

# Risk Factors for Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Industrial Regions of China: A Multicenter Cross-Sectional Study

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**Background:** The exacerbation of chronic obstructive pulmonary disease (COPD) seriously affects the patient's quality of life and prognosis. This multicenter cross-sectional study investigated the characteristics of stable COPD and risk factors for acute exacerbation of COPD (AECOPD) in patients in Changchun, Jilin Province, China.

**Methods:** The study included 400 outpatients admitted to four secondary hospitals and four tertiary hospitals in Jilin Province from March 2018 to March 2019. Data on the general condition of stable COPD patients, patient self-management, COPD Assessment Test (CAT) scores, number of acute exacerbations in the past 12 months, and medications received during the study period were collected using a questionnaire.

**Results:** Sociodemographic characteristics and clinical data were obtained from 306 patients, and drug prescription data were obtained from 329 patients. Pearson correlation analysis revealed that CAT scores were positively correlated with the number of acute exacerbations. Age, education level, smoking history, disease duration, number of comorbidities, and the presence of ischemic heart disease (IHD) were associated with AECOPD. Moreover, the level of education, disease duration, and the presence of IHD were independent risk factors for AECOPD. Poor compliance due to the lack of understanding of the disease and the high cost of treatment is a risk factor for AECOPD. In addition, increased air pollution in industrial cities and vitamin D deficiency are closely related to AECOPD.

**Conclusion:** Low education level, long disease duration, and the presence of IHD may promote the exacerbation and poor control of COPD in patients in Jilin Province.

**Keywords:** COPD, exacerbation, risk factors, Jilin Province

## Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation of the airways and has a high prevalence, morbidity, and mortality in many parts of the world.<sup>1-4</sup> Patients with stable COPD often have acute exacerbation due to risk factors, comorbidities, poor adherence to treatment, and insufficient treatment. AECOPD leads to lung function decline, reduced health-related quality of life, and poor prognosis.<sup>5-8</sup> In addition, AECOPD has a high economic and social cost and is associated with high morbidity and mortality.<sup>9</sup> The clinical manifestations and prevalence of COPD are variable,<sup>10,11</sup> which may be related to differences in the level of economic development between provinces and the degree of exposure to risk factors.<sup>12</sup> Therefore, further research on the management of COPD is needed to determine disease characteristics and risk factors.

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Jilin Province in northeastern China has a temperate climate and slow economic growth. In addition, coal-burning and industrial emissions increase air pollution. Air pollution is a significant contributor to AECOPD. Moreover, most patients with COPD have vitamin D deficiency,<sup>13</sup> which decreases lung function,<sup>14</sup> increases the risk of respiratory infections,<sup>15,16</sup> and may predispose to AECOPD. Long and cold winters in Jilin Province limit outdoor activities and may lead to vitamin D deficiency, which is linked to the clinical worsening of COPD. However, few studies have evaluated the characteristics of COPD and aggravating risk factors in patients in Jilin Province. This study reviews the risk factors for AECOPD in Jilin Province and can serve as a guideline for preventing and treating this disease in this province.

## Methods

### Study Design and Patients

This multicenter cross-sectional study continuously enrolled 400 stable COPD outpatients admitted to four secondary hospitals and four tertiary hospitals in Jilin Province from March 2018 to March 2019.

The inclusion criteria were diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), airflow limitation defined as forced expiratory volume in one second/forced vital capacity <70%, disease duration longer than 1 year, and written consent to participate in the investigation. The exclusion criteria were patients with heart, respiratory, or renal failure; current AECOPD; acute cerebrovascular disease with impaired consciousness; terminal cancer; pulmonary embolism; or active tuberculosis. The patients with missing data on COPD diagnosis and treatment, and those unwilling or unable to participate because of mental or neurological illnesses were also excluded. This study was approved by the research ethics committee of the Second Hospital of Jilin University. All patients signed informed consent.

### Data Collection

Demographic and socioeconomic data, including age, gender, BMI (weight [kg]/height [m]<sup>2</sup>), area of residence (rural or urban), level of education, occupation, and smoking history, were collected using a questionnaire. Clinical data included the number of acute exacerbations in the past 12 months (including acute episodes leading to hospital admission) and comorbidities during the course of the disease. Comorbidities included asthma, bronchiectasis, ischemic

heart disease (IHD), chronic cardiac insufficiency, diabetes, and hypertension. The CAT questionnaire contained eight questions with scores ranging from 0 to 5, and total scores of 0–10, 11–20, 21–30, and 31–40 represented mild, moderate, severe, and very severe symptoms, respectively.<sup>17</sup>

### Statistical Analysis

Statistical analysis was performed using SPSS software version 25.0. Continuous variables were presented as mean and standard deviation or percentage and were compared using an independent *t*-test. Categorical variables were analyzed using the Chi-square test. The association between demographic factors, risk factors, and AECOPD was evaluated by univariate analysis. The correlation between potential risk factors and AECOPD was analyzed by logistic regression. P-values of less than 0.05 were considered statistically significant. The associations were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). The relationship between CAT scores and the number of exacerbations was evaluated using Spearman correlation coefficient. The level of statistical significance was set at  $p < 0.05$ .

## Results

### Sociodemographic Characteristics and Clinical Data

A total of 400 questionnaires were distributed, and 306 questionnaires were valid. The mean age of our sample was  $67.08 \pm 11.41$  years. The baseline characteristics of our cohort are described in Table 1. Approximately 44.44% of the study population were rural residents, 56.86% were male, 74.84% had middle school education or lower, 35.62% were former smokers, and 35.95% were current smokers. The mean smoking history was  $25.97 \pm 23.42$  pack-years.

Clinical data, including comorbidities, are summarized in Table 2. The most common comorbidities were IHD (39.22%) and hypertension (27.45%). Only 26.80% of COPD patients had no comorbidities.

### Risk Factors for AECOPD

The CAT score was  $\leq 10$  in 15.03% of our sample. After adjusting for smoking status, CAT scores were weakly correlated with the number of acute exacerbations in the past 12 months ( $R = 0.394$ ,  $p < 0.0001$ ) (Figure 1). The clinical and demographic characteristics of patients with and without exacerbations are shown in Table 3. Patients with AECOPD were older ( $p = 0.0408$ ), had longer disease duration

**Table 1** General and Demographic Data of the Study Population

Male Gender	174 (56.86%)
Age (years)	
≤40	6 (1.96%)
41–60	79 (25.82%)
61–80	183 (59.8%)
>80	38 (12.42%)
BMI	
<18.5	41 (13.4%)
18.5–24.9	175 (57.19%)
≥25	90 (29.41%)
Level of education	
Middle school education or lower (≤9 years)	229 (74.84%)
High school education (9–12 years)	56 (18.3%)
University education or higher (>12 years)	21 (6.86%)
Occupation	
Workers, individuals, other workers	109 (35.62%)
Office, management, and technical staff	75 (24.51%)
Service workers	18 (5.88%)
Livestock and poultry industry workers	104 (33.99%)
Area of residence	
Rural	136 (44.44%)
Urban	170 (55.56%)
Smoking history	
Never	87 (28.43%)
Former	109 (35.62%)
Current	110 (35.95%)

( $p<0.0001$ ), lower education level ( $p=0.0149$ ), active smoking history ( $p=0.0474$ ), and more comorbidities ( $p=0.0011$ ) than the control group. The multivariate analysis showed that university education and higher (OR, 0.29; 95% CI, 0.08–0.86;  $P=0.0340$ ), disease duration of 3–5 years (OR, 3.73; 95% CI, 1.82–7.84;  $P<0.0001$ ), disease duration of 5–10 years (OR, 7.28; 95% CI, 3.34–16.59;  $P<0.0001$ ), disease duration longer than 10 years (OR, 6.01; 95% CI, 2.95–12.65;  $P<0.0001$ ), and IHD (OR, 2.01; 95% CI, 1.05–3.89;  $P=0.0352$ ) were significantly associated with AECOPD (Table 4).

## Treatment and Economic Burden of COPD

A total of 329 of 400 COPD patients answered questions about treatment (Table 5). The prescribed medications were inhaled bronchodilators (214, 65.05%), inhaled corticosteroids (ICSs) (213, 64.74%), or oral corticosteroids (OCS) (113, 34.35%). Of these, 20 (13.42%) used inhaled bronchodilators regularly in the

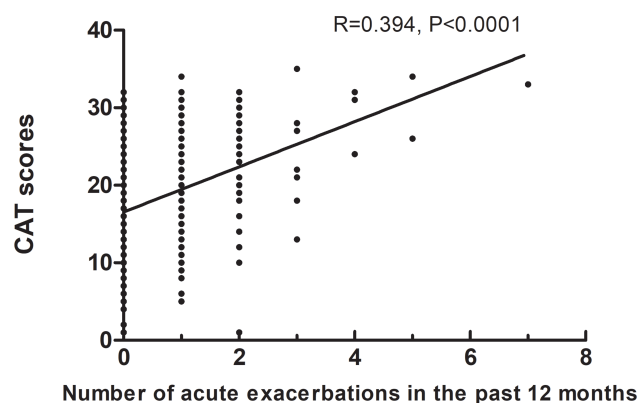
**Table 2** Clinical Characteristics of Patients with Chronic Obstructive Pulmonary Disease in Jilin Province, China, Admitted from March 2018 to March 2019

Variables (n=306)	N (%)
Duration of COPD (years)	
≤3	89 (29.08%)
3–5	69 (22.55%)
5–10	59 (19.28%)
≥10	89 (29.08%)
Comorbidities	
None	82 (26.80%)
Pulmonary embolism	1 (0.33%)
Interstitial lung disease	9 (2.94%)
Bronchiectasis	29 (9.48%)
Tuberculosis sequels	9 (2.94%)
Ischemic heart disease	120 (39.2%)
Chronic cardiac insufficiency	24 (7.84%)
Hypertension	84 (27.45%)
Diabetes	31 (10.13%)
Cerebrovascular disease	13 (4.25%)
Anxiety or depression	9 (2.94%)
Duration of oxygen therapy (hours per day)	
None	256 (83.66%)
<4	17 (5.56%)
4–8	15 (4.9%)
8–15	16 (5.23%)
>15	2 (0.65%)
Total number of acute exacerbations	
None	147 (48.04%)
1	95 (31.05%)
2	49 (16.01%)
≥3	15 (4.9%)
COPD Assessment Test scores	
0–10	46 (15.03%)
11–20	123 (40.2%)
21–30	120 (39.22%)
31–40	17 (5.56%)

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

past 12 months, and 19 (11.24%) used inhaled ICSs or hormones regularly in the past 12 months. The drugs prescribed to patients with and without AECOPD are shown in Table 6.

The cohort was divided into four groups based on the number of acute exacerbations, CAT scores, and hospitalization according to GOLD guidelines (A [N=27], B [N=190], C [N=2], and D [N=110]).<sup>18</sup> Group C was not included in the analysis because of the small sample size. The average monthly cost of treatment of COPD in the study period is shown in Figure 2.



**Figure 1** Association of CAT scores with the number of acute exacerbations of chronic obstructive pulmonary disease in the past 12 months.

### Discussion

This cross-sectional multicenter study analyzed baseline data of patients with stable COPD and the risk factors for AECOPD in Jilin Province, Northeast China. The CAT questionnaire is useful to evaluate health-related quality of life in patients with AECOPD.<sup>19</sup> CAT scores were weakly correlated with the number of acute exacerbations in the past 12 months (Figure 1). Consistent with our findings, Tu et al demonstrated that the frequency of COPD exacerbation frequency was positively correlated with CAT scores.<sup>20</sup> Furthermore, frequent exacerbations

**Table 4** Multivariate Regression Analysis of Risk Factors for Exacerbation of Stable Chronic Obstructive Pulmonary Disease in Patients in Jilin Province, China, Admitted from March 2018 to March 2019

Risk Factors (n=306)	OR	95% CI	P-value
University education or higher	0.29	0.08–0.86	0.0340*
Duration of COPD (years)			
3–5	3.73	1.82–7.84	<0.0001*
5–10	7.28	3.34–16.59	<0.0001*
≥10	6.01	2.95–12.65	<0.0001*
Ischemic heart disease	2.01	1.05–3.89	0.0352*

**Notes:** The variables considered significant in the univariate analysis were included in the multivariate regression model. The associations were expressed as odds ratio (OR) and 95% confidence interval (CI). \*p<0.05.

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

are linked to higher mortality.<sup>21</sup> However, the correlation between CAT and AECOPD in our study was weak, which might be due to differences in patient age, education level, and patient perception of disease severity. Therefore, whether CAT scores may predict the development of AECOPD is unknown.

AECOPD affects the natural history of the disease<sup>7</sup> and is associated with age, smoking, comorbidities, number of acute exacerbations, and patients’ socioeconomic level. In addition, AECOPD can decrease lung function,

**Table 3** Baseline Characteristics and Risk Factors for Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Patients in Jilin Province, China, Admitted from March 2018 to March 2019

		Exacerbations		
		No (n=141)	Yes (n=165)	P-value
Age		65.63±11.65	68.32±11.09	0.0408*
Gender <sup>#</sup>	Male	81 (57.45)	93 (56.36)	0.9403
Educational level <sup>#</sup>	Middle school and lower	99 (70.21)	130 (78.79)	0.0149*
Occupation <sup>#</sup>	Office, management, and technical staff	37 (26.24)	38 (23.03)	0.5263
Residence <sup>#</sup>	Urban	83 (58.87)	87 (52.73)	0.3362
Smoking history <sup>#</sup>	Current smoker	61 (43.26)	49 (29.7)	0.0474*
Amount smoked	Pack-years	24.79±21.98	27.11±24.80	0.6197
Duration of COPD	≤3 years	67 (47.52)	22 (13.33)	<0.0001*
Number of comorbidities <sup>#</sup>	None	52 (36.88)	30 (18.18)	0.0011*
Ischemic heart disease <sup>#</sup>	No	104 (73.76)	82 (49.7)	<0.0001*
Hypertension <sup>#</sup>	No	98 (69.5)	124 (75.15)	0.3295
Diabetes <sup>#</sup>	No	129 (91.49)	146 (88.48)	0.4976
Chronic cardiac insufficiency <sup>#</sup>	No	130 (92.2)	152 (92.12)	0.9999
Asthma <sup>#</sup>	No	119 (84.4)	126 (76.36)	0.1074
Bronchiectasis <sup>#</sup>	No	127 (90.07)	150 (90.91)	0.9571

**Notes:** The univariate analysis of the association between demographic and clinical factors and exacerbation of COPD was performed using an independent t-test. <sup>#</sup>Data were analyzed using the Chi-square test. Statistical significance was set at p<0.05. \*p<0.05.

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

**Table 5** Medications Prescribed to Patients with Chronic Obstructive Pulmonary Disease in Jilin Province, China, Admitted from March 2018 to March 2019

Medication (n=329)	N/%
Inhaled bronchodilator	214/65.05%
Inhaled corticosteroid	213/64.74%
Oral corticosteroid	113/34.35%
Theophylline	119/36.17%
Expectorants	125/37.99%
Others	26/7.9%
None	74/22.49%

increase mortality, affect the quality of life, and increase socioeconomic burden.<sup>5,9,22,23</sup> This study investigates the risk factors for AECOPD to help prevent and treat this disease and improve prognosis.

The main cause of COPD is smoking,<sup>24–26</sup> which is closely related to a decline in lung function.<sup>27</sup> Previous studies have shown that smoking cessation can delay lung function decline and improve survival.<sup>4</sup> However, in our cohort, smoking was not an independent risk factor for AECOPD, which might be due to the small sample size and geographic heterogeneity of the disease.

Previous studies have shown that age is a risk factor for AECOPD,<sup>28</sup> which may be due to the decline in lung function with age.<sup>29</sup> These findings agree with our study, wherein the risk of exacerbation increased as the disease progressed, probably because of poor lung function and other risk factors such as comorbidities and smoking. In addition, disease duration was an independent risk factor for AECOPD in our cohort.

Comorbidities are common in COPD patients and have a significant impact on patient outcomes, quality of life, and survival.<sup>30</sup> In our cohort, comorbid diseases were found in 224 patients, and the most common diseases were IHD and hypertension. IHD was an independent risk factor for AECOPD, and the number of comorbidities was positively correlated with the number of acute exacerbations. Furthermore, comorbidities significantly increase the cost of AECOPD treatment.<sup>31</sup> Therefore, preventing and managing comorbidities are crucial to reduce clinical deterioration, improve prognosis, and reduce disease burden.

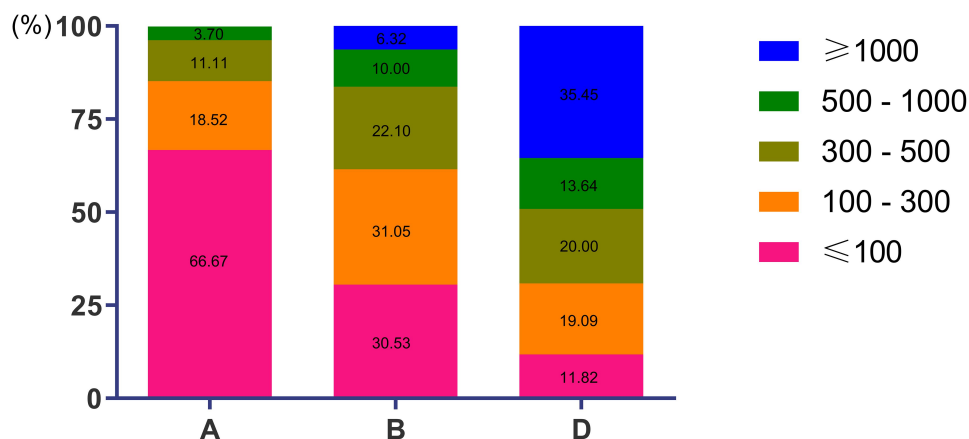
In our sample, 78.79% of patients with exacerbations had junior high school education or less, and this high percentage might be related to the lack of awareness of the disease among individuals with a lower educational level and limited self-management skills. In this respect, Yang

**Table 6** Drugs Prescribed to Patients with and without Chronic Obstruction Pulmonary Disease Exacerbation in Jilin Province, China, Admitted from March 2018 to March 2019

Exacerbations					
Medication		Yes (n=194)	No (n=135)	Total (n=329)	P-value
None	Yes	13 (17.6%)	61 (82.4%)	74	<0.0001
	No	181 (71%)	74 (29%)	255	
Bronchodilator	Yes	150 (70.1%)	64 (29.9%)	214	0.092
	No	44 (38.3%)	71 (61.7%)	115	
ICS	Yes	149 (70%)	64 (30%)	213	0.015
	No	45 (38.8%)	71 (61.2%)	116	
OCS	Yes	77 (68.1%)	36 (31.9%)	113	0.626
	No	117 (54.2%)	99 (45.8%)	216	
Theophylline	Yes	84 (70.6%)	35 (29.4%)	119	0.706
	No	110 (52.4%)	100 (47.6%)	210	
Expectorants	Yes	97 (77.6%)	28 (22.4%)	125	<0.0001
	No	97 (47.5%)	107 (52.5%)	204	
Others	Yes	177 (58.4%)	126 (41.6%)	303	0.037
	No	17 (65.4%)	9 (34.6%)	26	

**Abbreviations:** ICS, inhaled corticosteroid; OCS, oral corticosteroid.





**Figure 2** Monthly average cost of diagnosis and treatment of chronic obstructive pulmonary disease (COPD) in patients from groups A, B, and D. (group A, COPD Assessment Test [CAT] score <10, number of acute COPD exacerbations in the past 12 months ≤1, and no hospitalizations; group B, CAT score ≥10, number of acute COPD exacerbations in the past 12 months ≤1, and no hospitalizations; group D, CAT score ≥10, number of acute COPD exacerbations in the past 12 months ≥2, and hospitalizations).

et al found that COPD patients with more knowledge about the disease had better self-management,<sup>32</sup> which is consistent with other studies, demonstrating that increasing awareness about disease management is essential to improve prognosis.

The main drugs prescribed to COPD patients are bronchodilators and ICSs. The most commonly used medications in our cohort were inhaled bronchodilators (65.05%) and ICSs (64.74%).

During the study period, only 20 patients were regularly treated with inhaled bronchodilators, and 19 patients were regularly treated with ICSs, demonstrating that treatment compliance was poor. Poor treatment adherence is common in COPD patients and is a risk factor for AECOPD.<sup>33–35</sup> Poor compliance is associated with low education, older age, insufficient understanding of the disease, the misuse of inhalers,<sup>36</sup> and the high cost of COPD treatment. Furthermore, poor adherence may increase mortality, hospitalization, and medical costs, and reduce health-related quality of life.<sup>37,38</sup> ICSs are widely used in China to treat AECOPD. Compared with glucocorticoids, ICSs have higher local anti-inflammatory activity and produce fewer systemic side effects. Our results showed that 70% of COPD patients treated with ICS experienced AECOPD. The limited effectiveness of ICSs in our cohort may be due to the small sample size and disease heterogeneity and is worthy of further exploration.

The average cost of treatment of AECOPD in patients from groups A, B, and D was 500–1000 yuan and more than 1000 yuan, showing an upward trend. The cost of hospitalization and drug therapy is higher among patients with AECOPD, which increases economic burden, as

demonstrated in other studies.<sup>39,40</sup> Financial distress, poor treatment compliance, and the lack of understanding of COPD due to low education level may favor the occurrence of exacerbations. However, additional studies are necessary to confirm this hypothesis.

Climate and air pollution play an important role in AECOPD, especially in winter.<sup>41,42</sup> Because of greenhouse gas emissions from coal combustion, as well as emissions from fuel combustion and industrial activities (there is a large chemical complex in Jilin Province), atmospheric particulate matter (PM) and PM<sub>2.5</sub> levels are high in this province. Previous studies have shown that PM and other air pollutants increase the rate of AECOPD.<sup>43,44</sup> Therefore, the high prevalence of AECOPD in this province may be due to low temperatures in winter, coal-based heating, and industrial development.

Vitamin D deficiency is common in patients with COPD [13] and is associated with decreased lung function [46] and COPD exacerbation [14], indicating that this deficiency can potentially increase the risk of AECOPD; nonetheless, this relationship needs further investigation.

This study has limitations. First, the sample size was small, and larger studies are necessary to confirm our results. Second, the questionnaire was given to outpatients only, and drug treatment data were incomplete, underscoring the need to increase the number of follow-ups.

## Conclusion

Our research shows that most COPD patients in Changchun, Jilin Province, are older and male, with a history of smoking, lower education level, and comorbidities. Smoking, older

age, and comorbidities predispose to AECOPD. Other potential contributors to AECOPD are low education, insufficient knowledge of the disease, poor self-management, poor treatment compliance, air pollution, and long and cold winters, which limit outdoor activities and vitamin D synthesis. Notwithstanding, many known risk factors for AECOPD can be changed through patient management. Therefore, increasing awareness and knowledge about COPD and using targeted interventions can improve patient outcomes.

## Abbreviations

COPD, chronic obstructive pulmonary disease; CAT, COPD Assessment Test; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; IHD, ischemic heart disease; OD, odds ratio; ICS, inhaled corticosteroid; OCS, oral corticosteroid; PM, particulate matter.

## Data Sharing Statement

All data generated or analyzed during the study period are included in this article.

## Ethics Approval and Consent to Participate

The study protocol was approved by the research ethics committee of the Second Hospital of Jilin University, and all patients signed informed consent. The study was conducted in accordance with the Declaration of Helsinki.

## Author Contributions

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

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## Disclosure

The authors declare that they have no competing interests for this work.

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