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The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients☆

Sang-Do Lee [a], Ming-Shyan Huang [b], Jian Kang [c], Ching-Hsiung Lin [d], Myung Jae Park [e], Yeon-Mok Oh [a], Namhee Kwon [f], Paul W. Jones [g], Dimitar Sajkov [h],* on behalf of the Investigators of the Predictive Ability of CAT in Acute Exacerbations of COPD (PACE) Study

[a] *Division of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-2-dong, Songpa-gu, Seoul 138-736, Republic of Korea*
[b] *Department of Internal Medicine, Kaohsiung Medical University Hospital, School of Medicine, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan*
[c] *The Institute of Respiratory Diseases, The First Affiliated Hospital of China Medical University, No. 117, Nanjing Street (N), Shenyang 110001, Liaoning, China*
[d] *Division of Chest Medicine, Department of Internal Medicine, Changhua Christian Hospital, No. 135, Nan-Hsiao Street, Changhua City, Changhua County 500, Taiwan*
[e] *Division of Respiratory and Critical Care Medicine, Kyung Hee University Hospital, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul 130-702, Republic of Korea*
[f] *Asia Pacific Medical, GlaxoSmithKline, 150 Beach Road, #22-00 Gateway West, Singapore 189720, Singapore*
[g] *Division of Clinical Science, St George's University of London, Cranmer Terrace, London SW17 0RE, United Kingdom*
[h] *Australian Respiratory and Sleep Medicine Institute, Flinders Medical Centre, Bedford Park, Adelaide, SA 5042, Australia*

Summary
We evaluated the predictive value of the COPD assessment test (CAT™) for exacerbation in the following six months or time to first exacerbation among COPD patients with previous exacerbations.

* Corresponding author. Tel.: +61 8 8204 4623; fax: +61 8 8204 5632.
  E-mail addresses: dimitar.sajkov@health.sa.gov.au, dsajkov@hotmail.com (D. Sajkov).

COPD outpatients with a history of exacerbation from 19 hospitals completed the CAT questionnaire and spirometry over six months. Exacerbation events were prospectively collected using a structured questionnaire.

The baseline CAT score categorised into four groups (0–9, 10–19, 20–29, and 30–40) showed strong prediction for time to first exacerbation and modest prediction for any exacerbation or moderate-severe exacerbation (AUC 0.83, 0.64, and 0.63 respectively). In multivariate analyses, the categorised CAT score independently predicted all three outcomes ($p = 0.001$ or $p < 0.001$). Compared with the lowest CAT score category, the higher categories were associated with significantly shorter time to first exacerbation and higher exacerbation risks. The corresponding adjusted median time was >24, 14, 9, and 5 weeks and the adjusted RR was 1.00, 1.30, 1.37, and 1.50 in the category of 0–9, 10–19, 20–29, and 30–40 respectively. Exacerbation history (≥ 2 vs. 1 event in the past year) was related to time to first exacerbation (adjusted HR 1.35; $p = 0.023$) and any exacerbation during the study period (adjusted RR 1.15; $p = 0.016$).

The results of this study support the use of the CAT as a simple tool to assist in the identification of patients at increased risk of exacerbations. This could facilitate timely and cost-effective implementation of preventive interventions, and improve health resource allocation.

Trial registration: Clinicaltrials.gov: NCT01254032.

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) significantly impair health-related quality of life (QoL), are associated with poor prognosis [1,2] and place a huge economic burden on health services and society [3]. The Global initiative for chronic Obstructive Lung Disease (GOLD) strategy document recommends use of a multidimensional system based on post-bronchodilator forced expiratory volume in 1 s (FEV_1), exacerbation history and symptom scores to stratify COPD patients into GOLD A, B, C or D categories and guide the selection of pharmacological therapy [4]. A recent study showed that there is substantial heterogeneity in clinical characteristics among patients in group D and the highest exacerbation rates were recorded in this group [5]. This has led to the search for a tool to assist stratification of patients who are at high risk of exacerbations, particularly those placed in group D, according to their imminence or likelihood of exacerbations. This may facilitate initiation of prompt interventions and improve planning and distribution of health resources.

Few studies have evaluated the potential of exacerbation risk factors to stratify patients according to the imminence or likelihood of exacerbation [6,7]. The spirometric staging system defined by GOLD (GOLD stages 1–4) [4] was found to lack the potential for risk stratification [7] while the BMI/airflow obstruction/dyspnea/exercise capacity (BODE) index exhibits good prediction performance but was not practical to be used in clinical practice [6]. Therefore, there is a need for a simple and reliable tool to assist with the assessment of COPD exacerbation risk.

The recently developed CAT is a short self-administered QoL questionnaire [8]. It is readily available, easy to complete and interpret, suitable for routine clinical use [9,10]. The CAT has demonstrated good correlation with established QoL questionnaires and other relevant measures of disease severity [8,11–13]. Further, it provides a good sense of the health impact in COPD patients [14]. In an earlier study, the CAT score was significantly different between stable and exacerbated patients with COPD [8]. Moreover, longitudinal studies showed that the CAT score relates to exacerbation severity [15] and is responsive to changes in health status during and after exacerbations [13,15,16].

We hypothesised that health status could be a premonitory sign of exacerbation and the CAT could be a useful tool for predicting exacerbations. This study evaluates the predictive value of the CAT for exacerbations and moderate-severe exacerbations in the following six months, and time to first exacerbation in COPD outpatients who are at risk of exacerbations. It also examines the potential of the CAT to further stratify these patients according to the imminence or likelihood of exacerbations.

Methods

Study design and population

In this prospective observational 6-month study, we recruited 545 patients with COPD from outpatient clinics across 19 hospitals in Australia, China, Korea and Taiwan between August 2010 and April 2011. Patients were at least 40 years old, with smoking history of more than 10 pack-years, established diagnosis of COPD for at least six months, defined as FEV_1/forced vital capacity (FVC) ratio <0.7 [4], and with history of at least one COPD exacerbation, which required additional treatment in the previous 12 months. Patients with a current diagnosis of asthma were excluded.

All patients provided written informed consent and the study was approved by the local ethics committees or review boards prior to the initiation of any study-related activities. The study was conducted in accordance with Good Clinical Practice (GCP), all applicable patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki.

Study assessments

All patients attended the clinic every eight weeks and received a telephone call every eight weeks in between

study visits. Treatment history, COPD history, smoking history, and comorbidities were collected from the medical records at the baseline visit. A structured clinical interview was also conducted to record details of specific comorbidities, including lung cancer, diabetes, peripheral artery disease, rheumatoid disease, heart failure (any causes), ischaemic heart disease (IHD), hypertension, and cardiovascular disease. At the baseline visit and each study visit, health-related QoL, dyspnea, and lung function were evaluated using the local language version of the CAT questionnaire in each country, the Medical Research Council (MRC) dyspnea scale, and spirometry respectively. Spirometry was performed in accordance to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [17], and the predicted values were calculated using reference equations appropriate for each country [18–20]. GOLD stage was defined as post-bronchodilator FEV_1 % predicted values classified into 4 stages; stage 1: $\geq$80%, stage 2: 50–79%, stage 3: 30–49%, and stage 4: <30% [4]. Exacerbations in the previous month were assessed using a structured questionnaire at each study visit and telephone contact. An exacerbation was defined as worsening of symptoms of COPD for at least two consecutive days and was classified as mild when patients did not require treatment with systemic corticosteroids and/or antibiotics; moderate when treatment with systemic corticosteroids and/or antibiotics were required; or severe when hospitalisation or visit to the emergency care unit was required [21]. A separate exacerbation was considered when an interval of clinical improvement of at least 7 days was observed.

Statistical analysis

Predictive models for the outcome of at least one COPD exacerbation or moderate-severe exacerbation over the following six months were developed. The predictive index scores were obtained from two logistic regression models and two cox regression models on time to first exacerbation; based on baseline CAT score, uncategorised continuous variable or categorised into four CAT score groups (0–9, 10–19, 20–29, and 30–40). The predictive values of the CAT score in subgroups; patients with any cardiovascular comorbidity and patients with heart failure, IHD or both, were also evaluated. The predictive value of changes in CAT score over eight weeks (between two study visits) for COPD exacerbation in subsequent study periods were also evaluated.

Unadjusted and adjusted analyses were performed using Poisson regression to evaluate the relationship between baseline CAT scores and the occurrence of any exacerbation or moderate-severe exacerbation. The analyses were repeated using Cox regression to evaluate the relationship between baseline CAT scores and time to first COPD exacerbation. Relevant clinical factors that could affect the outcomes or baseline CAT scores were included in the adjusted analyses: age, gender, body mass index (BMI), GOLD stages (1–4), number of COPD exacerbations in the preceding year, duration of COPD, current smoking status, number of comorbidities, history of influenza vaccination, and country. The median time to first COPD exacerbation by categorised

baseline CAT score was estimated using the Kaplan–Meier technique. A p-value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS PASW Statistics 18 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 495 patients who had completed the CAT questionnaire at the baseline visit were included in the study population. Table 1 shows the demographics and characteristics at baseline for all patients and each baseline CAT score category. The mean age was 69.4 ± 8.8 years and 22% were current smokers. The mean CAT score was 14.8 ± 7.7 and 48% had a CAT score of 10–19. The median FEV_1 was 47.0% (range 13.0–121.0%) of predicted normal value. Nearly half of the patients (49%) had more than one COPD exacerbation in the preceding year. There was a trend for patients with higher baseline CAT scores to have longer COPD duration, poorer lung function, and more frequent exacerbations in the preceding year. Similarly, the prevalence of comorbidities and prior medication use tended to be higher with higher CAT scores.

During the study period, 338 patients (68%) and 226 patients (46%) experienced at least one COPD exacerbation and one moderate-severe exacerbation respectively (Supplementary Table 1). There was a trend for increased risk of exacerbations with higher baseline CAT scores (52%, 71%, 80%, and 100% for the four CAT score categories in ascending order). A similar trend was observed for the incidence of moderate-severe exacerbation (33%, 44%, 58%, and 95% respectively) (Supplementary Table 1). The median exacerbation rate for the study population was 1.00 (range 0.00–6.00) episodes over six months.

Predictive ability of the CAT for COPD exacerbations

The categorised CAT score showed a high predictive ability for time to first exacerbation (area under the receiver operating characteristic curve [AUC] 0.83) and a modest predictive ability for any COPD exacerbation (AUC 0.64) or moderate-severe exacerbation (AUC 0.63) in the following six months (Table 2). The uncategorised CAT score provided predictions of similar magnitude. In models adjusting for potential confounders, the uncategorised CAT score continued to show comparable prediction as the categorised CAT score. The sensitivity and specificity for prediction of time to first exacerbation at the uncategorised CAT score cut-off was 60% and 95% respectively. The probability cut-off of the uncategorised CAT score to observe a COPD exacerbation or moderate-severe exacerbation in a COPD patient was 11 and 17 respectively, with a sensitivity and specificity of 75% and 47%, and 52% and 69% respectively.

The categorised CAT score showed similar prediction performance when tested in subgroups of patients with cardiovascular comorbidity. The AUCs for time to first exacerbation, exacerbation, and moderate-severe exacerbation were 0.87, 0.66, and 0.60 respectively in patients

Table 1 Demographics and other baseline characteristics

Characteristics	Baseline CAT score category				
	0–9 (n = 134)	10–19 (n = 236)	20–29 (n = 104)	30–40 (n = 21)	All (n = 495)
Age (years)	69.0 ± 8.5	69.7 ± 8.9	69.4 ± 9.1	69.9 ± 7.9	69.4 ± 8.8
Male	120 (90)	207 (88)	91 (88)	17 (81)	435 (88)
Asians	129 (96)	201 (85)	74 (71)	11 (52)	415 (84)
BMI (kg/m^2)	23.7 (15.1–32.6)	23.1 (13.2–40.6)	22.0 (12.7–38.9)	21.1 (18.0–34.9)	23.0 (12.7–40.60)
COPD duration (months)	27.0 (6.0–379.0)	32.5 (6.0–323.0)	56.5 (6.0–240.0)	72.0 (19.0–280.0)	36.0 (6.0–379.0)
Current smoker	36 (27)	47 (20)	20 (19)	4 (19)	107 (22)
Smoking history (pack-years)	39.0 (10.0–150.0)	40.0 (10.0–138.0)	45.0 (11.0–175.0)	45.0 (19.0–196.0)	40.0 (10.0–196)
Post-bronchodilator FEV$_1$ (%predicted)	56.6 (19.4–101.0)	46.0 (13.0–99.0)	45.5 (14.0–121.0)	38.2 (14.5–92.0)	47.0 (13.0–121.0)
COPD exacerbation in the preceding year					
1	78 (58)	125 (53)	45 (43)	6 (29)	254 (51)
≥2	56 (42)	111 (47)	59 (57)	15 (71)	241 (49)
Comorbidities[a]					
0	88 (66)	142 (60)	49 (47)	4 (19)	283 (57)
1–2	35 (26)	71 (30)	37 (36)	11 (52)	154 (31)
≥3	11 (8)	23 (10)	18 (17)	6 (29)	58 (12)
Cardiovascular comorbidities[b]	39 (29)	85 (36)	49 (47)	16 (76)	189 (38)
CAT score					14.8 ± 7.7
Medication history					
Combination of ICS and LABA[c,d]	62 (46)	150 (64)	78 (75)	19 (91)	309 (62)
LABA[c,d]	9 (7)	15 (6)	2 (2.0)	0 (0)	26 (5)
Long-acting anticholinergic[c,d]	79 (59)	142 (60)	72 (69)	15 (71)	308 (62)
SABA[c,d]	41 (31)	108 (46)	59 (57)	12 (57)	220 (44)
Theophyllines (long- and short-acting)[d]	70 (52)	110 (47)	46 (44)	8 (38)	234 (47)
Systemic corticosteroids for COPD symptoms[e]	38 (28)	85 (36)	47 (45)	16 (76)	186 (38)
Antibiotics for RTI[e]	59 (44)	130 (55)	71 (68)	16 (76)	276 (56)
Influenza vaccination[e]	43 (32)	92 (39)	56 (54)	13 (62)	204 (41)

Data are presented as mean ± SD, n (%) or median (range).

BMI body mass index, CAT COPD assessment test, COPD chronic obstructive pulmonary disease, FEV$_1$ forced expiratory volume in 1 s, ICS inhaled corticosteroids, IHD ischaemic heart disease, LABA long-acting beta$_2$-agonist, RTI respiratory tract infection, SABA short-acting beta$_2$-agonist.

[a] Includes lung cancer, diabetes, peripheral artery disease, rheumatoid disease, heart failure (any causes), IHD, or on anti-hypertensive or other cardiovascular medication.

[b] Includes heart failure (any causes), IHD, or on anti-hypertensive or other cardiovascular medication.

[c] Inhalers.

[d] In the preceding 3 months.

[e] In the preceding 12 months.

with any cardiovascular comorbidity and 0.82, 0.72 and 0.62 respectively in patients with heart failure, IHD or both (Table 3).

Changes in CAT score between two study visits were associated with low-modest prediction of exacerbations in the subsequent study periods. Changes in CAT score at week 8 from baseline showed relatively low predictive value for exacerbations in the subsequent eight weeks (AUC 0.54; 95% CI 0.48–0.59) or 16 weeks (AUC 0.55; 95% CI 0.50–0.61). Changes in CAT score at week 16 from week 8 showed modest prediction (AUC 0.61; 95% CI 0.56–0.66) for exacerbations in the subsequent eight weeks.

Table 2 Predictive value of baseline COPD assessment test (CAT) score and other risk factors for exacerbation

Prediction models	AUC (95% CI)					
	Time to first exacerbation		Any exacerbation		Moderate-severe exacerbation	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Categorised CAT score	0.83 (0.79—0.87)	0.63 (0.57—0.68)	0.64 (0.59—0.70)	0.79 (0.75—0.84)	0.63 (0.58—0.68)	0.72 (0.68—0.77)
Uncategorised CAT score	0.83 (0.79—0.87)	0.64 (0.59—0.69)	0.65 (0.59—0.70)	0.79 (0.75—0.83)	0.63 (0.58—0.68)	0.72 (0.67—0.77)

AUC area under the receiver operating characteristic (ROC) curve, *BMI* body mass index, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease.

[a] Adjusted for age, gender, BMI, duration of COPD, current smoking status, number of comorbidities, history of influenza vaccination, and country. Categorised CAT score: baseline CAT score categorised into four groups (0—9, 10—19, 20—29, and 30—40).

Relationship between the CAT and exacerbations

The results of multivariate analyses evaluating the relationship between the CAT score and time to first exacerbation or risk of exacerbations are summarised in Table 4. In unadjusted analysis, the categorised CAT score was significantly associated with time to first exacerbation, and the risk of having any COPD exacerbation or moderate-severe exacerbation ($p < 0.001$ for all). These relationships remained significant even after adjusting for the effect of potential confounders ($p = 0.001$ or $p < 0.001$). Similarly, the uncategorised CAT score was also predictive of all three outcomes in both unadjusted ($p < 0.001$ for all) and adjusted analyses ($p < 0.001$, $p = 0.001$; $p = 0.002$ respectively) (Table 4).

The relationship between each CAT score category and each outcome was evaluated. Higher CAT score categories were associated with significantly shorter time to first exacerbation, compared with the lowest category (Table 4). The corresponding adjusted hazard ratios (HR) was 1.00, 1.73, 2.41, and 4.16 respectively (Table 4) and the adjusted median time was >24, 14, 9, and 5 weeks respectively (Fig. 1) for the four categories in ascending order. Similarly, higher CAT score categories were associated with significantly higher exacerbation risk; adjusted relative risks (RRs) 1.00, 1.30, 1.37, and 1.50 respectively (Table 4). Patients in the highest category were at twice the risk of having moderate-severe exacerbations (adjusted RR 2.01; $p < 0.001$) than patients in the lowest category (Table 4).

Relationship between other factors and exacerbations

Exacerbation history (≥ 2 vs. 1 event in the past year) was significantly associated with time to first exacerbation ($p = 0.023$) and risk of any exacerbation ($p = 0.016$) (Table 4). Compared with patients with less frequent prior exacerbations (1 event), those with frequent prior exacerbations (≥ 2 events) showed a shorter time to first exacerbation (adjusted HR 1.35) and increased risk of exacerbations (adjusted RR 1.15). However, exacerbation history was not associated with risk of moderate-severe exacerbations; adjusted RR 1.14; $p = 0.181$ (Table 4). GOLD stage was significantly associated with time to first exacerbation ($p = 0.029$) and risk of moderate-severe exacerbations ($p = 0.008$), but not risk of any exacerbation ($p = 0.128$) (Table 4).

Discussion

This is the first large, multinational study assessing the predictive value of the CAT for COPD exacerbations in COPD

Table 3 Predictive value of categorised COPD assessment test (CAT) score for exacerbation among patient subgroups

	AUC (95% CI)		
	Time to first exacerbation ($n = 431$)	Any exacerbation ($n = 491$)	Moderate-severe exacerbation ($n = 490$)
Overall cohort	0.83 (0.79—0.87)	0.64 (0.59—0.70)	0.63 (0.58—0.68)
Any cardiovascular comorbidity[a]			
Yes	0.87 (0.81—0.93)	0.66 (0.56—0.76)	0.60 (0.53—0.69)
No	0.82 (0.77—0.87)	0.65 (0.59—0.72)	0.62 (0.55—0.68)
Heart failure and/or IHD			
Yes	0.82 (0.68—0.95)	0.72 (0.58—0.86)	0.62 (0.48—0.76)
No	0.83 (0.79—0.87)	0.63 (0.58—0.69)	0.62 (0.57—0.68)

Among patients with available data.

AUC area under the receiver operating characteristic (ROC) curve, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *IHD* ischaemic heart disease.

[a] Includes heart failure (any causes), IHD, or on anti-hypertensive or other cardiovascular medications.

Table 4 Relationship between baseline COPD assessment test (CAT) score and exacerbations

Factor	Time to first exacerbation		Any exacerbation		Moderate-severe exacerbation	
	Hazard ratio (95% CI)	p-Value	Relative risk (95% CI)	p-Value	Relative risk (95% CI)	p-Value
Uncategorised CAT score[a] (unadjusted)	1.06 (1.04–1.07)	<0.001	1.02 (1.01–1.03)	<0.001	1.03 (1.02–1.04)	<0.001
Uncategorised CAT score[a,b] (adjusted)	1.05 (1.03–1.06)	<0.001	1.01 (1.01–1.02)	0.001	1.02 (1.01–1.03)	0.002
Categorised CAT score (unadjusted)		<0.001		<0.001		<0.001
0–9	1		1		1	
10–19	1.72 (1.17–2.54)	<0.001	1.35 (1.08–1.60)	0.004	1.31 (0.93–1.85)	0.174
20–29	2.64 (1.71–4.08)	<0.001	1.53 (1.21–1.92)	<0.001	1.73 (1.21–2.47)	<0.001
30–40	6.14 (3.19–11.82)	<0.001	1.91 (1.57–2.33)	<0.001	2.86 (2.08–3.92)	<0.001
Categorised CAT score (adjusted)		0.001		<0.001		<0.001
0–9	1		1		1	
10–19	1.73 (1.23–2.43)	0.001	1.30 (1.09–1.56)	0.004	1.18 (0.89–1.57)	0.251
20–29	2.41 (1.62–3.58)	<0.001	1.37 (1.14–1.65)	0.001	1.40 (1.03–1.90)	0.330
30–40	4.16 (2.26–7.64)	<0.001	1.50 (1.24–1.81)	<0.001	2.01 (1.45–2.80)	<0.001
Age (≤65 years vs. >65 years)	1.06 (0.79–1.42)	0.701	0.99 (0.87–1.13)	0.920	0.85 (0.67–1.06)	0.148
Gender (male vs. female)	0.86 (0.58–1.29)	0.469	1.01 (0.83–1.22)	0.958	1.17 (0.86–1.60)	0.319
BMI (≤21 kg/m^2 vs. >21 kg/m^2)	0.76 (0.57–1.02)	0.065	0.90 (0.79–1.03)	0.115	0.98 (0.80–1.20)	0.840
GOLD stage[c]		0.029		0.128		0.008
Stage 1	1		1		1	
Stage 2	0.91 (0.57–1.44)	0.674	0.92 (0.75–1.12)	0.391	0.86 (0.60–1.23)	0.396
Stage 3	1.32 (0.83–2.09)	0.242	1.07 (0.89–1.30)	0.476	1.25 (0.89–1.76)	0.201
Stage 4	1.54 (0.89–2.68)	0.124	1.02 (0.81–1.27)	0.883	1.02 (0.68–1.54)	0.919
COPD exacerbations in the preceding year (≥2 vs. 1)	1.35 (1.04–1.74)	0.023	1.15 (1.03–1.28)	0.016	1.14 (0.94–1.37)	0.181
Duration of COPD (months)[a]	1.00 (1.00–1.00)	0.684	1.00 (1.00–1.00)	0.445	1.00 (1.00–1.00)	0.506
Current smoking status (yes vs. no)	1.37 (1.00–1.88)	0.052	1.04 (0.92–1.17)	0.577	0.97 (0.77–1.22)	0.787
Number of comorbidities[d]		0.854		0.417		0.076
1–2 vs. none	1.08 (0.81–1.45)	0.593	1.08 (0.96–1.21)	0.186	1.25 (1.01–1.54)	0.041
≥3 vs. none	1.02 (0.68–1.51)	0.941	1.05 (0.90–1.22)	0.543	1.29 (0.99–1.67)	0.058
Influenza vaccination (yes vs. no)	1.33 (0.95–1.86)	0.098	1.07 (0.92–1.24)	0.376	1.47 (1.12–1.94)	0.005
Country	–	<0.001	–	<0.001	–	0.295

Results presented are adjusted values unless otherwise stated.

BMI body mass index, COPD chronic obstructive pulmonary disease, CI confidence interval, GOLD global initiative for chronic obstructive lung disease, IHD ischaemic heart disease.

[a] For continuous variables, the results are for per unit increase in variable.

[b] Full results of multivariate analyses of uncategorised CAT score are on file; covariables included in analyses are similar to those in multivariate analyses of categorised CAT score as shown in the table.

[c] GOLD stage: post-bronchodilator FEV$_1$ % predicted values classified into 4 stages (stage 1: ≥80%, stage 2: 50–79%, stage 3:30–49%, and stage 4: <30%).

[d] Includes lung cancer, diabetes, peripheral artery disease, rheumatoid disease, heart failure (any causes), IHD, or on anti-hypertensive or other cardiovascular medication.

outpatients who are at risk of exacerbations. Our study provides important evidence on the potential of the CAT for use as an additional tool to assist physicians to further stratify patients who are at risk of exacerbations, based on their exacerbation history, according to their imminence or likelihood of exacerbations.

Our study showed that the CAT score, categorised into four groups or used as a continuous variable, has a modest predictive value for exacerbations and moderate-severe exacerbations in the following six months (AUC 0.63–0.64).

A similar level of predictive ability for COPD exacerbation (AUC 0.62–0.69) was reported in other studies where the prediction models consisted of a combination of risk factors, which may not be practical to use in clinical practice. [7,22,23] These findings support the use of the CAT as a convenient and reliable alternative to these models to achieve the same level of prediction for exacerbations.

Our data suggest that the CAT score is consistent in its predictive ability in different subgroups of patients. Considering that heart disease is common among COPD
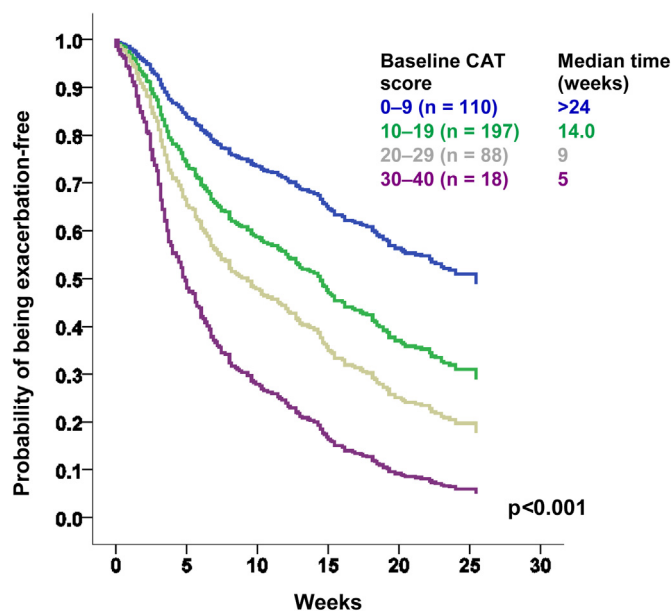
Figure 1   Adjusted time to first exacerbation by categorised baseline COPD assessment test (CAT) score. *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *GOLD* global initiative for chronic obstructive lung disease. Time to first exacerbation was adjusted for age, gender, BMI, GOLD stages (1—4), COPD exacerbation history in the preceding year, duration of COPD, current smoking status, number of comorbidities, history of influenza vaccination, and country.

patients and its symptoms may mimic those of COPD, we assessed the performance of the CAT score in predicting COPD exacerbations or time to first exacerbation in patients with cardiovascular comorbidity. We found predictions of similar magnitude as those observed with the overall study population. This observation is encouraging and suggests that the CAT score is reliable in predicting exacerbations in the presence of cardiovascular comorbidity. Further analysis on other patient subgroups is needed to confirm this observation.

Several factors have been previously reported to be associated with increased risk of exacerbation. These include poorer health status [24—27], worsening lung function [23,28], dyspnea [24], a history of exacerbation [26], and more severe disease [26]. Hurst and colleagues reported a history exacerbation (≥ 1 vs. 0 event) to be the strongest predictor of exacerbations among other significant factors [26]. Our findings extend previous findings and show that frequent-exacerbation in the past year (≥ 2 events) is a strong predictor of exacerbations among patients who are at higher risk of exacerbations. Importantly, we found that higher CAT scores remained associated with increased exacerbation risks and shorter time to first exacerbation after adjustment for relevant clinical factors. The highest category was also associated with twice the risk of moderate-severe exacerbations as the lowest category. In contrast, we did not observe such trends with GOLD stages. Taken together, these findings support the use of exacerbation history to identify patients who at risk of COPD exacerbation and the use of the CAT as a tool to further stratify these patients who are at increased risk for exacerbations according to the imminence and likelihood of exacerbation, thereby facilitating timely and cost-effective implementation of preventive interventions. Furthermore, our findings also support the use of the CAT in the design of

clinical trials where COPD exacerbation is an outcome to measure patients' health status and facilitate more accurate sample size calculation [29].

One of the strengths of this study is the large sample size, which allowed a reasonable level of precision to be achieved on the predictive power of the CAT for COPD exacerbation. Using the CAT score, assessments of onset or risk of COPD exacerbations can be performed easily and quickly as the CAT questionnaire is conveniently applicable in clinics; physicians need not collect a combination of other clinical information to achieve the same level of prediction.

However, our findings need to be interpreted in light of a few limitations. First, data on exacerbations were based on patient's recall, which may underestimate the exacerbation rates. Nonetheless, the use of a structured questionnaire to assess and classify exacerbations according to severity based on the consensus definition by the ERS and the ATS, improved the accuracy of patient recall and ensured consistency of data collection, which reduced recall bias to some extent. Furthermore, as the study was conducted over a 6-month period, exacerbation rates may have been influenced by seasonal variation, which could also impact upon the time to first exacerbation. Future studies conducted over a period of at least one year could overcome seasonal variations in exacerbations and provide more robust results. Our study recruited a specific population of COPD patients with prior exacerbations in the preceding year. Therefore, our prediction model may not be generally applicable to all patients with COPD, specifically those with a lower rate of exacerbations. Finally, the relatively short study duration only allowed small changes in patients' CAT score to be captured. Hence, only a preliminary evaluation of the predictive value of changes in CAT score for subsequent exacerbations can be made in this study. A study of a longer duration will provide further information.

Conclusions

In patients with a history of exacerbations in the preceding year, the CAT can identify patients at further risk of exacerbations in the following six months. This may allow better informed decisions in the clinical management of COPD patients and improve health resource allocation. The CAT may also be used in the design of clinical trials targeting COPD population at high risk of exacerbations.

Authors' contributions

SDL, YMO, NK, PWJ, and DS participated in the conception and design of the study. SDL, MSH, JK, CHL, MJP, YMO, NK, and DS contributed to the acquisition of the data. All authors participated in the analysis and the interpretation of the data, critical revisions of the manuscript drafts and approved the final manuscript for submission for publication.

Conflicts of interest

Sang-Do Lee served as a consultant to GlaxoSmithKline and Nycomed, and has received speakers' honoraria from GlaxoSmithKline, AstraZeneca, Boehringer, Nycomed, Takeda, Abbott, and Norvatis. Yeon-Mok Oh has received funding from GlaxoSmithKline, MSD Korea, AstraZeneca Korea, Boehringer Ingelheim Korea, Handok, Asan Institute for Life Science and University of Ulsan College of Medicine, speakers' honoraria from GlaxoSmithKline, MSD Korea, AstraZeneca Korea, Boehringer Ingelheim Korea, Handok, Pfizer Korea, and Korea Doctors' Weekly, and payment for development of a presentation for Diachi Sankyo Korea. Paul W Jones served as a consultant and speaker for GlaxoSmithKline and has received funding from GlaxoSmithKline. Namhee Kwon is an employee of GlaxoSmithKline and owns stocks in GlaxoSmithKline. The other authors declare they have no competing interests.

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Acknowledgements

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.12.014.

References

[1] Bourbeau J, Ford G, Zackon H, Pinsky N, Lee J, Ruberto G. Impact on patients' health status following early identification of a COPD exacerbation. Eur Respir J 2007;30:907—13.

[2] Suissa S, Dell'aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax 2012;67:957—63.

[3] Anzueto A. Impact of exacerbations on COPD. Eur Respir Rev 2010;19:113—8.

[4] Global Strategy for the Diagnosis. Management and prevention of COPD, global initiative for chronic obstructive lung disease (GOLD). Available from: http://www.goldcopd.org/; 2013.

[5] Sillen MJ, Franssen FM, Delbressine JM, et al. Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: findings of the DICES trial. Respir Med 2013;107:1186—94.

[6] Marin JM, Carrizo SJ, Casanova C, et al. Prediction of risk of COPD exacerbations by the BODE index. Respir Med 2009;103:373—8.

[7] Faganello MM, Tanni SE, Sanchez FF, Pelegrino NR, Lucheta PA, Godoy I. BODE index and GOLD staging as predictors of 1-year exacerbation risk in chronic obstructive pulmonary disease. Am J Med Sci 2010;339:10—4.

[8] Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34:648—54.

[9] COPD assessment test: http://www.catestonline.org. GlaxoSmithKline Group of companies.

[10] Kelly JL, Bamsey O, Smith C, et al. Health status assessment in routine clinical practice: the chronic obstructive pulmonary disease assessment test score in outpatients. Respiration 2012;84:193—9.

[11] Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J 2011;38:29—35.

[12] Kwon N, Amin M, Hui DS, et al. Validity of the chronic obstructive pulmonary disease assessment test translated into local languages for Asian patients. Chest 2013;143:703—10.

[13] Jones PW, Harding G, Wiklund I, et al. Tests of the responsiveness of the chronic obstructive pulmonary disease (COPD) assessment test following acute exacerbation and pulmonary rehabilitation. Chest 2012;142:134—40.

[14] Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD assessment test (CAT) scores. BMC Pulm Med 2011;11:42.

[15] Mackay AJ, Donaldson GC, Patel AR, Jones PW, Hurst JR, Wedzicha JA. Usefulness of the chronic obstructive pulmonary disease assessment test to evaluate severity of COPD exacerbations. Am J Respir Crit Care Med 2012;185:1218—24.

[16] Agusti A, Soler JJ, Molina J, et al. Is the CAT questionnaire sensitive to changes in health status in patients with severe COPD exacerbations? COPD 2012;9:492—8.

[17] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319—38.

[18] Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179—87.

[19] Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. Chest 2010;137:138—45.

[20] Pan WH, Chen JY, Haung SL, et al. Reference spirometric values in healthy Chinese neversmokers in two townships of Taiwan. Chin J Physiol 1997;40:165—74.

[21] Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008;31:416—69.

[22] Fan VS, Ramsey SD, Make BJ, Martinez FJ. Physiologic variables and functional status independently predict COPD hospitalizations and emergency department visits in patients with severe COPD. COPD 2007;4:29—39.

[23] Niewoehner DE, Lokhnygina Y, Rice K, et al. Risk indexes for exacerbations and hospitalizations due to COPD. Chest 2007; 131:20—8.

[24] Bahadori K, FitzGerald JM. Risk factors of hospitalization and readmission of patients with COPD exacerbation—systematic review. Int J Chron Obstruct Pulmon Dis 2007;2:241—51.

[25] Brusse-Keizer M, van der Palen J, van der Valk P, Hendrix R, Kerstjens H. Clinical predictors of exacerbation frequency in chronic obstructive pulmonary disease. Clin Respir J 2011;5: 227—34.

[26] Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. New Engl J Med 2010;363:1128—38.

[27] Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. Eur Respir J 2004;23:698—702.

[28] Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med 2008;178:332—8.

[29] Chetta A, Olivieri D. The COPD assessment test in the evaluation of chronic obstructive pulmonary disease exacerbations. Expert Rev Respir Med 2012;6:373—5.