CHEST

The COPD Assessment Test: What Do We Know So Far?

A Systematic Review and Meta-Analysis About Clinical Outcomes Prediction and Classification of Patients Into GOLD Stages

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BACKGROUND: The COPD Assessment Test (CAT) was developed as a simple instrument to assess health status in patients with COPD. This study aimed to systematically review the determinants of the CAT score, its ability to predict clinical outcomes, and the agreement between CAT ($\geq$ 10) and the modified Medical Research Council scale (mMRC $\geq$ 2) to categorize patients into the new Global Initiative for Chronic Obstructive Lung Disease classification system.

METHODS: From January 1, 2009, to June 30, 2015, databases were searched for studies using CAT in adults with COPD and in general populations aiming to detect COPD. Two investigators independently screened, selected, and extracted data by using a standardized form. Where appropriate, the results were combined in a random effects meta-analysis.

RESULTS: Of 453 studies, 17 were included, and eight were used in the meta-analysis. The models to predict the CAT score were able to explain < 50% of its variance. CAT scores can indicate risk of exacerbation, depression, acute deterioration in health status, and mortality. All studies found a different proportion of patients in each Global Initiative for Chronic Obstructive Lung Disease category using CAT $\geq$ 10 or mMRC $\geq$ 2. On average, the distribution was 13% different according to the instrument used. The κ agreement between CAT and mMRC ranged from 0.13 to 0.77.

CONCLUSIONS: CAT may be used as a complementary tool in a patient's clinical assessment to predict COPD exacerbation, health status deterioration, depression, and mortality. The interpretation of this meta-analysis does not support the use of the recommended cutoff points of $\geq$10 for CAT and $\geq$2 for mMRC as equivalents for the purpose of assessing patient symptoms.

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KEY WORDS: breathlessness; chronic obstructive pulmonary disease; COPD; COPD assessment test; health status

ABBREVIATIONS: AUC = area under the receiver-operating characteristic curve; CAT = COPD Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council scale

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COPD, a worldwide major cause of morbidity and mortality, is considered a serious public health problem of high and increasing prevalence.[1,2] It is an inflammatory disease of the lungs characterized by chronic, progressive, and not fully reversible airflow limitation. Although COPD is primarily a lung disease, it also produces significant systemic effects. These effects can result in reductions in functional and exercise capacity, health status, and/or quality of life.[2,3]

Since its 2011 update, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document added a new important recommendation that COPD management and treatment should be based not only on spirometric findings but also on disease impact (determined by using assessment of symptom burden and activity limitation) and future risk of disease progression and exacerbations.[2,4]

The disease burden and the impact of COPD on a patient's life are usually assessed according to self-reported health status and quality of life questionnaires.[5] A systematic review recently identified 13 disease-specific instruments to address these outcomes,[6] including the Chronic Respiratory Questionnaire[7] and St. George's Respiratory Questionnaire. Although widely used,[8] reliable, and valid, these questionnaires are lengthy[6,9] and have a complex scoring system that makes their use unsuitable in clinical settings.[9] Hence, the COPD Assessment Test (CAT) was developed as a short and simple instrument that could provide reliable measurement of COPD health status and facilitate communication between patient and health-care professionals.[9,10]

The CAT consists of eight items covering the most burdensome symptoms and limitations of COPD: cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep, and energy. The scale for each question ranges from 0 to 5, and the total score ranges from 0 to 40, with higher scores indicating poorer health status.[11] The 2011 GOLD revision recommends the use of the CAT to assess symptoms and assign patients to treatment groups based on a cutoff point of ≥10 on the CAT.[9]

Because this new integrated multidimensional COPD management has been emphasized by GOLD, the use of CAT in clinical and research settings has widely increased. Thus far, the assessment of CAT's psychometric properties suggests that it is a reliable, valid, and responsive tool to measure health status in patients with COPD.[12] The minimal clinically important difference is estimated to be 2 points.[13]

In addition to the important growth of evidence supporting the use of CAT, to the best of our knowledge, there are still some important issues regarding CAT that have not been addressed in the already published reviews.[6,12,14] Indeed, there is a need to gather information to aid in the interpretation of CAT scores and to ease its use into clinical practice. In this sense, it would be valuable to provide clear and practical evidence to help health professionals improve their understanding of the score's application, interpretation, and implications in various scenarios. The goal of the present study therefore was to perform a systematic review of the literature to summarize the determinants of the CAT score, the predictive ability of CAT to predict any clinical important outcomes, and the agreement between CAT (≥ 10) and the modified Medical Research Council scale (mMRC ≥ 2) to categorize patients into the new GOLD classification system.

Methods

Search Strategies and Selection

A systematic literature search was conducted by two investigators using OvidSP Embase, OvidSP Medline, and EBSCO Cinahl from 2009 (CAT's first publication) until June 30, 2015. The search terms used included "COPD," "CAT," and derivative terms (e-Appendix 1). Hand-searches of the included studies and other sources were also conducted.

Eligibility and Exclusion Criteria

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15] Scientific articles written in English, Spanish, and Portuguese published in peer-reviewed journals were included; meeting abstracts, case reports, editorials, commentaries, and reviews were excluded. Studies were also excluded if they were not the primary data source and/or they were a duplicate of a previously identified article. Two raters analyzed all titles and abstracts independently to find potentially eligible studies. In case of disagreement, a consensus meeting was held and, if necessary, a third rater decided the disagreement. Studies were included if they were full-text original articles that included patients with COPD or studies aiming to detect COPD, describing the predictive ability of CAT to predict any outcome, the determinants of the CAT score, or the agreement between CAT and other assessment tools.

Data Extraction

Data extraction was performed by two raters using a standardized form. The extracted information included: (1) study background, (2) sample characteristics, (3) factors that determine the CAT score,

(4) outcomes predictions, and (5) agreement between CAT and mMRC (cut points ≥ 10 and ≥ 2, respectively).

Quality Assessment

The revised tool for the Quality Assessment of Diagnostic Accuracy Studies[16] was used to assess the methodological quality of the included studies and was applied by two independent reviewers. Details of the quality assessment are provided in e-Appendix 2.

Analysis

The analyses of agreement data was performed by using MedCalc version 15.2.2, with ORs and 95% CIs for each effect (two-tailed). The inconsistency of effects between study findings was measured by using the I^2 statistic.

Results

Study Selection and Characteristics

Figure 1 displays a summary of the studies identified (n = 453), screened (n = 350), eligible (n = 22), and included (n = 17). Table 1 summarizes the main characteristics of the included studies. Two studies[17,18] assessed the determinants of the CAT score, six studies[18-23] assessed the prediction of other outcomes based on CAT, and 10 studies[24-33] assessed the agreement between symptoms vs health status to assign patients to each GOLD category.

Determinants for the CAT Score

Kelly et al[17] studied 224 patients from a COPD population in routine clinical practice. Three independent predictors of the CAT score were identified, generating the following equation: $CAT_{score} = 2.48 + 4.12$(mMRC [dyspnea,1-5]) + 0.08 (FEV_1%predicted) + 1.06 (exacerbation rate/year). A second equation was proposed for patients who had data from a body pletismography available: $CAT_{score} = 19.5 + 1.02$ (exacerbation rate/year) + 3.46 (mMRC[dyspnea,1-5]) – 0.092(total lung capacity % predicted). Both models explained 36% of the CAT score variance ($P < .05$).[17]

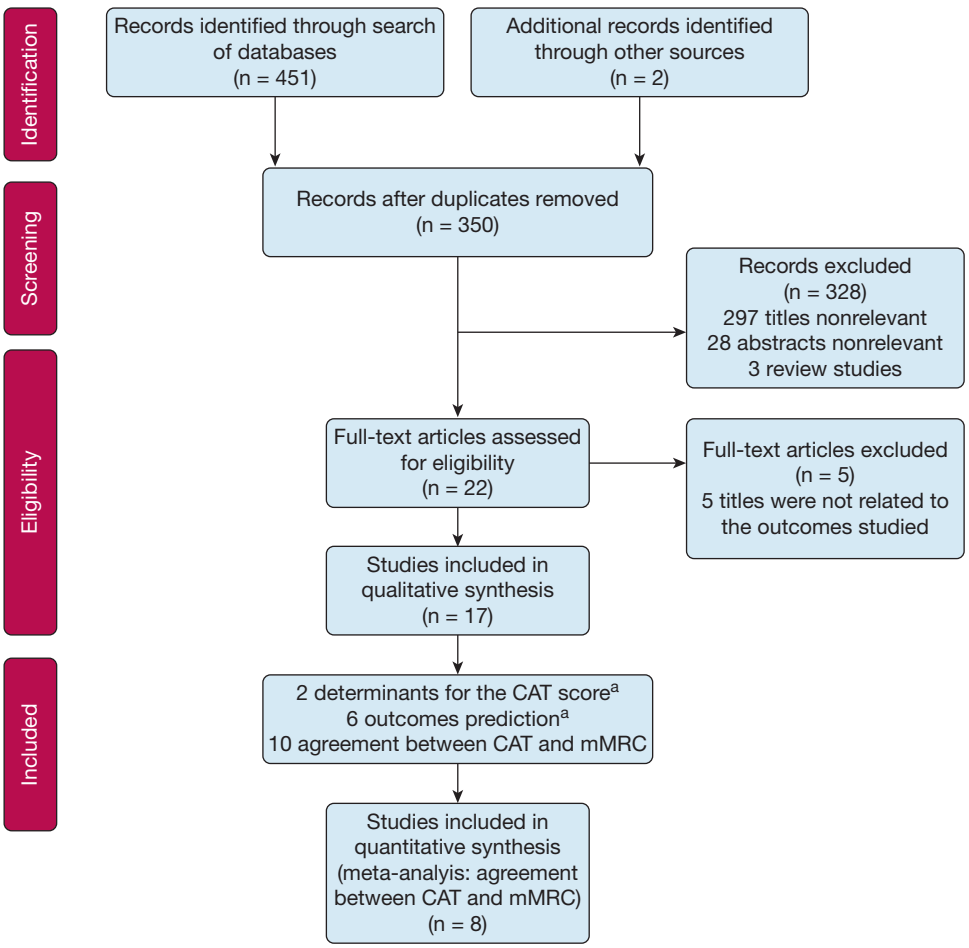

Figure 1 – *Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. [a]The study of Papaioannou et al[18] was used both in "determinants for the CAT score" and "prediction of outcomes." CAT = COPD Assessment Test; mMRC = modified Medical Research Council scale.*

TABLE 1] Study Characteristics

Study/Country	Aim	Design	Follow-up	Study Population	No. of Subjects	Male (%)	Age, Mean ± SD, y	FEV_1 % Predicted, Mean ± SD	Outcomes
Determinants for the CAT score									
Kelly et al[17], 2012/United Kingdom	Prediction of the CAT score	Cross-sectional	NA	COPD	224	64.0	63.5 ± 10.3	40.1 ± 17.9	Pulmonary function[a] Symptoms: mMRC Health status: CAT
Papaioannou et al[18], 2014/ Greece[b]	Prediction of the CAT score	Prospective observational cohort	1 y	COPD	111	84.7	71.7 ± 8.7	72 ± 21.5	Pulmonary function Health status: CAT
Outcomes prediction									
Raghavan et al[22], 2012/ Canada	Prediction of COPD diagnosis based on CAT	Cross-sectional	NA	General population	532	47.0	60.1 ± 11.4	98 ± 17	Pulmonary function mMRC dyspnea Health status: CAT
Lee et al[19], 2013/Korea	Prediction of depression based on CAT	Cross-sectional	NA	COPD	803	91.4	68.2 ± 8.2	52 ± 19.4	Health status: CAT Depression: PHQ-9
Lee et al[20], 2014/ Australia, China, Korea, Taiwan	Prediction of COPD exacerbation based on CAT	Prospective observational cohort	24 wk	COPD	495	88.0	69.4 ± 8.8	47 (13-121)[c]	Pulmonary function mMRC dyspnea Health status: CAT
Papaioannou et al[18], 2014/ Greece[b]	Prediction of COPD exacerbation based on CAT	Prospective observational cohort	1 y	COPD	111	84.7	71.7 ± 8.7	72 ± 21.5	Pulmonary function Health status: CAT

(Continued)

TABLE 1] *(Continued)*

Study/Country	Aim	Design	Follow-up	Study Population	No. of Subjects	Male (%)	Age, Mean ± SD, y	FEV_1 % Predicted, Mean ± SD	Outcomes
Pothirat et al[21], 2015/ Thailand	Prediction of acute deterioration in health status based on CAT	Prospective cohort	1-3 mo	COPD	140	56.4	71.1 ± 8.4	47.4 ± 18.2	Pulmonary function mMRC dyspnea Health status: CAT Exercise and functional capacity: 6MWT
Casanova et al[23], 2015/Spain	Prediction of all-cause mortality based on the CAT	Prospective observational cohort	38 mo	COPD	768	82.5	68 ± 9	60 ± 20	Spirometry, lung volumes, and CO diffusion capacity Comorbidities: Charlson Index mMRC dyspnea Health status: CAT and CCQ Exercise and functional capacity: 6MWT Mortality: BODE index
Agreement									
Han et al[24], 2013/United States	Agreement between symptoms vs health status measure to assign patients to GOLD categories	Prospective cohort	20 ± 11 mo	General population with positive smoking history (+ COPD)	4,484 COPD	Reported by category	Reported by category	Reported by category	Pulmonary function mMRC Health status: SGRQ (conversion of SGRQ to CAT) Exercise and functional capacity: 6MWT Multidimensional index: BODE

(Continued)

TABLE 1] *(Continued)*

Study/Country	Aim	Design	Follow-up	Study Population	No. of Subjects	Male (%)	Age, Mean ± SD, y	FEV_1 % Predicted, Mean ± SD	Outcomes
Jones et al[25], 2013/ Belgium, France, Germany, Italy, the Netherlands, Spain, United Kingdom	Agreement between symptoms vs health status measure to assign patients to GOLD categories	Cross-sectional observational	NA	COPD	1,817	71.5	65 (SD NR)	57 (SD NR) Reported by category	Pulmonary function Health status: CAT, SGRQ-C, SF-12, FACIT Symptoms: mMRC
Kim et al[26], 2013/South Korea	Agreement between symptoms vs health status measure to assign patients to GOLD categories	Prospective observation	NA	COPD	257	79.0	67.4 ± 9.4	74.6 ± 24.8	Pulmonary function Health status: CAT mMRC
Pillai et al[27], 2013/United Kingdom	Agreement between symptoms vs health status measure to assign patients to GOLD categories	Retrospective cohort	NA	α_1-antitrypsin deficiency	309	60.0	Reported by category	Reported by category	Pulmonary function Health status: CAT mMRC

(Continued)

TABLE 1] *(Continued)*

Study/Country	Aim	Design	Follow-up	Study Population	No. of Subjects	Male (%)	Age, Mean ± SD, y	FEV_1 % Predicted, Mean ± SD	Outcomes
Casanova et al[28], 2014/Spain	Agreement between symptoms vs health status measure to assign patients to GOLD categories	Prospective cohort	Annual visits (still running)	COPD	828	83	67 ± 9	56 ± 28	Pulmonary function mMRC Health status: CAT, CCQ Anxiety and Depression: HADS Exercise and functional capacity: 6MWT Multidimensional index: BODE Comorbidities: Charlson comorbidity index
Jones et al[29], 2014/ France, Germany, Italy, Spain, United Kingdom	Agreement between symptoms vs health status measure to assign patients to GOLD categories	Cross-sectional survey	NA	COPD	1,041	Reported by category	64.9 ± 9.9	62.5 ± 17.8	Health status: CAT Symptoms: mMRC

(Continued)

TABLE 1] *(Continued)*

Study/Country	Aim	Design	Follow-up	Study Population	No. of Subjects	Male (%)	Age, Mean ± SD, y	FEV_1 % Predicted, Mean ± SD	Outcomes
Price et al[30], 2014/ France, Germany, Spain, Italy, United Kingdom, United States	Agreement between symptoms vs health status measure to assign patients to GOLD categories	Retrospective, cross-sectional survey	NA	COPD	1,659	67.63	65.1 ± 10.4	[d]	Patient record form: spirometry and exacerbation history Patient self-completion form: EuroQol-5D, Work Productivity and Activity Impairment Questionnaire, CAT, mMRC
Rieger-Reyes et al[31], 2014/Spain	Agreement between symptoms vs health status measure to assign patients GOLD categories	Prospective cohort	Annual visits (still running)	COPD	283	92	71 ± 12	62.4 ± 20.3	Pulmonary function Health status: CAT mMRC Exercise and functional capacity: 6MWT
Zogg et al[32], 2014/ Switzerland	Agreement between symptoms vs health status measure to assign patients to each GOLD category	Cross-sectional	NA	COPD	87	58.6	67.6 ± 9.6	69.1 ± 24.3	Pulmonary function Health status: CAT mMRC Functional performance: physical activities in daily life (SenseWear; BodyMedia Inc)

(Continued)

TABLE 1] (Continued)

Study/Country	Aim	Design	Follow-up	Study Population	No. of Subjects	Male (%)	Age, Mean ± SD, y	FEV_1 % Predicted, Mean ± SD	Outcomes
Han et al[33], 2015/China	Agreement between symptoms vs health status measure to assign patients to each GOLD category	Prospective cohort	1 y	COPD	1,465	84.7	67.7 ± 9.3	45.3 ± 18.3	Pulmonary function Health status: CAT mMRC

6MWT = 6-min walk test; BODE = body-mass index, airflow obstruction, dyspnea, and exercise capacity index; CAT = COPD Assessment Test; CCQ = Clinical COPD Questionnaire; CO = carbon monoxide; EuroQol-5D = European Quality of Life Five Dimensions questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HADS = Hospital Anxiety and Depression Scale; mMRC = modified Medical Research Council scale; NA = not applicable; NR = not reported; PHQ-9 = Patient Health Questionnaire-9; SF-12 = Short-Form Health Survey; SGRQ = St. George's Respiratory Questionnaire.

[a]Spirometry, unless otherwise specified.

[b]The study of Papaioannou et al[18] was used in two analyses: determinants of the CAT score and prediction of outcomes.

[c]Median (range).

[d]Reported as number (%) by each FEV_1 group.

The prediction of CAT score at COPD diagnosis and at 1-year follow-up was reported by Papaioannou et al.[18] At diagnosis, $CAT_{score} = 14.818649 - 2.964921$(post-bronchodilator FEV_1) + 2.5106965(exacerbation/year) with an r^2 of 0.49 (P value not reported). The equation proposed to predict the CAT score after 12 months of treatment was: $CAT_{score} = 13.402661 - 2.932829$ (postbronchodilator FEV_1) + 2.4211109 (exacerbation/year), with an r^2 of 0.3 (P value not reported).

Outcomes Prediction

Six studies[18-23] described the use of CAT as a predictor of other outcomes, including COPD diagnosis,[22] exacerbation,[18,20,21] depression,[19] and mortality.[23] CAT score and its items breathlessness and phlegm were significantly ($P < .01$) related to spirometric diagnosis of COPD in a population-based sample of 532 participants,[22] but only the item breathlessness was retained in the linear regression model (in addition to age group and smoking status). This model, proposed as a screening tool for COPD diagnosis in the general population, resulted in an area under the receiver-operating characteristic curve (AUC) of 0.772, a sensitivity of 77.6%, and a specificity of 64.9%.

CAT can also be used to predict depression, which was assessed by using the Patient Health Questionnaire-9.[19] The AUC was 0.849 (95% CI, 0.819-0.880), and the optimal cutoff point was 19. The sensitivity, specificity, positive predictive value, and negative predictive value were 78%, 77.5%, 51.9%, and 91.7%, respectively.

The predictive value of CAT for disease exacerbation was also reported.[20] Both the uncategorized and the categorized CAT scores led to predictions of similar magnitude. The categorized model predicted the time to first exacerbation (AUC, 0.83 [95% CI, 0.79-0.87]), any exacerbation (AUC, 0.64 [95% CI, 0.59-0.70]), or moderate to severe exacerbation (AUC, 0.63 [95% CI, 0.58-0.68]). A cutoff point of 11 had a sensitivity and specificity of 75% and 47%, respectively, to predict an exacerbation. The cutoff of 17 had a sensitivity of 52% and a specificity of 69% to predict a moderate to severe exacerbation. In addition, the higher the CAT score, the shorter the time to first exacerbation. Although a CAT category of 0 to 9 suggested the probability of experiencing an exacerbation in $>$ 24 weeks, the category of 30 to 40 suggested the same chance in 5 weeks.[20] Another study[18] reported that the CAT score could predict future exacerbations in a cohort of 111 first-diagnosed COPD patients. A model of linear regression demonstrated that for each increased

TABLE 2] Agreement Between Patient's Assignment Into GOLD Categories Using the CAT Cut Point ≥ 10 or the mMRC Cut Point ≥ 2

Study	Assessment Tool	GOLD A		GOLD B		GOLD C		GOLD D		κ
		No.	%	No.	%	No.	%	No.	%	
Han et al[24], 2013	CAT	1,317	29.8	1,109	24.7	221	4.9	1,837	41	0.77
	mMRC	1,507	33.6	919	20.5	355	7.9	1,703	38	
	Δ	190	3.8	190	4.2	134	3	134	3	
Jones et al[25], 2013	CAT	149	8.1	351	19.2	167	9.1	1,150	63.3	0.63
	mMRC	373	20.5	124	6.8	667	36.7	653	35.9	
	Δ	224	12.4	227	12.4	500	27.6	497	27.4	
Kim et al[26], 2013	CAT	60	23.3	55	21.4	21	8.2	121	47.1	0.51
	mMRC	97	37.7	18	7	62	24.1	80	31.1	
	Δ	37	14.4	37	14.4	41	15.9	41	16	
Pillai et al[27], 2013	CAT	19	6.1	121	39.2	7	2.3	162	52.4	NR
	mMRC	61	20.3	74	24.7	15	5	150	50	
	Δ	42	14.2	47	14.5	8	2.7	12	2.4	
Casanova et al[28], 2014	CAT	214	27.2	223	28.3	102	12.9	249	31.6	0.53
	mMRC	316	38.2	146	17.6	131	15.8	235	28.4	
	Δ	102	11	77	10.7	29	2.9	14	3.2	
Jones et al[29], 2014	CAT	97	9.3	505	48.5	7	0.7	432	41.5	NR
	mMRC	393	37.8	209	20.1	139	13.4	300	28.8	
	Δ	296	28.5	296	28.4	132	12.7	132	12.7	
Price et al[30], 2014	CAT	83	5	448	27	116	7	1,012	61	0.13
	mMRC	365	22	166	10	713	43	415	25	
	Δ	282	17	282	17	597	36	597	36	
Rieger-Reyes et al[31], 2014	CAT	97	34.3	55	19.4	56	19.8	75	26.5	0.63
	mMRC	103	36.4	49	17.3	51	18	80	28.3	
	Δ	6	2.1	6	2.1	5	1.8	5	1.8	
Zogg et al[32], 2014	CAT	29	33	40	46	1	1	17	20	0.21
	mMRC	46	53	22	25	9	10	10	12	
	Δ	17	20	18	21	8	9	7	8	
Han et al[33], 2015	CAT	176	12.0	295	20.1	170	11.6	824	56.2	0.71
	mMRC	306	20.9	165	11.3	434	29.6	560	38.2	
	Δ	130	8.9	130	8.8	264	18	264	18	

Δ = difference between CAT and mMRC; NR = not reported. See Table 1 legend for expansion of other abbreviations.

point in the CAT score, the number of exacerbations increased 0.12 time. Pothirat et al[21] also showed that CAT could predict a worsening of symptoms and exacerbation (AUC, 0.89 [95% CI, 0.84-0.94]). More recently, Casanova et al[23] reported that CAT is a predictor of all-cause mortality in patients with COPD (AUC, 0.589) similar to the Clinical COPD Questionnaire (AUC, 0.588). However, both had inferior capacity to predict mortality compared with the mMRC dyspnea score (AUC, 0.649). The authors suggest that only a cutoff point of ≥17 for CAT has an ability similar to mMRC ≥ 2 for predicting mortality.

Agreement

Ten studies[24-33] have evaluated the distribution of patients in each stage of the new GOLD grading classification according to the tool used to assess symptoms. All studies found a different proportion of patients in each category using CAT ≥ 10 or mMRC ≥ 2. There was a misclassification of 13% in all GOLD categories (Table 2). Eight of them[24-26,28,30-33] reported agreement analysis comparing the frequencies of patients classified according to CAT or mMRC. The agreement between CAT and mMRC ranged from poor[30] to substantial.[24] The pooled κ is not presented

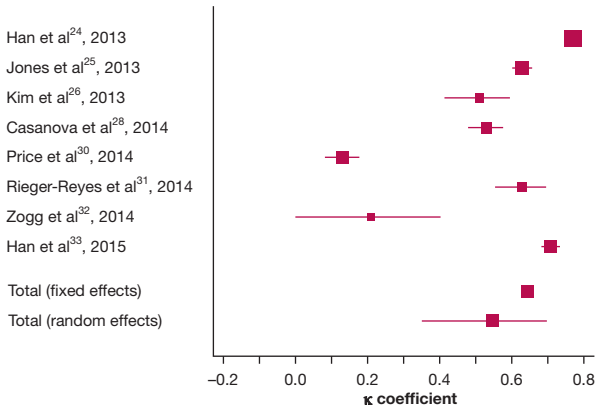

Figure 2 – Meta-analysis of inter-*rater agreement coefficients of CAT ≥ 10 and mMRC ≥ 2 to assign patients to each Global Initiative for Chronic Obstructive Lung Disease category (pooled κ coefficient of 0.548 [95% CI, 0.35-0.70;* $P < .0001$; $I^2 = 99.3$; $z = 4.84$*]). See Figure 1 legend for abbreviations.*

due to the high heterogeneity across studies (Fig 2). Based on the discrepancy with respect to the use of CAT or mMRC, Jones et al[25] suggested the cut point of ≥1 for the mMRC showing greater κ coefficients.[25,33]

Discussion

The goal of this systematic review was to summarize the determinants of the CAT score, its ability to predict other clinical outcomes, and the agreement between CAT ≥ 10 and mMRC ≥ 2 to categorize patients into the new GOLD classification.[2] The main findings were that the CAT is a tool which may help health professionals be aware of the risks of exacerbation, depression, acute deterioration in health status, and mortality. The results also showed that CAT and mMRC are not equivalent for the purpose of assessing a patient's symptoms.

CAT has been broadly used as a simple tool to assess health status in patients with COPD as part of the updated disease severity score system proposed by GOLD.[2] Only two studies that evaluated a total of 335 patients reported regression models to predict the CAT score, with r^2 values ranging from 0.30 to 0.49, explaining < 50% of its variance.[17,18] More important than predicting the score itself, these data are relevant to help us identify which factors are needed to determine the CAT score. Thus far, CAT is better associated with dyspnea during activities,[17] exacerbation frequency, and FEV_1.[17,18]

In addition to the already known CAT psychometric properties,[12] recent studies have shown that CAT has the ability to predict aspects relevant to clinical practice such as disease exacerbations,[18,20,21] depression,[19] and mortality.[23] Although the CAT score was significantly related to a COPD diagnosis in a random population sample,[22] only its domain breathlessness was included in the final logistic regression model to identify patients at risk for the disease. Based on what we currently know, predictions regarding the presence of COPD should not be made based only on CAT score until further studies are available.

The predictive validity of CAT to determine these aforementioned aspects is very useful and offers additional support for using CAT in clinical practice because it helps clinicians, physiotherapists, and health professionals to understand a patient's condition in a broader way. Furthermore, in addition to other clinical data, it can help to direct treatment management and referral to other health services.

Another important finding, based on the data of 10 studies[24-33] (Table 2), was that the classification of patients in each GOLD category is not identical, varying according to the instrument used to assess symptoms. The meta-analysis of eight studies[24-26,28,30-33] that reported agreement analysis showed a very high heterogeneity of the data available ($I^2 = 99.3$) despite the use of the same cutoff points for CAT (≥ 10) and for mMRC (≥ 2) across studies. It seems that these cutoff points are not equivalent for individual patients with less or more symptoms, determining inconsistency in the classification of patients in stages A-B-C-D. This discrepancy could lead to differences in a patient's management, including the choice of the best therapeutic strategy. Future studies should be able to recognize which thresholds are the best to make CAT and mMRC equivalent, thus refining recommendations of the current guidelines. Thus far, the new suggested cutoff point for mMRC, using a score ≥ 1 rather than ≥ 2,[25] resulted in better agreement between CAT and mMRC.[25,33] This approach would improve the probability of patients being classified into the same GOLD group regardless of the instrument used.

Conversely, the lack of agreement between GOLD group classifications using CAT or mMRC is not surprising because these two instruments differ in their purpose and symptom areas that are covered. Although CAT is a multidimensional scale, comprising seven other items rather than just breathlessness, mMRC is a unidimensional scale aimed at assessing only dyspnea.

This systematic review has some strengths and weaknesses to be acknowledged. A wide and complete

search strategy was performed in some of the most important databases. The study selection, data extraction, and analysis were performed independently by trained, experienced researchers in the field. Although a meta-analysis could be considered inappropriate in this context, it was still performed aiming to provide an exploratory analysis. The quality assessment of the studies that described the determinants of the CAT score,[17,18] and the outcomes prediction,[18-23] had an overall low risk of bias and concerns regarding applicability, although some "high-risk" or "unclear" points were observed.[16] Nevertheless, approximately 50% of the studies included in agreement analysis[24-33] had a "high" or "unclear" risk of bias, raising concerns regarding applicability[16] (e-Figure 1).

In the present review, the heterogeneity among studies was likely to be due to methodological differences among studies, including design, population, and settings (inpatient, outpatient, primary care, tertiary care, general population, α_1-antitrypsin COPD). These observations are relevant because they argue against the strength of the combined results and indicate the need for standardization to improve accuracy in estimating the agreement between CAT and mMRC. Nevertheless, it seemed relevant to present this analysis to stress that despite the heterogeneity, the lack of agreement between CAT and mMRC indicates that these two instruments should not be considered as interchangeable. Finally, it could be argued that the language restriction in this systematic review may have prevented the inclusion of researches published in other languages. However, we believe that was not the case because we found no other abstracts eligible for this review.

Conclusions

This present review used standardized methodology to summarize the available knowledge regarding CAT, presenting its usefulness to predict clinical aspects related to the disease and the agreement between CAT and mMRC to assign patients into the new GOLD grade system. It seems that CAT can be used as a complementary tool to help health professionals predict COPD exacerbations, depression, acute deterioration of health status, and mortality. In addition, the current studies do not support use of the cutoff points CAT $\geq$ 10 and mMRC $\geq$ 2 as equivalents for the purpose of assessing patient symptoms. Further studies are needed to evaluate which thresholds are the best for that goal.

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