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Factors related to the progression of chronic obstructive pulmonary disease: a retrospective case-control study

Fang Ding[1*], Wenjing Liu[2], Xiaoying Hu[1] and Chunyan Gao[1]

Abstract

Objectives To explore the factors related to the progression of chronic obstructive pulmonary disease (COPD).

Methods 80 COPD patients treated between January 2020 and December 2022. The patients' pulmonary functions at their first hospital admission were categorized into four groups: Grade I, Grade II, Grade III and Grade IV. Each group was further divided into a progression group and a non-progression group based on the disease progression over one year or several years of follow-up. Patients with other respiratory diseases, malignant tumors, severe heart, kidney, liver dysfunctions, or immune deficiencies affecting the prognosis were excluded. General information, clinical data, treatment data, and statistical analysis of the patients.

Results In comparison with the non-progression group, the progression group had significantly higher age, smoking behavior, COPD history, hemoptysis history, CRP levels, IL-6 levels, and Pneumonia Severity Index (PSI) scores, exhibiting significantly lower FEV1, FEV1% predicted, PaO2, and PaCO2. More frequent use of antibiotics, corticosteroids, oxygen therapy, and mechanical ventilation were observed in the progression group than that in the non-progression group ($P < 0.05$). As a consequence, the progression group had a worse prognosis as indicated by higher hospitalization costs, longer hospital stay, and higher rate of acute exacerbations than the non-progression group ($P < 0.05$). Multifactorial logistic regression analysis showed that age ≥ 65 years, PSI score ≥ 130 points, and multidrug-resistant bacteria infection were independent risk factors for the progression of COPD ($P < 0.05$).

Conclusions Older COPD patients, higher PSI score, and multidrug-resistant bacteria infection have a worse prognosis and need more intensive treatment and follow-up.

Keywords COPD, Progression, Age, PSI, Bacteria infection

*Correspondence:
Fang Ding
dingfan99g@126.com
[1]Department of Geriatrics, Harrison International Peace Hospital, Intersection of Renmin Road, Hongqi Street, Taocheng District, Hengshui City, Hebei Province 053000, China
[2]Department of Respiratory and Critical Care Medicine, Harrison International Peace Hospital, Hengshui, China

Introduction

Chronic obstructive pulmonary disease (COPD) is a common and preventable respiratory disease characterized by persistent airflow limitation and chronic inflammation [1]. COPD is a major cause of morbidity and mortality worldwide, which is associated with various comorbidities, such as cardiovascular disease, diabetes, osteoporosis, and depression [2]. The prevalence and burden of COPD are expected to increase in the coming decades, which can affect the quality of life of patients [3]. But COPD is a heterogeneous disease with different phenotypes, clinical manifestations, and disease courses, resulting in difficult in clinical management for patients [4]. Therefore, it is important to identify the factors that influence the progression and outcome of COPD in order to provide individualized treatment for patients.

The progression of COPD is usually measured by the decline rate of forced expiratory volume in one second (FEV1), which reflects the degree of airflow obstruction and lung function impairment [5]. However, FEV1 alone cannot capture the complexity and multidimensionality of COPD, and other indicators, such as acute exacerbations, quality of life, and mortality, should also be considered [6]. Several factors have been reported to affect the progression of COPD, such as comorbidities, inflammation, infection, and treatment [7]. However, the relative contribution and interaction of these factors are not fully understood, and there is a lack of studies on the progression of COPD in different severity stages and subgroups.

Therefore, this study was aimed to explore the factors related to the progression of COPD, which provided a basis for the prevention and treatment of COPD. We compared the general information, clinical symptoms and treatment regimens of the patients with progression and non-progression, and performed multifactorial logistic regression analysis to identify the independent risk factors for the progression of COPD.

Methods

Study design and subjects

This was a retrospective case-control study conducted in the respiratory department of a tertiary hospital and was approved by the ethics committee of the hospital. Due to the anonymized and de-identified nature of the data, there is no need to obtain informed consent from the patient after approval by the Medical Ethics Committee. We reviewed the medical records of COPD patients who were admitted to the hospital between January 2020 and December 2022. Inclusion criteria: (1) Meet the diagnostic criteria of COPD; (2) Complete clinical data; (3) Admission was due to an acute exacerbation of COPD. Exclusion criteria: (1) patients with other serious respiratory diseases or cardiovascular and cerebrovascular diseases; (2) patients with serious abnormalities of liver and renal functions; (3) patients with allergies to drugs; (4) patients in pregnancy or lactation; (5) patients with consciousness disorders or psychiatric anomalies; (6) patients with malignant tumors.

The diagnosis of COPD was based on the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2021[8], which included a history of exposure to risk factors, respiratory symptoms, and a post-bronchodilator FEV1/FVC ratio < 0.7. The patients' pulmonary functions at their first hospital admission were categorized into four groups according to the GOLD 2021 classification [8]: mild (Grade I, FEV1 ≥ 80% predicted), moderate (Grade II, 50% ≤ FEV1 < 80% predicted), severe (Grade III, 30% ≤ FEV1 < 50% predicted), and very severe (Grade IV, FEV1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure).

Patient data after initial in-patient recovery were collected as baseline data. Subsequently, lung function data were collected on an ongoing basis for the patient's subsequent revisits and follow-up. The criteria for disease progression included a decline rate in pulmonary function (annual FEV1 change rate) equal to or greater than the mean of the group. Each group above was divided into a progression group (top 50%) and a non-progression group (bottom 50%) based on the disease progression over two years of follow-up. The frequency and extent of acute exacerbations of COPD, lung function and other information were recorded during follow-up. Acute exacerbations were defined as episodes of worsening respiratory symptoms that required additional treatment. We measured the pulmonary function using a spirometer (Model SpiroPro-2000, by RespiraTech Health Solutions) before and after the administration of a bronchodilator (400 μg salbutamol) at each hospital visit. The frequency and severity of acute exacerbations was recorded by a standardized questionnaire. The overall flow of the study is shown in Fig. 1.

Data collection

We collected the following data from the hospital's electronic medical record system: general information, such as age, gender, body mass index (BMI), smoking behavior, drinking behavior, etc.; clinical data, such as pulmonary function, blood gas analysis, complete blood count, C-reactive protein (CRP), interleukin-6 (IL-6) levels at the first hospital admission, as well as changes in pulmonary function, acute exacerbations, and death during the follow-up period; and treatment data, such as the types, dosages, methods, and quantities of drugs used. Non-smoking is defined as never having smoked or having quit smoking > 1 year, and smoking is defined as currently smoking. Non-drinking is defined as never having consumed alcohol or having stopped drinking for > 1 year, and drinking is defined as currently consuming alcohol.

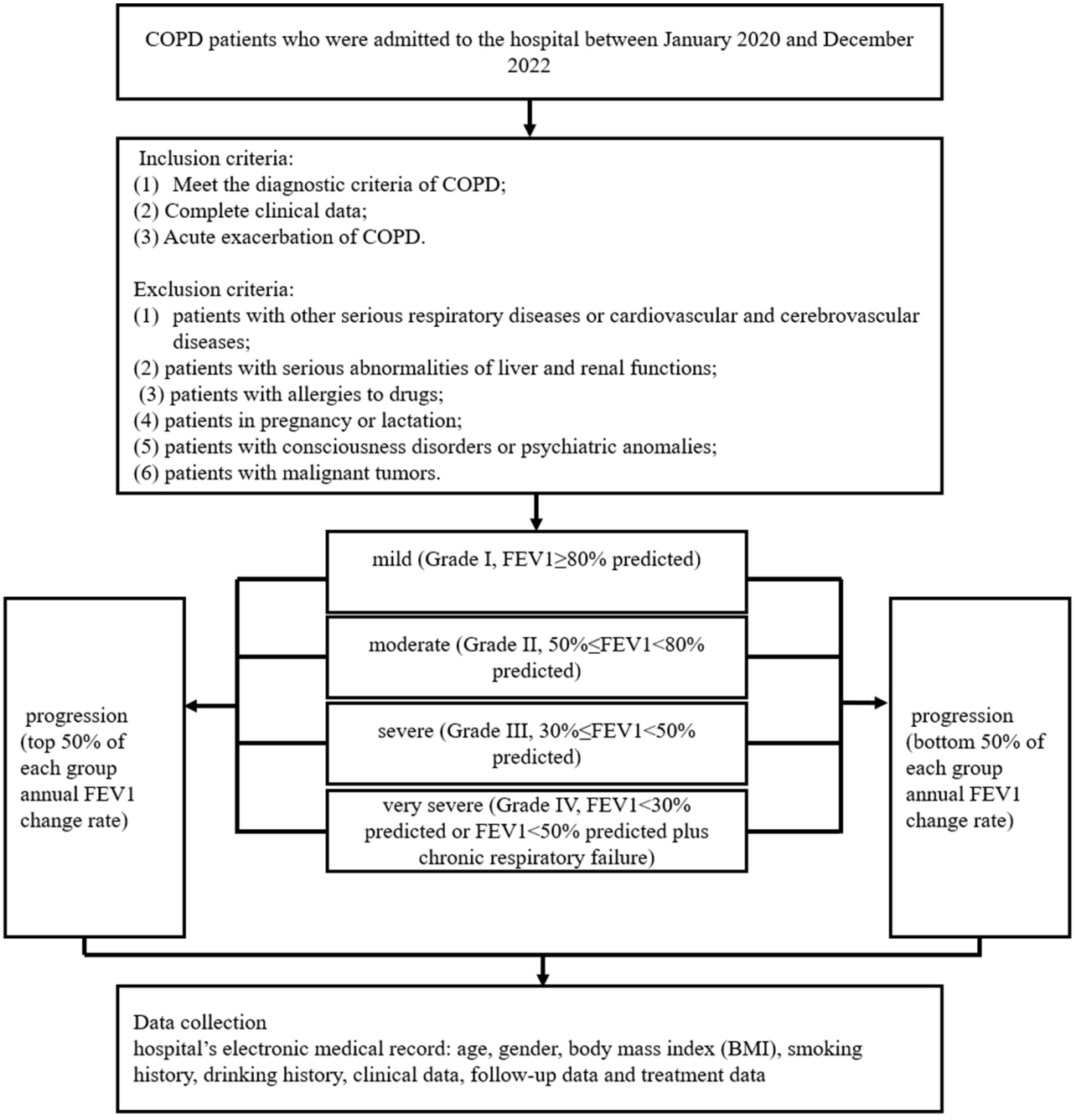

Fig. 1 Overall flow chart of the study

We checked the data for accuracy and completeness by comparing them with the paper records and contacting the patients or their relatives if necessary. We handled the missing values and outliers using multiple imputation and Winsorization methods, respectively. The following formula was used to calculate the study sample size:

$$n = \frac{2\sigma^2(Z + Z)^2}{(_1 - _2)^2}$$

Where n represents the required sample size; σ represents the overall standard deviation of the sample; μ_1 - μ_2 represents The differences between groups. The difference between the progressive and non-progressive groups in this study was predicted to be one standard deviation, with a test level of α=0.05, test efficacy (1-β)=0.9, a sample ratio of 1:1 (k=1) between the groups, and the number of people in each group should

Table 1 General characteristics of the patients

Variable	Progression group (n = 40)	Non-progression group (n = 40)	P-value
Age (years)	71.4 ± 9.6	64.2 ± 12.6	0.002
Gender (male)	28 (70.0%)	24 (60.0%)	0.132
Smoking behavior	16 (40.0%)	8 (20.0%)	0.003
Drinking behavior	8 (20.0%)	8 (20.0%)	1.000
BMI (kg/m^2)	24.2 ± 3.6	23.8 ± 3.4	0.542
Comorbidities	12 (30.0%)	10 (25.0%)	0.583

Table 2 Clinical characteristics of the patients at baseline

Variable	Progression group (n = 40)	Non-progression group (n = 40)	P-value
FEV1 (L)	1.24 ± 0.36	1.86 ± 0.42	< 0.001
FEV1% predicted (%)	42.6 ± 12.4	63.8 ± 14.2	< 0.001
PaO2 (mmHg)	58.6 ± 10.4	82.4 ± 12.6	< 0.001
PaCO2 (mmHg)	46.4 ± 8.6	38.6 ± 6.4	< 0.001
pH value	7.38 ± 0.04	7.42 ± 0.04	0.002
WBC count (×10^9/L)	10.82 ± 4.26	10.64 ± 4.22	0.812
Hemoglobin (g/L)	128.6 ± 16.4	128.4 ± 16.2	0.942
Platelet count (×10^9/L)	212.4 ± 60.2	210.2 ± 58.6	0.822
CRP (mg/L)	76.4 ± 38.6	49.6 ± 42.6	0.001
IL-6 (pg/mL)	18.6 ± 8.4	12.4 ± 8.6	< 0.001
PSI score	118.6 ± 26.4	112.6 ± 28.4	0.031
CURB-65 score	1.8 ± 0.8	1.6 ± 0.8	0.172

be not less than 21, and 80 subjects were finally considered for inclusion, 40 in each of the observational and control groups.

Statistical analysis

The data were processed and analyzed using SPSS software (version 26.0). Chi-square test or Fisher's exact test were used to compare categorical variables, and t-test or Mann-Whitney U test were used to compare continuous variables between the progression and non-progression groups. We tested the normality and homogeneity of variance of the data using Shapiro-Wilk and Levene's tests, respectively, and applied appropriate transformations if needed. Multifactorial logistic regression analysis was performed to explore the factors related to the progression of COPD in patients, calculating odds ratios (OR) and 95% confidence intervals (CI). We adjusted the model for potential confounders and interactions using backward elimination and likelihood ratio tests, respectively. A P-value < 0.05 was considered statistically significant. We reported the results using tables, figures, and text, following the STROBE guidelines for observational studies.

Table 3 Treatment characteristics and outcomes of the patients

Variable	Progression group (*n* = 40)	Non-progression group (*n* = 40)	*P*-value
Antibiotic combination therapy	32 (80.0%)	16 (40.0%)	< 0.001
Corticosteroid therapy	24 (60.0%)	12 (30.0%)	0.003
Oxygen therapy	32 (80.0%)	16 (40.0%)	< 0.001
Mechanical ventilation	16 (40.0%)	8 (20.0%)	0.023

Results

General characteristics

A total of 80 COPD patients were included in the study, with 40 patients in the progression group and 40 patients in the non-progression group. The general characteristics of the patients are shown in Table 1. The progression group had significantly higher age and smoking behavior than the non-progression group (71.4±9.6 vs. 64.2±12.6 years, $P=0.002$; 40.0% vs. 20.0%, $P=0.003$). The progression group also had a higher proportion of male patients than the non-progression group (70.0% vs. 60.0%, $P=0.132$), although the difference was not statistically significant. There was no significant difference in drinking behavior, BMI, and comorbidities between the two groups.

Clinical characteristics

The clinical characteristics of the patients at baseline are shown in Table 2. The progression group had significantly worse pulmonary function as indicated by lower FEV1, FEV1% predicted, PaO2, and PaCO2, compared with the non-progression group ($P<0.05$). For the inflammatory factors, the levels of CRP and IL-6 were significantly higher in the progression group with increased Pneumonia Severity Index (PSI) scores than the non-progression group ($P<0.05$). However, no significant difference was observed in hematology factors and CURB-65 score between the two groups.

Treatment characteristics and outcomes

The treatment characteristics and outcomes of the patients are shown in Table 3. The progression group had significantly higher rates of antibiotic combination therapy, corticosteroid therapy, oxygen therapy, and mechanical ventilation than the non-progression group ($P<0.05$). The most commonly used antibiotics were piperacillin-tazobactam, cefoperazone-sulbactam, and levofloxacin. The most commonly used corticosteroids were methylprednisolone and hydrocortisone. The outcomes of the patients are shown in Table 4. The progression group also had significantly higher hospitalization costs and longer hospital stay than the non-progression group ($P<0.05$), while no significant difference in acute exacerbation rate during follow-up visits ($P>0.05$). The

Table 4 Outcomes of the patients

Variable	Progression group (n = 40)	Non-progression group (n = 40)	P-value
Hospitalization cost (yuan)	28,642 ± 8642	18,624 ± 6428	< 0.001
Hospital stay (days)	18.6 ± 6.4	12.4 ± 4.2	< 0.001
Acute exacerbation rate in follow up	8 (20.0%)	4 (10.0%)	0.172
decline rate in pulmonary function (ml/year)	-65.4 ± 4.9	-35.1 ± 3.9	< 0.001

Table 5 Risk factors for the progression of COPD (OR and 95% CI)

Variable	OR	95% CI	P-value
Age ≥ 65 years	3.21	1.28–8.06	0.013
PSI score ≥ 130 points	4.37	1.76–10.84	0.001
Multidrug-resistant bacteria infection	5.23	2.01–13.62	< 0.001

progression group had higher decline rate in pulmonary function than the non-progression group (-65.4±4.9 ml/year vs. -35.1 ± 3.9 ml/year, $P<0.001$).

Risk factors for the progression of COPD

The results of the multifactorial logistic regression analysis are shown in Table 5. Age ≥ 65 years, PSI score ≥ 130 points, and multidrug-resistant bacteria infection with definition of simultaneous resistance of a microorganism to three or more classes of antibiotics were independent risk factors for the progression of COPD ($P<0.05$). The ORs and 95% CIs of these factors were 3.21 (1.28–8.06), 4.37 (1.76–10.84), and 5.23 (2.01–13.62), respectively.

Discussion

In this study, we explored the factors related to the progression of COPD in patients treated in the respiratory department of a tertiary hospital. COPD is a common and preventable respiratory disease that affects about 10% of the global population and causes significant morbidity and mortality [9]. The prognosis of COPD depends on the severity of the disease, the frequency and severity of acute exacerbations, and the presence of comorbidities [10]. The current treatment options for COPD include pharmacological and non-pharmacological interventions, such as bronchodilators, corticosteroids, oxygen therapy, pulmonary rehabilitation, and smoking cessation [11]. However, the effectiveness of these treatments varies among individuals and the disease progression is still unpredictable [12]. Therefore, it is important to identify the factors that influence the progression of COPD in patients and provide personalized and optimal management.

The independent risk factors for COPD progression

We hypothesized that some demographic, clinical, and treatment factors might be associated with the progression of COPD in patients. We defined the progression of COPD as a decline rate in pulmonary function (annual FEV1 change rate) equal to or greater than the mean of the group, acute exacerbations equal to or greater than the mean of the group, or death. The progression group had worse clinical characteristics, higher treatment intensity, and poorer outcomes than the non-progression group. These results were consistent with previous studies that showed that COPD progression was associated with lower lung function and higher exacerbation frequency [13, 14]. We also identified three independent risk factors for the progression of COPD: age ≥ 65 years, PSI score ≥ 130 points, and multidrug-resistant bacteria infection. These findings were in line with previous studies that showed that these factors were related to the severity and prognosis of COPD [15, 16]. These findings also supported and extended the existing theories and models of COPD, such as the inflammation-aging hypothesis [17], the pneumonia severity index [18], and the microbial-host interaction [19].

Age and progression of COPD

Age is a well-known risk factor for COPD, as it is associated with the decline of lung function, the increase of comorbidities, and the impairment of immune system [20]. Older COPD patients tend to have more severe airflow limitation, more frequent exacerbations, and higher mortality than younger COPD patients [21]. In our study, we found that age ≥ 65 years was an independent risk factor for the progression of COPD, which was consistent with previous studies [22]. Therefore, older COPD patients need more careful monitoring and management, and more attention should be paid to the prevention and treatment of comorbidities and complications.

PSI and progression of COPD

PSI score is a widely used tool to assess the severity and prognosis of community-acquired pneumonia (CAP), which is a common cause and complication of COPD exacerbations, with higher scores indicating higher risk of mortality [23]. In our study, we found that PSI score ≥ 130 points, which corresponds to the highest risk class V, was an independent risk factor for the progression of COPD. Therefore, PSI score can be used as a simple and effective tool to identify COPD patients with poor prognosis and guide the appropriate treatment and follow-up.

Multidrug-resistant bacteria infection and progression of COPD

Multidrug-resistant bacteria infection is a serious threat to the health and survival of COPD patients, as it can

cause severe and refractory pneumonia, sepsis, and organ failure [24]. Multidrug-resistant bacteria, such as Pseudomonas aeruginosa, Acinetobacter baumannii, and methicillin-resistant Staphylococcus aureus, are often isolated from the sputum or blood of COPD patients, especially those with severe disease, frequent exacerbations, or long-term antibiotic use [25]. In our study, we found that multidrug-resistant bacteria infection was an independent risk factor for the progression of COPD, which should be prevented and treated promptly and effectively in COPD patients, and rational use of antibiotics should be advocated to avoid the emergence and spread of resistance.

Impact of Individual and Social Environment on COPD

Although individual and socio-economic factors were not addressed in this study, the potential impact of socioeconomic factors, access to healthcare, and adherence to treatment regimens on COPD progression is substantial. Socioeconomic factors have a profound impact on the progression of COPD. People with low incomes may be at higher risk of environmental pollution and tobacco exposure, as they may live in areas with poorer environmental quality and work in environments that may be less conducive to respiratory health. In addition, low income may mean a lack of adequate health insurance coverage or an inability to afford high health care costs, which can lead to delays in medical appointments, an inability to receive regulated treatment, or an inability to purchase necessary medications. Low levels of education may also lead to a lack of disease awareness and health literacy, as well as poor choices in health behaviours. Occupational types may directly expose individuals to harmful gases, chemicals and dust, accelerating lung function decline and disease progression. Therefore, improving socio-economic conditions, providing equal access to health care, and enhancing educational and occupational health protections are essential to slowing the progression of COPD.

Recommendation for clinicians

Treatment for COPD patients aged ≥ 65 years with a PSI score ≥ 130 and multi-drug resistant bacterial infection should be personalized. This may include appropriate antibiotic therapy for the bacterial infection, supportive care, and medication management to control symptoms and slow disease progression. In addition to pharmacological treatment, supportive care is also a key component. This may include oxygen therapy, bronchodilators, and physical rehabilitation measures to help patients alleviate breathing difficulties, enhance lung function, and improve physical activity capacity. Furthermore, nutritional support and psychological support are also important components of the treatment plan to maintain the patient's nutritional status and improve quality of life. Active lifestyle interventions should also be incorporated into the treatment plan. This includes smoking cessation, avoiding air pollution, and regular physical exercise to reduce symptom exacerbation and disease progression. Rehabilitation programs can also help patients learn disease management, improve self-care skills, and provide social and psychological support to enhance their ability to cope with the disease. Finally, treatment planning should consider the patient's individual circumstances and clinical presentations. This may require collaboration with a multidisciplinary team, including pulmonologists, infectious disease specialists, dieticians, rehabilitation physicians, and psychologists, to develop a comprehensive treatment plan. Regular follow-up and assessment are also essential to monitor treatment efficacy and adjust the treatment plan to ensure patients receive optimal management and prognosis.

Limitations and future directions

This study has some limitations that should be acknowledged. First, the sample size was relatively small, and the study was conducted in a single center. Most of the studies were conducted in regional populations over 40 years of age where COPD is prevalent, which means that the results of the present study are less applicable to younger populations, and larger multi-center or multi-country studies are still needed to further explore the applicability of the conclusions at a more macroscopic level. Secondly, the study was retrospective in nature, and although we have considered strict inclusion and exclusion criteria in the study and have tried to ensure the accuracy of the information, some unnoticed aspects may introduce selection bias, information bias and confounding factors. Thirdly, the study did not include some potential factors that may influence the progression of COPD, such as genetic factors, biomarkers, microbiome, and environmental exposures, which will be examined in our future studies. Fourth, the study did not evaluate the quality of life, functional status, and psychological status of the patients, which are important aspects of COPD management and outcome. This is also a direction of interest in our subsequent research. Fifth, the study did not perform subgroup analysis based on the severity stages and phenotypes of COPD, which may reveal more specific and personalized factors for different subgroups of COPD patients. Moreover, future studies should focus on the mechanisms and pathways of how these factors influence the progression and outcome of COPD and develop more effective and targeted interventions and strategies to prevent and treat COPD and improve the prognosis and quality of life of COPD patients.

Conclusion

In conclusion, this study found that the patients with progression of COPD had worse clinical characteristics, higher treatment intensity, and poorer outcomes than the patients with non-progression disease. Independent risk factors of age ≥ 65 years, PSI score ≥ 130 points, and multidrug-resistant bacteria infection were also identified for the progression of COPD, which have important implications for the prevention and treatment of COPD and the improvement of the prognosis of COPD patients.

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Author contributions
Ding F conceived and designed the study. Liu WJ and Hu XY collected the data. Gao CY helped the date analysis and statistics. All authors took part in drafting the manuscript. All authors read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Harrison International Peace Hospital. Due to the anonymized and de-identified nature of the data, there is no need to obtain informed consent from the patient after approval by ethics committee of Harrison International Peace Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Agustí A, Celli BR, Criner GJ, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023;61(4):2300239. https://doi.org/10.1183/13993003.00239-2023.
2. Zaid AH, Thapamagar SB, Anholm JD et al. Effects of Dronabinol on Dyspnea and Quality of Life in Patients with COPD. Chronic Obstr Pulm Dis. 2024 Feb 2. https://doi.org/10.15326/jcopdf.2023.0401. Epub ahead of print.
3. McCormack M, Paczkowski R, Gronroos NN, et al. Outcomes of patients with COPD treated with ICS/LABA before and after initiation of single-inhaler Triple Therapy with Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI). Adv Ther. 2024;41(3):1245–61. https://doi.org/10.1007/s12325-023-02776-8.
4. Stephens CE, Utz R, Tay D, et al. Dying with dementia in nursing homes: a population-based study of decedents and their families. J Am Geriatr Soc. 2024 Feb;2. https://doi.org/10.1111/jgs.18770. Epub ahead of print.
5. Polverino E, De Soyza A, Dimakou K, et al. The Association between Bronchiectasis and Chronic Obstructive Pulmonary Disease: data from the European Bronchiectasis Registry (EMBARC). Am J Respir Crit Care Med. 2024 Jan;25. https://doi.org/10.1164/rccm.202309-1614OC. Epub ahead of print.
6. Jones PW, Agusti AG. Outcomes and markers in the assessment of chronic obstructive pulmonary disease. Eur Respir J. 2006;27(4):822–32. https://doi.org/10.1183/09031936.06.00145104.
7. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33(5):1165–85. https://doi.org/10.1183/09031936.00128008.
8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease report. 2023. Availble from: https://goldcopd.org/2023-gold-report-2/. Accessed Jan 12, 2024.
9. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: systematic review and meta-analysis. J Glob Health. 2015;5(2):020415. https://doi.org/10.7189/jogh.05.020415.
10. Hu W, Fang L, Zhang H, et al. Global disease burden of COPD from 1990 to 2019 and prediction of future disease burden trend in China. Public Health. 2022;208:89–97. https://doi.org/10.1016/j.puhe.2022.04.015.
11. Venkatesan P. GOLD COPD report: 2023 update. Lancet Respir Med. 2023;11(1):18. https://doi.org/10.1016/S2213-2600(22)00494-5.
12. Singh D, Agusti A, Anzueto A, et al. Global strategy for the diagnosis, management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J. 2019;53(5):1900164. https://doi.org/10.1183/13993003.00164-2019.
13. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med. 2008;178(4):332–8. https://doi.org/10.1164/rccm.200712-1869OC.
14. Wedzicha JA, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19–26. https://doi.org/10.1164/rccm.200707-973OC.
15. Mannino DM, Thorn D, Swensen A, et al. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J. 2008;32(4):962–9. https://doi.org/10.1183/09031936.00012408.
16. Almagro P, Cabrera FJ, Diez J, et al. Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en servicios de medicina interna (ESMI) study. Chest. 2012;142(5):1126–33. https://doi.org/10.1378/chest.11-2413.
17. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol Biol Sci Med Sci. 2014;69(Suppl 1):S4–9. https://doi.org/10.1093/gerona/glu057.
18. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336(4):243–50. https://doi.org/10.1056/NEJM199701233360402.
19. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med. 2008;359(22):2355–65. https://doi.org/10.1056/NEJMra0800353.
20. Rule AD, Grossardt BR, Weston AD et al. Older Tissue Age Derived From Abdominal Computed Tomography Biomarkers of Muscle, Fat, and Bone Is Associated With Chronic Conditions and Higher Mortality. Mayo Clin Proc. 2024 Feb 2:S0025-6196(23)00469-X. https://doi.org/10.1016/j.mayocp.2023.09.021. Epub ahead of print.
21. Le Rouzic O, Picaud M, Salvator H, et al. Residual reversibility in COPD patients already on long-acting bronchodilator: the OscilloRevers Study. Respir Med Res. 2024;85:101082. https://doi.org/10.1016/j.resmer.2023.101082. Epub ahead of print.
22. Menezes AM, Perez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five latin American cities (the PLATINO study): a prevalence study. Lancet. 2005;366(9500):1875–81. https://doi.org/10.1016/S0140-6736(05)67632-5.
23. Keene ON, Ruberg S, Schacht A, et al. What matters most? Different stakeholder perspectives on estimands for an invented case study in COPD. Pharm Stat. 2020;19(4):370–87. https://doi.org/10.1002/pst.1986.
24. Toychiev A, Gafner N, Belotserkovets V, et al. Impact of Ascaris lumbricoides infection on the development of chronic pulmonary aspergillosis in patients with COPD. Trop Doct. 2024;494755241226488. https://doi.org/10.1177/00494755241226488. Epub ahead of print.

25. Sethi S, Jones PW, Theron MS, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respir Res. 2010;11(1):10. https://doi.org/10.1186/1465-9921-11-10.

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