Association between measurements of functionining and multidimensional severity indexes in COPD

Associação entre medidas de funcionalidade e índices multidimensionais de gravidade em DPOC

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Resumo

Introdução: A Doença Pulmonar Obstrutiva Crônica (DPOC) desenvolve-se como uma afecção multifacetada e complexa, com manifestações clínicas e funcionais bastante variadas. Objetivo: Verificar a relação entre as variáveis funcionais e três formas de medir a gravidade da doença e do grau de risco para a saúde em pacientes com DPOC. Método: Quarenta e cinco pacientes com DPOC estáveis foram incluídos e avaliados, segundo nível de atividade de vida diária pelo *London Chest Activity of Daily Living* (LCADL); nível de incapacidade pelo *World Health Organization Disability Assessment Schedule* 2.0 (WHODAS 2.0); grau de obstrução do fluxo aéreo pelo volume expiratório forçado no primeiro segundo (VEF_1); escore prognóstico BODE (*Body mass index, airway Obstruction, Dyspnea and Exercise capacity*); avaliação combinada de risco em DPOC, segundo GOLD (grupos ABCD por VEF_1, grau de dispneia e histórico de exacerbações). Resultados: Foram encontradas correlações significativas entre LCADL e BODE (r=0,528; p=0,0001) e grupos ABCD (r=0,491; p=0,001), assim como WHODAS 2.0 e BODE (r=0,484; p=0,001) e grupos ABCD (r=0,481; p=0.001). O VEF_1 não se correlacionou com WHODAS 2.0 (r= -0,225, p=0,138), mas, sim, com LCADL (r= -0,314; p=0,036). Diferenças significativas foram encontradas ao comparar o LCADL e o WHODAS 2.0, entre os grupos, utilizando as três formas de estratificação de gravidade. Conclusões: Pacientes com DPOC apresentam incapacidades, em termos de atividades e participação social, que se correlacionam melhor com os índices multidimensionais de gravidade, mas, de modo pior, no caso do critério espirométrico. A utilidade do uso de instrumentos de medidas de funcionalidade e sua correlação com a avaliação combinada de risco da DPOC necessitam de avaliação em estudos prospectivos.

Palavras-chave: Doença Pulmonar Obstrutiva Crônica; Classificação Internacional de Funcionalidade; Incapacidade e Saúde; Atividades Cotidianas.

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Abstract

Introduction: The Chronic Obstructive Pulmonary Disease (COPD) develops as a multifactorial and complex disorder with highly varied clinical and functional manifestations. Objective: To verify correlations between functional variables and three classifications of disease severity and health risk in COPD patients. Methods: Forty-five stable COPD patients were enrolled in a cross-sectional study that assessed the level of activity of daily living by the London Chest Activity of Daily Living questionnaire (LCADL); disability by the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0); level of airway obstruction by the forced expiratory volume in the first second (FEV_1); assessment of prognostic risk by the BODE index (*Body mass index, airway Obstruction, Dyspnea and Exercise capacity*); GOLD-COPD risk assessment (ABCD groups by FEV_1, dyspnea and history of exacerbations). Results: Significant correlations were found between LCDAL and BODE index (r=0.528; p=0.0001) and ABCD groups (r=0.491; p=0.001) as well as WHODAS 2.0 and BODE index (r=0.484; p=0.001) and ABCD groups (r=0.481; p=0.001). There was a significant negative correlation between FEV_1 and LCADL was observed (r = -0.314; p=0.036), but not between FEV_1 and WHODAS 2.0 (r = -0.225, p=0.138). Significant differences were found when comparing the LCADL and the WHODAS 2.0 between groups using the three classifications of disease severity and health risk. Conclusions: Patients with COPD present disabilities in terms of activities and social participation that correlate better with multidimensional severity indices than severity using spirometry. The usefulness of measurements of functioning and their correlation with the combined assessment of COPD risk requires evaluation in prospective studies.

Keywords: Chronic Obstructive Pulmonary Disease; International Classification of Functioning; Disability and Health; Activities of Daily Living.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. Its impact and manifestations are determined by multiple factors, such as the occurrence of exacerbations and presence of comorbidities[1]. The extra-pulmonary effects, that include malnutrition, peripheral muscle dysfunction and depression, may complicate the clinical condition of these patients[2,3]. The clinical progression of COPD is associated with increase of dyspnea and other symptoms as well as a reduction in the functionality and perception of general health[4]. A variation in functional status and its implications may be found in these individuals[5].

According to the International Classification of Functioning, Disability and Health (ICF), the concept of *functioning* is based on a biopsychosocial model and is dimensioned by a multifactorial overview. This theoretical model assists in the understanding of the functional status of an individual or population, considering structure and body function, performance of daily activities and participation in society, besides contextual characteristics[6].

The scientific literature points out to the failure of pulmonary function variables as parameters to reflect COPD global consequences[7,8], including what has already been shown for functional outcomes[9].

Exacerbations are a key event in COPD since they have been associated with poorer quality of life and increased mortality risk. Besides the severity of airway obstruction (Global Initiative for

Chronic Obstructive Lung Disease – GOLD – I to IV spirometry stages), the history of exacerbations is an independent and good predictor of new exacerbations[10].

It was hypothesized that multidimensional stratification of risk, such as the BODE index or the GOLD ABCD stages, may provide a better prognostic marker for morbidity and mortality in COPD patients, as compared to classifications that use only single outcomes[1]. To the best of authors knowledge, the relationship between the markers of health risk and functioning has been little explored.

Thus, the aim of this study was to correlate functional outcomes, with emphasis on activities and social participation, with three different classifications of disease severity and health risk in patients with COPD. Secondly, comparisons of these indicators of functioning between COPD classifications were undertaken.

Methods

Study design and participants

A cross-sectional study was conducted in the Pulmonary Section of an university hospital, where ambulatory COPD patients were recruited between March 2015 and July 2016. Participants were COPD patients, diagnosed according to GOLD criteria[1], of all severity stages (GOLD stages), confirmed by spirometry in the previous 12 months. They must have had a post-bronchodilator forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) ratio of less than 0.70[1] and a bronchodilator response of less than 12% and 200 ml of FEV_1[11], coupled with absence of clinical history suggestive of asthma. Patients should be clinically stable, without recent hospitalization or exacerbation, at the minimum of 3 months and in a regular clinical follow-up program (at least at every six months) at the time of inclusion[12]. Patients would be excluded if presented musculoskeletal, neurological and peripheral vascular diseases, that might impair significantly mobility and functional limitation, any cognitive impairments that compromise the understanding of the questionnaires including the educational level of respondents using the Mini-Mental cutoffs points[13].

General assessment and multidimensional severity indexes

Patients' personal and clinical information such as age, gender, smoking load, body mass index (BMI) and use of oxygen therapy were collected. The socioeconomic level was assessed using a specific Brazilian economic classification[14], that takes into account the familiar income and considers the following classes: A and B1 = 11,307-6,006 brazilian reais (BRL); B2 = 3,118–6,006 BRL; C1 = 1,865–3,118 BRL; C2 = 1,277–1,865 BRL; D and E = 895–1,277 BRL. The presence of comorbidities was self-reported and determined by the number of diseases associated with COPD, among those recommended by GOLD[1] (coronary artery disease, heart failure, atrial fibrillation, hypertension, osteoporosis, lung cancer, infections, bronchiectasis, diabetes, metabolic syndrome, anxiety and depression). The multidimensional BODE index (*Body mass index, airway Obstruction, Dyspnea and Exercise capacity*), created by Celli *et al.*[15], developed as a predictor of morbidity and mortality, was calculated from four primary variables (BMI, FEV_1, walked distance on the six-minute walk test - 6MWT - and dyspnea scores in the Medical Research Council modified scale - mMRC). 6MWT was performed according to international guidelines[16,17], considering the highest distance walked in a corridor of 26.5 meters, performed within the previous 12 months without acute exacerbations. For

comparisons, it was used the following BODE categories: patients into the stages zero to 2, 3 to 4, 5 to 6 and 7 to 10.

The GOLD COPD combined risk strata (A to D)[1] include three aspects: FEV_1 (stages I – IV); the history of exacerbations in the previous year and the degree of dyspnea from the mMRC. The severity stages I to IV, based on lung function, indicate the strata A and B to the levels I and II, as well as C and D strata for levels III and IV. Milder respiratory symptoms (mMRC 0 or 1) indicate the stages A and C, while worse dyspnea (mMRC 2, 3 or 4) are linked to the strata B and D. None or one exacerbation in the last 12 months are linked to the strata A and B, as well as two or more exacerbations are linked to strata C and D. In case where patients could be classified as more than one possible strata, the worst was chosen.

Functioning measures

The activity and social participation, brought by ICF, were measured by two instruments. The *London Chest Activity of Daily Living* questionnaire (LCADL) was used to assess the degree of limitation of activities of daily living (ADL). This functional scale, developed by Garrod *et al.*[18] and validated to the Portuguese language by Carpes *et al.*[19], assess the ADL according to the areas of personal care, household, physical and leisure activities, resulting in total scores from zero to 75, with worse performance identified by higher scores. In this study, it inferential analyzes were used to the valid total score (in percentage), which eliminates responses in activities that the volunteer does not do for judging it irrelevant or does not have to do it anymore. In parallel, the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) developed in 2010[20,21] and adapted to Brazil in 2013[22] was employed. It evaluates the disability profile according to six domains (cognition, mobility, self-care, living with people, life activities and participation in society). The instrument provides a direct relation to items classified by the ICF model. The scores indicate the difficulty in different situations and range from one to five, with higher scores representative of worse performance. The scores of WHODAS 2.0 were calculated using its own software available for free, in percentages of the total and subscales[21]. The score used for the inferential analysis was the total of 32 items, which covers all areas of the questionnaire and eliminates work and school scores, because most of the sample is not inserted into any of these.

Statistical analysis and ethical aspects

Participants answered the questionnaires in individual sessions conducted by two trained researchers. The inter-examiner reliability was tested by reapplication of the instruments in a new visit after the period of one week, at the same period of the day and location of the first evaluation. This reliability was tested by the Intraclass Correlation Coefficient (ICC)[23] and presented excellent reliability with ICC of 0.942 and 0.992 for measures using LCADL and WHODAS 2.0, respectively.

All eligible patients were informed about the objectives and procedures of the research, as well as about the risks and benefits of it, as specified in the written informed consent term. The study was approved by the Ethics Committee of the Federal University of Minas Gerais (982.803 of 12 Mar 2015).

Results were expressed by descriptive and inferential statistical analysis. Due to non-normal distribution of data in both functional outcomes, the nonparametric Jonckheere-Terpstra was used to compare LCADL and WHODAS 2.0 variables between COPD groups (A to D), grades (I to IV) and BODE categories (α=0,05). Post-hoc pairwise comparisons among the four ABCD groups were

made using the Mann-Whitney test with corrected *p* value by Bonferroni method, being significant at p<0.008. To verify differences in GOLD grades and BODE categories, it was compared milder *versus* more severe stages with p<0.05. Correlations of the scores of LCADL and WHODAS 2.0 with the COPD severity classification (FEV_1, BODE index and stratification ABCD) were done using the Spearman correlation coefficient (α=0.05). Data analysis was performed using the Statistical Package for Social Sciences (SPSS 17.0, Chicago, IL, USA).

Results

General characteristics

Forty-five participants were included, mostly were elderly (mean age of 66.6 ± 8.5 years) and male (60%). The majority of them were classified as GOLD stages II and III (82.3%). The Table 1 provides the sample characteristics.

Tabela 1 | Characteristics of the participants.

Variables	Participants (n = 45)
Age (years)*	66.6 (8.5)
Gender, male (%)	60.0
Socioeconomic level (%)	
A/B1	11.1
B2	11.1
C1	24.4
C2	24.4
D/E	28.9
Smoking load (pack.years)**	45.0 (13.3 – 67.5)
BMI (kg/m^2)*	25.9 (4.0)
FEV$_1$ (% pred)*	48.2 (17.2)
GOLD I-IV stages (%)	
I	4.4
II	35.6
III	46.7
IV	13.3
GOLD ABCD stages (%)	
A	28.9
B	8.9
C	28.9
D	33.3
Comorbidities (%)	
None	33.3
1 or 2	57.8
3 or more	8.9
Oxygen therapy (%)	13.3
COPD exacerbations (%)	
None	75.6
1 or more	24.4
Dyspnea, mMRC (%)	
0	13.3
1	44.4
2	22.2
3	17.8
4	2.2
6MWTD (meters)**	460.80 (378.7 – 509.0)
BODE index (%)	
0 to 2	48.9
3 to 4	35.6
5 to 6	11.1
7 to 10	4.4

Legend: continuous variables presented as *mean (standard deviation) or **median (interquartile range), and categorical variables presented in percentages. BMI = body mass index; FEV1 = forced expiratory volume in the first second; GOLD = Global Initiative for Chronic Obstructive Pulmonary Disease; COPD = *Chronic Obstructive Pulmonary Disease*; mMRC = *Medical Research Council modified Scale*; 6MWTD = walked distance on the six-minute walk test; BODE = the Body mass index, airway Obstruction, Dyspnea and Exercise capacity index.

Correlations

There was a significant linear correlation amongst functional outcomes (LCADL and WHODAS 2.0) and classifications of severity and health risk in COPD, except between WHODAS 2.0 and FEV_1. The direction of the correlation indicated that a worse functioning occured in both more severe GOLD ABCD groups and worse BODE index. These results are depicted in Table 2.

Tabela 2 | Correlations between functional outcomes and classifications of severity in COPD.

| | LCADL | | WHODAS 2.0 | |
	valid total score	*p*	total (32-item)	*p*
ABCD groups	r = 0.491	0.001*	r = 0.481	0.001*
FEV_1	r = - 0.314	0.036*	r = - 0.225	0.138
BODE index	r = 0.528	0.0001*	r = 0.484	0.001*

Legend: COPD = Chronic Obstructive Pulmonary Disease; LCADL = *London Chest Activity of Daily Living questionnaire*; WHODAS 2.0 = *World Health Organization Disability Assessment Schedule*; GOLD = G*lobal Initiative for Chronic Obstructive Pulmonary Disease*; FEV1 = forced expiratory volume in one second; BODE = *the Body mass index, airway Obstruction, Dyspnea and Exercise capacity index*. * significant correlation p < 0,05.

Comparisons

The Table 3 shows the scores of functional outcomes for each group considering the three classifications in COPD patients.

In relation to the four combined risk strata (A to D groups), there were significant differences when comparing the LCADL valid total score (p=0.001) and the WHODAS 2.0 32-item score (p=0.001). In pairwise analysis, significant differences were found between A and B (p=0.003) and A and D groups (p=0.0001) when considering the LCADL, and between A and D (p=0.0001) and C and D groups (p=0.001) in the case of WHODAS 2.0.

In the evaluation of GOLD grades, there were significant differences among the four stages for LCADL (p=0.002) and WHODAS 2.0 (p=0.009). Between I and II *versus* III and IV grades, a significant difference was observed for LCADL (23.60 *vs.* 34.70, respectively; p=0.029), but not for WHODAS 2.0 (10.27 *vs.* 23.40, respectively; p=0.067).

Regarding the BODE categories, there were significant differences among the four strata for LCADL (p=0.005) and for WHODAS 2.0 (p=0.008). Significant differences between categories 0 – 2 and 3 – 4 *versus* 5 – 6 and 7 – 10 were found in LCADL (20.99 *vs.* 33.93, respectively; p=0.016) and in WHODAS 2.0 (20.89 *vs.* 34.43, respectively; p=0.012).

Tabela 3 | Functional outcomes and classification of severity in COPD.

	A (n=13)	B (n=4)	C (n=13)	D (n=15)	p value*
LCADL valid total score	22.7 (20.0 – 27.0)	43.6 (34.6 – 53.2)	27.1 (20.0 – 41.3)	44.0 (30.7 – 52.0)	0.001
WHODAS 2.0 total (32-item)	7.0 (4.9 – 15.1)	31.6 (20.6 – 57.7)	9.3 (3.9 – 19.7)	37.3 (18.8 – 42.2)	0.001
	I (n=2)	**II** (n=16)	**III** (n=21)	**IV** (n=6)	**p value***
LCADL valid total score	21.4 (20.0 – X)	24.8 (20.4 – 33.0)	33.3 (21.6 – 41.6)	49.4 (40.3 – 59.7)	0.002
WHODAS 2.0 total (32-item)	12.6 (3.3 – X)	10.3 (5.3 – 22.9)	16.0 (7.8 – 33.0)	41.8 (21.6 – 46.2)	0.009
	0 to 2 (n=22)	**3 to 4** (n=16)	**5 to 6** (n=5)	**7 to 10** (n=2)	**p value***
LCADL valid total score	23.8 (20.0 – 34.6)	33.8 (21.8 – 46.0)	44.0 (26.2 – 52.0)	54.7 (46.7 – X)	0.005
WHODAS 2.0 total (32-item)	10.3 (5.6 – 22.4)	17.2 (7.5 – 38.8)	35.2 (17.1 – 39.3)	43.7 (42.2 – X)	0.008

Legend: data presented as median (interquartile range). "X" represents the absence of the value. COPD = Chronic Obstructive Pulmonary Disease; LCADL = *London Chest Activity of Daily Living questionnaire*; WHODAS 2.0 = *World Health Organization Disability Assessment Schedule*; BODE =*the Body mass index, airway Obstruction, Dyspnea and Exercise capacity index*. *p values indicate between groups comparisons for each dependent variable.

Discussion

The results of this study suggest that functioning, with emphasis on activities and participation, correlates with the GOLD combined risk in COPD patients. Additionally, the correlations between BODE index and GOLD ABCD groups were stronger with functional outcomes than with classification using spirometry. When comparing functioning between ABCD strata, differences among these groups were clearly influenced by severity of symptoms.

A longitudinal study involving 6,628 COPD patients, that aimed to investigate the abilities of the combined assessment risk in the prediction of their clinical course, showed that GOLD A to D groups are better predictors of exacerbations than the GOLD I to IV stages. Group B patients, the more symptomatic group, had significantly poorer survival than patients in C in spite of having

higher FEV$_1$. The degree of dyspnea, as it was found in the present study, has been reported as a strong predictor of poor survival in COPD[24].

Boland et al.[25] conducted a cross-sectional study with 601 COPD patients and analyzed the potential association of GOLD combined risk assessment with health-related quality of life. This risk assessment was more strongly associated with disease-specific and generic quality of life measures than GOLD spirometry grades. The present study points to the same direction if the proximity between functioning and quality of life, its determinants and consequences, are taken into account.

Barusso et al.[26] evaluated ADL limitations and quality of life in 44 COPD patients. Similar to our results, they reported significant differences for LCADL among ABCD groups, with higher overall percentage score in groups B and D compared to group A. The subjects in the more symptomatic groups (B and D) had poorer quality of life measured by Saint George Respiratory Questionnaire (SGRQ). On the other hand, there was no association between the COPD ABCD groups and the presence of oxygen desaturation and dyspnea during ADL simulation test. However, this last finding could have been influenced by the small number of individuals in each ABCD strata, especially in B and C groups, what precluded the finding of a real significant difference.

The ABCD stratification for COPD patients was determined using different methods to assess symptoms. Kim et al.[27] ranked 257 COPD individuals and demonstrated that distribution in stages are different when using mMRC or COPD Assessment Test (CAT) with kappa agreement coefficient of only 0.510. In a different study, Casanova et al.[28] found also distinct distribution of ABCD groups in 828 COPD patients when using mMRC, CAT and Clinical COPD Questionnaire. These reports may suggest that only one instrument (mMRC or CAT) is enough for classification and that any change in method of evaluation of symptoms may alter the final ABCD stratification.

Our results corroborate other findings in the literature about the relationship between BODE index and functional outcomes. Sarkar et al.[29] found that BODE index is a better predictor of the health status than GOLD I to IV grades including sections of activity and psychosocial impact of SGRQ. Simon et al.[30] found a significant association between ADL limitation (valid total score of LCADL) and BODE index in 39 moderate to severe COPD patients ($r=0.65$ and $p<0.05$). Three of the four variables that compose this multidimensional index presented significant correlation, except the Body Mass Index. On the other hand, Mantoani et al.[31] assessed the association between the BODE index and the level of physical activity in daily life activities in 67 COPD patients. Unlike the use of questionnaire to assess ADL, which was used in the present study, the authors used activity monitors. Modest correlations between the BODE index and the time spent walking per day, the total daily energy expenditure and the time spent in moderate and vigorous activities per day were found ($-0.32 \leq r \leq -0.47$; $p \leq 0.01$). A significant association was observed between mild-to-moderate and severe-to-very severe COPD patients in relation to the walking time per day, the total daily energy expenditure and the time spent in moderate activities per day ($p<0.05$).

Moreira et al.[32] conducted a study with ninety COPD patients and found that GOLD B-C-D groups had a weak correlation with the LCADL ($r=0.26$; $p=0.01$) and no correlation was detected with the GOLD II-III-IV grades ($r=0.04$; $p=0.68$). In this sample, these two classifications were better associated with exercise capacity (6MWT) than with subjectively assessed ADL. Different from our work that considered the valid total score, authors considered the total score of LCADL, and the sample did not include patients in GOLD I- and A classifications. Besides, volunteers seem to have worse lung function compared with our sample (FEV$_1$ 39 ± 14 vs. 48 ± 17 % predicted).

A study with 119 COPD patients described their functioning according to the ICF framework. In general, functional categories at different stages of COPD (I to IV) were found to be similar, although the grade of airflow limitation was significantly associated with the presence and extent of some specific impairments[33]. These findings reinforce the relevance, but also the insufficiency of COPD severity staging in a perspective of functioning and rehabilitation.

This study has some limitations that must be pointed out. Firstly, the history of clinical exacerbations of each patient was obtained from patient's self-reporting. Besides the recall bias, this data may have been influenced by unclear definitions of exacerbations, especially the milder ones. Secondly, data of lung function test and 6MWT were obtained retrospectively in the last year. Despite the absence of acute exacerbations between the date of tests performance and the cross-sectional evaluation of the study, changes in these variables may not be discarded in that period of time. Thirdly, it was identified a lack of power in some pairwise comparisons, mainly in the case of group B (n=4), more severe categories of BODE index and GOLD I (n=2) and IV grades (n=6).

Conclusions

Our findings showed that multidimensional stratifications of severity and health risk seem to be more appropriate, especially when considering COPD functioning. This study reinforces the idea of insufficiency of spirometry grading to predict functional outcomes. Further studies are required to confirm these results using other variables of functioning and different statistical methods.

References

1. Global Initiative for Chronic Obstructive Pulmonary Disease. Global Strategy for the diagnosis, management, and prevention of COPD (Update 2017) [Internet]. Available from: http://www.goldcopd org.

2. Choudhury G, Rabinovich R, MacNee W. Comorbidities and systemic effects of chronic obstructive pulmonary disease. Clin Chest Med. 2014 Mar;35(1):101-30.

3. Sin DD, Man SF. Systemic inflammation and mortality in chronic obstructive pulmonary disease. Can J Physiol Pharmacol. 2007 Jan;85(1):141-7.

4. Park SK, Larson JL. Multiple symptoms, functioning, and general health perception in people with severe COPD over time. Appl Nurs Res. 2016 Feb;29:76-82.

5. Downs CA. Functional assessment of chronic obstructive pulmonary disease. J Am Acad Nurse Pract. 2011 Apr;23(4):161-7.

6. World Health Organization. International classification of functioning, disability and health: ICF. Geneva: WHO; 2001.

7. van der Molen T, Miravitlles M, Kocks JW. COPD management: role of symptom assessment in routine clinical practice. Int J Chron Obstruct Pulmon Dis. 2013;8:461-71.

8. Verhage TL, Heijdra YF, Molema J, Daudey L, Dekhuijzen PN, Vercoulen JH. Adequate Patient Characterization in COPD: Reasons to Go Beyond GOLD Classification. Open Respir Med J. 2009 Feb 13;3:1-9.

9. Athayde FT, Vieira DS, Britto RR, Parreira VF. Functional outcomes in patients with chronic obstructive pulmonary disease: a multivariate analysis. Braz J Phys Ther. 2014 Jan-Feb;18(1):63-71.

10. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010 Sep 16;363(12):1128-38.

11. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R et al. Interpretative strategies for lung function tests. Eur Respir J. 2005 Nov;26(5):948-68.

12. Takabatake N, Nakamura H, Abe S, Inoue S, Hino T, Saito H et al. The relationship between chronic hypoxemia and activation of the tumor necrosis factor-alpha system in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000 Apr;161(4 Pt 1):1179-84.

13. Brucki SM, Nitrini R, Caramelli P, Bertolucci PH, Okamoto IH. Suggestions for utilization of the mini-mental state examination in Brazil. Arq Neuropsiquiatr. 2003 Sep;61(3B):777-81.

14. Associação Brasileira de Empresas de Pesquisa. Critério de Classificação Econômica Brasil 2012. São Paulo: ABEP; 2012. 4 p. Available from: http://www.abep.org.

15. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004 Mar 4;350(10):1005-12.

16. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-7.

17. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014 Dec;44(6):1428-46.

18. Garrod R, Bestall JC, Paul EA, Wedzicha JA, Jones PW. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London Chest Activity of Daily Living scale (LCADL). Respir Med. 2000Jun;94(6):589-96.

19. Carpes MF, Mayer AF, Simon KM, Jardim JR, Garrod R. The Brazilian Portuguese version of the London Chest Activity of Daily Living scale for use in patients with chronic obstructive pulmonary disease. J Bras Pneumol. 2008 Mar;34(3):143-51.

20. Ustün TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J et al. Developing the World Health Organization Disability Assessment Schedule 2.0. Bull World Health Organ. 2010 Nov 1;88(11):815-23.

21. World Health Organization. Measuring Health and Disability: Manual for WHO Disability Assessment Schedule (WHODAS 2.0). Geneva: WHO; 2010. 152 p. Available from: http://www.who.int/en/

22. Silveira C, Parpinelli MA, Pacagnella RC, Camargo RS, Costa ML, Zanardi DM et al. Cross-cultural adaptation of the World Health Organization Disability Assessment Schedule (WHODAS 2.0) into Portuguese. Rev Assoc Med Bras. 2013 May-Jun;59(3):234-40. Available from: http://dx.doi.org/10.1016/j.ramb.2012.11.005

23. Portney LG, Watkins MP. Foundations of Clinical Research: Applications to Practice. 3rd ed. New Jersey: Prentice Hall; 2009. 892 p.

24. Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. Am J Respir Crit Care Med. 2012 Nov 15;186(10):975-81.

25. Boland MR, Tsiachristas A, Kruis AL, Chavannes NH, Rutten-van Mölken MP. Are GOLD ABCD groups better associated with health status and costs than GOLD 1234 grades? A cross-sectional study. Prim Care Respir J. 2014 Mar;23(1):30-7.

26. Barusso M, Gianjoppe-Santos J, Basso-Vanelli RP, Regueiro EM, Panin JC, Di Lorenzo VA. Limitation of Activities of Daily Living and Quality of Life Based on COPD Combined Classification. Respir Care. 2015 Mar;60(3):388-98.

27. 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 analysis. BMC Pulm Med. 2013 Jun 3;13:35.

28. 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 Jan 13;15:3.

29. Sarkar SK, Basuthakur S, Das SK, Das A, Das S, Choudhury S et al. Evaluation of correlation of BODE index with health-related quality of life among patients with stable COPD attending a tertiary care hospital. Lung India. 2015 Jan-Feb;32(1):24-8.

30. Simon KM, Carpes MF, Corrêa KS, dos Santos K, Karloh M, Mayer AF. Relationship between daily living activities (ADL) limitation and the BODE index in patients with chronic obstructive pulmonary disease. Rev Bras Fisioter. 2011 May-Jun;15(3):212-8.

31. Mantoani LC, Hernandes NA, Guimarães MM, Vitorasso RL, Probst VS, Pitta F. Does the BODE index reflect the level of physical activity in daily life in patients with COPD? Rev Bras Fisioter. 2011 Mar-Apr;15(2):131-7.

32. Moreira GL, Donária L, Furlanetto KC, Paes T, Sant'Anna T, Hernandes NA et al. GOLD B-C-D groups or GOLD II-III-IV grades: Which one better reflects the functionality of patients with chronic obstructive pulmonary disease? Chron Respir Dis. 2015 May;12(2):102-10.

33. Jácome C, Marques A, Gabriel R, Figueiredo D. Chronic obstructive pulmonary disease and functioning: implications for rehabilitation based on the ICF framework. Disabil Rehabil. 2013 Aug;35(18):1534-45.