

# Characteristics of 12-Month Readmission for Hospitalized Patients with COPD: A Propensity Score Matched Analysis of Prospective Multicenter Study

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**Purpose:** Hospitalization for acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is considered as severe exacerbations. Readmission for severe exacerbations is a crucial event for COPD patients. However, factors associated with readmission for severe exacerbations are incomplete. The study aimed to investigate different characteristics between the severe and non-severe exacerbation groups.

**Patients and Methods:** Patients hospitalized for severe AECOPD were included in multi-centers, and their exacerbations in next 12 months after discharge were recorded. According to exacerbations, patients were separated into the severe-exacerbation group and the non-severe exacerbation group. Propensity-score matching (PSM) and multivariable analyses were performed to compare the baseline characteristics of two groups. The Hosmer-Lemeshow test and receiver operating characteristic curve were applied to evaluate how well the model could identify clusters.

**Results:** The cohort included 550 patients with severe AECOPD across 27 study centers in China, and 465 patients were finally analyzed. A total of 41.5% of patients underwent readmission for AECOPD within 1 year. There were no significant differences in baseline characteristics between groups after PSM. Severe exacerbations in the 12 months were related to some factors, eg, the duration of COPD (13 vs 8 years,  $P<0.001$ ), the COPD Assessment Test (CAT) score (20 vs 17,  $P<0.001$ ), the blood eosinophil percentage (1.5 vs 2.0,  $P<0.05$ ), and their inhaler therapies. Patients readmitted with AECOPD had a longer time of diagnosis ( $\geq 9$  years), more symptoms (CAT  $\geq 10$ ), and lower blood eosinophils (Eos  $<2\%$ ). A clinical model was derived to help identify patients at risk of readmission with severe exacerbations.

**Conclusion:** These analyses confirmed the relevance of COPD at admission with future severe exacerbations. A lower blood eosinophils percentage appears to be related to readmission when combined with clinical history. Further studies are needed to evaluate whether this study can predict the risk of exacerbations.

**Keywords:** chronic obstructive pulmonary disease, acute exacerbation, eosinophils, prognosis

## Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease underpinned by diverse clinical phenotypes and biological endotypes,<sup>1,2</sup> with episodes of exacerbations leading to hospitalization and mortality.<sup>3–5</sup> There were 212.3 million cases of COPD globally with an estimated 3.3 million deaths relevant to COPD in 2019.<sup>6</sup> Acute exacerbation of COPD (AECOPD), defined as worsening of respiratory symptoms that results in additional therapy, is classified into mild, moderate and severe exacerbation. Patients are severe when the patient visits an emergency room or is hospitalized for the event.<sup>7,8</sup>

For patients underlying hospitalization for AECOPD, readmission to hospital is a vital problem. Hence, it is important to identify risk factors for severe exacerbation of COPD-related readmission in advance. Previous studies have identified various factors in predicting COPD outcomes. For example, Zemans et al reported that a combination of soluble Receptor for Advanced Glycation Endproducts and C-Reactive Protein may be predictive of total exacerbation frequency in the ECLIPSE study.<sup>9</sup> García-Sanz et al demonstrated that age, exacerbation severity and comorbidities influenced 5-year mortality in a retrospective study.<sup>10</sup> Furthermore, studies mostly focused on short-term readmission such as 30 days or 90 days after discharge.<sup>11,12</sup> Several studies have explored rates and risk factors related to readmission within 12 months, most were retrospective studies. The rates of readmission range from 25%–87%, and risk factors vary a lot among studies.<sup>13</sup> Notably, in our country, limited studies have been conducted to investigate factors relevant to 12-month readmission in a prospective way.

Severe exacerbations rely on self-reported symptoms and lack reliable biomarkers to distinguish future risk of exacerbations. Blood eosinophils tests are feasible in clinical practice. Furthermore, blood eosinophils are recommended as a biomarker to guide inhaled corticosteroids (ICS) use according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020<sup>8</sup>. However, there is controversy regarding the predictive value of blood eosinophil levels for severe exacerbation related readmission.<sup>14–20</sup> Whether eosinophil levels and other clinical characteristics at admission for AECOPD have an effect on readmission in the next year remains unclear and warrants investigation in large, longitudinal cohorts. Variation in the prevalence, and controversy in relationship between eosinophils and severe exacerbations demonstrate that risk factors cannot be generalized, which implies the interventions should be tailored to local healthcare system. Thus, the main objective of our study was to investigate the similarities and differences of patients with or without severe exacerbations of COPD in the following 12 months after discharge from the hospital.

## Materials and Methods

### Study Design

Our study is a multi-center, prospective, observational cohort study conducted in China. The study complied with the Declaration of Helsinki and Good Clinical Practice and was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University, China (2019-SR-129). The outbreak of coronavirus disease 2019 (COVID-19) influenced the number of enrolled patients, so we have to reapply to the hospital federal committee to prolong the study. All participants provided written informed consent. Respiratory physicians across 27 study centers enrolled patients with the main diagnosis of hospitalization for AECOPD from October 2019 to October 2020 and followed them in the next 12 months after discharge, due to the pandemic of COVID-19, sporadic cases make it difficult for all enrolled patients to attend the visit to the hospital, which pushes researchers to contact part of them online or by telephone.

### Study Patients

Patients were diagnosed with COPD by symptoms, spirometry and the standard definition of the Global Initiative for Chronic Obstructive Lung Disease.<sup>8</sup> In detail, the recruitment criteria included a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio <0.7, hospitalization for AECOPD and blood tests within 24 hours after admission. Blood tests included complete blood cell count which was collected from peripheral venous blood. Upon candidate reassessment, exclusion criteria were lack of pulmonary function test within five years, mislabeled

asthmatics, COPD without exacerbation and no access to 12-month follow-up. Patients with proceeding cancers and those taking systemic corticosteroids 48 hours before admission were also excluded.

## Study Variables

At baseline, some characteristics (eg, the patients' self-reported symptoms, smoking history, residence, time since COPD diagnosis, COPD Assessment Test (CAT) score, spirometry within 5 years, comorbid conditions, inhaler therapy and corticosteroid use within 48 hours before admission) were documented at study entry with the use of research collaborations platform of YiduCloud (<https://research.yiducloud.com.cn/>). Complete blood cell counts taken before the use of systemic corticosteroids were also documented and uploaded as pictures onto the platform. In line with previous studies, high eosinophil counts were defined as blood eosinophils  $\geq 2\%$  of the total white blood cell count, which has shown high sensitivity in identifying sputum eosinophilia.<sup>15,21</sup> Exacerbations in the next year after hospitalization were recorded by hospital database, telephone and internet due to the unexpected pandemic.<sup>22</sup>

## Study Outcomes

The occurrence of severe exacerbations was a critical outcome. Physicians were instructed to make their decision on common clinical practice without specific criteria of an exacerbation. The primary outcome was 12-month readmission for severe exacerbation of COPD after discharge. A severe exacerbation was defined as hospitalization for COPD.<sup>7</sup> To investigate the factors related to 12-month readmission after discharge, we divided patients into two groups: the severe exacerbation group and the non-severe exacerbation. The severe exacerbation group indicates patients who are hospitalized for AECOPD in the next 12 months, while patients without readmission for AECOPD are defined as the non-severe exacerbation group.

## Study Analysis

Demographic data were summarized using basic descriptive statistics. For continuous variables, data were presented as the means  $\pm$  standard deviations (SD) if they met normal distribution, or medians (25–75% interquartile range) if not. For categorical variables, data were presented as numbers (percentages). Continuous variables were analyzed using Student's *t*-test or nonparametric tests. Categorical variables were tested by the Chi-square test, Fisher's exact test or Mann–Whitney *U*-test, as appropriate. To help reduce the effects of confounding on nonrandomized design, propensity-score matching was applied. Considering the difficulty in conducting pulmonary function tests during acute exacerbations, the covariates (eg, age, sex, smoking status, body mass index, residence and FEV1% pre) were included in the PSM. Patients were 1:1 PS-matched by the near neighbor methodology with a maximum caliper of 0.02 of the deviation of the logit of the PS.

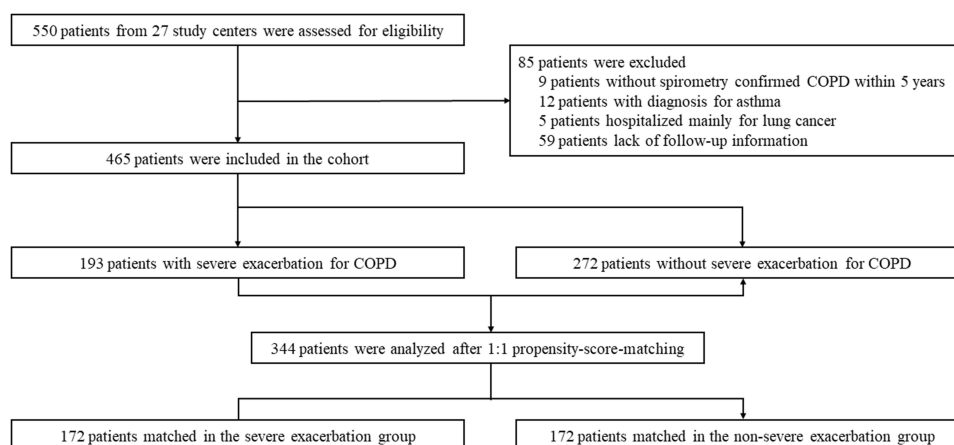
A binary logistic regression model was used to estimate factors associated with the probability of 12-month readmission for an individual. Variables that were explored in the univariate analysis were considered in the multivariate model, while a conservative significance threshold of 0.01 was applied to assess data for entry into or deletion from the model. Furthermore, the Hosmer-Lemeshow test was conducted to evaluate the goodness of fit of the binary logistic regression models. Receiver operating characteristic (ROC) curves were generated to assess the predictive ability of the models to correctly identify the onset of 12-month readmission. All statistical analyses were conducted using the IBM-SPSS version 26.0. Variables with a two-sided  $P < 0.05$  were accepted as statistically significant.

## Results

### Recruitment of Patients

The procedure of sample selection is shown in Figure 1. A total of 550 patients were assessed for eligibility from October 2019 to October 2020 in 27 study centers in China. Therein, 85 patients were excluded because they did not completely fulfill the enrollment criteria. Thus, 465 patients were included in the analysis.

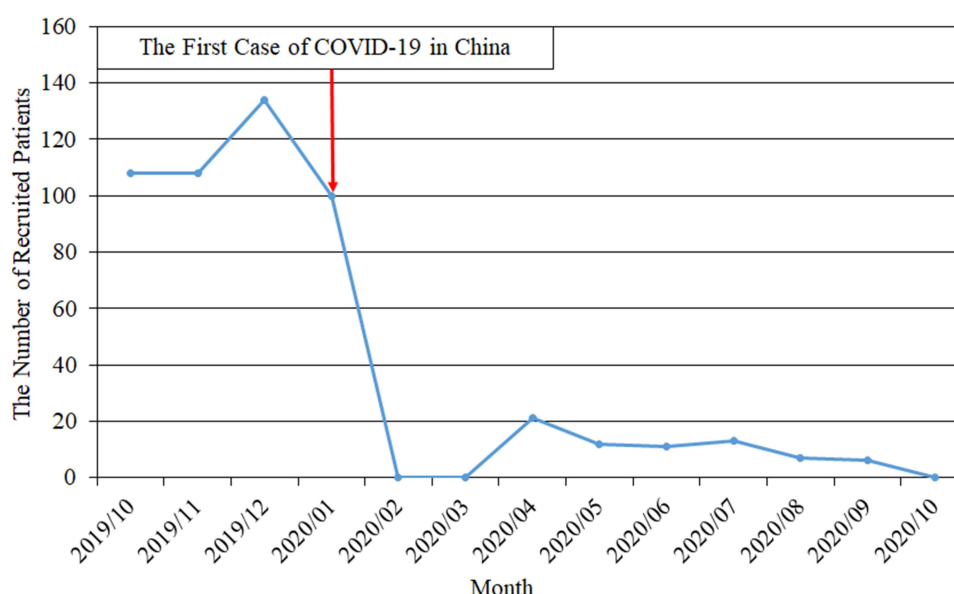
Since the unexpected COVID-19 pandemic, the number of recruited patients was sharply decreased from 90 to 5 patients per month (see Figure 2). Concerning the study centers, most of the hospitals attributed much to the study. Specifically, half of the centers enrolled more than 15 patients, and the most active center included 69 patients (Figure 3).



**Figure 1** Flowchart of cohort selection.

**Note:** Severe exacerbation indicates patients experienced readmission for exacerbations.

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



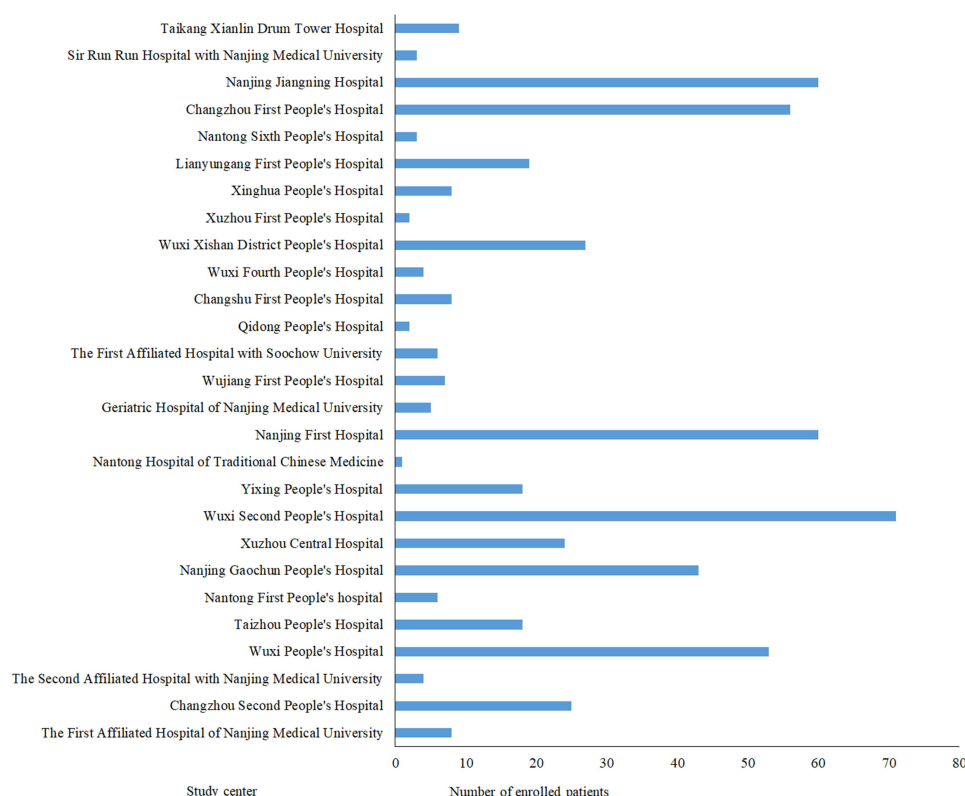
**Figure 2** The number of recruited patients over time.

**Abbreviation:** COVID-19, coronavirus disease 2019.

The demographic and baseline characteristics of the full cohort are presented in Table 1. Briefly, the enrolled patients were mostly men (71.8%) with smoking history. The primary symptoms were dyspnea, cough and expectoration. The mean (SD) duration of COPD diagnosis was 9.27 (9.36) years, the mean (SD) FEV1/FVC was 53.15% (12.16%), and the median (IQR) eosinophil percentage was 1.71 (3.07). Among those COPD patients, 41.5% (n=193) required hospitalization (range 1–8) with severe exacerbations in the following 12 months. In terms of COPD medications, most patients were prescribed ICS plus long-acting  $\beta_2$  agonist (LABA) combination or ICS plus LABA and long-acting muscarinic antagonist (LAMA) combination (24.1% and 29.5%, respectively).

## Characteristics of Patients with or Without Severe Exacerbations Before and After Propensity-Score Matching

Demographic According to the current GOLD strategy document, patients were categorized into severe exacerbation (termed group A) and non-severe exacerbation (termed group B) groups. The severe exacerbation group comprised 193 patients (41.5%)



**Figure 3** Number of patients from 27 study centers in China.

who experienced hospitalization for AECOPD and the non-severe exacerbation group consisted of 272 patients (58.5%) who were not hospitalized for COPD in the following 12 months. Baseline characteristics were compared between the two groups.

As shown in Table 2, patients with severe exacerbations in the next 12 months were older, which showed a greater proportion of the rural population, a lower ratio of current smokers, a longer duration of disease, a decreased eosinophil percentage, and fewer individuals with high blood eosinophils. Moreover, they complied with more respiratory symptoms, more severe airflow limitation, and more complex comorbidities. In addition, they were more likely to keep inhaling medicine regularly. The proportion of patients in the GOLD grade III was the highest in both the group A and the group B. In addition, the percentage of GOLD grade IV was significantly higher in group A than that in group B.

Given differences in the baseline characteristics between groups A and B, PSM was performed to reduce the effects of confounding. The following variables (eg, age, sex, residence, BMI, and smoking status) were included in the PSM model. Spirometry is crucial in the management of COPD; however, it is not routinely performed in AECOPD due to worsening symptoms and failure to cooperate effectively. Furthermore, it is necessary to explore factors regardless of pulmonary function test. Thus, FEV1 of predicted was also included in the model. Of the entire COPD patient cohort, 172 of 193 group A cases could be matched (1:1) to group B using the nearest neighbor method with a maximum caliper width equal to 0.02 of the PS. After matching, the two groups were well-balanced in baseline characteristics and showed a similar distribution of characteristics to the unmatched analysis. Notably, FVC% predicted and cor pulmonale were not included in the model but they were balanced after propensity-score adjustment, indicating that we were able to balance key unmeasured factors as far as feasible.

## Factors Independently Associated with Severe Exacerbations

Before matching, four factors were related to severe exacerbations in multivariable logistic regression analysis: years of COPD greater than or equal to 9 years, presence of dyspnea, CAT  $\geq 10$  and eosinophils  $< 2\%$ , as shown in Table 3. Nevertheless, no significant difference was observed in the comorbidity of cor pulmonale between two groups. After propensity matching, the

**Table I** Demographic and Clinical Data of Cohort Patients

Variable	Missing	Full Cohort
Number		465
Age -yr		70.1±9.3
Male sex -no. (%)		409(88)
Body-mass index -kg/m <sup>2</sup>	1	22.81±3.67
Smoking status -no. (%)		
Non-smoker		131(28.3)
Current smoker		101(21.7)
Ex-smoker		233(50.0)
Pack-years of smoking		40.92±23.77
Time since COPD diagnosis - yr		9.27±9.36
Severe exacerbations in the following 12 months -no. (%)		193(41.5)
Symptoms -no. (%)		
Dyspnea		310(66.7)
Wheezing		220(47.3)
Cough		280(60.2)
Sputum Production		259(55.7)
COPD Assessment Test score	13	18±6.9
FEV1/FVC		53.15±12.16
FEV1 -% predicted		44.14±17.31
FVC -% predicted		63.28±18.64
Blood eosinophil percentage -median (IQR)	6	1.71(3.07)
Comorbidities -no. (%)	45	
Cor pulmonale		25(5.38)
Osteoporosis		7(1.51)
Depression		2(0.43)
Hypertension		183(39.4)
Diabetes		46(9.9)
COPD inhaled treatment -no. (%)	28	
LAMA		46(9.9)
LABA plus LAMA		12(2.6)
LABA plus ICS		112(24.1)
LABA plus LAMA plus ICS		137(29.5)
Others		7(1.5)
Non-pharmacological treatments		
Flu, pneumonia vaccine		23(4.9)
Long-term oxygen therapy		27(5.8)
Contracted lips or abdominal breathing		7(1.5)

**Notes:** The body-mass index is the weight in kilograms divided by the square of the height in meters. The blood eosinophil percentage is of total leukocyte count. Scores on the COPD Assessment Test range from 0 to 40, with higher scores indicating more symptoms.

**Abbreviations:** yr, the year; no, number; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity ratio; FEV1 -% predicted, FEV1 of the predicted normal value; FVC -% predicted, FVC of the predicted normal value; IQR, interquartile range; LAMA, long-acting antimuscarinic antagonist; LABA, long-acting beta<sub>2</sub>-agonists; ICS, inhaled corticosteroids.

prevalence of cor pulmonale was similar between the two groups, and only three factors remained independently associated with severe exacerbation: years of COPD  $\geq 9$  years (odds ratio (OR), 2.16; 95% CI, 1.38 to 3.39;  $P < 0.001$ ), CAT  $\geq 10$  (OR, 3.40; 95% CI, 1.36 to 8.51;  $P < 0.001$ ), and eosinophils  $< 2\%$  (OR, 1.68; 95% CI, 1.07 to 2.64;  $P < 0.05$ ).

## Clinical Rules to Predict Future Severe Exacerbations

As shown in Table 4, the Hosmer-Lemeshow test was used to evaluate the goodness of fit in the model, and the H-L test values were 0.728 and 0.837, respectively, which suggested that the model was well-fitted. Moreover, we derived ROC



**Table 2** Characteristics of Patients with or Without Severe Exacerbations, Before and After 1:1 Propensity Score Matching

Variable	Unmatched Patients			Propensity-Score-Matched Patients		
	Severe Exacerbations	Non-Severe Exacerbations	P-value	Severe Exacerbations	Non-Severe Exacerbations	P-value
Number	193(41.5)	272(58.5)		172	172	
Age - yr	71.53±8.93	69.13±9.38	0.006	71.1±9.09	70.8±7.92	0.738
Male sex - no. (%)	167(86.5)	242(89.0)	0.425	147(85.5)	147(85.5)	1.000
Body-mass index- kg/m <sup>2</sup>	22.88±4.08	22.77±3.36	0.760	22.97±3.8	22.95±3.55	0.481
Residence			0.009			0.887
Urban	81(42.4)	144(54.8)		79(45.9)	77(44.8)	
Rural	110(57.6)	119(45.2)		91(52.9)	92(53.5)	
Smoking status - no. (%)			<0.001			0.969
Non-smoker	55(28.5)	76(27.9)		51(29.7)	53(30.8)	
Current smoker	26(13.5)	75(27.6)		26(15.1)	25(14.5)	
Ex-smoker	112(58.0)	121(44.5)		95(55.2)	94(54.7)	
Pack-years of smoking	42.79±22.24	39.59±24.77	0.230	41.74±21.13	40.31±26.83	0.649
Time since COPD diagnosis - yr	13.16±11.52	7.11±8.33	<0.001	13.06±11.12	7.75±7.32	<0.001
Symptoms - no. (%)						
Dyspnea	112(58.0)	108(39.7)	<0.001	100(58.1)	72(41.3)	<0.001
Cough	132(68.4)	148(54.4)	<0.001	117(68.0)	54(31.4)	<0.001
Sputum production	121(62.7)	138(50.7)	<0.001	107(62.2)	89(51.7)	<0.001
COPD Assessment Test score	20.3±6.5	16.3±6.7	<0.001	20.23±6.48	16.8±6.9	<0.001
FEV1- % predicted	41.45±17.00	46.05±17.32	0.005	43.07±17.09	43.27±16.47	0.911
Severity (% pre FEV1) - no. (%)			0.034			0.994
Mild (≥80%)	6(3.1)	13(4.8)		6(3.5)	7(4.1)	
Moderate (≥50% and <80%)	43(22.3)	84(30.9)		43(25.1)	43(25.1)	
Severe (≥30% and <50%)	88(46.6)	127(46.7)		83(48.5)	83(48.5)	
Very severe (<30%)	54(28)	46(16.9)		39(22.8)	39(22.8)	
FVC- % predicted	61.24±18.98	64.73±18.30	0.048	63.01±18.45	61.89±16.83	0.558
Blood eosinophil percentage-median (IQR)	1.51(3.16)	2.08(3.29)	0.002	1.5(3.18)	2.03(3.78)	0.047
Eos≥2% - no. (%)	74(38.5)	138(51.7)	0.005	68(29.8)	86(50.9)	0.039
Eos<2% - no. (%)	118(61.5)	129(48.3)		103(60.2)	83(49.1)	
Comorbidities - no. (%)						
Cor pulmonale	18(11.3)	7(3.6)	0.005	15(10.6)	6(4.6)	0.064
Osteoporosis	4(2.5)	3(1.5)	0.781	4(2.8)	2(1.5)	0.754
Depression	1(0.6)	1(0.5)	0.696	1(0.7)	1(0.7)	0.954
Hypertension	85(53.8)	97(49.2)	0.396	77(54.2)	68(51.9)	0.702
Diabetes	21(13.1)	25(12.7)	0.903	17(12.0)	19(14.5)	0.537
Cardiovascular disease	19(11.9)	16(8.1)	0.236	17(12.0)	8(6.1)	0.093
Cerebrovascular disease	18(11.3)	15(7.6)	0.238	16(11.3)	9(6.9)	0.208
Regular inhaler - no. (%)	128(66.3)	118(43.4)	<0.001	114(66.3)	83(48.3)	<0.001
COPD inhaled treatment - no. (%)						
LAMA	19(9.8)	27(9.9)	0.977	19(11.0)	16(9.3)	0.593
LABA+LAMA	2(1.0)	10(3.7)	0.141	1(0.6)	2(1.2)	0.562
ICS+LABA	59(30.6)	55(20.2)	0.011	54(31.4)	38(22.1)	0.051
ICS+LABA+LAMA	69(35.8)	68(25.0)	0.012	60(34.9)	42(24.4)	0.034
Others	3(1.6)	4(1.5)	1.000	2(1.2)	2(1.2)	1.000

**Note:** Severity (% pre FEV1) indicates the classification of airflow limitation of severity in COPD based on GLOD 2019 document.

**Abbreviations:** yr, the year; no, number; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity ratio; FEV1- % predicted, FEV1 of the predicted normal value; FVC- % predicted, FVC of the predicted normal value; IQR, interquartile range; Eos, eosinophil; LAMA, long-acting antimuscarinic antagonist; LABA, long-acting beta2-agonists; ICS, inhaled corticosteroids.

curves from the results of the multivariate logistic regression analysis. The AUCs of 0.727 (95% CI 0.681–0.773,  $P<0.05$ ) and 0.662 (95% CI 0.605–0.720,  $P<0.05$ ) demonstrated a fair accuracy of the model to predict the severe exacerbation (Figures 4 and 5).

**Table 3** Multivariate Regression Analysis of Associations with Severe Exacerbation (Group A)

Variable	Unmatched			Propensity Score Matched		
	OR	95% CI	P-value	OR	95% CI	P-value
Time since COPD diagnosis (reference: <9yr)	2.91	1.96–4.31	<0.001	2.16	1.38–3.39	<0.001
CAT score (reference: <10)	4.36	1.96–9.72	<0.001	3.40	1.36–8.51	0.009
Blood eosinophil percentage (reference: $\geq 2\%$ )	1.72	1.15–2.56	0.008	1.68	1.07–2.64	0.025
Cor pulmonale (reference: no)	2.56	1.00–6.56	0.05			NS

**Abbreviations:** yr, the year; no, number; COPD, chronic obstructive pulmonary disease; CAT, the COPD Assessment Test; OR, odds ratio; CI, confidence interval; NS, not significant.

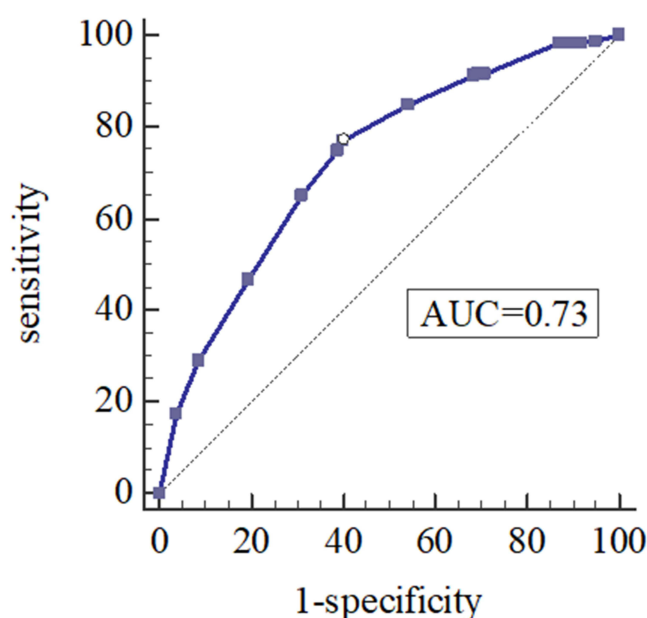
**Table 4** The Goodness of Fit and Accuracy of the Model

	AUC	95% CI	P-value	Sensitivity	Specificity	H-L Test	Omnibus
Unmatched	0.727	0.681–0.773	<0.001	77.2	59.93	0.728	<0.001
Matched	0.662	0.605–0.720	<0.001	55.81	68.02	0.837	<0.001

**Abbreviations:** AUC, area under the curve; CI, confidence interval; H-L, Hosmer-Lemeshow test.

## Discussion

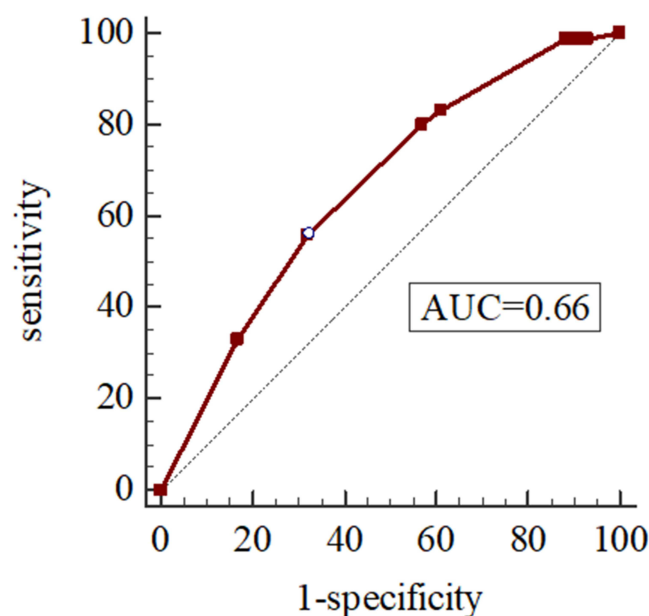
In this multicenter observational study, we found that patients admitted to the hospital with a COPD exacerbation were mostly male, and 41.5% of them would be readmitted within 1 year. For patients who were readmitted to the hospital with severe exacerbations in the following 12 months, they had a significantly longer duration of COPD (OR, 2.16; 95% CI, 1.38 to 3.39;  $P<0.001$ ), higher CAT score (OR, 3.40; 95% CI, 1.36 to 8.51;  $P<0.001$ ), and lower eosinophils (OR, 1.68; 95% CI, 1.07 to 2.64;  $P<0.05$ ) than those without severe exacerbations. There was a trend for a higher eosinophil percentage in patients without severe exacerbations, with a  $\geq 2\%$  blood eosinophils before and after PSM. To date, the relationship between the risk of severe exacerbation and blood eosinophil count remains controversial.<sup>14,15,17–20</sup> Our study may compensate for some information for those at risk of the most severe exacerbations (ie, those requiring hospitalization). However, given the observational design, the



**Figure 4** Receiver operating characteristic (ROC) curve for 12-month readmission of severe exacerbations using data from logistic model before propensity-score matching.

**Abbreviation:** AUC, area under the curve.





**Figure 5** Receiver operating characteristic (ROC) curve for 12-month readmission of severe exacerbations using data from logistic model after propensity-score matching. **Abbreviation:** AUC, area under the curve.

small sample size, and the loss of annual follow-up in 59 patients, the study should not be taken to extrapolate either low or high eosinophils in severe exacerbations. From a clinical perspective, it is challenging for doctors to identify patients at risk of exacerbations when insufficient follow-up is yet available to provide. Based on a real-world clinical setting, our study confirmed that long duration, multi-symptoms and low eosinophil percentage were associated with a higher incidence of severe exacerbation in the next 12 months, which may contribute to evaluating the severity of disease by history taking and blood eosinophils in clinical practice.

Among all study centers, tertiary referral centers enrolled more severe patients than rural hospitals, which may be due to the hierarchical medical system in our country. The system requires doctors to transfer severe patients from rural hospitals to referral hospitals, and transfer mild or moderate patients conversely. The severe exacerbation phenotype is defined as patients with COPD experiencing hospitalization or emergency room visits because of worsening symptoms, which leads to poorer outcomes.<sup>23</sup> Consistent with previous research, COPD patients were mainly male.<sup>24</sup> Non-pharmacological treatments for COPD are a crucial part of treatment plan, including vaccinations and pulmonary rehabilitation. Our study revealed patients were more likely to take pharmacotherapies than non-pharmacological treatments, and very few patients had access to Flu, pneumonia vaccine, pulmonary rehabilitation or other palliative care. Unlike our results, Mir et al reported that palliative care was similar with pulmonary rehabilitation and possibly involved in reducing COPD-related readmission rates.<sup>25</sup> Therefore, before widespread adoption, further studies and streamlined implementation of procedures are needed in our country to advocate non-pharmacological treatments.

Our results are partially concordant with some studies that found such differences between the two groups. For example, the EXACO study recorded the number of moderate and severe COPD exacerbations for 4 years and found that severe exacerbations were related to clinical variables including a COPD diagnosis of more than 7 years, daily sputum production and a modified Medical Research Council dyspnea score of 3–4.<sup>26</sup> However, the timepoints essential to COPD development might differ between individuals. Our mean time since COPD diagnosis was 9 years, which was employed as a cutoff value in our multivariate analysis. Moreover, the mean years of COPD diagnosis in the severe exacerbation group were nearly twice than non-severe exacerbation group. Pathological alterations of the airway structure and resistance to ICS might account for the phenomenon. At the early stage of COPD, inhaled exposures induce oxidant injury and reprogramming of airway epithelium to defend against damage.<sup>27,28</sup> At the advanced stage of COPD, accumulation of the epithelium reprogramming causes changes of airway microenvironment, immune responses and remodeling.<sup>29</sup> The structure alterations might result in increased

respiratory symptoms and accelerated decline of lung function, leading to the onset and progression of COPD.<sup>30</sup> Our findings emphasize the importance of early interventions to prevent from severe exacerbations of COPD, which has been verified by the Tie-COPD study.<sup>31</sup> Moreover, the CAT score involving cough, sputum production and dyspnea was calculated for a comprehensive assessment of symptoms, which has been widely used to evaluate the severity and prognosis of exacerbations. Previous studies analyzed participants with COPD of SPIROMICS cohort and IMPACT cohort, and revealed that higher CAT score was associated with increased rates of AECOPD.<sup>32,33</sup> Pulido Herrero et al had similar findings that the CAT score increased during exacerbation and decreased 2 months later.<sup>34</sup> These studies might indicate that symptom burden is related to the exacerbation status, which implies that reduction of symptoms probably contributes to preventing exacerbations.<sup>35</sup> An ICS in combination with a LABA or a LAMA is the mainstay therapy for managing severe COPD.<sup>36</sup> The link that we observed between severe exacerbation and inhale treatment has been partially noted previously.<sup>37</sup> In the ECLIPSE study, an independent association between worse quality of life and future risk of exacerbation was observed, and the proportion of medications for COPD raised as the severity increased.<sup>38</sup> In our study, patients in the severe exacerbation group had a higher tendency to use regular medications and more combinations of drugs, with the ratio of ICS/LABA/LAMA being nearly 1.5 times higher than that in the non-severe exacerbation group even after PSM (34.9% and 24.4%,  $P<0.05$ ). According to Palmiotti et al, patients with severe exacerbations were critically ill and primarily at GOLD IV stage, who showed better adherence to the GOLD guidelines using ICS/LABA/LAMA.<sup>39</sup>

The predicted value of eosinophils for the incidence and prognosis of future severe exacerbation was diverse, with either no relationship or a positive relationship reported.<sup>18,40,41</sup> Our findings are concordant with prior studies demonstrating a high prevalence (46%) of elevated eosinophil counts, defined as  $\geq 2\%$  of the total leukocyte count.<sup>14</sup> Many studies such as SUNSET, WISDOM and SPIROMICS have reported exacerbations correlating with blood eosinophils.<sup>15,16,42,43</sup> In our dataset, the proportion of high eosinophils in patients without severe exacerbation was approximately 1.7 times greater than that in the severe exacerbation group, and low eosinophil percentage was associated with increased 12-month COPD-related readmission before and after adjustment. Unlike our study, the SUNSET study reported that patients with higher blood eosinophils had a higher risk of future exacerbations, but their enrolled patients were stable COPD with a history of tobacco use and the endpoint was moderate or severe exacerbations.<sup>16</sup> On the other hand, the SPIROMICS cohort study, recruited for a range of COPD severity for smokers and a control group of non-smokers, reported that elevated blood eosinophils only in combination with elevated sputum eosinophils were associated with COPD exacerbations.<sup>32</sup> Consistent with our study, MacDonald et al found that the low eosinophil group was associated with increased mortality at 12 months, providing the clinical utility of eosinophils as biomarkers during acute exacerbations of COPD (AECOPD).<sup>18</sup> The DECAF score identified eosinopenia as one of five key predictors of inpatient mortality in severe exacerbation of COPD.<sup>44</sup> In addition, some studies comparing low and high eosinophil clusters have shown that high eosinophil was correlated with shorter length of hospital stay, lower risk of subsequent exacerbation, and better response to systemic corticosteroid treatment.<sup>19,45,46</sup> The biology underlying these discrepancies is uncertain, but there could be several reasons. First, the criteria of enrolled patients were different among studies, such as stable COPD, moderate and severe exacerbation of COPD or non-smokers without COPD. Such a recruitment strategy does not permit us to conclude the predictive value of blood eosinophils in all COPD groups. Second, the primary endpoints were diverse including mortality in hospital, 28-day readmission, first exacerbation time and 12-month readmission; however, the mechanisms lack molecular and biological research. Biologically, the high eosinophil group was related to fewer neutrophil percentages, a lower risk of bacterial infection at exacerbation, and a better response to systemic corticosteroid treatment, which may account for our results.<sup>47–50</sup>

The study has some strengths and limitations. A main strength of this work is the use of multiple centers in patients with severe exacerbations of COPD and the online access to follow-up data during the period of the COVID-19 pandemic, which may be representative of a real-world practice.<sup>51</sup> Another important strength is that we divided patients based on severe exacerbation in the following 12 months, which recorded comprehensive symptoms by CAT score and blood eosinophils at baseline to explore the relationship between eosinophil percentage and incidence of severe exacerbation within 1 year. Additionally, considering that pulmonary function is not recommended during severe acute exacerbation, we wanted to explore the characteristics between the two groups regardless of the severity of airflow

limitation. Hence, we adjusted for potential bias, including age, sex, residence, body mass index and predicted FEV1% by PSM and multiple regression. Despite this extensive adjustment, it is still possible that some amount of unmeasured confounding remains. Additional limitations of our study include the lack of follow-up of 59 patients, potential inaccuracies by telephone or internet, and failure to timely measure blood eosinophils and lung function after 1 year due to the COVID-19 pandemic, which somewhat restricts the generalizability of this study.<sup>52</sup> Large prospective studies are needed to further explore the impact of eosinophils on the clinical outcomes of AECOPD.

## Conclusion

In summary, for patients with or without 12-month readmission for AECOPD, their baseline characteristics differed greatly in past history, symptoms, eosinophils and prescriptions. Patients with duration  $\geq 9$  years, CAT  $\geq 10$  and eosinophil  $< 2\%$  tend to be associated with increased 12-month readmission for AECOPD. These results are clinically relevant and highlight the consideration of specific COPD phenotypes.

## Abbreviations

AECOPD, acute exacerbations of chronic obstructive pulmonary disease; PSM, propensity-score matching; ROC, receiver operating characteristic; CAT, COPD Assessment Test; Eos, eosinophil; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PS, propensity score; SD, standard deviation; IQR, interquartile range; COVID-19, coronavirus disease 2019; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; LAMA, long-acting muscarinic antagonist; AUC, area under the curve.

## Data Sharing Statement

The datasets used or analyzed in the study are not publicly available because the patients are still in follow-up for further data but are available from Ningfei Ji upon reasonable request.

## Ethics Approval and Informed Consent

The study complied with the Declaration of Helsinki and Good Clinical Practice. Besides, the study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University, China, with ethical approval reference number IRB-2019-SR-129. Before the actual data collection, written informed consent was obtained from the study participants. Our study is a multi-center, prospective, observational cohort study conducted in China.

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## Author Contributions

All authors made a significant contribution to the multi-center work, whether the contribution was in the conception, study design, execution, acquisition of data, analysis and interpretation of data, took part in drafting, revising or critically reviewing the article, and approved the final version of the manuscript before submission to an agreed upon journal. All authors agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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