J Bras Pneumol. 2021;47(5):e20210156
https://dx.doi.org/10.36416/1806-3756/e20210156

ORIGINAL ARTICLE

Respiratory symptoms (COPD Assessment Test and modified Medical Research Council dyspnea scores) and GOLD-ABCD COPD classification: the LASSYC study

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Submitted: 16 April 2021.
Accepted: 28 July 2021.

Study carried out in the Argentina, Chile, Colombia, Costa Rica, Guatemala, Mexico, and Uruguay.

ABSTRACT

Objective: To assess the frequency and severity of 24-hour respiratory symptoms according to COPD GOLD-ABCD classification (2017-version), the distribution of the patients with COPD into GOLD categories using mMRC (≥2) or CAT (≥10) scores, and agreement between these cut-off points. **Methods:** In this cross-sectional study (LASSYC study), 24-hour day respiratory symptoms were assessed by the Evaluating Respiratory Symptoms in COPD (E-RS) questionnaire, Nighttime Symptoms of COPD Instrument (NiSCI), Early Morning Symptoms of COPD Instrument (EMSCI), CAT and mMRC scores. **Results:** Among the 734 patients with COPD, 61% were male, age 69.6±8.7 years, FEV_1% post-BD 49.1±17.5%, mMRC 1.8±1.0 and CAT 15.3±.8.1. By mMRC 33.7% were group-A, 29.2% group-B, 10.2% group-C and 26.9% group-D. By CAT 22.3% were group-A, 41% group-B, 4.8% group-C and 31.9% group-D. Using the mMRC the severity of E-RS, NiSCI and EMSCI scores increased from group A to D. Using the CAT, the groups B and D had the higher scores. Agreement between mMRC and CAT was 89.5% (Kappa statistics=75.7%). For mMRC score of 2, CAT score of ≥11 showed the maximum Youden's index (1.34). For mMRC score of 1, CAT score of ≥9 and ≥10 showed the maximum Youden's index (1.48). **Conclusion:** GOLD COPD classification by CAT seems to better discriminate 24-hour symptoms. Results do not support the equivalent use of CAT≥10 and mMRC≥2 for assessing symptoms.

Keywords: Chronic obstructive pulmonary disease; Symptoms and COPD.

INTRODUCTION

The "ABCD" COPD assessment tool proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] is based on the combination of the patient's level of respiratory symptoms, and future risk of exacerbations. Spirometry is needed for diagnosis and extent of airflow limitation. To evaluate the symptoms, the GOLD document recommends the use of the modified British Medical Research Council dyspnea scale (mMRC) or the COPD assessment test (CAT) in an equivalent manner.[1]

The mMRC scale has been considered to be an adequate unidimensional tool for symptoms assessment in COPD due to its relationship with other health status measures and prognostic value.[2,3] It is recognized that COPD impacts patients beyond dyspnea,[4,5] therefore a comprehensive and multidimensional rather than a unidimensional assessment of symptoms is recommended. For this reason, and for its predictive value on important COPD outcomes, the CAT score has been proposed as a surrogate tool for assessing symptoms in COPD.[6-11]

We have previously reported that in patients with COPD the mMRC and CAT scores progressively increased as the intensity of daytime symptoms worsen (from mild to severe), and there was a relationship between daytime symptoms with mMRC and the CAT scores.[12] However, to our knowledge, no information exists regarding the presence of symptoms along the 24-hour day in patients classified in the different GOLD-ABCD subgroups using CAT or mMRC scores.

On the other hand, several reports have indicated that the GOLD group assignment of patients with COPD is different depending on the scale of symptoms used.[13-22] Although a simple breathlessness cutoff-point cannot be equated to a comprehensive or a full symptom score cutoff, and patients with mMRC <1 may also have a number of other COPD symptoms,[23] the use of the mMRC is widespread, and mMRC of ≥2 as a threshold

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Financial support: This observational study was funded by AstraZeneca Latin America. The funder had no input into the study design, analysis, or interpretation of the results.

for separating "less breathlessness" from "more breathlessness" is used together with a CAT ≥10 into the GOLD assessment tool. Controversies remain regarding the ideal CAT score cutoff-point equivalent to an mMRC value or the extent of agreement between the two scores.[24]

The **L**atin **A**merican **S**tudy of 24-hour **Sy**mptoms in **C**hronic Obstructive Pulmonary Disease (LASSYC) describes prevalence, severity and inter-relationship of early morning, day and night-time symptoms in patients with COPD recruited from clinics[12]outpatients. This study offers an opportunity to explore the distribution of respiratory 24-hour day symptoms according to the GOLD categories using the mMRC or CAT scores in a large sample of stable patients. Therefore, the main objective of the present study was to determine the frequency and severity of the 24-hour day symptoms according to GOLD-ABCD classification by mMRC and CAT scores. We also assess the distribution of the patients with COPD into each of the GOLD-ABCD categories by using the recommended mMRC or CAT scores cutoff-points (CAT ≥10 or mMRC ≥2), and analyze the agreement between the assigned patients into GOLD-ABCD categories using the GOLD cutoff-points.

METHODS

The LASSYC was a prospective observational, multicenter, multinational, cross-sectional, non-interventional study (Clinical Trial Registration: NCT02789540), in patients with COPD from seven Latin American countries: Argentina, Chile, Colombia, Costa Rica, Guatemala, Mexico, and Uruguay.[12] The main objective of the original study was to describe prevalence, severity and inter-relationship of early morning, day and night-time symptoms with COPD severity, exacerbations and patient reported outcomes (PROs) in stable patients.

A total of 795 patients with COPD were enrolled distributed among specialists in respiratory medicine in the selected countries. Each country recruited between 100-130 patients and each site around 10-15. The recruitment was competitive inside each country after the expected site recruitment time of one month, up to total of three months recruitment period. The study was approved by the ethics committees for each site and all patients provided written informed consent.

The methodology of the study has been previously[12,25] described; briefly, outpatients ≥40 years of age with a diagnosis of COPD for at least 1 year, at least one spirometric value with a COPD diagnosis using the post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.70 criteria in the previous 12 months, current or ex-smokers (≥10 pack-years), stable disease (without treatment for an exacerbation or changes in current treatment in the previous 2 months) were included in the study.[12,25] Patients with a diagnosis of sleep apnea or any other chronic respiratory disease, any acute or chronic condition that would limit a patient's ability to participate in the study were excluded.

The following information was collected for each patient: social demographics, health insurance system, lifestyle, smoking history, presence of comorbidities, level of dyspnea, disease severity, prescribed COPD treatments, exacerbation history, and healthcare resource utilization during the last 12 months. The level of dyspnea was measured using the mMRC scale[2] and the CAT score was used to evaluate the impact of the disease.[6]

COPD classification was performed according to the GOLD-ABCD categories (2017-version) using the CAT and mMRC scores separately.[1] The patients were categorized into GOLD-ABCD groups twice with mMRC or CAT score for symptom assessment, respectively.

Assessment of 24-hour day respiratory symptoms (early morning, daytime and night-time symptoms)

"Evaluating Respiratory Symptoms in COPD" E-RS™ 2016 (formerly EXACT-RS)[26] was used to assess daytime symptoms. The night-time and early morning symptoms were assessed with the Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI).[27-29] A detailed explanation of the methodology used in the study for the evaluation of 24-hour day respiratory symptoms and the validation of the instruments in Spanish have been previously[12,30] described.

Briefly, dichotomous variables for defining daytime, early morning and night-time symptoms were built. For daytime symptoms, the third tertile of the score were considered daytime symptoms; the early morning symptoms were defined according to the severity of dyspnea, classified as moderate or higher, added to other symptoms, classified as moderate or more severe; for night-time symptoms, we considered those who woke up at least once at night due to COPD symptoms.

Statistical analysis

Descriptive statistics included the absolute and relative frequencies for categorical variables and mean and standard deviation for numerical ones. No individual was excluded in the analysis.

We calculated the agreement of the GOLD-ABCD classification of COPD for the CAT and mMRC scales thresholds using Kappa statistics (weighted and unweighted). Also, we calculated the area under curve for the CAT score, using as reference the mMRC scale ≥ 2 drawing the graph. Sensitivity, specificity, positive (PPV) and negative (NPV) predicted values

for each of the cut off points in the mMRC scale were calculated with their respective 95% confidence interval. Additionally, the Youden's index ($\frac{sensitivity + specificity}{100}$) was calculated to establish the best value of the CAT score related to the mMRC scale.

We considered a p-value less than 5% as statistically significant. All analyzes were performed using Stata 13.1 (StatCorp LP, 2013. Stata Statistical Software: Release 13. College Station, TX, USA).

RESULTS

A total of 795 patients were included between May and August 2016, 61% were male with a mean age of 69.5±8.7 years, a mean post-bronchodilator FEV_1 of 49.1±17.5% of predicted mMRC score of 1.8±1.0 and 15.2±8.2CAT score . The general characteristics of the overall patient population and by country has been published elsewhere.[31]

The Figure 1 shows the patient's assignment into GOLD-ABCD categories using the CAT score cutoff-point ≥10 and the mMRC scale cutoff-point ≥2. When classification was performed according to mMRC scale the distribution (%) of patients in the ABCD groups were 33.7%, 29.2%, 10.2% and 26.9%, respectively; on the basis of the CAT score the distribution was 22.3%, 41%, 4.8% and 31.9%, respectively. When the stratification of symptom was done by CAT score, the proportion of high symptom groups (B and D) was increased.

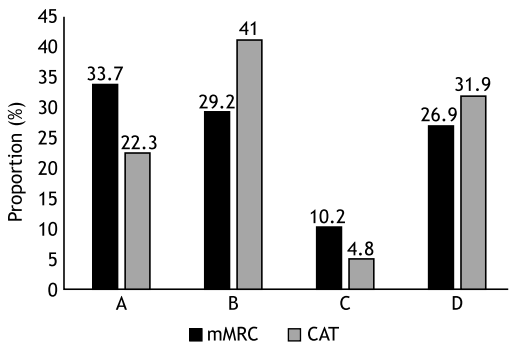

Figure 1. Patient's assignment into GOLD-ABCD categories using the CAT score cut point ≥10 or the mMRC scale cut point ≥2.

The frequency of the 24-hour day respiratory symptoms according to GOLD-ABCD classification by mMRC and CAT scores is shown in the Figure 2. The frequency of 24-hour day symptoms in all COPD categories is low reaching less than 50% of patients in the most severe group D.

The Figures 3-5 show the E-RS, NiSCI and EMSCI symptoms severity scores according to GOLD-ABCD classification by the mMRC and CAT scores, respectively. When the GOLD-ABCD classification was performed by using the mMRC scale, the severity of the symptoms scores E-RS, NiSCI and EMSCI progressively increased from GOLD groups A to D. In contrast, when the CAT score was used, the groups B and D were those with the higher scores. According to the definition of symptomatic patients by the E-RS score (10 units distinguish less vs. more symptomatic patients) when the GOLD-ABCD classification was performed by using the mMRC scale the mean score of patients in the groups B, C and D classified them as highly symptomatic, and those in group A as mild symptomatic. Using the CAT score only the patients in the groups B and D were classified as highly symptomatic and those in the group A and C as mildly symptomatic.

The agreement between the assignment of the patient into GOLD categories using the CAT score cutoff-point ≥10 and the mMRC scale cutoff-point ≥2 is shown in Table 1. The observed agreement for the GOLD groups by CAT and mMRC scores was 89.5%

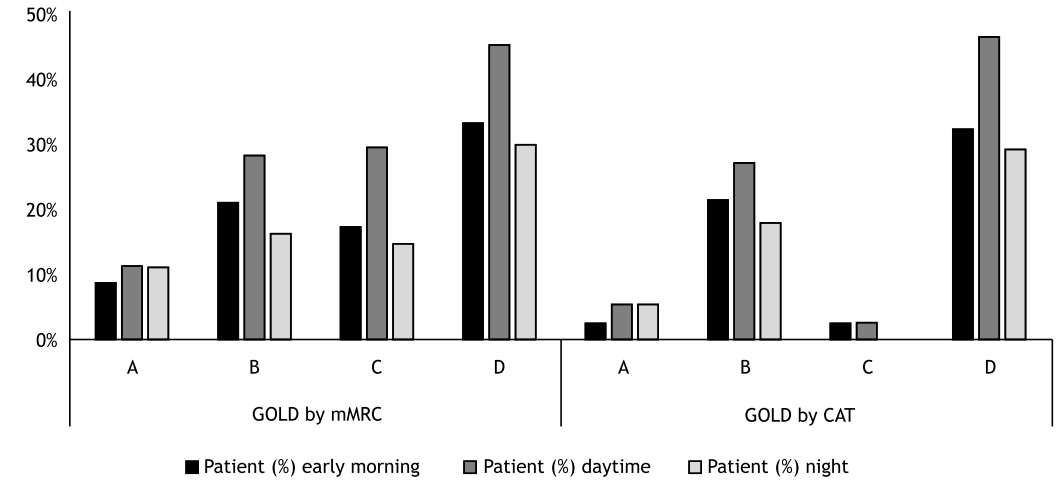

Figure 2. Frequency of the 24-hour day symptoms according to GOLD-ABCD categories by mMRC scale and CAT score.

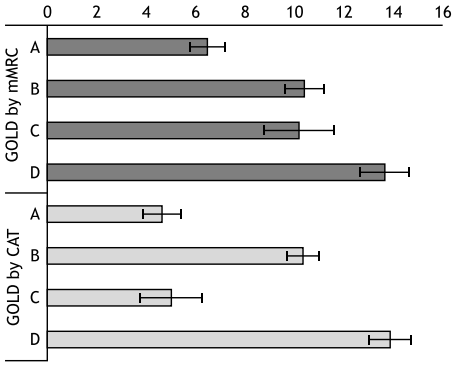

Figure 3. Daytime symptoms (E-RS) severity score according to GOLD-ABCD classification by the mMRC scale and CAT score.

(Kappa statistics= 75.7%), suggesting a substantial but not identical agreement (Table 1).

The agreement between mMRC and CAT scores for each cutoff-point is shown in Supplementary Table S1. For an mMRC score of 2, a CAT score of ≥11 showed the maximum Youden's index value (1.34) with a sensitivity and specificity of 84.8 and 49.3, respectively (AUC 67.1; 95%CI 63.9-70.2). For mMRC score of 1, a CAT score of ≥9 and ≥10 showed the maximum Youden index values (1.48). The sensitivity and specificity for the CAT score ≥9 were 80.8 and 67.3 (AUC 74.0; 95%CI 67.6- 80.5), respectively, and for the CAT score ≥10 the sensitivity and specificity were 77.4 and 70.9 (AUC 74.2; 95%CI 67.9- 80.4), respectively. Supplementary Figure S1 shows the

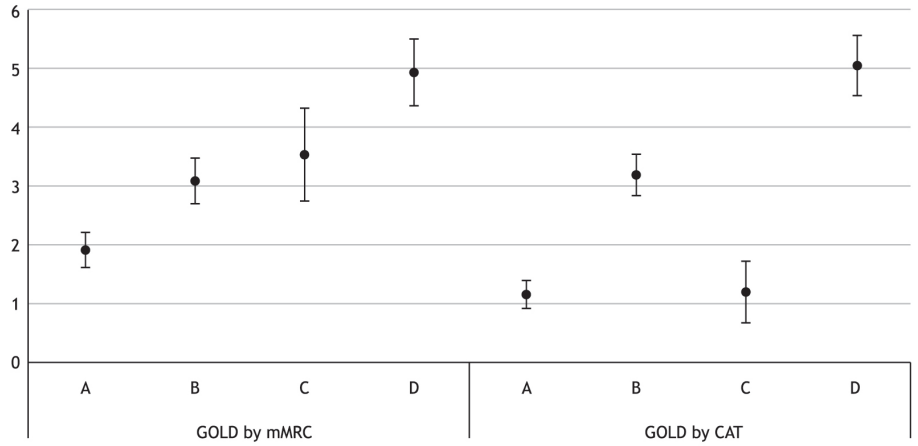

Figure 4. Early morning symptoms (EMSCI) severity score according to GOLD-ABCD classification by the mMRC scale and CAT score.

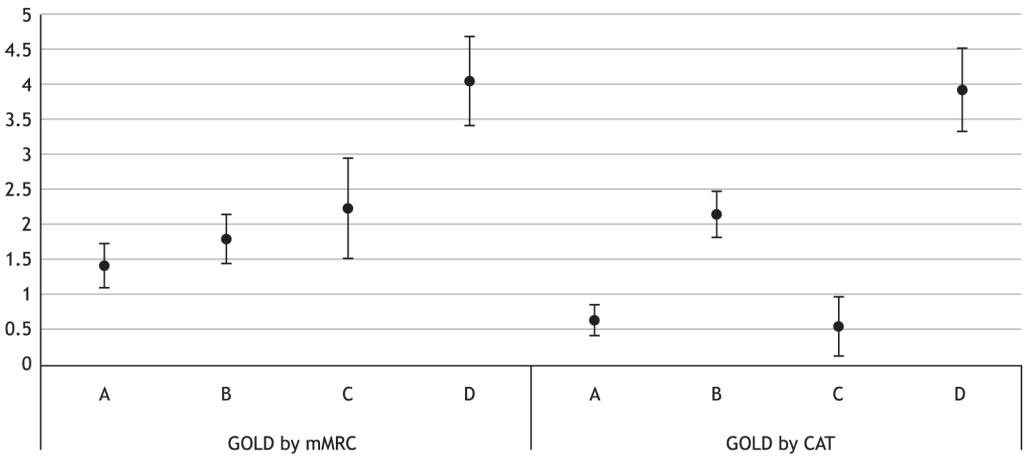

Figure 5. Night-time symptoms (NiSCI) severity score according to GOLD-ABCD classification by the mMRC scale and CAT score.

Table 1. Agreement between patient's assignments into GOLD categories using the CAT score cut point ≥10 or the mMRC scale cut point ≥2.

		CAT classification							
		A	B	C	D	Weighed analysis		Unweighted analysis	
						Observed agreement (%)	Kappa statistics	Observed agreement (%)	Kappa statistics
mMRC	A	140 (17.6)	128 (16.1)	0 (0.0)	0 (0.0)	89.5	75.7	69.2	56.9
	B	34 (4.3)	198 (24.9)	0 (0.0)	0 (0.0)				
	C	1 (0.1)	0 (0.0)	19 (2.4)	61 (7.7)				
	D	2 (0.3)	0 (0.0)	19 (2.4)	193 (24.3)				

ROC curve for the CAT score discriminating power for each cutoff-point of mMRC score. For a mMRC score ≥1 and ≥2, the AUC was 0.83 and 0.74, respectively, indicating that the CAT score had a better discriminating power for mMRC grade ≥1.

DISCUSSION

The main findings of this study on respiratory symptoms and GOLD-ABCD COPD classification in patients from Latin America were: first, the distribution of the patients with COPD into the GOLD categories by the mMRC or CAT scores is not equal, showing the stratification of symptoms by the CAT score a greater proportion of patients in the groups with high symptoms (B and D); second, the GOLD-ABCD classification by CAT score seems to better discriminate 24-hour day symptomatic patients than mMRC scale and third, the use of a mMRC score of 1 with a CAT score ≥10, and a mMRC score of 2 with a CAT score ≥11 seem to be in our population the best thresholds to make CAT and mMRC equivalent.

Several studies have reported differences in the patient's distribution into the GOLD-ABCD categories by using the scores of CAT ≥10 or mMRC ≥2.[13-22] Karloh et al.[24] performed a systematic review and meta-analysis about classification of patients into GOLD categories by CAT ≥10 or mMRC ≥ 2 scores based on the data of 10 studies. By using the mMRC scale the proportion of patients into the groups ranged from 20.3-53% (average 32%) in group-A, 6.8-24.7% (average 16%) in group-B, 5-36.7% (average 20.4%) in group-C, and 12-38.2% (average 31.6%) in group-D; by using the CAT score the proportion into the groups ranged from 5-34.3% (average 18.8%) in group-A, 19.2-48.5% (average 29.7%) in group-B, 0.7-19.8% (average 7.8%) in group-C, and 20-63.3% (average 44.1%) in group-D.[23] In all studies, the proportion of groups with high symptoms (B and D) increased when the stratification of symptoms was done by using the CAT score.[24] On average, the distribution was 13% different according to the instrument used. Another study showed that the most frequent discrepancy was to have a low level of dyspnea but a high CAT score, which in according with the authors opinion may be explained by variables impacting health status but with little impact on dyspnea, such as depression, anxiety or frequent exacerbations.[32]

The results of the present study are consistent with those reported in other populations showing that the proportion of patients categorized into groups A to D differed according to the use of a GOLD symptom cutoff-point of mMRC ≥2 or CAT score ≥10, therefore the choice of symptom scale can alter the group assignment in the GOLD-ABCD classification because mMRC and CAT scores do not behave in the same way in distinguishing symptom groups. These finding support the concept that the CAT and mMRC scores are not equivalent for the purpose of assessing the patients symptoms.

The symptoms of COPD vary throughout the 24-hours a day, so there is a growing interest in evaluating the patterns of 24- hours a day. Some authors suggest that the therapy adapted according to the pattern of the 24-hours a day symptom could provide important benefits in the management of patients with COPD.[33] According to the E-RS score a symptomatic patient is usually defined as the one having at least ten units in the score. This threshold was selected based on evidence suggesting that 10 units could distinguish between less symptomatic (GOLD groups A and C) and more symptomatic (GOLD groups B and D) patients.[34,35]

Results from an observational study in Europe have shown that more than 50% of patients with COPD report respiratory symptoms during the 24-hour day.[30] In addition, it showed a relationship between the 24-hour day symptoms and worse patient-reported outcomes.[30,36] We have previously reported the frequency of respiratory symptoms during the 24-hour day in patients with COPD from Latin America.[12] The frequency of the 24-hour day symptoms in our population was lower (20% and 18%) compared with others[5,30,37]. The study also showed that mMRC and CAT scores progressively increased as the intensity of daytime symptoms worsened (from mild to severe), and there was a strong correlation between E-RS global score with mMRC and the CAT score (r=0.715; p<0.001).[12]

To our knowledge, no previous study has evaluated the distribution of respiratory 24-hour day symptoms according to the GOLD-ABCD categories, as well as the differences in the frequency and severity of these

symptoms when GOLD stratification of the symptoms was performed using the mMRC or CAT scores.

The results of the present study show that the GOLD-ABCD classification by using the CAT score seems to better discriminate the more symptomatic patients (group B and D) by showing an E-RS score higher than 10 units only in the GOLD symptomatic groups B and D, and below this threshold in the low symptomatic groups A and C. In addition, the results expand the findings of other studies that demonstrate the predictive ability of CAT score on important COPD outcomes such as exacerbations, and mortality.[7-11] Interestingly, the GOLD-2019 document uses the multidimensional scores CAT to categorize patients as highly symptomatic in the high-risk group D (CAT ≥20) recommending the initial treatment with two bronchodilators, thus suggesting a central role of the CAT score for patients classification. Therefore, new classification schemes should be benchmarked against CAT score.

The agreement between CAT (≥10) and the (mMRC ≥2) to categorize patients into the GOLD classification system is another controversial issue. The results of a meta-analysis based on the data of 8 studies[13-21] indicate that using these cutoff-points the agreement between CAT and mMRC ranged from poor to substantial (k-coefficients between 0.13 to 0.77) with a pooled k coefficient of 0.548 (95% CI, 0.35-0.70; p< 0.0001) and high heterogeneity among the studies (I^2=99.3; z= 4.84). As a consequence of these, some authors have suggested using the cutoff-point for mMRC score of ≥1 rather than ≥2, for showing this the highest concordance (k-coefficient 0.66-0.79) with a CAT cutoff-point score of ≥10.[38]

Another study showed that a CAT score of ≥10 had 82% sensitivity but 24% specificity to identify mMRC grade ≥2, while a score of 17 had 98% specificity but a low sensitivity of 52% and did not improve the agreement.[39] The authors recommend that using mMRC ≥2 and CAT score ≥17 to identify more symptoms would avoid discordant categorization which is also consistent with the schema for exacerbation risk assessment.[39] Other authors performed a pooled analysis in order to find the best fitting cutoff-points for GOLD symptom measures, with a mMRC dyspnea grade of ≥2 as the point of reference in a total of 18,577 patients with COPD.[40] The results indicate that using mMRC ≥2 points as a reference, a CAT cutoff-point of ≥18 points reached the highest agreement.[40]

Our results are in line with previous studies[13-21] showing that the observed agreement for the GOLD groups by CAT score ≥10 and the mMRC ≥2 was substantial but not identical and that a mMRC score of 1, with a CAT score of ≥9 and ≥10 showed the maximum Youden's index value with an AUC of 74.0 and 74.2, respectively.[14,38] This approach would probably improve the patients being classified into the same GOLD group regardless of the instrument used for symptom assessment and avoid differences in a patient's management, including the choice of the appropriated pharmacological therapy.

This study has some limitations that should be mentioned. Despite the study includes a large number of patients with COPD from seven countries, is not possible to conclude that this sample is representative of the entire COPD population from Latin America; however, the sample included patients with different GOLD-ABCD categories and may provide a valid estimation of patients characteristics from the region. Finally, the definitions of severity of daytime symptoms and of "significant" morning and night-time symptoms are arbitrary as no universally accepted definitions exist. Therefore, the proposed definitions identified patients with different degrees of impairment and different outcomes. Although the use of questionnaires is the only way to investigate the frequency and severity of symptoms, their interpretation may be subjected to bias.

In conclusion, our results do not support the equivalent use of a CAT score of ≥10 and mMRC ≥2 for the purpose of assessing patient symptoms in the GOLD-ABCD classification. The GOLD-ABCD classification by CAT score seems to better discriminate the more 24-hour day symptomatic patients than mMRC scale.

ACKNOWLEDGMENTS

We would like to acknowledge all members of the LASSYC team of Argentina, Brazil, Colombia, Mexico, Uruguay, Chile, Costa Rica, Venezuela, and Spain: Alejandro Casas (Colombia), Maria Montes de Oca (Venezuela), Ana Menezes and Fernando C Wehrmeister (Brazil), Maria Victorina Lopez Varela (Uruguay), Luis Ugalde (Costa Rica), Alejandra Ramirez-Venegas (México), Laura Mendoza (Chile), Ana López (Argentina), Larissa Ramirez (Costa Rica), and Marc Miravitlles (Spain).

AUTHOR CONTRIBUTIONS

MMO, MVLV, AMBM, FCW, LR and MM, contributed substantially to the study design, data collection, interpretation, and reviewed the manuscript. AMBM and FCW performed the data analysis while all authors were involved with data interpretation. MMO wrote the manuscript. All authors approved the final version of the manuscript and agreed to its submission to Respiratory Medicine.

CONFLICTS OF INTEREST

MM has received speaker or consulting fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Laboratorios Esteve, Ferrer, Gebro Pharma, GlaxoSmithKline, Grifols, Menarini, Mereo Biopharma, Novartis, pH Pharma, Rovi, TEVA, Verona Pharma and Zambon, and research grants from GlaxoSmithKline and Grifols. AMBM has received consulting fees from AstraZeneca for the statistical analysis of the LASSYC study. MMO, MVLV, and FCW: no real or perceived conflicts of interest. Larissa LR: Employee of AstraZeneca.

REFERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195(5):557-82. http://dx.doi.org/10.1164/rccm.201701-0218PP. PMid:28128970.
2. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6. http://dx.doi.org/10.1136/thx.54.7.581. PMid:10377201.
3. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest. 2002;121(5):1434-40. http://dx.doi.org/10.1378/chest.121.5.1434. PMid:12006425.
4. Jones PW. Health status measurement in chronic obstructive pulmonary disease. Thorax. 2001;56(11):880-7. http://dx.doi.org/10.1136/thorax.56.11.880. PMid:11641515.
5. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respir Res. 2017;18(1):67. http://dx.doi.org/10.1186/s12931-017-0548-3. PMid:28431503.
6. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54. http://dx.doi.org/10.1183/09031936.00102509. PMid:19720809.
7. Papaioannou M, Pitsiou G, Manika K, Kontou P, Zarogoulidis P, Sichletidis L, et al. COPD assessment test: a simple tool to evaluate disease severity and response to treatment. COPD. 2014;11(5):489-95. http://dx.doi.org/10.3109/15412555.2014.898034. PMid:24766370.
8. Lee YS, Park S, Oh YM, Lee SD, Park SW, Kim YS, et al. Chronic obstructive pulmonary disease assessment test can predict depression: a prospective multi-center study. J Korean Med Sci. 2013;28(7):1048-54. http://dx.doi.org/10.3346/jkms.2013.28.7.1048. PMid:23853488.
9. Lee SD, Huang MS, Kang J, Lin CH, Park MJ, Oh YM, et al. The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients. Respir Med. 2014;108(4):600-8. http://dx.doi.org/10.1016/j.rmed.2013.12.014. PMid:24456695.
10. Pothirat C, Chaiwong W, Deesomchok A, Liwsrisakun C, Bumroongkit C, Theerakittikul T, et al. Detection of acute deterioration in health status visit among COPD patients by monitoring COPD assessment test score. Int J Chron Obstruct Pulmon Dis. 2015;10:277-82. http://dx.doi.org/10.2147/COPD.S76128. PMid:25678783.
11. Casanova C, Marin JM, Martinez-Gonzalez C, de Lucas-Ramos P, Mir-Viladrich I, Cosio B, et al. Differential Effect of Modified Medical Research Council Dyspnea, COPD Assessment Test, and Clinical COPD Questionnaire for Symptoms Evaluation Within the New GOLD Staging and Mortality in COPD. Chest. 2015;148(1):159-68. http://dx.doi.org/10.1378/chest.14-2449. PMid:25612228.
12. Miravitlles M, Menezes A, López Varela MV, Casas A, Ugalde L, Ramirez-Venegas A, et al. Prevalence and impact of respiratory symptoms in a population of patients with COPD in Latin America: the LASSYC observational study. Respir Med. 2018;134:62-9. http://dx.doi.org/10.1016/j.rmed.2017.11.018. PMid:29413510.
13. Han MK, Muellerova H, Curran-Everett D, Dransfield MT, Washko GR, Regan EA, et al. GOLD 2011 disease severity classification in COPDGene: a prospective cohort study. Lancet Respir Med. 2013;1(1):43-50. http://dx.doi.org/10.1016/S2213-2600(12)70044-9. PMid:24321803.
14. Jones PW, Adamek L, Nadeau G, Banik N. Comparisons of health status scores with MRC grades in COPD: implications for the GOLD 2011 classification. Eur Respir J. 2013;42(3):647-54. http://dx.doi.org/10.1183/09031936.00125612. PMid:23258783.
15. Kim S, Oh J, Kim YI, Ban HJ, Kwon YS, Oh IJ, et al. Differences in classification of COPD group using COPD assessment test (CAT) or modified Medical Research Council (mMRC) dyspnea scores: a cross-sectional analyses. BMC Pulm Med. 2013;13(1):35. http://dx.doi.org/10.1186/1471-2466-13-35. PMid:23731868.
16. Pillai AP, Turner AM, Stockley RA. Global Initiative for Chronic Obstructive Lung Disease 2011 symptom/risk assessment in α1-antitrypsin deficiency. Chest. 2013;144(4):1152-62. http://dx.doi.org/10.1378/chest.13-0161. PMid:23787410.
17. Casanova C, Marin JM, Martinez-Gonzalez C, de Lucas-Ramos P, Mir-Viladrich I, Cosio B, et al. New GOLD classification: longitudinal data on group assignment. Respir Res. 2014;15(1):3. http://dx.doi.org/10.1186/1465-9921-15-3. PMid:24417879.
18. Jones PW, Nadeau G, Small M, Adamek L. Characteristics of a COPD population categorised using the GOLD framework by health status and exacerbations. Respir Med. 2014;108(1):129-35. http://dx.doi.org/10.1016/j.rmed.2013.08.015. PMid:24041746.
19. Price DB, Baker CL, Zou KH, Higgins VS, Bailey JT, Pike JS. Real-world characterization and differentiation of the Global Initiative for Chronic Obstructive Lung Disease strategy classification. Int J Chron Obstruct Pulmon Dis. 2014;9:551-61. PMid:24920893.
20. Rieger-Reyes C, García-Tirado FJ, Rubio-Galán FJ, Marín-Trigo JM. Classification of chronic obstructive pulmonary disease severity according to the new Global Initiative for Chronic Obstructive Lung Disease 2011 guidelines: COPD assessment test versus modified Medical Research Council scale. Arch Bronconeumol. 2014;50(4):129-34. http://dx.doi.org/10.1016/j.arbr.2014.03.003. PMid:24268434.
21. Zogg S, Dürr S, Miedinger D, Steveling EH, Maier S, Leuppi JD. Differences in classification of COPD patients into risk groups A-D: a cross-sectional study. BMC Res Notes. 2014;7(1):562. http://dx.doi.org/10.1186/1756-0500-7-562. PMid:25148698.
22. Han J, Dai L, Zhong N, Young D. Breathlessness or health status in chronic obstructive pulmonary disease: the impact of different definitions. COPD. 2015;12(2):115-25. http://dx.doi.org/10.3109/15412555.2014.974741. PMid:25474373.
23. Jones PW, Adamek L, Nadeau G, Banik N. Comparisons of health status scores with MRC grades in COPD: implications for the GOLD 2011 classification. Eur Respir J. 2013;42(3):647-54. http://dx.doi.org/10.1183/09031936.00125612. PMid:23258783.
24. Karloh M, Fleig Mayer A, Maurici R, Pizzichini MMM, Jones PW, Pizzichini E. 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. Chest. 2016;149(2):413-25. http://dx.doi.org/10.1378/chest.15-1752. PMid:26513112.
25. Montes de Oca M, Menezes A, Wehrmeister FC, Lopez Varela MV, Casas A, Ugalde L, et al. Adherence to inhaled therapies of COPD patients from seven Latin American countries: the LASSYC study. PLoS One. 2017;12(11):e0186777. http://dx.doi.org/10.1371/journal.pone.0186777. PMid:29140978.
26. Leidy NK, Murray LT, Monz BU, Nelsen L, Goldman M, Jones PW, et al. Measuring respiratory symptoms of COPD: performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials. Respir Res. 2014;15(1):124. http://dx.doi.org/10.1186/s12931-014-0124-z. PMid:25287629.
27. Hareendran A, Palsgrove AC, Mocarski M, Schaefer ML, Setyawan J, Carson R, et al. The development of a patient-reported outcome measure for assessing nighttime symptoms of chronic obstructive pulmonary disease. Health Qual Life Outcomes. 2013;11(1):104. http://dx.doi.org/10.1186/1477-7525-11-104. PMid:23799883.
28. Mocarski M, Zaiser E, Trundell D, Make BJ, Hareendran A. Evaluation of the psychometric properties of the Nighttime Symptoms of COPD Instrument. Int J Chron Obstruct Pulmon Dis. 2015;10:475-87. PMid:25834415.
29. Stephenson JJ, Cai Q, Mocarski M, Tan H, Doshi JA, Sullivan SD. Impact and factors associated with nighttime and early morning symptoms among patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:577-86. http://dx.doi.org/10.2147/COPD.S76157. PMid:25844033.
30. Miravitlles M, Worth H, Soler Cataluña JJ, Price D, De Benedetto F, Roche N, et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res. 2014;15(1):122. http://dx.doi.org/10.1186/s12931-014-0122-1. PMid:25331383.
31. Casas Herrera A, Montes de Oca M, Menezes A, Wehrmeister FC, Lopez Varela MV, Mendoza L, et al. Respiratory medication used in COPD patients from seven Latin American countries: the LASSYC study. Int J Chron Obstruct Pulmon Dis. 2018;13:1545-56. http://dx.doi.org/10.2147/COPD.S154097. PMid:29785104.
32. Miravitlles M, Koblizek V, Esquinas C, Milenkovic B, Barczyk A, Tkacova R, et al. Determinants of CAT (COPD Assessment Test) scores in a population of patients with COPD in central and Eastern Europe: the POPE study. Respir Med. 2019;150:141-8. http://dx.doi.org/10.1016/j.rmed.2019.03.007. PMid:30961941.
33. Singh D, Miravitlles M, Vogelmeier C. Chronic obstructive pulmonary disease individualized therapy: tailored approach to symptom management. Adv Ther. 2017;34(2):281-99. http://dx.doi.org/10.1007/s12325-016-0459-6. PMid:27981495.
34. Jones PW, Leidy NK, Hareendran A, Lamarca R, Chuecos F, Garcia Gil E. The effect of aclidinium bromide on daily respiratory symptoms of COPD, measured using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) diary: pooled analysis of two 6-month Phase III studies. Respir Res. 2016;17(1):61. http://dx.doi.org/10.1186/s12931-016-0372-1. PMid:27215749.

35. Miravitlles M, Chapman K, Chuecos F, Ribera A, García-Gil E. The efficacy of aclidinium/formoterol on lung function and symptoms in patients with COPD categorized by symptom status: a pooled analysis. Int J Chron Obstruct Pulmon Dis. 2016;11:2041-53. http://dx.doi.org/10.2147/COPD.S114566. PMid:27621610.
36. Miravitlles M, Worth H, Soler-Cataluña JJ, Price D, De Benedetto F, Roche N, et al. The relationship between 24-hour symptoms and COPD exacerbations and healthcare resource use: results from an Observational Study (ASSESS). COPD. 2016;13(5):561-8. http://dx.doi.org/10.3109/15412555.2016.1150447. PMid:26983349.
37. Miravitlles M, Izquierdo JL, Esquinas C, Pérez M, Calle M, López-Campos JL, et al. The variability of respiratory symptoms and associated factors in COPD. Respir Med. 2017;129:165-72. http://dx.doi.org/10.1016/j.rmed.2017.06.017. PMid:28732827.
38. Rhee CK, Kim JW, Hwang YI, Lee JH, Jung KS, Lee MG, et al. Discrepancies between modified Medical Research Council dyspnea score and COPD assessment test score in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:1623-31. http://dx.doi.org/10.2147/COPD.S87147. PMid:26316736.
39. Mittal R, Chhabra SK. GOLD classification of COPD: discordance in criteria for symptoms and exacerbation risk assessment. COPD. 2017;14(1):1-6. http://dx.doi.org/10.1080/15412555.2016.1230844. PMid:27723367.
40. Smid DE, Franssen FME, Gonik M, Miravitlles M, Casanova C, Cosio BG, et al. 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. J Am Med Dir Assoc. 2017;18(12):1097.e11-24. http://dx.doi.org/10.1016/j.jamda.2017.09.003. PMid:29169740.