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Original Study

Redefining Cut-Points for High Symptom Burden of the Global Initiative for Chronic Obstructive Lung Disease Classification in 18,577 Patients With Chronic Obstructive Pulmonary Disease

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All authors have completed the ICMJE uniform disclosure form. Conflict of interest information is detailed in Appendix B.

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Keywords:
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GOLD
health status
clinical significance

ABSTRACT

Background: Patients with chronic obstructive pulmonary disease (COPD) can be classified into groups A/C or B/D based on symptom intensity. Different threshold values for symptom questionnaires can result in misclassification and, in turn, different treatment recommendations. The primary aim was to find the best fitting cut-points for Global initiative for chronic Obstructive Lung Disease (GOLD) symptom measures, with an modified Medical Research Council dyspnea grade of 2 or higher as point of reference.

Methods: After a computerized search, data from 41 cohorts and whose authors agreed to provide data were pooled. COPD studies were eligible for analyses if they included, at least age, sex, post-bronchodilator spirometry, modified Medical Research Council, and COPD Assessment Test (CAT) total scores.
Main outcomes: Receiver operating characteristic curves and the Youden index were used to determine the best calibration threshold for CAT, COPD Clinical Questionnaire, and St. Georges Respiratory Questionnaire total scores. Following, GOLD A/B/C/D frequencies were calculated based on current cut-points and the newly derived cut-points.
Findings: A total of 18,577 patients with COPD [72.0% male; mean age: 66.3 years (standard deviation 9.6)] were analyzed. Most patients had a moderate or severe degree of airflow limitation (GOLD spirometric grade 1, 10.9%; grade 2, 46.6%; grade 3, 32.4%; and grade 4, 10.3%). The best calibration threshold for CAT total score was 18 points, for COPD Clinical Questionnaire total score 1.9 points, and for St. Georges Respiratory Questionnaire total score 46.0 points.
Conclusions: The application of these new cut-points would reclassify about one-third of the patients with COPD and, thus, would impact on individual disease management. Further validation in prospective studies of these new values are needed.

The Global initiative for chronic Obstructive Lung Disease (GOLD) is a recent practice strategy on the diagnosis, prevention, and management of chronic obstructive pulmonary disease (COPD).[1] Patients with COPD are classified based on post-bronchodilator spirometry into grade I (forced expiratory volume in the first second, FEV_1 ≥80% predicted), grade II (FEV_1 50% to <80% predicted), grade III (FEV_1 30% to <50% predicted), or grade IV (FEV_1 <30% predicted). Additionally, patients are classified in groups A to D for specific therapeutic recommendations based on the degree of symptoms (low vs high), and the history of exacerbations and hospitalizations.

High symptoms are determined using various questionnaires: the modified Medical Research Council scale (mMRC, grade 2 or higher), the COPD Clinical Questionnaire (CCQ) total score (1 point or higher), the COPD Assessment test (CAT) total score (10 points or higher), and the St. Georges Respiratory Questionnaire (SGRQ) total score (25 points or higher).[1]

The choice of symptom questionnaire impacts the classification of patients with COPD in GOLD A/C or B/D groups.[2–5] mMRC only focusses on the impact of dyspnea, the most common symptom of patients with COPD. The other symptom questionnaires also take other aspects of health-related quality of life into consideration. Therefore, the CAT, CCQ, or SGRQ may be preferred over mMRC. However, mMRC is easy to obtain, and, it is the most frequently used in clinical practice and studies, and is suggested to be used to categorize patients into symptom severity groups for the purpose of treatment.[1,6]

Previous studies suggest that the current cut-points need proper validation.[4,7–10] Indeed, the GOLD Scientific Committee recognized that a calibration of the current cut-points of the symptom measures is an important topic that needs to be addressed in the next major revision of the GOLD document.[10] Then again, the former threshold values for mMRC, SGRQ, and CAT are still used in the GOLD 2017 strategy.[1] Interestingly, the GOLD document indicates that multidimensional scores like CAT do not categorize patients into symptom severity groups for the purpose of treatment, suggesting a central role of mMRC for patient classification. Therefore, new classification schemes should be benchmarked against mMRC.

The primary aim of this patient-level pooled analysis was to find best fitting cut-points for GOLD symptom measures, with a mMRC dyspnea grade of 2 or higher as the point of reference. Following, the impact of the newly derived cut-points of all questionnaires on the frequency distribution of the GOLD staging was studied.

Methods

This is a pooled analysis of concurrent cohort studies assessing mMRC and multidimensional evaluation systems in COPD. To identify the original cohorts, we performed a computerized search in the database Medline/Pubmed for reports published from the first CAT publication (September 2009) to June 2015.[11] D.S., S.H-W., or M.S. approached the corresponding authors to gather information about their readiness to partake and the availability of a minimum required set of individual data of patients with COPD, including age, sex, postbronchodilator FEV_1, CAT total score, and mMRC dyspnea grade. All participants within their respective studies gave their informed written consent to participate in the original study, and each study was approved by their respective ethics committee.

Measurements

The individual demographics and clinical characteristics [sex, age (years), height (m), weight (kg), smoking status (current/former/never), pack years, use of long-term oxygen therapy (yes/no), FEV_1 (liters), FEV_1 (% predicted), FEV_1/FVC (%), mMRC dyspnea grade, CAT total score (points), CCQ total score (points), SGRQ total score (points), and number of COPD exacerbations and/or hospitalizations in the last 12 months] were provided from each dataset. All data were pooled, and the dataset was cleaned.

Statistics

Mean (standard deviation), median (interquartile range), or proportions were calculated, whatever appropriate. Pearson product-moment correlations between mMRC dyspnea grade, CAT total score, CCQ total score, and SGRQ total score were performed. A r-value of <±0.20 indicates no meaningful correlation; ±0.20 to ±0.34, weak; ±0.35 to ±0.50, moderate; and >± 0.50, strong correlation.[12] Post-bronchodilator FEV_1 was used to classify patients into spirometric grades 1-4. Allocation to GOLD groups A-D was done using mMRC ≥2, CAT ≥10, CCQ ≥1, and SGRQ ≥25 in combination with exacerbations history. In addition, patients were re-allocated (if applicable) based on the newly derived cut-points in combination with exacerbations history.

Receiver operating characteristic (ROC) curves were used to reveal the cut-points for the GOLD symptom measures that discriminate best between the 2 clusters defined on mMRC dyspnea grade (2 or higher). ROC curve represented dependency between the sensitivity and

specificity of the binary classification for different cut-points of the GOLD symptom measures. The cut-point, which satisfied the optimal criterion of the Youden index,[13] was referred as the best calibration threshold. The optimal cut-points were calculated for CAT total score, CCQ total score, and SGRQ total score. A software environment R v 3.1.0 was used. The ROC function from the pROC package was used to visualize the ROC curves and calculate the best thresholds.

Graphs were created using GraphPad Prism v 6 (GraphPad Software Inc. San Diego, CA). Statistics were performed using SPSS for Windows, v 20.0 (IBM Corp, Armonk, NY). A P value of $\leq$.01 was interpreted as statistically significant, to obtain a greater statistical power than the usual P value of <.05.

Results

Overall, 337 reports were identified, of which 63 were eligible (Figure 1). Forty-five author groups were able and willing to participate. Finally, 41 datasets were included in the patient level pooled analysis. At the time of inclusion, 3 articles were published with the dataset of the COPD History Assessment In SpaiN (CHAIN) cohort,[14] 3 articles used the Adelphi Respiratory Disease Specific Program dataset (one of which is from another subcohort[15] than the other 2 articles[16,17]), 1 author group published 2 articles with the same dataset,[18,19] and 1 dataset did not have recently measured FEV_1 (% predicted).[5] In addition, the COPD and SYstemic consequences-COmorbidities NETwork (COSYCONET) steering committee approved to share their cohort baseline data.[20] Table 1 provides all details per study.

Demographic and clinical characteristics of 18,577 patients with COPD are presented in Table 2. Most patients had a moderate or severe degree of airflow limitation. Spirometric grade 2 was the most prevalent (46%). Using the GOLD 2017 cut-points, the majority of patients were classified in the high-symptom B/D groups: mMRC, 55.3%; CAT, 83.6%; CCQ, 78.8%; and SGRQ 83.0%.

The degree of airflow limitation correlated weakly-to-moderately with the mMRC dyspnea grade ($r = -0.40$, $P < .001$), CAT total score ($r = -0.26$, $P < .001$), CCQ total score ($r = -0.37$, $P < .001$), and SGRQ total score ($r = -0.36$, $P < .001$; Figure 2). Moreover, the symptom measures interrelated strongly, with the Pearson product-moment correlation coefficients ranging from 0.540 to 0.799 (all $P < .001$; Figure 3).

New Cut-Points

Figure 4 shows the newly proposed cut-points. A CAT cut-point of 18 points, a CCQ cut-point of 1.9 points, and a SGRQ cut-point of 46.0 points reached the highest sensitivity and specificity vs the mMRC dyspnea grade of 2 or higher as point of reference.

Frequency Distribution

GOLD A/B/C/D frequencies based on current cut-points and the newly derived cut points are shown in Figure 5. Compared with the existing CAT cut-point (≥10 points), the new cut-point (≥18 points) re-classified 30.2% of the GOLD B/D patients into GOLD A/C. Compared

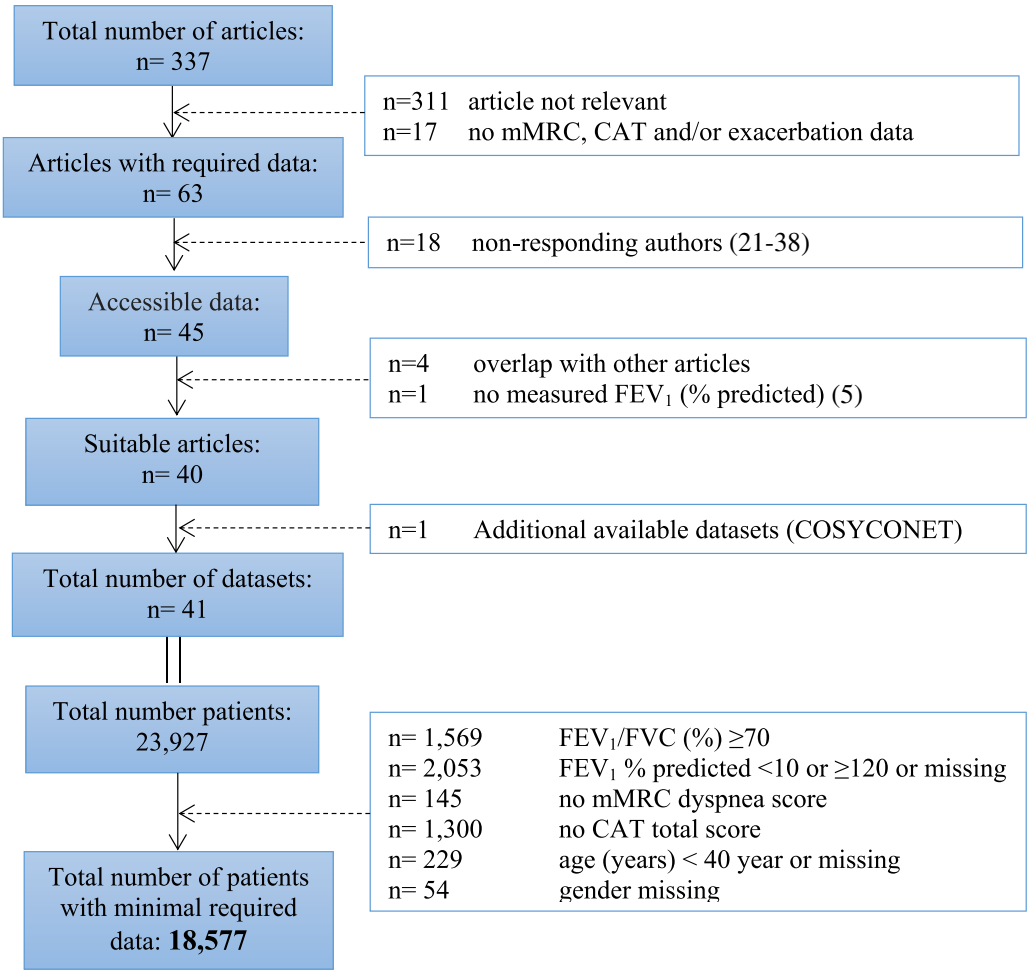

Fig. 1. Flow diagram of subject inclusion.

Table 1
General Characteristics per Resource Article

	Dataset Resource										
Lead author	Agusti[39]	Billington[40]	Boutou[41]	De Torres[42]	Casanova[43]	Casanova[43]	Chaplin[44]	Dodd[45]	Horita[46]	Jehn[47]	Jones[2]	Karch[20]
Journal/year	Qual Life Res, 2015	COPD, 2015	BMJ Open Respir Res, 2014	CHEST, 2014	Respir Res, 2014	Chest, 2014	J Cardiopulm Rehabil Prev, 2015	Thorax, 2011	Clin Respir J, 2013	Environ Health, 2013	ERJ, 2013	Respir Med, 2016
Country	Spain	UK	UK	Spain		UK	UK	Japan	Germany	Belgium, France, UK, Germany, Italy, The Netherlands, and Spain	Germany	
Cohort	GSK			CHAIN							HEED	COSYCONET
N	110	61	703	785		166	196	74	34	1725	2258	
Sex (male), n (%)	104 (94.5)	29 (47.5)	348 (49.5)	658 (83.8)		89 (53.6)	114 (58.2)	60 (81.1)	22 (64.7)	1251 (72.5)	1379 (61.1)	
Age, y	70.3 (9.7)	71.2 (10.0)	67.3 (9.8)	67.8 (8.8)		70.8 (8.7)	69.2 (9.0)	72.3 (9.4)	63.5 (9.9)	64.9 (9.7)	65.1 (8.4)	
Current smoker, n (%)	28 (25.5)	32 (52.5)	-	223 (28.4)		-	-	11 (14.9)	28 (82.4)	737 (42.7)	561 (24.8)	
Pack-y	40.0 (24.6-54.3)[a]	-	-	55.9 (28.0)[h]		-	-	51.6 (30.4)	15.7 (12.1)	38.4 (19.2)[p]	41.2 (22.0-63.0)[v]	
BMI, kg/m^2	-	26.1 (22.3-29.9)	26.0 (22.4 -30.0)[d]	27.8 (24.8-31.0)[i]		27.7 (7.0)[k]	27.6 (6.6)[l]	21.2 (3.0)	26.5 (19.9-29.8)	27.0 (4.9)[q]	26.2 (23.2-29.4)[w]	
FEV_1 (% pred.)	63.6 (20.0)	65.4 (15.8)	49.2 (18.8)	59.3 (20.2)		56.2 (24.4)	51.2 (19.4)	43.2 (12.7)	46.2 (13.4)	56.4 (19.7)	52.5 (18.5)	
FEV_1/FVC (%)	54.0 (11.2)[b]	53.0 (10.2)	43.9 (14.5)[e]	51.9 (11.3)		-	-	59.7 (7.7)	42.3 (13.2)[o]	56.2 (10.6)[r]	51.3 (11.0)	
LTOT, n (%)	-	-	-	69 (22.3)[j]		-	-	16 (21.6)	8 (23.5)	-	436 (19.3)	
GOLD stage, n (%)												
I	24 (21.8)	12 (19.7)	45 (6.4)	134 (17.1)		35 (21.1)	16 (8.2)	0 (0.0)	0 (0.0)	216 (12.5)	202 (8.9)	
II	57 (51.8)	39 (63.9)	289 (41.1)	377 (48.0)		55 (33.1)	86 (43.9)	20 (27.0)	14 (41.2)	827 (47.9)	956 (42.3)	
III	24 (21.8)	9 (14.8)	246 (35.0)	231 (29.4)		50 (30.1)	65 (33.2)	42 (56.8)	15 (44.1)	540 (31.3)	856 (37.9)	
IV	5 (4.5)	1 (1.6)	123 (17.5)	43 (5.5)		26 (15.7)	29 (14.8)	12 (16.2)	5 (14.7)	142 (8.2)	244 (10.8)	
Exacerbations previous 12 mo $\geq$2, n (%)	9 (8.2)	41 (67.2)	-	98 (12.5)		-	-	-	11 (32.4)	451 (29.9)[s]	633 (28.0)	
Hospitalizations previous 12 mo $\geq$1, n (%)	6 (5.5)	-	-	89 (11.3)		-	-	-	20 (58.8)	155 (10.3)[t]	453 (20.1)[x]	
mMRC dyspnea grade $\geq$2, n (%)	49 (44.5)	41 (67.2)	576 (81.9)	358 (45.6)		131 (78.9)	148 (75.5)	35 (47.3)	16 (47.1)	751 (43.5)	1090 (48.3)	
CAT total score, points	16.3 (8.2)	14.8 (6.8)	21.2 (7.5)	12.1 (7.6)		21.8 (7.6)	20.2 (7.5)	11.1 (7.9)	19.1 (5.7)	17.7 (8.4)	18.1 (7.4)	
CCQ total score, points	-	-	3.1 (1.2)[f]	1.6 (1.1)		-	2.9 (1.2)[m]	-	-	-	-	
SGRQ total score, points	44.5 (24.1)[c]	-	47.3 (16.4)[g]	-		-	45.7 (19.1)[n]	-	-	44.7 (19.4)[u]	43.6 (19.9)[y]	

BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CHAIN, COPD History Assessment In SpaiN; COPD, chronic obstructive pulmonary disease; COSYCONET, COPD and SYstemic consequences-COmorbidities NETwork; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HEED, Health-Related Quality of Life in COPD in Europe Study; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GSK, GlaxoSmithKline; IQR, interquartile range; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council dyspnea scale; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; UK, United Kingdom.

Values expressed as mean (SD), median (IQR) or number of patients (%).

[a]8 missing; [b]1 missing; [c]7 missing; [d]190 missing; [e]462 missing; [f]522 missing; [g]495 missing; [h]11 missing; [i]4 missing; [j]474 missing; [k]25 missing; [l]18 missing; [m]159 missing; [n]157 missing; [o]2 missing; [p]71 missing; [q]6 missing; [r]49 missing; [s]151 missing; [t]218 missing; [u]151 missing; [v]11 missing; [w]2 missing; [x]2 missing; [y]12 missing.

Dataset Resource											
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Journal/year	Respiration, 2012	Pulm Med, 2013	Thorax, 2014	CHEST, 2013	Respir Med, 2014	Rev Port Pneumol, 2015	Int J COPD, 2015	COPD, 2014	Coll Antropol, 2013	Eur Respir J, 2015	Pneumologia, 2015
Country	UK	South Korea	the UK	Indonesia, Korea, Vietnam, and Hong Kong	Australia, China, Korea and Taiwan	Portugal	Spain	Spain	Croatia	Chile	Romania
Cohort		-	-	GSK	GSK		On-Sint				
N	219	238	260	303	321	82	499	92	33	101	1082
Sex (male), n (%)	139 (63.5)	192 (80.7)	151 (58.1)	296 (97.7)	286 (89.1)	64 (78.0)	407 (81.6)	67 (72.8)	25 (75.8)	62 (61.4)	801 (74.0)
Age, y	64.0 (9.6)	67.8 (9.4)	71.0 (8.8)	69.0 (9.4)	69.7 (8.8)	70.2 (9.5)	67.1 (9.3)	66.1 (10.8)	62.6 (7.9)	68.8 (8.5)	63.1 (10.1)
Current smoker, n (%)	28 (12.8)	51 (21.4)	31 (11.9)	53 (17.5)	62 (19.3)	17 (20.7)	115 (23.0)[f]	4 (4.3)	12 (36.4)[l]	-	569 (52.6)
Pack-y	41.7 (23.2)[a]	27.9 (26.2)	41.1 (29.5)	30.0 (20.0-50.0)	40.0 (25.0-60.0)	41.5 (20.0-75.0)	38.3 (20.6)	33.0 (15.5-60.0)	41.6 (35.2)	40.5 (20.6)	-
BMI, kg/m^2	25.2 (5.4)[b]	22.9 (3.2)[c]	27.0 (23.7-31.0)	20.8 (3.6)	23.4 (4.1)	26.2 (5.0)	27.7 (4.3)[g]	26.2 (4.7)	24.5 (3.5)	26.9 (4.5)	-
FEV_1 (% pred.)	40.4 (17.9)	72.4 (23.7)	50.1 (20.6)	49.9 (18.0)	50.6 (19.3)	44.8 (16.3)	58.7 (18.4)	48.6 (17.2)	67.5 (16.9)	66.1 (19.5)	56.6 (17.8)
FEV_1/FVC (%)	36.9 (12.7)	54.5 (11.8)	50.4 (14.3)	50.0 (9.8)	46.5 (12.1)	67.0 (11.4)	54.6 (10.8)[h]	47.3 (11.6)	57.3 (7.9)	55.0 (9.5)	-
LTOT, n (%)	32 (14.6)	-	12 (4.6)	-	-	47 (57.3)	69 (14.2)[i]	7 (7.6)	-	3 (3.0)	-
GOLD stage, n (%)											
I	8 (3.7)	99 (41.6)	26 (10.0)	18 (5.9)	25 (7.8)	2 (2.4)	55 (11.0)	5 (5.4)	6 (18.2)	28 (27.7)	119 (11.0)
II	45 (20.5)	92 (38.7)	96 (36.9)	131 (43.2)	121 (37.7)	22 (26.8)	304 (60.9)	32 (34.8)	24 (72.7)	52 (51.5)	560 (51.8)
III	96 (43.8)	38 (16.0)	84 (32.3)	121 (39.9)	137 (42.7)	48 (58.5)	112 (22.4)	45 (48.9)	2 (6.1)	18 (17.8)	336 (31.1)
IV	70 (32.0)	9 (3.8)	54 (20.8)	33 (10.9)	38 (11.8)	10 (12.2)	28 (5.6)	10 (10.9)	1 (3.0)	3 (3.0)	67 (6.2)
Exacerbations previous, 12 mo $\geq$2, n (%)	132 (60.3)	126 (52.9)	117 (45.0)	95 (32.1)[d]	153 (47.7)	26 (31.7)	309 (62.6)[j]	29 (31.5)	-	-	470 (43.4)
Hospitalizations previous, 12 mo $\geq$1, n (%)	-	-	-	-	-	25 (30.5)	161 (33.8)[k]	15 (16.3)	-	-	-
mMRC dyspnea grade, $\geq$2, n (%)	183 (83.6)	93 (39.1)	185 (71.2)	169 (55.8)	153 (47.7)	54 (65.9)	247 (49.5)	51 (55.4)	6 (18.2)	49 (48.5)	665 (61.5)
CAT total score, points	23.1 (8.1)	16.0 (9.3)	20.7 (7.9)	17.8 (8.1)	14.8 (8.0)	17.3 (8.2)	18.4 (7.6)	12.8 (8.1)	14.6 (7.7)	16.0 (8.2)	17.8 (7.9)
CCQ total score, points	-	-	2.8 (1.2)	-	-	-	-	-	-	-	-
SGRQ total score, points	-	-	49.3 (16.4)	45.4 (17.8)[e]	-	-	-	-	-	42.8 (18.4)	-

BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council dyspnea scale; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; UK, United Kingdom.

Values expressed as mean (SD), median (IQR) or number of patients (%).

[a]125 missing; [b]8 missing; [c]3 missing; [d]7 missing; [e]1 missing; [f]3 missing; [g]6 missing; [h]125 missing; [i]14 missing; [j]5 missing; [k]23 missing; [l]21 missing.

Dataset Resource										
Lead author	Miravitlles[59]	Miravitlles[60]	Minami[61]	Nakken[62]	Nishijima[63]	Novotna[64]	Pothirat[65]	Pothirat[66]	Price[67]	Raghavan[68]
Journal/year	IJTLD, 2015	Respir Med, 2014	Multidiscip Respir Med, 2014	BMJ Open, 2014	Int J Chron Obstruct Pulmon Dis, 2015	IJCOPD, 2014	BMC Pulm Med, 2014	Int J Chron Obstruct Pulmon Dis, 2015	Int J COPD, 2014	COPD, 2012
Country	Spain	Spain	Japan	The Netherlands	Japan	The Czech republic	Thailand	Thailand	US, France, Spain, Germany, Italy, UK	Canada
Cohort	INSEPOC study					Czech Multicenter Research Database of COPD (CMRD)			Adelphi Respiratory DSP	COLD
N	2721	696	50	193	16	514	97	153	1070	111
Sex (male), n (%)	2251 (82.7)	585 (84.1)	47 (94.0)	101 (52.3)	15 (93.8)	374 (72.8)	80 (82.5)	89 (58.2)	734 (68.6)	63 (56.8)
Age, y	66.9 (9.7)	68.7 (9.3)	71.0 (8.9)	66.0 (8.7)	73.5 (6.6)	67.3 (8.1)	70.7 (8.2)	71.5 (8.5)	64.6 (10.4)	64.3 (10.6)
Current smoker, n (%)	1959 (72.0)[a]	156 (22.4)[f]	11 (22.0)	32 (16.6)	2 (12.5)	93 (18.1)	5 (5.2)	-	338 (31.6)	21 (18.9)
Pack-y	36.0 (24.0-50.0)[b]	43.2 (21.6)[g]	63.5 (32.2)	37.8 (28.3-51.4)	37.5 (24.6)[m]	38.0 (25.0-48.0)[n]	34.0 (19.0-59.5)	-	32.0 (20.0-48.0)[q]	19.6 (22.6)[u]
BMI, kg/m^2	27.7 (4.3)[c]	26.8 (24.7-30.0)[h]	22.9 (3.8)	26.3 (5.3)	20.6 (2.4)	27.2 (5.9)	20.9 (3.5)	20.2 (3.9)	26.4 (23.4-29.4)[r]	27.2 (24.3-30.8)
FEV_1 (% pred.)	52.6 (18.9)	53.2 (19.6)	51.5 (18.9)	47.3 (17.7)	54.8 (18.5)	43.3 (11.2)	56.4 (21.0)	47.8 (17.6)	60.5 (16.0)	86.7 (15.8)
FEV_1/FVC (%)	53.4 (11.1)[d]	53.1 (12.1)[i]	59.3 (9.5)	40.3 (12.7)	59.6 (9.6)	50.5 (10.7)	50.8 (12.1)	51.9 (10.3)	-	65.0 (60.0-67.6)
LTOT, n (%)	302 (11.8)[e]	163 (24.4)[j]	0 (0.0)	53 (27.5)	0 (0.0)	78 (15.2)	-	-	143 (13.4)	0 (0.0)

GOLD stage, n (%)										
I	232 (8.5)	46 (6.6)	4 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (14.4)	10 (6.5)	112 (10.5)	77 (69.4)
II	1202 (44.2)	347 (49.9)	22 (44.0)	93 (48.2)	10 (62.5)	168 (32.7)	42 (43.3)	58 (37.9)	711 (66.4)	32 (28.8)
III	984 (36.2)	229 (32.9)	17 (34.0)	62 (32.1)	3 (18.8)	278 (54.1)	27 (27.8)	61 (39.9)	203 (19.0)	2 (1.8)
IV	303 (11.1)	74 (10.6)	7 (14.0)	38 (19.7)	3 (18.8)	68 (13.2)	14 (14.4)	24 (15.7)	44 (4.1)	0 (0.0)
Exacerbations previous, 12 mo ≥2, n (%)	1402 (51.5)	420 (70.2)[k]	7 (14.0)	104 (53.9)	2 (12.5)	162 (31.5)	13 (13.4)	-	356 (33.4)[s]	-
Hospitalizations previous, 12 mo ≥1, n (%)	341 (12.5)	162 (27.1)[l]	6 (12.0)	81 (42.0)	2 (12.5)	141 (27.4)	-	-	150 (14.0)[t]	-
mMRC dyspnea grade, ≥2, n (%)	1526 (56.1)	449 (64.5)	34 (68.0)	150 (77.7)	7 (43.8)	391 (76.1)	39 (40.2)	96 (62.7)	377 (35.2)	8 (7.2)
CAT total score, points	19.2 (8.2)	21.3 (8.2)	11.6 (7.1)	21.2 (7.1)	16.0 (10.3)	16.6 (7.8)	12.3 (7.3)	12.4 (7.3)	20.6 (8.5)	8.4 (6.3)
CCQ total score, points	-	-	-	-	-	-	-	-	-	-
SGRQ total score, points	-	-	-	-	-	48.0 (18.5)[o]	38.3 (20.7)	42.1 (21.0)[p]	-	-

BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COLD, Canadian Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; DSP, disease specific program; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; INSEPOC, Impact of Socio-Economic Status on Quality of Life of COPD Patients; IQR, interquartile range; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council dyspnea scale; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; UK, United Kingdom.
Values expressed as mean (SD), median (IQR) or number of patients (%).
[a]145 missing; [b]717 missing; [c]28 missing; [d]2 missing; [e]153 missing; [f]10 missing; [g]35 missing; [h]2 missing; [i]1 missing; [j]29 missing; [k] 98 missing; [l]98 missing; [m]1 missing; [n]57 missing; [o]319 missing; [p]3 missing; [q]62 missing; [r]37 missing; [s]4 missing; [t]1 missing; [u]2 missing.

	Dataset Resource									
Lead author	Ringbaek[69]	Da Silva[18]	Da Silva[19]	Sigari[70]	Tsiligianni[71]	Tulek[72]	Jones[16] Vestbo[17]	Wilke[3]	Xie[73]	Yoshikawa[74]	Zogg[75]
Journal/year	COPD, 2012	Qual Life Res, 2014	J Bras Pneumol, 2013	Rheumatol Int, 2015	BMC Pulm Med, 2012	Respirology, 2014	Respir Med, 2014	J COPD F, 2014	Chin Med J, 2014	Respirology, 2014	BMC Res Notes, 2014
Country	Denmark	Brazil		Iran	Greece	Turkey	US, France, Germany, Italy, Spain, UK	The Netherlands	Shanghai	Japan	Switzerland
Cohort							Adelphi Respiratory DSP	-	-		
N	118	50		78	90	119	1491	698	844	58	68
Sex (male), n (%)	47 (39.8)	24 (48.0)		45 (57.7)	82 (91.1)	116 (97.5)	1019 (68.3)	391 (56.0)	659 (78.1)	56 (96.6)	41 (60.3)
Age, y	68.2 (9.6)	66.2 (8.5)		60.5 (8.0)	67.4 (8.7)	59.5 (9.3)	65.1 (10.2)	64.8 (8.9)	68.0 (9.1)	72.1 (9.2)	67.2 (10.4)
Current smoker, n (%)	22 (18.6)[a]	-		27 (34.6)	70 (77.8)	-	487 (32.9)[d]	166 (23.8)[g]	623 (73.8)	20 (34.5)	32 (47.1)
Pack-y	41.7 (22.6)[b]	-		29.1 (34.7)	60.0 (40.0-84.3)	38.3 (10.2)	30.0 (20.0-45.0)[e]	40.0 (28.0-50.0)[h]	22.5 (15.0-31.0)[k]	60.0 (45.8-80.0)	45.8 (32.5)[n]
BMI, kg/m^2	24.8 (5.8)	25.9 (5.1)		-	27.8 (5.1)	27.6 (5.3)	26.5 (23.4-29.4)[f]	26.1 (5.4)	22.9 (3.0)	21.0 (3.5)	25.1 (21.1-28.9)
FEV_1 (% pred.)	33.7 (9.3)	44.1 (13.8)		48.7 (17.4)	58.2 (18.8)	59.2 (20.0)	62.6 (17.1)	54.7 (22.3)	48.0 (17.2)	50.8 (19.7)	64.3 (21.9)
FEV_1/FVC (%)	-	48.7 (10.8)		56.1 (8.9)	55.7 (10.7)	-	-	42.3 (14.0)	54.7 (10.1)	43.5 (12.7)[l]	50.1 (12.4)
LTOT, n (%)	4 (3.4)	-		5 (6.4)	1 (1.1)	-	117 (7.8)	136 (19.5)	202 (23.9)	10 (17.2)	2 (3.1)[o]
GOLD stage, n (%)											
I	0 (0.0)	0 (0.0)		7 (9.0)	15 (16.7)	17 (14.3)	256 (17.2)	115 (16.5)	31 (3.7)	5 (8.6)	13 (19.1)
II	6 (5.1)	18 (36.0)		28 (35.9)	46 (51.1)	64 (53.8)	936 (62.8)	259 (37.1)	310 (36.7)	22 (37.9)	38 (55.9)
III	70 (59.3)	25 (50.0)		35 (44.9)	21 (23.3)	30 (25.2)	241 (16.2)	220 (31.5)	366 (43.4)	25 (43.1)	12 (17.6)
IV	42 (35.6)	7 (14.0)		8 (10.3)	8 (8.9)	8 (6.7)	58 (3.9)	104 (14.9)	137 (16.2)	6 (10.3)	5 (7.4)
Exacerbations previous 12 mo ≥2, n (%)	-	-		31 (39.7)	2 (2.2)	48 (40.3)	465 (31.2)	330 (47.3)	386 (45.7)	7 (12.1)	8 (11.8)
Hospitalizations previous 12 mo ≥1, n (%)	-	-		39 (50.0)	5 (5.6)	28 (23.5)	196 (13.1)	239 (34.3)	218 (25.8)	5 (8.6)	-
mMRC dyspnea grade ≥2, n (%)	118 (100.0)	25 (50.0)		70 (89.7)	22 (24.4)	64 (53.8)	758 (50.8)	490 (70.3)	534 (63.3)	36 (62.1)	28 (41.2)
CAT total score, points	18.3 (6.6)	20.8 (9.9)		25.1 (8.7)	12.9 (7.5)	13.1 (8.1)	21.0 (8.8)	20.0 (7.4)	18.3 (7.9)	15.2 (7.7)	13.3 (7.0)
CCQ total score, points	-	-		-	1.6 (1.0)	-	-	2.3 (1.1)[i]	-	-	-
SGRQ total score, points	42.8 (7.0)[c]	44.9 (20.4)		-	36.8 (18.3)	-	-	54.0 (22.0)[j]	-	42.0 (15.9)[m]	-

BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; DSP, disease specific program; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council dyspnea scale; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; UK, United Kingdom.
Values expressed as mean (SD), median (IQR) or number of patients (%).
[a]8 missing; [b]13 missing; [c]113 missing; [d]12 missing; [e]188 missing; [f]44 missing; [g]1 missing; [h]22 missing; [i]3 missing; [j]1 missing; [k]11 missing; [l]1 missing; [m]16 missing; [n]3 missing; [o]3 missing.

Table 2
General Characteristics of Total Population

Variables	N	n (%)
Sex (male)	18,577	13,370 (72.0)
Age, y	18,577	66.3 (9.6)
40-50		1122 (6.0)
51-60		3978 (21.4)
61-70		6985 (37.6)
71-80		5380 (29.0)
>80		1112 (6.0)
Current smoker	16,888	6626 (35.7)
Pack y	14,234	38.0 (23.0-52.5)
BMI, kg/m^2	16,934	26.5 (5.2)
FEV_1 (% pred.)	18,577	54.6 (19.5)
FEV_1/FVC (%)	13,692	51.8 (12.1)
LTOT	12,547	1903 (10.2)
GOLD spirometric grade	18,577	
1		2029 (10.9)
2		8611 (46.4)
3		6026 (32.4)
4		1911 (10.3)
Exacerbations previous 12 mo ≥2	16,607	6443 (38.8)
Hospitalizations previous 12 mo ≥1	13,881	2537 (18.3)
mMRC grade	18,577	
0		2183 (11.8)
1		6122 (33.0)
2		5474 (29.5)
3		3598 (19.4)
4		1200 (6.5)
mMRC dyspnea grade ≥2	18,577	10,272 (55.3)
CAT total score, points	18,577	18.4 (8.4)
Percentage participants with value ≥10		15,535 (83.6)
CCQ total score, points	2047	2.1 (1.3)
Percentage participants with value ≥1		1614 (78.8)
SGRQ total score, points	6159	45.4 (20.0)
Percentage participants with value ≥25		5114 (83.0)

LTOT, long-term oxygen therapy.
Values expressed as mean (standard deviation), median (interquartile range) or number of patients (%).

with the existing CCQ cut-point (≥1 point), the new cut-point (≥1.9 points) re-classified 23.9% of the GOLD B/D patients into GOLD A/C. Compared to the existing SGRQ cut-point (≥25 points), the new cut-point (≥46 points) re-classified 34.3% of the GOLD B/D patients into GOLD A/C.

Discussion

Healthcare professionals should be aware of the fact that the choice of symptom measure influences classification, and, in turn, also specific treatment recommendation in patients with COPD. Using mMRC ≥2 points as a reference, a CAT cut-point of 18 points, CCQ cut-point of 1.9 points, and SGRQ cut-point of 46.0 points reached the highest agreement. Implementation of these newly derived cut-points will influence the management of individual patients and the design and interpretation of clinical studies.

Recommendations

As the newly derived cut-points reached the highest sensitivity and specificity with the mMRC dyspnea grade of 2 or higher, guidelines committees may need to consider the use of a mMRC dyspnea grade 2 or higher, a CAT total score of 18 points or higher, a CCQ total score of 1.9 points or higher, or a total SGRQ score of 46.0 points or higher to classify patients with COPD as symptomatic (ie, GOLD B or D; Figure 6). This recommendation is supported by the fact that a CAT total score ≥10 points already occurs in 50% of current or former smokers without having any airway obstruction.[76] The newly derived cut-points enable healthcare professionals to classify the largest proportion of patients into the same GOLD quadrant regardless of their choice of symptom measure.

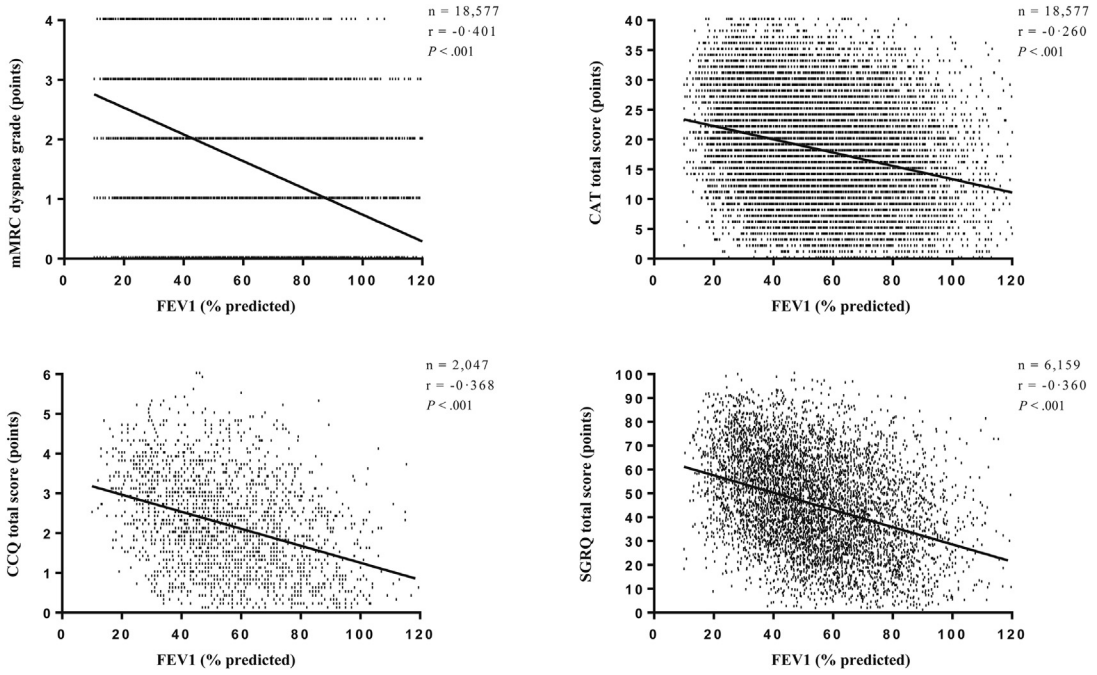

Fig. 2. Correlation between forced expiratory volume in the first second (FEV_1) and symptom measures

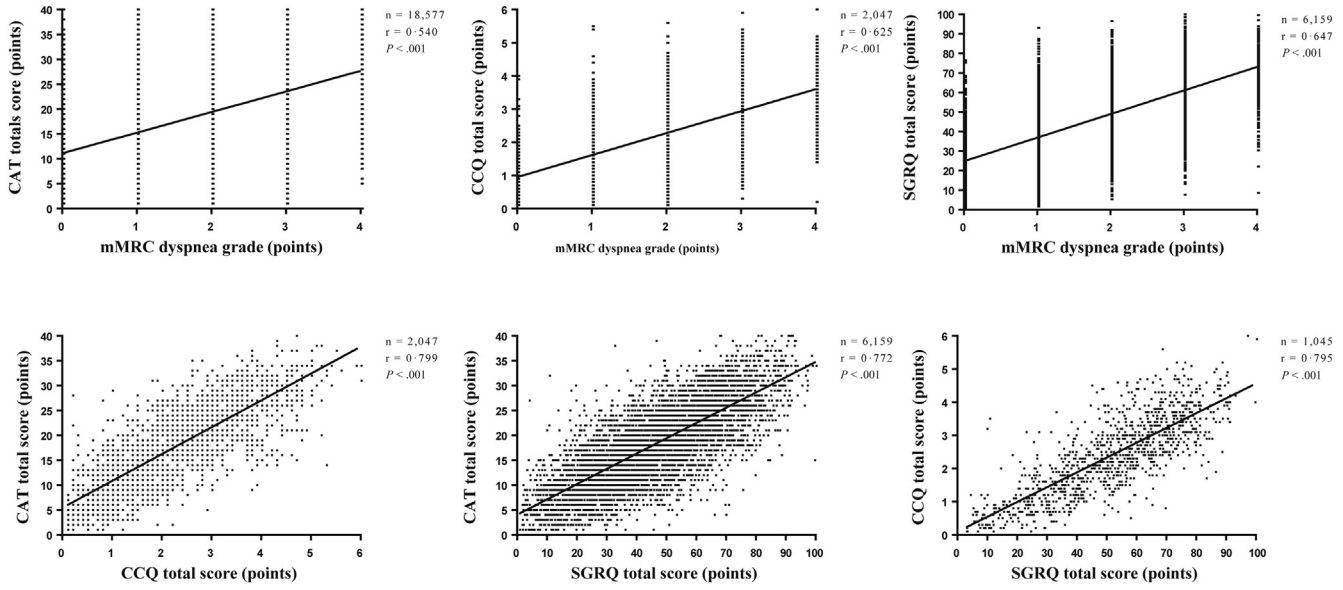

Fig. 3. Correlation between symptom measures

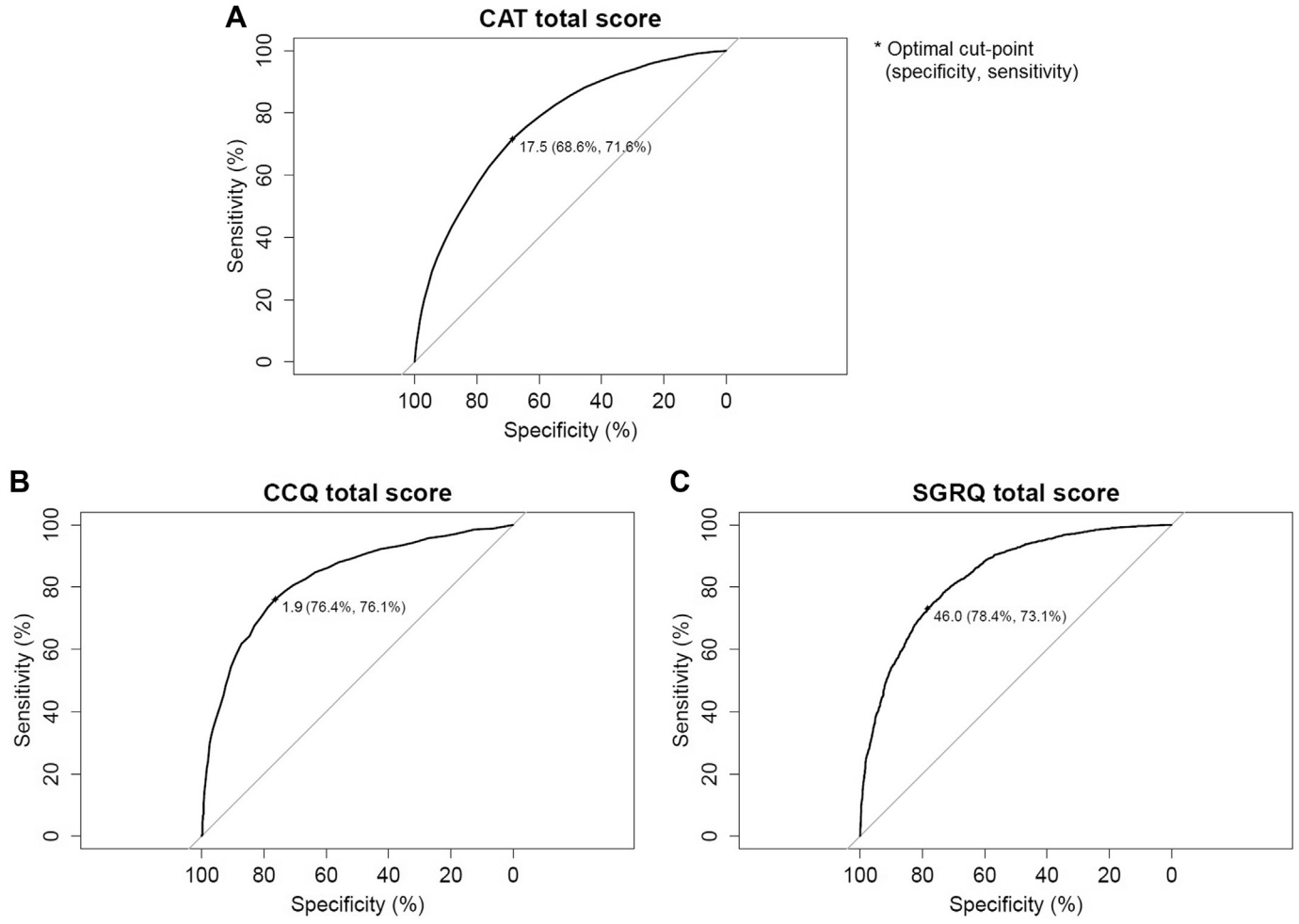

Fig. 4. ROC curves showing best pairwise classification thresholds. A) Best pairwise classification threshold between mMRC ≥2 points and the CAT; B) best pairwise classification threshold between mMRC ≥2 points and the CCQ; best pairwise classification threshold between mMRC ≥2 points and the SGRQ.

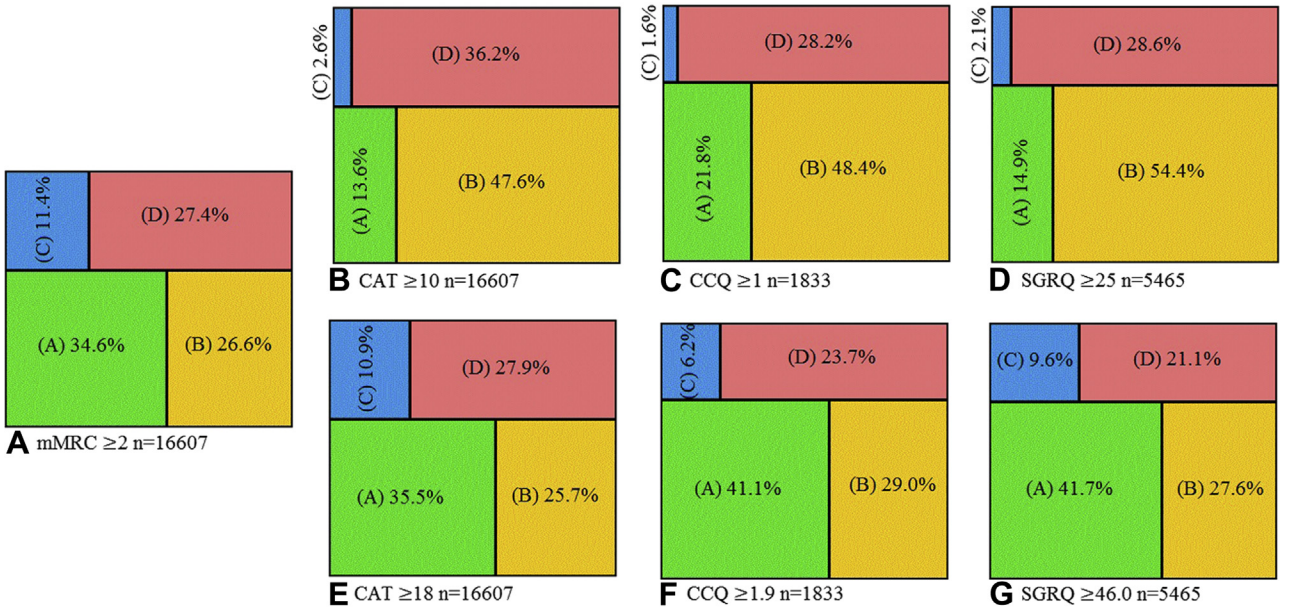

Fig. 5. Frequency distribution proportional rectangles based on the current GOLD 2017 strategy and newly derived GOLD cut-points combined with exacerbations.

Clinical Consequences

Future studies are needed to assess the effectiveness of bronchodilators in COPD patients with and without symptoms, using the newly derived cut-points. For example, GOLD A patients are advised to use short-acting bronchodilators, whereas GOLD B patients are advised to use long-acting bronchodilators.[1] Therefore, the new cut-points may reduce the prescription of long-acting bronchodilators in patients who are currently GOLD B, and will become GOLD A by applying the new cut-points. Obviously, the question arises what to do with COPD patients with a mMRC grade below 2 and a CAT score between 10 (current cut-point) and 18 points (newly derived cut point)? This combination of scores suggests that these patients suffer from other symptoms than dyspnea, which can most probably not be treated satisfactorily with the current pulmonary drug therapy.

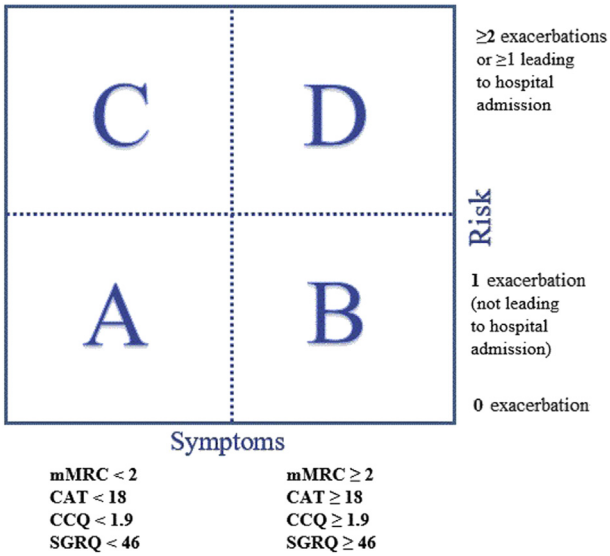

Fig. 6. Suggested GOLD ABCD diagram, using the new cut-points to assess symptoms.

The newly proposed cut-points may also affect recruitment criteria for upcoming trial designs. Indeed, studies that previously applied the current cut-points, will have an overrepresentation of GOLD B or D patients. Sillen et al[77] showed that there is a lot of heterogeneity in GOLD group D, when applying the existing cut-points. In turn, adjusting cut-points of the symptom measures to the newly derived cut-points will increase baseline homogeneity of patient populations within observational COPD studies and intervention trials.

The current analysis confirms that the degree of airflow limitation only moderately correlates with the symptom measures. So, the degree of symptom burden cannot accurately be derived from spirometry. Therefore, healthcare professionals need to regularly assess symptoms in patients with COPD. Indeed, a change in symptom scores may even have a prognostic value in patients with COPD.[78]

Strengths and Limitations

The pooled, multicenter, multinational, patient level dataset with a large number of patients and global coverage is a major strength. Indeed, this resulted in a heterogeneous sample of patients with COPD, also including a high number of patients with a low mMRC dyspnea grade (grade 0: 2183 patients; grade 1: 6122 patients), patients with a mild degree of airflow limitation (spirometric grade 1: 2029 patients), and 1,122 patients younger than 50 years of age. Moreover, patients were recruited from various care settings (ie, primary care, general population, hospital outpatients). This makes the results more generalizable.

A limitation of the current study is that the largest proportion of patients was male (72.0%). Although this seems to over-represent the male sex, it is probably a reliable representation of the current COPD population in the participating cohorts.[79] Less data were available for the CCQ total score (2047 patients) and SGRQ total score (6159 patients). Furthermore, the definition of COPD, current, former or never smoker and the definition of exacerbations and hospitalizations could differ between studies. Finally, the mMRC dyspnea grade solely captures symptoms of dyspnea, which may, together with spirometry and history of exacerbations/hospitalizations, be a suitable guidance for treatment recommendations. Nevertheless, mMRC dyspnea scale may

be too limited to truly understand the impact of COPD. Indeed, symptoms like fatigue, pain and insomnia, may also occur in patients with COPD.[80] Therefore, CAT, CCQ, or SGRQ may be preferred to more broadly characterize the daily symptoms of patients with COPD. Obviously, when CAT, CCQ, and SGRQ are applied for the binary classification of high vs low symptoms, there will still be discrepancy between these symptom measures. So, the GOLD Scientific Committee may want to consider the choice of 1 symptom measure or applying the worst scoring questionnaire to classify patients into groups A/C or B/D.

Conclusions

To objectively define a symptom burden score equivalent to a mMRC dyspnea grade of 2 or higher, a CAT total score of ≥18 points, a CCQ total score of ≥1.9 points, or a SGRQ total score of ≥46 points should be used. Following this grading, about one-third of the patients in GOLD groups B/D are re-classified to GOLD groups A/C. This implies that guidelines committees may consider adapting our evidence-based cut-points of symptom measures.

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Appendix A

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Appendix B

All authors completed the ICMJE uniform disclosure form and declare:

D.E. Smid, M. Gonik, B. G. Cosio, P. de Lucas-Ramos, J. M. Marin, C. Martinez, I. Mir, J.B. Soriano, J.P. de Torres, N.B. Atalay, J. Billington, A.K. Boutou, S. Brighenti-Zogg, E. Chaplin, S. Coster, J.W. Dodd, S. Dürr, A. Fernandez-Villar, M.T.J. Groenen, V. Higgins, N.S. Hopkinson, N. Horita, S. Houben-Wilke, D.J.A. Janssen, M. Jehn, R. Joerres, A. Karch, J.L Kelly, Y. I. Kim, J.W.H. Kocks, S. S. C. Kon, I. Ladeira, J. D. Leuppi, J.L. Lopez-Campos, L. Maricic, L. Mendoza, D. Miedinger, F. Mihaltan, S. Minami, T.J. Murrells, N. Nakken, Y. Nishijima, I.J. Norman, Y. Ogata, D.E. Pereira, J. Piercy, C. Pothirat, N. Raghavan, T. Ringbaek, D. Sajkov, N. Sigari, S. Singh, M. Small, G.F. da Silva, R.J. Tanner, I.G. Tsiligianni, B. Tulek, N. Tzanakis, L.E.G.W. Vanfleteren, K.A. Webb, E.F.M Wouters, G. G. Xie, M. Yoshikawa have no conflict of interest to declare.

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- Dr Price reports board membership with Aerocrine, Almirall, Amgen Inc., AstraZeneca plc, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis International AG and Teva, consultancy with Almirall, Amgen Inc., AstraZeneca plc, Boehringer Ingelheim, Chiesi, GlaxoSmithKline plc, Meda, Mundipharma, Napp, Novartis International AG, Pfizer, Inc., and Teva, grants and unrestricted funding for investigator-initiated studies (conducted through Research in Real-Life Ltd and Observational and Pragmatic Research Institute Pte Ltd) from UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca plc, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline plc, Meda, Merck & Co., Inc., Mundipharma, Napp, Novartis International AG, Orion, Pfizer, Inc., Respiratory Effectiveness Group, Takeda, Teva, and Zentiva, payments for lectures/speaking from Almirall, AstraZeneca plc, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline plc, Kyorin, Meda, Merck & Co., Inc., Mundipharma, Novartis International AG, Pfizer, Inc., Skyepharma, Takeda, and Teva, payment for manuscript preparation from Mundipharma and Teva, payment for travel/accommodations/meeting expenses from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis International AG, and Teva, funding for patient enrolment or completion of research from Almirall, Chiesi, Teva, and Zentiva, payment for the development of educational materials from GlaxoSmithKline plc, Novartis International AG, outside the submitted work; In addition, Dr Price has a patent AKL Ltd. pending and has shares in AKL Ltd which produces phytopharmaceuticals. He owns 80% of Research in Real Life Ltd (which is subcontracted by Observational and Pragmatic Research Institute Pte Ltd), 75% of the social enterprise Optimum Patient Care Ltd and 75% of Observational and Pragmatic Research Institute Pte Ltd.
- Dr Watz reports personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from BerlinChemie, personal fees from GlaxoSmithKline, personal fees from Chiesi, personal fees from Novartis, personal fees from Takeda (outside the submitted work).
- Prof Spruit discloses receiving personal remuneration for consultancy and/or lectures from Boehringer Ingelheim, GSK, and AstraZeneca outside the scope of this work.