitalised patients with AECOPD who were older (51.8% were >70 years of age), thus there may be a survivor bias in this study. It is possible for the bias created by these factors, to some extent, lead to a non-significant association between smoking and corticosteroid treatment failure, as well as the interaction between smoking and elevated blood eosinophils on the response to systematic corticosteroid therapy. Future prospective cohort studies or clinical trials are needed to confirm our findings.

Recently, a post hoc analysis of three RCTs has found that only eosinophil count and smoking status were independent predictors of response to budesonide in patients with COPD without asthma history, with the greatest benefit of corticosteroids treatment seen in current smokers with higher blood eosinophil.[40] Compared with RCT studies, our real-world study included a broader population with a diverse spectrum of patients with AECOPD. Different eligibility criteria might contribute to differences in results. A cohort study found an interaction between eosinophil and smoking status on COPD exacerbation risk.[20] But eosinophil count was measured at stable COPD, which might explain the inconsistency with our results. In addition, smoking status was categorised differently, and the study outcomes are also different. We focused on in-hospital outcomes and short-term exacerbation readmission (30-day), not on 1-year exacerbation risk. Some of the differences inevitably result from variability in eosinophil count, which is an inherent limitation of single measurement. Another real-world observational study conducted in 1290 Chinese patients admitted for AECOPD found that the hospitalisation time following treatment with systemic corticosteroids was shorter in patients with eosinophilia than patients without eosinophilia with smoking history (median 8 vs 9 days, p=0.046), and the results were similar between the two groups in patients without smoking history (p=0.376).[41] Another substudy analysis of the Corticosteroid Reduction in COPD (CORTICO-COP) RCT showed that smoking status did not influence the role of eosinophils as a biomarker in guiding corticosteroid treatment.[19] However, the small sample size (n=318) may have been insufficient to power the statistical analysis. Similarly, our study based on a real-world setting observed that regardless of smoking, higher levels of eosinophils reduced the risk of corticosteroid treatment failure. And there was no interaction between smoking and eosinophils on corticosteroids treatment. We also found a lower risk of corticosteroid treatment failure in patients receiving inhaled combined systemic corticosteroids, compared with only inhaled corticosteroids. It can thus be suggested that patients with eosinophilic AECOPD might benefit more from systemic corticosteroid treatment, regardless of whether they smoke. The mechanisms behind the complex interaction between active smoking and corticosteroid benefit remain unclear, and further research is needed to elucidate them.

The study has several key strengths. First, the present study assessed the interaction effect of smoking status with blood eosinophils on the effectiveness of systematic corticosteroid among inpatients with AECOPD. It provides the first evidence that higher eosinophil levels are associated with a lower risk of treatment failure, regardless of smoking, and thus smoking does not modify the association between higher eosinophil levels and better response to corticosteroids. Second, this study was of a 'real-life' nature, which made it more relevant to clinical management of patients with AECOPD. Third, we have adjusted for available confounding factors, such as age, gender, CCI, number of AECOPD hospitalisations in the previous year, white blood cell count and antibiotic usage, to ensure the reliability of the results.

This study also has some limitations. First, although potential risk factors were adjusted for, we still cannot

exclude the unavailable confounding factors which were not analysed in our study, such as socioeconomic status, exacerbation severity and pharmaceutical treatments, thus might bias our results to some extent. Second, lung function data before AECOPD hospitalisation was not available due to the retrospective nature of this study. In addition, the study population consisted mainly of elderly patients (mean age: 71.0 years), with only a limited number of patients (<10%) undergoing spirometry either during hospitalisation or at discharge. Third, the smoking status was collected from medical records and patient recall bias[42] may have biased the observed associations. Fourth, blood levels of eosinophils have variability,[43] but we only used the eosinophil count at admission. However, it is clinically unfeasible to measure peripheral blood eosinophils a few times before deciding whether corticosteroid therapy should be administered. In such cases, patients may miss the ideal timing to start corticosteroids treatment. Finally, this study used data from one of the top medical institutions in China that specialises in respiratory diseases, representing the highest standard of medical treatment for patients with AECOPD, enabling us to conduct this real-world study to assess the effectiveness of corticosteroid therapy. Nevertheless, it should be noted that our results and conclusions may not necessarily be representative of other hospital populations or generalisable to other levels of hospitals or regions. Further studies involving RCTs and prospective cohorts are necessary to confirm our findings.

CONCLUSIONS

In conclusion, our study showed that the eosinophilic phenotype was associated with a lower rate of corticosteroid treatment failure, whether smoking or not. And there was no interaction between smoking and eosinophils on corticosteroids treatment. Based on these findings, inpatients with eosinophilic AECOPD may benefit from corticosteroid treatment regardless of whether they smoke. Future study is required to validate our findings and elucidate the mechanisms underlying the complex interaction between smoking and blood eosinophils on corticosteroid benefit.

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