Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

COPD assessment tests scores are associated with exacerbated chronic obstructive pulmonary disease in Japanese patients

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ARTICLE INFO

Article history:
Received 20 February 2014
Received in revised form
3 April 2014
Accepted 30 April 2014
Available online 16 June 2014

Keywords:
COPD
Questionnaire
Quality of life
Respiratory function tests

ABSTRACT

Background: Guidelines recommend chronic obstructive pulmonary disease (COPD) assessment tests (CATs) for evaluation of symptoms and management risks. To investigate whether CAT can predict moderate or severe exacerbations in Japanese COPD patients, a single-blinded prospective study was performed.

Methods: A 123 Japanese COPD patients were classified into high-CAT ($n=64$) and low-CAT ($n=59$) groups. The frequencies and periods of moderate or severe exacerbation and hospitalization were compared between the two groups. Multivariate logistic regression analysis was performed to investigate whether CAT could predict exacerbations. A receiver operating characteristic (ROC) curve analysis was employed to find an appropriate CAT score for exacerbation.

Results: The high-CAT group was significantly older, had a lower body mass index, and had a lower airflow obstruction as compared to the low CAT group. The frequency of moderate or severe exacerbation (1.3 ± 1.3 events per patient per year, $p<0.0001$) and hospitalizations (0.2 ± 0.4, $p=0.0202$) in the high-CAT group was significantly higher than in the low-CAT group (0.4 ± 0.7 and 0.0 ± 0.1, respectively). Multivariate logistic regression analysis showed that both high CAT score and low airflow obstruction were independently predictive of frequent moderate or severe COPD exacerbation. ROC analysis showed that the best cut-off CAT score for moderate or severe COPD exacerbation was 8 points.

Conclusion: Our present results indicate that COPD Japanese patients showing high CAT scores have a poor prognosis, and that the CAT score is able to predict exacerbation in Japanese COPD.

http://dx.doi.org/10.1016/j.resinv.2014.04.004

1. Introduction

Exacerbation of chronic obstructive pulmonary disease (COPD) is associated with poorer health-related quality of life (HRQOL), hospitalization, and mortality [1–4]. HRQOL is an independent predictor of exacerbation and hospitalization in patients with COPD [5,6], and is associated with the severity of symptoms including chronic cough, sputum production, and dyspnea [7,8]. Chronic cough and sputum production in COPD patients are associated with progressive airflow obstruction, frequent exacerbation and hospitalization, and mortality [9–11]. Dyspnea is also a factor predictive of mortality in such patients [12–14]. Previous studies have demonstrated that evaluation of HRQOL using St. George's Respiratory Questionnaire (SGRQ) is useful for prognostication [4,15].

The COPD assessment test (CAT) has been shown to be a useful and readily applicable tool for optimization of the HRQOL in patients with COPD [16]. It is known that there is a good correlation between CAT score and total SGRQ score in patients with stable COPD, and that CAT evaluation can indicate the severity of exacerbation in progressive COPD [17]. Recently, we validated the Japanese version of the CAT for Japanese COPD patients [18]. However, it is still unknown whether the CAT score can be used as an indicator for prediction of exacerbation and hospitalization. Thus, the primary endpoint of the present single-blinded (investigator-blinded), prospective observation study was to investigate whether the CAT could be used to predict outcome in Japanese patients with COPD.

2. Materials and methods

2.1. Patients

Patients with COPD who had regularly attended each participating hospital for at least one year between September 2011 and August 2013 at the Chest Disease Center of Kurume University Hospital (Kurume, Japan), the Chikugo City Hospital (Chikugo, Japan), and Nagata Hospital (Yanagawa, Japan) were enrolled in this study. However, patients were excluded if they had a main diagnosis of bronchiectasis, asthma, interstitial pneumonia and pneumoconiosis based on medical history and chest high-resolution computed tomography (HRCT); active malignancies; and severe diseases of other organs such as dementia, cerebro- or cardio-vascular disease, hepatitis and cirrhosis, chronic kidney disease, and psychological disease. All patients were Japanese.

2.2. Study design

Each patient had been in stable condition with no history of exacerbation while receiving systemic antibiotics and corticosteroids, or had been hospitalized, for 4 weeks prior to study entry. Demographic data included body mass index, details of smoking habits, smoking index (packs per year), comorbidities, previous exacerbations and hospitalizations during the previous year, and medications were collected at baseline. Other baseline data included chest X-ray, chest HRCT, electrocardiography, and spirometry. The total CAT scores [16] for the previous 2 weeks were obtained from each patient through self-completed reports. For final analysis, the reports were kept in a designated box by special nurses and technicians in an investigator (single)-blinded manner.

The diagnosis of COPD was based on forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 0.7 after bronchodilator administration, and the classification of airflow obstruction after bronchodilator administration in COPD was in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2009 [19]. Spirometry was performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) task forces [20].

This prospective observation study was performed for one year after consent was obtained. Each patient self-reported his/her own condition in a daily journal and visited the chief physician monthly. Each physician then entered the monthly conditions, contents and periods of medication including treatments initiated for exacerbation, incidence of death, pulse oximetry oxygen status, and causes of death, hospitalization, or exacerbations, into the medical records. Exacerbation was defined on the basis of symptom-based diagnosis such as increased cough and sputum production, a change of sputum color, and worsening of dyspnea from a stable state and beyond-normal day-to-day variations, i.e., showing acute onset and necessitating a change in regular medication, in accordance with a previous report [21]. Moderate exacerbations required a prescription for antibiotics and/or systemic corticosteroids, and severe exacerbations required hospitalization [22]. COPD-related death was also counted as severe exacerbation. Mortality was also investigated for one year. The frequency of moderate or severe exacerbation and hospitalization due to

Abbreviations: ATS, American Thoracic Society; BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRCT, high-resolution computed tomography; HRQOL, health-related quality of life; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$ agonist; LAMA, long-acting muscarinic receptor antagonist; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; %FEV_1, percentage of predicted forced expiratory volume in 1 s; %FVC, percentage of predicted forced vital capacity

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severe COPD exacerbation per patient per year and the time until a first moderate or severe exacerbation and hospitalization from the baseline were obtained from each medical record and daily journal. The contents of the prescriptions did not change during the period of observation.

The study was conducted in accordance with the Good Clinical Practice guidelines and approved by the Ethics Committee of Kurume University and Chikugo City Hospital (Approval date: September 2011; Approved #: 11127). All of the study patients provided informed written consent.

2.3. *Statistical analysis*

An intention-to-treat analysis was performed in the study. All data were expressed as mean ± standard deviation (SD). Characteristics of COPD patients with low (<10 points) and high CAT (>10 points) scores in accordance with GOLD documents [19] at baseline were compared using Student's *t*-test. Differences in qualitative variables (e.g., gender, smoking status, comorbidities, GOLD classification, and treatments) were analyzed by χ^2 test. The period until the first moderate or severe COPD exacerbation and hospitalization after obtaining informed consent was analyzed using logistic multivariate regression tests. The odds ratio and 95% confidence interval (CI) of the predictive risk factors for moderate or severe COPD exacerbations and hospitalizations were analyzed by univariable and multivariable tests. The best sensitivity, specificity [sensitivity–(1–specificity)] and area under the receiver operating characteristic (ROC) curve (AUC) for the CAT score indicative of annual at least one moderate or severe COPD exacerbations and hospitalizations were determined by ROC analysis. Differences at $p<0.05$ were considered statistically significant. Kaplan–Meier analyses were performed using the statistical software package JMP version 9.0® (SAS Institute Japan Inc., Tokyo, Japan). However, hospitalizations except for COPD exacerbations were not counted in the analysis.

3. Results

3.1. *Patient characteristics*

In all, 154 patients with COPD provided informed consent, of which 139 patients were enrolled for this study (Fig. 1).

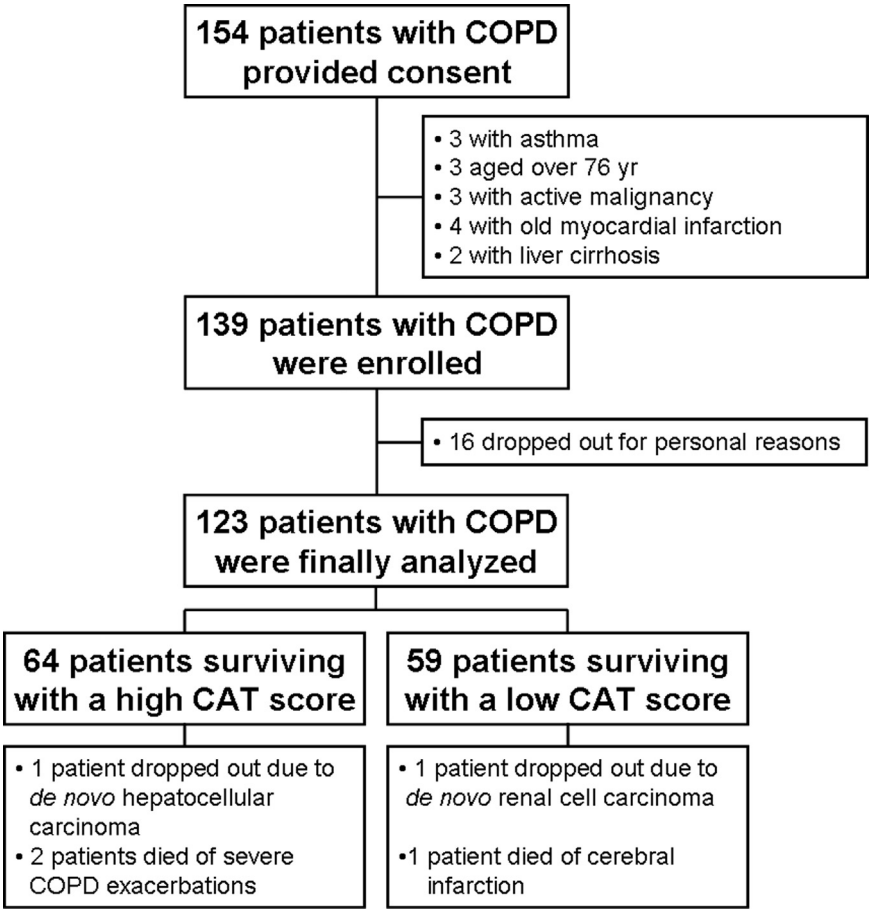

Fig. 1 – Study design. Informed consent was obtained from 154 patients with COPD. However, three patients with asthma were excluded. Three patients aged 76 years and older were also excluded. Three patients with active malignancy required anti-cancer drugs, 4 with old myocardial infarction, and 2 with liver cirrhosis due to hepatitis C virus infection were also excluded because of severe disease involving organs other than the lungs. Thus, 139 patients with COPD were enrolled. However, 16 patients for personal reasons and 2 who had de novo active malignancies were dropped out within 1 year after enrollment. CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease.

Sixteen patients were excluded from the final analysis because of withdrawal of consent for personal reasons during the observation period. Thus, 123 patients were included in the final analysis. Two patients were dropped out due to de novo malignancies. Two patients with a high CAT score died due to severe COPD exacerbations whereas a patient with a low CAT score died due to cerebral infarction without COPD exacerbation during the observation period (Fig. 1).

The baseline characteristics of the 123 patients are shown in Table 1. The numbers of GOLD stages I, II, III, and IV patients were 29, 57, 28, and 9, respectively. The respiratory medicines [long-acting muscarinic antagonists (LAMA), long-acting β_2 agonists (LABA), and/or inhaled corticosteroids (ICS)] were prescribed for 104 (84.6%) of the patients. Eighteen (14.6%) of the patients had inoculated the pneumococcal vaccination within 5 years prior to providing consent. All patients required influenza virus vaccinations.

In a comparison between the high- and low-CAT groups, the high-CAT group was significantly older ($p<0.0001$), had a lower body mass index (BMI) ($p<0.0001$), had a lower %FEV_1 predicted value ($p=0.006$) and FEV_1/FVC ($p=0.005$), and had a severe COPD stage ($p=0.035$) than the low-CAT group (Table 1). The number of patients who received LABA ($p=0.011$) and ICS ($p=0.015$) in the high-CAT group was significantly higher than in the low-CAT group, whereas there was no significant difference in the number of patients who received LAMA between the two groups. The numbers of the patients who received long-term oxygen therapy in high- and low-CAT groups were 3 and 1, respectively. None of the patients received noninvasive positive pressure ventilation at home.

3.2. Association of CAT with annual exacerbation and hospitalization

According to GOLD 2011 guidelines [19], we found that the high-CAT group had significantly higher annual frequencies of moderate or severe exacerbations (1.3±1.3 events per patient, $p<0.0001$) and hospitalizations (0.2±0.4 events per patient, $p=0.0202$) than the low-CAT group (0.4±0.7 and 0.0±0.1, respectively) (Fig. 2).

The Kaplan–Meier analysis showed that the high-CAT group had a significantly shorter time until the first moderate

Table 1 – Baseline characteristics of the study patients.

Characteristics	High-CAT group ($n=64$)	Low-CAT group ($n=59$)	p Value
Total CAT score,[a] points	17.9±8.0	4.9±3.0	<0.0001
Age, year	69.4±5.3	65.1±6.1	<0.0001
Male gender,[b] n (%)	54 (84.4)	53 (89.8)	0.4
Body mass index, kg/m^2	21.3±3.5	22.9±3.1	0.008
Current smoker,[b] n (%)	23 (35.9)	17 (28.8)	0.4
Smoking index, packs per year	60.1±25.4	52.2±27.8	0.1
Hypertension,[b] n (%)	10 (15.6)	8 (13.6)	0.8
Hyperlipidemia,[b] n (%)	3 (4.7)	3 (5.1)	1.0
Diabetes,[b] n (%)	17 (26.6)	16 (27.1)	1.0
Periods since COPD diagnosis,[a] year	6.3±4.1	4.9±4.0	0.06
Spirometry after bronchodilation			
FVC, L	3.3±0.8	3.8±0.8	0.005
%FVC predicted value, %	96.1±19.4	101.7±17.9	0.1
FEV_1, L	1.6±0.7	2.0±0.7	0.0004
%FEV_1 predicted value, %	58.2±22.0	69.2±21.3	0.006
FEV_1/FVC, %	46.0±13.8	52.9±13.0	0.005
GOLD stage I/II/III/IV,[b] n	10/31/15/8	19/26/13/1	0.035
Use of respiratory medicine,[c] n (%)			
Any	55 (85.9)	49 (83.1)	0.8
Long-acting beta agonists	21 (33.8)	7 (11.9)	0.011
Long-acting muscarinic agonists	49 (76.6)	48 (81.4)	0.7
Inhaled corticosteroids	14 (21.9)	3 (5.1)	0.015
Previous pneumococcal vaccination within 5 years, n (%)	13 (20.3)	5 (8.5)	0.1

All data are expressed as mean±standard deviation and compared between two groups using Student's t-test.
CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced expiratory capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
[a] Data were compared between groups by non-parametric Wilcoxon test.
[b] Data were compared between groups using χ^2 test.
[c] This agent was used either alone or as a fixed combination.

or severe exacerbation ($p<0.0001$), but not hospitalization ($p=0.064$), than the low-CAT group (Fig. 3).

3.3. *High CAT score as an independent predictor of exacerbation, but not hospitalization*

In univariable analysis for moderate or severe COPD exacerbation and hospitalization (Table 2), the odds ratio (95% CI) of the patients who had age >65 years, total CAT score >10 points, and GOLD stages III and IV, with at least one moderate or severe COPD exacerbation were 3.0 (1.4–6.3) ($p=0.006$), 5.1 (2.4–11.1) ($p<0.0001$), and 5.8 (2.4–13.9) ($p<0.0001$), respectively. The odds ratio (95% CI) of the patients who had age >65 years, total CAT score >10 points, and GOLD stages III and IV, with at least one hospitalization were 2.9 (0.8–10.7) ($p>0.05$), 4.3 (1.2–16.1) ($p=0.027$), and 4.3 (1.4–13.1) ($p=0.014$), respectively.

In multivariable analysis (Table 3), the odds ratio (95% CI) of the patients who had age >65 years, total CAT score >10 points, and GOLD stages III and IV, with at least one COPD exacerbation were 1.6 (0.6–4.0) ($p>0.05$), 4.5 (1.9–11.3) ($p=0.0005$), and 5.7 (2.3–15.3) ($p=0.0001$), respectively. The odds ratio (95% CI) of the patients who had total CAT score >10 points and GOLD stages III and IV with at least one hospitalization were 3.8 (1.1–17.7) ($p=0.035$) and 3.8 (1.2–12.6) ($p=0.020$), respectively.

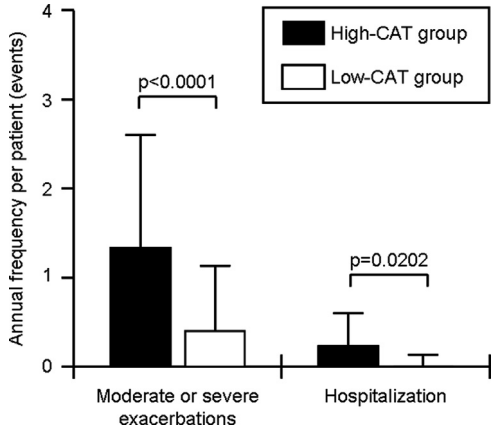

Fig. 2 – Annual frequency of exacerbation and hospitalization in COPD patients. All data are expressed as the annual frequency of moderate or severe COPD exacerbations and hospitalizations due to COPD exacerbations per patient per year (error bars=standard deviation). CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease.

3.4. *Cut-off points for exacerbation and hospitalization*

The AUC of the CAT score for patients with annual moderate or severe COPD exacerbations and hospitalizations was 0.77 and 0.79, respectively (Fig. 4). The best sensitivity and specificity for moderate or severe exacerbations were 0.90 and 0.47, respectively, when the cut-off CAT score was 8 points. The best sensitivity and specificity for hospitalizations were 0.53 and 0.49, respectively, when the cut-off CAT score was 29 points.

4. Discussion

In Japanese patients with COPD, the CAT score, but not hospitalization, is an independent predictor of annual moderate or severe COPD exacerbation. GOLD 2011 guidelines [19] recommended a CAT score of 10 points or higher as one of the indicators for appropriate management of patients with COPD. The patients with severe airflow obstruction such as GOLD stages II and III also had an independent predictive risk factor of moderate or severe COPD exacerbations and hospitalizations. In this study, we found that COPD patients with a high CAT score (>10 points) were significantly older, had a lower BMI, and had a severe airflow obstruction than those with a low CAT score (<10 points), despite the use of more advantaged respiratory medicines such as LABA and ICS in

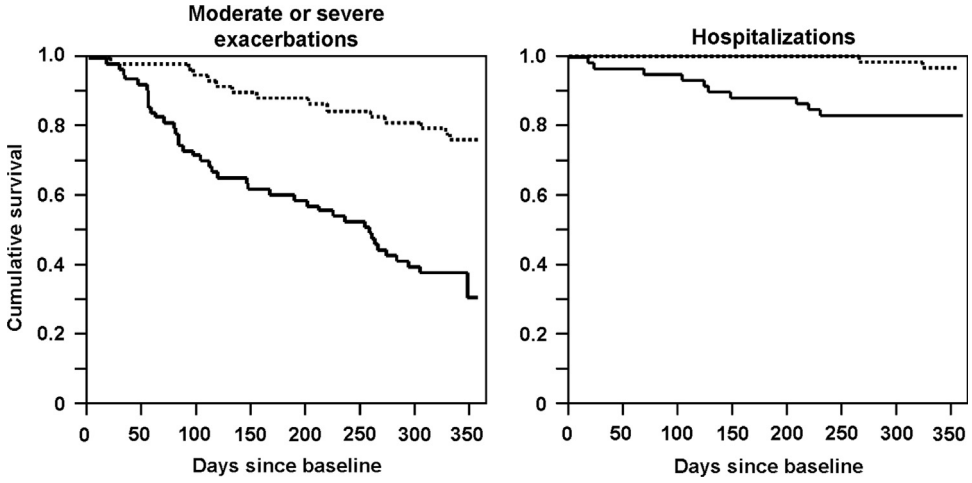

Fig. 3 – Cumulative survival curves for COPD patients with first exacerbation and hospitalization. Cumulative survival curves for patients with first moderate or severe exacerbation and hospitalization during one year. Solid line=high-CAT group; dashed line=low-CAT group. CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease.

the high-CAT group compared to the low-CAT group (Table 1). Moreover, the high-CAT group had a significantly higher frequency of moderate or severe COPD exacerbations and hospitalization, and a shorter period until the next moderate or severe COPD exacerbation than the low-CAT group.

Four stratifications, namely categories A, B, C, and D, in GOLD 2011 guidelines were well defined by identifying individuals at risk of exacerbation [19,23]. Using ROC curve analysis, we sought the optimal cut-off point that would serve as a predictor of exacerbation and hospitalization, as there has been little evidence that a CAT score of 10 points is a reliable cut-off point for this purpose. We found that the best predictive cut-off points for moderate or severe COPD exacerbations and hospitalization due to COPD exacerbations were 8 and 29 points, respectively. All of the enrolled patients

Table 2 – Univariable analysis for exacerbations and hospitalizations in COPD patients.

Characteristics	Exacerbation		Odds ratio (95% CI)	*p* Value	Hospitalization		Odds ratio (95% CI)	*p* Value
	(+) n/N	(−) n/N			(+) n/N	(−) n/N		
Age, ≥65 years	43/58	32/65	3.0 (1.4–6.3)	0.006	12/15	63/108	2.9 (0.8–10.7)	0.2
Total CAT score ≥10 points	42/58	22/65	5.1 (2.4–11.1)	<0.0001	12/15	52/108	4.3 (1.2–16.1)	0.027
GOLD stage III and IV	28/58	9/65	5.8 (2.4–13.9)	<0.0001	9/15	28/108	4.3 (1.4–13.1)	0.014

The number of patients and total number of patients with at least one moderate or severe COPD exacerbation or hospitalization due to COPD exacerbations are expressed as *n* and *N*, respectively.
CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 3 – Multivariable analysis for exacerbations and hospitalizations in COPD patients.

Characteristics	Exacerbation [odds ratio (95% CI)]	*p* Value	Hospitalization [odds ratio (95% CI)]	*p* Value
Age ≥65 years	1.6 (0.6–4.0)	0.3	–	–
Total CAT score ≥10 points	4.5 (1.9–11.3)	0.0005	3.8 (1.1–17.7)	0.035
GOLD stages III and IV	5.7 (2.3–15.3)	0.0001	3.8 (1.2–12.6)	0.020

CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

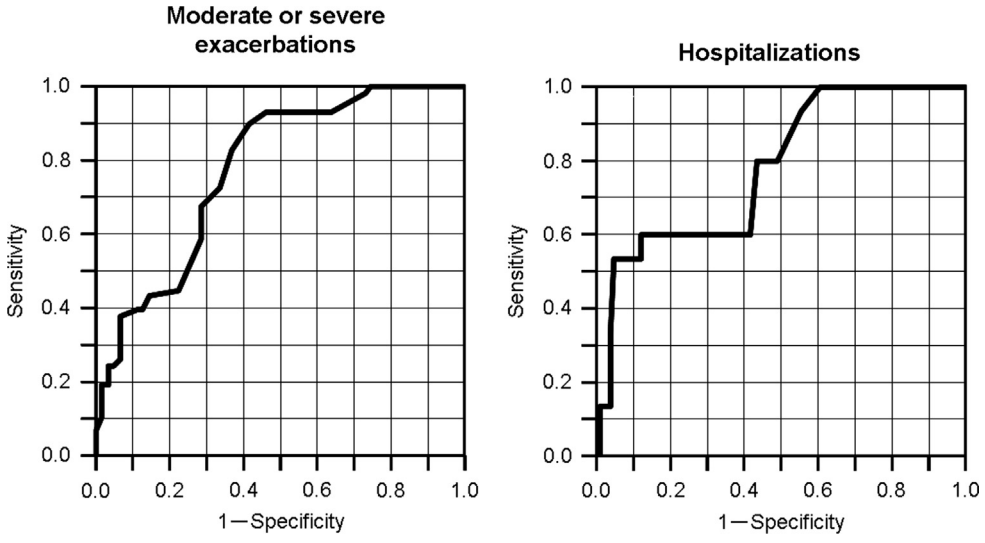

Fig. 4 – Receiver operating characteristic curves of the CAT scores for exacerbations and hospitalizations. The receiver operating characteristic curves of the CAT scores for annual moderate or severe COPD exacerbations and hospitalizations. CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease.

were Japanese. Previous studies have demonstrated that the frequency of annual moderate or severe exacerbations per patient in Japanese individuals (0.54–0.61 events) may be lower than that in the United States and Europe (0.81–0.88 events) [24,25]. Japanese people have significantly lower prevalence of obesity than Westerners [26]. Japanese patients with COPD have significantly lower BMI and less frequent chronic bronchitis with chronic coughing and sputum than Westerners [24,25,27]. All patients with COPD had emphysematous areas by HRCT in our study. Hence, the discrepancy in the best CAT score cut-off point between our results and GOLD 2011 guidelines [19] for exacerbations may have been due to differences in race or ethnicity. Our findings also suggest that CAT may be more suitable for predicting exacerbation rather than hospitalization in COPD patients. Further analysis will be needed to verify this hypothesis.

The CAT was originally developed as a tool to allow communication between physicians and patients about the impact of COPD [16]. The CAT has been shown to correlate well with HRQOL measured by the SGRQ and is simpler and easier to use than the latter [17]. The CAT can also help with diagnosis of COPD, its exacerbations, and their severity [26–31]. In this study, we found that the CAT score was an independent predictor of moderate or severe COPD exacerbations, but not hospitalizations due to COPD exacerbations, and was also predictive of a shorter period until the next moderate or severe COPD exacerbation in patients with COPD. Thus, the CAT score may be useful for devising changes in interventions to prevent exacerbations, as has been reported recently [32,33]. In this study, the reproducibility of the CAT has a limitation, because the CAT score was only measured one time in each patient. Further and longer trials will be necessary to clarify the reproducibility of the CAT and to investigate whether CAT can be used as a predictor of lung function decline and mortality in patients with COPD. In addition, investigations of future risks by using classification of category ABCD should be conducted in Japanese patients with COPD.

5. Conclusion

Our present results indicate that Japanese patients with COPD showing high CAT scores have a poor prognosis and that the CAT score is a promising tool to predict exacerbation in Japanese COPD.

Statement indicating the role of each author

Dr. M. Suetomo contributed to protocol design, data collection, analysis, and writing of the manuscript.
Dr. T. Kawayama contributed to protocol design and editing of the manuscript.
Dr. T. Kinoshita contributed to data collection.
Dr. S. Takenaka contributed to data collection.
Dr. M. Matsuoka contributed to data collection.
Dr. K. Matsunaga contributed to data collection.
Dr. T. Hoshino supervised the protocol design and edited the manuscript.

Conflict of interest

Tomotaka Kawayama received lecture fees from Novartis Pharmaceuticals Japan. Tomoaki Hoshino received a grant from GSK, Japan. There are no current funding sources, nor competing financial interests, associated with this work.

Acknowledgments

The authors extend special thanks to Professor Hisamichi Aizawa, M.D., Ph.D., Kurume University School of Medicine, for contributing to the protocol design. The authors are also grateful to Masaharu Kinoshita, M.D., Ph.D., Yanagawa Nagata Hospital, and Tatsuya Mukaino, MD, Social Insurance Tagawa Hospital, for collection of data on the study subjects. The authors are also grateful to Professor Howard A. Young, Ph.D., National Cancer Institute-Frederick, for English language support.

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