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Evaluation of COPD patients comparing CAT and mMRC: a retrospective, cross-sectional study

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Evaluation of COPD patients comparing CAT and mMRC: a retrospective, cross-sectional study

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ABBREVIATIONS

ABCD	Tool suggested by GOLD to graduate COPD severity in four grades (A-D)
CAT	COPD Assessment Test
CHUC	Coimbra Hospital and Universitary Centre
COPD	Chronic Obstructive Pulmonary Disease
FEV_1	Forced expiratory volume in 1 second
FEV_1/FVC	Ratio between forced expiratory volume in 1 second and functional vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
mMRC	modified Medical Research Council scale
MRC	Medical Research Council scale

ABSTRACT

Introduction Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous high prevalent disease with major impact on morbimortality. The instruments used to measure the impact of COPD in patients show different classifications, possibly leading to under or overtreatment. Given Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 recommendation, the goal of this study is to contribute, at a national level, to establish the agreement between COPD Assessment Test (CAT) and modified Medical Research Council scale (mMRC) to categorize patients into the new GOLD classification system, as well as how patient characteristics influence the differences.

Materials and Methods This was a retrospective and cross-sectional study conducted at Coimbra Hospital and Universitary Centre, Pulmonology A Service, during one month. The questionnaires, including an inquiry form with clinical and demographic data, CAT and mMRC, were administered only one time, on the same day and by the same interviewer. Statistical analysis included independent sample *t* test for continuous variables, chi-square test for categorical variables, Spearman correlation, one-way ANOVA and Cohen's kappa.

Results Assessing the classification of the 30 patients according to the method used, an overall correlation of *rho*=0.693, a degree of agreement of *k*=0.635 and a positive association with one-way ANOVA were obtained. Comparing concordant and discordant subgroups, there were not found statistically significant differences neither in continuous nor categorical variables. We verified as well weak and moderate correlations between mMRC and airflow limitation, age and exacerbations, between CAT and exacerbations and also between age and exacerbations.

Conclusions Similarly to previous literature, our study showed that the choice of symptom instrument can alter group assignment in GOLD category because mMRC and CAT do not perform identically in distinguishing symptom groups (26.7% of our sample was classified

differently). Differences in patients' characteristics did not seem to be statistically significant to draw firm results. Further longitudinal studies with standardization in other populations, with a larger sample size, documented exacerbation history and mortality data are required to validate our results and improve accuracy in estimating the agreement between CAT and mMRC.

Keywords Pulmonary Disease, Chronic Obstructive; COPD; COPD Assessment Test; CAT; modified Medical Research Council scale; mMRC.

RESUMO

Introdução A Doença Pulmonar Obstrutiva Crónica (DPOC) é uma doença heterogénea altamente prevalente com impacto elevado na morbimortalidade. Os instrumentos usados para medir o impacto da DPOC nos doentes revelam diferentes classificações, levando a possível sub ou sobretratamento. Dada a recomendação da Global Initiative for Chronic Obstructive Lung Disease (GOLD) de 2017, o objetivo deste estudo é contribuir, a nível nacional, para estabelecer a concordância entre o COPD Assessment Test (CAT) e o modified Medical Research Council scale (mMRC) na categorização dos doentes de acordo com o novo sistema de classificação GOLD, bem como as características do doente que influenciam as diferenças.

Materiais e Métodos Trata-se de um estudo retrospetivo e transversal, realizado no Centro Hospitalar e Universitário de Coimbra, no Serviço de Pneumologia A, durante um mês. Os questionários, incluindo um questionário com dados clínicos e demográficos, CAT e mMRC, foram administrados apenas uma vez, no mesmo dia e pelo mesmo entrevistador. A análise estatística incluiu teste *t* para amostras independentes (variáveis contínuas), teste qui-quadrado (variáveis categóricas), correlação de Spearman, ANOVA a um fator e kappa de Cohen.

Resultados Avaliando a classificação dos 30 doentes de acordo com o instrumento utilizado, obteve-se correlação global de *rho*=0,693, concordância de *k*=0,635 e associação positiva com ANOVA a um fator. Comparando os subgrupos concordante e discordante, não foram encontradas diferenças estatisticamente significantes, tanto nas variáveis contínuas como nas categóricas. Foram demonstradas também correlações fracas ou moderadas entre mMRC e limitação do fluxo aéreo, idade e exacerbações, entre CAT e exacerbações e também entre idade e exacerbações.

Conclusões De forma similar a estudos prévios, o nosso estudo demonstrou que a escolha do questionário pode alterar a categoria GOLD, uma vez que o CAT e o mMRC não se comportam

de forma idêntica na distinção dos grupos sintomáticos (26,7% da nossa amostra foi classificada de forma diferente). As diferenças nas características dos doentes não parecem ser estatisticamente significativas para produzir resultados consistentes. São necessários estudos longitudinais adicionais com padronização em outras populações, maior tamanho da amostra, história de exacerbação documentada e dados de mortalidade para validar os nossos resultados e melhorar a precisão na estimativa da concordância entre CAT e mMRC.

Palavras-Chave Doença Pulmonar Obstrutiva Crónica; DPOC; COPD Assessment Test; CAT; modified Medical Research Council scale; mMRC.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is considered a worldwide serious problem of public health, especially because of its high and increasing prevalence among adults.[1-4] It is already a major cause of morbidity and mortality,[1-4] achieving the fourth place in the major causes of death in the world and there are projections to be the third leading cause in 2020.[2] Despite the great impact on patient's quality of life,[1-4] it remains poorly diagnosed and many patients are only diagnosed when they present serious symptoms and signs, consistent with an advanced disease stage.[5] Globally, the COPD burden is projected to increase in the incoming decades because of continued exposure to COPD risks factors (like smoking and air pollution) and aging of the population.[2]

COPD is an inflammatory disease of the lungs characterized by chronic, progressive, and not fully reversible airflow limitation,[1,4] usually caused by significant exposure to noxious particles and gases.[2] This condition is characterized by a large variety of persistent respiratory symptoms, so its management and treatment is a major problem because of the heterogeneity of phenotypes.[2,5] These patients may experience an acute worsening of respiratory symptoms such as elevated sputum volume, purulence, and dyspnea, which is defined as an exacerbation.[4] Those are associated to health care utilization, such as emergency room visits and hospitalizations.[4] Despite its primary location at the lung, it also produces significant systemic effects, creating reductions in functional and exercise capacity, health status and/or quality of life.[1,3] Individual patients may have different reactions to the severity of the disease and comorbidities; therefore, the impact of the disease can be different among patients with the same severity.[5] COPD often coexists with other diseases (comorbidities) that may have a significant impact on disease course.[2] They can exist at any severity of COPD, influence mortality and hospitalizations and the differential diagnosis can be difficult.[2] The most common are lung cancer, cardiovascular diseases, osteoporosis, depression/anxiety, metabolic

syndrome, diabetes, gastroesophageal reflux, bronchiectasis and obstructive sleep apnea.[2] They should be looked routinely and treat appropriately, in any patient with COPD.[2]

The diagnosis of COPD requires exposure to risk factors (tobacco smoking, environmental exposures such as biomass fuel and air pollution, host factors such as genetic abnormalities, abnormal lung development, accelerated aging and hereditary deficiency of alpha-1 antitrypsin)[2], clinical and spirometric compatible data (ratio forced expiratory volume in 1 second / functional vital capacity, FEV_1/FVC, < 70% after bronchodilation, which confirms the presence of persistent airflow limitation).[2,5,6] The goals of COPD assessment are to determine the severity of airflow limitation (FEV_1% predicted), being important to establish the prognosis (according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 1-4) and assess the impact of the disease and the risk of future events (through the application of health status questionnaires, determining a classification of GOLD A-D), in order to decide the best treatment option.[2]

Since lung function may worsen over time, even with the best available care, routine follow-up of COPD patients is essential.[2] Symptoms, exacerbations and objective measures of airflow limitation should be monitored at each visit to determine when to modify management and to identify any complications and/or comorbidities that may develop.[2] Until 2009, GOLD classification of COPD severity was based on spirometry alone; from 2011 forward, it has started a concern about well-being or disease impact.[2-4,7,8] The spirometric classification of COPD has been advocated by GOLD; however, the cut-off points recommended are used for the purpose of simplicity and have not yet been clinically validated,[9] and it is now known that FEV_1 is an unreliable marker of symptoms and health status impairment.[2] The degree of airflow limitation was poorly predictive of dyspnea, quality of life and exacerbation frequency; also, lung function does not explain features of COPD.[8,10] So, this new classification incorporate the assessment of symptoms using either a dyspnea score or an health status measure in addition to

COPD exacerbation history and airflow limitation measured by FEV_1.[8,11] The GOLD strategy moved from a linear, one-dimensional classification for severity groups to a two-dimensional assessment.[11] In 2014, it was released an updated report from GOLD Initiative, still recommending the use of health status questionnaires as markers of burden disease, combined with the degree of airway obstruction and frequency of exacerbations, as markers for risks.[5,11] Since the 2017 update, the GOLD strategy document added a new important recommendation concerning management and treatment of COPD. GOLD proposes a refinement of the "ABCD" assessment tool that separates spirometric grades from the "ABCD" groups, which are now only derived exclusively from patient symptoms and their history of exacerbations.[2] This multidimensional approach should be based on the disease impact (determined by using the assessment of symptom burden and activity limitation) and on the future risk of disease progression and exacerbations (measured by the number of exacerbations in the previous year).[2,12] The burden disease and the impact of COPD on patient's life are usually evaluated using self-reported health status and quality of life questionnaires.[1,13] There are about 13 disease-specific instruments to address these outcomes, including the COPD Assessment Test (CAT), which is a short and simple instrument that could provide reliable measurement of COPD health status and facilitate communication between patient and health-care professionals.[1,13] The breathlessness is assessed using modified Medical Research Council scale (mMRC).[2] So, the most recent update recommends the use of CAT or mMRC to measure the impact of COPD on patient well-being.[2]

The CAT was developed in 2009[5] and it is a short, easy and very cheap way of measure health related quality of life like outcomes in clinical studies and help characterise patients, improving assessment of patients and communication between health professionals in routine practice.[14] Needs only 2 minutes to be completed[5] and consists of 8 items related to COPD symptoms and limitations: cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity

limitations at home, confidence leaving home and energy.[1,3,5,10,15,16] The scale for each question ranges from 0 to 5 and the total score ranges from 0 to 40, with higher scores indicating poorer health status.[1,3,5,10,15,16] The psychometric properties suggest that it is a reliable, valid and responsive tool to measure health status in patients with COPD.[1,6] The CAT score increases in stable COPD patients who have a history of frequent exacerbations (increased risk of hospitalization and mortality) and with the decrease of $FEV_{1,}$[17] which means that detects changes over time: diminishes score with pulmonary rehabilitation and exacerbation recovery and increases with the onset of an exacerbation; so, it should be considered as a marker of the effectiveness of treatment in COPD population.[6,17,18] It reveals also internal consistency and reproducibility over time, besides good construct validity.[6] The minimal clinically important difference is estimated to be 2 points, but it remains debatable.[1,3,6,15,18] Despite the large use of CAT in the clinical practice, there is still some issues on interpretation of the questionnaire, so it would be valuable to provide clear and practical evidence to help health professionals improve their understanding to the score's application, interpretation, and implications in various scenarios.[1]

The original Medical Research Council (MRC) was developed to help physicians establish clinical grades of breathlessness, based on the ability to perform physical activities and it ranged from 1 to 5.[7,19,20] Its modified version, mMRC, consists of an easy and safe self-reported questionnaire useful for examining current COPD symptoms.[21] It is a quantitative and one-dimensional tool assessing dyspnea during exercise in five levels.[3,5,9,10,16,19] Ranges from 0 (breathlessness only on strenuous exercise) to 4 (too breathless to leave the house or when getting dressed)[16,22] and the minimum clinically importance difference is 1.[3,5,19] More relevant to patient´s health and psychological status than FEV_1[9], mMRC has confirmed reliability and it can be used to predict hospitalization and exacerbation, as well as prognosis.[21]

The 2017 GOLD recommendation establishes the use of CAT or mMRC to evaluate symptoms and assign patients to treatment groups based on a cut-off point of ≥ 10 on the CAT and ≥ 2 on the mMRC.[1-3] As the GOLD classification of patients according to CAT or mMRC has already been proven to lead to a discrepancy in categorization, GOLD recommends assignment to the higher risk category.[3] There is strong evidence reporting inconsistencies in patient classification among CAT and mMRC.[4,11,19,20,23-26] The underestimating classification of COPD patients may lead to insufficient treatment; unfortunately, there is no definite evidence that any regular treatment can modify the course of the disease, except for smoking cessation.[25] On the other hand, over-classification could result in over-estimating and increasing medical costs.[25] Although COPD is considered a progressive disease, a reduction in treatment could positively affect health by, e.g., reducing troublesome side effects.[26] Because misclassification could lead to inconsistent management and treatment of the affected,[24,27] it could be useful to use only one tool to assess symptoms.[27]

The goal of the study is to contribute, at a national level, to establish the agreement between CAT (≥ 10) and mMRC (≥ 2) to categorize patients into the new GOLD classification system, updated in 2017, as well as how patient characteristics influence the differences.

MATERIALS AND METHODS

Study design and population

The data were obtained at Coimbra Hospital and Universitary Centre (CHUC), Pulmonology A Service, during one month, whereas qualified and actively involved in COPD management pulmonologists screened outpatients for study entry. The questionnaires included an inquiry form with clinical and demographic data, CAT and mMRC, and were administered on the same day and by the same interviewer. Patients aged 40 years or older with a confirmed diagnosis of COPD and a spirometric result taken from the last documented evidence before enrolment (FEV_1/FVC ratio < 0.7 after bronchodilation, according to the GOLD 2017 recommendation) were invited to participate. To assess the airflow limitation, patients were also classified into GOLD grades 1-4, according to FEV_1% predicted: GOLD 1 (FEV_1% predicted ≥ 80%), GOLD 2 (50% ≤ FEV_1% predicted < 80%), GOLD 3 (30% ≤ FEV_1% predicted < 50%) and GOLD 4 (FEV_1% predicted < 30%). Patients were excluded if they were pregnant, participated in interventional clinical trials in the previous year or did not complete both the CAT and mMRC. This study was approved by the hospital's ethics committee (approval number CHUC-067-17, **Appendix I**) and patient's confidentiality was maintained. All patients gave written informed consent.

Data collection

At a single visit, the investigator completed a detailed patient record form (**Appendix II**), which included baseline characteristics (gender, age), smoking history, occupational exposure, pulmonary function test results (asked to the physician), CAT score, mMRC scale and exacerbation history in the previous year. There were also questioned comorbidities of interest, including cardiovascular diseases (e.g., ischaemic heart disease, congestive heart failure, hypertension and arrhythmia) and chronic lung diseases (e.g., previous pulmonary tuberculosis,

bronchiectasis and pneumoconiosis). COPD group assignment for each participant was made according to the GOLD 2017 recommendation. After that, the patient record forms were collected for further data management and analysis.

Symptom assessment

According to GOLD 2017 recommendation, values of CAT ≥ 10 or mMRC ≥ 2 were classified as more symptomatic; scores of CAT < 10 or mMRC < 2 were identified as less symptomatic. In this study, despite the GOLD grouping (A-D) according to GOLD 2017 recommendation, symptom evaluation was carried out also using both questionnaires independently in each participant. Patients were asked which of five descriptions of breathlessness best describes their impairment to complete mMRC (**Appendix III**). In CAT (**Appendix IV**), patients decide where they fit on a scale of 0 to 5 for each statement. Both questionnaires are freely accessible on the online version of the Portuguese orientation regarding COPD.[16]

Exacerbation risk assessment

An exacerbation was defined as an acute worsening of respiratory symptoms that results in additional therapy,[2] emergency room visits or hospitalisations. In order to group participants into GOLD categories (A-D), patients were divided into two groups: participants with ≥ 2 exacerbations without hospitalisation or ≥ 1 exacerbation which required hospital admission (classified as high-risk) and participants with ≤ 1 exacerbation not leading to hospital admission (identified as low-risk).

COPD patient group

Participants were classified into four groups (A, B, C or D) by their COPD symptoms as determined by CAT or mMRC and exacerbation risk as determined by the history of exacerbations in the previous year, according to the GOLD 2017 recommendation.[2] The groups

were: A (less symptomatic and low-risk), B (more symptomatic and low-risk), C (less symptomatic and high-risk) and D (more symptomatic and high-risk). However, for this study, each participant was assigned twice (one with CAT and one with mMRC), so that we can analyse the discrepancies among these groups according to CAT *versus* mMRC settings.

COPD stage combined

In the 2017 GOLD update, airflow limitation is left apart from the "ABCD" tool; however, in clinical practice, it seems important to consider both classifications. Each treatment regimen needs to be individualized as the relationship between severity of symptoms, airflow limitation, and severity of exacerbations can differ between patients. So, in this study, we also generated COPD stage combined for each patient (using the GOLD grade according to FEV_1% predicted and the GOLD group according to "ABCD" tool).

Statistical analysis

Univariate analysis was used to compare demographic and clinical characteristics. Descriptive statistics such as means and standard deviations were presented for continuous measures. Number and percentage were presented for categorical measures. Comparisons were conducted using the independent sample *t*-test for continuous variables and chi-square test for categorical variables. First, we tested the normality of the variables. The relationship between CAT and mMRC was measured using Spearman correlation coefficient. Additionally, it was tested with the same correlation test the relationship between: post-bronchodilation FEV_1% predicted and CAT score, post-bronchodilation FEV_1% predicted and mMRC scale, post-bronchodilation FEV_1% predicted and total exacerbations, post-bronchodilation FEV_1% predicted and exacerbations requiring hospital admission, post-bronchodilation FEV_1% predicted and age, post-bronchodilation FEV_1/FVC% and CAT score, post-bronchodilation FEV_1/FVC% and

mMRC scale, post-bronchodilation FEV_1/FVC% and total exacerbations, post-bronchodilation FEV_1/FVC% and exacerbations requiring hospital admission, post-bronchodilation FEV_1/FVC% and age, total exacerbations and CAT score, total exacerbations and mMRC scale, total exacerbations and age, exacerbations requiring hospital admission and CAT score, exacerbations requiring hospital admission mMRC scale, exacerbations requiring hospital admission and age, CAT score and age, and finally, mMRC scale and age. Analysis of variance was applied to test the association between CAT and mMRC.

The extent of agreement between the two respiratory questionnaires (CAT and mMRC) was assessed using the Cohen's Kappa coefficient, where *kappa* < 0 indicates a "less than chance/poor" agreement and *kappa* = 1 indicates a "perfect" agreement (the intermediate values correspond to $0.00 \leq k \leq 0.20$ "slight", $0.21 \leq k \leq 0.40$ "fair", $0.41 \leq k \leq 0.60$ "moderate", $0.61 \leq k \leq 0.80$ "substantial" and $0.81 \leq k \leq 1.00$ "almost perfect").[10] Statistical significance was considered when $p < 0.05$ and all data analysis was conducted using SPSS software package version 24.0 (IBM® SPSS® Statistics Base 24.0) and GraphPad Prism® 5.

RESULTS

A total of 30 participants who completed the inclusion criteria and the questionnaires were included in this analysis. **Table 1** summarizes the participants' demographic and clinical characteristics. The population was composed of 7 female (23.3%) and 23 male patients (76.7%). Both female and male patients were mainly classified B and D. The overall mean age was 69.9 ± 11.18 years, with patients age going from 47 to 92 years. The sample consisted in 16.7% under 60 years, 23.3% over 80 years and the large majority (60.0%) has 60 to 79 years. Cigarette smoking was the leading apparent cause of COPD in 83.3% (25 of 30) of patients while compatible occupational exposure was identified in 22 patients (73.3% of the sample), with most of both groups being classified B and D. Finally, there were 15 patients with associated cardiovascular disease and 4 patients with other lung disease, which means percentages of 50 and 13.3% of these comorbidities, respectively. Despite the existence of comorbidity or not, the patients were also predominant in groups B and D. The exacerbation history was divided in total number of exacerbations, episodes of exacerbation requiring hospital admission and those without that need. Fourteen patients (46.7%) did not experience any exacerbation in the last year; of those, 26.7% were classified as group B and 20.0% as group A. We observed that most people with at least one exacerbation did not require hospital admission (5 patients); of those who needed (11 patients), the episodes of exacerbation varied between 1 and 2. Most patients needing hospital admission during at least an exacerbation were grouped as D (30.0%). There were 8 patients who had exacerbations without hospital admission (26.7%) and the number of exacerbations among them were between 1 and 3.

To assure COPD diagnosis, the FEV_1/FVC% was recorded after bronchodilation, achieving a mean value of 52.42 (standard deviation of 11.26); values varied between 31.72 e 69%. The mean FEV_1% predicted was 56.42% (standard deviation of 15.23), starting from 26.8 to 86. According to FEV_1% predicted, the number of individuals in GOLD grades 1, 2, 3 and 4 was

2, 18, 7 and 3, respectively, with an overwhelming proportion of GOLD 2 patients. More than one-half (60%) of the sample was classified as having moderate airflow obstruction (GOLD 2).

For this study, the GOLD groups were evaluated twice for each participant, once using the mMRC scale and again using the CAT score. With both scores (mMRC and CAT) we observed a preponderance of more symptomatic patients in this sample.

Table 1 Demographic and clinical characteristics of the study population

Demographic		**Total**
Gender	Female	7 (23.3%)
	Male	23 (76.7%)
Age (years)	Mean	69.9
	Standard deviation	11.18
	Minimum	47
	Maximum	92
Smoking history	Yes	25 (83.3%)
	No	5 (16.7%)
Occupational exposure	Yes	22 (73.3%)
	No	8 (26.7%)
Comorbidities		
Cardiovascular diseases	Yes	15 (50.0%)
	No	15 (50.0%)
Chronic lung diseases	Yes	4 (13.3%)
	No	26 (86.7%)
Exacerbation history (episodes)		
Total	0	14 (46.7%)
	≥1	16 (53.3%)
Hospital admission	0	19 (63.3%)
	≥1	11 (36.7%)
No hospital admission	0	22 (73.3%)
	1	5 (16.7%)
	≥2	3 (10.0%)
Spirometric		
FEV_1/FVC after bronchodilation (%)	Mean	52.42
	Standard deviation	11.26
	Minimum	31.72
	Maximum	69.00
FEV_1 after bronchodilation (% predicted)	Mean	56.42
	Standard deviation	15.23
	Minimum	26.80
	Maximum	86.00
Questionnaires		
mMRC score	<2	13 (43.3%)
	≥2	17 (56.7%)
	Mean	1.60
	Standard deviation	1.16
	Minimum	0
	Maximum	4
CAT score	<10	11 (36.7%)
	≥10	19 (63.3%)
	Mean	14.23
	Standard deviation	8.51
	Minimum	3
	Maximum	33

Table 1 Demographic and clinical characteristics of the study population (continuation)		
GOLD classification		**Total**
GOLD grade according to FEV_1	1	2 (6.7%)
	2	18 (60.0%)
	3	7 (23.3%)
	4	3 (10.0%)
GOLD group according to mMRC	A	10 (33.3%)
	B	7 (23.3%)
	C	3 (10.0%)
	D	10 (33.3%)
GOLD group according to CAT	A	7 (23.3%)
	B	10 (33.3%)
	C	4 (13.3%)
	D	9 (30.0%)
GOLD group according to "ABCD" tool	A	6 (20.0%)
	B	11 (36.7%)
	C	2 (6.7%)
	D	11 (36.7%)
GOLD stage combined 1	1A	0 (0.0%)
	1B	0 (0.0%)
	1C	1 (3.3%)
	1D	1 (3.3%)
GOLD stage combined 2	2A	5 (16.7%)
	2B	7 (23.3%)
	2C	1 (3.3%)
	2D	5 (16.7%)
GOLD stage combined 3	3A	1 (3.3%)
	3B	3 (10.0%)
	3C	0 (0.0%)
	3D	3(10.0%)
GOLD stage combined 4	4A	0 (0.0%)
	4B	1 (3.3%)
	4C	0 (0.0%)
	4D	2 (6.7%)

The values are expressed as numbers (percentages rounded to the tenths) or just numbers unless otherwise stated. Data are presented for 30 subjects from the single visit. Abbreviations: FEV_1/FVC = forced expiratory volume in 1 second / functional vital capacity; FEV_1 = forced expiratory volume in 1 s; CAT = COPD Assessment Test; mMRC = modified Medical Research Council scale; GOLD = Global Initiative for Chronic Obstructive Lung Disease; "ABCD" tool = Classification recommended by the 2017 updated guidelines.

mMRC formed two groups, less (mMRC < 2) or more (mMRC ≥ 2) symptomatic, according to the score: 43.3% constituted the less symptomatic group and 56.7% the more symptomatic group. CAT divided the patients into the less symptoms group (CAT < 10) and the more symptoms group (CAT ≥ 10): 36.7 and 63.3%, respectively. The total mean mMRC score was set at 1.60 (standard deviation of 1.16) and patient scores varied from the lowest to the highest grade of the scale (0 to 4). CAT scores demonstrated a mean of 14.23 (standard deviation of 8.51), varying from 3 to 33.

Based on the cut-off points of CAT score ≥ 10 and mMRC scale ≥ 2 recommended by the GOLD 2017 document, classifying patients by CAT resulted in 23.3, 33.3, 13.3 e 30.0% of patients in groups A, B, C and D, whereas the classification using the mMRC scale resulted in 33.3, 23.3, 10.0 e 33.3%, respectively.

Using the "ABCD" tool, the final distribution among the groups A, B, C and D was 20.0, 36.7, 6.7 and 36.7%, respectively.

Finally, combining "ABCD" tool and classification according to FEV_1, the most common group was 2B (23.3%), with moderate airflow obstruction, more symptoms and low-risk of exacerbations, followed closely by 2A and 2D, both corresponding to 16.7% of the patients.

Table 2 shows the distribution among concordance and discordance subgroups. Comparing the patients inside the discordance group, those with CAT < 10 and mMRC ≥ 2 have a higher preponderance of men, with 60 to 79 years, occupational exposure, cardiovascular diseases, total number of exacerbations and GOLD group D, according to "ABCD" tool.

Patients with CAT ≥ 10 and mMRC < 2 presented higher percentages of smoking history, exacerbations not requiring hospital admission and GOLD grade 2. Chronic lung comorbidities were absent in both.

Concerning to concordant group, patients with CAT < 10 and mMRC < 2 have tendentially higher proportions from masculine gender, ages between 60 and 79, smoking history, occupational exposure, GOLD grade 2 and GOLD group A, according to "ABCD" tool.

Patients with CAT ≥ 10 and mMRC ≥ 2 showed more chronic lung comorbidities, total number of exacerbations and GOLD group D, according to "ABCD" tool. There were no differences inside the concordant group regarding cardiovascular comorbidities.

Table 2 Detailed characteristics in COPD patients with discordant or concordant group assignment					
		Discordant group (n=8)		Concordant group (n=22)	
		CAT<10 and mMRC≥2 (n=3)	CAT≥10 and mMRC<2 (n=5)	CAT<10 and mMRC<2 (n=8)	CAT≥10 and mMRC≥2 (n=14)
Gender	Female	0 (0.0%)	2 (40.0%)	1 (12.5%)	4 (28.6%)
	Male	3 (100.0%)	3 (60.0%)	7 (87.5%)	10 (71.4%)
Age (years)	<60	0 (0.0%)	2 (40.0%)	2 (25.0%)	1 (7.1%)
	60-79	3 (100.0%)	3 (60.0%)	5 (62.5%)	7 (50.0%)
	≥80	0 (0.0%)	0 (0.0%)	1 (12.5%)	6 (42.9%)
Smoking history	Yes	2 (66.7%)	4 (80.0%)	7 (87.5%)	12 (54.5%)
	No	1 (33.3%)	1 (20.0%)	1 (12.5%)	2 (14.3%)
Occupational exposure	Yes	3 (100.0%)	2 (40.0%)	7 (87.5%)	10 (71.4%)
	No	0 (0.0%)	3 (60.0%)	1 (12.5%)	4 (28.6%)
Comorbidities					
Cardiovascular diseases	Yes	2 (66.7%)	2 (40.0%)	4 (50.0%)	7 (50.0%)
	No	1 (33.3%)	3 (60.0%)	4 (50.0%)	7 (50.0%)
Chronic lung diseases	Yes	0 (0.0%)	0 (0.0%)	2 (25.0%)	2 (14.3%)
	No	3 (100.0%)	5 (100.0%)	6 (75.0%)	12 (54.5%)
Exacerbation history (episodes)					
Total	0	0 (0.0%)	4 (80.0%)	6 (75.0%)	4 (28.6%)
	≥1	3 (100.0%)	1 (20.0%)	2 (25.0%)	10 (71.4%)
Hospital admission	0	1 (33.3%)	4 (80.0%)	6 (75.0%)	8 (57.1%)
	≥1	2 (66.7%)	1 (20.0%)	2 (25.0%)	6 (42.9%)
No hospital admission	0	2 (66.7%)	5 (100.0%)	8 (100.0%)	7 (50.0%)
	1	1 (33.3%)	0 (0.0%)	0 (0.0%)	4 (28.6%)
	≥2	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
GOLD grade according to FEV_1	1	1 (33.3%)	0 (0.0%)	1 (12.5%)	0 (0.0%)
	2	2 (66.7%)	4 (80.0%)	6 (75.0%)	6 (42.9%)
	3	0 (0.0%)	1 (20.0%)	1 (12.5%)	5 (35.7%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
GOLD group according to "ABCD" tool	A	0 (0.0%)	0 (0.0%)	6 (75.0%)	0 (0.0%)
	B	1 (33.3%)	4 (80.0%)	0 (0.0%)	6 (42.9%)
	C	0 (0.0%)	0 (0.0%)	2 (25.0%)	0 (0.0%)
	D	2 (66.7%)	1 (20.0%)	0 (0.0%)	8 (57.1%)

The values are expressed as numbers (percentages rounded to the tenths). Data are presented for 30 subjects from the single visit. Abbreviations: n = number of patients; mMRC = modified Medical Research Council scale; CAT = COPD Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV_1 = forced expiratory volume in 1 second; "ABCD" tool = Classification recommended by the 2017 updated guidelines.

The differences between concordant and discordant groups are showed in **table 3**. Comparing these subgroups using independent sample *t* test, there were no statistically significant differences in the continuous variables, regarding age, post-bronchodilation FEV_1/FVC%, post-bronchodilation FEV_1% predicted, CAT score and mMRC score, with values of p=0.14, p=0.24, p=0.148, p=0.464 and p=0.166, respectively. The categorical variables gender, smoking history, occupational exposure, cardiovascular comorbidities and chronic lung comorbidities were analysed with chi-square test and also did not present statistically significant differences, showing values of p=0.896, p=0.46, p=0.418, p=1 and p=0.195, respectively.

Table 3 Differences between concordant and discordant groups				
		Discordant group (n=8)	**Concordant group (n=22)**	***P* value**
Gender[a]	Female	2 (25.0%)	5 (22.7%)	0.896
	Male	6 (75.0%)	17 (77.3%)	
Age (years)[b]	<60	2 (25.0%)	3 (13.6%)	0.14
	60-79	6 (75.0%)	12 (54.5%)	
	≥80	0 (0.0%)	7 (31.8%)	
Smoking history[a]	Yes	6 (75.0%)	19 (86.4%)	0.46
	No	2 (25.0%)	3 (13.6%)	
Occupational exposure[a]	Yes	5 (62.5%)	17 (77.3%)	0.418
	No	3 (37.5%)	5 (22.7%)	
Comorbidities				
Cardiovascular diseases[a]	Yes	4 (50.0%)	11 (50.0%)	1
	No	4(50.0%)	11 (50.0%)	
Chronic lung diseases[a]	Yes	0 (0.0%)	4 (18.2%)	0.195
	No	8 (100.0%)	18 (81.8%)	
Exacerbation history (episodes)				
Total	0	4 (50.0%)	10 (45.5%)	-
	≥1	4 (50.0%)	12 (54.5%)	
Hospital admission	0	5 (62.5%)	14 (63.6%)	
	≥1	3 (37.5%)	8 (36.4%)	
No hospital admission	0	7 (87.5%)	15 (68.2%)	
	1	1 (12.5%)	4 (18.2%)	
	≥2	0 (0.0%)	3 (13.6%)	
FEV_1/FVC after bronchodilation (%)[b]	-	63.14 (13.99)	53.98 (15.22)	0.24
FEV_1 after bronchodilation (% predicted)[b]	-	56.48 (12.05)	50.94 (10.87)	0.148
CAT score[b]	-	-	-	0.464
mMRC score[b]	-	-	-	0.166
GOLD grade according to FEV_1	1	1 (12.5%)	1 (4.5%)	-
	2	6 (75.0%)	12 (54.5%)	
	3	1 (12.5%)	6 (27.3%)	
	4	0 (0.0%)	3 (13.6%)	
GOLD group according to "ABCD" tool	A	0 (0.0%)	6 (27.3%)	-
	B	5 (62.5%)	6 (27.3%)	
	C	0 (0.0%)	2 (9.1%)	
	D	3 (37.5%)	8 (36.4%)	

The values are expressed as numbers (percentages rounded to the tenths), means (standard deviations) or decimal numbers (for *p* values). Data are presented from the from the chi-square test (a) for categorical variables and independent sample *t* test (b) for continuous variables. Abbreviations: n = number of patients; mMRC = modified Medical Research Council scale; CAT = COPD Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV_1/FVC = forced expiratory volume in 1 second / functional vital capacity; FEV_1 = forced expiratory volume in 1 second; "ABCD" tool = Classification recommended by the 2017 updated guidelines.

We performed several correlations, using Spearman correlation. We observed a positive strong correlation between CAT and mMRC (*rho* of 0.693 and $p < 0.01$) in the sample study. Moreover, we also noted the presence of the following correlations: post-bronchodilation FEV_1/FVC% and mMRC (negative moderate correlation with *rho* of -0.43 and $p < 0.05$), post-bronchodilation FEV_1% predicted and mMRC (negative weak correlation with *rho* of -0.367 and $p < 0.05$), age and mMRC score (positive moderate correlation with *rho* of 0.466 and $p < 0.05$), total number of exacerbations and mMRC score (positive moderate correlation with *rho*

of 0.496 and $p < 0.05$), total number of exacerbations and CAT score (positive weak correlation with *rho* of 0.383 and $p < 0.05$) and total number of exacerbations and age (positive weak correlation with *rho* of 0.374 and $p < 0.05$).

One-way ANOVA was performed to evaluate the association between CAT score and mMRC scale; we identified a positive statistically significant association between both ($p < 0.05$), illustrated in **figure 1**.

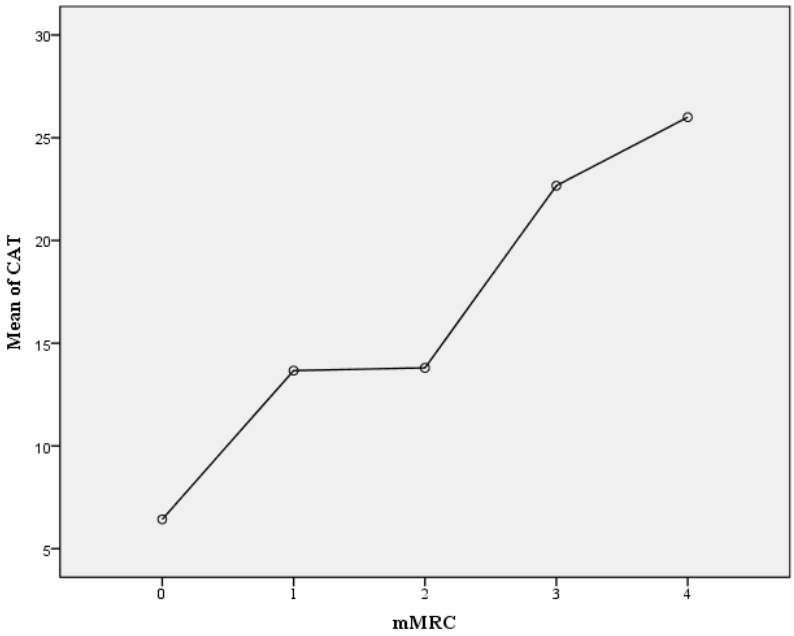

Figure 1 Association between CAT score and mMRC scale for the study sample. The values are expressed as numbers. Data are presented as means ($p < 0.05$) for the one-way ANOVA of the association between CAT score and mMRC scale. Abbreviations: mMRC = modified Medical Research Council scale; CAT = COPD Assessment Test.

The distribution of participants' demographic and clinical characteristics among the "ABCD" tool groups is presented in **table 4.** It also shows the discrepancies in the distribution between classifications made with the "ABCD" tool and the two symptoms scores. Groups A and C from the "ABCD" tool were classified equally with the two approaches; group B was distributed by groups A and B with mMRC, as well as with CAT, despite the last showing a lowest difference compared with "ABCD" tool; on the other hand, group D from "ABCD" tool showed also a distribution in the groups C and D using the questionnaires, but the difference was smaller with mMRC.

Table 4 Distribution of participants' demographic and clinical characteristics among the "ABCD" tool groups

		GOLD group according to "ABCD" tool			
Demographic characteristics		**A**	**B**	**C**	**D**
Gender	Female	1 (3.3%)	3 (10.0%)	0 (0.0%)	3 (10.0%)
	Male	5 (16.7%)	8 (26.7%)	2 (6.7%)	8 (26.7%)
Age (years)	<60	1 (3.3%)	1 (3.3%)	1 (3.3%)	2 (6.7%)
	60-79	5 (16.7%)	9 (30.0%)	0 (0.0%)	4 (13.3%)
	≥80	0 (0.0%)	1 (3.3%)	1 (3.3%)	5 (16.7%)
Smoking history	Yes	5 (16.7%)	8 (26.7%)	2 (6.7%)	10 (33.3%)
	No	1 (3.3%)	3 (10.0%)	0 (0.0%)	1 (3.3%)
Occupational exposure	Yes	5 (16.7%)	7 (23.3%)	2 (6.7%)	8 (26.7%)
	No	1 (3.3%)	4 (13.3%)	0 (0.0%)	3 (10.0%)
Comorbidities					
Cardiovascular diseases	Yes	3 (10.0%)	5 (16.7%)	1 (3.3%)	6 (20.0%)
	No	3 (10.0%)	6 (20.0%)	1 (3.3%)	5 (16.7%)
Chronic lung diseases	Yes	2 (6.7%)	1 (3.3%)	0 (0.0%)	1 (3.3%)
	No	4 (13.3%)	10 (33.3%)	2 (6.7%)	10 (33.3%)
Exacerbation history (episodes)					
Total	0	6 (20.0%)	8 (26.7%)	0 (0.0%)	0 (0.0%)
	≥1	0 (0.0%)	3 (10.0%)	2 (6.7%)	11 (36.7%)
Hospital admission	0	6 (20.0%)	11 (36.7%)	0 (0.0%)	2 (10.0%)
	≥1	0 (0.0%)	0 (0.0%)	2 (6.7%)	9 (30.0%)
No hospital admission	0	6 (20.0%)	8 (26.7%)	2 (6.7%)	6 (20.0%)
	1	0 (0.0%)	3 (10.0%)	0 (0.0%)	2 (6.7%)
	≥2	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (10.0%)
Questionnaires		**A**	**B**	**C**	**D**
mMRC score	<2	6 (20.0%)	3 (10.0%)	2 (6.7%)	1 (3.3%)
	≥2	0 (0.0%)	8 (26.7%)	0 (0.0%)	10 (33.3%)
CAT score	<10	6 (20.0%)	1 (3.3%)	2 (6.7%)	2 (6.7%)
	≥10	0 (0.0%)	10 (33.3%)	0 (0.0%)	9 (30.0%)
GOLD classification		**A**	**B**	**C**	**D**
GOLD grade according to FEV_1	1	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)
	2	5 (16.7%)	7 (23.3%)	1 (3.3%)	5 (16.7%)
	3	1 (3.3%)	3 (10.0%)	0 (0.0%)	3 (10.0%)
	4	0 (0.0%)	1 (3.3%)	0 (0.0%)	2 (6.7%)
GOLD group according to					
mMRC	A	6 (20.0%)	4 (13.3%)	0 (0.0%)	0 (0.0%)
	B	0 (0.0%)	7 (23.3%)	0 (0.0%)	0 (0.0%)
	C	0 (0.0%)	0 (0.0%)	2 (6.7%)	1 (3.3%)
	D	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)
CAT	A	6 (20.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
	B	0 (0.0%)	10 (33.3%)	0 (0.0%)	0 (0.0%)
	C	0 (0.0%)	0 (0.0%)	2 (6.7%)	2 (6.7%)
	D	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (30.0%)

The values are expressed as numbers (percentages rounded to the tenths). Data are presented for 30 subjects from the single visit. Abbreviations: "ABCD" tool = Classification recommended by the 2017 updated guidelines; mMRC = modified Medical Research Council scale; CAT = COPD Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV_1 = forced expiratory volume in 1 second.

Figure 2 illustrates the distribution of the study population by group (A-D), according to mMRC score, CAT score and "ABCD" tool, demonstrating that the COPD group assignment was not identical based on the questionnaire used. Concordance was defined as the COPD group being classified based on the CAT score that was consistent with that defined by the mMRC scale. Conversely, discordance was defined as the COPD group being classified based on the

CAT score, which was inconsistent with that defined by the mMRC scale. We found that 26.7% (8/30) of the enrolled participants had a discordance in the group assignment. It was observed for both sides, which means that the GOLD group by "ABCD" tool was achieved using cut-off points from mMRC in 3 patients (10.0%) and from CAT in 5 patients (16.7%).

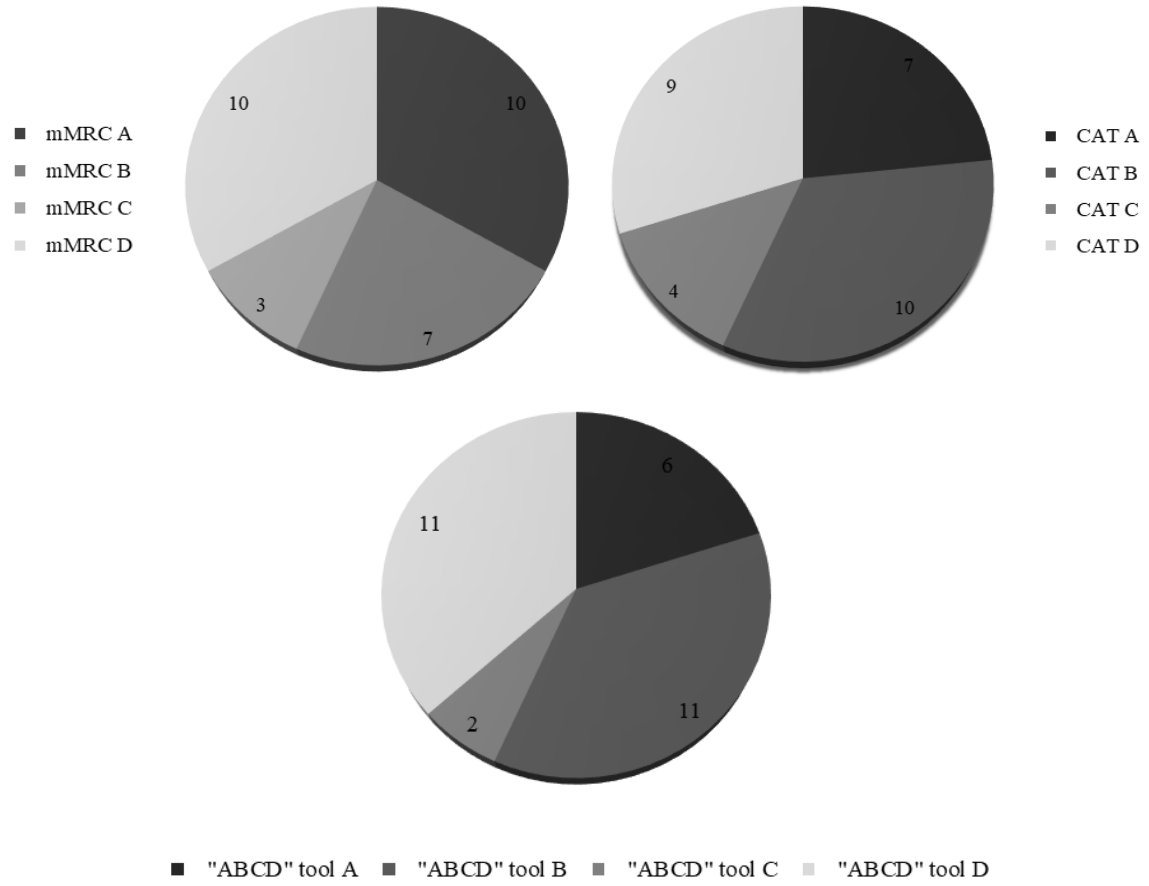

Figure 2 Distribution of the study population by group (A-D), according to mMRC score, CAT score and "ABCD" tool. The values are expressed as numbers. Data are presented for 30 subjects from the single visit. Abbreviations: mMRC = modified Medical Research Council scale; CAT = COPD Assessment Test; "ABCD" tool = Classification recommended by the 2017 updated guidelines.

Finally, based on the cut-off points recommended by GOLD 2017 update, we established a concordance between variables in GOLD classification of 73.3% of the sample study. **Table 5** shows the numbers and percentages of agreement between the two symptoms scores. When the results from the application of both evaluation methods were examined, we found that in category A, the classification of 6 patients coincided (85.7% of those classified using CAT and 60.0% of those classified with mMRC). In category B, there were also a match in 6 patients

(60.0% using CAT and 85.7% with mMRC). The category C was equally chosen in 2 patients (50.0% with CAT and 66.7% with mMRC). Finally, category D was set likewise in 8 patients (88.9% with CAT and 80.0% with mMRC). Cohen's kappa (which allows to exclude the concordance related to chance) revealed a statistically significant concordance of 63.5%, with $p < 0.05$ (illustrated in **table 6**), corresponding to a substantial agreement between CAT and mMRC.

Table 5 Crosstabulation of CAT and mMRC scores, according to GOLD 2017 update recommendations

			mMRC				Total
			A	B	C	D	
CAT	A	Count	6	1	0	0	7
		% within CAT	85.7%	14.3%	0.0%	0.0%	100.0%
		% within mMRC	60.0%	14.3%	0.0%	0.0%	23.3%
	B	Count	4	6	0	0	10
		% within CAT	40.0%	60.0%	0.0%	0.0%	100.0%
		% within mMRC	40.0%	85.7%	0.0%	0.0%	33.3%
	C	Count	0	0	2	2	4
		% within CAT	0.0%	0.0%	50.0%	50.0%	100.0%
		% within mMRC	0.0%	0.0%	66.7%	20.0%	13.3%
	D	Count	0	0	1	8	9
		% within CAT	0.0%	0.0%	11.1%	88.9%	100.0%
		% within mMRC	0.0%	0.0%	33.3%	80.0%	30.0%
Total		Count	10	7	10	10	30
		% within CAT	33.3%	23.3%	33.3%	33.3%	100.0%
		% within mMRC	100.0%	100.0%	100.0%	100.0%	100.0%

The values are expressed as numbers or percentages rounded to tenths. Data are presented for the 30 subjects of the sample study. Abbreviations: mMRC = modified Medical Research Council scale; CAT = COPD Assessment Test.

Table 6 Extent of agreement between CAT and mMRC, using Cohen's Kappa coefficient

	Symmetric Measures			
	Value	Asymptotic Standard Error[a]	Appoximate T[b]	Approximate Significance
Measurement of Agreement Kappa	0.635	0.107	5.889	0.000
Number of Valid Cases	30			

The values are expressed as numbers. Data are presented for the 30 subjects of the sample study. Abbreviations: a = Not assuming the null hypothesis; b = Using the asymptotic standard error assuming the null hypothesis; mMRC = modified Medical Research Council scale; CAT = COPD Assessment Test.

DISCUSSION

Interpretation of the main findings

The sample of the study was established mainly by men (76.7%), with a mean age of 69.9 years with previous history of smoking (83.3%). These findings are consistent with other studies, which reported also majority of men (53.0 to 96.2%) and mean ages from 65 to 72.2 years.[9,10,19,20,23,24,26-28] Smoking history (current and ex-smoker) was present in 38.4 to 96.2%.[9,10,19,23,27] There is also a systematic review including 28 countries reporting appreciably higher prevalence of COPD in men over 40 years, smokers and ex-smokers.[2] These findings can be explained by several ways: aging of the airways and parenchyma mimic structural changes associated with COPD, but gender may also influence certain occupational or environmental exposures and life expectancy that will allow greater lifetime exposure to risk factors.[2]

Cigarette smoking is the leading environmental risk factor for COPD, yet even for heavy smokers, fewer than 50% develop COPD during their lifetime.[2] Passive exposure to cigarette smoke may also contribute to respiratory symptoms and COPD by increasing the lung's total burden of inhaled particles and gases.[2] Reversely, and still controversial, some studies have suggested an equal to higher prevalence among women, reflecting the changing of tobacco smoking and the susceptibility to the effects of tobacco, leading to more severe disease for the equivalent quantity of cigarettes consumed.[2] On the other hand, occupational exposures are an under-appreciated risk factor for COPD.[2]

Some studies demonstrated not only an association with increased airflow limitation and respiratory symptoms, but also with emphysema and gas trapping assessed by computed tomography scan in both gender.[2] Accounts for 10-20% of symptoms or functional impairment consistent with COPD,[2] far below the one found in our study (73.3%).

The treatment of chronic diseases like COPD is complicated by the presence of comorbidities, which may have a direct impact on survival. In our study, cardiovascular comorbidities (50% of the sample) were mostly prevalent in groups B and D and revealed no differences between less and more symptomatic group, while other lung diseases affected only 13.3%. One study reported also these findings, but with cardiovascular comorbidities being more prevalent in higher score groups.[7] Evidence refers higher mortality from cardiovascular disease and cancer and poorer survival in group B compared to C, despite higher FEV_1.[7] So, it was suggested that there was a link between COPD severity and the prevalence of comorbidities.[7]

Before 2017, both exacerbation history and FEV_1 were used to stratify risk, but they do not behave identically in predicting risk because FEV_1 also relates to symptoms[8] and it is suggested that not only a $FEV_1 < 50\%$ but also a rate of annual hospitalizations ≥ 1 are the strongest and independent predictors of all-cause mortality.[28] So, measurement of FEV_1/FVC% and FEV_1% after bronchodilation continue to represent an important measurement of the disease status; our sample has mean values of 52.42% and 56.42% (moderate airflow obstruction or GOLD 2), respectively. These results are consistent with previous studies: post-bronchodilation FEV_1/FVC of 53-56.8%[9,23,28] and post-bronchodilation FEV_1 of 50.4-62.4%.[9,19,20,23,24,26,28] However, preventing exacerbations remains an essential step in the COPD management.[7] Some COPD patients are particularly susceptible to frequent exacerbations (defined as $\geq$ 2 exacerbations per year), and these patients have shown worse health status and morbidity than patients with less frequent exacerbations.[2] Patients at high risk of frequent exacerbations can be recognized across all disease severity groups and the strongest predictor of a patient's future exacerbation is the number of exacerbations that they have had in the previous year.[2] In our study, exacerbations were present in the majority of the sample (53.3%), but only 36.7% had exacerbations serious enough to need hospital assistance.

Consistent with the literature, we established positive correlations between total number of exacerbations and CAT, mMRC and age, meaning that those act as potential measures of predicting future exacerbations. Despite the newest update, it is important to remember that chronic respiratory symptoms may precede the development of airflow limitation with risk of acute respiratory events and vice versa.[2] So, chronic respiratory symptoms also exist in individuals with normal spirometry and people with airflow limitation may only have minor symptoms,[2] which can be problematic if FEV_1 evaluation is abandoned.

A large number of assessment tools have been developed in order to help measuring health status, symptoms, dyspnea and overall disease burden.[5] The main goal of this original article was to determine the agreement between CAT $\geq$ 10 and mMRC $\geq$ 2 to categorize patients according to the new GOLD classification.

In concordance with a recent study from Huang WC *et al.*[23], we showed that patients with worse health status and worse respiratory capacity (CAT $\geq$ 10 or mMRC $\geq$ 2) were older in age, have more presence of exacerbations in the previous year and more severe airflow limitation. Comparing with those of the less symptomatic group (CAT < 10 or mMRC < 2), they also presented less differences between genders (despite male still preponderant), smokers and non-smokers (despite smokers still in bigger number), occupational exposure (still higher number of exposure) and chronic lung comorbidities (despite higher number of disease absence).

Consonant with the present study (discordance of 26.7%), several previous studies found that the group assignment of patients with COPD using the symptom assessment methods (CAT or mMRC) was not consistent,[1] with discordances of 27.2% to 53.7%.[11,23,24]

Like in other studies,[7,10,19,25,27] CAT was major for symptom group classification; only 10.0% were classified into the more symptoms group based on the mMRC, against 16.7% classified into a superior group with CAT. The discrepancy is not surprising because these two

instruments differ in their purpose and evaluated areas, so, the choice of the symptom measure influenced category assignment.[3,8,11]

mMRC score is determined from only one question regarding the degree of dyspnea and CAT score is calculated using an eight-item questionnaire and covers many aspects of life.[1,19,23] mMRC has some advantages, like brevity,[8] easiness of use,[19] good correlation with COPD disability,[19] earlier detection of health related quality of life deterioration,[9] agreement with exacerbation risk and hospitalization,[22] and prediction of mortality risk and prognosis (better than CAT).[19,21,28] A study concluded that both patients and physicians consider breathlessness, fatigue and cough as the three symptoms that most concerned and affected the quality of life of COPD patients.[5,24] CAT has the capacity to discriminate health status in subsets of populations even with mild disease in all age groups,[15] good repeatability and responsiveness to pulmonary rehabilitation, exacerbation onset and recovery,[4,8,10,14] prediction of COPD diagnosis, time to exacerbation, depression and mortality,[1,28] sensitivity to effects of comorbidity[26] and validation in multiple languages.[19] As the category assignments produced by each symptom measure are not identical, it seems that a potential refinement of the GOLD classification scheme should be adopted: some studies cautiously recommend to discard mMRC;[8,14,19,27] others remain convinced of the important combination of the two scores to provide more stable and uniform COPD management.[1,11,23]

In our series, we obtained a statistically significant and positive strong Spearman correlation between CAT score and mMRC scale with *rho*=0.693 (similar to other studies, with *rho* of 0.613[24] and 0.63[4] and somewhat different from others, with *rho* of 0.45[27] and 0.49[19]). The association between CAT and mMRC using one-way ANOVA was also positive and statistically significant, like in other studies.[20,23] Other important correlations obtained in our study denote that mMRC may influence and be influenced by post-bronchodilation FEV_1/FVC%, post-bronchodilation FEV_1% predicted (weak negative correlation, like in other

study, indicating that with any pulmonary reserve, patients can range from no respiratory disability to almost complete incapacity[23]), age and total number of exacerbations; CAT is only correlated with total number of exacerbations.

Finally, we detected also that age may have some influence in the total number of exacerbations. So, it looks like older ages, worse health status and worse respiratory capacity may play a role on the development of exacerbations, as normally expected. A study suggests that this could be the reason why frequent exacerbators tend to have more exacerbation-related hospitalisations and poorer survival.[23] However, neither of the correlations was yet strong enough to predict a real influence on the variables.

Our analysis obtained a Cohen's kappa of 0.635 , revealing a substantial agreement between CAT and mMRC, similar to other studies that showed substantial[8,20,24,26] agreement and different from others, that showed fair[4,11,27] to moderate[10,19,23,28] agreements. Cohen's kappa is often used to test the interrater reliability, to understand the extent to which the data collected in the study are correct representations of the variables measured.[29]

Cohen's suggested interpretation may be too soft for health-related studies (k=0.41 as acceptable), because it seems that agreements below 0.8 correspond to 20% of erroneous data and below 0.6 about 50% erroneous; so, statistical significance means little with this amount of error.[29] This is the reason why many texts recommend 80% agreement as a minimum acceptable interrater agreement and any $k < 0.6$ indicates inadequate agreement among raters and little confidence should be attributable to results.[29] Nevertheless, low levels of interrater reliability should not be considered acceptable in clinical research, especially when it may change clinical practice.[29] So, according to an alternative interpretation,[29] our study has a moderate agreement (0.6 to 0.79, with 35 to 63% of the data considered reliable[29]).

Strengths and limitations

This original article has some strengths and weaknesses to be acknowledged. The major advantage of this study was that mMRC and CAT were compared directly regarding to the recent GOLD report; then, it was also achieved a relatively recent recruitment to reflect current prescribing practices. Other main point was the age of patients, because one review reported the need of data in patients under 50 and over 70 and in grade 4,[14] a failure filled in this study. But there are also several limitations, like the type of study (a cross-sectional non-interventional method) which does not permit assessment of disease changes over time and therefore we cannot speculate about movements across categories, missing the longitudinal follow-up.

We also could not perform the investigation about the effect of any exposure and/or COPD pharmacological treatment and the influence of other medications. Another issue is the small sample size. We think that the numbers were too small to draw strong conclusions; female patients were in a very small number.

Regarding to COPD groups, C was particularly underrepresented because of the population-based sampling; therefore, the present study was not representative for COPD risk group C. The comparison between exacerbation risk using severity grades or past-year exacerbations may be biased and inaccurate, because the history of exacerbation was self-reported and there was missed information about the time from exacerbation. Another concern is that the study was conducted only at a central hospital (one single hospital); therefore, it may not be applicable to the general COPD population and does not represent patients with undiagnosed disease. Some comorbidities may have been missed, because we recorded the comorbidities of major interest. We did not establish any correlation with comorbidities between different categories, despite they could have a significant effect on disease prognosis and should also be considered for the combined evaluation of COPD in any future revision of the GOLD guidelines. Other risk factors, mentioned at 2017 update guidelines, like socioeconomic status and infections

(severe childhood respiratory infection; human immunodeficiency virus; tuberculosis)[2] probably need to be considered.

Conclusions

The present study provides cross-sectional data concerning the allocation of COPD patients across COPD groups according to 2017 updated guidelines, using either CAT or mMRC scores in a Portuguese sample. To our knowledge, this was the first study addressing these aspects in our country.

In summary, this study found that there were several differences in GOLD category depending on the method of symptom assessment applied (26.7% of our sample was classified differently). We showed that the choice of symptom scale can alter group assignment of COPD because mMRC and CAT do not perform identically in distinguishing symptom groups. So, the appropriate clinical management of COPD patients may require alignment of questionnaires' cut-off points and/or co-administration of these tools. Despite the findings of some correlations, differences in patients' characteristics did not seem to be statistically significant to draw firm results. Further longitudinal studies with standardization in other populations, with a larger sample size, documented exacerbation history and mortality data are required to validate our results and improve accuracy in estimating the agreement between CAT and mMRC.

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APPENDICES

Appendix I Document of Ethics Committee approval

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

CHUC CENTRO HOSPITALAR E UNIVERSITÁRIO DE COIMBRA

Comissão de Ética para a Saúde

Visto/ À U.I.D.
para difusão

30/11/2017
Dr. Francisco Parente
Diretor Clínico
C.H.U.C. - EPE

Exmo. Senhor
Dr. Francisco Parente
Digmº Director Clínico do CHUC

SUA REFERÊNCIA	SUA COMUNICAÇÃO DE	NOSSA REFERÊNCIA	DATA
		Nº 0209/CES	24-11-2017
		Proc. Nº **CHUC-067-17**	

ASSUNTO: *Estudo Observacional "Avaliação de doentes com DPOC, comparando CAT e mMRC: estudo retrospetivo transversal."* – Ana Rita Monteiro Laranjeiro, aluna do Mestrado Integrado em Medicina da Faculdade de Medicina da Universidade de Coimbra (estudo a ser realizado no Serviço de Pneumologia A do CHUC).
(Reentrada do processo na CES a 22.09.2017)

Cumpre informar Vossa Ex.ª de que a Comissão de Ética para a Saúde do Centro Hospitalar e Universitário de Coimbra, reunida em 24 de Novembro de 2017, com a presença da maioria dos seus membros, após análise dos esclarecimentos adicionais enviados pela investigadora e ouvido o relator, emitiu parecer favorável à sua realização. Parecer aprovado por unanimidade.

Mais se informa que a CES do CHUC deve ser semestralmente actualizada em relação ao desenvolvimento dos estudos favoravelmente analisados e informada da data da conclusão dos mesmos, que deverá ser acompanhada de relatório final.

Com os melhores cumprimentos.

A COMISSÃO DE ÉTICA PARA A SAÚDE
DO CHUC, E.P.E.

C.H.U.C. E.P.E. Comissão de Ética para a Saúde

Prof. Doutor José Sousa Barros
Vice-Presidente da CES do CHUC

LP/CES

A CES do CHUC: Prof. Doutor José Joaquim Sousa Barros; Prof.ª Doutora Maria Fátima Pinto Saraiva Martins; Dr. Mário Rui Almeida Branco; Enf.º Adélio Tinoco Mendes; Prof. Doutor Carlos Alberto Fontes Ribeiro; Padre José António Afonso Pais; Dr. José António Feio; Dr. José Alves Grilo Gonçalves; Enf.º Fernando Mateus; Dr. José António Pinheiro; Dra. Cláudia Santos; Dr. Paulo Figueiredo

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REPÚBLICA PORTUGUESA
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CHUC CENTRO HOSPITALAR E UNIVERSITÁRIO DE COIMBRA

10.6

UNIDADE DE INOVAÇÃO E DESENVOLVIMENTO

A CA
21/12/17

Prof. Doutor Fernando J. Regateiro
Presidente do Conselho de Administração
C.H.U.C. - EPE

Exmo Senhor
Prof. Doutor Fernando Regateiro
Presidente do Conselho de Administração
Centro Hospitalar e Universitário de Coimbra, EPE

SUA REFERÊNCIA	SUA COMUNICAÇÃO DE	NOSSA REFERÊNCIA	DATA
		CHUC-067-17	05-12-2017

ASSUNTO: Aprovação do Projeto de Investigação CHUC-067-17

A pedido de ***Ana Rita Monteiro Laranjeiro***, recebeu esta Unidade um pedido de autorização de um Projeto de Investigação sobre ***"AVALIAÇÃO DE DOENTES COM DPOC, COMPARANDO CAT E mMRC: ESTUDO RETROSPETIVO TRANSVERSAL"***, ao qual não se aplicam as normas previstas na Lei n.º 21/2014 de 16 de Abril e colheu parecer **favorável** da Comissão de Ética deste Hospital.

Informa-se V. Exª. que este projecto não acarreta qualquer encargo financeiro adicional para o CHUC.

Solicita-se assim a autorização do Conselho de Administração para este Projecto.

Com os mais respeitosos cumprimentos,

C.H.U.C. - EPE - Conselho de Administração
Aprovado
04.01.2018

(Prof. Doutor Fernando J. Regateiro - Presidente)
(Dr. Diogo Reis Afonso - Vogal)
(Dr.ª Manuela Mota Pinto - Vogal)
(Dr. Francisco Parente - Dir. Clínico)
(Enf.ª Áurea Andrade - Enf.ª Directora)

C.H.U.C. - EPE
CONSELHO DE ADMINISTRAÇÃO
Reg. N.º 9678 PCA
Origem
Data 6 / 12 / 2017

Pl'A Coordenadora da Unidade de Inovação e Desenvolvimento

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Appendix II **“**Questionário Individual de Dados Clínicos”

QUESTIONÁRIO INDIVIDUAL DE DADOS CLÍNICOS

- **Género:** Feminino___ Masculino___
- **Idade:** ___ anos
- **Residência:** _____
- **Profissão** (se desempregado ou reformado, indicar a última profissão)**:** _____

_____

- **História tabágica:** Sim___ Não___
- **Carga tabágica:** _____UMA
- **Exposição ocupacional:** Sim___ Não___ Qual? _____
- **Idade de diagnóstico de DPOC:** ____ anos
- **Estádio GOLD atual:** ___
- **Último resultado da Espirometria:** VEMS_____% Tiffeneau_____%
- **Número de exacerbações no último ano:** _____
- **Exacerbação com necessidade de hospitalização no último ano:** Sim__ Não__ Quantas? ____
- **Outras patologias:** Sim___ Não___ Qual? _____

_____

- **Outras informações relevantes:** _____

_____

_____

_____

_____

_____

Appendix III modified Medical Research Council scale (mMRC)[16]

modified Medical Research Council scale (mMRC)[16]

Assinale com uma cruz (X), o quadrado ☐ correspondente à afirmação que melhor descreve a sua sensação de falta de ar.

GRAU 0
Sem problemas de falta de ar exceto em caso de exercício intenso.
"Só sinto falta de ar em caso de exercício físico intenso". ☐

GRAU 1 Falta de fôlego em caso de pressa ou ao percorrer um piso ligeiramente inclinado.
"Fico com falta de ar ao apressar-me ou ao percorrer um piso ligeiramente inclinado". ☐

GRAU 2
Andar mais devagar que as pessoas da minha idade devido a falta de fôlego, ou necessidade de parar para respirar quando anda no seu passo normal.

"Eu ando mais devagar que as restantes pessoas devido à falta de ar, ou tenho de parar para respirar quando ando no meu passo normal". ☐

GRAU 3
Paragens para respirar de 100 em 100 metros ou após andar alguns minutos seguidos.

"Eu paro para respirar depois de andar 100 metros ou passados alguns minutos". ☐

GRAU 4 Demasiado cansado/a ou sem fôlego para sair de casa, vestir ou despir.
"Estou sem fôlego para sair de casa". ☐

Appendix IV COPD Assessment Test (CAT)[16]

COPD Assessment Test (CAT)[16]