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

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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.

Design A retrospective cohort study.

Setting Data were obtained from patients enrolled in a database setup by Second Xiangya Hospital of Central South University.

Participants 1729 stable COPD patients listed from September 2017 to December 2019 in the database. The patients were classified into more and less symptomatic groups based on GOLD 2017 report.

Outcomes 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre study and the data derived from outpatient chronic obstructive pulmonary disease (COPD) database, which included several hospitals.
⇒ This study is the first to explore the independent risk factors for future exacerbation and mortality among more symptomatic patients with COPD according to Global Initiative for Chronic Obstructive Lung Disease report.
⇒ A key limitation is that 281 of the more symptomatic patients were lost to follow-up.
⇒ This study did not discuss the comorbidities that 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 dyspnoea. This disease has brought a huge burden of mortality to humanity[1 2]; 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 dyspnoea, 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 patients with COPD.[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 patients with COPD 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, dyspnoea, exercise capacity) index includes dyspnoea as a meaningful marker of future exacerbation risk.[9] In fact, some patients with COPD only experience cough or breathlessness, whereas others have multiple respiratory symptoms, including cough, expectoration, chest tightness and dyspnoea.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 evaluated patients with COPD 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 patients with COPD 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 more symptomatic patients with COPD 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 patients with COPD remained unclear. Therefore, our purpose was to analyse 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 Affiliated Hospital of Shaoyang University, the Eighth Hospital in Changsha and the Longshan Hospital of Traditional Chinese Medicine (Hunan, China). The inclusion criterion for patients with COPD 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.

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

Data collection and definitions

The baseline clinical characteristics included demographics, smoking 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 exacerbation and hospitalisation in the past year. Furthermore, we recorded mortality, and the number of exacerbation and hospitalisation 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] Exacerbation was defined as disease progression that requires antibiotics, oral corticosteroids or hospitalisation for treatment or was determined by a sputum colour 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 1 year. Occupational exposure was defined as exposure to dust, metals, chemical substances or other

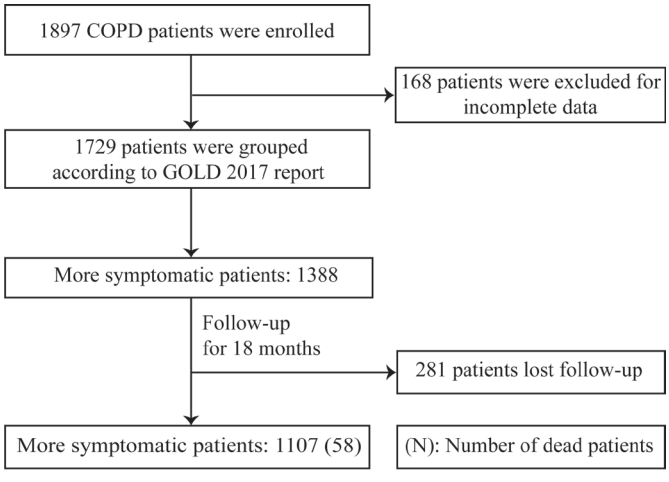

Figure 1 Flow chart. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 1 The baseline characteristics of the patients with COPD

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
Smoking 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)
Exacerbation in the past year, mean±SD	1.7±3.1
Exacerbation in the past year, n (%)	
0	753 (43.6)
1	412 (23.8)
≥2	564 (32.6)
Hospitalisation in the past year, mean±SD	0.7±1.3
Hospitalisation in the past year, n (%)	
0	1132 (65.5)
≥1	597 (34.5)

BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; PEF, peak expiratory flow.

environmental agents for at least 8 hours a day for at least 1 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 manoeuvre that started without hesitation from a position of maximal lung inflation.[21]

Statistical analysis

Continuous variables were presented as the mean±SD. The X^2 and Fisher's tests were used to analyse categorical variables. An independent-sample Student's t-test was used to analyse continuous variables. For variables with non-normal distribution or uneven variance, we used non-parametric tests. The variously adjusted OR was calculated using multivariate logistic regression. Two-sided p values of <0.05 were considered to be statistically significant. SPSS V.26.0 (IBM) was used to perform all statistical analyses.

Table 2 The clinical characteristics of more symptomatic patients with COPD

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
Smoking 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)	
Exacerbation in the past year, mean±SD	1.9±3.3	0.8±1.8	<0.001
Exacerbation 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)	
Hospitalisation in the past year, mean±SD	0.7±1.4	0.3±0.8	<0.001
Hospitalisation in the past year, n (%)			<0.001
0	872 (62.8)	260 (76.2)	
≥1	516 (37.2)	81 (23.8)	

BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; PEF, peak expiratory flow.

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 on 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 exacerbation and hospitalisation less than once per year (table 1).

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

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
Exacerbation in the past year	1.114	1.025–1.211	0.011

Adjusted for age, education level, biofuel exposure, FEV1, FEV1 %pred, FVC, GOLD stages, BMI and hospitalisation in the past year. P<0.05 is statistically significant in accordance with logistic regression analysis.
BMI, body mass index; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PEF, peak expiratory flow.

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

Variables	Total (n=1407)	More symptomatic (n=1107)	Less symptomatic (n=300)	P value
Exacerbation, mean±SD	0.7±1.3	0.8±1.4	0.5±1.1	<0.001
Exacerbation, 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)	
Hospitalisation, mean±SD	0.4±0.8	0.4±0.9	0.2±0.6	<0.001
Hospitalisation, 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

COPD, chronic obstructive pulmonary disease.

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 were found in the more symptomatic group (p<0.05). Furthermore, more symptomatic patients with COPD had higher CCQ scores and a higher number of exacerbation and hospitalisation in the past year (p<0.001) (table 2).

Multivariate analysis of risk factors associated with more symptomatic patients with COPD

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 ORs 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 exacerbation in the past year were positively correlated with the more symptomatic, with ORs of 1.200 (95% CI=1.169–1.232) and 1.114 (95% CI=1.025–1.211), respectively (p<0.05) (table 3).

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 exacerbation and hospitalisation were 0.7±1.3 and 0.4±0.8, respectively. Most of the patients suffered exacerbation and hospitalisation less than once per year and the mortality rate was 4.6%.

After 18 months of follow-up, 1107 more symptomatic patients with COPD were analysed for future exacerbation and mortality. The results show that the more symptomatic patients with COPD suffered from a higher number of exacerbation and hospitalisation (p<0.001). The proportion of more symptomatic patients who suffered from exacerbation and hospitalisation at least once per year was higher (p<0.001), with rates of 40.8%

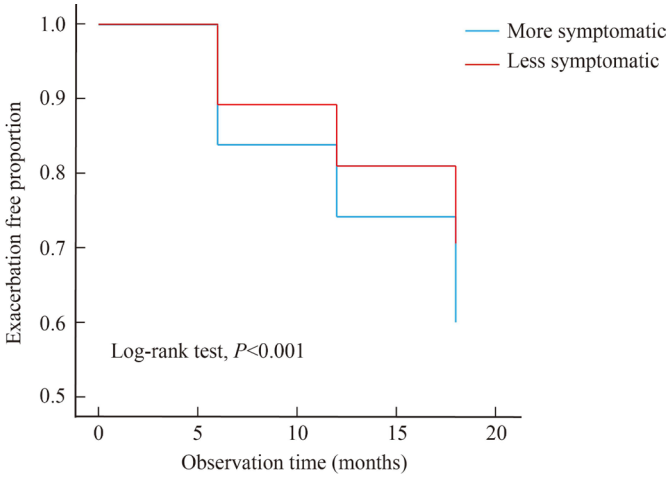

Figure 2 Kaplan-Meier curves of the exacerbation-free proportion between more and less symptomatic patients with COPD; p<0.05 was considered to be statistically significant. COPD, chronic obstructive pulmonary disease.

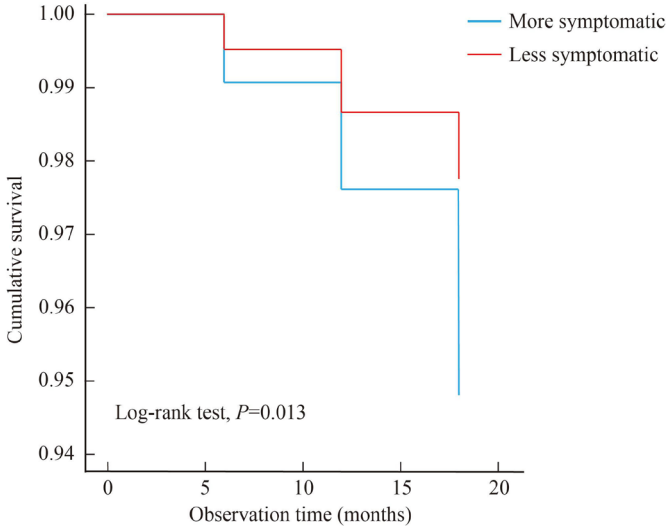

Figure 3 Kaplan-Meier curves of the overall survival between more and less symptomatic patients with COPD; p<0.05 was considered to be statistically significant. COPD, chronic obstructive pulmonary disease.

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

	Univariate			Multivariate		
Variables	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			
Smoking 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			

Continued

Table 5 Continued

Variables	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Oxygen therapy						
No	Reference					
Yes	1.526	0.986–2.363	0.058			
Exacerbation in the past year	1.057	1.001–1.117	0.049	1.016	0.933–1.107	0.711
Hospitalisation in the past year	1.143	1.014–1.289	0.029	1.108	0.948–1.295	0.198

BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; PEF, peak expiratory flow.

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 patients with COPD 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 analyses of risk factors for mortality in more symptomatic patients with COPD

Of the 1107 more symptomatic patients with COPD, 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), exacerbation in the past year (OR=1.057, 95% CI=1.001–1.117, p=0.049) and hospitalisation 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 patients with COPD (table 5).

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

In total, 428 of 1107 more symptomatic patients with COPD 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 20–29 (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), exacerbation in the past year (OR=1.098, 95% CI=1.049–1.149, p<0.001) and hospitalisation 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 exacerbation 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 patients with COPD (table 6).

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, patients with COPD with biofuel exposure experienced more dyspnoea.[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 patients with COPD had a higher biofuel exposure rate. Maintenance of inhaled bronchodilators and ICS could reduce respiratory symptoms and exacerbation, and 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 a study done by Kobayashi *et al*.[11]

Pulmonary function is used to evaluate airflow limitation and severity of patients with COPD. Our research also found that more symptomatic patients with COPD 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

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

	Univariate			Multivariate		
Variables	**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
Smoking 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			

Continued

Table 6 Continued

Variables	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
LAMA+LABA+ICS	0.813	0.635–1.041	0.100			
Oxygen therapy						
No	Reference					
Yes	1.755	0.806–3.818	0.156			
Exacerbation in the past year	1.098	1.049–1.149	<0.001	1.061	1.013–1.112	0.013
Hospitalisation in the past year	1.208	1.094–1.335	<0.001	1.078	0.965–1.204	0.183

BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; PEF, peak expiratory flow.

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 dyspnoea were inversely related to pulmonary function. Another study found that initial FEV1 level was lower in patients with dyspnoea 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 patients with COPD.[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 exacerbation in the past year. Moreover, the higher the number of exacerbation, the more symptoms the patients experienced. Miravitlles *et al*[33] also found that more exacerbation 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 exacerbation 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 hospitalisation 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*[16] 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*,[35] which showed that underweight participants had a significantly higher risk of death and severe exacerbation.

Death is the most serious malignant event associated with COPD,[36] and it is vital to analyse the risk factors for death in patients with COPD. Our results showed that age, smoking (packs/year) and CAT scores were positively correlated with mortality. Age and smoking are important risk factors associated with COPD development,[37 38] 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 exacerbation is an important deterioration event in patients with COPD during follow-up. Therefore, it is necessary to analyse 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 exacerbation in the past year were positively correlated with future exacerbation. It is implied that the higher the mMRC scores and number of exacerbation in the past year, the higher the future exacerbation risk.

Smoking is an important risk factor for COPD development,[38] and it is important to demonstrate the effects of smoking on COPD exacerbation. Therefore, we further analysed the exacerbation and mortality after 18 months of follow-up in patients with COPD with different smoking histories. We found that current smokers had higher exacerbation and hospitalisation rates than former smokers and never smokers (online supplemental table 1). Furthermore, patients with COPD who smoked more than 10 packs/year had higher mortality (online supplemental table 2). This implies that smoking cessation may decrease the risk of exacerbation and mortality in patients with COPD. A study by Pezzuto and Carico[39] 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 patients with COPD were lost to follow-up. However, we found that the characteristics of the patients

who were lost to follow-up and those who remained in the study were not significantly different (online supplemental 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 and because there were relatively few female patients who smoked.[40 41] Furthermore, several studies showed that the proportion of female patients was relatively small in China.[42–44] 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 would have an impact on future exacerbation and mortality.

In summary, our study revealed that the majority of patients with COPD 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 patients with COPD were identified, including age, smoking, mMRC scores, CAT scores and exacerbation in the past year. Therefore, clinicians should be aware of the risk factors and take them into account for interventions in more symptomatic patients with COPD.

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