



## Muscle mass and function are related to respiratory function in chronic obstructive pulmonary disease

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### Abstract

**Background:** Chronic obstructive pulmonary disease (COPD), as an airway limitation condition, is accompanied by alteration of muscle mass and function. We aimed to determine the relationship between disease severity and body composition, muscle function, and nutritional status in COPD patients.

**Methods:** This cross-sectional study was conducted on 129 COPD participants. Muscle strength, body composition, and calf circumference (CC) were measured using a hydraulic hand dynamometer, bioelectrical impedance analysis (BIA), and a tape measure, respectively. Furthermore, fat-free mass index (FFMI), body mass index (BMI) and muscle mass value were calculated by equations. Forced expiratory volume in one second (FEV1) was assessed as well. Nutritional status was also evaluated by subjective global assessment (SGA) questionnaire. SPSS software (version 21) was used, chi-square, Fisher's exact test, univariate and multivariate linear regression models were used for statistical analysis. P-values less than 0.05 were considered significant.

**Results:** Based on FEV1 classification, 52.7% of the patients had severe conditions. The reports indicated that the prevalence of low CC was 54.2%, low muscle mass 38.7%, low FFMI 34.8%, low right handgrip strength 61.2% and low left handgrip strength 64.3%. Furthermore, there was an increasing trend based on FEV1 in low CC ( $p=0.032$ ), low muscle mass ( $p=0.005$ ), low FFMI ( $p=0.002$ ), low right handgrip strength ( $p=0.004$ ) and low left handgrip strength ( $p=0.014$ ). The results of univariate analysis showed muscle mass ( $p=0.036$ ), total protein ( $p=0.043$ ), FFM ( $p=0.047$ ), FFMI ( $p=0.007$ ), SGA ( $p=0.029$ ), right handgrip strength ( $p=0.004$ ) and left handgrip strength ( $p=0.023$ ) were associated with FEV1. In addition, the results of multivariate analysis demonstrated low values of FFMI ( $p=0.005$ ) and right handgrip strength ( $p=0.042$ ) were the main detrimental factors for FEV1. The results of multivariate analysis were confirmed by stepwise model.

**Conclusion:** Low values of muscle mass and function are prevalent among COPD patients. The present study revealed that low FFMI and handgrip strength were closely related to disease severity.

**Keywords:** Muscle Mass, Lean Body Mass, Nutritional Status, Muscle Strength, Respiratory Disease

**Conflicts of Interest:** None declared

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### Introduction

Chronic obstructive pulmonary disease (COPD), as a complicated and heterogeneous condition, is characterized

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#### ↑What is "already known" in this topic:

COPD is a heterogeneous condition with a rapid rise. Poor nutritional status and muscle mass alteration are prevalent in this population, which can worsen the disease complications.

#### →What this article adds:

Our study proposed anthropometric and body composition indices to be able to rapidly evaluate nutritional status with regard to the severity of the respiratory distress in patients with chronic lung failure at clinics and hospitals.

by airway limitation and extrapulmonary manifestations (1, 2). Based on the World Health Organization's (WHO) reports, COPD has a rapid progression and is one of the main causes of morbidity and mortality worldwide (3). COPD can also increase the health care system costs and worsen the quality of life and daily living (4). Aging, smoking tobacco, air pollution, and social and economic situation have been reported to be the related causes of the increasing rates of COPD (5).

Systemic inflammation has a crucial role in the pathology of COPD. Evidence has shown that it is accompanied by high oxidative stress and increased proinflammatory cytokines and plasma levels of neutrophils, macrophages, and T lymphocytes (6). These markers might also be involved in the related comorbidities, such as cachexia, osteoporosis, cardiovascular disease, and muscle proteolysis, which can cause skeletal muscle waste and dysfunction (2, 7). On the other hand, nutritional deprivation, respiratory disorders, such as hypoxia and hypercapnia, drug therapy, and infection could result in metabolic changes and hypermetabolism in COPD. Moreover, activation of catabolic pathways could inhibit protein synthesis and promote gluconeogenesis and proteolysis, which could in turn aggravate the patients' health conditions (8).

Poor nutritional status and muscle mass alteration can deteriorate exercise capacity and airflow and decrease survival rates over time (9, 10). Due to the rapid rise in COPD population, assessment, diagnosis, and management of its complications are essential. To achieve this goal, evaluation of body composition and nutritional status is necessary (11). However, to the best of our knowledge, very few publications are available in the literature around this area. Therefore, the primary objective of this study was to assess the relationship between respiratory status and anthropometric indices, and the secondary objective was to evaluate the relationship between respiratory status and muscle strength and nutritional status. Thus, this study aimed to draw attention to the nutritional status, anthropometric measurements, and muscle mass and strength in COPD patients in Iran and to characterize the relationship between the aforementioned parameters and disease severity.

## Methods

### Study design

This cross sectional survey as a screening study was conducted on patients with COPD and data were collected from September to December 2018. The participants were selected from the patients with medical records for the past 7 years (March 2011 to June 2018) from 4 medical centers affiliated to Shiraz University of Medical Sciences, Shiraz, Iran (Rajai, Nemazee, Shahid Faghihi, and Ali-Asghar hospitals) and specialized respiratory clinics. Then, through calling and asking some questions, patients who wanted to cooperate were referred to Imam Reza clinic (a clinic affiliated to Shiraz University of Medical Sciences). Meanwhile, the records of those patients who were diagnosed as COPD were checked and reassessed using a spirometry test by a trained person and based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee; FEV1/FVC <0.70 value and fixed FEV1 values were used

for prognosis of the disease and classify severity. Finally, patients' affliction with COPD was again confirmed by a pulmonary specialist. The inclusion criteria of the study were being a male outpatient aged 40-70 years, having suffered from COPD based on one's medical history for 7 years, having been diagnosed as COPD for at least 3 months, and residence in Shiraz. However, women and individuals with infections, malignancies, other inflammatory disease, any other organs failure, and those with supplement consumption were not eligible to participate in the research. The study protocol was reviewed and approved by the Ethics Committee of Shiraz University of Medical Sciences. All patients who were enrolled into the study were requested to sign informed consent forms. A total of 1957 patients were screened for participation, and the census method was used. However, only 132 patients were satisfied and eligible to take part in the study.

### Disease severity

Spirometry test was done for all patients to assess the disease severity. From the 132 patients recruited, only 3 were not capable of completing the spirometry test. Finally, 129 patients were included in the study. Spirometry is the standard respiratory function test for patients with COPD. This method (Vitalograph Pneumotrac 77000PC based spirometry, England) was performed by an experienced operator to characterize disease progression and classify the COPD patients by severity based on the forced expiratory volume in 1 second (FEV1). Accordingly, FEV1 values  $\geq 80\%$ ,  $50\% \leq FEV1 < 80\%$ ,  $30\% \leq FEV1 < 50\%$ , and  $FEV1 < 30\%$  were considered as mild, moderate, severe and very severe intensity, respectively (12). The protocol of this process was first fully explained to the patient; then, spirometry test was performed for each patient. On the other hand, these patients had previously undergone spirometry test and were familiar with the administration protocol. After 3 times of repeating the FEV1 measurements, the highest value was selected (13).

### Participants' characteristics

In this study, 129 patients were interviewed by the researchers to complete their lifestyle, demographic, and disease-related information. Information about age, educational degree, job circumstances, smoking habits, type of tobacco used and age of onset, duration of smoking, and medical history was also gathered by the researchers.

### Nutritional assessment

Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire was used by the main investigator to evaluate the nutrition-associated complications, which is correlated to patient history (Body weight, % weight loss, dietary intake, gastrointestinal symptoms, functional capacity, and respiratory stress) and physical examination (muscle wasting, subcutaneous fat loss, and edema). Finally, each patient received a score, and scores  $>17$  were considered as severe malnutrition (14,15).

### Anthropometric measurements and body composition

Weight, height, and calf circumference (CC) of all patients were measured by a well-trained nutritionist according to the standard methods. Body weight measurement was performed using a calibrated scale (Omron, Korea) with an accuracy of 0.1 kg with light clothing. The participants' height was measured by a stadiometer to the nearest 0.1 cm without shoes. To calculate BMI, weight (kg) was divided by height squared (cm) (16). In this respect, the reference values  $< 20 \text{ kg/m}^2$  were adopted as the cutoff point (17). CC was measured using a nonstretching flexible tape to the nearest 0.1 cm in seated position (16). Based on different references, CC values lower than 32 cm or 34 cm were considered as low (18, 19). Two cutoffs from 2 different references were considered for evaluation of CC in this study in order not to miss any significant correlations. Segmental lean body mass, fat mass, and fat free mass (FFM) were assessed via segmental multifrequency bioelectrical impedance analysis (BIA) and InBody S10 analyzer (BioSpace Co., Ltd., South Korea) (16). Muscle mass values were also calculated by dividing Segmental lean body mass to height squared ( $\text{m}^2$ ) and values less than  $< 7 \text{ kg/m}^2$  were defined as low (20). Fat-free mass index (FFMI) was also calculated by dividing FFM to height squared ( $\text{m}^2$ ) and values less than  $17 \text{ kg/m}^2$  were considered as low body muscle mass (21).

### Muscle strength assessment

Hydraulic hand dynamometer (model MSD, Sihan, Korea) was used as a simple tool to measure muscular strength in seated position 3 times for each hand. The mean of 3 measurements of grip strength was calculated for both hands (22). Handgrip strength values  $< 26 \text{ kg}$  were determined as the cutoff point (20). Body position was set according to the same device working protocol, which was both written and available visually on the device's instruction.

### Statistical analysis

Statistical analysis was done using the SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA). The results for categorical data were expressed as percentages. Moreover, chi-square test was employed to compare the categorical variables. Fisher's exact test was also used for SGA since there was not enough frequency to perform chi-square test. The normality of the distribution of quantitative data was assessed using Kolmogorov-Smirnov test. Moreover, multiple linear regression model was used to explore the relationship between nutritional status and anthropometric variables and disease severity (FEV1). Based on the stepwise model, independent factors with  $p \leq 0.2$  in univariate analysis were included in the Linear model and variance inflation factor (VIF) was used to determine the collinearity diagnostic.  $P < 0.05$  was considered as statistically significant.

### Results

The characteristics of the 129 patients are summarized in Table 1. Almost 85 (66%) patients were older than 60

years, 27 (20.9%) were illiterate, and 16 (12.4%) had a university degree. Considering job circumstances, 78 (60.5%) participants had exposure to dust, chemical agents, or both. Moreover, 105 (81.4%) participants were smokers and 58 (55.2%) had started smoking before the age of 20. Of 132 patients who were enrolled into the study, 3 were unable to perform the respiratory test.

Classification of FEV1 showed that 68 (52.7%), 49 (38%), and 12 (9.3%) participants had severe, moderate, and mild conditions, respectively. The SGA score was below 17 in most of the patients ( $n = 121$ , 93.8%). Considering anthropometric indicators, BMI was higher than  $20 \text{ kg/m}^2$  in 100 (77.6%), CC was less than 32 cm in 48 (37.2%), muscle mass value was lower than  $7 \text{ kg/m}^2$  in 50 (38.7%), and FFMI was higher than 17 for most of the participants ( $n = 83$ , 65.2%). Furthermore, approximately 83 and 79 (64.3% and 61.2%) patients had less than 26 kg of left and right handgrip strengths, respectively.

### Prevalence of malnutrition according to body composition, body strength, and SGA indicators

The analysis of body composition, body strength, and SGA has been indicated in Table 2. The findings showed 29 (22.4%) patients had low BMIs. Moreover, based on different classifications of CC, 48 and 70 (37.2% and 54.2%) patients had low CC values ( $\text{CC} \leq 32 \text{ cm}$  or  $\text{CC} \leq 34 \text{ cm}$ ). Also, the prevalence of low muscle mass and low FFMI was reported in 50 and 45 (38.7% and 34.8%) patients, respectively. Considering the assessment of body strength, 79 and 83 (61.2% and 64.3%) participants had low right and left handgrip strengths, respectively. Overly, 8 (6.2%) participants obtained SGA scores higher than 17.

There has been an increasing trend in the prevalence of the previously listed markers based on the COPD severity. Nevertheless, these values were statistically significant just for CC ( $\leq 34 \text{ cm}$ ), muscle mass value, FFMI, and right and left handgrip strengths ( $p=0.032$ ,  $p=0.005$ ,  $p=0.002$ ,  $p=0.004$  and  $p=0.014$ ).

### FEV1 and the associated markers

As shown in Table 3, muscle mass, total protein, FFM, FFMI, SGA, and left and right handgrip strengths were associated with FEV1. In multivariate linear regression analysis, low FFMI ( $\beta=6.52$ ,  $p=0.005$ ) and right handgrip values ( $\beta=0.79$ ,  $p=0.042$ ) were the significant determinants of FEV1. Similar results were also obtained in the stepwise model after elimination of body components assessed by BIA, including protein and FFM as confounders. The results were as follow: for FFMI ( $\beta=1.66$ , 95% CI = 0.33-2.99,  $p=0.015$ ) and for right handgrip strength ( $\beta=0.69$ , 95% CI = 0.19-1.19,  $p=0.007$ ).

### Discussion

The findings of this cross sectional study showed that the disease was severe in 53% of the patients. Also, there was a significant relationship between FEV1 and CC, low lean mass, FFMI, and muscle strength values. On the other hand, FFMI and right handgrip strength values were the two determinants of FEV1.

Table 1. Characteristics of the participants

Variable	N (%)	Variable	N (%)
<b>Age, years</b>		<b>FEV1, %</b>	
40-50	3 (2.3)	Mild	12 (9.3)
51-60	41 (31.8)	Moderate	49 (38.0)
61-70	63 (48.8)	Severe and very severe	68 (52.7)
>70	22 (17.1)		
<b>Education</b>		<b>Anthropometrics data and body composition indicators and SGA</b>	
Illiterate	27 (20.9)	BMI, kg/m <sup>2</sup>	
Elementary	54 (41.9)	≤20	29 (22.4)
Intermediate	17 (13.2)	>20	100 (77.6)
Diploma	15 (11.6)		
>Diploma	16 (12.4)	<b>CC, cm<sup>b</sup></b>	
<b>Job</b>		≤32	48 (37.2)
Exposure to dust	27 (20.9)	>32	80 (62.8)
Exposure to chemicals	26 (20.2)		
Exposure to dust and chemicals	25 (19.4)	<b>CC, cm</b>	
Driver	24 (18.6)	≤34	70 (54.2)
Other	27 (20.9)	>34	58 (45.8)
<b>Type of tobacco or opioid used<sup>a</sup></b>		<b>Muscle mass value, kg/m<sup>2c</sup></b>	
Cigarette	105 (81.4)	≤7	50 (38.7)
Opium	76 (58.9)	>7	78 (61.3)
Hookah	12 (9.3)		
Methadone	9 (9.97)	<b>FFMI, kg/m<sup>2</sup></b>	
Heroin	1 (0.77)	≤17	45 (34.8)
		>17	83 (65.2)
<b>Smoking status (cigarette and hookah)<sup>a</sup></b>		<b>Right handgrip, kg<sup>d</sup></b>	
Have already consumed	105 (81.4)	≤26	79 (61.2)
Now they consume	62 (48.1)	>26	49 (38.8)
Have never consumed	24 (18.6)		
<b>Age at onset of smoking, years</b>		<b>Left handgrip, kg<sup>e</sup></b>	
9-20	58 (55.2)	≤26	83 (64.3)
21-30	26 (24.8)	>26	43 (35.7)
31-40	15 (14.3)		
>40	6 (5.7)	<b>SGA score</b>	
<b>Years of smoking</b>		≤17	121 (93.8)
3-20	16 (15.2)	>17	8 (6.2)
21-40	48 (45.7)		
>40	41 (39.1)		

FEV1, forced expiratory volume in one second; BMI, body mass index; CC, calf circumference; FFMI, fat free mass index; SGA, subjective global assessment.

<sup>a</sup> The percentages were reported to be over 100, because each individual might have had multiple answers.

<sup>b</sup> No measurements were taken for one person due to a leg amputation.

<sup>c</sup> Body composition could not be measured in one person because of a quiver in his body.

<sup>d</sup> Due to amputation of both hands, measurement was not performed in one person.

<sup>e</sup> Except for one person with defects in both hands, the other two had defects in their left fingers due to an occupational accident.

One of the gold standards for determining COPD severity is FEV1 according to spirometric criteria (23). FEV1 is an important index for evaluation of pulmonary obstruction, exacerbations, lung dysfunction, and disease mortality (24). On the other hand, FEV1 can be positively correlated to health status, treatment outcomes, and body composition, including lean mass and dry lean mass (25, 26). In this context, Menezes et al showed that FEV1 could be a predictor of overall mortality in COPD (27).

Although several studies have indicated body composition and body strength alterations in various conditions and ages (28, 29), little attention has been paid to COPD population. One prevalent observation in COPD is low handgrip strength, and the results of the present research showed the prevalence of this marker was more than 60% in these patients. Handgrip strength is a measurement tool for assessing upper limb muscle capability and is correlated to

other complications and mortality among COPD patients (30). Ozyemisci-Taskiran et al. reported a positive correlation between handgrip strength and functional capacity indicators in COPD (31). The results of this study demonstrated that low handgrip strength could estimate FEV1. Shah et al. also confirmed these findings and claimed that reduced muscle strength might be responsible for other respiratory disturbances (32). On the other hand, lower muscle strength could cause high exacerbations and lower health-related quality of life in COPD patients (33). On the contrary, Jeong et al. found no significant differences between COPD and non-COPD individuals with respect to muscle mass strength. Nonetheless, handgrip strength was associated with low quality of life, including mobility and daily activity, in COPD patients (34). Recently, several authors have proposed different mechanisms leading to this com-



**Table 2.** The prevalence of malnutrition according to anthropometric indices and SGA and their relationship with disease severity

Disease severity	FEV1				P value <sup>a*</sup>
	Total <sup>#</sup> n=129	Mild <sup>#</sup> n=12	Moderate <sup>#</sup> n=49	Severe <sup>#</sup> n=68	
Nutrition status:					
Low BMI	29 (22.4)	3 (2.3)	6 (4.7)	20 (15.5)	0.088
Low CC ( $\leq 32$ cm)	48 (37.2)	3 (2.3)	13 (10.2)	32 (25)	0.057
Low CC ( $\leq 34$ cm)	70 (54.2)	6 (4.7)	20 (15.6)	44 (34.4)	0.032*
Low Muscle mass	50 (38.7)	2 (1.6)	13 (10.2)	35 (27.3)	0.005*
Low FFMI	45 (34.8)	2 (1.6)	10 (7.8)	33 (25.8)	0.002*
Low right handgrip	79 (61.2)	2 (1.6)	29 (22.7)	48 (37.5)	0.004*
Low left handgrip	83 (64.3)	3 (2.4)	31 (24.6)	49 (38.9)	0.014*
SGA score $\geq 17$	8 (6.2)	0 (0)	1 (0.8)	7 (5.4)	0.158

#Data are expressed as frequency (percentage); FEV1, forced expiratory volume in one second; BMI, body mass index; CC, calf circumference; FFMI, fat free mass index; SGA, subjective global assessment. <sup>a</sup>P obtained from chi-square and Fisher's exact test. <sup>\*</sup>P<0.05 considered significant.

**Table 3.** The factors associated with FEV1 based on the multiple linear regression test

Variables	FEV1			
	Univariate analysis $\beta$ (95% CI)	P <sup>a</sup>	Multivariate analysis $\beta$ (95% CI)	P value <sup>b</sup>
Age, per 1 year	-0.21 (-0.70, 0.28)	0.397	-	-
Weight, per 1 kg	0.08 (-0.13, 0.29)	0.459	-	-
BMI, per 1 kg/m <sup>2</sup>	0.29 (-0.33, 0.93)	0.355	-	-
Muscle mass per 1 kg/m <sup>2</sup>	3.20 (0.21, 6.19)	0.036*	-8.18 (-20.97, 4.67)	0.211
Protein, per 1 unit	2.05 (0.07, 4.04)	0.043*	-2.03 (-7.62, 3.55)	0.472
FFM, per 1 kg	0.40 (0.00, 0.80)	0.047*	-	-
FFMI, per 1 kg/m <sup>2</sup>	1.88 (0.53, 3.23)	0.007*	6.52 (2.05, 10.99)	0.005*
CC, per 1 cm	0.70 (-0.14, 1.55)	0.102	-0.38 (-1.95, 1.18)	0.627
Right handgrip, per 1 kg	0.74 (0.24, 1.24)	0.004*	0.79 (0.02, 1.54)	0.042*
Left handgrip, per 1 kg	0.55 (0.08, 1.03)	0.023*	-0.01 (-0.75, 0.72)	0.961
SGA score, per 1 unit	-0.8 (-1.51, -0.08)	0.029*	-0.7 (-1.46, 0.05)	0.074

P<sup>a</sup> and P<sup>b</sup> obtained from univariate and multivariate linear regression. <sup>\*</sup>P<0.05 considered as significant.

plication. High oxidative stress, malnutrition, airflow obstruction, hypoxemia, and inflammation are some possible factors that can cause muscle dysfunction and impaired structure in COPD (8, 9, 35).

Low lean mass as a common manifestation in COPD is associated with a higher risk of death. In the present study, the prevalence of low muscle mass was 38.7%, following a positive trend based on FEV1. In the same line, the previous studies reported muscle mass as an accurate marker to express disease severity. Therefore, muscle mass could be valuable for the clinical assessment of COPD patients (36, 37). A similar trend was also observed in the research by Graumam et al. Accordingly, the patients with severe COPD (GOLD 3 and 4) demonstrated a higher rate of low lean mass and lower skeletal mass index compared to those with milder disease (GOLD 1 and 2) and healthy individuals (36). As body composition abnormalities are prevalent in COPD, it is important to point out that a whole cascade of modifications come together in this condition. Hypoxemia, high transcription of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), and downregulation of peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) might be involved in metabolic pathways and result in increased levels of glycolytic enzymes and low levels of antioxidative and fatty acid oxidative enzymes (38, 39). On the other hand, alteration in the levels of anabolic hormones like testosterone and insulin-like growth factor 1 (IGF-1) and even corticosteroid therapy could contribute to muscle atrophy in COPD (40).

FFMI is another proper index, which is a reflector of muscle mass and respiratory function (41). Based on the findings of this study, low FFMI was highly prevalent among COPD patients and was a major risk factor for

FEV1. In this regard, other studies have expressed FFMI as an essential factor involved in disease deterioration, exercise capacity, dyspnea, and muscle atrophy in COPD, which could predict disease severity (42, 43). Slinde et al. investigated the long-term effect of COPD on mortality rate in a 1-year multidisciplinary rehabilitation project and showed that an increase in FFMI might decrease the mortality risk (44). Ischaki et al. also mentioned that FFMI seemed to be an accurate indicator in expressing the disease severity and was a predictor of COPD stage (45). Moreover, Kim et al. discovered a decrease in FFMI in COPD patients, which was more prominent in the lower body and was accompanied with significantly lower FEV1 (46). FFMI is also an important indicator of sarcopenia. McIntosh et al. reported a significant correlation between this index and circumference measures in elderly individuals, which could affect muscle function and mass (47). There are different complications involved in COPD that can worsen the above-mentioned disease symptoms. Systemic inflammation is an underlying factor related to COPD, which can exacerbate cachexia and muscle quality and quantity by the production of cytokines (7, 48). Deterioration of protein synthesis and an increase in protein degradation are secondary to systemic inflammation (49). Furthermore, evidence has demonstrated COPD patients had less physical activity levels and would become even less active over time, which would result in muscle mass and strength alteration (50, 51).

Malnutrition, as a major problem in COPD, can influence quality of life, health care costs, and pulmonary function. An imbalance between energy requirements and energy expenditure might lead to a negative impact on body weight

and even muscle depletion and mortality in COPD (5, 52). Zapatero et al. reported that malnutrition was closely associated with mortality rate and risk of hospital admission in COPD patients (53). Burak Mete et al. also confirmed that malnutrition was associated with spirometric values and low BMI (52). However, the present study findings showed no significant relationship between SGA score and FEV1. It should be mentioned that SGA is an assessment tool, which is appropriate for the evaluation of malnutrition in hospitalized patients (54). However, the present study only included outpatients and SGA lacked a significant predictive value in this group. On the other hand, the chance of false-negative cases was increased due to the specific scoring of the SGA and its items as well as the better performance of outpatients compared to hospitalized patients. FEV1, however, was not correlated to BMI even though some previous studies considered BMI as a tool for evaluation of nutritional status and COPD severity (55, 56). In this regard, Fukahori et al. indicated higher pulmonary dysfunction in patients with low BMI (57). Moreover, CC was found to be a reflector of health, performance, nutritional status, and survival (58). Shu-Chuan Hoet al also suggested CC as an accurate predictor of long-term risk of mortality in COPD (59). Consistently, other studies performed among elderly individuals have identified CC as an indicator of skeletal muscle mass, which could be used for diagnosing sarcopenia (58, 60). As shown in the 'Results' section in the present study, CC values  $\leq 34$  cm could be a predictor of FEV1. However, no significant correlation was observed between CC  $\leq 32$  cm and disease severity. This controversy originates from different cutoff points considered for CC. Nevertheless, BMI status or CC values alone cannot be proper predictors of muscle mass and function.

In this study, multiple anthropometric indices including body composition, muscle strength, and nutritional status were considered simultaneously. On the other hand, given that this cross-sectional study was a screening study, there was no information on this disease and its related variables in Fars province, which could be of great importance to check the patients' nutritional status in hospitals and clinics in early phases of the disease and this study could suggest the best anthropometric parameters appropriate for COPD patients' nutritional screening. This study had some limitations. First, casual relationships could not be determined due to the cross-sectional study design. Moreover, although some women had COPD and its related complications, they could not be enrolled in this study due to the lack of enough number of women who were eligible for participation. In other words, the inclusion of a few women might disturb sex distribution in the study that could become a confounding factor, which possibly could affect the results of interpretation. Further nutrition research in COPD is desirable to extend the knowledge around the identification of the influential factors in the progression and management of the disease.

### Conclusion

To sum up, the results showed some indicators of malnutrition such as low muscle strength and FFMI were present in the COPD patients, which were highly associated with

the disease severity. Although COPD is a progressive condition, its severity and progression can be modulated by appropriate diagnosis and management, which needs proper assessment. Since there are still some questions and inconclusive results regarding this issue, further studies are warranted.

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### Conflict of Interests

The authors declare that they have no competing interests.

### References

- Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;11(1):122.
- Zhang Y, Zuo H, Tian D, Ouyang X, Wang X. Correlation between peripheral skeletal muscle functions and the stable phase of COPD in older patients. *Eur Rev Med Pharmacol Sci*. 2018;22(16):5317-26.
- Crisafulli E, Alfieri V, Chetta A. Clinical Factors Associated with an Increased Risk of Death at and During Hospitalization for an Acute Exacerbation of COPD (AECOPD) and for a Short Period after Discharge. *J Respir Res*. 2016;2(2):44-6.
- Byng D, Lutter JI, Wacker ME, Jörres RA, Liu X, Karrasch S, et al. Determinants of healthcare utilization and costs in COPD patients: first longitudinal results from the German COPD cohort COSYCONET. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1423.
- Nguyen HT, Collins PF, Pavey TG, Nguyen NV, Pham TD, Gallegos DL. Nutritional status, dietary intake, and health-related quality of life in outpatients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2019;14:215.
- Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of 'overspill' of inflammatory mediators from the lungs? Review of the evidence. *Thorax*. 2010;65(10):930-6.
- Byun MK, Cho EN, Chang J, Ahn CM, Kim HJ. Sarcopenia correlates with systemic inflammation in COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:669.
- Ezzell L, Jensen GL. Malnutrition in chronic obstructive pulmonary disease. Oxford University Press; 2000.
- Hallin R, Gudmundsson G, Ulrik CS, Nieminen MM, Gislason T, Lindberg E, et al. Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). *Respir Med*. 2007;101(9):1954-60.
- Gea J, Sancho-Muñoz A, Chalela R. Nutritional status and muscle dysfunction in chronic respiratory diseases: stable phase versus acute exacerbations. *J Thorac Dis*. 2018 May;10(Suppl 12):S1332.
- De Blasio F, de Blasio F, Berlingieri GM, Bianco A, La Greca M, Franssen FM, et al. Evaluation of body composition in COPD patients using multifrequency bioelectrical impedance analysis. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2419.
- Vogelmeier C, Criner G, Martinez F. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Revisions 2001-2017: Historical and Critical Perspective. *Barc Respir Netw*. 2017;3(3).
- Johns DP, Walters JA, Walters EH. Diagnosis and early detection of COPD using spirometry. *J Thorac Dis*. 2014;6(11):1557.
- Bauer J, Egan E, Clavarino A. The scored patient-generated subjective global assessment is an effective nutrition assessment tool in subjects with chronic obstructive pulmonary disease. *E Spen Eur E J Clin Nutr Metab*. 2011;6(1):e27-e30.
- Gupta B, Kant S, Mishra R. Subjective global assessment of nutritional status of chronic obstructive pulmonary disease patients on admission. *Int J Tuberc Lung Dis*. 2010;14(4):500-5.
- Ramachandran K, McCusker C, Connors M, Zuwallack R, Lahiri B. The influence of obesity on pulmonary rehabilitation outcomes in

- patients with COPD. *Chron Respir Dis*. 2008 Nov;5(4):205-9.
17. Mahan LK, Escott-Stump S, Raymond J. Krause's food & the nutrition care process: Elsevier Health Sciences. Saunders, Elsevier. 2012.
  18. Kim S, Kim M, Lee Y, Kim B, Yoon TY, Won CW. Calf circumference as a simple screening marker for diagnosing sarcopenia in older Korean adults: the Korean frailty and aging cohort study (KFACS). *J Korean Med Sci*. 2018;33(20).
  19. Kawakami R, Murakami H, Sanada K, Tanaka N, Sawada SS, Tabata I, et al. Calf circumference as a surrogate marker of muscle mass for diagnosing sarcopenia in Japanese men and women. *Geriatr Gerontol Int*. 2015;15(8):969-76.
  20. Chen L-K, Liu L-K, Woo J, Assantachai P, Auyeung T-W, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc*. 2014;15(2):95-101.
  21. Schols AM, Ferreira IM, Franssen FM, Gosker HR, Janssens W, Muscaritoli M, et al. Nutritional assessment and therapy in COPD: a European Respiratory Society statement. *Eur Respir Soc*. 2014.
  22. Massy-Westropp NM, Gill TK, Taylor AW, Bohannon RW, Hill CL. Hand Grip Strength: age and gender stratified normative data in a population-based study. *BMC Res Notes*. 2011;4(1):127.
  23. Sterk P. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. *Eur Respir Soc*. 2004.
  24. Tashkin DP, Goodin T, Bowling A, Price B, Ozol-Godfrey A, Sharma S, et al. Effect of smoking status on lung function, patient-reported outcomes, and safety among COPD patients treated with glycopyrrolate inhalation powder: pooled analysis of GEM1 and GEM2 studies. *Respir Res*. 2019;20(1):135.
  25. Roca M, Mitu F, Roca IC, Mihăescu T. Body composition alterations in chronic obstructive pulmonary disease. *Rev Med Chir Soc Med Nat Iasi*. 2013;117(2):337-43.
  26. Jones P, Miravittles M, van der Molen T, Kulich K. Beyond FEV1 in COPD: a review of patient-reported outcomes and their measurement. *Int J Chron Obstruct Pulmon Dis*. 2012;7:697.
  27. Menezes AMB, Pérez-Padilla R, Wehrmeister FC, Lopez-Varela MV, Muiño A, Valdivia G, et al. FEV1 is a better predictor of mortality than FVC: the PLATINO cohort study. *PLoS One*. 2014;9(10).
  28. Nasimi N, Dabbaghmanesh MH, Sohrabi Z. Nutritional status and body fat mass: Determinants of sarcopenia in community-dwelling older adults. *Exp Gerontol*. 2019;122:67-73.
  29. Poggiogalle E, Lubrano C, Sergi G, Coin A, Gnassi L, Mariani S, et al. Sarcopenic obesity and metabolic syndrome in adult Caucasian subjects. *J Nutr Health Aging*. 2016;20(9):958-63.
  30. Burtin C, Ter Riet G, Puhana MA, Waschki B, Garcia-Aymerich J, Pinto-Plata V, et al. Handgrip weakness and mortality risk in COPD: a multicentre analysis. *Thorax*. 2016;71(1):86-7.
  31. Ozyemisci-Taskiran O, Erden Z, Kokturk N, Karatas GK. Hand grip strength in patients engaged in pulmonary rehabilitation program during COPD exacerbation. *Eur Respir Soc*. 2011.
  32. Shah S, Nahar P, Vaidya S, Salvi S. Upper limb muscle strength & endurance in chronic obstructive pulmonary disease. *Indian J Med Res*. 2013;138(4):492.
  33. Silva Neto LS, Karnikowski MG, Tavares AB, Lima RM. Association between sarcopenia, sarcopenic obesity, muscle strength and quality of life variables in elderly women. *Braz J Phys Ther*. 2012;16(5).
  34. Jeong M, Kang HK, Song P, Park HK, Jung H, Lee S-S, et al. Hand grip strength in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2385.
  35. Barreiro E. Chronic Obstructive Pulmonary Disease and Oxidative Damage. *Protein Carbonylation: Principles, Analysis, and Biological Implications*. 2017:241-71.
  36. Graumam R, Pinheiro M, Nery L, Castro C. Increased rate of osteoporosis, low lean mass, and fragility fractures in COPD patients: association with disease severity. *Osteoporos Int*. 2018;29(6):1457-68.
  37. Marquis K, Debigaré R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166(6):809-13.
  38. Huss JM, Levy FH, Kelly DP. Hypoxia inhibits the peroxisome proliferator-activated receptor  $\alpha$ /retinoid X receptor gene regulatory pathway in cardiac myocytes a mechanism for  $O_2$ -dependent modulation of mitochondrial fatty acid oxidation. *Int J Biol Chem*. 2001;276(29):27605-12.
  39. Raguso CA, Luthy C. Nutritional status in chronic obstructive pulmonary disease: role of hypoxia. *Nutrition*. 2011;27(2):138-43.
  40. Gupta M, Vardey S, Sinha M, Joshi N, Dixit R, Gupta R. Evaluation of anabolic hormone status in patients with COPD during stable and acute exacerbation state. *Biomed Res*. 2014.
  41. Gologanu D, Ionita D, Gartonea T, Stanescu C, Bogdan MA. Body composition in patients with chronic obstructive pulmonary disease. *Maedica*. 2014;9(1):25.
  42. Luo Y, Zhou L, Li Y, Guo S, Li X, Zheng J, et al. Fat-free mass index for evaluating the nutritional status and disease severity in COPD. *Respir Care*. 2016;61(5):680-8.
  43. Sarc I, Kosten T, Hafner T, Zupanc B, Zihlerl K. Low FFMI according to ESPEN cut-offs is a strong independent predictor of mortality in patients with COPD. *Eur Respir Soc*. 2018.
  44. Slinde F, Grönberg A, Engström CP, Rossander-Hulthén L, Larsson S. Body composition by bioelectrical impedance predicts mortality in chronic obstructive pulmonary disease patients. *Respir Med*. 2005;99(8):1004-9.
  45. Ischaki E, Papatheodorou G, Gaki E, Papa I, Koulouris N, Loukides S. Body mass and fat-free mass indices in COPD: relation with variables expressing disease severity. *Chest*. 2007;132(1):164-9.
  46. Kim S, Kang Y, Jung J, Park M, Kim Y, Kim S, et al. Body mass index and fat free mass index in obstructive lung disease in Korea. *Int J Tuberc Lung Dis*. 2014;18(1):102-8.
  47. McIntosh EI, Smale KB, Vallis LA. Predicting fat-free mass index and sarcopenia: a pilot study in community-dwelling older adults. *Age*. 2013;35(6):2423-34.
  48. Morello Gearhart A, Fernandez-Botran R, Peyrani P, Wiemken T, Reyes A, Gauhar U, et al. Role Of Cytokines In The Lung And Systemic Inflammation In Patients With COPD. *Proc Am Thorac Soc*. 2017. p. A6307-A.
  49. Bolton CE, Broekhuizen R, Ionescu AA, Nixon LS, Wouters EF, Shale DJ, et al. Cellular protein breakdown and systemic inflammation are unaffected by pulmonary rehabilitation in COPD. *Thorax*. 2007;62(2):109-14.
  50. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of COPD. *Chest*. 2006;129(3):536-44.
  51. Vaes AW, Garcia-Aymerich J, Marott JL, Benet M, Groenen MT, Schnohr P, et al. Changes in physical activity and all-cause mortality in COPD. *Eur Respir J*. 2014;44(5):1199-209.
  52. Mete B, Pehlivan E, Gülbaş G, Günen H. Prevalence of malnutrition in COPD and its relationship with the parameters related to disease severity. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3307.
  53. Zapatero A, Barba R, Ruiz J, Losa J, Plaza S, Canora J, et al. Malnutrition and obesity: influence in mortality and readmissions in chronic obstructive pulmonary disease patients. *J Hum Nutr Diet*. 2013;26:16-22.
  54. Stratton RJ, Hackston A, Longmore D, Dixon R, Price S, Stroud M, et al. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. *Br J Nutr*. 2004;92(5):799-808.
  55. Baig MMA, Hashmat N, Adnan M, Rahat T. The relationship of dyspnea and disease severity with anthropometric indicators of malnutrition among patients with chronic obstructive pulmonary disease. *Pak J Med Sci*. 2018;34(6):1408.
  56. Zhou Y, Wang D, Liu S, Lu J, Zheng J, Zhong N, et al. The association between BMI and COPD: the results of two population-based studies in Guangzhou, China. *COPD*. 2013;10(5):567-72.
  57. Fukahori S, Matsuse H, Takamura N, Tsuchida T, Kawano T, Fukushima C, et al. Body mass index correlated with forced expiratory volume in 1 second/forced vital capacity in a population with a relatively low prevalence of obesity. *Chin Med J*. 2010;123(20):2792-6.
  58. Tosato M, Marzetti E, Cesari M, Saveria G, Miller RR, Bernabei R, et al. Measurement of muscle mass in sarcopenia: from imaging to biochemical markers. *Aging Clin Exp Res*. 2017;29(1):19-27.
  59. Ho SC, Wang JY, Kuo HP, Huang CD, Lee KY, Chuang HC, et al. Mid-arm and calf circumferences are stronger mortality predictors than body mass index for patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2075.
  60. Pagotto V, Santos KFd, Malaquias SG, Bachion MM, Silveira EA. Calf circumference: clinical validation for evaluation of muscle mass in the elderly. *Rev Bras Enferm*. 2018;71(2):322-8.