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ORIGINAL RESEARCH

Real-world characterization and differentiation of the Global Initiative for Chronic Obstructive Lung Disease strategy classification

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Background: This study aimed to characterize and differentiate the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy 2011 cut points through the modified Medical Research Council dyspnea scale (mMRC) and chronic obstructive pulmonary disease (COPD) assessment test (CAT).

Methods: Analysis of COPD patient data from the 2012 Adelphi Respiratory Disease Specific Program was conducted in Europe and US. Matched data from physicians and patients included CAT and mMRC scores. Receiver operating characteristic curves and kappa analysis determined a cut point for CAT and mMRC alignment and thus defined patient movement ("movers") within GOLD groups A–D, depending on the tool used. Logistic regression analysis, with a number of physician- and patient-reported covariates, characterized those movers.

Results: Comparing GOLD-defined high-symptom patients using mMRC and CAT cut points (≥2 and ≥10, respectively), there were 890 (53.65%) movers; 887 of them (99.66%) moved from less symptomatic GOLD groups A and C (using mMRC) to more symptomatic groups B and D (using CAT). For receiver operating characteristic (area under the curve: 0.82, $P<0.001$) and kappa (maximized: 0.45) recommended CAT cut points of ≥24 and ≥26, movers reduced to 429 and 403 patients, respectively. Logistic regression analysis showed variables significantly associated with movers were related to impact on normal life, age, cough, and sleep (all $P<0.05$). Within movers, direction of movement was significantly associated with the same variables (all $P<0.05$).

Conclusion: Use of current mMRC or CAT cut points leads to inconsistencies for COPD assessment classification. It is recommended that cut points are aligned and both tools administered simultaneously for optimal patient care and to allow for closer management of movers. Our research may suggest an opportunity to investigate a combined score approach to patient management based on the worst result of mMRC and CAT. The reduced number of remaining movers may then identify patients who have greater impact of disease and may require a more personalized treatment plan.

Keywords: GOLD classification, mMRC, CAT, cut points, kappa analysis, receiver operating curves

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex global disease, which requires a simple approach to management. In recognition of these complexities, the Global initiative for Chronic Obstructive Lung Disease (GOLD) group has provided recommendations for appropriate diagnosis and treatment of COPD. In 2011, the GOLD strategy[1] moved away from a linear, one-dimensional classification of severity groups, defined solely by degree of airflow limitation (forced expiratory volume [FEV_1]), to a two-dimensional assessment that takes into account exacerbation risk, measured by

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exacerbation history and/or FEV_1, and current symptoms, measured by either the modified Medical Research Council dyspnea scale (mMRC) or the COPD assessment test (CAT).[2] An updated GOLD report was released in January 2014 based on further published scientific research since completion of the 2011 document but maintains the same treatment paradigm.[3]

This new classification creates four GOLD groups stratified by exacerbation risk (low, high) and symptoms (low, high), with patient treatment recommendations dependent on group allocation: A: low risk, low symptoms; B: low risk, high symptoms; C: high risk, low symptoms; D: high risk, high symptoms.[2] Exacerbation risk is defined by the greater level of either history of exacerbations in the previous year (0–1, low risk and 2+, high risk) or by spirometry-determined airflow limitation (GOLD stages 1 and 2, low risk [$FEV_1 \geq 50\%$ predicted] and stages 3 and 4, high risk [$FEV_1 < 50\%$ predicted]). However, it should be noted that one or more hospitalizations for COPD exacerbations should be considered high risk.[3] Current symptoms are measured by either the mMRC (0 or 1, low symptoms and 2+, high symptoms) or the CAT (<10, low symptoms and ≥ 10, high symptoms). GOLD recognizes that COPD is multisymptomatic and that mMRC measures breathlessness only. It therefore recommends that additional comprehensive symptom assessment is undertaken using questionnaires such as CAT.[3]

Real-world evidence has become an established method for examining treatment practices in primary and specialist care across a large number of disease areas, and demand continues for better evidence of the practical and real-world effects of treatments.[4] It is complementary to data provided by randomized clinical trials and addresses gaps in current knowledge. In this research, the matched elements of physician-reported (exacerbations/FEV_1) and patient-reported (mMRC and CAT) variables provided a unique data source to enable the categorization of patients into the GOLD groups A to D.

This research sought to assess the implications of the revised GOLD strategy on the consulting population by understanding the degree of CAT and mMRC alignment given the cut points recommended by GOLD. Additionally, it aimed to characterize the patients who have a different GOLD classification depending on which instrument is used – the movers – and to determine a CAT cut point that would more closely align the two populations in order to provide a consistent approach to patient classification and treatment.

Materials and methods

Study design and population

Data were from a retrospective analysis of the Adelphi Real World Respiratory Disease Specific Program (DSP) conducted from September to December 2012 in France, Germany, Spain, Italy, UK, and USA. These surveys are large, multinational, and cross-sectional and collect data from physicians and patients in real-world clinical settings thereby providing a holistic picture of a disease and its treatment. They do not aim to demonstrate cause and effect and have no set hypothesis. The DSP is an established method for investigating multicenter treatment practices across a variety of disease areas. The full methodology has been published previously.[5]

Physicians were a geographically representative sample of primary care physicians and pulmonologists, who had qualified between 1977 and 2006, were actively involved in COPD management, and saw three or more COPD patients per physician in a typical week. Included subjects were the next six consulting patients of 40 years of age and older, with a history of smoking and with a confirmed diagnosis of COPD (COPD-only or with mixed COPD and asthma). For the purposes of this analysis, patients with a mixed asthma diagnosis were excluded. It was also deemed irrelevant for the purposes of this observational survey if physicians had applied, or were even aware of, GOLD criteria to their patients as GOLD categorization was performed retrospectively on the dataset.

Data collection

Physicians completed a detailed patient record form, which included spirometry and exacerbation history, for the next six consecutive consulting COPD patients. The same patients were invited to fill out a voluntary, confidential, anonymized patient self-completion form. Unique numerical identifiers allowed matching of physician and patient recorded data. Questions related primarily to demographics, symptomology, quality of life, and disease burden, including EuroQol-5D[6] and the Work Productivity and Activity Impairment Questionnaire.[7] Mandatory questions for inclusion in this analysis included completion of both the CAT[8] and the mMRC.[9,10]

The mMRC is a patient-reported ordinal-rating scale measuring levels of dyspnea. Patients are asked which of five descriptions of breathlessness best describes their impairment, with a choice of 0, "only breathless with serious exercise", to 4, "I am too breathless to leave the house"; high symptoms according to current GOLD recommendations equal ≥ 2.[2] The CAT questionnaire measures the health status

of COPD patients. Eight statements describe best and worst case scenarios; patients decide where they fit on a scale of 0–5 (best to worst) for each statement. The total score range is 0–40.[8] High symptoms according to current GOLD recommendation are ≥10.[3]

Symptom evaluation for a GOLD group (A–D) is defined by the results of one of these two questionnaires. For the purposes of this research, patients who were classified into different symptom groups, depending on the symptom questionnaire and cut point being used, were termed as movers.

The survey was performed according to the European Pharmaceutical Market Research Association guidelines[11] and in full accordance with the US Health Insurance Portability and Accountability Act 1996[12] and European equivalents.[11,13] Each patient provided consent for deidentified and aggregated reporting of research findings as required by the guidelines. Data were deidentified prior to receipt by Adelphi.

Statistical analysis

Receiver operating characteristic (ROC) curves analysis[14] was conducted to determine the optimal cut point of CAT to match the mMRC cut point of ≥2 recommended by the GOLD strategy. We employed nonparametric estimation of the ROC curve and selected the most appropriate CAT cut point by maximizing the Youden index,[15–17] the sum of sensitivity and specificity. The area under the curve (AUC) was calculated using the Mann–Whitney–Wilcoxon test method; this can range between 0 and 1, representing expected performance. An AUC of 0.5 is equivalent to random guessing or the lack of a relationship, whereas an AUC of 1 is equivalent to the reference standard. Preliminary ROC curves analysis was also conducted to determine the optimal cut point of mMRC to match the CAT cut point of ≥10 recommended by the GOLD strategy. However, in all further analysis, mMRC was selected as the reference as it is more evenly split between low and high, and CAT has more granularity and potential cut points.

Furthermore, the kappa statistic[18] was used as a measure of interrater agreement for qualitative (categorical) items, scaled to be 0 when the amount of agreement is what would be expected to be observed by chance and 1 when there is perfect agreement. We determined which CAT cut point maximized the agreement with the mMRC cut point of ≥2 in determining presence of current symptoms (low, high) per patient, as recommended by the GOLD group.

In order to investigate what characterized a mover and what characterized those who moved left/right, we ran separate logistic regression analyses, respectively, for the following dependent variables: 1) whether or not a patient has been categorized differently by CAT and mMRC cut points (movers versus non movers), and 2) whether the patient moved left or right (movers-left versus movers-right) in the GOLD classification (for those categorized differently by CAT and mMRC cut points).

Standard errors were computed by adjusting for possible intragroup correlation within reporting physician. A list of covariates was as follows (all physician-reported): country, age, sex, ethnicity, smoking status, body mass index, physician comanagement of patients, rapid decliners, and Deyo–Charlson comorbidity index (CCI).[19] Additionally, patient-reported variables, general non validated questions in the survey, were included as covariates: presence in past 4 weeks of phlegm, general chest tightness, cough, tiredness through lack of sleep, lack of energy, compromised daily activities, getting up and ready for the day, ability to lead a normal life due to COPD, and the Jenkins Sleep Questionnaire score.[20] Variables with two-sided $P<0.05$ were retained in final regression models.

Regressions were repeated for the following cut points: CAT cut point as recommended by the GOLD group, optimal CAT cut points recommended by the ROC curves analysis, and CAT cut points recommended by the kappa statistic analysis.

Continuous variables were split into three binary variables according to tertiles where possible (or four variables in the case of body mass index). This allowed for nonlinear effects and to make interpretation easier for clinicians. Therefore, all variables used in regression analysis were discrete variables.

Statistical analyses were performed using STATA version 12.1 (StataCorp, College Station, TX, USA).[21]

Results

General patient population

Primary care physicians (318) and pulmonologists (319) from Europe and the US included a total of 3,830 patients, with each physician completing a patient record form for each patient. Of these patients, 2,054 completed a voluntary patient self-completion questionnaire and from this group, 1,659 were COPD-only and had completed both mMRC and CAT and were therefore included in the analysis. Patients were recruited in France (254, 15.3%), Germany (454, 27.3%), Italy (209, 12.6%), Spain (302, 18.2%), UK (52, 3.13%), and the US (388, 23.39%). Patient characteristics are summarized in Table 1.

Table 1 Physician-reported patient characteristics (n=1,659 unless otherwise stated)

Patient characteristics	Category	n (%) or mean (SD)
Sex	M	1,122 (67.63)
	F	537 (32.37)
Age in years		65.14 (10.44)
Ethnicity (1,644 patients)	White/Caucasian	1,517 (91.4)
BMI (1,594 patients)	$kg \cdot m^{-2}$	26.77 (4.93)
Smoking status	Current smokers	533 (32.13)
	Ex-smokers	1,126 (67.87)
Lung function (FEV_1) (1,073 patients)	$FEV_1 < 30$	45 (4.19)
	$FEV_1 \geq 30, FEV_1 < 50$	203 (18.92)
	$FEV_1 \geq 50, FEV_1 < 80$	713 (66.45)
	$FEV_1 \geq 80$	112 (10.44)
COPD comanaged (more than one doctor), (1,645 patients)		685 (41.29)
How quickly disease is progressing (1,631 patients)	Slowly/average	1,542 (92.95)
	Rapid	89 (5.36)
Deyo–Charlson comorbidity index (CCI)[a] (1,528 patients)		1.40 (0.74)

Notes: [a]Comorbid conditions as described by Deyo–Charlston index[19] are mapped from as many as ten reported ICD-9-CM secondary diagnosis codes. A single summary cumulative value is represented. A score of 0 represents no comorbidities. Since COPD was a prerequisite in this research, minimum score was 1. Out of the 17 conditions, this research could accommodate 12: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, diabetes mellitus, cerebrovascular disease, COPD, connective tissue disease, mild liver disease, any malignancy including lymphoma and leukemia, AIDS, metastatic solid tumor.

Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; F, female; FEV_1, forced expiratory volume in 1 second; ICD-9-CM, international classification of disease, ninth revision, clinical modification; M, male; SD, standard deviation.

Patient-reported COPD symptoms

Patient-reported general symptoms present in the previous 4 weeks included tightness in the chest, cough and coughing up of mucus, effect of their COPD on daily activities on a scale of 1–10 (no effect to prevented daily activities), whether they were restricted in their normal life because of COPD on a scale of 1–5 (not restricted at all to completely restricted), whether they ever lacked energy, and whether they ever experienced tiredness through lack of sleep. Patients also reported on the impact of COPD on getting up and ready for the day. A complete breakdown of patient-reported COPD characteristics can be seen in Table 2.

ROC curves and kappa statistic analysis

Table 3 provides the results of the ROC and kappa statistic analyses. For each cut point of the CAT score, the sensitivity, specificity, Youden index, and the kappa statistic are presented. The Youden index is maximized at ≥24 and the kappa statistic is maximized at ≥26.

The AUC of 0.82 (with 95% confidence interval [CI] 0.80–0.84) in Figure 1 is significantly greater than 0.5 ($P<0.001$), which indicates that the CAT score has good discriminating power for the GOLD-recommended mMRC cut point of ≥2.

Of note, for an mMRC cut point of ≥1, the Youden index is maximized at the CAT cut point of ≥19 (0.52, 95% CI 0.47–0.56), with an AUC of 0.83 (95% CI 0.81–0.85), $P<0.001$. The kappa measure of agreement is maximized at the CAT cut point of ≥17 (0.47, 95% CI 0.42–0.51).

GOLD groups and definition of movers

GOLD-recommended cut point

Out of the total 1,659 patients, there were 890 (53.65%) movers under the GOLD-recommended cut points (GOLD-recommended mMRC cut point ≥2 versus the GOLD-recommended CAT cut point of ≥10), three (0.34%) patients moved left, from mMRC higher symptomatic GOLD groups B and D to the lower CAT-defined symptomatic GOLD groups of A and C. Conversely, 887 (99.66%) patients moved right from mMRC lower symptomatic GOLD groups A and C to the higher CAT-defined symptomatic GOLD groups of B and D (see Figure 2).

ROC-recommended cut point

Of the total number of patients who moved under the ROC-recommended cut point of ≥24 (429), 170 (39.63%) moved left from mMRC higher symptomatic groups B and D to the newly defined CAT A and C lower symptomatic groups. The majority of patients, 259 (60.37%), still moved to the right from mMRC lower symptomatic groups A and C to the higher symptomatic ROC CAT-defined groups B and D, albeit to a lesser degree (see Figure 3).

Kappa statistic-recommended cut point

Of the total number of patients who moved under the kappa statistic-recommended cut point of ≥26 (403), 230 (57.07%) patients moved left from mMRC higher symptomatic groups B and D to the newly defined CAT lower symptomatic groups A and C. Fewer patients 173 (42.92%) moved to the right from mMRC lower symptomatic groups A and C to the higher symptomatic groups of B and D defined by kappa statistic (see Figure 3).

Table 2 Patient-reported patient COPD characteristics (n=1,659 unless otherwise stated)

Questions	Description	n (%) or mean (SD)
Breathing symptoms present in last 4 weeks, (1,514 patients)	Coughing up mucus and phlegm	649 (39.12)
	General tightness in chest	340 (20.49)
	Cough	878 (52.92)
Breathing condition's effect on daily activities in past week: (1,631 patients)	0 No effect on daily activities	127 (7.66)
	1	194 (11.69)
	2	232 (13.98)
	3	262 (15.79)
	4	185 (11.15)
	5	130 (7.84)
	6	151 (9.10)
	7	124 (7.47)
	8	134 (8.08)
	9	55 (3.32)
	10 Condition prevented daily activities	37 (2.23)
Extent breathing condition has restricted normal life: (1,625 patients)	1 Not at all restricted	226 (13.62)
	2	460 (27.73)
	3	482 (29.05)
	4	353 (21.28)
	5 Completely restricted	104 (6.27)
Do you ever experience the following feelings, (1,623 patients)	Constant lack of energy	588 (35.44)
	Tiredness through lack of sleep	476 (28.69)
Impact breathing condition has on getting up and ready for the day: (1,634 patients)	1 No impact	413 (24.89)
	2	412 (24.83)
	3	268 (16.15)
	4	201 (12.12)
	5	167 (10.07)
	6	103 (6.21)
	7 Constant impact	70 (4.22)
Jenkins sleep scale (1,588 patients)	(scale 0–20, where 0= no problems with sleep and 20= high impact on sleep),	5.12 (4.65)

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Regression analysis on movers

GOLD-recommended cut point

The following were significantly associated with being a mover when defined according to the GOLD-recommended CAT cut point: being less than 70 years of age ($P<0.001$), being a smoker ($P=0.042$), having a cough in the previous 4 weeks ($P=0.011$), COPD having a medium effect (3–5 on a scale of 0–10, where 0 is no effect and 10 prevented from undertaking daily activities) on daily activities in the previous week ($P<0.001$), COPD having low restriction (1–3 on a scale of 1–5, where 1 is no restriction and 5 is complete restriction) on living a completely normal life ($P<0.001$), not experiencing constant lack of energy ($P=0.001$), COPD having no to medium impact (1–4 on a scale of 1–7, where 1 is no impact and 7 is constant impact) on getting up and ready for the day ($P<0.001$), and an increased Jenkins sleep scale score (≥3 on a scale of 0–20, where 0 is no impact with sleep and 20 is high impact on sleep; $P=0.001$).

Cut point recommended by ROC analysis

The following were significantly associated with being a mover when defined according to the ROC-recommended CAT cut point: the presence of a cough in the last 4 weeks ($P=0.040$), COPD having restricted or completely restricted impact (3–5 on a scale of 1–5) on living a normal life ($P<0.001$), COPD having no to medium impact (1–4 on a scale of 1–7) on getting up and ready for the day ($P=0.003$), and increased Jenkins sleep scale score (≥3 on a scale of 0–20; $P<0.001$).

Cut point recommended by the kappa statistic

The following were significantly associated with being a mover when defined according to the kappa-recommended CAT cut point: being 55 or more years of age ($P=0.017$),

Table 3 ROC curves analysis and kappa statistic analysis

Cut point	ROC Points			Kappa statistic (95% CI)
	Sensitivity (%)	Specificity (%)	Youden index (bootstrap 95% CI)	
≥0	100.00	0.00		
≥1	100.00	0.65	0.01 (0.00–0.01)	0.00 (0.00–0.01)
≥2	100.00	1.47	0.01 (0.01–0.02)	0.01 (0.01–0.02)
≥3	100.00	2.40	0.02 (0.01–0.03)	0.02 (0.01–0.02)
≥4	100.00	3.96	0.04 (0.03–0.05)	0.03 (0.02–0.04)
≥5	100.00	5.53	0.06 (0.04–0.07)	0.04 (0.03–0.05)
≥6	100.00	7.00	0.07 (0.06–0.08)	0.05 (0.04–0.06)
≥7	99.83	9.12	0.09 (0.07–0.11)	0.06 (0.05–0.07)
≥8	99.83	10.97	0.11 (0.09–0.13)	0.08 (0.06–0.09)
≥9	99.83	15.21	0.15 (0.13–0.17)	0.11 (0.09–0.13)
≥10	99.48	18.25	0.18 (0.15–0.20)	0.13 (0.11–0.15)
≥11	98.95	22.95	0.22 (0.19–0.24)	0.16 (0.14–0.19)
≥12	98.61	27.93	0.27 (0.24–0.29)	0.20 (0.18–0.23)
≥13	97.91	32.26	0.30 (0.27–0.33)	0.23 (0.21–0.26)
≥14	96.86	35.67	0.33 (0.30–0.36)	0.25 (0.22–0.29)
≥15	95.99	39.54	0.36 (0.32–0.38)	0.28 (0.25–0.31)
≥16	94.60	42.49	0.37 (0.34–0.41)	0.30 (0.27–0.33)
≥17	93.38	47.28	0.41 (0.37–0.44)	0.33 (0.30–0.39)
≥18	90.07	50.14	0.40 (0.36–0.44)	0.34 (0.30–0.37)
≥19	88.15	54.84	0.43 (0.39–0.47)	0.37 (0.33–0.40)
≥20	86.06	58.53	0.45 (0.41–0.49)	0.39 (0.35–0.43)
≥21	81.71	62.49	0.44 (0.40–0.48)	0.39 (0.35–0.43)
≥22	78.40	67.56	0.46 (0.42–0.50)	0.42 (0.38–0.46)
≥23	73.34	71.61	0.45 (0.40–0.50)	0.42 (0.42–0.38)
≥24	70.38	76.13	**0.47 (0.42–0.51)**	0.45 (0.40–0.49)
≥25	64.46	80.00	0.44 (0.40–0.49)	0.44 (0.40–0.49)
≥26	59.93	84.06	0.44 (0.40–0.49)	**0.45 (0.40–0.50)**
≥27	53.48	87.83	0.41 (0.36–0.46)	0.44 (0.40–0.48)
≥28	46.86	91.34	0.38 (0.34–0.42)	0.42 (0.37–0.46)
≥29	39.20	94.01	0.33 (0.29–0.38)	0.38 (0.33–0.42)
≥30	33.97	96.13	0.30 (0.26–0.34)	0.35 (0.30–0.39)
≥31	29.27	97.70	0.27 (0.23–0.30)	0.32 (0.28–0.36)
≥32	25.09	98.43	0.24 (0.20–0.27)	0.28 (0.24–0.32)
≥33	19.34	99.26	0.19 (0.15–0.22)	0.23 (0.19–0.27)
≥34	15.51	99.63	0.15 (0.12–0.18)	0.19 (0.15–0.22)
≥35	11.32	99.83	0.11 (0.09–0.14)	0.14 (0.11–0.17)
≥36	7.49	99.83	0.07 (0.05–0.09)	0.09 (0.07–0.12)
≥37	5.57	99.83	0.05 (0.03–0.07)	0.07 (0.05–0.09)
≥38	3.83	99.91	0.04 (0.02–0.05)	0.05 (0.02–0.07)
≥39	2.79	99.91	0.02 (0.01–0.04)	0.03 (0.02–0.05)
≥40	1.39	99.91	0.01 (0.00–0.02)	0.02 (0.00–0.03)
≥41	0.00	100.00		

Notes: ROC: 1,659 patients; Area under the curve (standard error) =0.82 (0.01); 95% CI 0.80, 0.84. Bold font indicates where the Youden index and kappa statistic are maximized.
Abbreviations: CI, confidence interval; ROC, receiver operating characteristic.

COPD having restricted or complete impact (3–5 on a scale of 1–5) on living a completely normal life ($P<0.001$), COPD having a medium impact (3–4 on a scale of 1–7) on getting up and ready for the day ($P<0.001$), and increased Jenkins sleep scale score (≥3 on a scale of 0–20; $P=0.003$). Results from the three regression analyses are shown in Table 4.

Regression analysis on moving left (from B/D to A/C) or right (from A/C to B/D)

There were insufficient patients moving left (n=3) for the GOLD-recommended cut points to run the regression. However, analysis of the ROC-recommended cut points showed the following were significantly associated with

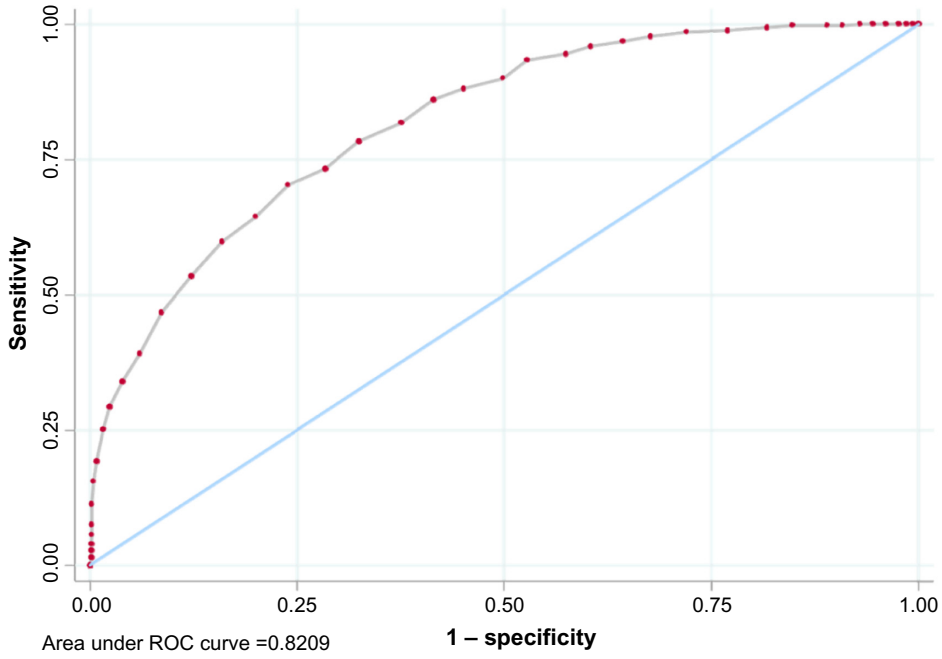


Figure 1 Graphical representation of the ROC curves analysis for CAT and mMRC.
Abbreviations: CAT, Chronic Obstructive Pulmonary Disease (COPD) Assessment Test; mMRC, modified Medical Research Council dyspnea scale; ROC, receiver operating characteristic.

moving to the right: not being from France (*P*=0.014), being less than 55 years of age (*P*=0.005), the presence of a cough in the last 4 weeks (*P*=0.003), COPD having little or no impact (1–2 on a scale of 1–7) on getting up and ready for the day (*P*=0.032), and an increased Jenkins sleep scale score (≥7 on a scale of 0–20; *P*=0.001).

Analysis of the kappa statistic-recommended cut points showed the following were significantly associated with moving to the right: not being from France (*P*=0.047), being less than 55 years of age (*P*=0.002), being a smoker (*P*=0.018), the presence of a cough in the last 4 weeks (*P*=0.001), COPD having little or no impact (1–2 on a scale of 1–7) on getting

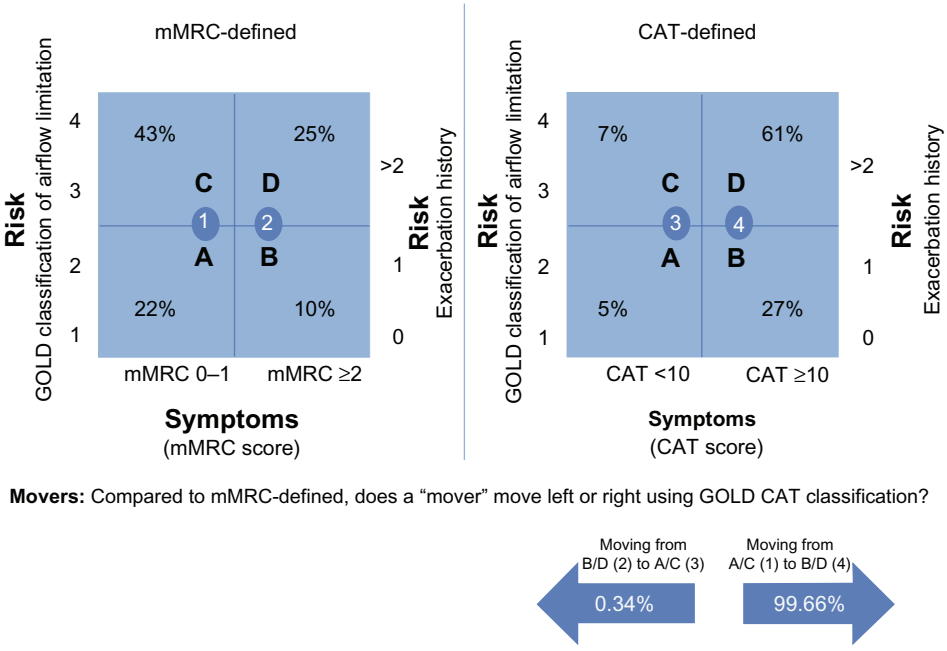
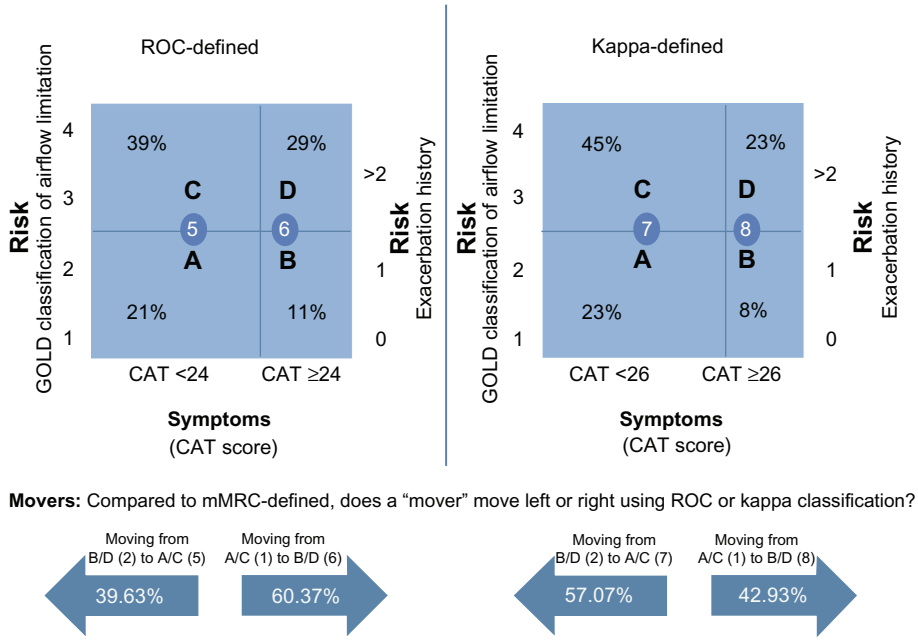


Figure 2 mMRC and CAT sized groups as defined by GOLD-recommended cut point (1,653 patients).
Abbreviations: CAT, Chronic Obstructive Pulmonary Disease (COPD) Assessment Test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea scale.



Movers: Compared to mMRC-defined, does a "mover" move left or right using ROC or kappa classification?

Figure 3 ROC and Cohen's kappa-statistic sized segments as defined by ROC and kappa cut point (1,653 patients).
Abbreviations: CAT, Chronic Obstructive Pulmonary Disease (COPD) Assessment Test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea scale; ROC, receiver operating characteristic.

up and ready for the day (P=0.007), and an increased Jenkins sleep scale score (≥7 on a scale of 0–20) (P=0.001). Detailed results are presented in Table 5.

Discussion

Our data would suggest that relying on one marker of COPD symptoms may potentially result in under treatment for many patients if based on mMRC. Indeed, GOLD recommends further symptom assessment in conjunction with mMRC administration. However, alignment of the two measures by moving the cut point will only be partially successful in better categorizing and stabilizing patients to their respective groups. There will likely still be some movers, though greatly reduced as we have shown, and it is these patients

Table 4 Regression analysis on movers

	Odds ratio	95% CI	*P*-value
GOLD-recommended cut points			
Age <70 years	1.62	1.25–2.10	<0.001
Smoker	1.31	1.01–1.70	0.042
Cough in last 4 weeks	1.47	1.08–1.98	0.013
Condition having medium (3–5 on scale 0–10)[a] effect on daily activities in past week	1.79	1.34–2.40	<0.001
Condition having low restriction (1–3 on scale 1–5)[b] on living a normal life	2.76	1.86–4.09	<0.001
Not experiencing constant lack of energy	1.77	1.30–2.42	<0.001
Condition having no/low impact (1–2 on scale 1–7)[c] on getting up and ready for the day	2.84	1.75–4.60	<0.001
Condition having medium impact (3–4 on scale 1–7)[c] on getting up and ready for the day	1.85	1.17–2.93	0.009
Increased Jenkins sleep scale score (≥3 on a scale of 0–20)[d]	1.78	1.28–2.47	0.001
ROC-recommended cut points			
Presence of cough in last 4 weeks	1.34	1.01–1.76	0.040
Condition having medium restriction (3 on a scale 1–5)[b] on living a normal life	4.15	2.79–6.17	<0.001
Condition having high restriction (4–5 on a scale 1–5)[b] on living a normal life	2.23	1.36–3.67	0.001
Condition having no/low/medium impact (1–4 on scale 1–7)[c] on getting up and ready for the day	1.96	1.27–3.04	0.003
Increased Jenkins sleep scale score (≥3 on a scale of 0–20)[d]	2.06	1.45–2.91	<0.001
Kappa statistic-recommended cut points			
Age ≥55 years	1.56	1.08–2.24	0.017
Condition having medium/high restriction (3–5 on a scale 1–5)[b] on living a normal life	3.27	2.19–4.89	<0.001
Condition having medium impact (3–4 on scale 1–7)[c] on getting up and ready for the day	1.66	1.21–2.28	0.002
Condition having high impact (5–7 on scale 1–7)[c] on getting up and ready for the day	0.64	0.41–0.99	0.047
Increased Jenkins sleep scale score (≥3 on a scale of 0–20)[d]	1.72	1.20–2.47	0.003

Notes: [a]Where 0= no effect and 10= prevented from undertaking daily activities; [b]where 1= no restriction and 5= complete restriction on normal living; [c]where 1= no impact and 7= constant impact on getting up and ready for the day; [d]where 0= no impact on sleep and 20= high impact on sleep.
Abbreviations: CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ROC, receiver operating characteristic.

Table 5 Regression analysis on moving left or right[a]

	Odds ratio	95% CI	*P*-value
ROC-recommended cut points			
Not from France	2.45	1.20–5.02	0.014
Age <55 years	4.07	1.51–10.96	0.005
Presence of cough in last 4 weeks	2.11	1.29–3.43	0.003
Condition having little or no impact (1–2 on scale 1–7)[b] On getting up and ready for the day	1.82	1.05–3.16	0.032
Increased Jenkins sleep scale score (≥7 on a scale 0–20)[c]	2.53	1.47–4.37	0.001
Kappa statistic-recommended cut points			
Not from France	2.12	1.01–4.46	0.047
Age <55 years	3.78	1.62–8.80	0.002
Smoker	1.82	1.11–2.99	0.018
Presence of cough in last 4 weeks	2.38	1.41–4.02	0.001
Condition having little or no impact (1–2 on scale 1–7)[b] On getting up and ready for the day	2.18	1.24–3.84	0.007
Increased Jenkins sleep scale score (≥7 on a scale 0–20)[c]	2.38	1.41–4.02	0.001

Notes: [a]There were insufficient patients moving left to run this regression for GOLD-recommended cut points; [b]where 1= no impact and 7= constant impact on getting up and ready for the day; [c]where 0= no impact on sleep and 20= high impact on sleep.
Abbreviations: CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ROC, receiver operating characteristic.

who will need additional and possibly more personalized treatment.

When modifying the cut point from the GOLD-recommended values (mMRC ≥2; CAT ≥10) to those which identified best alignment using the kappa statistic cut point (mMRC ≥2; CAT ≥26), the number of movers declines from 890 to 403. These movers are significantly associated with being older, with their COPD condition restricting or completely restricting their lives, with COPD having a medium or high impact on their ability to get up and ready for the day, and with an increased Jenkins sleep scale score. These remaining movers may represent patients who are more difficult to treat and who may require additional follow-up.

It is worth noting that movers from B/D to A/C are also significantly likely to be from France. However, as this is a borderline significance, it should be viewed with caution, as geographic regions should not affect COPD characteristics.

The results of our research concur broadly with a number of studies published in the last 2 years since GOLD 2011, which have shown that the heterogeneity of COPD does not easily translate to "grouping"; that the presence of comorbidities complicates diagnosis;[22] and that group C, with less symptoms, does not necessarily translate into better outcomes.[23] Since the GOLD strategy 2011, four large retrospective analyses of COPD cohorts[24–27] have examined the relationships among the four GOLD groups. These have been synthesized by Agusti et al, finding that the prevalence of patients in each group may depend on the population studies and whether they are treated through a primary or secondary health setting.[24]

Further research on misalignment has been produced in analyses by Jones et al,[29,30] which indicate as our current research does, that the two cut points for mMRC and CAT are not equivalent. Jones et al[29] suggested that an mMRC score of ≥1 is approximately equal to a CAT score of ≥10 when diagnosing low symptom patients. Having examined the current GOLD cut points and noted, in Jones' more limited analysis, the suggested mMRC/CAT score equivalent of ≥1/≥10, we chose to use as our starting point the baseline of mMRC cut point ≥2 since this is the midpoint between low and high symptoms. CAT offers more granularity and breadth of potential cut points to align against mMRC at ≥2 and thus, harmonizing the tools via this approach makes for a potentially more accurate "fine-tuning" of the cut points.

A study published in 2009 by Lacoma et al[31] concluded that the influence of a number of factors, such as disease severity, comorbidities, and treatment, was more important in COPD management, with individual monitoring, than establishing cut points for the COPD population as a whole.[31] While we acknowledge this point, we believe that our research offers the potential for more accurate grouping, while also advocating more personalized management for those who move groups and are likely more disease impacted patients than nonmovers. Moreover, our research suggests that with better aligned cut points, those in need of such individualized support will be a smaller number than those who currently move groups with the GOLD recommended cut points.

It may be questioned whether such studies present the clinician with more questions than answers. However, COPD is a global disease, and as an editorial by Franssen and Han[32] reminds us, GOLD is a global strategy, and a simple, more uniform approach to COPD disease assessment, management, and treatment is key. Any COPD classification must therefore

be easy to use but also provide sufficient information on the disease. Would a more precise alignment of mMRC and CAT therefore provide greater accuracy of grouping?

Ultimately, mMRC is a less sensitive tool than CAT for classifying COPD patients. It provides a baseline measurement of a patient's COPD status through measuring breathlessness. Indeed, GOLD recommends use of a second measure of symptoms, such as CAT, in addition to mMRC for comprehensive symptom assessment.[3] CAT addresses a broader scope of COPD factors, is sensitive to change and consequently management of exacerbations,[8] and is thus well placed as an ongoing assessment tool. Our analysis shows that the two tools misclassify a substantial number of patients; a combination of the two, particularly if realigned, could therefore potentially provide more stable and uniform management and treatment of COPD patients.

Data collection through the DSP has some limitations. The collected sample is not truly random as it uses the next six eligible patients who consult the physician. It may, therefore, not represent the overall COPD population as it would capture those patients who may be more symptomatic or consult their doctors more frequently. Patient selection bias is therefore possible. Additionally, only data from those patients who chose to complete the voluntary patient self-completion form were used in this analysis. There could be potential differences between those patients who chose to complete the form and those who do not, possibly introducing additional bias. The quality of data collected depended on accurate reporting of information by both physicians and patients. However, as data for these analyses were collected at the time of the consultation and relate only to that consultation, recall bias is unlikely to be an issue. Finally, while minimal inclusion criteria governed the selection of participating physicians, inclusion will have been influenced by willingness to take part and practical considerations of location.

Despite these limitations, our research provides valuable real-world physician and patient matched data. The misalignment shown and statistical evidence for a possible change of cut points, to measure disease severity, would indicate that further research is necessary to understand, characterize, and differentiate the GOLD classification through mMRC and CAT.

Conclusion

Use of mMRC or CAT leads to inconsistencies for COPD assessment classification. The optimal clinical management of COPD patients, and a closer and more personalized approach to the treatment of movers in particular, may require alignment of assessment tool cut points, coadministration of these tools, and consideration of whether a higher cut point for CAT is appropriate. Our research may suggest an opportunity to investigate a combined score approach to patient management based on the worst result of mMRC and CAT. Subsequently, the reduced number of remaining movers may then identify patients who have greater impact of disease and may require a more personalized treatment plan.

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Author contributions

DBP provided clinical direction and input to the objective of the analysis, made substantial contributions to the interpretation of data, critical revisions, and approved the final version for submission. CLB made substantial contributions to the design of the study, interpretation of the data, critical revisions, and approved the final version for submission. KHZ made substantial contributions to the statistical analysis and interpretation of the data, critical revisions, and approved the final version for submission. JTB made substantial contributions to the concept and design of the study and interpretation of the data. He was involved in the drafting of the article, critical revisions, and approved the final version for submission. JSP made substantial contributions to the statistical analysis and interpretation of the data, critical revisions, and approved the final version for submission. VSH made substantial contributions to the concept and design of the study and interpretation of the data. She was involved in the drafting of the article, critical revisions, and approved the final version for submission. VSH also takes responsibility for the integrity of the work as a whole, from inception to finished article.

Disclosure

CLB and KHZ are employees of Pfizer Inc, which sponsored this analysis. DBP was a paid consultant to Pfizer in connection with this analysis. VSH, JTB, and JSP are employees of Adelphi Real World. The authors report no other conflicts of interest in this work.

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