



ISSN: 2320-8090

Available online at <http://www.journalijcst.com>

International Journal of Current Science and Technology
Vol.5, Issue, 8, pp. 489-493, August, 2017

IJCST

RESEARCH ARTICLE

SARCOPENIA PREVALENCE IN COPD PATIENTS-COMPARISON AMONG FOUR DIFFERENT CRITERIA

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ARTICLE INFO

Article History:

Received 19th May, 2017

Received in revised form 10th June, 2017

Accepted 25th July, 2017

Published online 28th August, 2017

Key words:

Body Composition, COPD, Criteria of sarcopenia, FNIH, Sarcopenia

ABSTRACT

To examine the prevalence and the agreement among different diagnosis criteria of pre-sarcopenia and sarcopenia in a population of COPD patients. All patients underwent a DXA body composition exam, and for physical capacity, patients underwent a six-minute walk test. We defined pre-sarcopenia and sarcopenia by four different criteria: Baumgartner, Newman, Mixed, and Foundation for the National Institutes of Health (FNIH). 121 patients were studied. Pre-sarcopenia was observed in 19.8 to 46.3% depending on the criterion, higher with the FNIH criterion. The agreement among the criteria was poor. The positive percent agreements (%PPA) between the FNIH criterion and other criteria were low. However, the negative percent agreement (%NPA) was higher. The prevalence of sarcopenia was 4.9 to 12.4% depending on the criterion, also higher with the FNIH criterion. The agreement among the criteria was fair-to-good. The %PPA between the FNIH criterion and other criteria were higher than in pre-sarcopenia and also the %NPA was very high. In our study, the prevalence of pre-sarcopenia and sarcopenia was greater with the FNIH criterion. The agreement among the methods was better in sarcopenia than in pre-sarcopenia. We suggest that the FNIH criteria would be more suitable for this population of patients.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent condition, affecting up to 10% of adults, with high rates of mortality (1). COPD is associated with several extra-pulmonary disorders. Previous studies indicate an association of lower body mass index (BMI) with shorter survival in these patients. However, more recent data demonstrate that changes in body composition, especially the decrease in lean mass, are more reliable than the unique analysis of BMI. These changes have been shown to be related to low exercise capacity and increased mortality in patients with COPD (2,3).

Pre-sarcopenia is characterized by low muscle mass, and sarcopenia is a severe syndrome characterized by low muscle mass and weakness, which results in impairment of functional capacity and disability in older persons (4). Prevalence of pre-sarcopenia ranges between 20-50% and sarcopenia 1.5-15% among the elderly (5,6). In COPD patients, pre-sarcopenia has been reported in approximately 20-40% and sarcopenia in 10-15% (7,8).

Although the term "sarcopenia" has become widespread, the criteria for an operational definition vary among studies. Initial work on defining sarcopenia was based on measures of muscle mass alone,

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particularly the appendicular skeletal muscle mass (ASM) quantified by dual X-ray absorptiometry (DXA), which is the method officially recommended in clinical practice (6). However, a growing body of research suggests that there is a disconnection between muscle mass and strength. Thus, recent definitions of sarcopenia have incorporated elements of strength and physical performance in addition to muscle mass in the criteria for sarcopenia (9-12).

The purpose of this study was to examine the prevalence and the agreement among four different diagnosis criteria of pre-sarcopenia and sarcopenia in a population of patients with COPD.

METHODS

Subjects

This is part of a cross-sectional study with patients with COPD treated at the Pulmonary Outpatient Clinic of the Hospital de Clinicas at Universidade Federal do Paraná, from 2010 to 2014, where the total body densitometry exam was performed as part of their routine evaluation. All patients signed an informed consent and the study was approved by the Ethics Committee on Human Research of our institution. The inclusion criteria was patients with tobacco-induced COPD, of both sexes and over 50 years old, who had undergone a spirometry exam using a Koko spirometer PFT (nSpire Health (EUA), 2007) and who had been diagnosed with COPD by the spirometry parameter of post-bronchodilator FEV1/FVC <0.70

defined by the Global Initiative for Chronic Obstructive Lung Disease(13). Patients were excluded if they did not have all the required tests, were taking medications, or had another disease known to interfere with body composition

Body mass index (BMI) was determined by weight (kg)/height² (m²) and the group was classified as underweight (BMI < 22 kg/m²), normal weight (BMI 22 and < 27 kg/m²), and overweight/obese (BMI 27 kg/m²), which, according to Lipschitz *et al.*(14), are more suitable measurements for the elderly.

All patients underwent a total body exam assessment of body composition using dual energy x-ray absorptiometry (DXA) on a Lunar Prodigy whole-body scanner (GE Medical Systems, Madison, WI) and Encore 2002 software. The software provides data about lean body mass(bone mass plus fat-free mass), bone-free lean mass (lean mass minus fat-free mass), fat mass, and bone mineral density. For the determination of physical capacity, all patients underwent a six-minute walk test and the gait speed was calculated. Patients with 0.8 m/s were classified as having slow walking speed(4).

Sarcopenia Definitions

We defined pre-sarcopenia as low lean mass, diagnosed by the following four different criteria:

- Baumgartner: RSMI (Relative Skeletal Muscle Index): ALM (appendicular lean mass)/height² were 7.26 kg/m² for men and 5.45 kg/m² for women(5);
- Newman: measurement of relative lean mass derived by adjusting the lean mass for fat mass (in kilograms) in addition to height (in meters). The residuals of the regression were used to identify those individuals whose amount of ALM was lower than expected (obtained by an equation derived from the model) for a given amount of fat mass. A positive residual would indicate a relatively muscular individual, whereas negative values would indicate relatively sarcopenic individuals(15,16). For this study, the equation resultant from the model was as follows: for men, ALM (Kg) = -36.9307 + 32.8261 x height (m) + 0.1181 x fat mass (kg) and for women, ALM (kg) = -20.6479 + 20.7699 x height (m) + 0.1387x fat mass (kg). The 20th percentile of the distribution of residuals was used as the cutoff for the diagnosis of sarcopenia, according to ALM adjusted for fat, as defined by Newman's criterion. This cutoff corresponded to a residual of -2.1924 for men and -1.1713 for women in our population.
- Mixed criterion, based on two recently Brazilian studies that compared both criteria and concluded that the cutoff of BMI (22 kg/m²) defined the choice of the criteria for low lean mass (17,18), Baumgartner were applied to define low lean mass for individuals with BMI < 22 kg/m², and Newman were applied for individuals with BMI 22kg/m².
- Criterion of the Foundation for the National Institutes of Health(FNIH): ALM divided by body size (ALM/BMI) to determine lean mass. Men with ALM/BMI less than 0.789 and women with ALM/BMI less than 0.512 were classified as low lean mass(12).

The diagnosis of sarcopenia was defined by low lean mass plus low performance (gait speed 0.8m/s)(4).

Statistical Analysis

Data are presented as mean ± SD. All analyses were performed using SPSS v.20.0, 2011 IBM software group, Chicago, IL. The condition of normality of variables was evaluated by the Kolmogorov-Smirnov test. The comparison between two groups of quantitative variables was performed considering Student's t test for independent samples or the nonparametric Mann-Whitney test. For the preliminary statistical analysis, we used the Fisher's exact test and the chi-square test to assess the association between two qualitative variables. P-values below 0.05 were considered statistically significant.

Descriptive statistics were examined across sets of criteria. We described the agreement between the criteria by the Cohen's kappa () coefficient calculated by the McNemar test, with confidence intervals of 95%. Kappa () values less than 0.20 are considered poor reliability; between 0.21–0.40, weak reliability; between 0.41-0.60, fair-to-good;between 0.61-0.80, good; and greater than 0.80, excellent reliability. Analogous to a sensitivity estimation, we calculated the positive percent agreement (PPA%): the proportion of participants who were categorized as having the condition by both the FNIH criteria (more actual) and a second set of criteria divided by the number of participants who were categorized as having the condition by the second set of criteria. And similar to a specificity estimation, we calculated the negative percent agreement (NPA%): the proportion of participants who were categorized as not having the condition by both the FNIH criteria and a second set of criteria divided by the number of participants who were categorized as not having the condition by the second set of criteria(6).

RESULTS

From the 126 consecutive patients, 5 were excluded because they did not perform all the required tests of the protocol. Final analysis was carried out in 121 patients (65 women, mean age 67.9 ± 8.6 years, mean BMI 26.5 ± 6.2 kg/m²). Thirty-four patients (28%) had normal weight, 32 (26.4%) were underweight, and 55 (45.5%) were overweight. The average tobacco use was 58.9 ± 40.8years/pack. Twenty-three patients (19.1%) were still smokers at the time of the study evaluation. The percentage of total body fat mass (%TFM) was 33.1% ± 11.4 (38.3% ± 9.6 in women and 27.2% ± 10.5 in men, p=0.000), the total lean mass (TLM) (kg) was 41.8 ± 10 (41.6 ± 8.5 in women and 42.1 ± 11.7 in men, p=0.780), RSMI was 6.67 ± 1.16 (6.58 ± 1.08 for women and 6.76 ± 1.24 for men, p=0.403), ALM (kg) was 17.2 ± 4.4 (14.6 ± 2.7 for women and 20.2 ± 4.2 for men, p<0.001) and ALM (kg)/IMC was 0.67 ± 0.17 (0.55 ± 0.1 for women 0.8 ± 0.12 for men, p<0.001). The prevalence of pre-sarcopenia was as follows: Newman 23 (19.8%), Baumgartner 45 (37.2%), Mixed 43 (36.3%), and FNIH 56 (46.5%). There was a significant difference between the Newman method and the other three (p<0.001). The coefficient among the four criteria was 0.29. The comparison of the methods two by two were the following: (Table 1)

Table 1 Agreement among the four different criteria for the diagnosis of pre-sarcopenia

Criterion 1	Criterion 2	Agreement	p	kappa
Newman	Mixed	83%	<0.001*	0.60
Baumgartner	Mixed	86%	1	0.70
Newman	Baumgartner	69%	0.001*	0.28
Newman	FNIH	62%	<0.001*	0.20
Mixed	FNIH	54%	0.142	0.06
Baumgartner	FNIH	53%	0.185	0.04

Legend: *p<0.05. Cohen's kappa () coefficient less than 0.20, poor reliability; between 0.21–0.40, weak reliability; between

0.41-0.60, fair-to-good; between 0.61-0.80; and greater than 0.80, good-to-excellent reliability
 The %PPA between the FNIH criterion and other criteria were low, ranging from 30.4% to 39.3%. However, the %NPA was higher, 63.2% to 89.2% (Table 2).

Table 2 Agreement comparing the FNIH criterion with other operational criteria for pre-sarcopenia

Criterion 1	Criterion 2	PPA (%)	NPA (%)
FNIH	Newman	30.4%	89.2%
FNIH	Mixed	39.3%	63.2%
FNIH	Baumgartner	39.3%	64.6%

Legend: FNIH: Foundation of the National Institute of Health. PPA% (positive percent agreement): the proportion of participants who were categorized as having the condition by both the FNIH criteria and a second set of criteria divided by the number of participants who were categorized as having the condition by the second set of criteria. NPA% (negative percent agreement): the proportion of participants who were categorized as not having the condition by both the FNIH criteria and a second set of criteria divided by the number of participants who were categorized as not having the condition by the second set of criteria

The mean gait speed (m/s) was 1.03 ± 0.26 . The number of patients with gait speed < 0.8 was 23 (19%). Patients with pre-sarcopenia by different criteria had a low gait speed except when the Newman criterion was applied (Table 3).

Table 3 Mean gait speed and presence of pre-sarcopenia between different criteria of diagnosis.

Criterion	Pre-sarcopenia	n	m/s	p
Baumgartner	No	76	1.09 ± 0.25	0.001*
	Yes	45	0.93 ± 0.26	
Newman	No	97	1.04 ± 0.26	0.206
	Yes	24	0.97 ± 0.29	
Mixed	No	77	1.07 ± 0.27	0.043*
	Yes	44	0.96 ± 0.25	
FNIH	No	65	1.09 ± 0.25	0.009*
	Yes	56	0.96 ± 0.27	

Legend: * p<0.05, m/s: meters by second

The prevalence of sarcopenia was as follows: Newman 6 (4.9%), Baumgartner 13 (10.7%), Mixed 11 (9.1%), and FNIH 15 (12.4%), Figure 1.

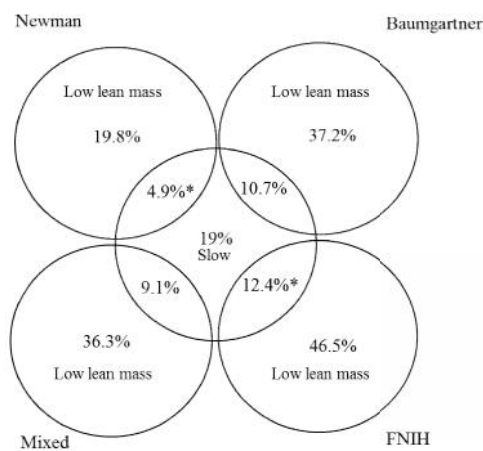


Figure 1 Percentage of sarcopenic patients using the four different criteria of diagnosis.

Legend: *p<0.05 between FNIH and Newman. The external circles show the percentage of pre-sarcopenia with each criterion and the internal circle shows the percentage of low

gait speed. The interaction between them shows the agreement between the diagnosis of pre-sarcopenia and low gait speed. There was a significant difference between the Newman and FNIH (p=0.012). The coefficient of the four criteria was 0.57. Table 4 shows the comparison of the four methods two by two.

Table 4 Comparison of the four different criteria of sarcopenia

Criterion 1	Criterion 2	Agreement	p	kappa
Newman	Mixed	95.9%	0.062	0.69
Baumgartner	Mixed	95%	0.687	0.72
Newman	Baumgartner	90.9%	0.065	0.38
Newman	FNIH	90.9%	0.012*	0.44
Mixed	FNIH	91.7%	0.344	0.57
Baumgartner	FNIH	91.7%	0.754	0.60

Legend: *p<0.05. Cohen's kappa () coefficient less than 0.20, poor reliability; between 0.21-0.40, weak reliability; between 0.41-0.60, fair-to-good; 0.61-0.80, good; and greater than 0.80, excellent reliability

The %PPA between the FNIH and other criteria ranged from 33.3% to 60% (FNIH to Newman 33.3%; FNIH to Mixed 53.3% and FNIH to Baumgartner 60%). However, the %NPA was very high (all >96%).

When patients with or without sarcopenia defined by FNIH (more actual and prevalent) showed no difference in relation to BMI (p=0.342), gender (p=1), actual tobacco use (p=0.48), average tobacco use (p=0.966), %TFM (p=0.130), TLM (p=0.261), and RSMI (p=0.076). The unique difference was age; sarcopenic patients were older (73.4 ± 8.8 years) than nonsarcopenic patients (67 ± 8.2 , p=0.006).

DISCUSSION

The prevalence of pre-sarcopenia in this study ranged from 19.8 to 46.3% depending on the criterion. Reliable data in the literature on COPD patients reports from 15% to 40% (19,20). Cesari *et al.* (21) found pre-sarcopenia in 30% of COPD patients; when adjusted for fat mass, the prevalence rose to 42.5. In the current study, the prevalence of pre-sarcopenia was higher with the FNIH criteria and significantly different between the Newman and the others.

The first most widely used criteria in the literature to diagnose sarcopenia was proposed by Baumgartner (5). Sarcopenia was defined by the ratio RSMI lower than 2 standard deviations or more below the normal means for a younger reference group measured using DXA. The cutoffs were 7.26 kg/m² for men and 5.45 kg/m² for women. However, when the normal reference was extrapolated to other populations showed lower prevalence than would be expected, 3 to 16% (ages 22-24), probably due to the interference of the increasing prevalence of obesity in the world. An alternative method, considering the residuals, proposed by Newman, is a criterion that considers fat mass in addition to height, which seems to identify more individuals with sarcopenia, particularly in obese subjects (15,16).

Two Brazilian studies evaluated the prevalence of sarcopenia, applying these two criteria in community-dwelling older men and women (17,18). These articles demonstrated that the criterion based on ASM adjusted for fat identified a greater number of older sarcopenic men and women, although the authors of those articles suggested that the ASM/height² should be used for underweight subjects (BMI <22 kg/m²). In the

current study, the findings were diverse: by Baumgartner, pre-sarcopenia was diagnosed in 37.2% of patients and by Newman, in 19.8% of patients, mainly due to the lower mean BMI in our population, compared to the other studies(15-18). When we mixed the two criteria, employing the Baumgartner for BMI <22 kg/m² and Newman for the BMI >22 kg/m², the prevalence was 36.3%, very similar to the Baumgartner, demonstrating again that our population of COPD patients had lower mean BMI than those in the other studies(15-18).

The coefficient among the four criteria was 0.29, considered a poor reliability. Comparing the methods two by two, we had better reliability between Newman versus Mixed (fair-to-good) and Baumgartner versus Mixed (good). To date, no other studies have compared different criteria of pre-sarcopenia in patients with COPD.

Several groups have published operational criteria to define sarcopenia, including the International Working Group (IWG)(10) and the European Working Group on Sarcopenia Older Persons (EWGSOP)(4); These recommendations combined lean mass with a strength and/or physical performance measure. The EWGSOP (4) differentiated pre-sarcopenia (low mass) from sarcopenia (low mass + low strength or low performance) and severe sarcopenia (low mass + low strength + low performance). Several possible performance measures (grip strength, chair stand, gait speed), lean mass assessment methods (DXA, bioimpedance, and magnetic resonance imaging), and different cutpoints were suggested by the EWGSOP(4).

These consensus statements were based on expert opinions and lacked access to large data sets to validate their recommendations(6). Thus, more recently the FNIH Sarcopenia Project has created a data-driven set of criteria for clinically relevant weakness and low lean mass using pooled data from multiple studies(12). The goal was to provide data-driven evidence to the field in order to advance professional consensus regarding clinically relevant cutpoints and terminology. The FNIH analyses used ALM by DXA, grip strength, and gait speed as measures of muscle mass, strength, and physical performance and used similar cut points that were recently published to operationalize the EWGSOP(4)criteria. Participants with gait speed less than or equal to 0.8 m/s were classified as having slow walking speed. ALM was divided by BMI to determine lean mass(12).

The best test to define physical capacity in patients with COPD is the 6-minute walk test(13). Among this study's population, 19% of the patients had a gait speed 0.8. The comparison between patients with and without pre-sarcopenia showed that lower mean gait speed was associated with the diagnosis of pre-sarcopenia when the Baumgartner, Mixed, and FNIH criteria were applied.

The prevalence of sarcopenia ranged from 4.9% to 12.4% depending on the criteria, with a significant difference observed between the Newman and FNIH. The data were consistent with the literature on COPD patients that reports around 15%[25] prevalence. Considering the FNIH criterion, the prevalence of sarcopenia in COPD patients was much higher than that observed in elderly people without the disease (12.4% vs. 2.3%)(6).The possible reasons for progressive loss of tissue mass include the following: increased load on the respiratory muscles, a high level of proinflammatory cytokines and basic metabolism, expressed hypoxia and tissue oxygen

debt, oxidative stress, the use of long acting b2-agonists and theophylline, smoking, hypoandrogenism, impaired regulation of hormones that reduces food intake and increased protein degeneration(26).

The coefficient among the four methods was 0.57, considered a fair-to-good reliability. Comparing the methods two by two we had better reliability between: Baumgartner x FNIH (fair-to-good), Newman x Mixed (fair-to-good), and Baumgartner x Mixed (good). To date, in the literature, no studies have compared different criteria of sarcopenia in patients with COPD. However, in a study with 10.000 individuals older than 65 that compared different criteria of sarcopenia, the prevalence was 2.3% (FNIH), 11.8% (EWGSOP), and 13.3% (IWG). And the reliability between the criteria was low. The PPA% between the FNIH criterion and other criteria ranged from 4% to 30% and the NPA% >95% (6). In this study we found a higher PPA% between the FNIH and other criteria (33.3% to 60%), and also a very high NPA% (all >96%), suggesting that there was good agreement on the absence of the condition.

An important finding was the lack of relationship between sarcopenia and BMI. It was believed that the diagnosis of sarcopenia was present only in skinny patients (27). However, recent studies have also shown that around 10 to 15% of normal weight people can have sarcopenia as well as overweight or obese individuals (28). The prevalence of sarcopenia in patients with a BMI > 25 kg/m² was 15% in patients with severe COPD (29). In the study of Koo *et al.*(30), 30% of patients were diagnosed as sarcopenic and half of them were obese.

CONCLUSIONS

One limitation of our study was that muscle strength was not assessed. In conclusion, many different methods diagnosis of sarcopenia and pre-sarcopenia have been used in the literature. In our study with COPD patients, the prevalence of pre-sarcopenia was high and greater with the FNIH criteria. The diagnosis of sarcopenia was most correlated with the performance using the Baumgartner and the FNIH criteria. In addition, the prevalence of sarcopenia was high and also greater when the FNIH criteria were used. We suggest that the FNIH criteria would be more suitable for this population of patients.

Disclosure Statement

The authors declare that they have no conflict of interest. And the article has not been published or sent for publication elsewhere.

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