



## REVIEW ARTICLE

## COVID-19 related to sarcopenia: Current perspectives on etiology, clinical implications, and nutritional rehabilitation

*Sarcopenia relacionada à COVID-19: Perspectivas atuais da etiologia, implicações clínicas e reabilitação nutricional*

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## KEYWORDS

Inflammation  
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## ABSTRACT

Sarcopenia is a progressive skeletal muscle disorder characterized by reduced strength and quality. Pathophysiological mechanisms, clinical aspects, and nutritional points were related to sarcopenia in COVID-19 found in skeletal muscle during and after the disease course, which corroborated the development of adverse events. Declining physical activity, insufficient protein intake, and worsened proinflammatory response have been shown to have negative consequences on muscle protein synthesis, potentiating the risk of acute sarcopenia. Obesity sarcopenia has also been shown to worsen the prognosis of patients with SARS-CoV-2. Nutritional rehabilitation is used to prevent or minimize the development of acute sarcopenia. Dietary recommendations include increased energy supply and protein intake of 1.2 to 2.0 g/kg of body weight. Evidence suggests that aging with sedentary behaviors, pathophysiological changes, and inflammation alter body composition. In addition, nutritional deficiencies are predictors and aggravators of acute sarcopenia in COVID-19.

## PALAVRAS-CHAVE

Inflamação  
Massa muscular  
esquelética  
Nutrição  
Sarcopenia  
SARS-CoV-2

## RESUMO

Sarcopenia é um distúrbio progressivo do músculo esquelético caracterizado pela redução da força e qualidade. Mecanismos fisiopatológicos, aspectos clínicos e nutricionais foram relacionados à sarcopenia no COVID-19 encontrada no músculo esquelético, durante e após o curso da doença, o que corroborou para o desenvolvimento de eventos adversos. O declínio da atividade física, a ingestão insuficiente de proteínas e piora da resposta pró-inflamatória demonstraram ter consequências negativas na síntese de proteínas musculares, potencializando risco de sarcopenia. A obesidade sarcopênica também demonstrou piorar o prognóstico de pacientes infectados com SARS-CoV-2. A reabilitação nutricional pode prevenir ou minimizar o desenvolvimento de sarcopenia. As recomendações dietéticas incluem maior oferta de energia e maior ingestão de proteínas de 1,2 a 2,0 g/kg de peso corporal. Evidências sugerem que o envelhecimento com comportamentos sedentários, alterações fisiopatológicas e inflamação, alterações na composição corporal, deficiências nutricionais são preditores e agravantes da sarcopenia aguda na COVID-19.

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## INTRODUCTION

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As a new disease, its pathophysiology is still being studied; however, it is known that COVID-19 is associated with systemic inflammation, with a broad response in the inflammatory cascade, especially with the increased production of pro-inflammatory cytokines. Serum concentrations of inflammatory cytokines, including tumor necrosis factor-alpha (TNF- $\alpha$ ), were shown to be higher in patients with severe<sup>1-5</sup>.

This inflammatory condition has negative consequences on muscle protein synthesis. TNF- $\alpha$  decreases the messenger ribonucleic acid (mRNA) translation efficiency and increases ubiquitin ligase activation, proteins that are markers of the muscle atrophy process. In turn, establishing an anabolic resistance state favors acute sarcopenia<sup>2,4,5</sup>.

The term "sarcopenia" was conceptualized in 2010 as "muscle mass reduction", a widely accepted definition conceived by *the European Working Group on Sarcopenia in Older People*<sup>6</sup>. However, in 2019, this concept was updated, characterizing sarcopenia as a "reduction in muscle strength and quality"<sup>7</sup>. Sarcopenia is considered a progressive and generalized skeletal muscle disorder inherent to aging, which exposes the individual to greater risks of adverse outcomes, including trauma, physical disability, and mortality<sup>7</sup>. Current evidence shows that, after a stressful event, such as a SARS-CoV-2 infection, hospitalized patients have an increased potential for acute sarcopenia, which develops in less than six months<sup>8</sup>.

According to the literature, patients with COVID-19 are more likely to lose weight during and after hospitalization. In addition, inflammation caused by the disease and the weight loss etiology was the reduction of food intake and essential nutrients, accompanied by inappetence, ageusia, fever, and use of sedative drugs, which can contribute to malnutrition and acute sarcopenia<sup>3</sup>. According to the *Global Leadership Initiative on Malnutrition (GLIM)*, malnutrition is based on the criteria of non-voluntary weight loss, low body mass index (BMI), loss of muscle mass, reduced food intake, and disease-related inflammation<sup>9</sup>. Still, it is important to highlight that patients with an inadequate earlier nutritional status are more susceptible to worse clinical outcomes<sup>10</sup>.

Thus, immediate assessment of nutritional status and body composition, focusing on muscle quality and strength, is crucial for diagnosing sarcopenia in patients with COVID-19 during hospitalization and post-discharge period<sup>11</sup>. Data on this topic increases the need to explore information currently available in the literature. Thus, this review aims to compile the findings of existing studies and clarify the etiological factors, pathophysiological mechanisms, clinical implications, and nutritional points of view related to sarcopenia in COVID-19.

## SARCOPENIA ETIOLOGY IN COVID-19

Global exposure to SARS-CoV-2 has forced governments to decide on restriction measures to reduce

its spread. Closing shops, restaurants, and schools are examples of restrictive measures that have led to changes in the world's population routine. Due to restrictions in limiting people's movement, the decline of physical activity was favored<sup>12,13</sup>. Deficient food intake, increased levels of stress and anxiety during the pandemic, and disease-related inflammation are considered to be possible etiologic factors of COVID-19-related sarcopenia<sup>14,15</sup>.

Physical inactivity and sedentary behaviors favor skeletal muscle loss through mechanisms such as induced anabolic resistance, insulin resistance, mitochondrial dysfunction, and oxidative stress, which inhibit pathways related to muscle protein synthesis and activate muscle protein catabolism pathways<sup>14</sup>. The muscle degradation process corresponds to muscle loss through myocyte atrophy and hypoplasia. Hypoplasia is believed to occur secondary to motor neuron death, denervation, and atrophy of muscle fibers secondary to proteolytic pathways, further contributing to sarcopenia and worsening of the general condition<sup>16</sup>.

In addition, it is noted that poor/insufficient food intake and increased stress and anxiety levels in the population are also factors that promote muscle homeostasis imbalance<sup>2,12,17</sup>. Considering the current scenario, a concern related to preexisting sarcopenia in patients with COVID-19 is the increased hospitalization risk<sup>18</sup>.

In this follow-up, disease progression is reflected by excessive drug administration, multiple organ failure, admission to the intensive care unit (ICU), increased need for mechanical ventilation, and mortality<sup>5</sup>. In addition, prolonged mechanical ventilation can lead to diaphragm atrophy, resulting in a decrease in muscle thickness, accompanied by below-normal respiratory effort<sup>19</sup>. However, because of the pulmonary complications caused by COVID-19, it is often necessary to use mechanical ventilation to avoid even worse prognoses<sup>19-22</sup>. Since the beginning of the SARS-CoV-2 pandemic, other common manifestations have been detected among those affected, such as fever, dry cough, dyspnea, generalized myalgia, migraine, tonsillitis, viral pneumonia, worsened inflammatory response and pathophysiological changes, and reduction in skeletal muscle mass<sup>14,20</sup>.

## HISTOPATHOLOGICAL CHANGES IN SKELETAL MUSCLE, INFLAMMATION, AND SARCOPENIA IN COVID-19

Skeletal muscle mass undergoes some histopathological changes during the disease course, which can result in sequelae even after infection. After entering the human body, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), which acts as a virus receptor on the cell surface. ACE2 is present in human organs, including the nasal and oral mucosa, lungs, stomach, intestines, kidneys, liver, and brain<sup>23,24</sup>.

After the virus adheres to the cell membrane, its entry is facilitated by the transmembrane enzyme serine protease type 2 (TMPRSS2). In the intracellular environment, the virus replicates and disrupts cellular functions, which can lead to cell death and tissue dysfunction<sup>25,26</sup>. In muscle tissue, unprogrammed cell death is visualized through the presence of tissue

necrotic fibers, resulting primarily from the inflammatory process and infiltration of immune cells at the muscle site<sup>25</sup>.

To reduce necrotic tissue, the organism reacts by proliferating fibroblastic cells, which replace the affected tissue with fibrous connective tissue. The mechanisms implicated include dysregulation of transforming growth factor beta (TGF- $\beta$ ) and activation of genes involved in fibrosis<sup>27</sup>.

In this context, the development of pulmonary fibrosis in COVID-19 patients is an important pathological change that can compromise the respiratory muscles<sup>27</sup>. Pulmonary involvement generates an overload of work in respiratory muscles, especially in the diaphragm, making gas exchange difficult and reducing tissue oxygenation. Thus, symptoms such as dyspnea, fatigue, and respiratory failure are part of the clinical picture of the disease<sup>28,29</sup>.

Furthermore, lung tissue damage caused by SARS-CoV-2, in addition to the deregulation of the innate immune system due to high viral load, is a clinical complication responsible for the excessive secretion of proinflammatory cytokines and chemokines in the body (IL-6, IP-10, IFN $\gamma$ , IL-2, IL-10, G-CSF, MIP1 $\alpha$ , TNF and chemokines) by macrophages, monocytes, and T cells<sup>30</sup>. This characteristic hyperinflammatory response in COVID-19 represents the severe pathophysiological form of the disease<sup>31</sup>.

In addition, high concentrations of inflammatory cytokines enable the activation of biochemical pathways involved in skeletal muscle loss<sup>32,33</sup>. This pathway involves changes in the availability of eukaryotic translation initiation factor 4E (eIF-4E). Activation of this pathway positively regulates MuRF1, a protein that mediates muscle atrophy<sup>8</sup>.

Unprogrammed cell death is visualized through the presence of necrotic fibers in muscle wasting, mainly resulting from the high COVID-19 inflammatory processes with infiltration of immune cells in the skeletal muscle tissue<sup>25</sup>.

Worsening lung function generates an overload of work on the respiratory muscles, especially on the diaphragm, making gas exchange difficult and reducing tissue oxygenation. Thus, symptoms such as dyspnea, fatigue, and respiratory failure are part of the clinical disease<sup>28,29</sup>.

Therefore, clinical conditions with a high inflammatory response, such as COVID-19, can harm the patient's strength and muscle mass<sup>5</sup>. Intense proteolysis and muscle atrophy are even more frequent in critically ill patients because of greater activation of genes related to the ubiquitin-proteasome system<sup>32</sup> and proteases, such as calpain<sup>34</sup>. Other musculoskeletal changes include rupture of the sarcomere structure and loss of myosin<sup>25</sup>.

Although the development of acute sarcopenia in COVID-19 involves particularities, the hyperinflammatory state promoted by the disease is one of the main precipitating factors of this condition<sup>4</sup>. Even patients with myopathy associated with COVID-19 demonstrated alterations in genes involved in skeletal muscle regeneration and extracellular matrix deposition. This fact explains muscle catabolism potentiation, with consequent persistence of symptoms, even in the post-COVID-19 period<sup>25,35,36</sup>.

Based on the critical relationship between inflammatory cytokines and sarcopenia, studies suggest that serum cytokine levels could be biological markers of sarcopenia. However, this statement is still quite conflicting<sup>37</sup> since the literature shows that aging-related biochemical changes are an important risk factor for acute sarcopenia in COVID-19. Elevated levels of TNF- $\alpha$  and IL-6 are observed in the skeletal muscles of older individuals, mediating the promotion of catabolic signals<sup>38</sup>. Furthermore, decreased anabolic hormone concentrations, including growth hormone (GH), testosterone, thyroid hormones, and insulin-like growth factor (IGF-1), lead to reduced anabolic hormonal signals<sup>8</sup>.

Therefore, the elderly is considered to be the most vulnerable population to develop negative clinical outcomes. Similarly, patients with sarcopenic obesity also have a greater potential for adverse events throughout the disease and after infection<sup>39</sup>.

## SARCOPENIC OBESITY AND ITS IMPLICATIONS IN THE DISEASE COURSE

Sarcopenic obesity is defined as the simultaneous presence of obesity and sarcopenia with increased risks of disability, mortality, and metabolic diseases<sup>40</sup>. Furthermore, individuals with sarcopenic obesity have a higher risk of infection and a worse prognosis for COVID-19 and are more susceptible to developing the severe form of the disease<sup>41</sup>.

Obesity alone increases the chances of developing severe COVID-19 by 1.8 times<sup>42</sup>. In sarcopenic obesity, where there is excess adipose tissue and impairment of muscle mass and strength, the chances increase 2.6 times<sup>41</sup>. Kara et al.<sup>43</sup> also highlighted a positive relationship between sarcopenic obesity and increased risk of severity and mortality from the disease. Thus, losses in the patient's nutritional status are proportionally related to COVID-19 infection severity, recovery time, incidence of complications, and higher mortality<sup>11,43,44</sup>.

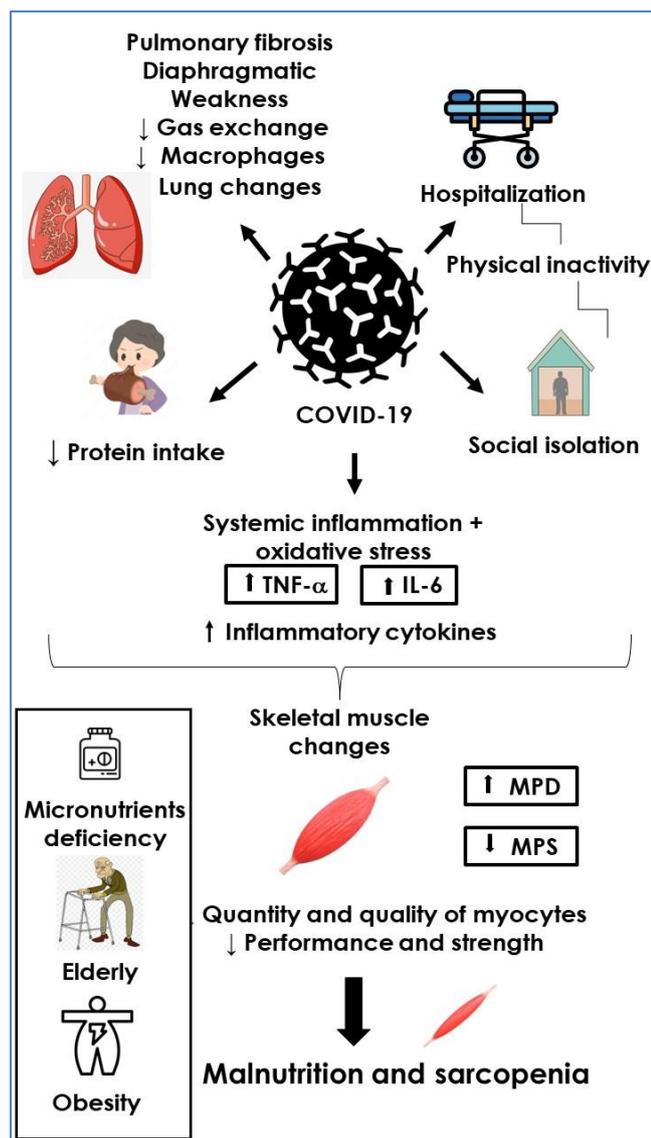
Contributing factors to the worsening prognosis in sarcopenic obese individuals include the increased susceptibility of this population to metabolic disorders such as insulin resistance, cardiovascular complications, immune dysregulation, including failures in innate and adaptive immune responses, and chronic systemic inflammation<sup>45,46</sup>. Peripheral insulin resistance has been identified as one of the main complications responsible for this outcome. A defect in insulin action inhibits the Akt-kinase pathway, increasing gene expression related to muscle atrophy, such as MAFbx/atrogen 1, MuRF1, which alters muscle turnover<sup>25</sup>.

It should also be noted that obesity is commonly associated with a micronutrient deficiency (vitamins A, B6, B12, folate, vitamin C, D, E, zinc, selenium, and copper) and alterations in the intestinal microbiota, which increases the immunosuppression risk in obese patients<sup>47</sup>. Thus, preventive or in-hospital interventions, such as individualized nutritional therapy, are essential for better clinical outcomes and patient recovery.

Figure 1 illustrates how COVID-19 triggers significant pulmonary changes, including decreased gas exchange, pulmonary fibrosis, and diaphragmatic

weakness. Furthermore, reduced protein intake and physical inactivity caused by hospitalization or social isolation promote the activation of protein degradation pathways, predisposing the patient to malnutrition and sarcopenia. Elderly, obese, or micronutrient-deficient patients are at a greater risk of developing this scenario.

Nevertheless, COVID-19 symptoms and their clinical and nutritional implications may persist even after infection. Although the individual no longer has the active virus in the body, disease sequelae still exist, a situation currently described as “post-COVID-19 syndrome”.



**Figure 1** – Sarcopenia etiology associated with COVID-19 and its clinical and nutritional implications. MPD - Muscle protein degradation; MPS - Muscle protein synthesis.

### POST-COVID-19 SYNDROME: IMPACT AT HOSPITAL DISCHARGE

It is estimated that mortality rates of COVID-19 vary between 1% and 7%<sup>48</sup>; that is, most of those affected by the disease recover. However, the long-term implications mediated by the virus in the body are still

being studied. Some post-COVID-19 symptoms already described are fatigue, dyspnea, angina and migraine, cognitive disorders, hair loss, ageusia, anosmia, digestive symptoms, and muscle wasting<sup>49</sup>. The continuity of symptoms may be related to cell damage and the innate immune response with inflammatory cytokine production induced by SARS-CoV-2 infection<sup>50</sup>.

The amplitude of virus action in human organisms may be related to the manner in which it infects cells. complications Despite the severe effects on the respiratory system, the abundant ACE2 presence in the gastrointestinal tract cells also causes in this system<sup>51</sup>. Frequently reported gastrointestinal symptoms include anorexia, vomiting, nausea, abdominal pain, diarrhea, and gastrointestinal bleeding<sup>48</sup>. Still, 70-80% of patients have taste alterations. Changes also include ageusia, hypogeusia and dysgeusia<sup>52</sup>.

These symptoms, along with anosmia and dysphagia, are also common in these patients and can lead to reduced food intake. Furthermore, increased inflammation promoted by COVID-19 is associated with increased catabolism and anabolic resistance, leading to increased energy demand<sup>4</sup>.

Changes in food consumption resulting from gastrointestinal symptoms and anorexia, an increase in cellular catabolism processes, damage caused by worsened inflammatory processes, and physical inactivity are some of the factors related to the development of sarcopenia in the post-COVID-19 period<sup>5</sup>.

In addition, COVID-19 has the potential to alter the gut microbiota, including the multiplication of opportunistic infectious microorganisms and the reduction of beneficial commensal bacteria. In COVID-19, *Faecalibacterium prausnitzii*, a gut probiotic bacterium, is usually associated with good gastrointestinal health and is inversely correlated with disease severity<sup>50,53</sup>. Although the relationship between microbiota and sarcopenia is not fully understood, the influence of some gut microbiota bacteria on muscle mass has been observed, particularly among the elderly<sup>51,54</sup>.

### NUTRITIONAL SUPPORT AND REHABILITATION IN COVID-19-RELATED SARCOPENIA

Although COVID-19-related sarcopenia is a multifactorial condition<sup>25</sup>, nutritional interventions are adjuvant measures to optimize the recovery muscle mass and strength of patients, thus improving their clinical and nutritional prognosis (Figure 2). Diet therapy aimed at preventing COVID-19-related sarcopenia mainly consists of meeting the increased energy and protein requirements due to fever, mechanical ventilation, exacerbated work of respiratory muscles, increased immune response, and metabolic disorders<sup>55</sup>. Nutritional therapy for COVID-19 prevents or improves sarcopenia and attenuates oxidative stress and inflammation produced by the disease, enhancing the immune response to fight the infection<sup>56</sup>.

For eutrophic critically ill patients, the energy recommendation is 25 to 30 kcal/kg/day. For critically overweight and obese patients, this recommendation decreases to 21 kcal/kg/day<sup>55</sup>. Considering the daily

fluid intake, it is recommended that patients consume 2.5-3 L/day, preferably including water, but also milk, fruit juice, broth, sports drinks, coffee, and tea<sup>56</sup>.

Furthermore, a higher protein intake favors a positive nitrogen balance. Promoting greater muscle protein synthesis than degradation enables muscle mass maintenance and prevents a sarcopenic scenario<sup>57</sup>. Thus, the recommended protein supply for critically ill patients during the clinical disease course is 1.2 to 2.0 g/kg of body weight. For the malnourished elderly or those at risk of malnutrition, the suggested values are 1.2 to 1.5 g/kg<sup>55,58</sup>.

It is even recommended that protein consumption should be made with proteins of high biological value<sup>59</sup>. According to Ferrara et al.<sup>60</sup>, amino acid supplementation can also help prevent skeletal muscle loss and improve respiratory muscle strength. The amino acid leucine has been shown to be of greater importance for muscle protein synthesis<sup>32,61</sup>.

Barazzoni et al. (The European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines)<sup>47</sup> also recommend optimizing protein intake in obese COVID-19 patients (1.0 kg/day). Concurrently, slow and gradual weight loss is also suggested. Due to the risk of inducing or aggravating muscle wasting, caloric restriction is limited to a daily deficit of 500 kcal.

In addition, supplying nutrients and bioactive compounds with anti-inflammatory and antioxidant properties, such as omega-3 fatty acids, vitamin C, vitamin A, vitamin D, zinc, and phytochemicals (polyphenols and carotenoids)<sup>62</sup>, exert effects on response modulation inflammation and oxidative stress associated with COVID-19. Such substances avoid activation of the NF-κB transcription pathway, thereby preventing muscle atrophy<sup>8,62-64</sup>.

The recommendation of administering probiotics, particularly *Lactobacillus plantarum* DK119 or *L. casei* DN-114001, is also under study. The potential of these bacteria to increase the production of interleukin 12 and interferon  $\gamma$ , modulate macrophage and dendritic cell activity, and reduce inflammatory responses has the potential to protect the host from common infectious respiratory diseases and reduce disease duration<sup>65</sup>.

Thus, an adequate diet with nutrients that develop a healthy microbiota will help promote physical and psychological well-being among patients with post-COVID-19 syndrome<sup>56</sup>. Therefore, a diet rich in fiber, low in refined carbohydrates and trans-fat, and high in bioactive compounds, such as omega-3 fatty acids, may play a key role in recovery from post-COVID-19 syndrome<sup>56</sup>.

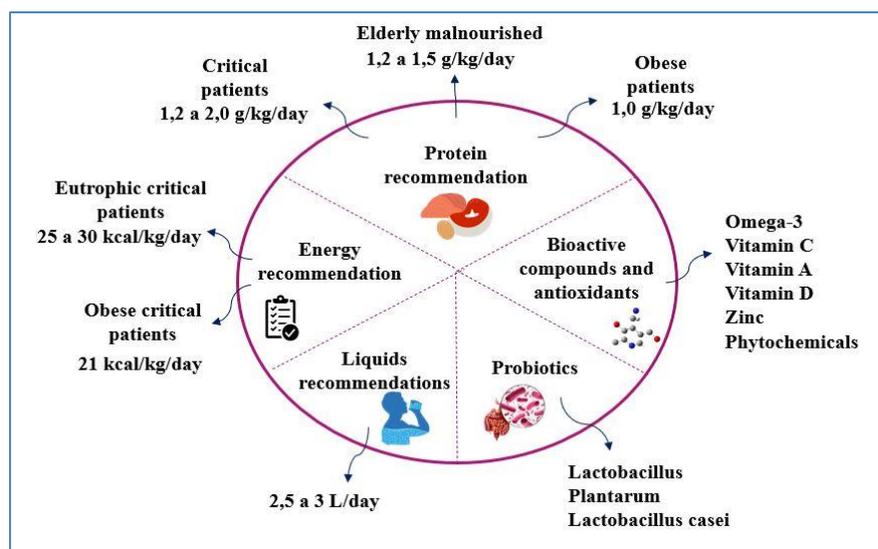


Figure 2 – Nutritional recommendations in COVID-19 and post-infection period.

## CONCLUSION

Finally, the current evidence suggests that aging in conjunction with sedentary behaviors, pathophysiological changes in skeletal muscle, disease-caused inflammation, changes in body composition, and nutritional deficiencies are predictors and aggravators of

acute sarcopenia in COVID-19.

Furthermore, more studies, mainly longitudinal and randomized clinical trials, are needed to detect early sarcopenia in patients with COVID-19 and to conduct clinical and nutritional treatments to improve the quality of life through muscle mass and function muscular reestablishment.

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