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ORIGINAL

Patients with Post-Covid-19 Syndrome are at risk of malnutrition and obesity: findings of outpatient follow-up

Pacientes com Síndrome Pós-Covid-19 apresentam risco de desnutrição e obesidade: achados de um ambulatório de seguimento

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ABSTRACT

Objective

To evaluate the nutritional and functional status, swallowing disorders, and musculoskeletal manifestations of patients with Post-Covid-19 Syndrome, stratified by the Appendicular Skeletal Muscle Mass Index.

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Methods

This is a cross-sectional study with patients diagnosed with Post-Covid-19 Syndrome after discharge from the intensive care unit of a university hospital. The evaluated outcomes were: nutritional status (Mini Nutritional Assessment, bioimpedance and anthropometry), swallowing disorders (Dysphagia Risk Evaluation Protocol), functional status (Post-Covid-19 Functional Status Scale), and musculoskeletal manifestations. According to the Appendicular Skeletal Muscle Mass Index, patients were stratified in terms of loss or not loss of muscle mass.

Results

Thirty-eight patients were included in the study, 20 stratified into the no loss of muscle mass group (17 females; 49.45±12.67 years) and 18 into the loss of muscle mass group (18 males; 61.89±12.49 years). Both groups were at risk of malnutrition (Mini Nutritional Assessment scores between 17–23.5 points; No Loss of Muscle Mass Group: 21.82±3.93; Loss of Muscle Mass Group: 23.33±3.41) and obesity (No Loss of Muscle Mass Group: 33.76±6.34; Loss of Muscle Mass Group: 30.23±3.66). The groups differed in terms of bioimpedance parameters (except fat mass) and age. However, there were no differences in swallowing alterations, functional status, and musculoskeletal manifestations.

Conclusion

Patients with Post-Covid-19 Syndrome, stratified according to the Appendicular Skeletal Muscle Mass Index, were at risk of malnutrition and obesity. The persistence of fatigue, weakness, myalgia and arthralgia at 6 months after hospital discharge is noteworthy. These findings emphasize the importance of comprehensive care for patients with Post-Covid-19 Syndrome.

Keywords: Coronavirus infections. Functional status. Intensive care units. Muscles. Nutrition assessment.

RESUMO

Objetivo

Avaliar o estado nutricional, status funcional, alterações de deglutição e manifestações musculoesqueléticas de pacientes com Síndrome Pós-Covid-19, estratificados pelo Índice de Massa Muscular Esquelética Apendicular.

Métodos

Estudo transversal composto por pacientes diagnosticados com a Síndrome Pós-Covid-19 que estiveram internados na Unidade de Terapia Intensiva de um hospital universitário. Os desfechos avaliados foram: estado nutricional (Mini Avaliação Nutricional; bioimpedância e antropometria), alterações de deglutição (Protocolo Fonoaudiológico de Avaliação do Risco de Disfagia), status funcional (Post-Covid-19 Functional Status Scale) e manifestações musculoesqueléticas. Os pacientes foram classificados, quanto à perda de massa muscular conforme o Índice de Massa Muscular Esquelética Apendicular, em grupo sem e com perda de massa muscular.

Resultados

Foram inseridos no estudo 38 pacientes, 20 no grupo sem perda de massa muscular (17 deles do sexo feminino; 49,45±12,67 anos) e 18 no grupo com perda de massa muscular (todos do sexo masculino; 61,89±12,49 anos). Os pacientes de ambos os grupos apresentaram risco de desnutrição (escores Mini Avaliação Nutricional entre 17-23.5 pontos; Grupo Sem Perda de Massa Muscular: 21,82±3,93; Grupo Com Perda de Massa Muscular: 23,33±3,41) e obesidade (Grupo Sem Perda de Massa Muscular: 33,76±6,34; Grupo Com Perda de Massa Muscular: 30,23±3,66). Os grupos diferiram quanto aos parâmetros da bioimpedância (exceto massa gorda) e idade. Entretanto, não foram observadas diferenças na deglutição, status funcional e manifestações musculoesqueléticas.

Conclusão

Os pacientes com Síndrome Pós-Covid-19, estratificados conforme o Índice de Massa Muscular Esquelética Apendicular, apresentaram risco de desnutrição e obesidade. Destaca-se a persistência de fadiga, fraqueza, mialgia e artralgia após seis meses da alta hospitalar. Esses achados ressaltam a importância do cuidado integral ao paciente com a Síndrome Pós-Covid-19.

Palavras-chave: *Infecções por Coronavirus. Estado funcional. Unidades de terapia intensiva. Músculos. Avaliação nutricional.*

INTRODUCTION

Coronavirus disease - 2019 (Covid-19) is a systemic disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It usually manifests with mild symptoms, although in some cases,

especially in the elderly, men, and people with obesity and/or comorbidities, it can progress to a severe form [1-5]. Among hospitalized patients, over 12% require treatment in the Intensive Care Unit (ICU), which may involve endotracheal intubation and nutritional therapy [6]. In Brazil, among the first 250.000 hospitalizations for Covid-19, 39% of patients were admitted to the ICU and 59% died, with 80% receiving invasive mechanical ventilation. The proportion of deaths was higher in men (56%) and patients with a mean age of 60±17 years [7].

Weight loss, especially of muscle mass, is common among critically ill patients and those recovering from Covid-19 [8-10]. The causes involve previous health conditions, gastrointestinal symptoms (nausea, vomiting, diarrhea, mild abdominal pain, and lack of appetite) from the direct action of the virus, the repercussions of ICU treatment, and the inflammatory reaction of the disease [8,9]. Studies have indicated that acute or chronic inflammation can induce malnutrition [11,12], and patients with severe Covid-19 are susceptible to it due to cytokine storms (higher blood levels of interleukin [IL] IL-6, IL-8, IL-10, and fractalkine), intubation and mechanical ventilation, persistent dysphagia, and malnutrition associated with a deficient or inadequate nutritional formula. This scenario may compromise the patients' nutritional status, influencing changes in the body-composition, primarily the amount, structure, and function of skeletal muscles [13]. Muscle damage is also associated with prolonged bed rest and medications such as dexamethasone, neuromuscular blockers, sedatives, opioids, and hypercortisolemia, and the latter may even contribute to intestinal dysmotility and weight loss [9,12].

A successful rehabilitation after the acute period of the disease, with improved functionality, is associated with adequate nutrition. Although most patients affected by Covid-19 are obese, few studies have shown their nutritional conditions after the ICU discharge [12,14]. The loss of muscle mass and function which characterizes sarcopenia has even more significant implications when it affects people with obesity [15]. In light of these findings, the nutritional and functional status due to muscle damage must be better investigated. Moreover, Post-Covid-19 Syndrome is defined by persistent clinical signs and symptoms that appear during or after Covid-19, and it may persist for over 12 weeks and cannot be explained by an alternative diagnosis that may have implications for the rehabilitation of these patients [16]. Given this context, this study aimed to evaluate the nutritional and functional status, swallowing disorders, and musculoskeletal manifestations of patients with Post-Covid-19 Syndrome, stratified by the Appendicular Skeletal Muscle Mass Index (ASMI).

METHODS

A cross-sectional study was conducted at the University Hospital of the Federal University of *Santa Maria, Rio Grande do Sul*, Brazil. The study was approved by the Ethics Committee (Process nº 4.527.287) and performed in accordance with the Declaration of Helsinki. All subjects provided written informed consent before participating, and the recruitment took place between January and May 2021. All patients were recruited from the waiting list for rehabilitation at the Post-covid-19 Syndrome Outpatient Rehabilitation Program of the same hospital. The criteria of eligibility included adult patients (≥18 years of both sexes) with Covid-19 admitted to intensive care and who presented Post-Covid-19 Syndrome six months after being discharged from the hospital (convenience sample). The exclusion criteria were non-attendance at outpatient appointments.

An initial anamnesis was performed to collect sociodemographic data, previous diseases, and aspects of hospitalization such as the length of stay and the need for invasive mechanical ventilation. The self-reported Body Mass Index (BMI) was assessed during the first outpatient nutritional assessment after the hospital discharge; the current complaints of musculoskeletal manifestations were also recorded.

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The multidisciplinary team assessed the nutritional status using a nutritional questionnaire Mini Nutrition Assessment (MNA) and anthropometric and body composition assessment using a hand-to-foot bioelectrical impedance method (Tanita BC 601, Tokyo, Japan). The MNA has high sensitivity, specificity, and prognostic value for malnutrition; it is a validated screening method for the elderly and it is used with hospitalized adult patients. According to the sum of the obtained scores, the patient is classified as having adequate or normal nutritional status (MNA ≥24), being at risk of malnutrition (MNA 17–23.5), or malnourished (MNA <17) [17-19].

The anthropometric evaluation measured the most voluminous point of the right calf and the brachial region with an inelastic measuring tape. The height was checked with a stadiometer (Personal Caprice – Sanny ES2060) with the patient standing with his back to the evaluator, feet together, and arms along the body. The measurement of the right calf circumference ≤31 cm was considered indicative of loss of muscle mass [20]. The formula for BMI is weight in kilograms divided by height in meters squared and classified, and according to the World Health Organization, classified as underweight (BMI ≤18.5 kg/m^2), appropriate weight (18.5 <BMI <25 kg/m^2), overweight (25 ≤BMI <30 kg/m^2), and obese (BMI ≥30 kg/m^2). The body composition was measured according to the procedures of Domingos *et al.* [21].

The patients were stratified by loss of muscle mass according to ASMI (lean limb mass/height^2) with values below 6.76 kg/m^2 for women and below 10.76 kg/m^2 for men into the Loss of Muscle Mass Group (LMG) and No Loss of Muscle Mass Group (NLMG) [22].

The functional status was assessed using the Post-Covid-19 Functional Status Scale (PCFS), which has four questions to classify each patient into one of five categories with different degrees of functional limitation [23].

An experienced speech therapist evaluated swallowing disorders according to the Dysphagia Risk Evaluation Protocol (DREP) [24].

The data were analyzed using the GraphPad Prism 5 statistical software (GraphPad Software Inc., San Diego, CA, USA) The normality of the variables was verified by the Shapiro-Wilk test. The continuous variables are reported as a mean±standard deviation (SD) and 95% confidence interval (95% CI), and the categorical variables are presented in absolute frequencies and percentages. The comparisons between the groups were performed by the independent t-test and Fisher's exact test. The significance level was set at 5% for all analyses (p<0.05).

RESULTS

Thirty-eight patients were included in this study; 20 were classified as NLMG and 18 as LMG. Patient demographics are described in Table 1. According to the MNA scores, individuals from both groups were at risk of malnutrition (Figure 1). Obesity prevailed in the NLMG and LMG. With the exception of fat mass, body composition, and anthropometry were significantly different between patients with and without loss of muscle mass (Table 2).

The functional status in both groups is shown in Figure 2; 50% of the patients with loss of muscle mass reported mild limitations, and 38% reported moderate limitations with the need for some adaptations in their daily activities. The functional impairment was moderate to severe in patients without muscle loss, although no differences were observed between the groups.

Table 1 – Characterization of patients with Post-Covid-19 Syndrome in groups with and without loss of muscle mass. *Santa Maria* (RS), Brazil, 2021.

Characteristics	Total (n=38)		NLMG (n=20)		LMG (n=18)		*p*-value
Sex - n(%)							
Male	21	(55.26)	3	(15.00)	18	(100.00)	0.001*
Female	17	(44.74)	17	(85.00)	-	-	
Age - M±SD	55.39±13.92		49.45±12.67		61.89±12.49		0.001**
School characteristics - n(%)							
Elementary	5	(13.16)	3	(15.00)	2	(11.11)	0.15
High school	25	(65.79)	10	(50.00)	15	(83.34)	
Higher education	8	(21.05)	7	(35.00)	1	(5.55)	
Previous diseases - n(%)							
Hipertension	26	(68.42)	12	(60.00)	14	(77.78)	0.24
Diabetes	14	(36.84)	6	(30.00)	8	(44.45)	0.36
Dyslipidemics	12	(31.58)	6	(30.00)	6	(33.34)	0.82
COPD	5	(13.16)	1	(5.00)	4	(22.23)	0.12
Heart disease	5	(13.16)	2	(10.00)	3	(16.67)	0.54
Asthma	2	(5.26)	2	(10.00)	-	-	
Kidney disease	1	(2.63)	-	-	1	(5.56)	
Hospitalization							
LOS - M±SD (days)	18.54±10.89		15.45±10.56		16.78± 9.38		0.69
IMV - n(%)	14	(36.84)	8	(40.00)	6	(33.33)	0.75
Post discharge							
Weight loss - M±SD	8.89±6.07		8.3±5.6		9.6±6.6		0.49
Swallowing disorders - n(%)							
DREP level I	31	(81.58)	16	(80.00)	15	(83.33)	0.99
DREP level II	7	(18.42)	4	(20.00)	3	(16.67)	0.99
Musculoskeletal manifestations - n(%)							
Fatigue	14	(36.84)	8	(40.00)	6	(33.33)	0.74
Weakness	15	(39.47)	6	(30.00)	9	(50.00)	0.32
Myalgia	12	(31.58)	5	(25.00)	7	(38.89)	0.49
Arthralgia	10	(26.32)	3	(15.00)	7	(38.89)	0.14

Note: *$p<0.05$ Fisher's exact test; **$p<0.05$ independent samples t-test. DREP: Dysphagia Risk Evaluation Protocol; IMV: Invasive Mechanical Ventilation; LMG: Loss of Muscle Mass Group; LOS: Length of hospital stay; NLMG: No Loss of Muscle Mass Group; M: Mean; SD: Standard Deviation.

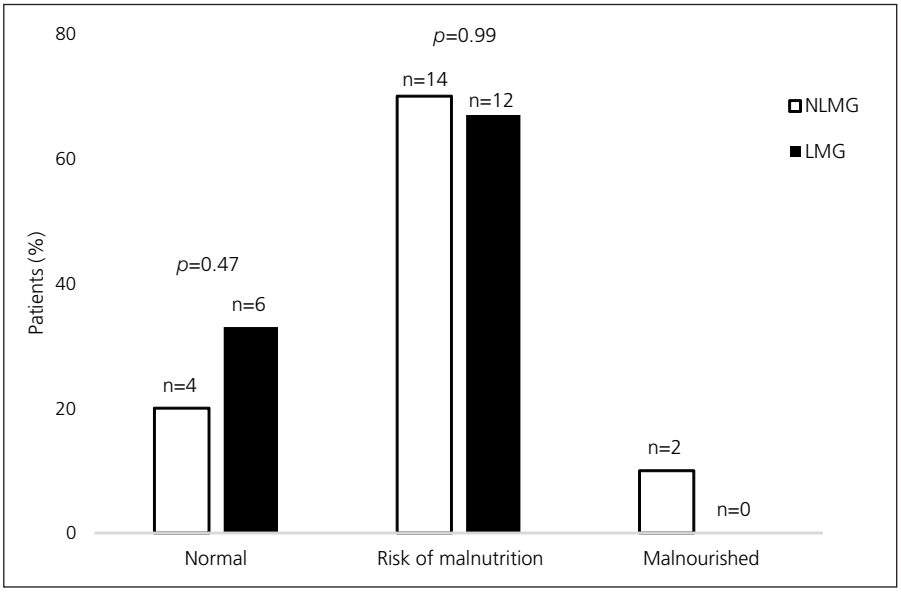

Figure 1 – Nutritional status of patients with Post-Covid-19 Syndrome in: No Loss of Musce Mass Group (NLMG) and Loss of Muscle Mass Group (LMG). *Santa Maria* (RS), Brazil, 2021.

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T**able 2** – Comparison of nutritional status between patients with Post-Covid-19 Syndrome with and without loss of muscle mass. *Santa Maria* (RS), Brazil, 2021.

Nutrition	Total (n=38)	NLMG (n=20)	LMG (n=18)	Difference	95% CI	*p*-value
	M±SD	M±SD	M±SD	M±SD		
MNA	22.54±3.58	21.82±3.93	23.33±3.06	1.51±1.15	0.83;3.85	0.20
Anthropometry						
BMI	32.09±5.48	33.76±6.34	30.23±3.66	-3.53±1.71	6.99;-0.07	0.05
Calf circumference	40.08±4.26	41.92±4.34	38.14±3.27	-3.69±1.24	6.21;-1.17	0.01
Body composition						
Muscle mass	54.73±9.54	51.28±9.52	58.56±8.20	7.28±2.90	1.39;13.16	0.02
Fat mass	32.65±16.30	37.57±17.07	27.89±15.35	-9.68±5.09	20.00;0.64	0.07
Bone mass	2.89±0.46	2.73±0.47	3.08±0.41	0.34±0.14	0.05;0.63	0.02
Water	47.71±6.45	44.33±5.29	51.48±5.86	7.15±1.76	3.58;10.72	0.001
% body fat	34.66±9.17	39.99±8.17	28.76±6.64	-11.23±2.37	16.03;6.42	0.001

Note: BMI: Body Mass Index; CI: Confidence Interval; LMG: Loss of Muscle Mass Group; MNA: Mini Nutritional Assessment; NLMG: No Loss of Muscle Mass Group; M: Mean; SD: Standard Deviation.

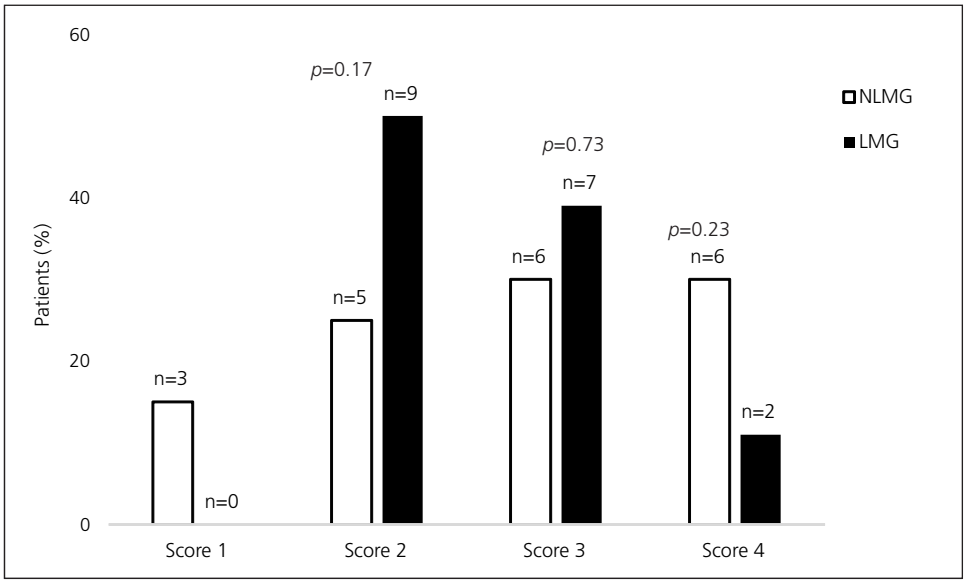

Figure 2 – Post-Covid-19 Functional Status (PCFS) in: No Loss of Muscle Mass Group (NLMG) and Loss of Muscle Mass Group (LMG). *Santa Maria* (RS), Brazil, 2021.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the nutritional status, functional status, swallowing alterations, and musculoskeletal manifestations of patients with Post-Covid-19 Syndrome. Other studies have not investigated these outcomes, stratified by the ASMI, in the post-discharge follow-up based on specialized and interdisciplinary assessments. The main findings demonstrated the risk of malnutrition and obesity. The persistence of fatigue, weakness, myalgia, and arthralgia at 6 months after hospital discharge are noteworthy. The results showed that the loss of muscle mass prevailed in the male participants. The variables associated with nutritional assessment, such as the BMI, calf circumference, and body composition, were significantly different between the groups with and without loss of muscle mass,

although these groups did not differ in MNA scores. We also demonstrated mild functional limitations, assessed by PCFS scale, at 6 months after hospital discharge; however, no differences were observed between the groups. Patients in both groups were not at risk of dysphagia. The skeletal muscle manifestations of fatigue, weakness, myalgia, and arthralgia were present in all patients.

Our study demonstrated that patients with and without loss of muscle mass, classified by BMI, showed overweight/obesity, therefore, without differences regarding fat mass in the bioimpedance evaluation. Several studies showed that patients with obesity are more likely to be hospitalized with Covid-19, and overweight and class I–III obese individuals were at a higher risk of mechanical ventilation and mortality [2,4,25-27]. There is increased expression of the Angiotensin-Converting Enzyme 2 (ACE2) receptor in adipose tissue, allowing SARS-CoV-2 to enter cells and thus working as a functional virus reservoir [28]. Hence, both obesity and SARS-CoV-2 infection can cause hyperglycemia. The former occurs by insulin resistance and the latter is caused by damage to pancreatic B cells, contributing to the worsening of metabolic dysfunction. The pro-inflammatory state and metabolic dysregulation of people with obesity may favor cytokine storm, leading to a worse prognosis. Other implications of obesity occur in respiration mechanics, altered vitamin D levels, and modified intracellular pH, and these aspects presumably have significant consequences for patients with Covid-19 [29].

Despite being overweight and obese (according to the NMA), most patients with Post-Covid-19 Syndrome were at risk of malnutrition, with a prevalence of 70% in the NLMG and 66.67% in the LMG; malnutrition was present in 10% of NLMG patients. Li *et al.*, observed the risk of malnutrition in 27.5% and malnutrition in 52.7% of patients hospitalized with Covid-19 [28]. Few studies have assessed the nutritional status of Covid-19 patients after the ICU discharge. Bedock *et al.*, used the Global Leadership Initiative on Malnutrition criteria and reported an overall prevalence of malnutrition of 42.1%, and the prevalence of malnutrition reached 66.7% in patients admitted to the ICU [30]. Haraj *et al.*, found that 65.9% of patients, assessed by the MNA, were at risk of malnutrition and 14.6% were malnourished [31]. In our study, during the first outpatient nutritional assessment, the patients self-reported a loss of 8 kg immediately after hospital discharge. Notably, monitoring the nutritional status and body composition after the ICU discharge is essential and often neglected, even for cultural reasons [8]. In a nested cohort study within a randomized controlled trial in critically ill patients, Ridley *et al.*, showed that energy and protein intake in the post-ICU hospitalization period was less than the estimated and measured energy requirements [32]; moreover, identifying malnourished patients or patients at risk of malnutrition is crucial in the Post-Covid-19 recovery process [18]. Gobbi *et al.*, assessed the presence of a malnutrition condition in SARS-CoV2 patients after the acute phase and the effects of a multidisciplinary rehabilitation program on nutritional and functional status. The authors dignosed a malnutrition condition in 60% of patients and demostranted that the individualized nutritional intervention with adequate energy and protein intake combined with aerobic and strengthening exercise improved nutritional and functional status [12].

The loss of muscle mass in male patients could be explained by sex-based differences, specifically to higher type-IIA muscle fiber size. Generally, male muscles are more fatigable than female muscles. The female sex hormones, through the estrogen receptor-mediated signaling have been shown to exert protective effects on skeletal muscle mitochondrial biogenesis, muscle mass, regeneration, and satellite cell growth [33]. Furthermore, in our study, given the higher age in the loss of muscle mass group, we postulate that the findings of body composition could be associated with the variables age and sex. The calf circumference was significantly different between the groups, although the values were above the cutoff point for mass loss in both groups, and the more significant amount of adipose tissue may have interfered in the measurement. In obesity, alterations in skeletal muscle metabolism may modify body composition, with greater fat mass and substantial loss in mass and muscle function [15,34]. The analysis of body composition

by bioelectric impedance of Covid-19 patients admitted to the ward or ICU did not differ in the study of Moonen *et al.* [35]. However, in other studies, increased adipose/muscle tissue ratio was associated with higher Covid-19 mortality rates [5,36].

The exact mechanisms of muscle wasting in Covid-19 are unclear. Studies suggest that the cytokine storm associated with oxidative stress severely damages myocytes and that interrelated factors (*e.g.*, advanced age, metabolic diseases, inflammatory response, malnutrition, disease severity, need for orotracheal intubation, among other factors) are involved, justifying muscle loss and functional impairment in the post-Covid-19 stage [8,10,13]. Older age and male sex were associated with worse functional scores on the Barthel scale in Covid-19 patients discharged from hospital [37]. Another study with 444 patients showed a significant variation in the PCFS scale according to sex, age, comorbidities, oxygen requirements, and ICU stays [38]. Taboada and collaborators demonstrated that the age and length of hospital stay were associated with higher risk of limitations in the functional status (grade II-IV of the PCSF) [39]. Nevertheless, in this study, there were no differences in the assessment of functional status between patients with muscle depletion. The fact that Covid-19 severity (as observed by need for invasive mechanical ventilation) and the length of hospital stay did not differ between the groups may justify the similar functional impairment between the groups as well as the similar symptoms of musculoskeletal manifestations and dysphagia.

Between 10% and 65% of survivors who had mild/moderate Covid-19 present symptoms of Post-Covid-19 Syndrome for 12 weeks or more [40]. It has been reported in patients with mild or severe Covid-19 and irrespective of the severity of the symptoms during the acute phase [40,41]. Our findings corroborate the conclusions of several other studies. Huang *et al.*, evaluated 1,773 patients 6 months after hospital discharge and reported fatigue or muscle weakness (63%) were the most common symptoms [42]. Carfi *et al.*, reported that 87% of 143 Covid-19 survivors reported symptoms of fatigue (53.1%), dyspnea (43.4%), arthralgia (27.3%), and chest pain (21.7%) [43].

Despite the relevance of our results, some limitations should be considered. First, we did not use dual-energy X-ray absorptiometry or magnetic resonance imaging to evaluate the body composition and skeletal muscle quantity and quality. In association with computed tomography scans for the diagnostic accuracy, these screening tools are considered the most precise [44]. Second, we did not evaluate swallowing with videofluoroscopy (the gold standard exam). Third, this is a single-center study with a relatively small number of patients. Forth, we did not investigate the existence sarcopenia (defined by the muscle strength, physical performance, and muscle mass). Future research should be directed toward addressing these limitations.

CONCLUSION

Patients with Post-Covid-19 Syndrome, stratified according to the ASMI, were at risk of malnutrition and obesity. The persistence of fatigue, weakness, myalgia and arthralgia at 6 months after hospital discharge is noteworthy. These findings corroborate the establishment of specialized interdisciplinary post-Covid-19 outpatient clinics and the importance to provide these patients with comprehensive care, as well as conduct further research and develop new therapeutic options for patients with Post-Covid-19 Syndrome.

CONTRIBUTORS

JA SOUZA, IM ALBUQUERQUE, and AS PASQUALOTO conceptualized the study; collected the data, supervised, analysed and/or interpreted it; they also worked on the writing, revising and/or editing the manuscript; TD SANTOS, VB

BERNI, and TD FELTRIN worked in the data acquisition, supervision, analysis and/or interpretation; writing, revising and/or editing the manuscript.

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