

The role of CAT in evaluating the response to treatment of patients with AECOPD

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Background: The chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) questionnaire is a short patient-completed questionnaire, which is used to assess the health status of patients with stable COPD. However, whether it is a good tool to evaluate the response to treatment in acute exacerbation of COPD (AECOPD) has been less studied.

Methods: The patients were assessed at two visits, at admission and on the seventh day. Anthropometric variables were collected at admission. CAT and lung function were measured twice at the above time points. At the second visit, the health status of the patients were divided into five groups based on a 5-point Likert scale, ranging from 1 to 5, which represents “much better,” “slightly better,” “no change,” “slightly worse,” and “much worse.” Responders were those who reported “much better” or “slightly better,” and nonresponders were those who claimed “no change,” “worse,” or “much worse.”

Results: In total, 225 patients were recruited. The average CAT score at admission was 24.82 ± 7.41 , which declined to 17.41 ± 7.35 on the seventh day. There were 81.33% responders, whose improvement in CAT score (9.37 ± 5.24) was much higher than that of the nonresponders (-1.36 ± 4.35). A moderate correlation was observed between the changes in CAT score and improvement in FEV₁, FEV₁%, and the length of hospital stay. There was a strong correlation between the changes in CAT score and health status. A 3.5-unit improvement in the CAT score, with highest area under the curve, was the cutoff to differentiate responders from nonresponders.

Conclusion: The evolution of CAT scores during exacerbation can provide useful information to assess the health status of patients with AECOPD. A 3.5-unit improvement in CAT score is the best cutoff to differentiate between patients who have a response or no response to treatment, which offers a convenient and easy way for clinicians to monitor the health status of patients with an AECOPD.

Keywords: COPD, acute exacerbation, CAT, curative effect

Introduction

COPD is defined by the GOLD as a disease characterized by airflow limitation, which is not fully reversible; it will represent the fourth leading cause of mortality worldwide by 2020.¹ The progress of COPD can always be deteriorated by the incidence of exacerbations. It was proved that exacerbation was an important life-threatening event for patients with COPD.^{2,3} Patients who suffer frequent and repeated exacerbations within 1 year have a poor prognosis,⁴ low HRQOL,⁵ rapid decline in lung function,⁶⁻⁸ and high mortality.⁹ Effective treatment could improve the quality of life and decrease the economic burden of these patients. However, patients with AECOPD have various phenotypes¹⁰ and often present different responses to treatment.^{11,12} Thus, to make timely and reasonable changes of the therapy for those who have no response to the

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treatment, it is essential to find an efficient tool to evaluate the curative effect of the therapy.

As we all know, the diagnosis, stage of severity, and treatment recommendations of COPD have been guided by the degree of airflow limitation (ie, the ratio of FEV₁ and FVC, and FEV₁%) for many years.¹³ However, COPD is a heterogeneous disease, and spirometry only captures some of the disease variety.^{14,15} In addition, a study¹⁶ showed the airway function of some patients could not return to pre-exacerbation levels within 91 days, which indicates lung function was not able to sensitively reflect the health status of the patients. Thus, to better classify the patients for prognostic purposes and to guide treatment, the GOLD 2011¹⁷ Executive Summary made great modifications in the disease classification. Instead of relying on FEV₁ only, it classified the patients according to the level of dyspnea, exacerbation history, and FEV₁, which pointed out the importance of clinical symptoms.

The CAT and mMRC dyspnea scale were the main questionnaires to evaluate the symptoms in the GOLD document. mMRC is a simple questionnaire that can only evaluate the dyspnea of the patient.¹⁸ However, the impact of COPD on individuals is multifaceted and it causes impairment not only in the lungs but also in other organs, and even psychological conditions.¹⁷ The CAT was designed by Jones et al¹⁹ in 2009, and it consists of eight items, including cough, expectoration, dyspnea, chest tightness, confidence, limitation of daily activities, quality of sleep, and levels of energy. The score of each item ranges from 0 to 5 (0=no impairment, 5=greatest impairment). The total score is calculated by adding the points of the eight questions ranging from 0 to 40, where 0 means the best status and 40 means the worst status. This questionnaire is completed by the patients themselves, and it can assess the impact of COPD on the health status of patients within a few minutes. In recent years, the CAT has been proven to be very useful in evaluating the health status of patients with stable COPD.^{20,21} Also, it has been used to assess the severity of exacerbations^{22–24} and the health status of patients with an AECOPD.^{25–27} The CAT score is a potential indicator to assess the response to treatment.

Thus, in this study, we aim to assess the sensitivity of the CAT score to assess the response to the treatment of patients with an AECOPD and find the cutoff CAT score to define the responders among patients with an AECOPD.

Methods

The research protocol was approved by the local Ethics Committee of the Second Xiangya Hospital of Central South

University (number: zay0410), and all subjects provided written informed consent to participate in the study. The study was approved by the ethics committee. The study was registered in the Chinese Clinical Trial Registry (ChiCTR-ROC-16009087; <http://www.chictr.org.cn/>).

Inclusions and exclusions of the patients

Patients with a clinician-diagnosed AECOPD from the Second Xiangya Hospital of Central South University in China from February 2016 to December 2017 were recruited. Patients with a history of COPD, confirmed by spirometry in stable phase showing a post-bronchodilator FEV₁/FVC ratio <0.7, with a primary diagnosis of AECOPD without respiratory tract infection, and aged over 40 years were included in the study. Patients with a history of asthma or other respiratory diseases (ie, lung cancer, interstitial lung disease, bronchiectasis, or pulmonary thromboembolism), severe heart failure (New York Heart Association stage IV), and malignant comorbidities were excluded from the study. All diagnoses were established by the clinicians and were independently verified by physicians specializing in respiratory medicine. COPD was defined as progressive, irreversible airway obstruction associated with airway inflammation primarily caused by cigarette smoking, in agreement with GOLD 2013 guidelines. AECOPD was defined as increased dyspnea, cough, or sputum expectoration (quality or quantity) that led the subjects to seek medical care. Smoking subjects were defined as those who still smoked tobacco daily. Ex-smokers had stopped smoking at least 6 months prior to inclusion in the study.

Study design

Anthropometric and clinical variables were collected: smoking, drug treatment, and comorbidities, which included cardiovascular disease, OSAHS, diabetes, and hypertension. The comorbidities would be recorded, no matter whether a history of diagnosis at admission or diagnosed by clinicians during the hospital stay. CAT and lung function were measured at two time points: within 24 hours of hospital admission and on the seventh day. If the hospital stay was less than 7 days, the second visit would be performed at discharge. Treatment during hospitalization was determined by the clinicians based on GOLD guidelines. Treating clinicians were not directly involved in the study and were blinded to the results of the CAT. After treatment, the health status was divided into five groups based on a 5-point Likert scale, ranging from 1 to 5, which represents “much better,” “slightly better,” “no change,” “slightly worse,” and “much worse,” respectively.

Responders were defined as reporting “much better” or “slightly better” at the second visit. Nonresponders were defined as claiming “no change,” “worse,” or “much worse.”

Statistical analyses

Sociodemographic and clinical characteristics of patients were summarized descriptively. SPSS software version 25.0 was used for statistical analysis. Data are reported as mean±SD. The level of statistical significance was set at 0.05 (two-sided). Changes in the CAT at hospital admission and discharge showing a normal distribution were tested using paired *t*-tests, while the variables showing non-normal distribution were analyzed by rank test. Spearman rank correlation coefficient method was used to analyze the relationship between the health status and CAT, and Pearson correlation analysis was used to analyze the relationship between the CAT and hospital stay. Group comparisons were tested using analysis of variance or *t*-tests. ROC curve analysis was performed to derive the optimum cutoff value for the CAT, and a value of the AUC above 0.8 on ROC analysis was considered to provide good discrimination.

Results

Patient demographics

A total of 356 subjects were screened, and 126 patients were excluded because of pneumonia, lung cancer, asthma, interstitial lung disease, bronchiectasis, and severe heart failure. In total, 230 subjects were recruited in the first visit. Among them, five patients failed to complete the second visit because of serious deterioration (Figure 1). Thus, just 225 patients succeeded to complete two visits and 55 of them completed lung function testing. Demographic and clinical data are presented in Table 1. Mean±SD age was 67.08±10.03 years, with 89.3% males and 10.7% females in the study. Mean±SD FEV₁% was 42.13%±16.14% and mean±SD FEV₁/FVC ratio was 44.87±11.07, which included 103 smokers and 122 ex-smokers. Most of the patients were also diagnosed with hypertension (44.89%) and cardiovascular disease (40.89%). Patients receiving regular ICS therapy and bronchodilators totaled 195, while 190 patients received antibiotics. The type of antibiotic was decided by the clinicians. Because of dyspnea, 116 patients were given doxofylline, and 43 of them accepted intravenous prednisone due to wheezing (Table 1).

The changes of CAT

Most of the patients with an AECOPD (81.33%) reported improved health status at the second visit. Among these

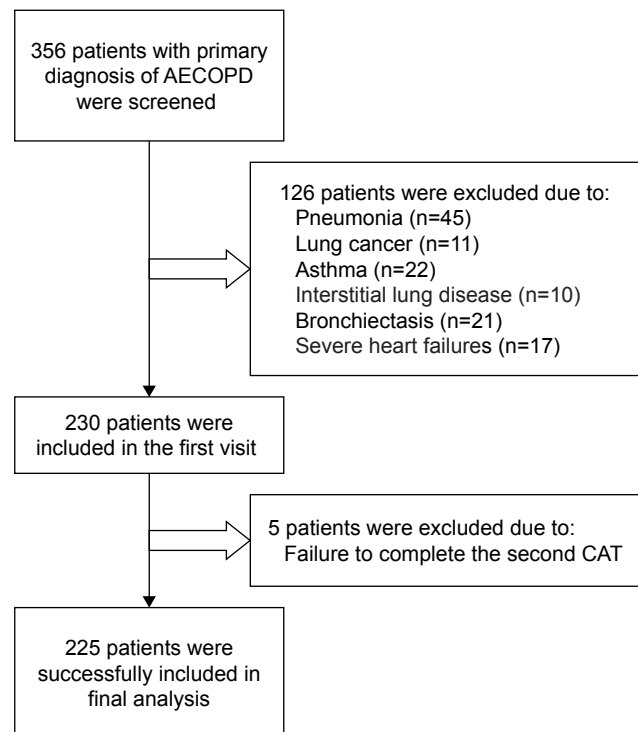


Figure 1 The flowchart for screening patients.

Abbreviations: AECOPD, acute exacerbation of COPD; CAT, COPD assessment test.

patients, 49.78% reported their health status as much improved and 31.56% reported slightly improved. The mean±SD of changes in the CAT score of all patients was 7.37±6.60. The mean±SD of changes in the much improved group was 12.07±4.48 and slightly better was 5.24±3.51, while the mean±SD of changes in the no change, slightly worse, and much worse groups were 1.24±1.53, -3.23±2.31, and -11.50±3.11, respectively. The changes between two visits in each group presented great differences, except in the much worse group (Table 2). In addition, the comparison of changes in the CAT between the two visits among the five groups is shown in Figure 2. There are significant differences between the five groups.

The comparison between responders and nonresponders

Of the 225 patients, 183 (81.33%) were responders and 42 (18.67%) were nonresponders. The mean initial CAT values before treatment in the responders and nonresponders were 25.87±6.94 and 20.26±7.75, respectively. There was a statistically significant difference between the groups. After treatment, the CAT score improvement in the responders group was 9.37±5.24, which was significantly higher than the

Table 1 Clinical characteristics of the patients

Variables	Characteristics	N	Mean±SD (%)
Sex	Male	201	89.3%
	Female	24	10.7%
Age		225	67.08±10.03
Smoke	Ex-smokers	122	54.22%
	Current smokers	103	45.78%
	Smoking index	225	58.69±58.07
Lung function	FEV ₁ %	55	42.13±16.14
	FEV ₁ /FVC	55	44.87±11.07
Comorbidities	Cardiovascular disease	92	40.89%
	OSAHS	18	8.0%
	Diabetes	24	10.67%
	Hypertension	101	44.89%
Treatment	Antibiotics	190	84.44%
	ICS or bronchodilator	195	86.67%
	Intravenous prednisone	116	51.56%
	Theophylline	43	19.11%
CAT	0–10	12	8.08±1.78
	11–20	48	16.83±2.75
	21–30	108	25.60±2.62
	31–40	57	33.60±2.27
mMRC	0–1	17	0.88±0.33
	2–4	208	3.02±0.67
GOLD grades	Mild	5	2.22%
	Moderate	21	9.33%
	Severe	189	84.0%
	Very severe	10	4.45%

Abbreviations: CAT, COPD assessment test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; mMRC, modified Medical Research Council; OSAHS, obstructive sleep apnea–hypopnea syndrome.

nonresponders group (−1.36±4.35). There was a statistically significant difference between the two groups (Table 3).

The correlation between CAT score both with health status and lung function

Spearman rank correlation coefficient method was used to analyze the relationship between the health status and CAT score. The initial CAT score in the acute exacerbation period was negatively correlated with the patient's

self-assessment of health status, and the correlation coefficient was −0.331. In addition, there was a significant negative correlation between the CAT score changes and the health status of the patients. The correlation coefficient was −0.824. A positive relationship was observed between the CAT score at discharge and the health status of the patients. The correlation coefficient was 0.333. As for the lung function, a total of 55 patients completed lung function testing during the exacerbations. Pearson correlation analysis was used to analyze the relationship between the CAT score and FEV₁ and FEV₁%. The changes in the CAT score had moderate correlation with increases of FEV₁ and FEV₁%. The correlation index was 0.363 and 0.387, respectively, while the CAT score either at admission or at the second visit had no relationship with changes in FEV₁ and FEV₁% (Table 4).

The correlation between CAT and hospital stay

Pearson correlation analysis was used to analyze the relationship between the CAT and hospital stay. The average length of stay was 9.24±5.36 days. There was no significant relationship between the CAT score obtained at admission and length of hospital stay ($r=0.10$; $P=0.143$; Figure 3), and there was a moderate correlation between the CAT score obtained on the second visit and the length of hospital stay ($r=0.403$; $P<0.001$; Figure 4). In addition, a slightly negative relationship was observed between the changes in CAT score and length of hospital stay ($r=-0.35$; $P<0.001$; Figure 5).

Cutoff of changes in CAT to predict response to treatment

The ROC curve analysis identified a decrease of 3.5 units in the CAT score between admission and discharge as the cutoff point with the greatest predictive value for treatment failure (AUC=0.973, sensitivity=86.9%, and specificity=97.4%;

Table 2 Changes in CAT scores between the two visits in different health statuses

Health status	Cases	CAT score at admission	CAT score at the second visit	Changes in CAT score	P-value
Total	225	24.82±7.41	17.41±7.35 ^a	7.37±6.60	<0.001
Much better	112	27.13±6.18	15.06±5.29 ^a	12.07±4.48	<0.001
Slightly better	71	23.87±7.61	18.63±7.63 ^a	5.24±3.51	<0.001
No change	25	19.16±8.79	17.92±8.64 ^a	1.24±1.53	<0.001
Slightly worse	13	22.30±6.56	25.53±7.23 ^a	−3.23±2.31	<0.001
Much worse	4	20.50±1.29	32.00±4.08	−11.50±3.11	0.178

Note: ^aSignificant difference in CAT score between the two visits.

Abbreviation: CAT, COPD assessment test.

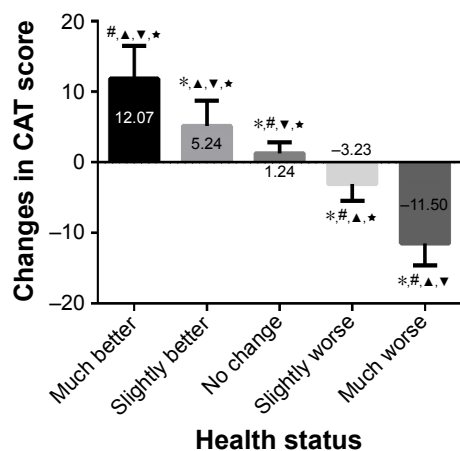


Figure 2 The comparison of the changes in CAT score in AECOPD patients with different health statuses.

Notes: * $P < 0.05$ vs much better group; # $P < 0.05$ vs slightly better group; * $P < 0.05$ vs no change group; * $P < 0.05$ vs slightly worse group; * $P < 0.05$ vs much worse group.
Abbreviations: AECOPD, acute exacerbation of COPD; CAT, COPD assessment test.

Figure 6). Moreover, a decrease of 3.5 units in the CAT score was also the optimum cutoff to differentiate patients reporting slightly better and no change (AUC=0.900, sensitivity=70%, and specificity=96%; Figure 7).

Discussion

This study showed that monitoring the changes of the CAT score during an AECOPD could assess the curative effect of treatment. Previous studies have observed a difference in the CAT score of between 4 and 10 points for patients with COPD on different time points during exacerbation.^{22,25,28,29} In our study, the difference in CAT scores observed was 7.37 ± 6.60 , which was similar to previous studies. In addition, we also found the changes in CAT scores in the much better to much worse groups declined in turn, with statistically significant differences, while the changes of CAT scores in the responder group were much higher than those in the nonresponder group, indicating CAT score was very sensitive to the changes of the health status of patients. However, we found the CAT score in the much better group was significantly improved by 12.07 ± 4.48 , which was much higher than that in other studies.^{25,31} We suppose it may have relation to the fact that most patients in China do not

have sufficient knowledge of the disease and always have difficulty in adhering to regular treatment. One of our previous prospective studies showed only one-third of patients adhered to the treatments suggested by doctors (Figure S1). In addition, another study showed that the patients who received regular treatment achieved a significant decrease in CAT score.³⁰ Therefore, we speculate that the CAT score would be a little higher than expected when the patients presented for medical care because of the absence of receiving regular treatment. Moreover, the distribution of medical resources in China is unbalanced. The primary care units and community hospitals are not always equipped with very professional physicians and advanced instruments. Our hospital is a comprehensive third-grade hospital, which represents the highest medical level in Hunan Province. Thus, most of the patients admitted to our hospital had significant improvement. Actually, in another Chinese study, the CAT score changed by as much as 15 units.²⁹ Interestingly, in the patients reporting no change, there was also a statistically significant difference between the CAT values during the two visits. We suppose it may have relation to the complex condition of the patients. Nearly half of the patients had some comorbidities, which would affect their self-assessment. In this study, six patients reported a three-unit improvement of CAT values but reported no change in their health status. We found three of them also had coronary heart disease, two of them also had diabetes, and one also had OSAHS (Table S1). Although respiratory symptoms, including cough and sputum, were relieved, some other manifestations, such as angina and dizziness, were not improved, which may have resulted in the final reply of no change in patients.

In this study, we analyzed the correlation between CAT score and FEV_1 , $FEV_1\%$, health status, and the length of hospital stay. We found that when compared with CAT score, no matter whether at admission or at discharge, the changes in CAT score had better correlation with health status, which indicated dynamically monitoring CAT score would be more useful than a one-time measure of CAT score in predicting the health status of the patients. In addition, the changes in CAT score also had a positive correlation with FEV_1 or $FEV_1\%$,

Table 3 Changes in CAT scores between responders and nonresponders

Subjects	Cases	CAT score at admission	CAT score at the second visit	Changes in CAT score	P-value
Responders	183	25.87 ± 6.94	16.45 ± 6.52	9.37 ± 5.24	<0.001
Nonresponders	42	20.26 ± 7.75	21.62 ± 9.18	-1.36 ± 4.35	

Abbreviation: CAT, COPD assessment test.

Table 4 The correlation between CAT score and health status, and improvement in FEV₁% and FEV₁

CAT score (N=225)	Health status (N=225)		ΔFEV ₁ % (N=55)		ΔFEV ₁ (N=55)	
	Rho	P-value	r	P-value	r	P-value
CAT at admission	-0.331	<0.001 ^a	0.16	0.23	0.17	0.22
CAT at the second visit	0.333	<0.001 ^a	-0.22	0.11	-0.19	0.16
Changes in CAT	-0.824	<0.001 ^a	0.387	0.001 ^a	0.363	0.007 ^a

Notes: Δ means the changes of the parameters between the two visits. ^aStatistic difference of the correlation between the two parameters.

Abbreviation: CAT, COPD assessment test.

which was similar to other studies.^{24,32} As we all know, in other previous studies, FEV₁ and FEV₁% were often used to assess the response to treatment not only in stable COPD but also in acute exacerbations.³³⁻³⁵ In this study, a positive moderate correlation was observed between the improvement in CAT score and ΔFEV₁ and ΔFEV₁%, suggesting that for those patients who could not afford lung function testing or who were too ill, the CAT was a good alternative. In terms of the length of hospital stay, there was a relationship with the CAT score at the second visit and the improvement of the CAT score, indicating the changes of CAT and the CAT value at the second visit can predict the length of hospital stay for patients with an AECOPD. This result was similar to Dai’s study.³⁶ However, there was no relationship between the CAT score at admission and length of hospital stay, which was different from another study.³⁷ We speculate the reason was related to the fact that nearly one-third of the patients with COPD did not obey physician recommendations to get regular treatment, resulting in a higher CAT score at admission (Figure S1). After receiving professional treatment, they were likely to have obvious improvement as well as a shorter hospital stay. In addition, the hospital stay can be influenced

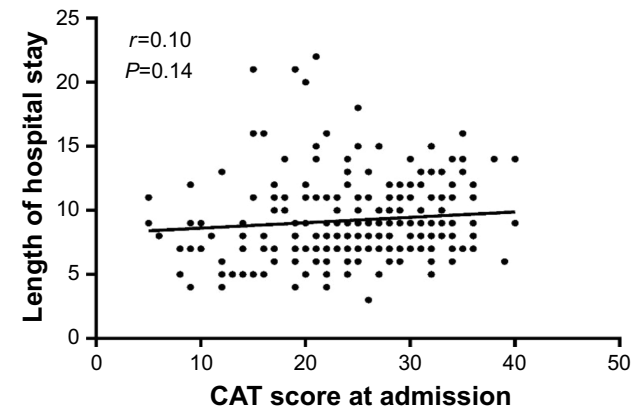


Figure 3 Relationship between the CAT score at admission and length of hospital stay.

Abbreviation: CAT, COPD assessment test.

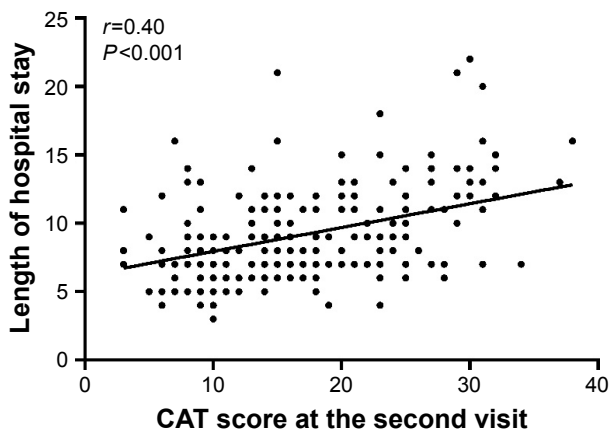


Figure 4 Relationship between the CAT score at the second visit and length of hospital stay.

Abbreviation: CAT, COPD assessment test.

by many factors, including the financial condition, education background, insurance policy, and even family relationship of the patient.³⁸

An improvement of more than 3.5 units in the CAT score between hospital admission and discharge was the cutoff with the highest predictive value to differentiate responders from nonresponders. In one previous study, García-Sidro et al³⁹ collected CAT scores on 106 patients with an AECOPD on the first day, third day of admission, and at discharge. They found that patients with a CAT improvement value of <4 were more likely to suffer another exacerbation and readmission. Kon et al⁴⁰ used a different method to calculate the MCID value for the CAT. The distribution method recommended 3.75 units, whereas the ROC curve identified 2 units. Two recent studies suggested 2–3 and 3 units, respectively, as the MCID for the CAT.^{41,42} In this study, the ROC curve was used to differentiate patients reporting slightly better

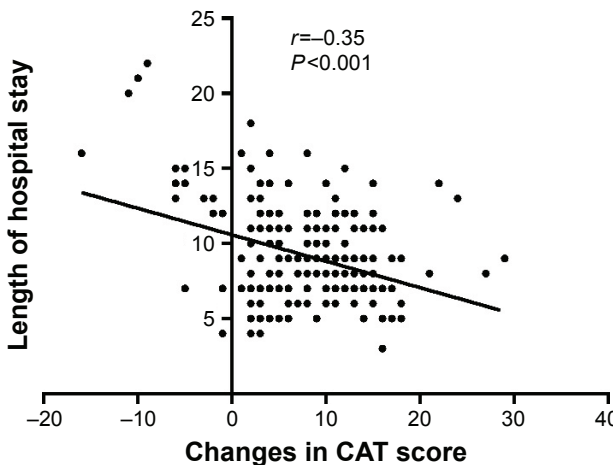


Figure 5 Relationship between the changes in CAT score and length of hospital stay.

Abbreviation: CAT, COPD assessment test.

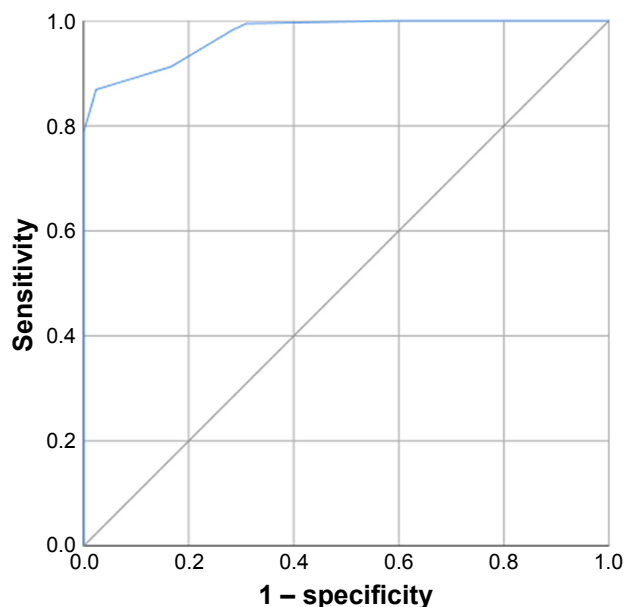


Figure 6 The ROC curve for the cutoff point of CAT score improvements to differentiate responders and nonresponders.

Notes: The AUC was 0.973; the sensitivity and specificity were 86.9% and 97.4%, respectively.

Abbreviations: AUC, area under the curve; CAT, COPD assessment test; ROC, receiver operating characteristic.

and no change, with the cutoff being 3.5 units. The above differences may be related to many factors, such as the difference in the sample size, design of the study, and calculation method for MCID.

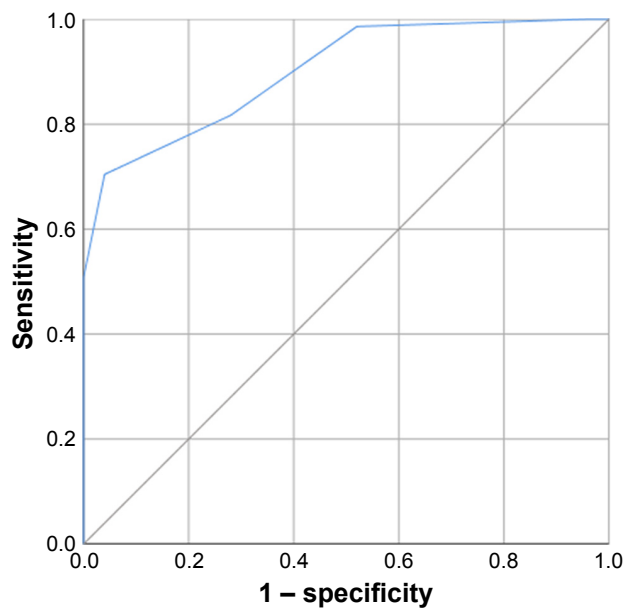


Figure 7 The ROC curve for the cutoff point of CAT score improvements to differentiate between patients in the slightly better group and no-change group.

Note: The AUC was 0.900; the sensitivity and specificity were 70% and 96%, respectively.

Abbreviations: AUC, area under the curve; CAT, COPD assessment test; ROC, receiver operating characteristic.

Our study has some limitations. The sample size in the nonresponder group is much smaller than that in the responder group owing to the medical condition in our hospital, which may result in the initial CAT score in nonresponders being lower than that in responders. In the future, a larger study, which includes patients with stable COPD, is required to address this issue. Moreover, there is no gold standard to assess the curative effect of the treatment. We used the self-reported health status of patients as the standard to assess the role of the CAT score, which may be affected by the subjective consciousness of the patients. But we believe that it would have a small effect on the relationship between the CAT score and health status, since both of them were completed by the patients themselves. Finally, this is not a multicenter study, which will limit the application of the conclusion. For this issue, a multicenter study should be conducted, which may be beneficial to the management of COPD.

In conclusion, this study found that the evaluation of CAT scores between admission and discharge can provide useful additional information to assess the health status of patients with an AECOPD. Also, CAT score would be a good alternative for lung function testing, especially for those who cannot afford the expense of lung function testing. CAT scores that improved 3.5 units were regarded as the cutoff to differentiate responders from nonresponders, which would be useful to guide clinicians toward a timely change in therapy.

Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AUC, area under the curve; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQOL, health-related quality of life; ICS, inhaled corticosteroid; MCID, minimum clinically important difference; mMRC, modified Medical Research Council; OSAHS, obstructive sleep apnea–hypopnea syndrome; ROC, receiver operating characteristic.

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Author contributions

PC and AZ contributed to the study design; AZ contributed to the drafting of the manuscript; PC contributed to critically

revising the manuscript for important intellectual content. AZ, ZZ, YP, YZ, and JD contributed to data collection. All authors contributed toward data analysis, drafting, and revising the paper, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

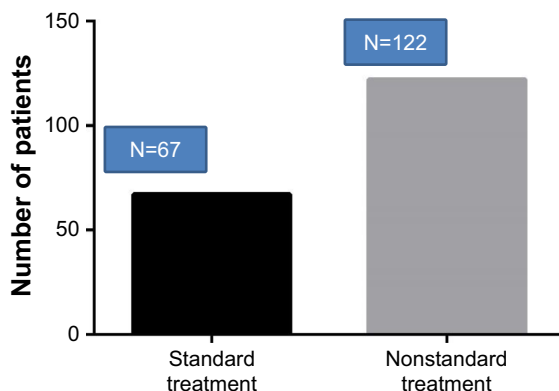


Figure S1 The number of the patients who received standard treatment.

Notes: This was a one-year follow-up study. In total, 189 patients were recruited into our study. All of them accepted three visits after being recruited (at 3 months, at 6 months, and at 12 months). If the patients reported they took their drugs everyday based on the prescription at every visit, they would be classified as those who received regular treatment. The rest were those who didn't receive regular treatment. We found that only one-third of the patients received regular treatment.

Table S1 The detailed information of the comorbidities of patients who reported no change

Health status	CAT score at admission	CAT score at the second visit	Changes in CAT	Comorbidities
No change	25	25	0	N
No change	14	14	0	N
No change	28	30	-2	N
No change	12	9	3	Diabetes
No change	20	20	0	H
No change	6	6	0	N
No change	28	25	3	CHD
No change	10	10	0	N
No change	5	3	2	N
No change	16	15	1	N
No change	17	15	2	N
No change	5	5	0	N
No change	26	26	0	H
No change	17	14	3	CHD, H
No change	25	23	2	N
No change	18	18	0	N
No change	29	29	0	H
No change	9	9	0	N
No change	28	24	4	CHD, H
No change	24	21	3	CHD
No change	33	31	2	N
No change	22	20	2	N
No change	9	6	3	Diabetes
No change	34	31	3	OSAHS
No change	19	19	0	N

Abbreviations: CAT, COPD assessment test; CHD, coronary heart disease; H, hypertension; N, no comorbidity; OSAHS, obstructive sleep apnea-hypopnea syndrome.

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