BMJ Open

Clinical-functional characteristics and risk of exacerbation and mortality in more symptomatic patients with chronic obstructive pulmonary disease

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065625
Article Type:	Original research
Date Submitted by the Author:	14-Jun-2022
Complete List of Authors:	Song, Qing; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Lin, Ling; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Cheng, Wei; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Zhao, Yi-Yang; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Zeng, Yu-Qin; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Liu, Cong; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Deng, Min-Hua; PLA Rocket Force Characteristic Medical Center, Department of Respiratory Liu, Dan; The Eighth Hospital in Changsha, Department of Respiratory Yu, Zhi-Ping; Longshan Hospital of Traditional Chinese Medicine, Department of Respiratory Li, Xin; Central South University Ma, Li-Bing; Affiliated Hospital of Guilin Medical University, Department of respiratory and critical care medicine Chen, Yan; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Cai, Shan; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Chen, Ping; Central South University, Department of Respiratory and Critical Care Medicine; Central South University
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Respiratory physiology < THORACIC MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Title: Clinical-functional characteristics and risk of exacerbation and mortality in more symptomatic patients with chronic obstructive pulmonary disease

Authors: Qing Song[1,2,3], Ling Lin[1,2,3], Wei Cheng[1,2,3], Yi-Yang Zhao[1,2,3], Yu-Qin Zeng[1,2,3], Cong Liu[1,2,3], Min-Hua Deng[4], Dan Liu[5], Zhi-Ping Yu[6], Xin Li[7], Li-Bing Ma[8], Yan Chen[1,2,3], Shan Cai[1,2,3], Ping Chen[1,2,3]

Affiliations:[1]Department of Respiratory and Critical Care Medicine, the Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China.

[2]Research Unit of Respiratory Disease, Central South University, Changsha, Hunan 410011, China.

[3]Diagnosis and Treatment Center of Respiratory Disease, Central South University, Changsha, Hunan 410011, China.

[4]Department of Respiratory, PLA Rocket Force Characteristic Medical Center, Beijing 100088, China.

[5]Department of Respiratory, The Eighth Hospital in Changsha, Hunan 410000, China.

[6]Department of Respiratory, Longshan Hospital of Traditional Chinese Medicine, Hunan 410000, China.

[7]Division 4 of Occupational Disease, Hunan Occupational Disease Prevention and Treatment Hospital, Changsha, Hunan 410000, China.

[8]Department of respiratory and critical care medicine, Affiliated Hospital of Guilin Medical University, Guilin, Guangxi 541000, China.

Corresponding author: Ping Chen, Department of Respiratory and Critical Care Medicine, the Second Xiangya Hospital, Central South University, 139 Renmin Middle

Road, Changsha, Hunan 410011, China. Tel +86 731 8529 5248; Fax +86 731 8529 5848.

Email: pingchen0731@csu.edu.cn

Abstract

Objectives: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 classified chronic obstructive pulmonary disease (COPD) patients into more symptomatic group. Our purpose was to analyze the clinical characteristics and risk of exacerbation and mortality in more symptomatic patients.

Methods: This cohort study including stable COPD patients who were classified into more symptomatic group based on GOLD 2017. All patients were followed up for 18 months. We collected baseline data and recorded the number of exacerbations, hospitalizations and mortality during follow-up. A logistic regression was conducted to determine the independent risk factors for mortality and future exacerbation.

Results: The more symptomatic patients were older, with higher Clinical COPD Questionnaire (CCQ), and more severe airflow limitation, as well as higher number of exacerbations and hospitalizations in the past year ($P < 0.05$). The logistic regression showed that having more symptoms was correlated with CCQ and exacerbations in the past year ($P < 0.05$). After patients were followed up, there were a higher number of exacerbations and hospitalizations, as well as higher mortality rates in more symptomatic patients ($P < 0.05$). The multivariate model showed that age (OR = 1.050, 95% CI = 1.012-1.090), smoking (OR = 1.012, 95% CI = 1.003-1.020), and COPD assessment test (OR = 1.101, 95% CI = 1.049-1.155) were independently associated with mortality, while current-smoker (OR = 1.411, 95% CI = 1.066-1.869), modified Medical Research Council (OR = 1.301, 95% CI = 1.131-1.497) and exacerbations in the past year (OR = 1.081, 95% CI = 1.035-1.130) were independently associated with future exacerbation in more symptomatic COPD patients ($P < 0.05$).

Conclusions: More symptomatic COPD patients have worse outcomes. In addition, several independent risk factors for exacerbation and mortality were identified. Therefore, clinicians should be aware of these risk factors and take them into account during interventions.

Keywords: COPD, more symptomatic, Mortality, Exacerbation, GOLD

Strengths and limitations of this study

The main strength of the paper is that it uses the realistic data to reveal the symptomatic COPD patients have worse lung function and outcomes and explores the independent risk factors for future exacerbation and mortality in more symptomatic COPD patients according to GOLD guidelines.

The main limitation of this study is that there are 281 more symptomatic COPD patients lost to contact during follow-up and lacking data on comorbidities.

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious chronic respiratory disease that typically features persistent respiratory symptoms, such as cough, expectoration, and dyspnea. This disease has brought a huge burden of mortality to humanity;[1-2] therefore, prevention and treatment is urgent.

Breathlessness, cough, and sputum production are common symptoms of COPD, bringing a huge burden to patients. Some may experience deterioration of their symptoms and need additional treatment.[3] The COPD assessment test (CAT) and modified Medical Research Council (mMRC) cover several dimensions, such as dyspnea, cough, expectoration, confidence, limitation of daily activities and chest tightness, and are used as an indicator to measure the effect of symptoms on the health of COPD patients.[4-5] The higher the CAT and mMRC scores, the more symptoms the patients have, and the greater the impact on patient's health.[6] Ding et al.[7] found that as the CAT score increased, the frequency of primary care physician visits also increased. Kim et al.[8] found that COPD patients with increased mMRC scores had a higher risk of exacerbation, more severe airflow limitation and respiratory symptoms when compared with patients with unchanged mMRC scores after one year of follow-up. In addition, a study showed that the BODE (body mass index, air-flow obstruction, dyspnea, exercise capacity) index includes dyspnea as a meaningful marker of future exacerbation risk.[9] In fact, some COPD patients only experience cough or breathlessness, while some patients have multiple respiratory symptoms, including cough, expectoration, chest tightness and dyspnea.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 evaluated COPD patients based on CAT or mMRC, and exacerbation risk to better guide treatment, dividing patients into those with more symptomatic and less symptomatic.[10] A Japanese study found that the COPD patients in the more symptomatic group were older, with more severe airflow limitation and higher exacerbation rates according to the GOLD 2017 classification; however, the number of patients with more symptomatic in this study was small.[11] In addition, several studies have shown that more symptomatic COPD patients account for the majority.[12-15] In addition, Cabrera López et al.[16] found that the risk of mortality was higher in Groups B and D than in Groups A and C according to the GOLD 2017 classification. However, the clinical characteristics and outcomes in more symptomatic COPD patients remained unclear. Therefore, our purpose was to analyze the clinical-functional characteristics and related risk factors, as well as risk of future exacerbation and mortality in more symptomatic COPD patients.

Methods

Study participants

We conducted observational cohort study that captured the patients listed from September 2017 to December 2019 in the outpatient department database. The study was registered in the Chinese Clinical Trial Registry (ChiCTR-POC-17010431). The inclusion criterion for COPD patients was a ratio of forced expiratory volume in 1s to forced vital capacity (FEV1/FVC) < 0.70 after bronchodilator administration. Patients with interstitial lung disease, bronchiectasis, pneumonia, asthma, pleural effusion, lung cancer or active tuberculosis were excluded from the study.

We confirm that this study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. All patients in this study were written informed consent.

Patient and public involvement

Patients and the public were not involved in the conception of this study, development of the research question, interpretation of the results or manuscript writing.

Study procedures

All included COPD patients underwent 18 months of follow-up. Furthermore, at the 6th, 12th and 18th months, we recorded the number of exacerbations, hospitalizations and deaths among these patients. According to the GOLD 2017 guidelines, the COPD patients were assigned to the more and less symptomatic groups. Briefly, the more symptomatic group was defined by mMRC scores ≥ 2 and/or CAT scores ≥ 10, with or without a history of exacerbations and hospitalizations. The less symptomatic group was defined by mMRC scores < 2 and CAT scores < 10, with or without a history of exacerbations and hospitalizations.[10]

Data collection and definition

The baseline clinical characteristics included demographics, smoke history, biofuel and occupational exposure history, pulmonary function results, symptoms scores (including CAT and mMRC), Clinical COPD Questionnaire (CCQ), treatment regimens and number of exacerbations and hospitalizations in the past year. Furthermore, we recorded mortality, and the number of exacerbations and hospitalizations during follow-up.

A current-smoker was defined as having smoking exposure of more than 10 pack-years, while a former-smoker was defined as having smoking exposure of at least 10 pack-years, but smoking cessation of more than half a year.[17] An exacerbation was defined as disease progression that requires antibiotics, oral corticosteroids or hospitalization for treatment, or was determined by a sputum color change (to green or yellow).[18] Biofuel exposure was defined as continuous exposure to biofuels for at least two hours a day, for at least one year. Occupational exposure was defined as exposure to dust, metals, chemical substances or other environmental agents for at least eight hours a day for at least one year.[19] According to the GOLD 2017 guidelines, GOLD grade 1 (FEV1 ≥ 80 %pred), GOLD grade 2 (FEV1 50-79 %pred), GOLD grade 3 (FEV1 30-49 %pred) and GOLD grade 4 (FEV1 < 30 %pred).[10]

Statistical analysis

The continuous variables were tested for normality and presented as mean ± standard deviation (SD), or median and interquartile range (IQR). The Chi-squared and Fisher's tests were used to analyze categorical variables. An independent-samples Student's t-test was used to analyze continuous variables. For variables with non-normal distribution or uneven variance, we used non-parametric tests. The variously adjusted odds ratio was calculated using multivariate logistic regression. Two-sided and *P* values < 0.05 were considered to be statistically significant. SPSS version 26.0 (IBM, Armonk, NY, USA) was used to perform all statistical analyses.

Results

Baseline characteristics

A total of 1729 patients with COPD were included (Figure 1). The mean age was 65.1 ± 8.2 years, and 89.1% of them were male. More than half of the patients were current-smokers, with no biofuel or occupational exposure. Most of the patients were in GOLD grades 2-3 and treatment with long-acting muscarinic antagonist (LAMA), LAMA + long-acting β2-agonist (LABA) + inhaled corticosteroid (ICS). The mean CAT and CCQ were 15.4 ± 6.6 and 21.9 ± 7.2, respectively. Most patients suffered from exacerbation and hospitalization less than once per year (Table 1).

Table 1. The baseline characteristics of the COPD patients.

Variables	Total (n = 1729)
Age (years)	65.1 ± 8.2
Sex, n (%)	
Male	1541 (89.1)
Female	188 (10.9)
Education level, n (%)	
Primary school	713 (41.2)
Junior high school	618 (35.8)
High school	289 (16.7)
University	108 (6.3)
BMI (kg/m^2)	22.5 ± 3.6
Smoke history, n (%)	
Never-smoker	288 (16.7)
Former-smoker	576 (33.3)
Current-smoker	865 (50.0)
Smoking, (pack/year) (Median, IQR)	35 (30)
Biofuel exposure, n (%)	
Yes	659 (38.1)
No	1070 (61.9)
Occupational exposure, n (%)	
Yes	660 (38.2)
No	1069 (61.8)
Pulmonary function, (Mean ± SD)	
FEV1	1.3 ± 0.6
FEV1 %pred	52.1 ± 20
FVC	2.7 ± 0.7
FEV1/FVC	46.5 ± 16.1

PEF	3.5 ± 1.6
GOLD grade, n (%)	
1	171 (9.9)
2	709 (41.0)
3	596 (34.5)
4	253 (14.6)
CAT, (Mean ± SD)	15.4 ± 6.6
mMRC, (Median, IQR)	2 (2)
CCQ, (Mean ± SD)	21.9 ± 7.2
Treatments, n (%)	
LAMA	622 (36.0)
LABA + ICS	136 (7.9)
LAMA + LABA	33 (1.9)
LAMA + LABA + ICS	797 (46.1)
Exacerbations in the past year, (Median, IQR)	1 (2)
Exacerbations in the past year, n (%)	
0	753 (43.6)
1	412 (23.8)
≥2	564 (32.6)
Hospitalizations in the past year, (Median, IQR)	0 (1)
Hospitalizations in the past year, n (%)	
0	1132 (65.5)
≥1	597 (34.5)

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow.

According to the GOLD 2017 guidelines, 1388 (80.3%) were more symptomatic patients. more symptomatic patients were older (65.5 ± 8.0 vs 63.4 ± 8.8 years, $P < 0.001$), and had a lower education level, BMI, FEV1, FEV1 %pred, FVC, FEV1/FVC and peak expiratory flow (PEF) ($P < 0.001$). However, there was a higher proportion of biofuel exposure history and GOLD grades 3-4 patients ($P < 0.001$). In addition, there were a higher proportion of biofuel exposure history, GOLD grade 3-4 patients, treatment with LAMA+LABA+ICS ($P < 0.001$). more symptomatic COPD patients had a higher CCQ

scores, and a higher number of exacerbations and hospitalizations in the past year ($P <$ 0.001) (Table 2).

Table 2. The clinical characteristics of more symptomatic COPD patients.

Variables	More symptoms (n = 1388)	Less symptoms (n = 341)	*P* - value
Age (years)	65.5 ± 8.0	63.4 ± 8.8	<0.001
Sex, n (%)			0.858
Male	1238 (89.2)	303 (88.9)	
Female	150 (10.8)	38 (11.1)	
Education level, n (%)			<0.001
Primary school	585 (42.1)	128 (37.5)	
Junior high school	516 (37.2)	102 (29.9)	
High school	222 (16.0)	67 (19.6)	
University	65 (4.7)	44 (13.0)	
BMI (kg/m^2)	22.3 ± 3.7	23.2 ± 3.1	<0.001
Smoke history, n (%)			0.142
Never-smoker	240 (17.3)	48 (14.1)	
Former-smoker	469 (33.8)	107 (31.4)	
Current-smoker	679 (48.9)	186 (54.5)	
Smoking, (pack/year) (Median, IQR)	35 (30)	38 (30)	0.629
Biofuel exposure, n (%)			<0.001
Yes	558 (40.2)	102 (29.9)	
No	830 (59.8)	239 (70.1)	
Occupational exposure, n (%)			0.706
Yes	526 (37.9)	133 (39)	
No	862 (62.1)	208 (61)	
Pulmonary function, (Mean ± SD)			
FEV1	1.2 ± 0.5	1.7 ± 0.6	<0.001
FEV1 %pred	48.7 ± 19.0	65.7 ± 19.4	<0.001
FVC	2.6 ± 0.7	3.1 ± 0.8	<0.001
FEV1/FVC	44.4 ± 12.2	54.9 ± 12.9	<0.001
PEF	3.2 ± 1.4	4.7 ± 1.9	<0.001
GOLD grade, n (%)			<0.001
1	90 (6.5)	81 (23.8)	
2	518 (37.3)	191 (56.0)	
3	536 (38.6)	60 (17.6)	
4	244 (17.6)	9 (2.6)	
CAT, (Mean ± SD)	17.6 ± 5.3	6.5 ± 2.2	<0.001
mMRC, (Median, IQR)	2 (1)	1 (1)	<0.001

CCQ, (Mean ± SD)	23.6 ± 6.5	15.1 ± 5.8	<0.001
Treatments, n (%)			
LAMA	464 (33.4)	158 (46.3)	<0.001
LABA + ICS	97 (7.0)	39 (11.4)	0.006
LAMA + LABA	27 (1.9)	6 (1.8)	0.822
LAMA + LABA + ICS	695 (50.1)	102 (29.9)	<0.001
Exacerbations in the past year, (Median, IQR)	1 (2)	c0 (1)	<0.001
Exacerbations in the past year, n (%)			<0.001
0	555 (40.0)	198 (58.1)	
1	325 (23.4)	87 (25.5)	
≥2	508 (36.6)	56 (16.4)	
Hospitalizations in the past year, (Median, IQR)	0 (1)	0 (0)	<0.001
Hospitalizations in the past year, n (%)			<0.001
0	872 (62.8)	260 (76.2)	
≥1	516 (37.2)	81 (23.8)	

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow.

Multivariate analysis of risk factors associated with more symptomatic COPD patients

Results were adjusted for age, education level, biofuel exposure, FEV1, FEV1 %pred, FVC, GOLD grade and BMI. A logistic regression analysis showed that FEV1/FVC and PEF were negatively correlated with more symptomatic, with an OR of 0.980 (95% CI = 0.964 - 0.995) and 0.774 (95% CI = 0.688 - 0.872) ($P < 0.05$), respectively. However, CCQ and exacerbations in the past year were positively correlated with more symptomatic, with an OR of 1.200 (95% CI = 1.169 - 1.232) and 1.114 (95% CI = 1.025 - 1.211) ($P < 0.05$), respectively (Table 3).

Table 3. Multivariate analysis of risk factors associated with more symptomatic COPD patients.

Variables	OR	95% CI	*P* - value

FEV1/FVC	0.980	0.964 – 0.995	0.010
PEF	0.774	0.688 – 0.872	<0.001
CCQ	1.200	1.169 – 1.232	<0.001
Exacerbations in the past year	1.114	1.025 - 1.211	0.011

Notes: After adjusted for age, education level, biofuel exposure, FEV1, FEV1 %pred, FVC, GOLD grade, BMI and hospitalizations in the past year. $P < 0.05$ are statistically significant in accordance with Logistic regression analysis.

Abbreviations: BMI, Body Mass Index; CI, Confidence interval; COPD, Chronic Obstructive Pulmonary Disease; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PEF, Peak Expiratory Flow; OR, Odds Ratio.

Exacerbation and mortality after 18 months of follow-up

As shown in Table 4, after 18 months of follow-up, a total of 1407 patients were included. The median (IQR) of exacerbations and hospitalizations were 0 (1) and 0 (1) respectively. Most of patients suffered from exacerbation and hospitalization less than once per year and the mortality rate was 4.6%.

Table 4. Exacerbation and mortality after 18 months of follow-up in more symptomatic COPD patients.

Variables	Total (n = 1407)	More symptomatic (n = 1107)	Less symptomatic (n = 300)	*P* - value
Exacerbations (Median, IQR)	0 (1)	0 (1)	0 (1)	<0.001
Exacerbations, n (%)				<0.001
0	836 (62.2)	621 (59.2)	215 (73.4)	
1	259 (19.4)	217 (20.7)	42 (14.3)	
≥2	247 (18.4)	211 (20.1)	36 (12.3)	
Hospitalizations (Median, IQR)	0 (1)	0 (1)	0 (0)	<0.001
Hospitalizations, n (%)				0.001
0	1004 (77.7)	762 (72.6)	242 (82.6)	
≥1	338 (22.3)	287 (27.4)	51 (17.4)	
Mortality, n (%)	65 (4.6)	58 (5.2)	7 (2.3)	0.033

Note: COPD, Chronic Obstructive Pulmonary Disease.

After 18 months of follow-up, 1107 more symptomatic COPD patients were analyzed for future exacerbation and mortality. The results show that more symptomatic COPD

patients suffered from higher exacerbations and hospitalizations ($P < 0.001$). The proportion of more symptomatic patients who suffered from exacerbations and hospitalizations at least once per year was higher ($P < 0.001$), with rates of 40.8% and 27.4%, respectively. A comparison of the exacerbation free proportion using a Kaplan–Meier curve revealed that there was a significant difference between the more and less symptomatic groups ($P < 0.001$) (Figure 2). In addition, 58 (5.2%) more symptomatic COPD patients died during the 18 months of follow-up, higher than in the less symptomatic group ($P < 0.001$). A comparison of the overall survival using the Kaplan–Meier curve revealed that survival was significantly different between the more and less symptomatic groups ($P = 0.013$) (Figure 3).

Univariate and stepwise multivariate analysis of risk factors for mortality in more symptomatic COPD patients

Fifty-eight of the 1107 more symptomatic COPD patients died during follow-up. Univariate analysis showed that there were several factors were risk factors for mortality, including age (OR = 1.057, 95% CI = 1.021-1.095, $P = 0.002$), smoking (pack/year) (OR = 1.012, 95% CI = 1.003-1.020, $P = 0.005$), CAT (OR = 1.102, 95% CI = 1.054-1.151, $P < 0.001$), mMRC (OR = 1.490, 95% CI = 1.107-2.006, $P = 0.009$), CCQ (OR = 1.091, 95% CI = 1.048-1.137, $P < 0.001$), exacerbations in the past year (OR = 1.057, 95% CI = 1.001-1.117, $P = 0.049$) and hospitalizations in the past year (OR = 1.143, 95% CI = 1.014-1.289, $P = 0.029$). The multivariate model showed that age (OR = 1.050, 95% CI = 1.012-1.090, $P = 0.010$) smoking (pack/year) (OR = 1.012, 95% CI = 1.003-1.020, $P = 0.006$), and CAT (OR = 1.101, 95% CI = 1.049-1.155, $P < 0.001$) were independently associated with mortality in more symptomatic COPD patients (Table 5).

Table 5. Univariate and stepwise multivariate analysis of risk factors for mortality in more symptomatic COPD patients.

Variables	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.057	1.021-1.095	0.002	1.050	1.012-1.090	0.010
Sex						
Male	Reference					
Female	0.439	0.135-1.425	0.170			
Education level						
Primary school	Reference			Reference		
Junior high school	0.372	0.194-0.714	0.003	0.446	0.227-1.352	0.328
High school	0.655	0.308-1.394	0.272	0.710	0.323-1.561	0.394
University	0.239	0.032-1.781	0.162	0.331	0.043-2.543	0.288
BMI	0.950	0.881-1.023	0.173			
Smoke history						
Former-smoker	Reference					
Never-smoker	0.517	0.196-1.362	0.182			
Current-smoker	1.363	0.782-2.374	0.275			
Smoking (pack/year)	1.012	1.003-1.020	0.005	1.012	1.003-1.020	0.006
Biofuel exposure						
Yes	Reference					
No	0.736	0.416-1.302	0.292			
Occupational exposure						
Yes	Reference					
No	0.642	0.378-1.089	0.100			
Pulmonary function						
FEV1	0.713	0.407-1.246	0.235			
FEV1 %pred	1.000	0.986-1.014	0.993			
FVC	0.573	0.387-0.848	0.005	0.738	0.431-1.263	0.267
FEV1/FVC	1.013	0.991-1.034	0.246			
PEF	0.898	0.731-1.102	0.303			
GOLD grade						
1	0.314	0.071-1.394	0.128	0.489	0.106-2.241	0.357
2	0.676	0.355-1.290	0.304	0.930	0.462-1.873	0.838
3	0.394	0.193-0.806	0.011	0.398	0.191-0.830	0.014
4	Reference			Reference		
CAT	1.102	1.054-1.151	<0.001	1.101	1.049-1.155	<0.001
mMRC	1.490	1.107-2.006	0.009	0.945	0.647-1.382	0.772
CCQ	1.091	1.048-1.137	<0.001	1.034	0.982-1.088	0.202
Treatments						
LAMA	0.918	0.519-1.625	0.770			
LABA + ICS	0.670	0.205-2.189	0.507			
LAMA + LABA	2.670	0.773-9.225	0.121			
LAMA + LABA + ICS	1.057	0.623-1.794	0.837			
Exacerbations in the past year	1..057	1.001-1.117	0.049	1.016	0.931-1.108	0.721
Hospitalizations in the past year	1.143	1.014-1.289	0.029	1.084	0.925-1.270	0.317

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow, OR = Odds Ratio, CI = Confidence Interval.

Univariate and stepwise multivariate analysis of risk factors for future exacerbation in more symptomatic COPD patients

In total, 428 of 1107 more symptomatic COPD patients suffered from exacerbation during follow-up. Univariate analysis showed that several factors were risk factors for future exacerbation, including age (OR = 1.019, 95% CI = 1.003-1.035, *P* = 0.017), current-smoker (OR = 1.480, 95% CI = 1.125-1.948, *P* = 0.005), CAT (OR = 1.043, 95% CI = 1.019-1.067, *P* < 0.001), mMRC (OR = 1.375, 95% CI = 1.199-1.576, *P* < 0.001), CCQ (OR = 1.025, 95% CI = 1.006-1.045, *P* = 0.012), exacerbations in the past year (OR = 1.098, 95% CI = 1.049-1.149, *P* < 0.001) and hospitalizations in the past year (OR = 1.208, 95% CI = 1.094-1.335, *P* < 0.001). The multivariate model showed that current-smoker (OR = 1.411, 95% CI = 1.066-1.869, *P* = 0.016), mMRC (OR = 1.301, 95% CI = 1.131-1.497, *P* < 0.001) and exacerbations in the past year (OR = 1.081, 95% CI = 1.035-1.130, *P* = 0.001) were independently associated with future exacerbation in more symptomatic COPD patients (Table 6).

Table 6. Univariate and stepwise multivariate analysis of risk factors for future exacerbation in more symptomatic COPD patients.

Variables	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.019	1.003-1.035	0.017	1.002	0.985-1.020	0.810
Sex						
Male	Reference					
Female	0.749	0.500-1.123	0.162			
Education level						
Primary school	Reference			Reference		
Junior high	0.701	0.531-0.925	0.012	0.733	0.548-0.981	0.056

school						
High school	0.884	0.613-1.274	0.507	0.983	0.670-1.442	0.931
University	0.903	0.427-1.424	0.737	1.163	0..627-2.157	0.631
BMI	0.956	0.924-0.989	0.010	0.963	0.930-0.997	0.034
Smoke history						
Former-smoker	Reference			Reference		
Never-smoker	1.064	0.751-1.508	0.728	1.032	0.723-1.474	0.861
Current-smoker	1.480	1.125-1.948	0.005	1.411	1.066-1.869	0.016
Smoking (pack/year)	1.002	0.997-1.006	0.469			
Biofuel exposure						
No	Reference					
Yes	1.159	0.901-1.491	0.252			
Occupational exposure						
No	Reference					
Yes	1.065	0.826-1.373	0.627			
Pulmonary function						
FEV1	0.768	0.600-0.983	0.036	1.754	0.988-3.113	0.055
FEV1 %pred	0.994	0.988-1.001	0.093			
FVC	0.779	0.653-0.931	0.006	0.764	0.562-1.039	0.087
FEV1/FVC	0.994	0.984-1.004	0.224			
PEF	0.891	0.813-0.977	0.015	0.917	0.767-1.097	0.345
GOLD grade						
1	0.557	0.313-0.994	0.068			
2	0.699	0.490-0.997	0.100			
3	0.760	0.536-1.078	0.124			
4	Reference					
CAT	1.043	1.019-1.067	<0.001	1.009	0.978-1.040	0.590
mMRC	1.375	1.199-1.576	<0.001	1.301	1.131-1.497	<0.001
CCQ	1.025	1.006-1.045	0.012	0.993	0.970-1.017	0.585
Treatments						
LAMA	0.918	0.705-1.194	0.523			
LABA + ICS	0.660	0.404-1.078	0.097			
LAMA + LABA	0.902	0.370-2.195	0.820			
LAMA + LABA + ICS	0.813	0.635-1.041	0.100			
Exacerbations in the past year	1.098	1.049-1.149	<0.001	1.081	1.035-1.130	0.001
Hospitalizations in the past year	1.208	1.094-1.335	<0.001	1.080	0.967-1.206	0.170

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow, OR = Odds Ratio, CI = Confidence Interval.

Discussion

In this study, we found that more symptomatic patients accounted for the majority and several studies have yielded the same results.[12-15] In addition, patients with COPD typically do not go to the hospital until they have severe respiratory symptoms in China. We also found that more symptomatic patients were older, and a similar result was observed by Han et al.[20] Biofuel exposure also is one of main risk factors of COPD.[21-22] A study showed that, compared with smoking, COPD patients with biofuel exposure experienced more dyspnea.[23] In addition, Dutt et al.[24] found that people exposed to biofuel may suffer from more respiratory symptoms. The results of our research also confirmed that more symptomatic COPD patients had a higher biofuel exposure rate. Maintenance of inhalation bronchodilators and ICS could reduce respiratory symptoms and exacerbations, improve pulmonary function in patients with COPD. Our research results showed that more symptomatic patients were more likely to use triple inhalers, whereas less likely to use monotherapy with LAMA. This was consistent with Kobayashi et al.[11]

Pulmonary function is used to evaluate airflow limitation and severity of in COPD patients. Our research also found that more symptomatic COPD patients had worse pulmonary function, and that deterioration in pulmonary function was significantly associated with respiratory symptoms. This was consistent with a study by Boezen et al.[25] that showed that both FEV1 and PEF decreased as symptom number increased, and the risk of having a FEV1 or PEF value of < 70% was increased with increasing symptom number. Brodkin et al.[26] also found that cough, phlegm, wheeze, and dyspnea were inversely related to pulmonary function. Another study found that initial FEV1 level was lower in patients with dyspnea appearing during follow-up than in the never-symptom

group.[27] The GOLD 2013 guidelines also recommend CCQ as a symptom measure,[28] and state that it is predictive of mortality in COPD patients.[29] Our study showed that more symptomatic patients had higher CCQ scores, which were positively correlated with more symptomatic.

Exacerbation is an important risk factor for stable COPD, leading to pulmonary function decline, and poor prognosis.[30] Our study found that more symptomatic patients suffered from higher number of exacerbations in the past year. Moreover, the more exacerbations, the more symptomatic patients experienced. Miravitlles et al.[31] also found that more exacerbations in the past year was associated with variability in symptom number. In addition, Kobayashi et al.[11] found that more symptomatic patients suffered higher number of exacerbations in the past year, which is consistent with our research. However, it is unclear whether more symptomatic patients have worse outcomes. Therefore, we performed 18 months of follow-up to observe the patients' future exacerbation and mortality. The results showed that there were higher exacerbation and hospitalization rates in more symptomatic patients, along with higher mortality rates. In addition, Kim et al.[32] found that the more symptomatic patients had significantly higher future exacerbation risk among patients with FEV1 ≥ 50%. A study by Cabrera López et al.[33] also found a similar result, with more symptomatic patients showing a higher mortality rate at five years of follow-up. In addition, our research results show that more symptomatic patients had lower BMI, but a higher risk of future exacerbation and mortality. This was consistent with a study by Putcha et al.[34] study that showed that underweight participants had a significantly higher risk of death and severe exacerbations

Death is the most serious malignant event associated with COPD[35] and it is vital to analyze the risk factors for death in COPD patients. Our results showed that age, smoking (pack/year) and CAT were positively correlated with mortality. Age and smoking are important risk factors associated with COPD development,[36-37] and our study also found the same result. At the same time, it implied that improved pulmonary function, reduced respiratory symptoms and quitting smoking are important interventions to reduce the occurrence of malignant events in COPD.

Acute exacerbations are important deterioration events in patients with COPD during follow-up. Therefore, it is necessary to analyze the independent risk factors of the more symptomatic patients who suffered from exacerbation during the 18 months of follow-up in order to better guide the prevention and treatment. In this study, we found that mMRC scores, current-smoker and exacerbations in the past year were positively correlated with future exacerbation. It is implied that the higher the mMRC scores and number of exacerbations in the past year, the higher the future exacerbation risk.

Smoking is an important risk factor of COPD development,[37] and it is important to demonstrate the effects of smoking on COPD exacerbation. Therefore, we further analyzed the exacerbations and mortality after 18 months of follow-up in COPD patients with different smoke history. We found that current-smokers had a higher exacerbation and hospitalization rates than former-smokers and never-smokers (Supplementary Table 1). Furthermore, COPD patients who smoked more than 10 packs/years had higher mortality (Supplementary Table 2). This implies that smoking cessation may decrease the risk of exacerbation and mortality in COPD patients. A study by Pezzuto e al.[38] had a

similar result, showing that smoking cessation notably improved pulmonary functional parameters, oxygen desaturation and walking test, as well as decreasing CAT scores.

This study has some limitations. First, there were 281 more symptomatic COPD patients lost to contact during follow-up. However, we found that the characteristics of the patients lost to follow-up patients and those that remained in the study were not significantly different (Supplementary Table 3). Then, the number of female patients in this study was small. In fact, The prevalence of COPD differed significantly between male and female in China and prevalence was higher in male, mainly because smoking was the main risk factor for COPD, but there were relatively few female smoking patients.[39-40] Furthermore, several studies showed that the proportion of female patients was relatively small in China.[41-43] In addition, the number of low education level patients was higher. In fact, China is a developing country, the overall level of education is not high in early time. Finally, this study lacked data on comorbidities which placed a symptom burden on patients with COPD and have an impact on future exacerbation and mortality.

In summary, our study revealed that the majority of COPD patients have more symptoms, which are associated with worse pulmonary function. more symptomatic patients also have worse outcomes. Reducing respiratory symptoms might improve patients' pulmonary function and outcomes. In addition, several independent risk factors for exacerbation and mortality in more symptomatic COPD patients were identified, including age, smoke, mMRC, CAT and exacerbation in the past year. Therefore, clinicians should be aware of the risk factors and take them into account in interventions in more symptomatic COPD patients.

Abbreviations

BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CI, Confidence interval; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, Interquartile Range; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, Modified Medical Research Council; OR, Odds Ratio; PEF, Peak Expiratory Flow.

Funding

This work was supported by the National Key Clinical Specialty Construction Projects((2012)No. 650), the National Natural Science Foundation of China (NSFC, Grants 81970044) and Xiangya Mingyi grant (2013).

Acknowledgments

We would like to thank the staff of the hospitals for their cooperation in collecting the study data.

Ethics approval and consent to participate

This study was approved by an institutional review board from the Second Xiangya Hospital of Central South University and conducted in accordance with the Declaration of Helsinki. This study was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR-POC-17010431). Informed consent was obtained from all patients for being included in the study.

Competing interests

All authors of this study have no conflicts of interests for this work.

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 agreed to be accountable for all aspects of the work.

Data sharing statement

The datasets are available in the Department of Pulmonary and Critical Care Medicine, the Second Xiangya Hospital repository (http://218.4.234.74:9007/a/login). The data that support the findings of this study are available upon reasonable request from the corresponding author Ping Chen.

References

1. Lareau SC, Fahy B, Meek P, Wang A. Chronic Obstructive Pulmonary Disease (COPD). Am J Respir Crit Care Med. 2019;199(1):P1-P2. doi: 10.1164/rccm.1991P1.
2. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585-596. doi: 10.1016/S2213-2600(20)30105-3.
3. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respir Res. 2017;18(1):67. doi: 10.1186/s12931-017-0548-3.

4. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54. doi: 10.1183/09031936.00102509.
5. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6. doi: 10.1136/thx.54.7.581.
6. Global Initiative for Chronic Obstructive Lung Disease Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease; 2020 [updated 2020 Nov 4; accessed 2020 Oct 25]. Available from: http://www.goldcopd.org/].
7. Ding B, Small M, Bergström G, Holmgren U. COPD symptom burden: impact on health care resource utilization, and work and activity impairment. Int J Chron Obstruct Pulmon Dis. 2017;12:677-689. doi: 10.2147/COPD.S123896.
8. Kim MA, Suh MK, Park J, Kim JH, Kim TH, Kim EK, et al. Impact of symptom variability on clinical outcomes in COPD: analysis of a longitudinal cohort. Int J Chron Obstruct Pulmon Dis. 2019;14:2135-2144. doi: 10.2147/COPD.S203715.
9. Praveen CK, Manu M, Mohapatra AK, Pentapati KC. Power of BODE Index in Predicting Future Exacerbations of COPD: A Prospective Observational Study in Indian Population. J Assoc Physicians India. 2019;67(4):14-16.
10. GOLD Executive Committee, Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (2017 REPORT). Available online: https://goldcopd.org/. Accessed Nov 2016.

11. Kobayashi S, Hanagama M, Ishida M, Sato H, Ono M, Yamanda S, et al. Clinical characteristics and outcomes in Japanese patients with COPD according to the 2017 GOLD classification: the Ishinomaki COPD Network Registry. Int J Chron Obstruct Pulmon Dis. 2018;13:3947-3955. doi: 10.2147/COPD.S182905.
12. Le LAK, Johannessen A, Hardie JA, Johansen OE, Gulsvik A, Vikse BE, et al. Prevalence and prognostic ability of the GOLD 2017 classification compared to the GOLD 2011 classification in a Norwegian COPD cohort. Int J Chron Obstruct Pulmon Dis. 2019;14:1639-1655. doi: 10.2147/COPD.S194019.
13. Lee SJ, Yun SS, Ju S, You JW, Cho YJ, Jeong YY, et al. Validity of the GOLD 2017 classification in the prediction of mortality and respiratory hospitalization in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2019;14:911-919. doi: 10.2147/COPD.S191362.
14. Kahnert K, Alter P, Young D, Lucke T, Heinrich J, Huber RM, et al. The revised GOLD 2017 COPD categorization in relation to comorbidities. Respir Med. 2018;134:79-85. doi: 10.1016/j.rmed.2017.12.003. Epub 2017 Dec 5.
15. Song Q, Zhao YY, Zeng YQ, Liu C, Cheng W, Deng MH, et al. The Characteristics of Airflow Limitation and Future Exacerbations in Different GOLD Groups of COPD Patients. Int J Chron Obstruct Pulmon Dis. 2021;16:1401-1412. doi: 10.2147/COPD.S309267.
16. Cabrera López C, Casanova Macario C, Marín Trigo JM, de-Torres JP, Sicilia Torres R, González JM, et al. Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes. Am J Respir Crit Care Med. 2018;197(4):463-469. doi: 10.1164/rccm.201707-1363OC.

17. Zhao YY, Liu C, Zeng YQ, Zhou AY, Duan JX, Cheng W, et al. Modified and simplified clinically important deterioration: multidimensional indices of short-term disease trajectory to predict future exacerbations in patients with chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2020;14:1753466620977376. doi: 10.1177/1753466620977376.

18. Hirschmann JV. Do bacteria cause exacerbations of COPD? Chest. 2000;118(1):193-203. doi: 10.1378/chest.118.1.193.

19. Duan JX, Cheng W, Zeng YQ, Chen Y, Cai S, Li X, et al. Characteristics of Patients with Chronic Obstructive Pulmonary Disease Exposed to Different Environmental Risk Factors: A Large Cross-Sectional Study. Int J Chron Obstruct Pulmon Dis. 2020;15:2857-2867. doi: 10.2147/COPD.S267114.

20. Han MZ, Hsiue TR, Tsai SH, Huang TH, Liao XM, Chen CZ. Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3425-3433. doi: 10.2147/COPD.S179048.

21. Po JY, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. Thorax. 2011;66(3):232-9. doi: 10.1136/thx.2010.147884. Epub 2011 Jan 19.

22. Pathak U, Gupta NC, Suri JC. Risk of COPD due to indoor air pollution from biomass cooking fuel: a systematic review and meta-analysis. Int J Environ Health Res. 2020;30(1):75-88. doi: 10.1080/09603123.2019.1575951.

23. Cheng LL, Liu YY, Su ZQ, Liu J, Chen RC, Ran PX. Clinical characteristics of tobacco smoke-induced versus biomass fuel-induced chronic obstructive pulmonary

disease. J Transl Int Med. 2015;3(3):126-129. doi: 10.1515/jtim-2015-0012.

24. Dutt D, Srinivasa D.K, Rotti S.B, Sahai A.K. Effect of indoor air pollution on the respiratory system of women using different fuels for cooking in an urban slum of Pondicherry. Natl. Med J. India. 1996;9:113–117.

25. Boezen HM, Schouten JP, Postma DS, Rijcken B. Relation between respiratory symptoms, pulmonary function and peak flow variability in adults. Thorax. 1995;50(2):121-6. doi: 10.1136/thx.50.2.121.

26. Brodkin CA, Barnhart S, Anderson G, Checkoway H, Omenn GS, Rosenstock L. Correlation between respiratory symptoms and pulmonary function in asbestos-exposed workers. Am Rev Respir Dis. 1993;148(1):32-7. doi: 10.1164/ajrccm/148.1.32.

27. Krzyzanowski M, Camilli AE, Lebowitz MD. Relationships between pulmonary function and changes in chronic respiratory symptoms. Comparison of Tucson and Cracow longitudinal studies. Chest. 1990;98(1):62-70. doi: 10.1378/chest.98.1.62.

28. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2013.

29. Sundh J, Janson C, Lisspers K, Montgomery S, Ställberg B. Clinical COPD Questionnaire score (CCQ) and mortality. Int J Chron Obstruct Pulmon Dis. 2012;7:833-42. doi: 10.2147/COPD.S38119.

30. Dong H, Hao Y, Li D, Su Z, Li W, Shi B, Gao P. Risk Factors for Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Industrial Regions of China: A Multicenter Cross-Sectional Study. Int J Chron Obstruct Pulmon Dis.

2020;15:2249-2256. doi: 10.2147/COPD.S270729.

31. Miravitlles M, Izquierdo JL, Esquinas C, Pérez M, Calle M, López-Campos JL, et al. The variability of respiratory symptoms and associated factors in COPD. Respir Med. 2017;129:165-172. doi: 10.1016/j.rmed.2017.06.017.

32. Kim J, Lee CH, Lee MG, Shin KC, Yoo KH, Lim SY, et al. Acute Exacerbation According to GOLD 2017 Categories in Patients with Chronic Obstructive Pulmonary Disease. Arch Bronconeumol (Engl Ed). 2019;55(8):414-420. English, Spanish. doi: 10.1016/j.arbres.2019.02.004.

33. Cabrera López C, Casanova Macario C, Marín Trigo JM, de-Torres JP, Sicilia Torres R, González JM, et al. Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes. Am J Respir Crit Care Med. 2018;197(4):463-469. doi: 10.1164/rccm.201707-1363OC.

34. Putcha N, Anzueto AR, Calverley PMA, Celli BR, Tashkin DP, Metzdorf N, et al. Mortality and Exacerbation Risk by Body Mass Index in Patients with COPD in TIOSPIR® and UPLIFT®. Ann Am Thorac Soc. 2021. doi: 10.1513/AnnalsATS.202006-722OC.

35. Flattet Y, Garin N, Serratrice J, Perrier A, Stirnemann J, Carballo S. Determining prognosis in acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:467-475. doi: 10.2147/COPD.S122382.

36. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. Thorax. 2015;70(5):482-9. doi: 10.1136/thoraxjnl-2014-206084.

37. Olloquequi J, Jaime S, Parra V, Cornejo-Córdova E, Valdivia G, Agustí À, et al. Comparative analysis of COPD associated with tobacco smoking, biomass smoke

exposure or both. Respir Res. 2018;19(1):13. doi: 10.1186/s12931-018-0718-y.

38. Pezzuto A, Carico E. Effectiveness of smoking cessation in smokers with COPD and nocturnal oxygen desaturation: Functional analysis. Clin Respir J. 2020;14(1):29-34. doi: 10.1111/crj.13096.

39. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet. 2018;391(10131):1706-1717. doi: 10.1016/S0140-6736(18)30841-9.

40. Fang L, Gao P, Bao H, Tang X, Wang B, Feng Y, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med. 2018;6(6):421-430. doi: 10.1016/S2213-2600(18)30103-6.

41. Han MZ, Hsiue TR, Tsai SH, Huang TH, Liao XM, Chen CZ. Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3425-3433. doi: 10.2147/COPD.S179048.

42. Hu YH, Liang ZY, Xu LM, Xu WH, Liao H, Li R, et al. Comparison of the clinical characteristics and comprehensive assessments of the 2011 and 2017 GOLD classifications for patients with COPD in China. Int J Chron Obstruct Pulmon Dis. 2018;13:3011-3019. doi: 10.2147/COPD.S174668.

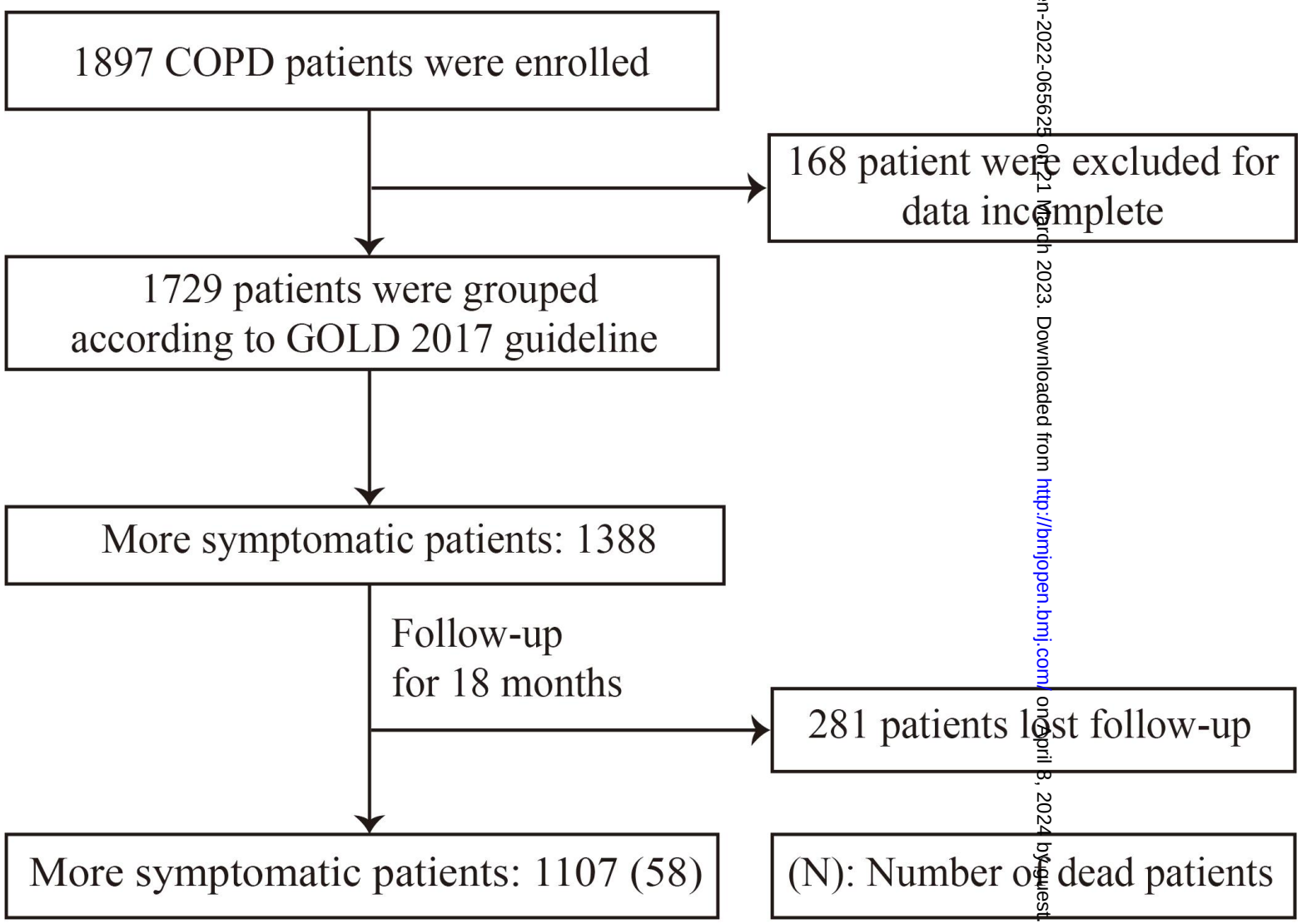
43. Zha Z, Leng R, Xu W, Bao H, Chen Y, Fang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in Anhui Province, China: a population-based survey. BMC Pulm Med. 2019;19(1):102. doi: 10.1186/s12890-019-0864-0.

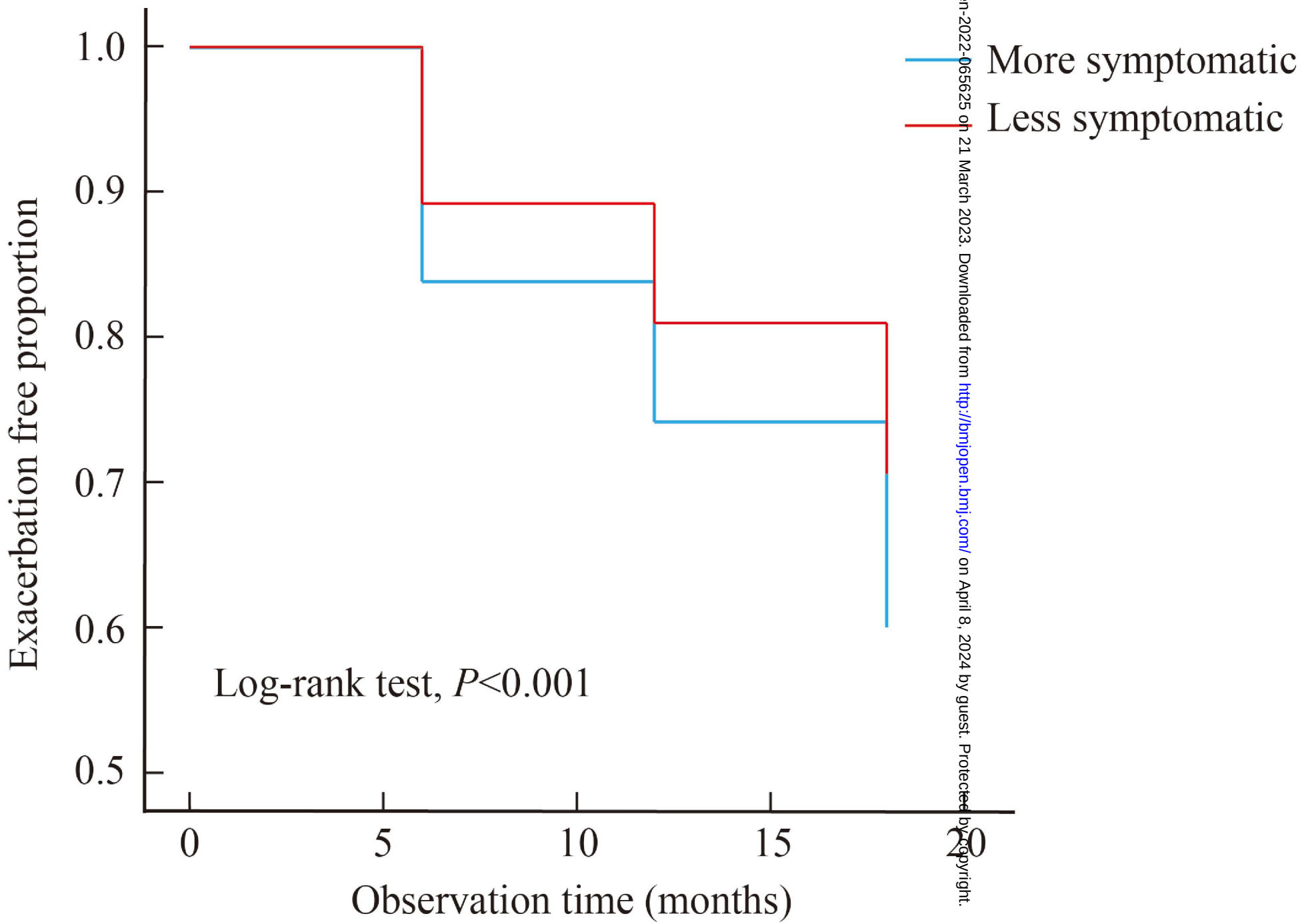
Figure captions

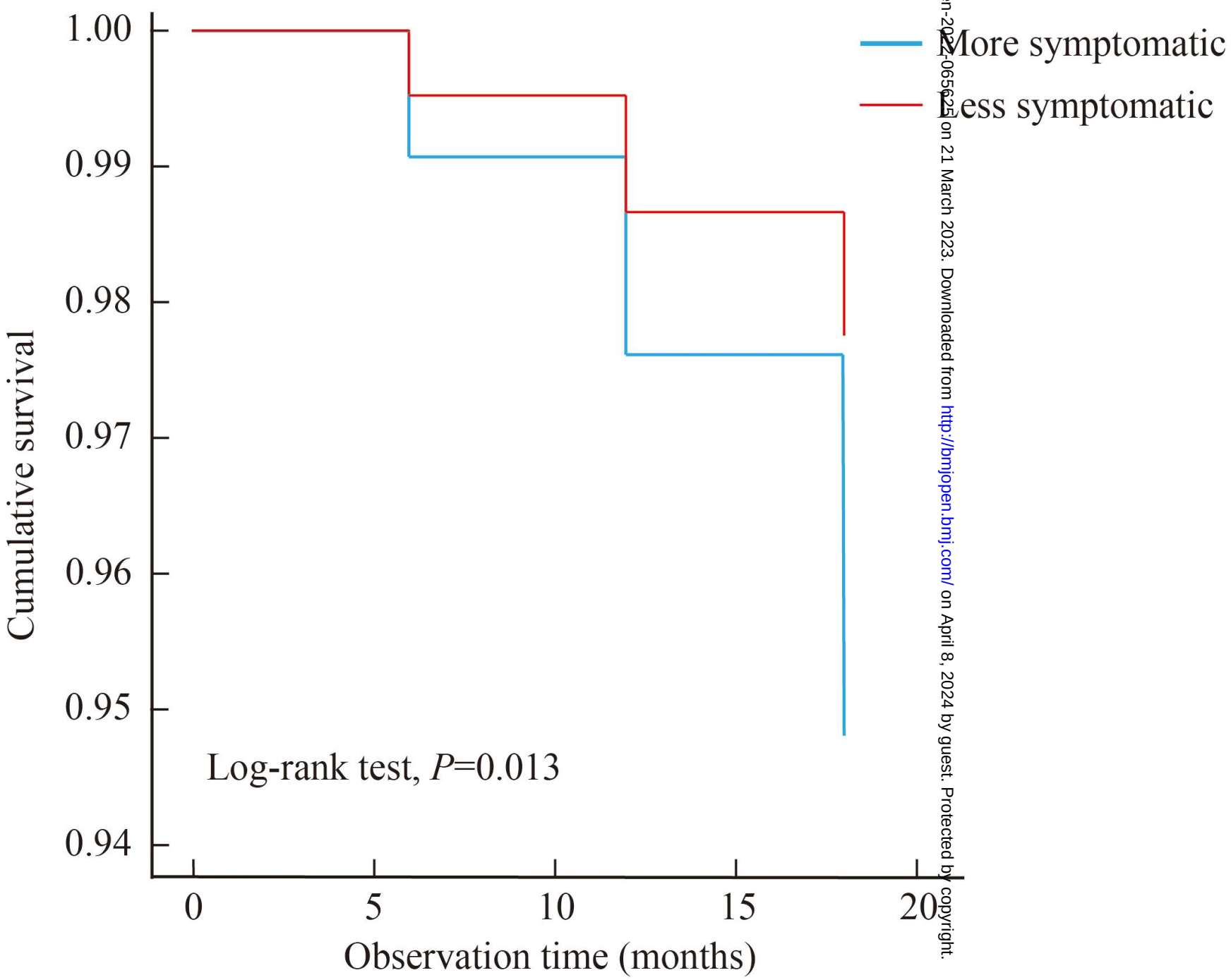
Figure 1. Flow chart. COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Figure 2. Kaplan-Meier curves of the exacerbation free proportion between more and less symptomatic COPD patients; $P < 0.05$ was considered to be statistically significant. COPD, Chronic Obstructive Pulmonary Disease.

Figure 3. Kaplan-Meier curves of the overall survival between more and less symptomatic COPD patients; $P < 0.05$ was considered to be statistically significant. COPD, Chronic Obstructive Pulmonary Disease.







Supplementary Table 1. Exacerbation and mortality after 18 months of follow-up in COPD patients with different smoke history.

Variables	Never-smoker (n = 234)	Former-smoker (n = 478)	Current-smoker (n = 695)	*P* - value
Exacerbations (Median, IQR)	0 (1)	0 (1)	1 (1) [a,b]	0.008
Exacerbations, n (%)				0.006
0	178 (73.6)	327 (70.2)	438 (66.1) [a,b]	
1	28 (13.2)	63 (14.4)	108 (16.3)	
≥2	22 (13.2)	61 (15.4)	117 (17.6) [a,b]	
Hospitalizations (Median, IQR)	0 (0)	0 (1)	0 (1) [a,b]	0.045
Hospitalizations, n (%)				0.035
0	182 (79.8)	361 (78.8)	480 (73.2) [a,b]	
≥1	46 (20.2)	97 (21.2)	176 (26.8) [a,b]	
Mortality, n (%)	6 (2.6)	20 (4.2)	39 (5.6)	0.135

Notes: [a] Compared with the Never-smoker, $P < 0.05$; b Compared with the Former-smoker, $P < 0.05$.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease.

Supplementary Table 2. Exacerbation and mortality after 18 months of follow-up in COPD patients with different amounts of smoking.

Variables	< 10 pack/year (n = 239)	≥ 10 pack/year (n = 1168)	*P* - value
Exacerbations (Median, IQR)	0 (1)	0 (1)	0.306
Exacerbations, n (%)			0.949
0	147 (62.8)	692 (62.5)	
1	39 (16.7)	194 (17.5)	
≥2	48 (20.5)	222 (20.0)	
Hospitalizations (Median, IQR)	0 (0)	0 (0)	0.753
Hospitalizations, n (%)			0.298
0	180 (76.9)	816 (73.6)	
≥1	54 (23.1)	292 (26.4)	
Mortality, n (%)	5 (2.5)	60 (5.1)	0.045

Note: COPD, Chronic Obstructive Pulmonary Disease.

Supplementary Table 3. The baseline characteristics of more symptomatic COPD patients who remained in the study and lost to follow-up.

Variables	More symptomatic patients (n=1388)		*P* - value
	A_1 (n=1107)	A_2 (n=281)	
Age (years)	65.5 ± 8.0	65.6 ± 8.0	0.813
Sex, n (%)			0.892
Male	988 (89.3)	250 (89.0)	
Female	119 (10.7)	31 (11.0)	
Education level, n (%)			0.158
Primary school	455 (41.1)	130 (46.3)	
Junior high school	428 (38.7)	88 (31.3)	
High school	173 (15.7)	49 (17.4)	
University	51 (4.6)	14 (5.0)	
BMI (kg/m^2)	22.3 ± 3.7	22.5 ± 3.7	
Smoke history, n (%)			0.290
Never-smoker	187 (16.9)	53 (18.9)	
Former-smoker	385 (34.8)	84 (29.9)	
Current-smoker	535 (48.3)	144 (51.2)	
Smoking, (pack/year) (Median, IQR)	35 (30)	40 (30)	0.433
Biofuel exposure, n (%)			0.493
Yes	440 (39.8)	118 (42.0)	
No	667 (60.2)	163 (58.0)	
Occupational exposure, n (%)			0.629
Yes	416 (37.6)	110 (39.1)	
No	691 (62.4)	171 (60.9)	
Pulmonary function, (Mean ± SD)			
FEV1	1.8 ± 0.5	1.2 ± 0.5	0.908
FEV1 %pred	48.6 ± 19.0	49.5 ± 19.1	0.480
FVC	2.6 ± 0.7	2.6 ± 0.7	0.439
FEV1/FVC	44.4 ± 12.2	44.7 ± 12.1	0.664
PEF	3.2 ± 1.4	3.1 ± 1.4	0.498
GOLD grade, n (%)			0.706
1	71 (6.4)	19 (6.8)	
2	408 (36.9)	110 (39.1)	
3	427 (38.6)	109 (38.8)	
4	201 (18.1)	43 (15.3)	
CAT, (Mean ± SD)	17.6 ± 5.4	17.3 ± 5.2	0.400
mMRC, (Median, IQR)	2 (1)	2 (1)	0.885
CCQ, (Mean ± SD)	23.7 ± 6.5	23.2 ± 6.4	0.206
Treatments, n (%)			
LAMA	363 (32.8)	101 (35.9)	0.317
LABA + ICS	82 (7.4)	15 (5.3)	0.224
LAMA + LABA	24 (2.2)	3 (1.1)	0.233

LAMA + LABA + ICS	558 (50.4)	137 48.8)	0.621
Exacerbations in the past year, (Median, IQR)	1 (2)	1 (2)	0.603
Hospitalizations in the past year, (Median, IQR)	0 (1)	0 (1)	0.467

Notes: A_1: The COPD patients who remained in the study after 18 months of follow-up; A_2: The COPD patients who lost to follow-up.

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) If applicable, explain how loss to follow-up was addressed	6-8
		(*e*) Describe any sensitivity analyses	6-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-11
		(b) Give reasons for non-participation at each stage	8-11
		(c) Consider use of a flow diagram	8-11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-11
		(b) Indicate number of participants with missing data for each variable of interest	8-11
		(c) Summarise follow-up time (eg, average and total amount)	8-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(*b*) Report category boundaries when continuous variables were categorized	8-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Clinical-functional characteristics and risk of exacerbation and mortality in more symptomatic patients with chronic obstructive pulmonary disease: A prospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065625.R1
Article Type:	Original research
Date Submitted by the Author:	16-Jan-2023
Complete List of Authors:	Song, Qing; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Lin, Ling; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Cheng, Wei; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Li, Xueshan; The Second Xiangya Hospital of Central South University Zeng, Yu-Qin; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Liu, Cong; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Deng, Min-Hua; PLA Rocket Force Characteristic Medical Center, Department of Respiratory Liu, Dan; The Eighth Hospital in Changsha, Department of Respiratory Yu, Zhi-Ping; Longshan Hospital of Traditional Chinese Medicine, Department of Respiratory Li, Xin; Central South University Ma, Li-Bing; Affiliated Hospital of Guilin Medical University, Department of respiratory and critical care medicine Chen, Yan; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Cai, Shan; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Chen, Ping; Central South University, Department of Respiratory and Critical Care Medicine; Central South University
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Smoking and tobacco, Medical management
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Respiratory physiology < THORACIC MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Title: Clinical-functional characteristics and risk of exacerbation and mortality in more symptomatic patients with chronic obstructive pulmonary disease: A prospective study

Authors: Qing Song[1,2,3], Ling Lin[1,2,3], Wei Cheng[1,2,3], Xue-Shan Li[1,2,3], Yu-Qin Zeng[1,2,3], Cong Liu[1,2,3], Min-Hua Deng[4], Dan Liu[5], Zhi-Ping Yu[6], Xin Li[7], Li-Bing Ma[8], Yan Chen[1,2,3], Shan Cai[1,2,3], Ping Chen[1,2,3]

Affiliations:[1]Department of Respiratory and Critical Care Medicine, the Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China.

[2]Research Unit of Respiratory Disease, Central South University, Changsha, Hunan 410011, China.

[3]Diagnosis and Treatment Center of Respiratory Disease, Central South University, Changsha, Hunan 410011, China.

[4]Department of Respiratory, PLA Rocket Force Characteristic Medical Center, Beijing 100088, China.

[5]Department of Respiratory, The Eighth Hospital in Changsha, Hunan 410000, China.

[6]Department of Respiratory, Longshan Hospital of Traditional Chinese Medicine, Hunan 410000, China.

[7]Division 4 of Occupational Disease, Hunan Occupational Disease Prevention and Treatment Hospital, Changsha, Hunan 410000, China.

[8]Department of respiratory and critical care medicine, Affiliated Hospital of Guilin Medical University, Guilin, Guangxi 541000, China.

Corresponding author: Ping Chen, Department of Respiratory and Critical Care Medicine, the Second Xiangya Hospital, Central South University, 139 Renmin Middle

Road, Changsha, Hunan 410011, China. Tel +86 731 8529 5248; Fax +86 731 8529 5848.

Email: pingchen0731@csu.edu.cn

Abstract

Objectives: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 classified chronic obstructive pulmonary disease (COPD) patients into a more symptomatic group. Our purpose was to analyze the clinical characteristics and risk of exacerbation and mortality in more symptomatic patients.

Methods: This prospective study enrolled 1729 stable COPD patients from a database setup by the Second Xiangya Hospital of Central South University. Then, the patients were classified into a more symptomatic group based on GOLD 2017 report. All patients were followed up for 18 months. We collected baseline data and recorded the number of exacerbations, hospitalizations and mortality during follow-up.

Results: The more symptomatic patients were older, had higher Clinical COPD Questionnaire (CCQ) score, more severe airflow limitation and a higher number of exacerbations and hospitalizations in the past year ($P < 0.05$). Logistic regression showed that having more symptoms correlated with the CCQ score and exacerbations in the past year ($P < 0.05$). After patients were followed up, there were higher numbers of exacerbations, hospitalizations and mortality rates in more symptomatic patients ($P < 0.05$). The multivariate model showed that age (OR = 1.050, 95% CI = 1.012-1.090), smoking (OR = 1.012, 95% CI = 1.003-1.020), and COPD assessment test score (OR = 1.101, 95% CI = 1.049-1.155) were independently risk factors for mortality, whereas current-smoker (OR = 1.411, 95% CI = 1.066-1.869), modified Medical Research Council score (OR = 1.301, 95% CI = 1.131-1.497) and exacerbations in the past year (OR = 1.081, 95% CI = 1.035-1.130) were independently risk factors for exacerbation in more symptomatic patients ($P < 0.05$).

Conclusions: More symptomatic COPD patients have worse outcomes. In addition, several independent risk factors for exacerbation and mortality were identified. Therefore, clinicians should be aware of these risk factors and take them into account during interventions.

Keywords: COPD, More symptomatic, Mortality, Exacerbation, GOLD

Strengths and limitations of this study

- This study used the realistic data to reveal that the symptomatic COPD patients have worse pulmonary function and outcomes.
- Also, we explore several independent risk factors for future exacerbation and mortality in more symptomatic COPD patients.
- The main limitation is that there are 281 more symptomatic COPD patients lost to contact during follow-up and data on comorbidities were lacking.

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious chronic respiratory disease that typically features persistent respiratory symptoms, such as cough, expectoration and dyspnea. This disease has brought a huge burden of mortality to humanity [1-2] and therefore prevention and treatment are urgent.

Breathlessness, cough and sputum production are common symptoms of COPD, bringing a huge burden to patients. Some may experience deterioration of their symptoms and need additional treatment [3]. The COPD assessment test (CAT) and modified Medical Research Council (mMRC) scale cover several dimensions, such as dyspnea, cough, expectoration, confidence, limitation of daily activities and chest tightness, and are used as indicators to measure the effect of symptoms on the health of COPD patients [4-5]. The higher the CAT and mMRC scores, the more symptoms the patients have and the greater the impact on patients' health [6]. Ding et al. [7] found that as the CAT score increased, the frequency of primary care physician visits also increased. Kim et al. [8] found that COPD patients with increased mMRC scores had a higher risk of exacerbation, more severe airflow limitation and respiratory symptoms when compared with patients with unchanged mMRC scores after 1 year of follow-up. In addition, one study showed that the BODE (body mass index (BMI), airflow obstruction, dyspnea, exercise capacity) index includes dyspnea as a meaningful marker of future exacerbation risk [9]. In fact, some COPD patients only experience cough or breathlessness, whereas others have multiple respiratory symptoms, including cough, expectoration, chest tightness and dyspnea.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 evaluated COPD patients based on the CAT/mMRC and exacerbation risk to better guide the treatment, dividing patients into more symptomatic and less symptomatic groups [10]. A Japanese study found that the COPD patients in the more symptomatic group were older and had more severe airflow limitation and higher exacerbation rates according to the GOLD 2017 classification; however, the number of more symptomatic patients in this study was small [11]. Several studies have shown that the more symptomatic COPD patients account for the majority [12-15]. In addition, Cabrera López et al. [16] found that the risk of mortality was higher in Groups B and D than in Groups A and C according to the GOLD 2017 classification. However, the clinical characteristics and outcomes in the more symptomatic COPD patients remained unclear. Therefore, our purpose was to analyze the clinical-functional characteristics and related risk factors, as well as the risk of future exacerbation and mortality in the more symptomatic COPD patients.

Methods

Study participants

We conducted a prospective study that captured the patients listed from September 2017 to December 2019 in the outpatient COPD database (Register number: ChiCTR-POC-17010431; http://120.77.177.175:9007/a/login), which includes the Second Xiangya Hospital of Central South University, the Zhuzhou Central Hospital, the Hunan Prevention and Treatment Institute for Occupational Diseases, the First Attached Hospital of Shaoyang University, the Eighth Hospital in Changsha and the Longshan Hospital of Traditional Chinese Medicine (Hunan, China). The inclusion criterion for COPD patients was a ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) of <

0.70 after bronchodilator administration. Patients with interstitial lung disease, bronchiectasis, pneumonia, asthma, pleural effusion, lung cancer or active tuberculosis were excluded from the study.

We confirm that this study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. All patients in this study were provided written informed consent.

Patient and public involvement

Patients and the public were not involved in the conception of this study, development of the research question, interpretation of the results or manuscript writing.

Study procedures

All included COPD patients underwent 18 months of follow-up. Furthermore, at the 6, 12 and 18 months, we recorded the number of exacerbations, hospitalizations and deaths among these patients. According to the GOLD 2017 report, the COPD patients were assigned to more and less symptomatic groups. Briefly, the more symptomatic group was defined by mMRC scores ≥ 2 and/or CAT scores ≥ 10, with or without a history of exacerbations and hospitalizations. The less symptomatic group was defined by mMRC scores < 2 and CAT scores < 10, with or without a history of exacerbations and hospitalizations [10].

Data collection and definitions

The baseline clinical characteristics included demographics, smoke history, biofuel and occupational exposure history, pulmonary function results, symptoms scores (including CAT and mMRC), Clinical COPD Questionnaire (CCQ) score, treatment regimens and

number of exacerbations and hospitalizations in the past year. Furthermore, we recorded mortality, and the number of exacerbations and hospitalizations during follow-up.

A current-smoker was defined as having a smoking exposure of more than 10 packs/year, whereas a former-smoker was defined as having a smoking exposure of at least 10 packs/year, but with smoking cessation for more than half a year [17]. An exacerbation was defined as disease progression that requires antibiotics, oral corticosteroids or hospitalization for treatment or was determined by a sputum color change (to green or yellow) [18]. Biofuel exposure was defined as continuous exposure to biofuels for at least 2 hours a day, for at least one year. Occupational exposure was defined as exposure to dust, metals, chemical substances or other environmental agents for at least eight hours a day for at least one year [19]. According to the GOLD 2017 report, GOLD stage 1 (FEV1 ≥ 80 %pred), GOLD stage 2 (FEV1 50-79 %pred), GOLD stage 3 (FEV1 30-49 %pred) and GOLD stage 4 (FEV1 < 30 %pred) [10]. Oxygen therapy included home oxygen therapy and non-invasive positive pressure ventilation in this study [20].

The pulmonary function test was measured by a spirometer (MasterScreen-Body/Diff, CareFusion, Germany) according to the American Thoracic Society guidelines. FEV1 was defined as the time in seconds, measured from Time 0 to 1, of the expiration after maximal forced inspiration. FVC was defined as the largest expiration volume immediately after maximal forced inspiration. Peak expiratory flow (PEF) was defined as the highest flow achieved from a maximum forced expiratory maneuver started without hesitation from a position of maximal lung inflation [21].

Statistical analysis

Continuous variables were presented as the mean ± standard deviation (SD). The Chi-squared and Fisher's tests were used to analyze categorical variables. An independent-sample Student's *t*-test was used to analyze continuous variables. For variables with non-normal distribution or uneven variance, we used non-parametric tests. The variously adjusted odds ratio was calculated using multivariate logistic regression. Two-sided *P* values of < 0.05 were considered to be statistically significant. SPSS version 26.0 (IBM, Armonk, NY, USA) was used to perform all statistical analyses.

Results

Baseline characteristics

A total of 1729 patients with COPD were included (Figure 1). The mean age was 65.1 ± 8.2 years, 89.1% were male and more than half of the patients were current-smokers. Most of the patients were in GOLD stages 2-3 and treatment with a long-acting muscarinic antagonist (LAMA), LAMA + long-acting β2-agonist (LABA) + inhaled corticosteroid (ICS). The mean CAT and CCQ scores were 15.4 ± 6.6 and 21.9 ± 7.2, respectively. Most patients suffered from an exacerbation and hospitalization less than once per year (Table 1).

Table 1. The baseline characteristics of the COPD patients.

Variables	Total (n = 1729)
Age (years)	65.1 ± 8.2
Sex, n (%)	
Male	1541 (89.1)
Female	188 (10.9)
Education level, n (%)	
Primary school	713 (41.2)
Junior high school	618 (35.8)
High school	289 (16.7)
University	108 (6.3)

BMI (kg/m^2)	22.5 ± 3.6
Smoke history, n (%)	
Never-smoker	288 (16.7)
Former-smoker	576 (33.3)
Current-smoker	865 (50.0)
Smoking, (packs/year), (Mean ± SD)	37.4 ± 28.2
Biofuel exposure, n (%)	
Yes	660 (38.2)
No	1069 (61.8)
Occupational exposure, n (%)	
Yes	659 (38.1)
No	1070 (61.9)
Pulmonary function, (Mean ± SD)	
FEV1	1.3 ± 0.6
FEV1 %pred	52.1 ± 20
FVC	2.7 ± 0.7
FEV1/FVC	46.5 ± 16.1
PEF	3.5 ± 1.6
GOLD stages, n (%)	
1	171 (9.9)
2	709 (41.0)
3	596 (34.5)
4	253 (14.6)
CAT, (Mean ± SD)	15.4 ± 6.6
mMRC, (Mean ± SD)	2.1 ± 1.0
CCQ, (Mean ± SD)	21.9 ± 7.2
Treatments, n (%)	
LAMA	622 (36.0)
LABA + ICS	136 (7.9)
LAMA + LABA	33 (1.9)
LAMA + LABA + ICS	797 (46.1)
Oxygen therapy, n (%)	
Yes	121 (7.0)
No	1608 (93.0)
Exacerbations in the past year, (Mean ± SD)	1.7 ± 3.1
Exacerbations in the past year, n (%)	
0	753 (43.6)
1	412 (23.8)
≥2	564 (32.6)
Hospitalizations in the past year, (Mean ± SD)	0.7 ± 1.3
Hospitalizations in the past year, n (%)	

0	1132 (65.5)
≥1	597 (34.5)

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow; SD, Standard Deviation.

According to the GOLD 2017 report, 1388 (80.3%) were more symptomatic patients. These patients were older (65.5 ± 8.0 vs 63.4 ± 8.8 years, $P < 0.001$) and had lower education level, BMI, FEV1, FEV1 %pred, FVC, FEV1/FVC and PEF ($P < 0.001$). In addition, a higher proportion of biofuel exposure history, GOLD stages 3-4 patients, treatment with LAMA+LABA+ICS and oxygen therapy in more symptomatic group ($P < 0.001$). Furthermore, more symptomatic COPD patients had higher CCQ scores and a higher number of exacerbations and hospitalizations in the past year ($P < 0.001$) (Table 2).

Table 2. The clinical characteristics of more symptomatic COPD patients.

Variables	More symptoms (n = 1388)	Less symptoms (n = 341)	*P* - value
Age (years)	65.5 ± 8.0	63.4 ± 8.8	<0.001
Sex, n (%)			0.858
Male	1238 (89.2)	303 (88.9)	
Female	150 (10.8)	38 (11.1)	
Education level, n (%)			<0.001
Primary school	585 (42.1)	128 (37.5)	
Junior high school	516 (37.2)	102 (29.9)	
High school	222 (16.0)	67 (19.6)	
University	65 (4.7)	44 (13.0)	
BMI (kg/m^2)	22.3 ± 3.7	23.2 ± 3.1	<0.001
Smoke history, n (%)			0.142
Never-smoker	240 (17.3)	48 (14.1)	
Former-smoker	469 (33.8)	107 (31.4)	
Current-smoker	679 (48.9)	186 (54.5)	

Smoking, (packs/year) (Mean ± SD)	37.2 ± 28.3	38.0 ± 27.9	0.629
Biofuel exposure, n (%)			<0.001
Yes	558 (40.2)	102 (29.9)	
No	830 (59.8)	239 (70.1)	
Occupational exposure, n (%)			0.706
Yes	526 (37.9)	133 (39)	
No	862 (62.1)	208 (61)	
Pulmonary function, (Mean ± SD)			
FEV1	1.2 ± 0.5	1.7 ± 0.6	<0.001
FEV1 %pred	48.7 ± 19.0	65.7 ± 19.4	<0.001
FVC	2.6 ± 0.7	3.1 ± 0.8	<0.001
FEV1/FVC	44.4 ± 12.2	54.9 ± 12.9	<0.001
PEF	3.2 ± 1.4	4.7 ± 1.9	<0.001
GOLD stages, n (%)			<0.001
1	90 (6.5)	81 (23.8)	
2	518 (37.3)	191 (56.0)	
3	536 (38.6)	60 (17.6)	
4	244 (17.6)	9 (2.6)	
CAT, (Mean ± SD)	17.6 ± 5.3	6.5 ± 2.2	<0.001
mMRC, (Mean ± SD)	2.3 ± 0.9	1.2 ± 0.8	<0.001
CCQ, (Mean ± SD)	23.6 ± 6.5	15.1 ± 5.8	<0.001
Treatments, n (%)			
LAMA	464 (33.4)	158 (46.3)	<0.001
LABA + ICS	97 (7.0)	39 (11.4)	0.006
LAMA + LABA	27 (1.9)	6 (1.8)	0.822
LAMA + LABA + ICS	695 (50.1)	102 (29.9)	<0.001
Oxygen therapy, n (%)			0.001
Yes	111 (8.0)	10 (2.9)	
No	1277 (92.0)	331 (97.1)	
Exacerbations in the past year, (Mean ± SD)	1.9 ± 3.3	0.8 ± 1.8	<0.001
Exacerbations in the past year, n (%)			<0.001
0	555 (40.0)	198 (58.1)	
1	325 (23.4)	87 (25.5)	
≥2	508 (36.6)	56 (16.4)	
Hospitalizations in the past year, (Mean ± SD)	0.7 ± 1.4	0.3 ± 0.8	<0.001
Hospitalizations in the past year, n (%)			<0.001
0	872 (62.8)	260 (76.2)	
≥1	516 (37.2)	81 (23.8)	

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung

Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow; SD, Standard Deviation.

Multivariate analysis of risk factors associated with more symptomatic COPD patients

Results were adjusted for age, education level, biofuel exposure, FEV1, FEV1 %pred, FVC, GOLD stages and BMI. Logistic regression analysis showed that FEV1/FVC and PEF were negatively correlated with the more symptomatic, with an OR of 0.980 (95% CI = 0.964 - 0.995) and 0.774 (95% CI = 0.688 - 0.872), respectively ($P < 0.05$). However, CCQ and exacerbations in the past year were positively correlated with the more symptomatic, with an OR of 1.200 (95% CI = 1.169 - 1.232) and 1.114 (95% CI = 1.025 - 1.211), respectively ($P < 0.05$) (Table 3).

Table 3. Multivariate analysis of risk factors associated with more symptomatic COPD patients.

Variables	OR	95% CI	*P* - value
FEV1/FVC	0.980	0.964 – 0.995	0.010
PEF	0.774	0.688 – 0.872	<0.001
CCQ	1.200	1.169 – 1.232	<0.001
Exacerbations in the past year	1.114	1.025 - 1.211	0.011

Notes: After adjusted for age, education level, biofuel exposure, FEV1, FEV1 %pred, FVC, GOLD stages, BMI and hospitalizations in the past year. $P < 0.05$ are statistically significant in accordance with Logistic regression analysis.
Abbreviations: BMI, Body Mass Index; CI, Confidence interval; COPD, Chronic Obstructive Pulmonary Disease; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PEF, Peak Expiratory Flow; OR, Odds Ratio.

Exacerbation and mortality after 18 months of follow-up

As shown in Table 4, after 18 months of follow-up, a total of 1407 patients were included. The mean values for exacerbations and hospitalizations were 0.7 ± 1.3 and 0.4 ± 0.8

respectively. Most of the patients suffered an exacerbation and hospitalization less than once per year and the mortality rate was 4.6%.

Table 4. Exacerbation and mortality after 18 months of follow-up in more symptomatic COPD patients.

Variables	Total (n = 1407)	More symptomatic (n = 1107)	Less symptomatic (n = 300)	*P* - value
Exacerbations, (Mean ± SD)	0.7 ± 1.3	0.8 ± 1.4	0.5 ± 1.1	<0.001
Exacerbations, n (%)				<0.001
0	836 (62.2)	621 (59.2)	215 (73.4)	
1	259 (19.4)	217 (20.7)	42 (14.3)	
≥2	247 (18.4)	211 (20.1)	36 (12.3)	
Hospitalizations, (Mean ± SD)	0.4 ± 0.8	0.4 ± 0.9	0.2 ± 0.6	<0.001
Hospitalizations, n (%)				0.001
0	1004 (77.7)	762 (72.6)	242 (82.6)	
≥1	338 (22.3)	287 (27.4)	51 (17.4)	
Mortality, n (%)	65 (4.6)	58 (5.2)	7 (2.3)	0.033

Note: COPD, Chronic Obstructive Pulmonary Disease; SD, Standard Deviation.

After 18 months of follow-up, 1107 more symptomatic COPD patients were analyzed for future exacerbation and mortality. The results show that the more symptomatic COPD patients suffered from a higher number of exacerbations and hospitalizations ($P < 0.001$). The proportion of more symptomatic patients who suffered from exacerbations and hospitalizations at least once per year was higher ($P < 0.001$), with rates of 40.8% and 27.4%, respectively. Comparison of the exacerbation free proportion using a Kaplan–Meier curve revealed that there was a significant difference between the more and less symptomatic patients ($P < 0.001$) (Figure 2). In addition, 58 (5.2%) more symptomatic COPD patients died during the 18 months of follow-up, which is a higher number than in the less symptomatic group ($P < 0.001$). Comparison of overall survival using the

Kaplan–Meier curve revealed that survival was significantly different between the more and less symptomatic patients ($P = 0.013$) (Figure 3).

Univariate and stepwise multivariate analysis of risk factors for mortality in more symptomatic COPD patients

Of the 1107 more symptomatic COPD patients, 58 died during follow-up. Univariate analysis showed that there were several risk factors for mortality, including age (OR = 1.057, 95% CI = 1.021-1.095, $P = 0.002$), smoking (packs/year) (OR = 1.012, 95% CI = 1.003-1.020, $P = 0.005$), CAT score (OR = 1.102, 95% CI = 1.054-1.151, $P < 0.001$), mMRC score (OR = 1.490, 95% CI = 1.107-2.006, $P = 0.009$), CCQ score (OR = 1.091, 95% CI = 1.048-1.137, $P < 0.001$), exacerbations in the past year (OR = 1.057, 95% CI = 1.001-1.117, $P = 0.049$) and hospitalizations in the past year (OR = 1.143, 95% CI = 1.014-1.289, $P = 0.029$). The multivariate model showed that age (OR = 1.050, 95% CI = 1.012-1.090, $P = 0.010$), smoking (packs/year) (OR = 1.012, 95% CI = 1.003-1.020, $P = 0.006$), and CAT score (OR = 1.101, 95% CI = 1.049-1.155, $P < 0.001$) were independently associated with mortality in more symptomatic COPD patients (Table 5).

Table 5. Univariate and stepwise multivariate analysis of risk factors for mortality in more symptomatic COPD patients.

Variables	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.057	1.021-1.095	0.002	1.050	1.012-1.090	0.010
Sex						
Male	Reference					
Female	0.439	0.135-1.425	0.170			
Education level						
Primary school	Reference			Reference		
Junior high school	0.372	0.194-0.714	0.003	0.446	0.227-1.352	0.328
High school	0.655	0.308-1.394	0.272	0.710	0.323-1.561	0.394
University	0.239	0.032-1.781	0.162	0.331	0.043-2.543	0.288
BMI	0.950	0.881-1.023	0.173			
Smoke history						

Former-smoker	Reference					
Never-smoker	0.517	0.196-1.362	0.182			
Current-smoker	1.363	0.782-2.374	0.275			
Smoking (packs/year)	1.012	1.003-1.020	0.005	1.012	1.003-1.020	0.006
Biofuel exposure						
Yes	Reference					
No	0.736	0.416-1.302	0.292			
Occupational exposure						
Yes	Reference					
No	0.642	0.378-1.089	0.100			
Pulmonary function						
FEV1	0.713	0.407-1.246	0.235			
FEV1 %pred	1.000	0.986-1.014	0.993			
FVC	0.573	0.387-0.848	0.005	0.738	0.431-1.263	0.267
FEV1/FVC	1.013	0.991-1.034	0.246			
PEF	0.898	0.731-1.102	0.303			
GOLD stages						
1	0.314	0.071-1.394	0.128	0.489	0.106-2.241	0.357
2	0.676	0.355-1.290	0.304	0.930	0.462-1.873	0.838
3	0.394	0.193-0.806	0.011	0.398	0.191-0.830	0.014
4	Reference			Reference		
CAT	1.102	1.054-1.151	<0.001	1.101	1.049-1.155	<0.001
mMRC	1.490	1.107-2.006	0.009	0.945	0.647-1.382	0.772
CCQ	1.091	1.048-1.137	<0.001	1.034	0.982-1.088	0.202
Treatments						
LAMA	0.918	0.519-1.625	0.770			
LABA + ICS	0.670	0.205-2.189	0.507			
LAMA + LABA	2.670	0.773-9.225	0.121			
LAMA + LABA + ICS	1.057	0.623-1.794	0.837			
Oxygen therapy						
No	Reference					
Yes	1.526	0.986-2.363	0.058			
Exacerbations in the past year	1..057	1.001-1.117	0.049	1.016	0.931-1.108	0.721
Hospitalizations in the past year	1.143	1.014-1.289	0.029	1.084	0.925-1.270	0.317

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow, OR = Odds Ratio, CI = Confidence Interval.

Univariate and stepwise multivariate analysis of risk factors for future exacerbation in more symptomatic COPD patients

In total, 428 of 1107 more symptomatic COPD patients suffered from exacerbation during follow-up. Univariate analysis showed that there were several risk factors for future exacerbation, including age (OR = 1.019, 95% CI = 1.003-1.035, *P* = 0.017), being a current-smoker (OR = 1.480, 95% CI = 1.125-1.948, *P* = 0.005), CAT score (OR = 1.043, 95% CI = 1.019-1.067, *P* < 0.001), mMRC score (OR = 1.375, 95% CI = 1.199-1.576, *P* < 0.001), CCQ score (OR = 1.025, 95% CI = 1.006-1.045, *P* = 0.012), exacerbations in the past year (OR = 1.098, 95% CI = 1.049-1.149, *P* < 0.001) and hospitalizations in the past year (OR = 1.208, 95% CI = 1.094-1.335, *P* < 0.001). The multivariate model showed that being a current-smoker (OR = 1.411, 95% CI = 1.066-1.869, *P* = 0.016), mMRC score (OR = 1.301, 95% CI = 1.131-1.497, *P* < 0.001) and exacerbations in the past year (OR = 1.081, 95% CI = 1.035-1.130, *P* = 0.001) were independently associated with future exacerbation in more symptomatic COPD patients (Table 6).

Table 6. Univariate and stepwise multivariate analysis of risk factors for future exacerbation in more symptomatic COPD patients.

Variables	Univariate			Multivariate		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	1.019	1.003-1.035	0.017	1.002	0.985-1.020	0.810
Sex						
Male	Reference					
Female	0.749	0.500-1.123	0.162			
Education level						
Primary school	Reference			Reference		
Junior high school	0.701	0.531-0.925	0.012	0.733	0.548-0.981	0.056
High school	0.884	0.613-1.274	0.507	0.983	0.670-1.442	0.931
University	0.903	0.427-1.424	0.737	1.163	0..627-2.157	0.631
BMI	0.956	0.924-0.989	0.010	0.963	0.930-0.997	0.034
Smoke history						
Former-smoker	Reference			Reference		
Never-smoker	1.064	0.751-1.508	0.728	1.032	0.723-1.474	0.861
Current-smoker	1.480	1.125-1.948	0.005	1.411	1.066-1.869	0.016
Smoking (packs/year)	1.002	0.997-1.006	0.469			
Biofuel exposure						

No	Reference					
Yes	1.159	0.901-1.491	0.252			
Occupational exposure						
No	Reference					
Yes	1.065	0.826-1.373	0.627			
Pulmonary function						
FEV1	0.768	0.600-0.983	0.036	1.754	0.988-3.113	0.055
FEV1 %pred	0.994	0.988-1.001	0.093			
FVC	0.779	0.653-0.931	0.006	0.764	0.562-1.039	0.087
FEV1/FVC	0.994	0.984-1.004	0.224			
PEF	0.891	0.813-0.977	0.015	0.917	0.767-1.097	0.345
GOLD stages						
1	0.557	0.313-0.994	0.068			
2	0.699	0.490-0.997	0.100			
3	0.760	0.536-1.078	0.124			
4	Reference					
CAT	1.043	1.019-1.067	<0.001	1.009	0.978-1.040	0.590
mMRC	1.375	1.199-1.576	<0.001	1.301	1.131-1.497	<0.001
CCQ	1.025	1.006-1.045	0.012	0.993	0.970-1.017	0.585
Treatments						
LAMA	0.918	0.705-1.194	0.523			
LABA + ICS	0.660	0.404-1.078	0.097			
LAMA + LABA	0.902	0.370-2.195	0.820			
LAMA + LABA + ICS	0.813	0.635-1.041	0.100			
Oxygen therapy						
No	Reference					
Yes	1.755	0.806-3.818	0.156			
Exacerbations in the past year	1.098	1.049-1.149	<0.001	1.081	1.035-1.130	0.001
Hospitalizations in the past year	1.208	1.094-1.335	<0.001	1.080	0.967-1.206	0.170

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow, OR = Odds Ratio, CI = Confidence Interval.

Discussion

In this study, we found that the more symptomatic patients accounted for the majority, and several studies have yielded the same results [12-15]. In addition, patients with COPD in China typically do not go to the hospital until they have severe respiratory symptoms. We also found that the more symptomatic patients were older, and a similar

result was observed by Han et al. [22] Biofuel exposure is one of the main risk factors of COPD [23-24]. A study showed that compared with smoking, COPD patients with biofuel exposure experienced more dyspnea [25]. In addition, Dutt et al. [26] found that people exposed to biofuel may suffer from more respiratory symptoms. The results of our research confirmed that more symptomatic COPD patients had a higher biofuel exposure rate. Maintenance of inhalation bronchodilators and ICS could reduce respiratory symptoms and exacerbations, improve pulmonary function in patients with COPD. Our research results showed that more symptomatic patients were more likely to use triple inhalers and less likely to use monotherapy with LAMA. This was consistent with the results of Kobayashi et al. [11].

Pulmonary function is used to evaluate airflow limitation and severity of COPD patients. Our research also found that more symptomatic COPD patients had worse pulmonary function and that deterioration of pulmonary function was significantly associated with respiratory symptoms. This was consistent with a study by Boezen et al. [27], which showed that both FEV1 and PEF decreased as the number of symptoms increased and that the risk of having a FEV1 or PEF value of < 70% increased with increasing symptoms. Brodkin et al. [28] also found that cough, phlegm, wheeze and dyspnea were inversely related to pulmonary function. Another study found that initial FEV1 level was lower in patients with dyspnea appearing during follow-up than in the group without symptoms [29]. The GOLD 2013 report also recommends the CCQ as a symptom measure [30] and states that it is predictive of mortality in COPD patients [31]. Our study showed that more symptomatic patients had higher CCQ scores, which were positively correlated with more symptoms.

Exacerbation is an important risk factor for stable COPD, leading to pulmonary function decline and poor prognosis [32]. Our study found that more symptomatic patients suffered from a higher number of exacerbations in the past year. Moreover, the higher the number of exacerbations, the more symptoms the patients experienced. Miravitlles et al. [33] also found that more exacerbations in the past year was associated with variability in symptom number. In addition, Kobayashi et al. [11] found that more symptomatic patients suffered a higher number of exacerbations in the past year, which is consistent with our research. However, it is unclear whether more symptomatic patients have worse outcomes. Therefore, we performed 18 months of follow-up to observe the patients' future exacerbation and mortality. The results showed that there were higher exacerbation and hospitalization rates in more symptomatic patients, along with higher mortality rates. In addition, Kim et al. [34] found that the more symptomatic patients had significantly higher future exacerbation risk among patients with FEV1 ≥ 50%. A study by Cabrera López et al. [35] also found a similar result, with more symptomatic patients showing a higher mortality rate at 5 years of follow-up. In addition, our research results show that more symptomatic patients had a lower BMI but a higher risk of future exacerbation and mortality. This was consistent with a study by Putcha et al. [36], which showed that underweight participants had a significantly higher risk of death and severe exacerbations

Death is the most serious malignant event associated with COPD [37] and it is vital to analyze the risk factors for death in COPD patients. Our results showed that age, smoking (packs/year) and the CAT score were positively correlated with mortality. Age and smoking are important risk factors associated with COPD development [38-39], and our study also found the same result. At the same time, it implied that improved pulmonary

function, reduced respiratory symptoms and quitting smoking are important interventions to reduce the occurrence of malignant events in COPD.

Acute exacerbations are important deterioration events in patients with COPD during follow-up. Therefore, it is necessary to analyze the independent risk factors of the more symptomatic patients who suffered from exacerbation during the 18 months of follow-up in order to better guide the prevention and treatment. In this study, we found that the mMRC score, being a current-smoker and the number of exacerbations in the past year were positively correlated with future exacerbation. It is implied that the higher the mMRC score and number of exacerbations in the past year, the higher the future exacerbation risk.

Smoking is an important risk factor for COPD development [39] and it is important to demonstrate the effects of smoking on COPD exacerbation. Therefore, we further analyzed the exacerbations and mortality after 18 months of follow-up in COPD patients with different smoking histories. We found that current-smokers had a higher exacerbation and hospitalization rates than former-smokers and never-smokers (Supplementary Table 1). Furthermore, COPD patients who smoked more than 10 packs/year had higher mortality (Supplementary Table 2). This implies that smoking cessation may decrease the risk of exacerbation and mortality in COPD patients. A study by Pezzuto et al. [40] had a similar result, showing that smoking cessation notably improved pulmonary functional parameters, oxygen desaturation and the walking test, as well as decreasing the CAT scores.

This study has some limitations. First, there were 281 more symptomatic COPD patients lost to contact during follow-up. However, we found that the characteristics of the

patients lost to follow-up and those that remained in the study were not significantly different (Supplementary Table 3). Also, the number of female patients in this study was small. In fact, the prevalence of COPD differed significantly between males and females in China, with the prevalence being higher in males, mainly because smoking was the main risk factor for COPD but also because there were relatively few female patients who smoked [41-42]. Furthermore, several studies showed that the proportion of female patients was relatively small in China [43-45]. In addition, the number of patients with a low education level was higher. In fact, China is a developing country and the overall level of education is not high in early time. Finally, this study lacked data on comorbidities, which placed a symptom burden on patients with COPD and has an impact on future exacerbation and mortality.

In summary, our study revealed that the majority of COPD patients have more symptoms, which is associated with worse pulmonary function. More symptomatic patients also have worse outcomes. Reducing respiratory symptoms might improve patients' pulmonary function and outcomes. In addition, several independent risk factors for exacerbation and mortality in more symptomatic COPD patients were identified, including age, smoking, mMRC score, CAT score and exacerbations in the past year. Therefore, clinicians should be aware of the risk factors and take them into account for interventions in more symptomatic COPD patients.

Abbreviations

BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CI, Confidence interval; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global

Initiative for Chronic Obstructive Lung Disease; IQR, Interquartile Range; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, Modified Medical Research Council; OR, Odds Ratio; PEF, Peak Expiratory Flow; SD, Standard Deviation.

Funding

This work was supported by the National Natural Science Foundation of China (NSFC, Grants 81970044) and Xiangya Mingyi grant (2013).

Acknowledgments

We would like to thank the staff of the hospitals for their cooperation in collecting the study data.

Ethics approval and consent to participate

This study was approved by an institutional review board from the Second Xiangya Hospital of Central South University and conducted in accordance with the Declaration of Helsinki. This study was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR-POC-17010431). All patients in this study were provided written informed consent.

Competing interests

All authors of this study have no conflicts of interests for this work.

Author contributions

QS performed the data collection, statistical analyses, and drafted the manuscript. LL, WC, XS L, YQ Z and CL performed the data collection, statistical analyses. MH D, DL,

ZP Y, XL and LB M performed the data collection. PC, YC and SC designed, coordinated the research and helped with editing of the paper. All authors revised the article critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published.

Data sharing statement

The datasets are available in the Department of Pulmonary and Critical Care Medicine, the Second Xiangya Hospital repository (http://120.77.177.175:9007/a/login). The data that support the findings of this study are available upon reasonable request from the corresponding author Ping Chen.

References

1. Lareau SC, Fahy B, Meek P, Wang A. Chronic Obstructive Pulmonary Disease (COPD). Am J Respir Crit Care Med. 2019;199(1):P1-P2. doi: 10.1164/rccm.1991P1.
2. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585-596. doi: 10.1016/S2213-2600(20)30105-3.
3. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respir Res. 2017;18(1):67. doi: 10.1186/s12931-017-0548-3.
4. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54. doi: 10.1183/09031936.00102509.
5. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of

the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6. doi: 10.1136/thx.54.7.581.

6. Global Initiative for Chronic Obstructive Lung Disease Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease; 2020 [updated 2020 Nov 4; accessed 2020 Oct 25]. Available from: http://www.goldcopd.org/].
7. Ding B, Small M, Bergström G, Holmgren U. COPD symptom burden: impact on health care resource utilization, and work and activity impairment. Int J Chron Obstruct Pulmon Dis. 2017;12:677-689. doi: 10.2147/COPD.S123896.
8. Kim MA, Suh MK, Park J, Kim JH, Kim TH, Kim EK, et al. Impact of symptom variability on clinical outcomes in COPD: analysis of a longitudinal cohort. Int J Chron Obstruct Pulmon Dis. 2019;14:2135-2144. doi: 10.2147/COPD.S203715.
9. Praveen CK, Manu M, Mohapatra AK, Pentapati KC. Power of BODE Index in Predicting Future Exacerbations of COPD: A Prospective Observational Study in Indian Population. J Assoc Physicians India. 2019;67(4):14-16.
10. GOLD Executive Committee, Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (2017 REPORT). Available online: https://goldcopd.org/. Accessed Nov 2016.
11. Kobayashi S, Hanagama M, Ishida M, Sato H, Ono M, Yamanda S, et al. Clinical characteristics and outcomes in Japanese patients with COPD according to the 2017 GOLD classification: the Ishinomaki COPD Network Registry. Int J Chron Obstruct Pulmon Dis. 2018;13:3947-3955. doi: 10.2147/COPD.S182905.

12. Le LAK, Johannessen A, Hardie JA, Johansen OE, Gulsvik A, Vikse BE, et al. Prevalence and prognostic ability of the GOLD 2017 classification compared to the GOLD 2011 classification in a Norwegian COPD cohort. Int J Chron Obstruct Pulmon Dis. 2019;14:1639-1655. doi: 10.2147/COPD.S194019.

13. Lee SJ, Yun SS, Ju S, You JW, Cho YJ, Jeong YY, et al. Validity of the GOLD 2017 classification in the prediction of mortality and respiratory hospitalization in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2019;14:911-919. doi: 10.2147/COPD.S191362.

14. Kahnert K, Alter P, Young D, Lucke T, Heinrich J, Huber RM, et al. The revised GOLD 2017 COPD categorization in relation to comorbidities. Respir Med. 2018;134:79-85. doi: 10.1016/j.rmed.2017.12.003. Epub 2017 Dec 5.

15. Song Q, Zhao YY, Zeng YQ, Liu C, Cheng W, Deng MH, et al. The Characteristics of Airflow Limitation and Future Exacerbations in Different GOLD Groups of COPD Patients. Int J Chron Obstruct Pulmon Dis. 2021;16:1401-1412. doi: 10.2147/COPD.S309267.

16. Cabrera López C, Casanova Macario C, Marín Trigo JM, de-Torres JP, Sicilia Torres R, González JM, et al. Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes. Am J Respir Crit Care Med. 2018;197(4):463-469. doi: 10.1164/rccm.201707-1363OC.

17. Zhao YY, Liu C, Zeng YQ, Zhou AY, Duan JX, Cheng W, et al. Modified and simplified clinically important deterioration: multidimensional indices of short-term disease trajectory to predict future exacerbations in patients with chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2020;14:1753466620977376. doi:

10.1177/1753466620977376.

18. Hirschmann JV. Do bacteria cause exacerbations of COPD? Chest. 2000;118(1):193-203. doi: 10.1378/chest.118.1.193.

19. Duan JX, Cheng W, Zeng YQ, Chen Y, Cai S, Li X, et al. Characteristics of Patients with Chronic Obstructive Pulmonary Disease Exposed to Different Environmental Risk Factors: A Large Cross-Sectional Study. Int J Chron Obstruct Pulmon Dis. 2020;15:2857-2867. doi: 10.2147/COPD.S267114.

20. Zeng Y, Cai S, Chen Y, Duan J, Zhao Y, Li X, et al. Current Status of the Treatment of COPD in China: A Multicenter Prospective Observational Study. Int J Chron Obstruct Pulmon Dis. 2020;15:3227-3237. doi: 10.2147/COPD.S274024.

21. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88. doi: 10.1164/rccm.201908-1590ST.

22. Han MZ, Hsiue TR, Tsai SH, Huang TH, Liao XM, Chen CZ. Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3425-3433. doi: 10.2147/COPD.S179048.

23. Po JY, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. Thorax. 2011;66(3):232-9. doi: 10.1136/thx.2010.147884. Epub 2011 Jan 19.

24. Pathak U, Gupta NC, Suri JC. Risk of COPD due to indoor air pollution from biomass cooking fuel: a systematic review and meta-analysis. Int J Environ Health

Res. 2020;30(1):75-88. doi: 10.1080/09603123.2019.1575951.

25. Cheng LL, Liu YY, Su ZQ, Liu J, Chen RC, Ran PX. Clinical characteristics of tobacco smoke-induced versus biomass fuel-induced chronic obstructive pulmonary disease. J Transl Int Med. 2015;3(3):126-129. doi: 10.1515/jtim-2015-0012.
26. Dutt D, Srinivasa D.K, Rotti S.B, Sahai A.K. Effect of indoor air pollution on the respiratory system of women using different fuels for cooking in an urban slum of Pondicherry. Natl. Med J. India. 1996;9:113–117.
27. Boezen HM, Schouten JP, Postma DS, Rijcken B. Relation between respiratory symptoms, pulmonary function and peak flow variability in adults. Thorax. 1995;50(2):121-6. doi: 10.1136/thx.50.2.121.
28. Brodkin CA, Barnhart S, Anderson G, Checkoway H, Omenn GS, Rosenstock L. Correlation between respiratory symptoms and pulmonary function in asbestos-exposed workers. Am Rev Respir Dis. 1993;148(1):32-7. doi: 10.1164/ajrccm/148.1.32.
29. Krzyzanowski M, Camilli AE, Lebowitz MD. Relationships between pulmonary function and changes in chronic respiratory symptoms. Comparison of Tucson and Cracow longitudinal studies. Chest. 1990;98(1):62-70. doi: 10.1378/chest.98.1.62.
30. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2013.
31. Sundh J, Janson C, Lisspers K, Montgomery S, Ställberg B. Clinical COPD Questionnaire score (CCQ) and mortality. Int J Chron Obstruct Pulmon Dis. 2012;7:833-42. doi: 10.2147/COPD.S38119.

32. Dong H, Hao Y, Li D, Su Z, Li W, Shi B, et al. Risk Factors for Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Industrial Regions of China: A Multicenter Cross-Sectional Study. Int J Chron Obstruct Pulmon Dis. 2020;15:2249-2256. doi: 10.2147/COPD.S270729.

33. Miravitlles M, Izquierdo JL, Esquinas C, Pérez M, Calle M, López-Campos JL, et al. The variability of respiratory symptoms and associated factors in COPD. Respir Med. 2017;129:165-172. doi: 10.1016/j.rmed.2017.06.017.

34. Kim J, Lee CH, Lee MG, Shin KC, Yoo KH, Lim SY, et al. Acute Exacerbation According to GOLD 2017 Categories in Patients with Chronic Obstructive Pulmonary Disease. Arch Bronconeumol (Engl Ed). 2019;55(8):414-420. English, Spanish. doi: 10.1016/j.arbres.2019.02.004.

35. Cabrera López C, Casanova Macario C, Marín Trigo JM, de-Torres JP, Sicilia Torres R, González JM, et al. Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes. Am J Respir Crit Care Med. 2018;197(4):463-469. doi: 10.1164/rccm.201707-1363OC.

36. Putcha N, Anzueto AR, Calverley PMA, Celli BR, Tashkin DP, Metzdorf N, et al. Mortality and Exacerbation Risk by Body Mass Index in Patients with COPD in TIOSPIR® and UPLIFT®. Ann Am Thorac Soc. 2021. doi: 10.1513/AnnalsATS.202006-722OC.

37. Flattet Y, Garin N, Serratrice J, Perrier A, Stirnemann J, Carballo S. Determining prognosis in acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:467-475. doi: 10.2147/COPD.S122382.

38. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts.

Thorax. 2015;70(5):482-9. doi: 10.1136/thoraxjnl-2014-206084.

39. Olloquequi J, Jaime S, Parra V, Cornejo-Córdova E, Valdivia G, Agustí À, et al. Comparative analysis of COPD associated with tobacco smoking, biomass smoke exposure or both. Respir Res. 2018;19(1):13. doi: 10.1186/s12931-018-0718-y.

40. Pezzuto A, Carico E. Effectiveness of smoking cessation in smokers with COPD and nocturnal oxygen desaturation: Functional analysis. Clin Respir J. 2020;14(1):29-34. doi: 10.1111/crj.13096.

41. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet. 2018;391(10131):1706-1717. doi: 10.1016/S0140-6736(18)30841-9.

42. Fang L, Gao P, Bao H, Tang X, Wang B, Feng Y, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med. 2018;6(6):421-430. doi: 10.1016/S2213-2600(18)30103-6.

43. Han MZ, Hsiue TR, Tsai SH, Huang TH, Liao XM, Chen CZ. Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3425-3433. doi: 10.2147/COPD.S179048.

44. Hu YH, Liang ZY, Xu LM, Xu WH, Liao H, Li R, et al. Comparison of the clinical characteristics and comprehensive assessments of the 2011 and 2017 GOLD classifications for patients with COPD in China. Int J Chron Obstruct Pulmon Dis. 2018;13:3011-3019. doi: 10.2147/COPD.S174668.

45. Zha Z, Leng R, Xu W, Bao H, Chen Y, Fang L, et al. Prevalence and risk factors of

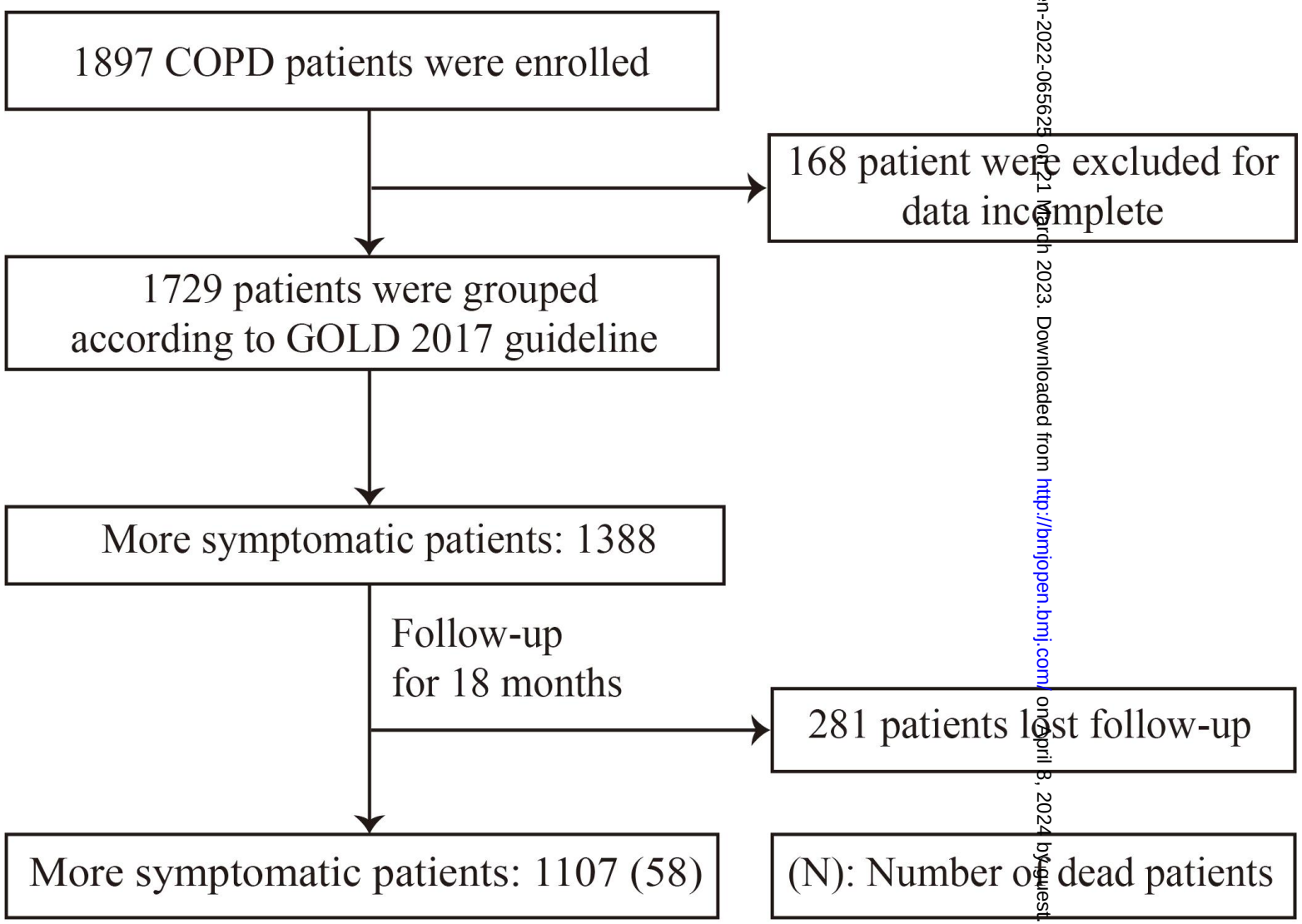
chronic obstructive pulmonary disease in Anhui Province, China: a population-based survey. BMC Pulm Med. 2019;19(1):102. doi: 10.1186/s12890-019-0864-0.

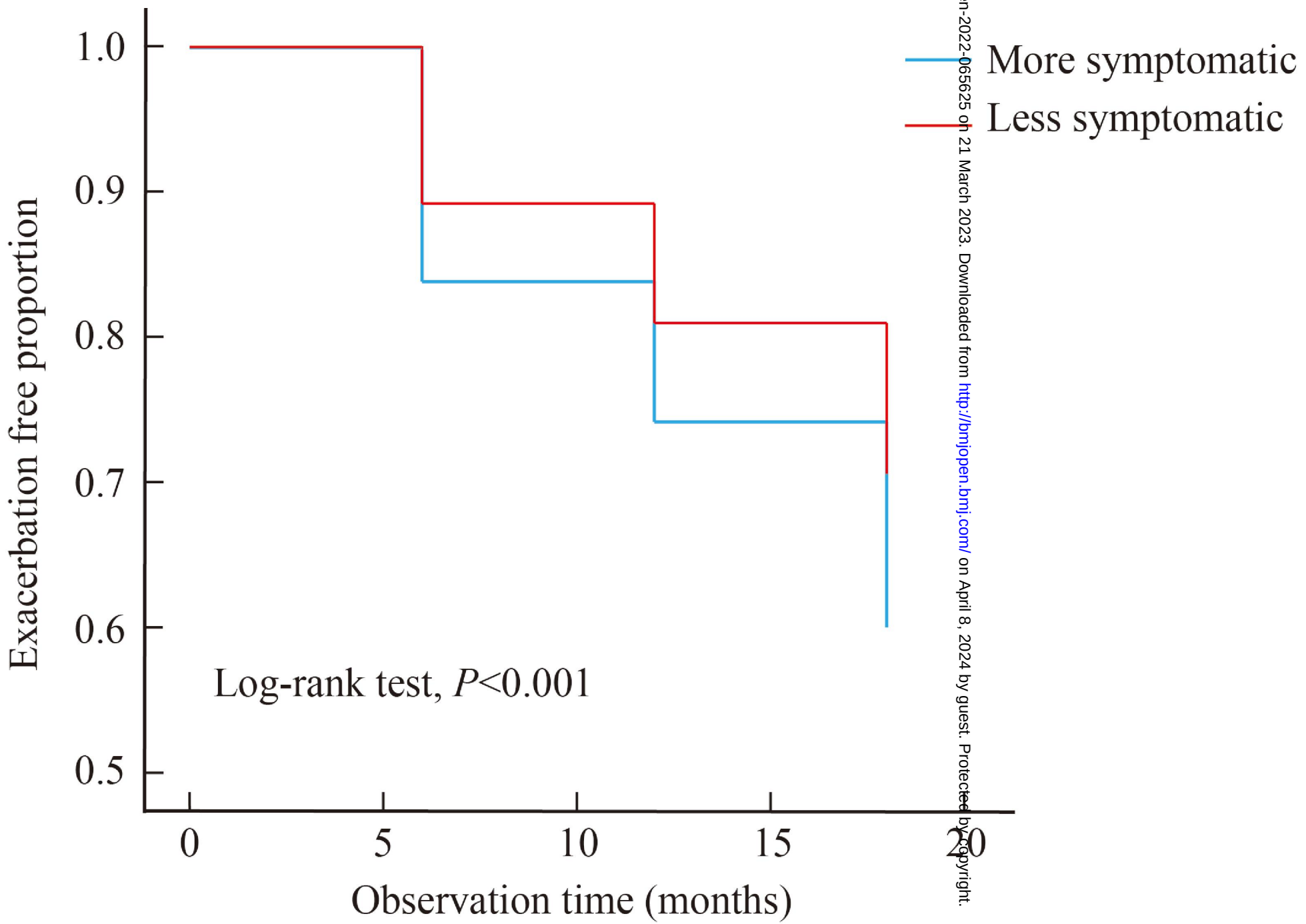
Figure captions

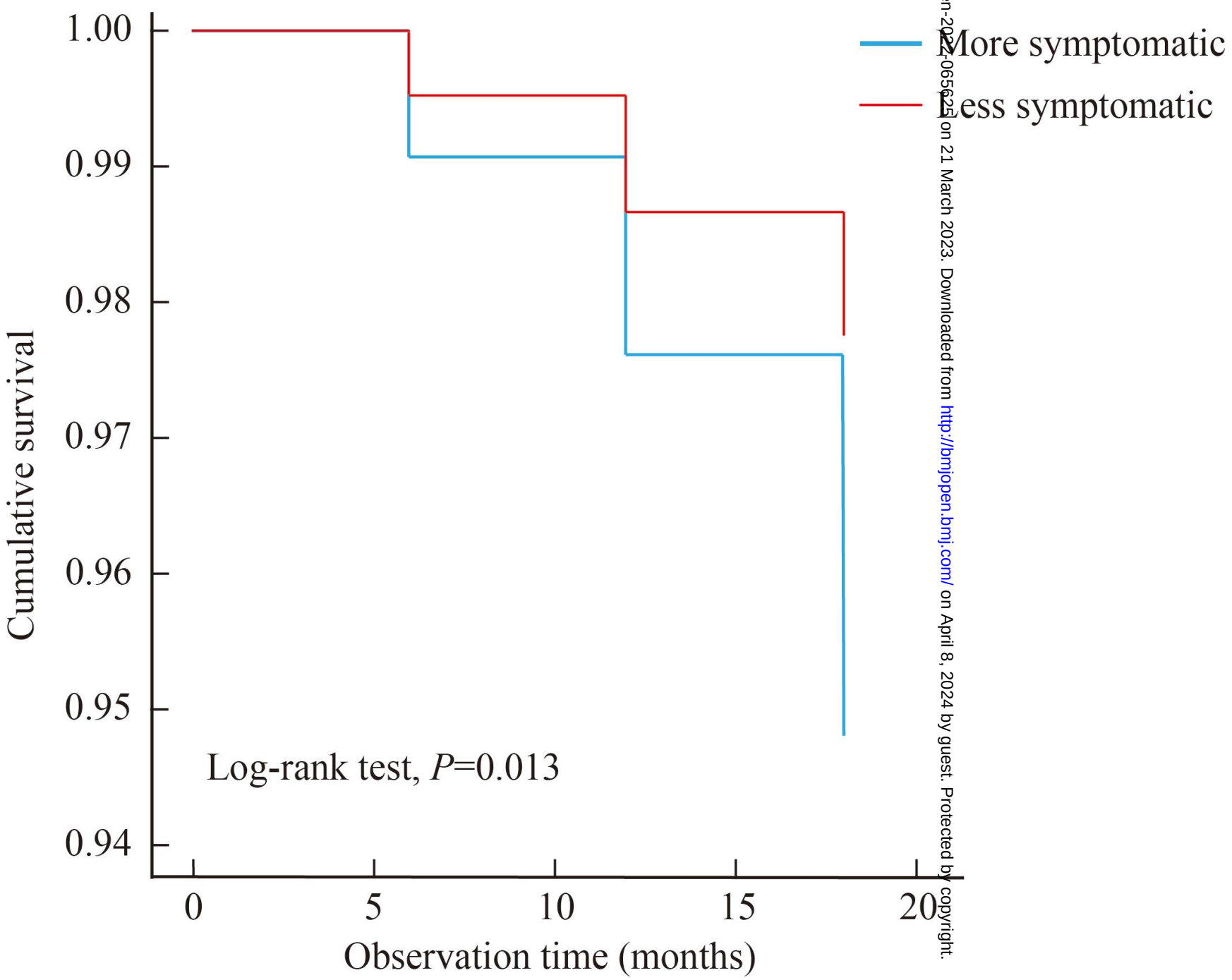
Figure 1. Flow chart. COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Figure 2. Kaplan-Meier curves of the exacerbation free proportion between more and less symptomatic COPD patients; $P < 0.05$ was considered to be statistically significant. COPD, Chronic Obstructive Pulmonary Disease.

Figure 3. Kaplan-Meier curves of the overall survival between more and less symptomatic COPD patients; $P < 0.05$ was considered to be statistically significant. COPD, Chronic Obstructive Pulmonary Disease.







Supplement table 1. Exacerbation and mortality after 18 months of follow-up in COPD patients with different smoke history.

Variables	Never-smoker (n = 234)	Former-smoker (n = 478)	Current-smoker (n = 695)	*P* - value
Exacerbations, (Mean ± SD)	0.8 ± 1.5	0.9 ± 1.4	1.5 ± 1.9 [a, b]	0.008
Exacerbations, n (%)				0.006
0	178 (73.6)	327 (70.2)	438 (66.1) [a, b]	
1	28 (13.2)	63 (14.4)	108 (16.3)	
≥2	22 (13.2)	61 (15.4)	117 (17.6) [a, b]	
Hospitalizations, (Mean ± SD)	0.4 ± 1.0	0.4 ± 0.8	0.6 ± 1.2 [a, b]	0.045
Hospitalizations, n (%)				0.035
0	182 (79.8)	361 (78.8)	480 (73.2) [a, b]	
≥1	46 (20.2)	97 (21.2)	176 (26.8) [a, b]	
Mortality, n (%)	6 (2.6)	20 (4.2)	39 (5.6)	0.135

Notes: [a] Compared with the Never-smoker, $P < 0.05$; [b] Compared with the Former-smoker, $P < 0.05$.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; SD, Standard Deviation.

Supplement table 2. Exacerbation and mortality after 18 months of follow-up in COPD patients with different amounts of smoking (packs/year).

Variables	< 10 packs/year (n = 239)	≥ 10 packs/year (n = 1168)	*P*-value
Exacerbations, (Mean ± SD)	0.8 ± 1.5	0.7 ± 1.3	0.306
Exacerbations, n (%)			0.949
0	147 (62.8)	692 (62.5)	
1	39 (16.7)	194 (17.5)	
≥2	48 (20.5)	222 (20.0)	
Hospitalizations, (Mean ± SD)	0.4 ± 1.0	0.4 ± 0.8	0.753
Hospitalizations, n (%)			0.298
0	180 (76.9)	816 (73.6)	
≥1	54 (23.1)	292 (26.4)	
Mortality, n (%)	5 (2.5)	60 (5.1)	0.045

Note: COPD, Chronic Obstructive Pulmonary Disease; SD, Standard Deviation.

Supplement table 3. The baseline characteristics of more symptomatic COPD patients who remained in the study and lost to follow-up.

Variables	More symptomatic patients		*P*-value
	A_1 (n=1107)	A_2 (n=281)	
Age (years)	65.5 ± 8.0	65.6 ± 8.0	0.813
Sex, n (%)			0.892
Male	988 (89.3)	250 (89.0)	
Female	119 (10.7)	31 (11.0)	
Education level, n (%)			0.158
Primary school	455 (41.1)	130 (46.3)	
Junior high school	428 (38.7)	88 (31.3)	
High school	173 (15.7)	49 (17.4)	
University	51 (4.6)	14 (5.0)	
BMI (kg/m^2)	22.3 ± 3.7	22.5 ± 3.7	
Smoke history, n (%)			0.290
Never-smoker	187 (16.9)	53 (18.9)	
Former-smoker	385 (34.8)	84 (29.9)	
Current-smoker	535 (48.3)	144 (51.2)	
Smoking, (packs/year), (Mean ± SD)	37.5 ± 28.6	36.1 ± 26.7	0.433
Biofuel exposure, n (%)			0.493
Yes	440 (39.8)	118 (42.0)	
No	667 (60.2)	163 (58.0)	
Occupational exposure, n (%)			0.629
Yes	416 (37.6)	110 (39.1)	
No	691 (62.4)	171 (60.9)	
Pulmonary function, (Mean ± SD)			
FEV1	1.8 ± 0.5	1.2 ± 0.5	0.908
FEV1 %pred	48.6 ± 19.0	49.5 ± 19.1	0.480
FVC	2.6 ± 0.7	2.6 ± 0.7	0.439
FEV1/FVC	44.4 ± 12.2	44.7 ± 12.1	0.664
PEF	3.2 ± 1.4	3.1 ± 1.4	0.498
GOLD stages, n (%)			0.706
1	71 (6.4)	19 (6.8)	
2	408 (36.9)	110 (39.1)	
3	427 (38.6)	109 (38.8)	
4	201 (18.1)	43 (15.3)	
CAT, (Mean ± SD)	17.6 ± 5.4	17.3 ± 5.2	0.400
mMRC, (Mean ± SD)	2.3 ± 0.9	2.3 ± 0.9	0.885
CCQ, (Mean ± SD)	23.7 ± 6.5	23.2 ± 6.4	0.206
Treatments, n (%)			
LAMA	363 (32.8)	101 (35.9)	0.317
LABA + ICS	82 (7.4)	15 (5.3)	0.224
LAMA + LABA	24 (2.2)	3 (1.1)	0.233
LAMA + LABA + ICS	558 (50.4)	137 48.8)	0.621

Oxygen therapy, n (%)			0.393
Yes	92 (8.3)	19 (6.8)	
No	1015 (91.7)	262 (93.2)	
Exacerbations in the past year, (Mean ± SD)	1.8 ± 3.3	1.9 ± 3.5	0.603
Hospitalizations in the past year, (Mean ± SD)	0.8 ± 1.5	0.7 ± 1.3	0.467

Notes: A_1: The COPD patients who remained in the study after 18 months of follow-up; A_2: The COPD patients who lost to follow-up.

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow; SD, Standard Deviation.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) If applicable, explain how loss to follow-up was addressed	6-8
		(*e*) Describe any sensitivity analyses	6-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-11
		(b) Give reasons for non-participation at each stage	8-11
		(c) Consider use of a flow diagram	8-11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-11
		(b) Indicate number of participants with missing data for each variable of interest	8-11
		(c) Summarise follow-up time (eg, average and total amount)	8-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(*b*) Report category boundaries when continuous variables were categorized	8-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Clinical-functional characteristics and risk of exacerbation and mortality among more symptomatic patients with chronic obstructive pulmonary disease: A retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065625.R2
Article Type:	Original research
Date Submitted by the Author:	27-Feb-2023
Complete List of Authors:	Song, Qing; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Lin, Ling; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Cheng, Wei; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Li, Xueshan; The Second Xiangya Hospital of Central South University Zeng, Yu-Qin; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Liu, Cong; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Deng, Min-Hua; PLA Rocket Force Characteristic Medical Center, Department of Respiratory Liu, Dan; The Eighth Hospital in Changsha, Department of Respiratory Yu, Zhi-Ping; Longshan Hospital of Traditional Chinese Medicine, Department of Respiratory Li, Xin; Central South University Ma, Li-Bing; Affiliated Hospital of Guilin Medical University, Department of respiratory and critical care medicine Chen, Yan; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Cai, Shan; Central South University, Department of Respiratory and Critical Care Medicine; Central South University Chen, Ping; Central South University, Department of Respiratory and Critical Care Medicine; Central South University
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Smoking and tobacco, Medical management
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Respiratory physiology < THORACIC MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Title: Clinical-functional characteristics and risk of exacerbation and mortality among more symptomatic patients with chronic obstructive pulmonary disease: A retrospective cohort study

Authors: Qing Song[1,2,3], Ling Lin[1,2,3], Wei Cheng[1,2,3], Xue-Shan Li[1,2,3], Yu-Qin Zeng[1,2,3], Cong Liu[1,2,3], Min-Hua Deng[4], Dan Liu[5], Zhi-Ping Yu[6], Xin Li[7], Li-Bing Ma[8], Yan Chen[1,2,3], Shan Cai[1,2,3], Ping Chen[1,2,3]

Affiliations:[1]Department of Respiratory and Critical Care Medicine, the Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China.

[2]Research Unit of Respiratory Disease, Central South University, Changsha, Hunan 410011, China.

[3]Diagnosis and Treatment Center of Respiratory Disease, Central South University, Changsha, Hunan 410011, China.

[4]Department of Respiratory, PLA Rocket Force Characteristic Medical Center, Beijing 100088, China.

[5]Department of Respiratory, The Eighth Hospital in Changsha, Hunan 410000, China.

[6]Department of Respiratory, Longshan Hospital of Traditional Chinese Medicine, Hunan 410000, China.

[7]Division 4 of Occupational Disease, Hunan Occupational Disease Prevention and Treatment Hospital, Changsha, Hunan 410000, China.

[8]Department of respiratory and critical care medicine, Affiliated Hospital of Guilin Medical University, Guilin, Guangxi 541000, China.

Corresponding author: Ping Chen, Department of Respiratory and Critical Care Medicine, the Second Xiangya Hospital, Central South University, 139 Renmin Middle Road, Changsha, Hunan 410011, China. Tel +86 731 8529 5248; Fax +86 731 8529 5848. Email: pingchen0731@csu.edu.cn

Abstract

Objectives: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 classified chronic obstructive pulmonary disease (COPD) patients into more and less symptomatic groups. This study aimed to analyze the clinical characteristics, risk of future exacerbation and mortality among patients in more symptomatic group.

Methods: This retrospective cohort study enrolled 1729 stable COPD patients from a database setup by Second Xiangya Hospital of Central South University. The patients were classified into more and less symptomatic groups based on GOLD 2017 report. All patients were followed up for 18 months. We collected baseline data and recorded the number of exacerbations and mortality during follow-up.

Results: The more symptomatic patients were older, had higher Clinical COPD Questionnaire (CCQ) scores, more severe airflow limitation and higher number of exacerbations and hospitalizations in the past year ($P < 0.05$). Logistic regression showed that having more symptoms correlated with the CCQ scores and exacerbations in the past year ($P < 0.05$). After patients were followed up, there were higher numbers of exacerbations, hospitalizations and mortality rates in more symptomatic patients ($P < 0.05$). The multivariate model showed that age more than 65 years (OR = 2.047, 95% CI = 1.020-4.107) and COPD assessment test scores more than 30 (OR = 2.609, 95% CI = 1.339-5.085) were independent risk factors for mortality, whereas current smoker (OR = 1.565, 95% CI = 1.052-2.328), modified Medical Research Council scores (OR = 1.274, 95% CI = 1.073-1.512) and exacerbations in the past year (OR = 1.061, 95% CI = 1.013-1.112) were independent risk factors for exacerbation in more symptomatic patients ($P < 0.05$).

Conclusions: More symptomatic COPD patients have worse outcomes. In addition, several independent risk factors for exacerbation and mortality were identified. Therefore, clinicians should be aware of these risk factors and take them into account during interventions.

Keywords: COPD, More symptomatic, Mortality, Exacerbation, GOLD

Strengths and limitations of this study

- This is a multicenter study and the data derived from outpatient COPD database which including several hospitals.
- This study is the first to explore the independent risk factors for future exacerbation and mortality among more symptomatic COPD patients according to GOLD report.
- A key limitation is that 281 of the more symptomatic patients were lost to follow-up.
- This study did not discuss the comorbidities which might place a symptom burden on patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious chronic respiratory disease that typically features persistent respiratory symptoms, such as cough, expectoration and dyspnea. This disease has brought a huge burden of mortality to humanity [1-2] and therefore prevention and treatment are urgent.

Breathlessness, cough and sputum production are common symptoms of COPD, bringing a huge burden to patients. Some may experience deterioration of their symptoms and need additional treatment [3]. The COPD assessment test (CAT) and modified Medical Research Council (mMRC) scales cover several dimensions, such as dyspnea, cough, expectoration, confidence, limitation of daily activities and chest tightness, and are used as indicators to measure the effect of symptoms on the health of COPD patients [4-5]. The higher the CAT and mMRC scores, the more symptoms the patients have and the greater the impact on patients' health [6]. Ding et al. [7] found that as the CAT scores increased, the frequency of primary care physician visits also increased. Kim et al. [8] found that COPD patients with increased mMRC scores had a higher risk of exacerbation, more severe airflow limitation and respiratory symptoms when compared with patients with unchanged mMRC scores after 1 year of follow-up. In addition, one study showed that the BODE (body mass index (BMI), airflow obstruction, dyspnea, exercise capacity) index includes dyspnea as a meaningful marker of future exacerbation risk [9]. In fact, some COPD patients only experience cough or breathlessness, whereas others have multiple respiratory symptoms, including cough, expectoration, chest tightness and dyspnea.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 evaluated COPD patients based on the CAT/mMRC scores and exacerbation risk to better guide the treatment, dividing patients into more symptomatic and less symptomatic groups [10]. A Japanese study found that the COPD patients in the more symptomatic group were older and had more severe airflow limitation and higher exacerbation rates according to the GOLD 2017 classification; however, the number of more symptomatic patients in this study was small [11]. Several studies have shown that the more symptomatic COPD patients account for the majority [12-15]. In addition, Cabrera López et al. [16] found that the risk of mortality was higher in Groups B and D than in Groups A and C according to the GOLD 2017 classification. However, the clinical characteristics and outcomes among more symptomatic COPD patients remained unclear. Therefore, our purpose was to analyze the clinical characteristics and related risk factors, as well as the risk of future exacerbation and mortality among patients in more symptomatic group.

Methods

Study participants

We conducted a retrospective cohort study that captured the patients listed from September 2017 to December 2019 in the outpatient COPD database (Register number: ChiCTR-POC-17010431; http://120.77.177.175:9007/a/login), which includes the Second Xiangya Hospital of Central South University, the Zhuzhou Central Hospital, the Hunan Prevention and Treatment Institute for Occupational Diseases, the First Attached Hospital of Shaoyang University, the Eighth Hospital in Changsha and the Longshan Hospital of Traditional Chinese Medicine (Hunan, China). The inclusion criterion for COPD patients was a ratio of forced expiratory volume in 1 s to forced vital capacity

(FEV1/FVC) of < 0.70 after bronchodilator administration. Patients with interstitial lung disease, bronchiectasis, pneumonia, asthma, pleural effusion, lung cancer or active tuberculosis were excluded from the study.

We confirm that this study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. All patients in this study were provided written informed consent.

Patient and public involvement

Patients and the public were not involved in the conception of this study, development of the research question, interpretation of the results or manuscript writing.

Study procedures

All included COPD patients underwent 18 months of follow-up. Furthermore, at the 6, 12 and 18 months, we recorded the number of exacerbations, hospitalizations and deaths among these patients. According to the GOLD 2017 report, the COPD patients were assigned to more and less symptomatic groups. Briefly, the more symptomatic group was defined by mMRC scores ≥ 2 and CAT scores ≥ 10, with or without a history of exacerbations and hospitalizations. The less symptomatic group was defined by mMRC scores < 2 and/or CAT scores < 10, with or without a history of exacerbations and hospitalizations [10].

Data collection and definitions

The baseline clinical characteristics included demographics, smoke history, biofuel and occupational exposure history, pulmonary function results, symptoms scores (including CAT and mMRC), Clinical COPD Questionnaire (CCQ) scores, treatment regimens and

number of exacerbations and hospitalizations in the past year. Furthermore, we recorded mortality, and the number of exacerbations and hospitalizations during follow-up.

A current smoker was defined as having a smoking exposure of more than 10 packs/year, whereas a former smoker was defined as having a smoking exposure of at least 10 packs/year, but with smoking cessation for more than half a year [17]. An exacerbation was defined as disease progression that requires antibiotics, oral corticosteroids or hospitalization for treatment or was determined by a sputum color change (to green or yellow) [18]. Biofuel exposure was defined as continuous exposure to biofuels for at least 2 hours a day, for at least one year. Occupational exposure was defined as exposure to dust, metals, chemical substances or other environmental agents for at least eight hours a day for at least one year [19]. According to the GOLD 2017 report, GOLD stage 1 (FEV1 ≥ 80 %pred), GOLD stage 2 (FEV1 50-79 %pred), GOLD stage 3 (FEV1 30-49 %pred) and GOLD stage 4 (FEV1 < 30 %pred) [10]. Oxygen therapy included home oxygen therapy and non-invasive positive pressure ventilation in this study [20].

The pulmonary function test was measured by a spirometer (MasterScreen-Body/Diff, CareFusion, Germany) according to the American Thoracic Society guidelines. FEV1 was defined as the time in seconds, measured from time 0 to 1, of the expiration after maximal forced inspiration. FVC was defined as the largest expiration volume immediately after maximal forced inspiration. Peak expiratory flow (PEF) was defined as the highest flow achieved from a maximum forced expiratory maneuver started without hesitation from a position of maximal lung inflation [21].

Statistical analysis

Continuous variables were presented as the mean ± standard deviation (SD). The Chi-squared and Fisher's tests were used to analyze categorical variables. An independent-sample Student's *t*-test was used to analyze continuous variables. For variables with non-normal distribution or uneven variance, we used non-parametric tests. The variously adjusted odds ratio was calculated using multivariate logistic regression. Two-sided *P* values of < 0.05 were considered to be statistically significant. SPSS version 26.0 (IBM, Armonk, NY, USA) was used to perform all statistical analyses.

Results

Baseline characteristics

A total of 1729 patients with COPD were included (Figure 1). The mean age was 65.1 ± 8.2 years, 89.1% were male and more than half of the patients were current smokers. Most of the patients were in GOLD stages 2-3 and treatment with a long-acting muscarinic antagonist (LAMA), LAMA + long-acting β2-agonist (LABA) + inhaled corticosteroid (ICS). The mean CAT and CCQ scores were 15.4 ± 6.6 and 21.9 ± 7.2, respectively. Most patients suffered from an exacerbation and hospitalization less than once per year (Table 1).

Table 1. The baseline characteristics of the COPD patients.

Variables	Total (n = 1729)
Age (years), (Mean ± SD)	65.1 ± 8.2
Age, n (%)	
<65	755 (43.7)
≥65	974 (56.3)
Sex, n (%)	
Male	1541 (89.1)
Female	188 (10.9)
Education level, n (%)	
Primary school	713 (41.2)

Junior high school	618 (35.8)
High school	289 (16.7)
University	108 (6.3)
BMI (kg/m^2)	22.5 ± 3.6
Smoke history, n (%)	
Never smoker	288 (16.7)
Former smoker	576 (33.3)
Current smoker	865 (50.0)
Smoking, (packs/year), (Mean ± SD)	37.4 ± 28.2
Biofuel exposure, n (%)	
Yes	660 (38.2)
No	1069 (61.8)
Occupational exposure, n (%)	
Yes	659 (38.1)
No	1070 (61.9)
Pulmonary function, (Mean ± SD)	
FEV1	1.3 ± 0.6
FEV1 %pred	52.1 ± 20
FVC	2.7 ± 0.7
FEV1/FVC	46.5 ± 16.1
PEF	3.5 ± 1.6
GOLD stages, n (%)	
1	171 (9.9)
2	709 (41.0)
3	596 (34.5)
4	253 (14.6)
CAT, (Mean ± SD)	15.4 ± 6.6
mMRC, (Mean ± SD)	2.1 ± 1.0
CCQ, (Mean ± SD)	21.9 ± 7.2
Treatments, n (%)	
LAMA	622 (36.0)
LABA + ICS	136 (7.9)
LAMA + LABA	33 (1.9)
LAMA + LABA + ICS	797 (46.1)
Oxygen therapy, n (%)	
Yes	121 (7.0)
No	1608 (93.0)
Exacerbations in the past year, (Mean ± SD)	1.7 ± 3.1
Exacerbations in the past year, n (%)	
0	753 (43.6)
1	412 (23.8)

≥2	564 (32.6)
Hospitalizations in the past year, (Mean ± SD)	0.7 ± 1.3
Hospitalizations in the past year, n (%)	
0	1132 (65.5)
≥1	597 (34.5)

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow; SD, Standard Deviation.

According to the GOLD 2017 report, 1388 (80.3%) were more symptomatic patients. These patients were older (65.5 ± 8.0 vs 63.4 ± 8.8 years, $P < 0.001$) and had lower education level, BMI, FEV1, FEV1 %pred, FVC, FEV1/FVC and PEF ($P < 0.001$). In addition, a higher proportion of biofuel exposure history, GOLD stages 3-4 patients, treatment with LAMA+LABA+ICS and oxygen therapy in more symptomatic group ($P < 0.05$). Furthermore, more symptomatic COPD patients had higher CCQ scores and a higher number of exacerbations and hospitalizations in the past year ($P < 0.001$) (Table 2).

Table 2. The clinical characteristics of more symptomatic COPD patients.

Variables	More symptoms (n = 1388)	Less symptoms (n = 341)	*P* - value
Age (years) , (Mean ± SD)	65.5 ± 8.0	63.4 ± 8.8	<0.001
Age, n (%)			0.003
<65	582 (41.9)	173 (50.2)	
≥65	806 (58.1)	168 (49.3)	
Sex, n (%)			
Male	1238 (89.2)	303 (88.9)	
Female	150 (10.8)	38 (11.1)	
Education level, n (%)			<0.001
Primary school	585 (42.1)	128 (37.5)	
Junior high school	516 (37.2)	102 (29.9)	
High school	222 (16.0)	67 (19.6)	

University	65 (4.7)	44 (13.0)	
BMI (kg/m^2)	22.3 ± 3.7	23.2 ± 3.1	<0.001
Smoke history, n (%)			0.142
Never smoker	240 (17.3)	48 (14.1)	
Former smoker	469 (33.8)	107 (31.4)	
Current smoker	679 (48.9)	186 (54.5)	
Smoking, (packs/year), (Mean ± SD)	37.2 ± 28.3	38.0 ± 27.9	0.629
Biofuel exposure, n (%)			<0.001
Yes	558 (40.2)	102 (29.9)	
No	830 (59.8)	239 (70.1)	
Occupational exposure, n (%)			0.706
Yes	526 (37.9)	133 (39)	
No	862 (62.1)	208 (61)	
Pulmonary function, (Mean ± SD)			
FEV1	1.2 ± 0.5	1.7 ± 0.6	<0.001
FEV1 %pred	48.7 ± 19.0	65.7 ± 19.4	<0.001
FVC	2.6 ± 0.7	3.1 ± 0.8	<0.001
FEV1/FVC	44.4 ± 12.2	54.9 ± 12.9	<0.001
PEF	3.2 ± 1.4	4.7 ± 1.9	<0.001
GOLD stages, n (%)			<0.001
1	90 (6.5)	81 (23.8)	
2	518 (37.3)	191 (56.0)	
3	536 (38.6)	60 (17.6)	
4	244 (17.6)	9 (2.6)	
CAT, (Mean ± SD)	17.6 ± 5.3	6.5 ± 2.2	<0.001
mMRC, (Mean ± SD)	2.3 ± 0.9	1.2 ± 0.8	<0.001
CCQ, (Mean ± SD)	23.6 ± 6.5	15.1 ± 5.8	<0.001
Treatments, n (%)			
LAMA	464 (33.4)	158 (46.3)	<0.001
LABA + ICS	97 (7.0)	39 (11.4)	0.006
LAMA + LABA	27 (1.9)	6 (1.8)	0.822
LAMA + LABA + ICS	695 (50.1)	102 (29.9)	<0.001
Oxygen therapy, n (%)			0.001
Yes	111 (8.0)	10 (2.9)	
No	1277 (92.0)	331 (97.1)	
Exacerbations in the past year, (Mean ± SD)	1.9 ± 3.3	0.8 ± 1.8	<0.001
Exacerbations in the past year, n (%)			<0.001
0	555 (40.0)	198 (58.1)	
1	325 (23.4)	87 (25.5)	
≥2	508 (36.6)	56 (16.4)	
Hospitalizations in the past year, (Mean ± SD)	0.7 ± 1.4	0.3 ± 0.8	<0.001

Hospitalizations in the past year, n (%)			<0.001
0	872 (62.8)	260 (76.2)	
≥1	516 (37.2)	81 (23.8)	

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow; SD, Standard Deviation.

Multivariate analysis of risk factors associated with more symptomatic COPD patients

Results were adjusted for age, education level, biofuel exposure, FEV1, FEV1 %pred, FVC, GOLD stages and BMI. Logistic regression analysis showed that FEV1/FVC and PEF were negatively correlated with the more symptomatic, with an OR of 0.980 (95% CI = 0.964 - 0.995) and 0.774 (95% CI = 0.688 - 0.872), respectively ($P < 0.05$). However, CCQ scores and exacerbations in the past year were positively correlated with the more symptomatic, with an OR of 1.200 (95% CI = 1.169 - 1.232) and 1.114 (95% CI = 1.025 - 1.211), respectively ($P < 0.05$) (Table 3).

Table 3. Multivariate analysis of risk factors associated with more symptomatic COPD patients.

Variables	OR	95% CI	*P* - value
FEV1/FVC	0.980	0.964 – 0.995	0.010
PEF	0.774	0.688 – 0.872	<0.001
CCQ	1.200	1.169 – 1.232	<0.001
Exacerbations in the past year	1.114	1.025 - 1.211	0.011

Notes: After adjusted for age, education level, biofuel exposure, FEV1, FEV1 %pred, FVC, GOLD stages, BMI and hospitalizations in the past year. $P < 0.05$ are statistically significant in accordance with logistic regression analysis.
Abbreviations: BMI, Body Mass Index; CI, Confidence interval; COPD, Chronic Obstructive Pulmonary Disease; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PEF, Peak Expiratory Flow; OR, Odds Ratio.

Exacerbation and mortality after 18 months of follow-up

As shown in Table 4, after 18 months of follow-up, a total of 1407 patients were included. The mean values for exacerbations and hospitalizations were 0.7 ± 1.3 and 0.4 ± 0.8 respectively. Most of the patients suffered an exacerbation and hospitalization less than once per year and the mortality rate was 4.6%.

Table 4. Exacerbation and mortality after 18 months of follow-up in more symptomatic COPD patients.

Variables	Total (n = 1407)	More symptomatic (n = 1107)	Less symptomatic (n = 300)	*P* - value
Exacerbations, (Mean ± SD)	0.7 ± 1.3	0.8 ± 1.4	0.5 ± 1.1	<0.001
Exacerbations, n (%)				<0.001
0	836 (62.2)	621 (59.2)	215 (73.4)	
1	259 (19.4)	217 (20.7)	42 (14.3)	
≥2	247 (18.4)	211 (20.1)	36 (12.3)	
Hospitalizations, (Mean ± SD)	0.4 ± 0.8	0.4 ± 0.9	0.2 ± 0.6	<0.001
Hospitalizations, n (%)				0.001
0	1004 (77.7)	762 (72.6)	242 (82.6)	
≥1	338 (22.3)	287 (27.4)	51 (17.4)	
Mortality, n (%)	65 (4.6)	58 (5.2)	7 (2.3)	0.033

Note: COPD, Chronic Obstructive Pulmonary Disease; SD, Standard Deviation.

After 18 months of follow-up, 1107 more symptomatic COPD patients were analyzed for future exacerbation and mortality. The results show that the more symptomatic COPD patients suffered from a higher number of exacerbations and hospitalizations ($P < 0.001$). The proportion of more symptomatic patients who suffered from exacerbations and hospitalizations at least once per year was higher ($P < 0.001$), with rates of 40.8% and 27.4%, respectively. Comparison of the exacerbation free proportion using a Kaplan–Meier curve revealed that there was a significant difference between the more and less symptomatic patients ($P < 0.001$) (Figure 2). In addition, 58 (5.2%) more symptomatic COPD patients died during the 18 months of follow-up, which is a higher number than in

the less symptomatic group ($P < 0.001$). Comparison of overall survival using the Kaplan–Meier curve revealed that survival was significantly different between the more and less symptomatic patients ($P = 0.013$) (Figure 3).

Univariate and stepwise multivariate analysis of risk factors for mortality in more symptomatic COPD patients

Of the 1107 more symptomatic COPD patients, 58 died during follow-up. Univariate analysis showed that there were several risk factors for mortality, including age more than 65 years (OR = 2.925, 95% CI = 1.532-5.586, $P = 0.001$), smoking (packs/year) (OR = 1.012, 95% CI = 1.003-1.020, $P = 0.005$), CAT scores more than 30 (OR = 3.341, 95% CI = 1.923-5.805, $P < 0.001$), mMRC scores (OR = 1.490, 95% CI = 1.107-2.006, $P = 0.009$), CCQ scores (OR = 1.091, 95% CI = 1.048-1.137, $P < 0.001$), exacerbations in the past year (OR = 1.057, 95% CI = 1.001-1.117, $P = 0.049$) and hospitalizations in the past year (OR = 1.143, 95% CI = 1.014-1.289, $P = 0.029$). The multivariate model showed that age more than 65 years (OR = 2.047, 95% CI = 1.020-4.107, $P = 0.044$), smoking (packs/year) (OR = 1.014, 95% CI = 1.005-1.023, $P = 0.002$), and CAT scores more than 30 (OR = 2.609, 95% CI = 1.339-5.085, $P = 0.005$) were independent risk factors for mortality in more symptomatic COPD patients (Table 5).

Table 5. Univariate and stepwise multivariate analysis of risk factors for mortality in more symptomatic COPD patients.

Variables	Univariate			Multivariate		
	OR	95% CI	*P* - value	OR	95% CI	*P* - value
Age						
<65	Reference			Reference		
≥65	2.925	1.532-5.586	0.001	2.047	1.020-4.107	0.044
Sex						
Male	Reference					
Female	0.439	0.135-1.425	0.170			
Education level						
Primary school	Reference			Reference		

Junior high school	0.372	0.194-0.714	0.003	0.453	0.230-1.350	0.325
High school	0.655	0.308-1.394	0.272	0.758	0.341-1.689	0.499
University	0.239	0.032-1.781	0.162	0.325	0.041-2.547	0.284
BMI	0.950	0.881-1.023	0.173			
Smoke history						
Former smoker	Reference					
Never smoker	0.517	0.196-1.362	0.182			
Current smoker	1.363	0.782-2.374	0.275			
Smoking (packs/year)	1.012	1.003-1.020	0.005	1.014	1.005-1.023	0.002
Biofuel exposure						
Yes	Reference					
No	0.736	0.416-1.302	0.292			
Occupational exposure						
Yes	Reference					
No	0.642	0.378-1.089	0.100			
Pulmonary function						
FEV1	0.713	0.407-1.246	0.235			
FEV1 %pred	1.000	0.986-1.014	0.993			
FVC	0.573	0.387-0.848	0.005	0.667	0.394-1.130	0.132
FEV1/FVC	1.013	0.991-1.034	0.246			
PEF	0.898	0.731-1.102	0.303			
GOLD stages						
1	0.314	0.071-1.394	0.128	0.862	0.155-4.796	0.865
2	0.676	0.355-1.290	0.304	1.359	0.600-3.080	0.462
3	0.394	0.193-0.806	0.011	0.553	0.251-1.220	0.142
4	Reference			Reference		
CAT						
10-19	Reference			Reference		
20-29	2.927	0.835-10.257	0.093	1.538	0.354-6.680	0.566
≥30	3.341	1.923-5.805	<0.001	2.609	1.339-5.085	0.005
mMRC	1.490	1.107-2.006	0.009	0.911	0.626-1.325	0.626
CCQ	1.091	1.048-1.137	<0.001	1.039	0.988-1.092	0.135
Treatments						
LAMA	0.918	0.519-1.625	0.770			
LABA + ICS	0.670	0.205-2.189	0.507			
LAMA + LABA	2.670	0.773-9.225	0.121			
LAMA + LABA + ICS	1.057	0.623-1.794	0.837			
Oxygen therapy						
No	Reference					
Yes	1.526	0.986-2.363	0.058			
Exacerbations in the past year	1.057	1.001-1.117	0.049	1.016	0.933-1.107	0.711
Hospitalizations in the past year	1.143	1.014-1.289	0.029	1.108	0.948-1.295	0.198

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-

Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow, OR, Odds Ratio; CI, Confidence Interval.

Univariate and stepwise multivariate analysis of risk factors for future exacerbation in more symptomatic COPD patients

In total, 428 of 1107 more symptomatic COPD patients suffered from exacerbation during follow-up. Univariate analysis showed that there were several risk factors for future exacerbation, including being a current smoker (OR = 1.480, 95% CI = 1.125-1.948, *P* = 0.005), CAT scores 20 to 29 (OR = 1.428, 95% CI = 1.087-1.877, *P* = 0.011) and CAT scores more than 30 (OR = 3.225, 95% CI = 1.531-6.793, *P* = 0.002), mMRC scores (OR = 1.375, 95% CI = 1.199-1.576, *P* < 0.001), CCQ scores (OR = 1.025, 95% CI = 1.006-1.045, *P* = 0.012), exacerbations in the past year (OR = 1.098, 95% CI = 1.049-1.149, *P* < 0.001) and hospitalizations in the past year (OR = 1.208, 95% CI = 1.094-1.335, *P* < 0.001). The multivariate model showed that being a current smoker (OR = 1.565, 95% CI = 1.052-2.328, *P* = 0.027), mMRC scores (OR = 1.274, 95% CI = 1.073-1.512, *P* = 0.006) and exacerbations in the past year (OR = 1.061, 95% CI = 1.013-1.112, *P* = 0.013) were independent risk factors for future exacerbation in more symptomatic COPD patients (Table 6).

Table 6. Univariate and stepwise multivariate analysis of risk factors for future exacerbation in more symptomatic COPD patients.

Variables	Univariate			Multivariate		
	OR	**95% CI**	***P* - value**	**OR**	**95% CI**	***P* - value**
Age						
<65	Reference					
≥65	1.264	0.982-1.627	0.069			
Sex						
Male	Reference					
Female	0.749	0.500-1.123	0.162			
Education level						
Primary school	Reference			Reference		

Junior high school	0.701	0.531-0.925	0.012	0.728	0.545-1.072	0.052
High school	0.884	0.613-1.274	0.507	0.978	0.667-1.435	0.911
University	0.903	0.427-1.424	0.737	1.169	0..631-2.168	0.621
BMI	0.956	0.924-0.989	0.010	0.962	0.927-0.998	0.040
Smoke history						
Former smoker	Reference			Reference		
Never smoker	1.064	0.751-1.508	0.728	1.066	0.725-1.567	0.746
Current smoker	1.480	1.125-1.948	0.005	1.565	1.052-2.328	0.027
Smoking (packs/year)	1.002	0.997-1.006	0.469			
Biofuel exposure						
No	Reference					
Yes	1.159	0.901-1.491	0.252			
Occupational exposure						
No	Reference					
Yes	1.065	0.826-1.373	0.627			
Pulmonary function						
FEV1	0.768	0.600-0.983	0.036	1.757	0.992-3.113	0.054
FEV1 %pred	0.994	0.988-1.001	0.093			
FVC	0.779	0.653-0.931	0.006	0.758	0.563-1.020	0.067
FEV1/FVC	0.994	0.984-1.004	0.224			
PEF	0.891	0.813-0.977	0.015	0.921	0.770-1.102	0.368
GOLD stages						
1	0.557	0.313-0.994	0.068			
2	0.699	0.490-0.997	0.100			
3	0.760	0.536-1.078	0.124			
4	Reference					
CAT						
10-19	Reference			Reference		
20-29	1.428	1.087-1.877	0.011	1.173	0.854-1.613	0.325
≥30	3.225	1.531-6.793	0.002	1.874	0.819-4.288	0.137
mMRC	1.375	1.199-1.576	<0.001	1.274	1.073-1.512	0.006
CCQ	1.025	1.006-1.045	0.012	0.991	0.968-1.204	0.433
Treatments						
LAMA	0.918	0.705-1.194	0.523			
LABA + ICS	0.660	0.404-1.078	0.097			
LAMA + LABA	0.902	0.370-2.195	0.820			
LAMA + LABA + ICS	0.813	0.635-1.041	0.100			
Oxygen therapy						
No	Reference					
Yes	1.755	0.806-3.818	0.156			
Exacerbations in the past year	1.098	1.049-1.149	<0.001	1.061	1.013-1.112	0.013
Hospitalizations in the past year	1.208	1.094-1.335	<0.001	1.078	0.965-1.204	0.183

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-

Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow, OR, Odds Ratio, CI, Confidence Interval.

Discussion

In this study, we found that the more symptomatic patients accounted for the majority, and several studies have yielded the same results [12-15]. In addition, patients with COPD in China typically do not go to the hospital until they have severe respiratory symptoms. We also found that the more symptomatic patients were older, and a similar result was observed by Han et al. [22] Biofuel exposure is one of the main risk factors of COPD [23-24]. A study showed that compared with smoking, COPD patients with biofuel exposure experienced more dyspnea [25]. In addition, Dutt et al. [26] found that people exposed to biofuel may suffer from more respiratory symptoms. The results of our research confirmed that more symptomatic COPD patients had a higher biofuel exposure rate. Maintenance of inhalation bronchodilators and ICS could reduce respiratory symptoms and exacerbations, improve pulmonary function in patients with COPD. Our research results showed that more symptomatic patients were more likely to use triple inhalers and less likely to use monotherapy with LAMA. This was consistent with the results of Kobayashi et al. [11].

Pulmonary function is used to evaluate airflow limitation and severity of COPD patients. Our research also found that more symptomatic COPD patients had worse pulmonary function and that deterioration of pulmonary function was significantly associated with respiratory symptoms. This was consistent with a study by Boezen et al. [27], which showed that both FEV1 and PEF decreased as the number of symptoms increased and that the risk of having a FEV1 or PEF value of < 70% increased with increasing

symptoms. Brodkin et al. [28] also found that cough, phlegm, wheeze and dyspnea were inversely related to pulmonary function. Another study found that initial FEV1 level was lower in patients with dyspnea appearing during follow-up than in the group without symptoms [29]. The GOLD 2013 report also recommends the CCQ as a symptom measure [30] and states that it is predictive of mortality in COPD patients [31]. Our study showed that more symptomatic patients had higher CCQ scores, which were positively correlated with more symptoms.

Exacerbation is an important risk factor for stable COPD, leading to pulmonary function decline and poor prognosis [32]. Our study found that more symptomatic patients suffered from a higher number of exacerbations in the past year. Moreover, the higher the number of exacerbations, the more symptoms the patients experienced. Miravitlles et al. [33] also found that more exacerbations in the past year was associated with variability in symptom number. In addition, Kobayashi et al. [11] found that more symptomatic patients suffered a higher number of exacerbations in the past year, which is consistent with our research. However, it is unclear whether more symptomatic patients have worse outcomes. Therefore, we performed 18 months of follow-up to observe the patients' future exacerbation and mortality. The results showed that there were higher exacerbation and hospitalization rates in more symptomatic patients, along with higher mortality rates. In addition, Kim et al. [34] found that the more symptomatic patients had significantly higher future exacerbation risk among patients with FEV1 $\geq$ 50%. A study by Cabrera López et al. [35] also found a similar result, with more symptomatic patients showing a higher mortality rate at 5 years of follow-up. In addition, our research results show that more symptomatic patients had a lower BMI but a higher risk of future exacerbation and

mortality. This was consistent with a study by Putcha et al. [36], which showed that underweight participants had a significantly higher risk of death and severe exacerbations Death is the most serious malignant event associated with COPD [37] and it is vital to analyze the risk factors for death in COPD patients. Our results showed that age, smoking (packs/year) and the CAT scores were positively correlated with mortality. Age and smoking are important risk factors associated with COPD development [38-39], and our study also found the same result. At the same time, it implied that improved pulmonary function, reduced respiratory symptoms and quitting smoking are important interventions to reduce the occurrence of malignant events in COPD.

Acute exacerbations are important deterioration events in patients with COPD during follow-up. Therefore, it is necessary to analyze the independent risk factors of the more symptomatic patients who suffered from exacerbation during the 18 months of follow-up in order to better guide the prevention and treatment. In this study, we found that the mMRC scores, being a current smoker and the number of exacerbations in the past year were positively correlated with future exacerbation. It is implied that the higher the mMRC scores and number of exacerbations in the past year, the higher the future exacerbation risk.

Smoking is an important risk factor for COPD development [39] and it is important to demonstrate the effects of smoking on COPD exacerbation. Therefore, we further analyzed the exacerbations and mortality after 18 months of follow-up in COPD patients with different smoking histories. We found that current smokers had a higher exacerbation and hospitalization rates than former smokers and never smokers (Supplementary table 1). Furthermore, COPD patients who smoked more than 10

packs/year had higher mortality (Supplementary table 2). This implies that smoking cessation may decrease the risk of exacerbation and mortality in COPD patients. A study by Pezzuto et al. [40] had a similar result, showing that smoking cessation notably improved pulmonary functional parameters, oxygen desaturation and the walking test, as well as decreasing the CAT scores.

This study has some limitations. First, 281 of the more symptomatic COPD patients lost to follow-up. However, we found that the characteristics of the patients lost to follow-up and those that remained in the study were not significantly different (Supplementary table 3). Also, the number of female patients in this study was small. In fact, the prevalence of COPD differed significantly between males and females in China, with the prevalence being higher in males, mainly because smoking was the main risk factor for COPD but also because there were relatively few female patients who smoked [41-42]. Furthermore, several studies showed that the proportion of female patients was relatively small in China [43-45]. In addition, the number of patients with a low education level was higher. In fact, China is a developing country and the overall level of education is not high in early time. Finally, the comorbidities including interstitial lung disease, bronchiectasis, asthma and lung cancer were excluded from this study, which placed a symptom burden on patients with COPD and has an impact on future exacerbation and mortality.

In summary, our study revealed that the majority of COPD patients have more symptoms, which is associated with worse pulmonary function. More symptomatic patients also have worse outcomes. Reducing respiratory symptoms might improve patients' pulmonary function and outcomes. In addition, several independent risk factors for exacerbation and mortality in more symptomatic COPD patients were identified, including age, smoking,

mMRC scores, CAT scores and exacerbations in the past year. Therefore, clinicians should be aware of the risk factors and take them into account for interventions in more symptomatic COPD patients.

Abbreviations

BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CI, Confidence interval; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, Modified Medical Research Council; OR, Odds Ratio; PEF, Peak Expiratory Flow; SD, Standard Deviation.

Funding

This work was supported by the National Natural Science Foundation of China (NSFC, Grants 81970044) and Xiangya Mingyi grant (2013).

Acknowledgments

We would like to thank the staff of the hospitals for their cooperation in collecting the study data.

Ethics approval and consent to participate

This study was approved by an institutional review board from the Second Xiangya Hospital of Central South University and conducted in accordance with the Declaration of Helsinki. This study was registered in the Chinese Clinical Trial Registry (Registration

number: ChiCTR-POC-17010431). All patients in this study were provided written informed consent.

Competing interests

All authors of this study have no conflicts of interests for this work.

Author contributions

QS performed the data collection, statistical analyses, and drafted the manuscript. LL, WC, XS L, YQ Z and CL performed the data collection, statistical analyses. MH D, DL, ZP Y, XL and LB M performed the data collection. PC, YC and SC designed, coordinated the research and helped with editing of the paper. All authors revised the article critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published.

Data sharing statement

The datasets are available in the Department of Pulmonary and Critical Care Medicine, the Second Xiangya Hospital repository (http://120.77.177.175:9007/a/login). The data that support the findings of this study are available upon reasonable request from the corresponding author Ping Chen.

References

1. Lareau SC, Fahy B, Meek P, Wang A. Chronic Obstructive Pulmonary Disease (COPD). Am J Respir Crit Care Med. 2019;199(1):P1-P2. doi: 10.1164/rccm.1991P1.
2. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the

Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585-596. doi: 10.1016/S2213-2600(20)30105-3.

3. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respir Res. 2017;18(1):67. doi: 10.1186/s12931-017-0548-3.

4. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54. doi: 10.1183/09031936.00102509.

5. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6. doi: 10.1136/thx.54.7.581.

6. Global Initiative for Chronic Obstructive Lung Disease Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease; 2020 [updated 2020 Nov 4; accessed 2020 Oct 25]. Available from: http://www.goldcopd.org/].

7. Ding B, Small M, Bergström G, Holmgren U. COPD symptom burden: impact on health care resource utilization, and work and activity impairment. Int J Chron Obstruct Pulmon Dis. 2017;12:677-689. doi: 10.2147/COPD.S123896.

8. Kim MA, Suh MK, Park J, Kim JH, Kim TH, Kim EK, et al. Impact of symptom variability on clinical outcomes in COPD: analysis of a longitudinal cohort. Int J Chron Obstruct Pulmon Dis. 2019;14:2135-2144. doi: 10.2147/COPD.S203715.

9. Praveen CK, Manu M, Mohapatra AK, Pentapati KC. Power of BODE Index in Predicting Future Exacerbations of COPD: A Prospective Observational Study in Indian Population. J Assoc Physicians India. 2019;67(4):14-16.
10. GOLD Executive Committee, Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (2017 REPORT). Available online: https://goldcopd.org/. Accessed Nov 2016.
11. Kobayashi S, Hanagama M, Ishida M, Sato H, Ono M, Yamanda S, et al. Clinical characteristics and outcomes in Japanese patients with COPD according to the 2017 GOLD classification: the Ishinomaki COPD Network Registry. Int J Chron Obstruct Pulmon Dis. 2018;13:3947-3955. doi: 10.2147/COPD.S182905.
12. Le LAK, Johannessen A, Hardie JA, Johansen OE, Gulsvik A, Vikse BE, et al. Prevalence and prognostic ability of the GOLD 2017 classification compared to the GOLD 2011 classification in a Norwegian COPD cohort. Int J Chron Obstruct Pulmon Dis. 2019;14:1639-1655. doi: 10.2147/COPD.S194019.
13. Lee SJ, Yun SS, Ju S, You JW, Cho YJ, Jeong YY, et al. Validity of the GOLD 2017 classification in the prediction of mortality and respiratory hospitalization in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2019;14:911-919. doi: 10.2147/COPD.S191362.
14. Kahnert K, Alter P, Young D, Lucke T, Heinrich J, Huber RM, et al. The revised GOLD 2017 COPD categorization in relation to comorbidities. Respir Med. 2018;134:79-85. doi: 10.1016/j.rmed.2017.12.003. Epub 2017 Dec 5.
15. Song Q, Zhao YY, Zeng YQ, Liu C, Cheng W, Deng MH, et al. The Characteristics of Airflow Limitation and Future Exacerbations in Different GOLD Groups of COPD

Patients. Int J Chron Obstruct Pulmon Dis. 2021;16:1401-1412. doi: 10.2147/COPD.S309267.

16. Cabrera López C, Casanova Macario C, Marín Trigo JM, de-Torres JP, Sicilia Torres R, González JM, et al. Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes. Am J Respir Crit Care Med. 2018;197(4):463-469. doi: 10.1164/rccm.201707-1363OC.
17. Zhao YY, Liu C, Zeng YQ, Zhou AY, Duan JX, Cheng W, et al. Modified and simplified clinically important deterioration: multidimensional indices of short-term disease trajectory to predict future exacerbations in patients with chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2020;14:1753466620977376. doi: 10.1177/1753466620977376.
18. Hirschmann JV. Do bacteria cause exacerbations of COPD? Chest. 2000;118(1):193-203. doi: 10.1378/chest.118.1.193.
19. Duan JX, Cheng W, Zeng YQ, Chen Y, Cai S, Li X, et al. Characteristics of Patients with Chronic Obstructive Pulmonary Disease Exposed to Different Environmental Risk Factors: A Large Cross-Sectional Study. Int J Chron Obstruct Pulmon Dis. 2020;15:2857-2867. doi: 10.2147/COPD.S267114.
20. Zeng Y, Cai S, Chen Y, Duan J, Zhao Y, Li X, et al. Current Status of the Treatment of COPD in China: A Multicenter Prospective Observational Study. Int J Chron Obstruct Pulmon Dis. 2020;15:3227-3237. doi: 10.2147/COPD.S274024.
21. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med.

2019;200(8):e70-e88. doi: 10.1164/rccm.201908-1590ST.

22. Han MZ, Hsiue TR, Tsai SH, Huang TH, Liao XM, Chen CZ. Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3425-3433. doi: 10.2147/COPD.S179048.
23. Po JY, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. Thorax. 2011;66(3):232-9. doi: 10.1136/thx.2010.147884. Epub 2011 Jan 19.
24. Pathak U, Gupta NC, Suri JC. Risk of COPD due to indoor air pollution from biomass cooking fuel: a systematic review and meta-analysis. Int J Environ Health Res. 2020;30(1):75-88. doi: 10.1080/09603123.2019.1575951.
25. Cheng LL, Liu YY, Su ZQ, Liu J, Chen RC, Ran PX. Clinical characteristics of tobacco smoke-induced versus biomass fuel-induced chronic obstructive pulmonary disease. J Transl Int Med. 2015;3(3):126-129. doi: 10.1515/jtim-2015-0012.
26. Dutt D, Srinivasa D.K, Rotti S.B, Sahai A.K. Effect of indoor air pollution on the respiratory system of women using different fuels for cooking in an urban slum of Pondicherry. Natl. Med J. India. 1996;9:113–117.
27. Boezen HM, Schouten JP, Postma DS, Rijcken B. Relation between respiratory symptoms, pulmonary function and peak flow variability in adults. Thorax. 1995;50(2):121-6. doi: 10.1136/thx.50.2.121.
28. Brodkin CA, Barnhart S, Anderson G, Checkoway H, Omenn GS, Rosenstock L. Correlation between respiratory symptoms and pulmonary function in asbestos-exposed workers. Am Rev Respir Dis. 1993;148(1):32-7. doi:

10.1164/ajrccm/148.1.32.

29. Krzyzanowski M, Camilli AE, Lebowitz MD. Relationships between pulmonary function and changes in chronic respiratory symptoms. Comparison of Tucson and Cracow longitudinal studies. Chest. 1990;98(1):62-70. doi: 10.1378/chest.98.1.62.
30. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2013.
31. Sundh J, Janson C, Lisspers K, Montgomery S, Ställberg B. Clinical COPD Questionnaire score (CCQ) and mortality. Int J Chron Obstruct Pulmon Dis. 2012;7:833-42. doi: 10.2147/COPD.S38119.
32. Dong H, Hao Y, Li D, Su Z, Li W, Shi B, et al. Risk Factors for Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Industrial Regions of China: A Multicenter Cross-Sectional Study. Int J Chron Obstruct Pulmon Dis. 2020;15:2249-2256. doi: 10.2147/COPD.S270729.
33. Miravitlles M, Izquierdo JL, Esquinas C, Pérez M, Calle M, López-Campos JL, et al. The variability of respiratory symptoms and associated factors in COPD. Respir Med. 2017;129:165-172. doi: 10.1016/j.rmed.2017.06.017.
34. Kim J, Lee CH, Lee MG, Shin KC, Yoo KH, Lim SY, et al. Acute Exacerbation According to GOLD 2017 Categories in Patients with Chronic Obstructive Pulmonary Disease. Arch Bronconeumol (Engl Ed). 2019;55(8):414-420. English, Spanish. doi: 10.1016/j.arbres.2019.02.004.
35. Cabrera López C, Casanova Macario C, Marín Trigo JM, de-Torres JP, Sicilia Torres R, González JM, et al. Comparison of the 2017 and 2015 Global Initiative for

Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes. Am J Respir Crit Care Med. 2018;197(4):463-469. doi: 10.1164/rccm.201707-1363OC.

36. Putcha N, Anzueto AR, Calverley PMA, Celli BR, Tashkin DP, Metzdorf N, et al. Mortality and Exacerbation Risk by Body Mass Index in Patients with COPD in TIOSPIR® and UPLIFT®. Ann Am Thorac Soc. 2021. doi: 10.1513/AnnalsATS.202006-722OC.
37. Flattet Y, Garin N, Serratrice J, Perrier A, Stirnemann J, Carballo S. Determining prognosis in acute exacerbation of COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:467-475. doi: 10.2147/COPD.S122382.
38. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. Thorax. 2015;70(5):482-9. doi: 10.1136/thoraxjnl-2014-206084.
39. Olloquequi J, Jaime S, Parra V, Cornejo-Córdova E, Valdivia G, Agustí À, et al. Comparative analysis of COPD associated with tobacco smoking, biomass smoke exposure or both. Respir Res. 2018;19(1):13. doi: 10.1186/s12931-018-0718-y.
40. Pezzuto A, Carico E. Effectiveness of smoking cessation in smokers with COPD and nocturnal oxygen desaturation: Functional analysis. Clin Respir J. 2020;14(1):29-34. doi: 10.1111/crj.13096.
41. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet. 2018;391(10131):1706-1717. doi: 10.1016/S0140-6736(18)30841-9.
42. Fang L, Gao P, Bao H, Tang X, Wang B, Feng Y, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med.

2018;6(6):421-430. doi: 10.1016/S2213-2600(18)30103-6.

43. Han MZ, Hsiue TR, Tsai SH, Huang TH, Liao XM, Chen CZ. Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3425-3433. doi: 10.2147/COPD.S179048.

44. Hu YH, Liang ZY, Xu LM, Xu WH, Liao H, Li R, et al. Comparison of the clinical characteristics and comprehensive assessments of the 2011 and 2017 GOLD classifications for patients with COPD in China. Int J Chron Obstruct Pulmon Dis. 2018;13:3011-3019. doi: 10.2147/COPD.S174668.

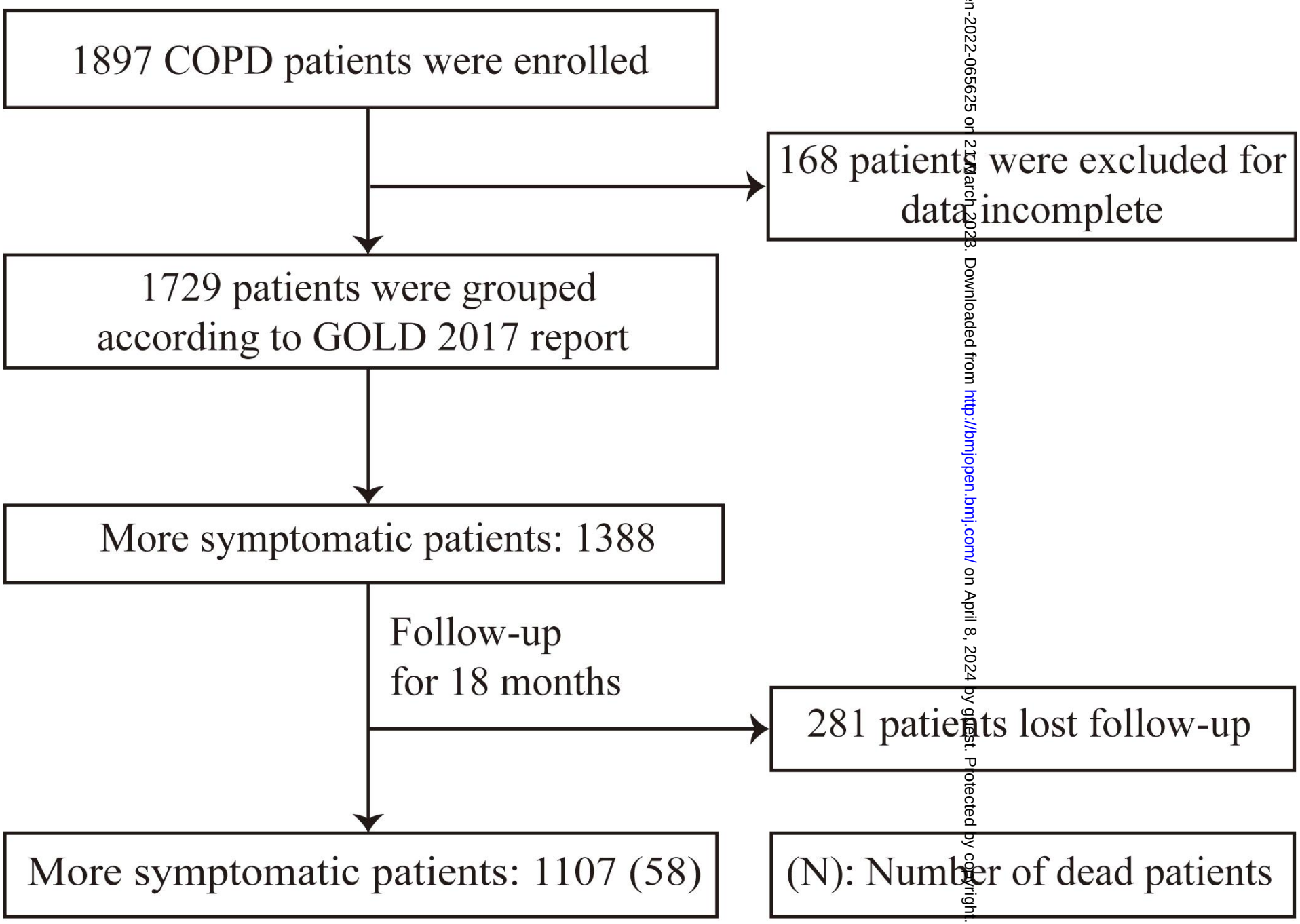
45. Zha Z, Leng R, Xu W, Bao H, Chen Y, Fang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in Anhui Province, China: a population-based survey. BMC Pulm Med. 2019;19(1):102. doi: 10.1186/s12890-019-0864-0.

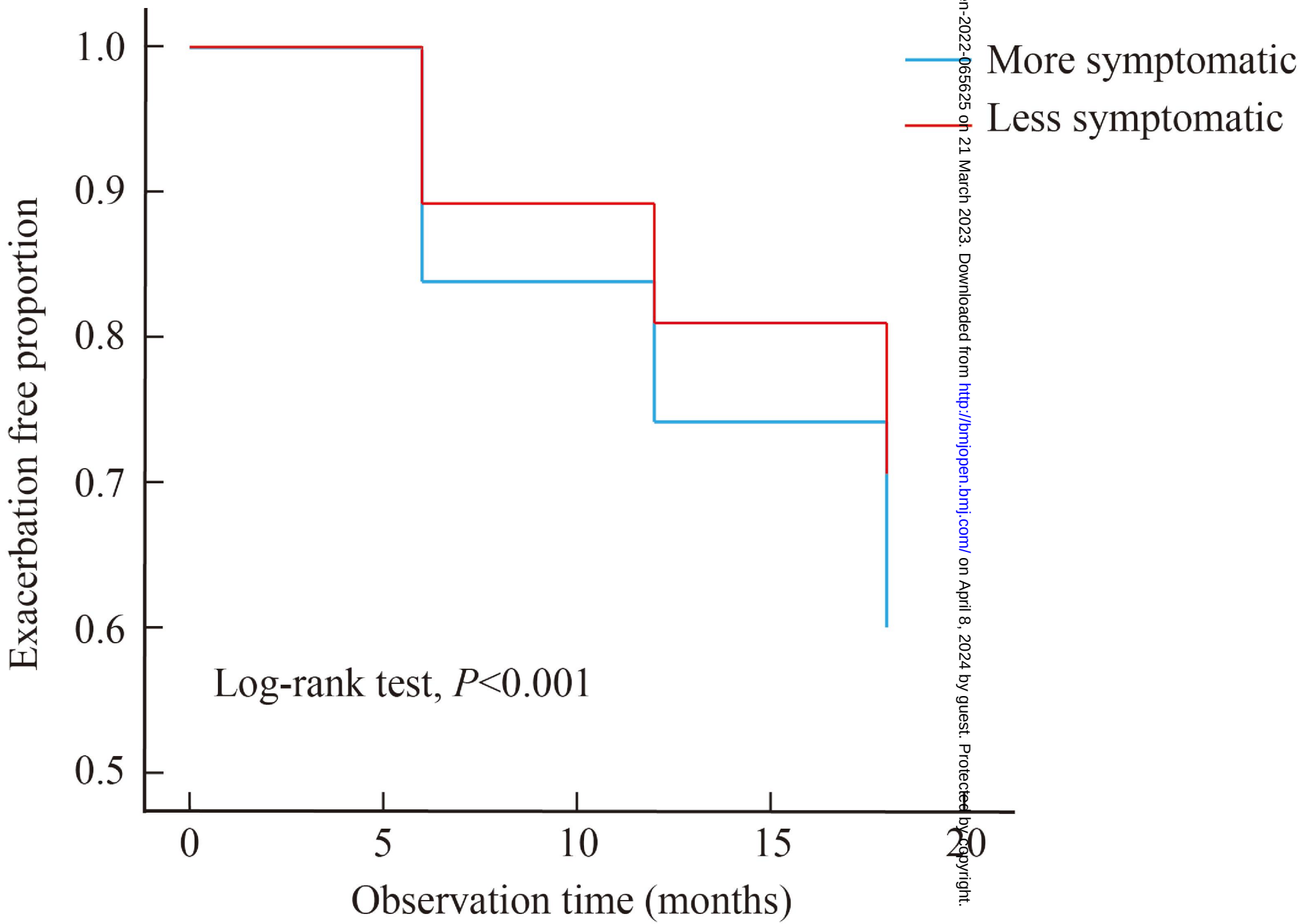
Figure captions

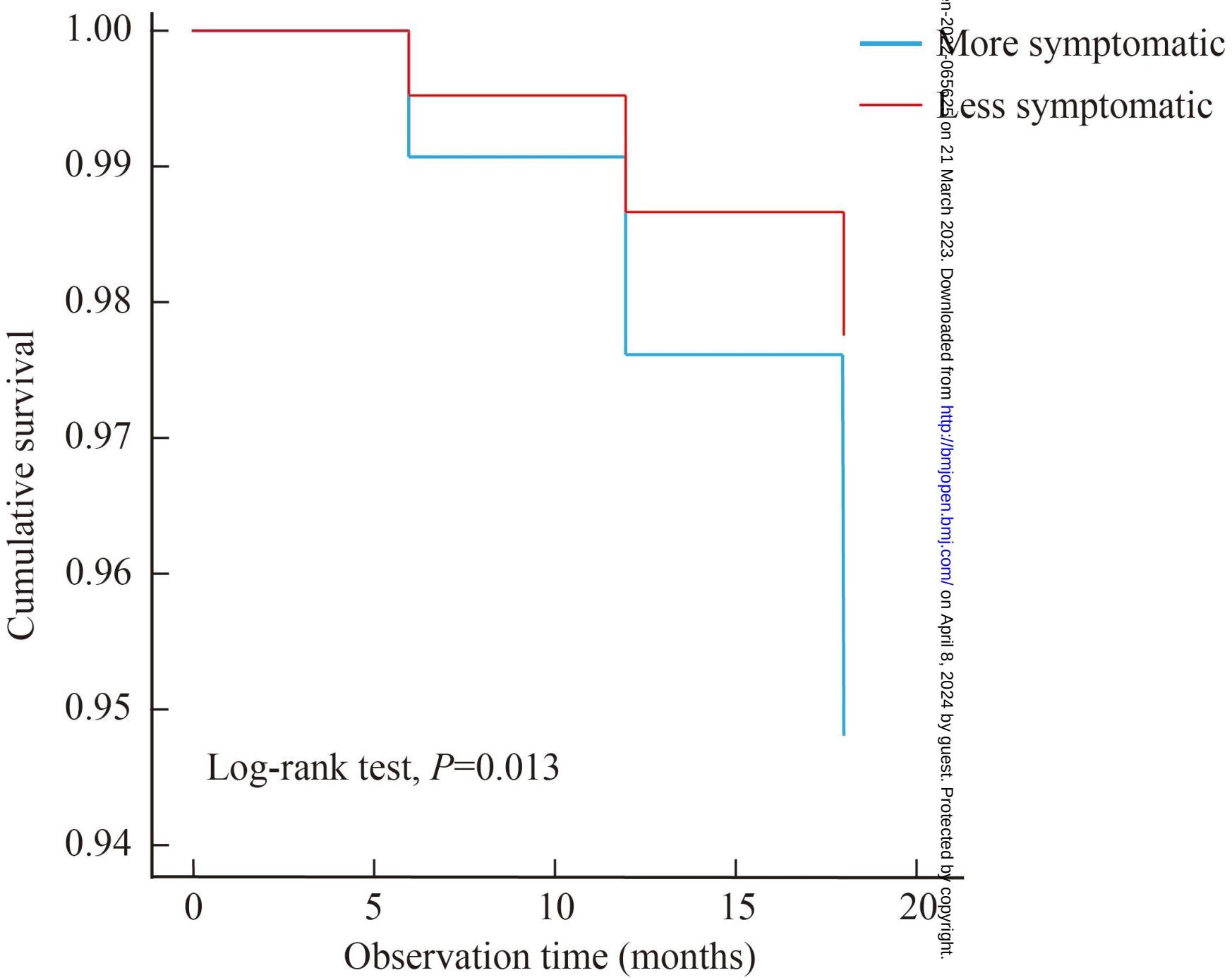
Figure 1. Flow chart. COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Figure 2. Kaplan-Meier curves of the exacerbation free proportion between more and less symptomatic COPD patients; $P < 0.05$ was considered to be statistically significant. COPD, Chronic Obstructive Pulmonary Disease.

Figure 3. Kaplan-Meier curves of the overall survival between more and less symptomatic COPD patients; $P < 0.05$ was considered to be statistically significant. COPD, Chronic Obstructive Pulmonary Disease.







Supplementary table 1. Exacerbation and mortality after 18 months of follow-up in COPD patients with different smoke history.

Variables	Never smoker (n = 234)	Former smoker (n = 478)	Current smoker (n = 695)	*P* - value
Exacerbations, (Mean ± SD)	0.8 ± 1.5	0.9 ± 1.4	1.5 ± 1.9 [a, b]	0.008
Exacerbations, n (%)				0.006
0	178 (73.6)	327 (70.2)	438 (66.1) [a, b]	
1	28 (13.2)	63 (14.4)	108 (16.3)	
≥2	22 (13.2)	61 (15.4)	117 (17.6) [a, b]	
Hospitalizations, (Mean ± SD)	0.4 ± 1.0	0.4 ± 0.8	0.6 ± 1.2 [a, b]	0.045
Hospitalizations, n (%)				0.035
0	182 (79.8)	361 (78.8)	480 (73.2) [a, b]	
≥1	46 (20.2)	97 (21.2)	176 (26.8) [a, b]	
Mortality, n (%)	6 (2.6)	20 (4.2)	39 (5.6)	0.135

Notes: [a] Compared with the Never smoker group, $P < 0.05$; [b] Compared with the Former smoker group, $P < 0.05$.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; SD, Standard Deviation.

Supplementary table 2. Exacerbation and mortality after 18 months of follow-up in COPD patients with different amounts of smoking (packs/year).

Variables	< 10 packs/year (n = 239)	≥ 10 packs/year (n = 1168)	*P*-value
Exacerbations, (Mean ± SD)	0.8 ± 1.5	0.7 ± 1.3	0.306
Exacerbations, n (%)			0.949
0	147 (62.8)	692 (62.5)	
1	39 (16.7)	194 (17.5)	
≥2	48 (20.5)	222 (20.0)	
Hospitalizations, (Mean ± SD)	0.4 ± 1.0	0.4 ± 0.8	0.753
Hospitalizations, n (%)			0.298
0	180 (76.9)	816 (73.6)	
≥1	54 (23.1)	292 (26.4)	
Mortality, n (%)	5 (2.5)	60 (5.1)	0.045

Note: COPD, Chronic Obstructive Pulmonary Disease; SD, Standard Deviation.

Supplementary table 3. The baseline characteristics of more symptomatic COPD patients who remained in the study and lost to follow-up.

Variables	More symptomatic patients		*P*-value
	A_1 (n=1107)	A_2 (n=281)	
Age (years), (Mean ± SD)	65.5 ± 8.0	65.6 ± 8.0	0.813
Sex, n (%)			
Male	988 (89.3)	250 (89.0)	
Female	119 (10.7)	31 (11.0)	
Education level, n (%)			0.158
Primary school	455 (41.1)	130 (46.3)	
Junior high school	428 (38.7)	88 (31.3)	
High school	173 (15.7)	49 (17.4)	
University	51 (4.6)	14 (5.0)	
BMI (kg/m^2)	22.3 ± 3.7	22.5 ± 3.7	
Smoke history, n (%)			0.290
Never smoker	187 (16.9)	53 (18.9)	
Former smoker	385 (34.8)	84 (29.9)	
Current smoker	535 (48.3)	144 (51.2)	
Smoking, (packs/year), (Mean ± SD)	37.5 ± 28.6	36.1 ± 26.7	0.433
Biofuel exposure, n (%)			0.493
Yes	440 (39.8)	118 (42.0)	
No	667 (60.2)	163 (58.0)	
Occupational exposure, n (%)			0.629
Yes	416 (37.6)	110 (39.1)	
No	691 (62.4)	171 (60.9)	
Pulmonary function, (Mean ± SD)			
FEV1	1.8 ± 0.5	1.2 ± 0.5	0.908
FEV1 %pred	48.6 ± 19.0	49.5 ± 19.1	0.480
FVC	2.6 ± 0.7	2.6 ± 0.7	0.439
FEV1/FVC	44.4 ± 12.2	44.7 ± 12.1	0.664
PEF	3.2 ± 1.4	3.1 ± 1.4	0.498
GOLD stages, n (%)			0.706
1	71 (6.4)	19 (6.8)	
2	408 (36.9)	110 (39.1)	
3	427 (38.6)	109 (38.8)	
4	201 (18.1)	43 (15.3)	
CAT, (Mean ± SD)	17.6 ± 5.4	17.3 ± 5.2	0.400
mMRC, (Mean ± SD)	2.3 ± 0.9	2.3 ± 0.9	0.885
CCQ, (Mean ± SD)	23.7 ± 6.5	23.2 ± 6.4	0.206
Treatments, n (%)			
LAMA	363 (32.8)	101 (35.9)	0.317
LABA + ICS	82 (7.4)	15 (5.3)	0.224
LAMA + LABA	24 (2.2)	3 (1.1)	0.233
LAMA + LABA + ICS	558 (50.4)	137 48.8)	0.621

Oxygen therapy, n (%)			0.393
Yes	92 (8.3)	19 (6.8)	
No	1015 (91.7)	262 (93.2)	
Exacerbations in the past year, (Mean ± SD)	1.8 ± 3.3	1.9 ± 3.5	0.603
Hospitalizations in the past year, (Mean ± SD)	0.8 ± 1.5	0.7 ± 1.3	0.467

Notes: A_1: The COPD patients who remained in the study after 18 months of follow-up; A_2: The COPD patients who lost to follow-up.

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; LAMA, Long-Acting Muscarinic Antagonist; LABA, Long-Acting β2-Agonist; mMRC, modified Medical Research Council; PEF, Peak Expiratory Flow; SD, Standard Deviation.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) If applicable, explain how loss to follow-up was addressed	6-8
		(*e*) Describe any sensitivity analyses	6-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-11
		(b) Give reasons for non-participation at each stage	8-11
		(c) Consider use of a flow diagram	8-11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-11
		(b) Indicate number of participants with missing data for each variable of interest	8-11
		(c) Summarise follow-up time (eg, average and total amount)	8-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(*b*) Report category boundaries when continuous variables were categorized	8-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.