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Determinants of Clinical COPD Questionnaire in Patients with COPD: A Cross-Sectional Observational Study

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Keywords
Chronic obstructive pulmonary disease · Clinical COPD Questionnaire · Health-related quality of life

Abstract

Background: The Clinical COPD Questionnaire (CCQ) has been suggested by the Global Initiative of Chronic Obstructive Lung Disease (GOLD) as a comprehensive symptom measurement tool, which helps to classify patients in order to direct pharmacological treatment. Therefore, it is essential to understand its determinants. ***Objectives:*** To identify the determinants of the overall CCQ score and scores of its 3 subdomains among chronic obstructive pulmonary disease (COPD) patients from China. ***Methods:*** A total of 1,241 COPD patients in the outpatient department of the Second Xiangya Hospital in China were recruited. Basic information and clinical data were collected. Differences in the GOLD categories based on Modified Medical Research Council Dyspnea Scale (mMRC), COPD Assessment Test (CAT), and CCQ were compared. Multiple linear regression analyses were performed to evaluate determinant factors of the total CCQ and subdomain scores. ***Results:*** The total CCQ and/or separate domain scores significantly differed with sex, age, BMI, smoking status, biomass fuel exposure, exacerbation frequency, mMRC, CAT, and GOLD grades and groups. Subjects with asthma-COPD overlap (ACO) had worse health status based on CCQ than those with COPD alone. As for the 16 subgroups based on GOLD 2017, statistical differences in the total CCQ and functional domain scores were found among subgroups 1A–4A, 1B–4B, and 1D–4D. The mMRC classified much more patients into more symptom groups than CAT and CCQ. No significant difference was observed in the GOLD categories between the CAT and CCQ (cut point = 1.5). Multiple linear regression analysis showed that smoking status, underweight, ACO, post-bronchodilator FEV1% predicted <50%, exacerbation history, and mMRC were independently associated with the total CCQ score. Only 3 variables were significantly associated with the symptom domain: ACO, exacerbations, and mMRC; for the functional domain, age ≥75 years, ACO, post-bronchodilator FEV1% predicted <50%, exacerbation history, and mMRC were significant; female sex, underweight, frequent exacerbations (≥2), and mMRC were significantly associated with higher scores in the mental do-

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main. ***Conclusions:*** The classification of COPD produced by mMRC, CAT, and CCQ was not identical. Smoking status, underweight, ACO, post-bronchodilator FEV1% predicted <50%, exacerbation history, and mMRC were associated with lower health-related quality of life assessed by the total CCQ score, while different subdomains of CCQ had different determinant factors.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation, which creates substantial social and economic burden worldwide, including China [1]. The importance of comprehensive assessment of symptoms has been acknowledged by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline. Both the COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ) were suggested by GOLD as comprehensive health status evaluation tools [2], which help to classify patients in order to direct pharmacological treatment, and due to their relevant role in the management of COPD, it is essential to understand their determinants.

However, compared with CAT, the CCQ has been much less studied in clinical practice. The CCQ was developed in 2003 and consists of 3 subdomains: symptom, functional, and mental [3]. It is a simple and practical tool, and commonly used in clinical populations with good reliability, validity, and responsiveness to interventions [4]. Importantly, it has been reported that more than half of patients preferred CCQ instead of CAT, because the CCQ had more details on breathing problems, and it was easier to understand the response option system as compared to the CAT [5].

Although, previous findings have shown that the overall CCQ score can distinguish COPD patients with different characteristics [6–10]; moreover, determinants of the CCQ have also been studied in the populations mainly from Sweden and Netherlands [10, 11]. However, the impact of different factors on the overall CCQ score and its 3 subdomains still remains an understudied area in real-life outpatients with COPD from China. Chinese patients with COPD have unique features compared with those from Western countries. Generally, they had lower BMI and more severe airflow limitation and experienced more exacerbations [12–17]. This is probably due to the delayed diagnosis and intervention for COPD in China [18]. In addition, biomass fuel, which is frequently used in rural areas of China, is one of the most important risk factors for COPD and has also been considered as an important feature for patients from developing countries [18–20]. It would be interesting and valuable to identify the association between CCQ and these important clinical variables, which enables Chinese health care professionals to improve their understanding of the score's application and interpretation in a heterogeneous sample of COPD patients.

In the present work, we evaluate the determinant factors of the overall CCQ score and its 3 subdomains among COPD patients with distinct characteristics from China, in addition, we also compare the differences in the GOLD categories based on Modified Medical Research Council Dyspnea Scale (mMRC), CAT, and CCQ.

Methods

Study Sample

This was a cross-sectional observational study aimed to investigate the clinical usage of CCQ among COPD patients in China (Registration number: ChiCTR-OOC-15007352). The study was approved by the Institutional Review Board of the Second Xiangya Hospital of Central South University (Hunan, China) and conducted in accordance with the Declaration of Helsinki. Patients diagnosed with stable COPD in the outpatient department from November 2015 to December 2018 were enrolled. All patients were aged over 40 years. All patients received pulmonary function tests and had a ratio of the forced expiratory volume in 1 s to the forced vital capacity (FEV1/FVC) lower than 0.70 after bronchodilation. Patients who refused to participate in this survey or complete questionnaires (mMRC, CAT, and CCQ) or were under active treatment, such as for tuberculosis or pneumonia, were excluded.

Data Collection and Definitions

All participants in this study provided written informed consent. Information on age, sex, education level, BMI, smoking status, biomass fuel exposure, exacerbation history, history of asthma, lung function, and scores of mMRC, CAT, and CCQ were recorded.

The overall CCQ score ranges from 0 to 6 for 10 items, and it is divided into symptom, functional, and mental domains. The total score is calculated by adding all scores and dividing them by the number of questions, that is, 10. Similarly, domains are calculated by adding each domain's score and dividing by 4 for the symptom and functional domains and by 2 for the mental domain [3]. Higher scores indicate poorer quality of life.

The diagnosis of asthma-COPD overlap (ACO) was based on the GINA-GOLD consensus [21] and was identified by the features that it shares with both asthma and COPD. Current smokers are people who have smoked over 100 cigarettes in their lifetime and have smoked in the last 30 days; ex-smokers are people who have smoked over 100 cigarettes in their lifetime but have not smoked in the last 30 days; never-smokers are people who have

Table 1. Baseline characteristics of COPD patients included in this study

Characteristic	*n*	Value
Sex	1,241	
Male		1,066 (85.9)
Female		175 (14.1)
Age, years	1,241	63.31±8.93
BMI, kg/m^2	1,241	22.36±3.56
Education level	851	
Low		376 (44.2)
Middle		315 (37.0)
High		160 (18.8)
Smoking status	1,241	
Never smoker		263 (21.2)
Ex-smoker		562 (45.3)
Current smoker		416 (33.5)
Biomass fuel exposure	819	
No		386 (47.1)
Yes		433 (52.9)
Previous exacerbations in the last year	1,241	
0		525 (42.3)
1		303 (24.4)
2		170 (13.7)
≥3		243 (19.6)
FEV1/FVC	1,241	44.98±12.10
Post-bronchodilator FEV1% predicted	1,241	50.15±19.49
Comorbid with asthma (ACO)	1,241	
No		1,024 (82.5)
Yes		217 (17.5)
GOLD 2007	1,241	
GOLD I		101 (8.1)
GOLD II		461 (37.2)
GOLD III		510 (41.1)
GOLD IV		169 (13.6)
GOLD 2017	1,241	
Group A		123 (9.9)
Group B		579 (46.7)
Group C		30 (2.4)
Group D		509 (41.0)
mMRC	1,241	2.13±1.00
CAT	1,241	16.48±5.93
CCQ	1,241	
Total score		2.14±0.66
Symptom domain		2.47±0.79
Functional domain		1.84±0.76
Mental domain		2.04±1.14

Data are presented as absolute patient numbers (% of total population) or mean ± SD. BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified Medical Research Council Dyspnea Scale; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire.

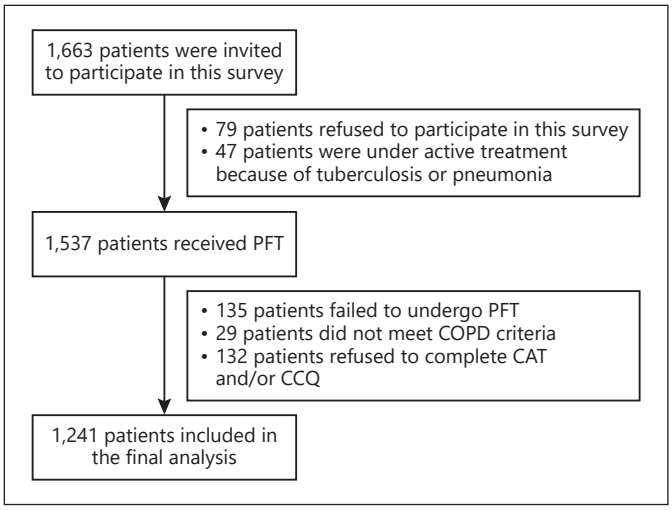

Fig. 1. Flowchart of patient selection. PFT, pulmonary function tests; COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire.

not smoked over 100 cigarettes in their lifetime and do not currently smoke. Exposure to biomass fuel was defined as the use of biofuel (wood, charcoal, grass, and crop residues) for cooking or heating ≥1 year [22].

According to GOLD 2017, an exacerbation was defined as an acute worsening of respiratory symptoms that results in additional therapy [23]. Therefore, the details about the definition of AECOPD in this study were as follows: acute worsening or new onset of any respiratory symptoms (cough, sputum volume or purulence, wheezing, or dyspnea) for at least 3 days that leads to any one of following situations: (1) requiring prescription change: increase in the dose or/and frequency of bronchodilator at home or requiring treatment with oral corticosteroids or/and antibiotics under the guidance of a physician in the outpatient department; (2) requiring hospitalization and diagnosed with AECOPD; (3) requiring an emergency room visit and diagnosed with AECOPD.

For disease severity, participants were classified into GOLD grades 1–4 based on spirometry. According to GOLD 2017, we used exacerbation history and CAT score (cut point: 10) to determine ABCD groups; moreover, we further subdivided subjects into 16 subgroups (1A–4D) based on their lung function [23].

Statistical Analysis

Differences in the total CCQ score and all separate domains among patients with distinct characteristics were compared using the Student *t* test or Mann-Whitney U test for two-group comparisons and using ANOVA for multiple-group comparisons. The χ^2 test was used to compare the differences in the GOLD categories based on mMRC, CAT, and CCQ. Back stepwise linear regression analysis using the total CCQ score and 3 subdomain scores as dependent variables was conducted to identify their determinants. All covariates were included in the multivariate models. An adjusted coefficient of determination (R^2) was also calculated. All statistical analyses were performed using SPSS 23, and a p value <0.05 was considered statistically significant.

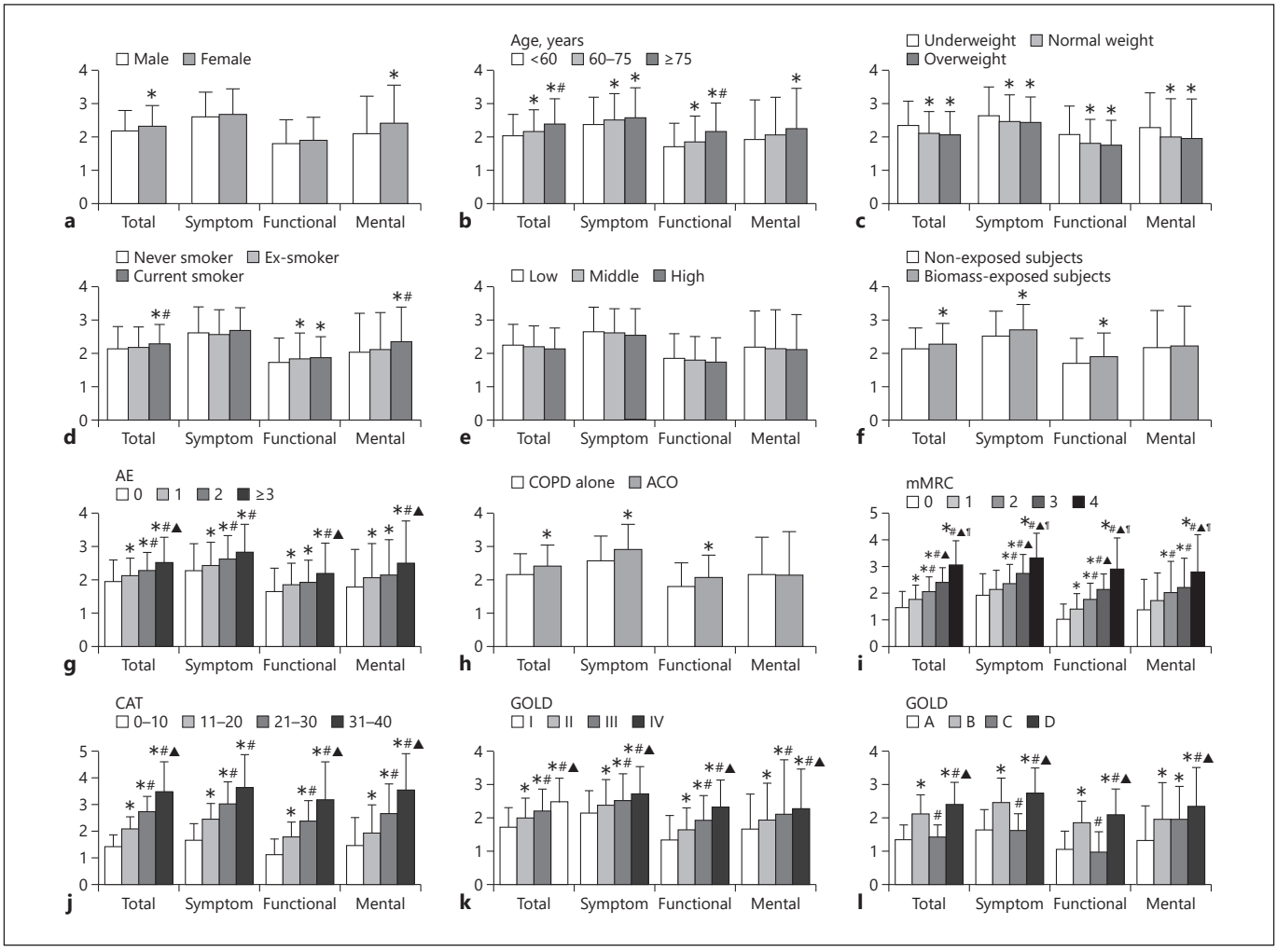

Fig. 2. CCQ total and domain scores according to COPD subpopulations. **a** CCQ according to sex. * $p < 0.05$ vs. male patients. **b** CCQ score according to age. * $p < 0.05$ vs. age <60 years; # $p < 0.05$ vs. 60≤ age <75 years. **c** CCQ score according to BMI. * $p < 0.05$ vs. underweight. **d** CCQ score according to smoking status. * $p < 0.05$ vs. never smoker; # $p < 0.05$ vs. ex-smoker. **e** CCQ score according to education level. **f** CCQ score according to biomass exposure. * $p < 0.05$ vs. non-exposed subjects. **g** CCQ score according to exacerbation frequency in the last year. * $p < 0.05$ vs. AE = 0; # $p < 0.05$ vs. AE = 1; ▲ $p < 0.05$ vs. AE = 2. **h** CCQ score according to comorbidity. * $p < 0.05$ vs. COPD alone. **i** CCQ score according to mMRC. * $p < 0.05$ vs. mMRC = 0; # $p < 0.05$ vs. mMRC = 1; ▲ $p < 0.05$ vs. mMRC = 2; ❡ $p < 0.05$ vs. mMRC = 3. **j** CCQ score according to CAT. * $p < 0.05$ vs. CAT = 0–10; # $p < 0.05$ vs. CAT = 11–20. ▲ $p < 0.05$ vs. CAT = 21–30. **k** CCQ score according to GOLD 2007. * $p < 0.05$ vs. GOLD I; # $p < 0.05$ vs. GOLD II; ▲ $p < 0.05$ vs. GOLD III. **l** CCQ score according to GOLD 2017. * $p < 0.05$ vs. GOLD A; # $p < 0.05$ vs. GOLD B; ▲ $p < 0.05$ vs. GOLD C. BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ACO, asthma-chronic obstructive pulmonary disease overlap; mMRC, Modified Medical Research Council Dyspnea Scale; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire.

Results

Study Population

A total of 1,241 subjects with stable COPD from the outpatient department were finally included in this analysis (Fig. 1). Table 1 describes their demographic and clinical characteristics. The majority of patients were male (85.9%), with an average age of 63.31 years, and the mean BMI of 22.36 kg/m^2. The mean (SD) FEV1/FVC was 44.98% (12.10%) and the mean (SD) post-bronchodilator FEV1% predicted was 50.15% (18.4%). More than half of the patients had experienced one or more exacerbations in the past year. The average scores (mean ± SD) of the overall CCQ and symptom, functional, and mental

Table 2. CCQ score according to GOLD 2017 classification (n = 1,241)

Obstruction	n (%)	CCQ			
		total	symptom	functional	mental
Group A					
GOLD I (1A)	26 (21.1)	1.06±0.38	1.39±0.55	0.76±0.52	1.02±0.92
GOLD II (2A)	55 (44.7)	1.33±0.22	1.31±0.47	0.95±0.49	1.38±1.25
GOLD III (3A)	38 (30.9)	1.36±0.44	1.79±0.49	1.31±0.46	1.20±0.92
GOLD IV (4A)	4 (3.3)	1.51±0.35	1.68±0.65	1.37±0.52	1.53±1.11
p value		<0.001	0.037	<0.001	0.187
Group B					
GOLD I (1B)	45 (7.8)	1.99±0.46	2.38±0.55	1.67±0.64	1.82±1.11
GOLD II (2B)	228 (39.4)	2.01±0.43	2.37±0.65	1.69±0.49	1.91±1.01
GOLD III (3B)	245 (42.3)	2.18±0.64	2.49±0.79	1.92±0.72	1.99±1.15
GOLD IV (4B)	61 (10.5)	2.46±0.47	2.75±0.76	2.28±0.55	2.06±1.03
p value		<0.001	0.004	<0.001	0.592
Group C					
GOLD I (1C)	5 (16.7)	1.30±0.2	1.63±0.43	0.56±0.43	2.13±1.03
GOLD II (2C)	15 (50.0)	1.41±0.36	1.71±0.41	0.86±0.49	1.89±1.13
GOLD III (3C)	7 (23.3)	1.48±0.40	1.29±0.56	1.29±0.77	2.25±0.61
GOLD IV (4C)	3 (10.0)	1.75±0.71	2.13±0.18	1.63±0.18	1.25±0.35
p value		0.496	0.124	0.079	0.642
Group D					
GOLD I (1D)	25 (4.9)	1.95±0.51	2.42±0.61	1.45±0.62	2.02±0.80
GOLD II (2D)	163 (32.0)	2.33±0.61	2.76±0.73	1.96±0.65	2.21±1.16
GOLD III (3D)	220 (43.2)	2.43±0.58	2.74±0.74	2.10±0.70	2.40±1.14
GOLD IV (4D)	101 (19.9)	2.59±0.78	2.81±0.81	2.41±0.93	2.47±1.23
p value		<0.001	0.137	<0.001	0.125

Data are presented as absolute patient numbers (% of total population) or mean ± SD. GOLD, Global Initiative for Chronic Obstructive Lung Disease; CCQ, Clinical COPD Questionnaire.

domains were 2.14 ± 0.66, 2.47 ± 0.79, 1.84 ± 0.76, and 2.04 ± 1.14, respectively. 17.5% of participants were diagnosed with ACO. According to GOLD spirometry-based severity criteria, 8.1% of patients had mild COPD (GOLD I), 37.2% had moderate disease (GOLD II), 41.1% had severe disease (GOLD III), and 13.6% had very severe disease (GOLD IV). Based on the GOLD 2017, 9.9% of patients were classified into group A, 46.7% in group B, 2.4% in group C, and 41% into group D.

CCQ Total and Domain Scores according to COPD Subpopulations

The total CCQ score and scores of the 3 domains were significantly higher in subjects with age ≥75 years, underweight, poorer health status assessed by mMRC and CAT, more severe airflow limitation, and exacerbations in the previous year (Fig. 2b, c, g, i–k). CCQ total and mental domain scores were significantly lower in men than in women (Fig. 2a). No statistical differences were found in CCQ symptom and functional domain scores between men and women. In addition, patients with different education levels had no significant differences in the total CCQ or domain scores (Fig. 2e). Current smokers showed increased total CCQ and mental domain scores compared to ex-smokers and never-smokers (Fig. 2d). The total CCQ, symptom, and functional domain scores were significantly higher in biomass-exposed subjects than in non-exposed subjects (Fig. 2f) and in subjects with ACO than in those with COPD alone (Fig. 2h).

Based on GOLD 2017, the degree of airflow limitation was removed; however, the ABCD classification was solely based on the symptom burden and exacerbation history. Subjects in group D had higher total CCQ and domain scores than those in the other 3 groups. No significant differences were found in the scores of total CCQ and symptom and functional domains between group A

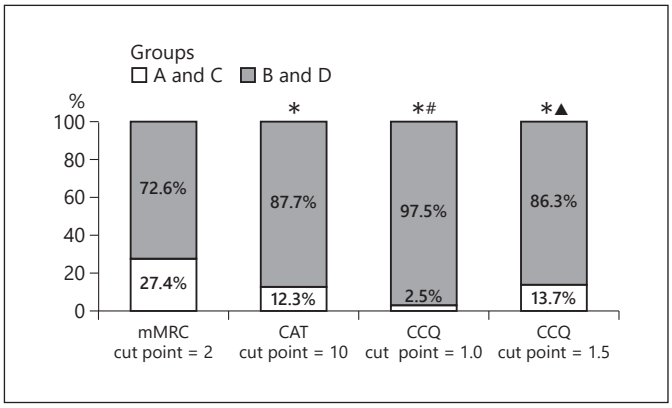

Fig. 3. Differences in classification of symptom groups using mMRC, CAT, and CCQ. * $p < 0.05$ vs. mMRC cut point = 2; # $p < 0.05$ vs. CAT cut point = 10; ▲ $p < 0.05$ vs. CCQ cut point = 1.0. mMRC, Modified Medical Research Council Dyspnea Scale; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire.

and C (Fig. 2l). We further subdivided the patients into 16 subgroups (1A–4D) based on the lung function. The total CCQ and functional domain scores were significantly increased in subgroups 1–4A, 1–4B, and 1–4D. The total CCQ and symptom, functional, and mental domain scores were not statistically different among subgroups 1–4C. Although the mental domain score gradually increased from 1 to 4B and from 1 to 4D, no significant differences were observed among the subgroups (Table 2).

Differences in the GOLD Categories Based on mMRC, CAT, and CCQ

The mMRC classified 72.6% of patients into more symptom groups (groups B and D), which is statistically lower compared with the CAT (87.7%, cut point = 10) and CCQ (97.5% for cut point = 1.0 and 86.3% for cut point = 1.5). In addition, the CCQ cut point of 1.0 classified much more patients into more symptom groups than CAT. However, no significant difference was observed in the GOLD categories (groups AC vs. BD) between the CAT and CCQ with the cut point of 1.5 (Fig. 3).

Determinant Factors of Total CCQ and Domain Scores

In 819 subjects with complete data, the multiple linear regression analysis after including all covariates showed that smoking status, underweight, ACO, post-bronchodilator FEV1% predicted <50%, exacerbation history, and mMRC were significantly associated with the CCQ total score. Only 3 variables were independently associated with the symptom domain: ACO, exacerbation history, and mMRC. For the functional domain, age ≥75 years, ACO, post-bronchodilator FEV1% predicted <50%, exacerbation history, and mMRC remained significant, while female sex, underweight, frequent exacerbations (≥2) in the previous year, and mMRC were significantly associated with mental domain score (Table 3). The explained variance (adjusted R^2) of the multivariable models for the overall CCQ and symptom, functional, and mental domain scores were 39.4, 24.0, 40.7, and 8.4%, respectively.

Discussion

Our previous studies revealed that CCQ could classify patients into more severe categories compared to CAT, and the overall CCQ and 3 domain scores could discriminate among subjects with different disease severities [24]. In order to make a better understanding of the clinical usage of CCQ and its determinants in China, we enrolled participants for the past 2 years to increase the sample size, including those diagnosed with ACO. The major findings were as follows: (1) the total CCQ and/or 3 subdomain scores were statistically different among COPD subjects with distinct characteristics and disease severities; (2) as for the 16 subgroups based on GOLD 2017, significant differences in the total CCQ and functional domain scores were observed in subgroups 1A–4A, 1B–4B, and 1D–4D; (3) the classification of COPD produced by different status questionnaires was not identical; (4) smoking status, underweight, ACO, post-bronchodilator FEV1% predicted <50%, exacerbation history, and mMRC were significantly associated with the total CCQ score. However, different subdomains had different determinant factors: ACO, exacerbations, and mMRC were significantly associated with the symptom domain; age ≥75 years, ACO, post-bronchodilator FEV1% predicted <50%, exacerbation history, and mMRC were significant for the functional domain; higher scores in the mental domain were associated with female sex, underweight, frequent exacerbations (≥2), and mMRC.

In this study, significantly higher total CCQ scores were observed in women and older subjects. This result was consistent with the results of Joseph et al. [7]. However, Sundh et al. [8] did not find any significant difference in CCQ between men and women, and this could be explained by the distinct characteristics of the study population. Moreover, we found that the higher total CCQ score in women was mainly attributed to the worse psy-

Table 3. Multiple linear regression analyses to determine factors associated with the total CCQ and its individual domains (n = 819)

	β	95% CI	p value
CCQ total score			
BMI			
Underweight vs. normal	0.139	0.038–0.240	0.007
Smoking status	0.117	0.031–0.203	0.008
Comorbidity			
ACO vs. COPD alone	0.135	0.032–0.238	0.010
Post-bronchodilator FEV1% predicted <50% vs. ≥50%	0.086	0.012–0.159	0.023
Number of exacerbations in the previous year			
1 vs. 0	0.140	0.051–0.230	0.002
2 vs. 0	0.385	0.278–0.492	<0.001
≥3 vs. 0	0.451	0.357–0.545	<0.001
mMRC	0.232	0.196–0.268	<0.001
CCQ symptom domain			
Comorbidity			
ACO vs. COPD alone	0.257	0.122–0.393	<0.001
Number of exacerbations in the previous year			
1 vs. 0	0.160	0.041–0.279	0.008
2 vs. 0	0.436	0.295–0.577	<0.001
≥3 vs. 0	0.487	0.363–0.610	<0.001
mMRC	0.204	0.158–0.251	<0.001
CCQ functional domain			
Age (≥75 vs. <60)	0.203	0.073–0.333	0.002
Comorbidity			
ACO vs. COPD alone	0.170	0.052–0.287	0.005
Post-bronchodilator FEV1% predicted <50% vs. ≥50%	0.146	0.063–0.229	0.001
Number of exacerbations in the previous year			
1 vs. 0	0.126	0.023–0.229	0.017
2 vs. 0	0.382	0.258–0.505	<0.001
≥3 vs. 0	0.385	0.277–0.493	<0.001
mMRC	0.305	0.263–0.348	<0.001
CCQ mental domain			
Sex			
Female vs. male	0.306	0.093–0.520	0.005
BMI			
Underweight vs. normal	0.281	0.060–0.502	0.013
Number of exacerbations in the previous year			
2 vs. 0	0.291	0.067–0.514	0.011
≥3 vs. 0	0.463	0.270–0.655	<0.001
mMRC	0.156	0.079–0.233	<0.001

β, coefficient of regression; CI, confidence interval; BMI, body mass index; mMRC, Modified Medical Research Council Dyspnea Scale; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; CCQ, Clinical COPD Questionnaire.

chological conditions assessed by the CCQ mental subdomain: female sex was significantly associated with the mental domain in the multiple regression analysis. Our result confirmed the earlier findings that women with COPD had higher levels of depression and anxiety with worse health-related quality of life [25–27].

Older subjects had statistically higher score in total CCQ and all separate domains, but the multiple regression analysis showed that age ≥75 years was independently associated with the functional domain alone. This result might be explained by the stronger correlation between post-bronchodilator FEV1% predicted and the

functional domain than the other 2 subdomains [5, 28]. Further, progressive reduction in FEV1 was closely associated with increasing age [29]. In addition, post-bronchodilator FEV1% predicted <50% was significantly associated with the total CCQ score and functional domain in the multiple regression analysis, which was in agreement with previous studies either using CCQ [8] or other symptom assessment tools [17]. An explanation for the non-significant association between symptom domain, mental domain, and post-bronchodilator FEV1% predicted could be the heterogeneity of COPD and that airflow limitation alone cannot reflect all subjective clinical symptoms and psychological conditions in the real life. Either weak or no correlations among symptom domain, mental domain, and post-bronchodilator FEV1% predicted were observed in previous studies [30–32]. Our study also revealed that underweight was independently associated with higher score on the total CCQ and mental domain, which was consistent with the results of Sundh et al. [8, 11]; in addition, BMI <25 kg/m^2 was significantly associated with lower health-related quality of life assessed by CCQ in a prospective study with 7 years of follow-up [33].

Cigarette smoking is considered as the most common risk factor for COPD, and our study showed that smoking status was significantly associated with the total CCQ score in the multiple regression analysis, which confirmed the results of previous studies. Papadopoulos et al. [34] found that smoking cessation led to significant reduction in the CCQ score in a sample of 26 COPD patients; Joseph et al. [7] observed that cumulative cigarette smoking was an independent predictor of higher CCQ scores. Biomass fuel exposure has also been identified as a risk factor for COPD [23] and considered as a phenotype of COPD [35]. Compared with Western countries, biomass fuel is commonly used in developing countries, especially in Chinese rural areas. It was reported that solid fuels, such as wood, crop residues, and coal, were used in >70% of Chinese households, whereas in rural areas, the rate increased to 90% [36, 37]. Our work demonstrated that the total CCQ and symptom and functional domain scores in subjects who had a biomass fuel exposure history were higher than in those who did not. Our unpublished data revealed that subjects with biomass fuel exposure had worse quality of sleep and more frequent exacerbations in the past year compared to non-exposed subjects, which could partially explain the higher CCQ score in the biomass fuel-exposed group.

Our study revealed that previous exacerbations were an independent factor for the overall CCQ and symptom and functional domain scores, and frequent exacerbations (≥2) were significantly associated with the mental domain. All these findings confirmed the important role of CCQ in predicting future exacerbations and mortality among COPD patients, concluded by earlier studies [38, 39]. In contrast, one study reported that the significance of the association between CCQ and exacerbations disappeared in the multivariate analysis [40]; therefore, the association between CCQ and COPD exacerbations will need more rigorous investigations.

We found that 17.5% of the participants in the outpatient department had ACO according to the GINA-GOLD consensus [21]. ACO was considered as one of the phenotypes of COPD. Our study showed that ACO was independently associated with the total CCQ and symptom and functional domain scores, which was consistent with findings of other studies, in which subjects with ACO suffered from higher symptom burden than those with COPD alone [41–43].

Statistical differences in both total CCQ and 3 subdomain scores were found in patients with different GOLD grades, which was in line with previous findings [3]. In 2017, GOLD modified the grading system, in which the ABCD groups were based only on their level of respiratory symptoms and risk of exacerbations. To the best of our knowledge, this is the first study to compare the values of the overall CCQ score and its separate domains among the 16 subgroups based on GOLD 2017. The overall CCQ score or the 3 subdomain scores did not show any statistical difference among subgroups 1C–4C. This might be because of the fewer patients categorized into group C by GOLD 2017, which was consistent with the results of other studies [44, 45]. Additionally, our work also found that the mean change of total CCQ score between patients from more symptom groups and those from less symptom groups was 0.94; besides, the CCQ total scores of COPD patients with high risk (groups C and D) were significantly higher than those of COPD patients with low risk (groups A and B), and the mean change was 0.37. Previous studies identified that the mean MCID of the CCQ was 0.4 [46, 47]; therefore, our results indicated that the CCQ might be a useful tool to distinguish patients with different disease severity.

The choice of thresholds for mMRC, CAT, and CCQ are important, because COPD assessment classification depending on the cutoff value of questionnaires has different treatment recommendations. Our results showed that mMRC (with cut point ≥2), CAT (with cut point ≥10), and CCQ (with cut point ≥1.0) lead to inconsisten-

cies in symptom classification. We also demonstrated that the categories of COPD identified by CAT and CCQ cutoff point of 1.5 were similar, and further found that the agreement was 89% (data not shown), indicating 1.5 rather than 1.0 might be a better cutoff point for the CCQ, which was consistent with our previous findings [24] and those of Kon et al. [48]. So far, the cutoff points for mMRC, CAT, and CCQ are still under debate and need to be studied further. It seems that CCQ ≥1.0 or CAT ≥10 did not correspond well with SGRQ ≥25 (used as the standard marker of more symptomatic patients by GOLD) [49, 50]. New thresholds for these questionnaires based on future adverse events were also suggested by other studies.

Our study has several strengths and limitations. Compared with previous studies which investigated the relationship of CCQ with demographic and clinical variables, our study also investigated its association with ACO and biomass exposure; in addition, we also compared the values of the overall CCQ score and its separate domains among the 16 subgroups based on GOLD 2017. To the best of our knowledge, these have not been documented before. On the other hand, because of limited data on comorbidities, we did not analyze the association between CCQ and comorbidities, such as heart disease and depression. COPD often coexists with other diseases, which may have a significant impact on the disease course. Some studies have revealed that patients with heart disease, depression, urinary incontinence, or fatigue had statistically higher CCQ scores [8, 10, 51, 52]. In particular, heart disease and anxiety or depression significantly affected the overall CCQ score [8, 10, 11]. Urff et al. [10] showed that heart failure and depression explained 23% of the variance in the total CCQ score; moreover, heart failure alone explained 27% of the variance in the functional domain, and depression alone explained 22% of the variance in the mental domain, which indicated the important role of heart disease and depression in COPD and may also explain the smaller adjusted coefficient of determination (R^2, 8.4%) for the mental domain in this study.

In conclusion, the overall CCQ and subdomain scores could distinguish COPD subjects with distinct characteristics and disease severities. The classification of COPD produced by mMRC, CAT, and CCQ was not identical. Smoking status, underweight, ACO, post-bronchodilator FEV1% predicted <50%, exacerbation history, and mMRC were associated with lower health-related quality of life assessed by the total CCQ score, while different subdomains of CCQ had different determinant factors.

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Statement of Ethics

The study was approved by the Institutional Review Board of the Second Xiangya Hospital of Central South University (Hunan, China) and conducted in accordance with the Declaration of Helsinki. All participants in the cohorts provided written informed consent.

Disclosure Statement

None of the authors have a conflict of interest that could affect this article.

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Author Contributions

P.C. is the guarantor and takes responsibility for the content of this article. Z.Z. wrote the manuscript. Z.Z., A.Z., Y.P., Y.Z., J.D., Y.Z., and W.C. contributed to the data collection. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. The authors would like to thank all the patients and their families, the team of investigators and research nurses.

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