



Pulmonary function and functional capacity cut-off point to establish sarcopenia and dynapenia in patients with COPD

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ABSTRACT

Objective: To establish a cut-off point for clinical and functional variables to determinate sarcopenia and dynapenia in COPD patients, and to analyze the impact of skeletal muscle dysfunction (SMD) on these variables. **Methods:** Cross-sectional study, screened COPD patients for sarcopenia or dynapenia through low muscle mass and hand grip strength (HGS). Clinical variables: pulmonary function, respiratory muscle strength and functional capacity (FC). The precision of the variables in determining points of predictive cut-off for sarcopenia or dynapenia were performed using the Receiver Operating Characteristic curve and two-way analysis of variance. **Results:** 20 COPD patients stratified for sarcopenia (n = 11) and dynapenia (n = 07). Sarcopenia group presented lower lean mass and lower maximal inspiratory pressure (MIP), decreased HGS, reduced FC (p<0.050). Dynapenia group presented reduced MIP, lower HGS and walked a shorter distance at Incremental shuttle walk test (ISWT) (p<0.050). We found cut-off points of forced expiratory volume in one second (FEV₁), MIP and maximal expiratory pressure (MEP) and ISWT. It is possible to identify sarcopenia or dynapenia in these patients. We found the coexistence of the conditions (SMD effect) in COPD – reduction in the distance in the ISWT (p = 0.002) and %ISWT (p = 0.017). **Conclusion:** In moderate to very severe COPD patients the sarcopenia could be predicted by FEV₁ (%predicted) < 52, MIP < 73 cmH₂O, MEP < 126 cmH₂O and distance traveled of < 295 m in ISWT. Whereas dynapenia could be predicted by FEV₁ < 40%, MIP < 71 cmH₂O, MEP < 110 cmH₂O and distance of < 230 m traveled in ISWT.

Keywords: Sarcopenia; Chronic obstructive pulmonary disease; Musculoskeletal system.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by a persistent airflow limitation initially associated with abnormal inflammatory response in the airways and lungs.⁽¹⁾ Secondarily, its progression reflects on multisystemic symptoms and the presence of comorbidities such as skeletal muscle dysfunctions (SMD), obstructive sleep apnea, cardiovascular disease, metabolic syndrome, osteoporosis, mental disorders and lung cancer.^(2,3) Systematic inflammation in COPD increases the presence of inflammatory mediators on bloodstream, promoting oxidative stress, consequently resulting on protein degradation, causing SMD.⁽⁴⁻⁶⁾ Nutritional imbalance and hypoxemia are also potential contributors for this condition, which results in a poor prognosis independent of lung function.⁽⁷⁾

SMD is composed by peripheral muscle weakness, a shift from type I and II to a higher presence of type II

fibers and muscular atrophy. COPD patients usually have decreased tolerance to physical exercise and difficulties in performing activities of daily living. Hence studying skeletal muscle function, structure and its dysfunction in this population is important because its repercussions bring to low exercise performance, poor health status and premature mortality.^(7,8)

Age-related loss of muscle strength is known as dynapenia,⁽⁹⁾ which leads to functional impairment of the skeletal muscle system and is associated with diminished physical performance.⁽¹⁰⁾ Loss of skeletal muscle mass is referred as sarcopenia⁽¹¹⁾ and its etiology could have genetic, physiological, and environmental factors.⁽¹²⁾ It is noteworthy that there is no global consensus on the term sarcopenia.⁽¹³⁾ Both conditions are linked to reduction in muscle performance leading to exercise intolerance and sedentary behaviors.⁽¹⁴⁾ It is already known that sarcopenia could coexist with

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other disorders,⁽¹⁵⁾ but the presence and prevalence of the overlapping between dynapenia and sarcopenia is still unknown.

The prevalence of sarcopenia in stable COPD patients is around 15%, which increased with age and GOLD stages.⁽¹⁶⁾ The prevalence of dynapenia in COPD patients needs to be investigated. It is important to emphasize that COPD is characterized by two different phenotypes that have their own particularities, which we should take in account when thinking on how much sarcopenia and dynapenia are related to these phenotypes.⁽¹⁷⁾ Therefore, our aim was to establish a cut-off point for clinical and functional variables to determinate sarcopenia and dynapenia in COPD patients and to analyze the impact of skeletal muscle dysfunction on the evaluated variables. We hypothesized that in COPD patients, sarcopenia and dynapenia could be predicted by reduced functional capacity, respiratory muscle strength and airway obstruction.

METHODS

Study design

This was a cross-sectional study performed on a convenience non-probability sample, conducted in the Santa Cruz Hospital's Cardiorespiratory Rehabilitation Program (Santa Cruz do Sul, RS, Brazil). The sample of our study was constituted of patients who attend the pneumology outpatient clinic of the Santa Cruz Hospital for follow-up and treatment of their conditions and were requested to join the Cardiorespiratory Rehabilitation Program through the pulmonologist or general practitioner referral. The Research was approved by the Research Ethics Committee of University of Santa Cruz do Sul, protocol n. 1.514.705. All volunteers signed an informed consent statement prior to participation.

Subjects and selection

Subjects with clinical diagnosis of COPD confirmed by pulmonary function test, adequate cognition, no disease exacerbation 30 days prior to the study who signed the informed consent statement were included in the study. The exclusion criteria were musculoskeletal or neurological disorders that affected the locomotor system in such a way that would impede participation in the research protocol, clinical diagnosis of lung cancer, current alcoholism, arrhythmias, uncontrolled metabolic disease, or electrocardiogram alterations.

Measurements

The research was conducted in an acclimated laboratory at a temperature of 22 °C and relative humidity between 50% and 60%, during the morning (between 8 a.m. to 12 a.m.). Subject's clinical characteristics were reviewed and recorded including age, sex, height, weight and medications used.

Dynapenia screening

Hand-grip strength (HGS) was measured to evaluate muscle strength (Jamar Hydraulic Dynamometer, Bolingbrook, IL, USA). To perform the maneuver, volunteers were sitting on a standard height chair without armrest with their shoulder adducted, elbow flexed at 90°, forearm in neutral position, and wrists with 15° extension.⁽¹⁸⁾ Participants were asked to grasp the dynamometer at their maximal power. Three attempts on both hands were performed with a one-minute rest between each of them. The mean value of each hand was used in the analysis. We considered dynapenia when our patients presented cut-off values of < 30 kg/f for men and < 20 kg/f for women.⁽¹⁹⁾

Sarcopenia screening

The skeletal muscle mass was assessed by the appendicular skeletal muscle mass (ASM) and defined skeletal muscle mass index (SMI) as ASM/height² (kg/m²).⁽²⁰⁾ Sarcopenia was diagnosed according to the criteria proposed by the European Working Group for Sarcopenia in Older People.⁽¹¹⁾ Were considered sarcopenic those patients with low muscle mass defined as SMI below 7.26 kg/m² for men and below 5.45 kg/m² for women.⁽¹¹⁾

To evaluate the lean mass, patients' body composition was assessed by means of electrical bioimpedance with Biodynamics® (model 420, international version 5.1). The exam was performed according to the National Institutes of Health Technology Assessment Conference statement.⁽²¹⁾

Pulmonary function test

To assess pulmonary function a digital spirometer (Microloop®, MK8, Care Fusion, Hoechberg, Germany) was used. The test was performed in accordance to the American Thoracic Society recommendations,⁽²²⁾ and the results were interpreted according to the values predicted by Pereira et al.⁽²³⁾ The variables analyzed were: forced expiratory volume in 1 s (FEV₁), and the FEV₁/FVC ratio. Airflow limitation was categorized in agreement to the Global Initiative for Chronic Obstructive Lung Disease 2018 recommendations, where patients were classified as mild (GOLD I), moderate (GOLD II), severe (GOLD III), or very severe (GOLD IV).⁽¹⁾

Respiratory muscle strength

Respiratory muscle strength (RMS) was evaluated through digital manometer (MDI®, MVD300, Porto Alegre, Brazil), where we obtained measures of the maximum inspiratory pressure (MIP) and the maximum expiratory pressure (MEP). MIP was obtained after the individual expired to the residual volume and carried out the inspiration until total lung capacity. For the measurement of the MEP, the patient underwent an inspiration to total lung capacity, expiring until the residual volume. The values were later compared with those described in the literature for Brazilian population⁽²⁴⁾ and expressed as a percentage of predicted values.

Respiratory muscle weakness was determined for a MIP of < 60 cmH₂O.⁽²⁵⁾

Functional capacity

The incremental shuttle walking test (ISWT) aims to assess one's performance considering the individuals' limiting symptoms used to evaluate functional capacity as described in Singh et al.⁽²⁶⁾ The test has 12 stages with one minute each, with initial velocity of 0.5 m/s, with each minute being added 0.17 m/s (equivalent to 10 m/min). There was provided a standardized verbal command at the end of each stage to inform the individual of increasing walking speed. The walking speed is determined by two distinct types of beeps: a single beep indicating a change of direction, and a triple (beep) signal that indicates a change of direction and stage. The percentage of the predicted walked distance ISWT (% predicted) was calculated considering sex, age, height and weight of each patient according to Dourado et al.⁽²⁷⁾

Statistical analyses

Data were analyzed using the Sigmaplot® statistical package (version 11.0, Systat Software Inc., San Jose, CA, USA). Data were tested for normality through the Shapiro-Wilk test and presented descriptively as mean and STD (parametric) or as median and minimum and maximum interval (non-parametric). The analyses between the groups were performed through Student T test or Mann Whitney.

The precision of the clinical variables, pulmonary function (FEV₁ % predicted), respiratory muscle strength (MIP) and functional capacity (ISWT) in determining points of predictive cut-off sarcopenia and dynapenia were performed using the Receiver Operating Characteristic (ROC) curves.⁽²⁸⁾ The total area under the ROC curve was determined between FEV₁ (% predicted), MIP, ISWT, and sarcopenia and dynapenia indexes. The greater area under the ROC curve represented greater discriminatory power of clinical variables to establish sarcopenia or dynapenia in individuals with COPD.⁽²⁹⁾ The 95% confidence interval (95% CI) was used to determine the ability of the clinical variables to predict sarcopenia and dynapenia, with the lower limit being greater than 0.50.⁽²⁴⁾ Subsequently, the cut-off points of the clinical variables that obtained significant areas under the ROC curve, with the respective values of sensitivity and specificity, balanced among themselves. Values lower than 60% were identified.

The results were compared using two-way analysis of variance on ranks with post-hoc Bonferroni, in order to identify statistically significant differences in: (i) functional capacity; and (ii) pulmonary function. For these analyses, subjects were categorized according to SMD effect (dynapenia vs sarcopenia) and Non SMD effect (non dynapenia vs non sarcopenia). Residuals were evaluated under the assumptions of normality, constant variance, and independence. $P \leq 0.05$ was considered significant.

RESULTS

A total of 20 subjects were enrolled in the study. Of them, 11 were stratified with sarcopenia, 7 with dynapenia and 7 with overlapping between the conditions. In COPD patients with sarcopenia there were found lower lean mass and lower MIP, decreased HGS and reduced functional capacity than non-sarcopenia group. The patients with dynapenia presented reduced MIP, lower HGS and walked a shorter distance in the ISWT, when compared with non-dynapenia group (Table 1). There were no significant differences of the groups for age, BMI, pulmonary function, GOLD stages and MEP. It is important to highlight that we did not find any significant difference between overlapping and dynapenia and sarcopenia groups in isolation.

The cut-off points, the areas under the ROC curve and 95% CI of clinical variables, as well as the sensitivity and specificity of the clinical variables as predictors of sarcopenia and dynapenia are showed in Table 2. According to the prediction model, FEV₁ < 52%, MIP < 73 cmH₂O, MEP < 126 cmH₂O identified sarcopenia in these patients and FEV₁ < 40%, MIP < 71 cmH₂O, MEP < 110 cmH₂O identified dynapenia. The distance walked on the ISWT was significantly able to determine the presence of sarcopenia and dynapenia in patients with COPD, with walked distance of 295 and 230 m respectively. There was established as cut-off point according to the adopted sensitivity and specificity.

When applying two-way ANOVA, there was found that COPD patients with dynapenia and sarcopenia (SMD effect) presented a reduction in the distance walked in the ISWT ($p = 0.002$) and the %ISWT ($p = 0.017$) (Figure 1), demonstrating the impact of SMD on the functional capacity of these patients. We emphasize that there were not significant results for FEV₁.

DISCUSSION

COPD patients with sarcopenia or dynapenia present reduced inspiratory muscular strength, handgrip strength and distance walked in the ISWT. COPD patients with sarcopenia also presented a reduction in lean mass. According to ROC curve, it was possible to establish that COPD patients with FEV₁ (%pred) < 52%, MIP < 73 cmH₂O, MEP < 126 cmH₂O identified sarcopenia; and FEV₁ < 40%, MIP < 71 cmH₂O, MEP < 110 cmH₂O identified dynapenia. Furthermore, a distance walked in the ISWT of 295 and 230 m can determine sarcopenia or dynapenia, respectively.

SMD is associated with diminished physical performance and functional capacity. Moreover, skeletal muscle impairment could provoke physiological, metabolic and functional repercussions.^(30,31) In COPD patients, the SMD affects both ventilatory and non-ventilatory muscle groups, contributing to greater energy expenditure for the individual to execute his activities of daily living, it also leads to decreased quality of life and the aftermath is a poor prognosis.⁽³⁾ Our study is in congruence with these findings, where we found an impact on handgrip and respiratory muscle strength

Table 1. COPD patients' clinical characteristics stratified by sarcopenia and dynapenia.

Variables	Non-Dynapenia (n = 13)	Non-Sarcopenia (n = 9)	Dynapenia (n = 7)	Sarcopenia (n = 11)	Dynapenia + Sarcopenia (n = 7)	P#	P*
Age (years)	65.0±4.0	65.6±5.1	66.5±4.1	65.7±5.0	65.0±5.3	0.34	0.98
Sex, Male n (%)	11 (84.6)	6 (66.6)	4 (57.1)	10 (90.9)	5 (71.4)	0.30	0.26
Height (cm)	1.5±0.1	1.6±0.1	1.6±0.3	1.6±0.1	1.6±0.1	0.85	0.86
BMI (Kg/m ²)	26.0±6.6	25.7±5.6	24.6±4.9	25.5±6.6	25.9±3.4	0.48	0.73
Lean Mass (Kg)	43.9±15.0	53.9±12.8	37.8±6.6	34.2±6.9	30.1±5.3	0.02	0.20
Spirometrics							
FEV ₁ (L/s)	1.1±0.7	1.2±0.6	0.9±0.1	0.9±0.4	1.0±0.5	0.09	0.53
FEV ₁ (%predicted)	38.3±24.1	44.8±23.6	37.6±11.0	33.6±18.3	39.1±18	0.10	0.88
FEV ₁ /FVC (L/s)	0.50±0.16	0.53±0.19	0.44±0.13	0.44±0.11	0.44±0.13	0.26	0.44
FEV ₁ /FVC (%predicted)	64.4±23.6	68.8±28.2	56.7±17.1	57.3±16.0	56.7±17.1	0.26	0.42
Staging (GOLD) COPD, n (%)						0.60	0.35
Stage II	5 (38.4)	4 (44.4)	1 (14.2)	2 (18.1)	1 (14.3)		
Stage III	4 (30.7)	2 (22.2)	4 (57.1)	4 (36.3)	4 (57.1)		
Stage IV	4 (30.7)	3 (33.3)	2 (28.5)	5 (45.4)	2 (28.6)		
Respiratory muscle strength							
MIP (cmH ₂ O)	78.2±27.6	82.3±18.0	52.1±21.8	62.4±31.4	67.5±27.1	0.04	0.03
MIP (% predicted)	79.5±29.1	86.0±18.2	55.9±24.9	63.3±30.6	70.5±28.5	0.20	0.73
MEP (cmH ₂ O)	114.8±43.6	124.1±32.5	89.1±33.1	95.8±44.5	101.8±32.5	0.15	0.26
MEP (% predicted)	106.3±36.0	121.2±26.7	90.2±34.8	88.3±35.2	95.1±18.5	0.10	0.35
Inspiratory Muscle Weakness (MIP < 60 cmH₂O), n (%)						0.06	0.04
Yes	1 (7.6)	1 (11.1)	5 (71.5)	7 (63.7)	5 (71.4)		
No	12 (92.4)	8 (88.9)	2 (28.5)	4 (36.3)	2 (28.6)		
Hand Grip Strength							
Hand Grip (kg/f)	39.2±10.0	37.7±12.9	21.0±5.1	31.1±11.3	22.3±5.4	0.04	<0.01
Functional capacity							
ISWT (m)	326.1±77.5	347.5±57.7	251.6±77.8	270.0±86.0	215.7±118.7	0.02	0.03
ISWT (% predicted)	47.9±16.0	55.4±13.3	38.3±9.3	37.2±10.7	33.9±16.9	0.05	0.16

Data are presented as mean ± standard deviation; n (%): number of patients (% of sample size); P# < 0.050 between sarcopenia vs no sarcopenia; P* < 0.050 between dynapenia vs non dynapenia; COPD: Chronic Obstructive Pulmonary Disease; BMI: body mass index; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Lung Disease; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; ISWT: incremental shuttle walking test.

Table 2. Cut-off values, sensitivity and specificity of variable clinics with prediction of sarcopenia and dynapenia in COPD patients.

Variables	Sarcopenia (n = 20)				Dynapenia (n = 20)			
	Cut-off	Sensitivity	Specificity	AUC [Interval Confidence 95%]	Cut-off	Sensitivity	Specificity	AUC [Interval Confidence 95%]
Spirometrics								
FEV ₁ (L/s)	1.0	75	71	0.726 [0.477-0.902]	0.97	57	50	0.580 [0.336-0.798]
FEV ₁ (% predicted)	0.52	83	57	0.738 [0.489-0.909]	0.40	57	41	0.580 [0.336-0.798]
Respiratory muscle strength								
MIP (cm H ₂ O)	73	66	85	0.696 [0.447-0.882]	71	62	72	0.545 [0.305-0.771]
MIP (% predicted)	70	66	85	0.690 [0.441-0.878]	70	71	67	0.534 [0.295-0.762]
MEP (cm H ₂ O)	126	58	43	0.649 [0.400-0.850]	110	50	72	0.597 [0.351-0.811]
MEP (% predicted)	100	66	85	0.750 [0.502-0.917]	101	75	72	0.659 [0.410-0.857]
Functional capacity								
ISWT (m)	295	66	85	0.774 [0.527-0.931]	230	71	80	0.855 [0.592-0.977]
ISWT (% predicted)	45	75	71	0.774 [0.527-0.931]	45	71	58	0.532 [0.288-0.766]

COPD: Chronic Obstructive Pulmonary Disease; AUC: Area under curve; FEV₁: forced expiratory volume in 1 s; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; m: meters; n: number of patients; ISWT: incremental shuttle walk test. Statistical significance p < 0.05.

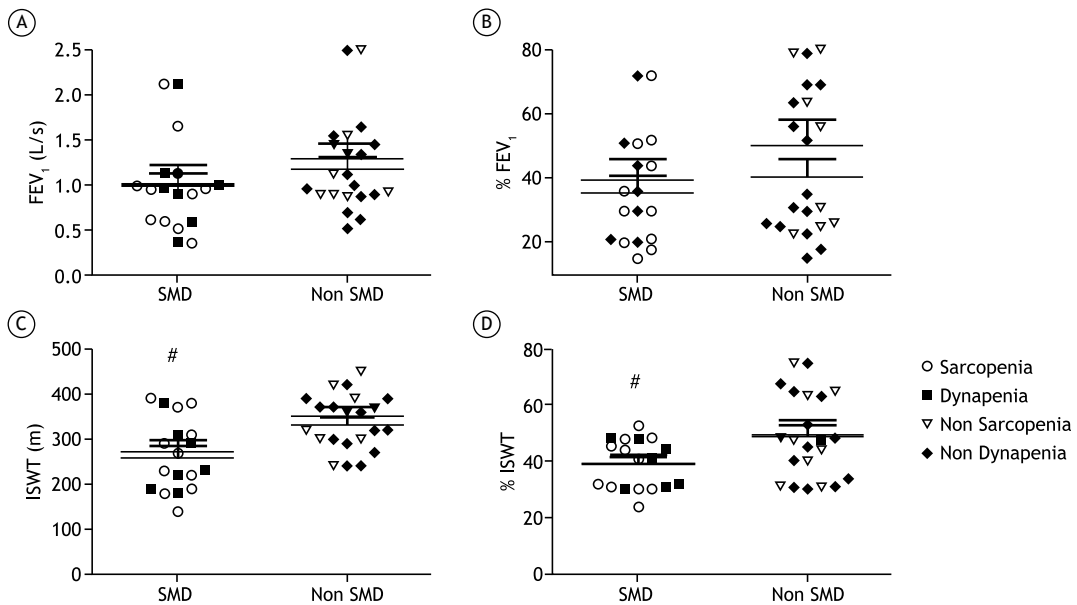


Figure 1. Comparison of functional capacity and FEV_1 in COPD patients with MSD and without MSD. # $p < 0.050$ for MSD. FEV_1 : forced expiratory volume in one second; ISWT: Incremental shuttle walk test; MSD: muscular skeletal dysfunction. (A) Comparison between FEV_1 (L/s) of MSD and non-MSD groups; (B) Comparison between % FEV_1 of MSD and non-MSD groups; (C) Comparison between ISWT (m) of MSD and non-MSD groups; (D) Comparison between % ISWT of MSD and non-MSD groups.

as well as in functional capacity on both patients with sarcopenia or dynapenia.

SMD pathophysiology is complex and involves fiber damage and catabolic events that worsen with ageing and the presence of comorbidities.⁽³⁰⁾ Byun et al.⁽⁴⁾ found correlation between sarcopenia, old age, low body mass index, presence of comorbidities and systemic inflammation in COPD patients. Therefore, considering that our sample was composed by elderly subjects, we can hypothesize that muscle wasting in our patients was due to natural physiological reasons, like an imbalance between muscle protein synthesis and muscle protein breakdown and changes associated with COPD consequences, such as chronic inflammation and functional decline. It is important to emphasize that the loss of 1% of lean mass is equivalent to a reduction of 3% in muscle strength in elderly, something that could have an impact on one's functionality.⁽²⁷⁾

Sarcopenia and dynapenia are two conditions related to muscle mass and its function, and for identifying them there are several methods that could be used. Bone et al.,⁽³¹⁾ in a review paper, listed handgrip strength and low gait speed as instruments for defining sarcopenia. Handgrip measurement has the advantage of being simple and easy and sometimes used as an index of muscular strength for the whole body. When it comes to muscle mass evaluation we used bioelectrical impedance analysis, considered by Maddocks et al.⁽³²⁾ a more practical tool for this purpose. There are other methods used for muscle mass assessment as seen in Bone et al.,⁽³¹⁾ who cited dual X-ray absorptiometry and computational tomography. Specifically to determinate

dynapenia, Morley et al.⁽³³⁾ mentioned evaluating walking speed, walking distance and stair climbing as screening tools. Whilst for identifying sarcopenia in COPD patients, most studies used Six-minute walk test for functional capacity evaluation, to our knowledge no study has used ISWT for this purpose.⁽³⁴⁻³⁶⁾

To date, there is still no consensus on measurement tools or diagnostic cut-off to determinate these two conditions, but it is known that diagnosis could be done by assessing muscle mass and functional performance.⁽⁵⁾ The diversity of methods available to measure these variables could lead to several cut-off as well underestimate the presence of this condition in COPD patients. We emphasize that this is a relevant and original study where we evaluated sarcopenia and dynapenia in moderate to very severe COPD patients. With a pulmonary function test, through FEV_1 (%pred) < 52 and assessing physical performance by means of ISWT, the distance traveled of < 295 m is able to predict sarcopenia, and a distance in ISWT of < 230 m is able to predict dynapenia.

Our findings are important because they allow clinical practitioners to apply feasible methods to assess sarcopenia and dynapenia on their routine, like a spirometry and a 10 m hall to perform ISWT. Additionally, the results demonstrate that a careful evaluation of these patients is required, as well as a future focus on SMD based mechanisms and its relationship with activity of daily living execution, physical activity levels and quality of life in a COPD population.

Some limitations pointed out are due to our strict inclusion and exclusion criteria, resulting in a number of

subjects that might be considered small. We emphasize that our results should be considered only for patients with COPD. This study is of clinical relevance since SMD in COPD impacts on anatomical, physiological and functional systems. Identifying these conditions could help health care professionals to assess in a feasible and workable way, to understand and treat patients with specifically interventions (e.g multidisciplinary rehabilitation programs), it is already known that physical exercise can reverse sarcopenia in COPD patients and improve the condition in older adults⁽³⁷⁾. Regarding nutritional treatment strategies there is still a lack of specific recommendations.⁽³⁸⁾ Knowing that skeletal muscles perform essential functions for the whole organism, we highlight the importance of early recognition of these disorders for patients'

risk stratification and prevention, which may reduce the development of comorbidities, delay functional decline and improve prognosis in patients with chronic obstructive pulmonary disease.

In conclusion, this study was able to give variables' cut-off points for identifying or predicting sarcopenia and dynapenia in moderate to very severe COPD patients. Moreover, these SMD cause negative impact on the peripheral muscular strength and functional capacity. Sarcopenia could be predicted by FEV_1 (%predicted) < 52, MIP < 73 cmH₂O, MEP < 126 cmH₂O and distance traveled of < 295 m in ISWT. Whereas, dynapenia could be predicted by FEV_1 < 40%, MIP < 71 cmH₂O, MEP < 110 cmH₂O and distance of < 230 m traveled in ISWT.

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