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Review Article

Sarcopenia in Coronavirus Disease (COVID-19): All to Know from Basic to Nutritional Interventions from Hospital to Home

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Coronavirus Disease (COVID-19) became a worldwide pandemic with a high hospitalisation rate in March 2020. COVID-19 infection and sarcopenia concentrate on the same pathway that increases the risk of sarcopenia. The resulting sarcopenia can cause severity of the disease, lower treatment efficiency, and physical disabilities for surviving COVID-19 patients. This review provides a practical overview of the importance, metabolism, mechanism, and link of COVID-19 with sarcopenia. In addition, all the concerns and treatments that healthcare experts need to consider from the hospital to the patients' homes with their timeline are explained. Nevertheless, sarcopenia is not limited to the hospital and can continue developing long after COVID-19 recovery. This situation makes continuous follow-up, sarcopenia monitoring, and interventions necessary until the removal of risks, even after recovery. Otherwise, a higher prevalence of sarcopenia and, as a result, higher morbidity, mortality, dependency, and disabilities in surviving COVID-19 patients can be expected.

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Highlights

- The mechanism of sarcopenia can be so close to COVID-19 pathology that it requires special care.
- Sarcopenia in COVID-19 patients is not limited to the hospital and can develop after recovery through the muscle-fat interaction cycle.
- COVID-19-related sarcopenia can become the leading cause of disabilities, morbidity, and mortality in the future.
- SARC-F, PG-SGA, MNA tools, and EWGSOP sarcopenia criteria can be proper tools for sarcopenia assessment during hospitalisation.
- Nutrition therapy can be the key intervention in stopping sarcopenia.
- Some interventions are better to be continued for months after discharge.

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Introduction

The 2019 novel coronavirus disease (COVID-19) became a worldwide pandemic on March 11, 2020, as reported by the World Health Organization (WHO) [1]. According to reports, more than 508 million cases and about 6.21 million deaths were caused by this disease until May 2022. Although standard diagnostic and prevention methods for COVID-19 have been established, a suitable effective treatment method is still lacking [2]. While most researchers have tried to solve the pandemic by studying medications and developing vaccines, the destructive effect of most co-diseases is not considered [2].

One of these diseases is "sarcopenia," defined as a decrease in muscle strength, mass, or performance [3]. Sarcopenia in the 1980s was defined as a progressive and generalised skeletal muscle disorder and has been classified as a disease since 2016 by the World Health Organization (WHO) [3][4]. Sarcopenia can lead to a higher mortality risk during hospitalisation or disabilities, falling, and functional limitations after discharge [3][4]. The leading cause of sarcopenia is ageing (usually more than 65 years old) or facing any catabolic situation. However, lifestyle, nutritional pattern, socio-economic status, and physical activity are other risk factors [4][5].

By considering the destructive effects of sarcopenia during hospitalisation and changes in the lifestyle of COVID-19 patients after hospitalisation, controlling this disease in COVID-19 patients is necessary. This review aims to examine sarcopenia in COVID-19 from basic to clinical science and provide considerations for treatment within the hospital and beyond.

Importance and the triangle link of Sarcopenia, COVID-19, and outcome

Sarcopenia is one of the most common hospitalization outcomes among all hospitalized patients [6][7]. The previous studies that assessed the effect of sarcopenia on the survival of patients with cancer [8], hepatocellular carcinoma [9], cardiovascular [10], and critical illness [6][7] also showed the importance of this disease. A higher length of stay, more inflammatory response, lower response to treatment, severe clinical status, and higher morbidity and mortality are sarcopenia's main impacts on hospitalized patients [11]. There is also evidence that sarcopenia impacts mechanical ventilation efficiency, which is essential during COVID-19 hospitalization [6][7]. All these effects are independent of the effect of the main illness, which shows its impact.

At the same time, COVID-19 hospitalisation, in many cases, is considered a critical illness [2][12][13]. Despite strong evidence specifying that critical illness caused by COVID-19 is qualitatively different from other diseases, making its treatment harder, this situation can still elevate the process of sarcopenia [6][7][13]. In fact, these differences are in patterns of symptoms and responses to treatment that make COVID-19 unpredictable [13]. For example, a trend indicates that treatment with corticosteroids is harmful in mild COVID-19 patients, whereas there is a substantial benefit among patients with critical respiratory failure [13]. A high inflammatory and metabolic response caused by COVID-19 also impacts treatment and sarcopenia [12][13][14]. While having any non-communicable diseases (NCDs) is another factor that can increase the risk of mortality in COVID-19 patients [3][4][12][13][14][15], all these conditions show the complexity of COVID-19 treatment, which can get more difficult with sarcopenia.

Things get harder when we consider the fact that sarcopenia is not just a passive disease. Sarcopenia has long-term effects that can cause obstinate functional disability one year after discharge [7]. There is also a significantly increased risk of readmission in older adults hospitalised with sarcopenia than in people without sarcopenia [16]. The concern grows when, despite knowing the importance of preventing sarcopenia, it is still not a significant concern in COVID-19 patients.

The danger of mortality and morbidity can remain even after hospitalisation. Sarcopenia is a complex multifactorial disease that is not limited to the hospital [3][4][5]. One of the harmful effects of sarcopenia with long-term self-effect is the muscle-fat interaction cycle [17] (Figure 1). In this cycle that repeats and self-increases the severity of sarcopenia, energy expenditure decreases the muscle mass while the dietary intake may stay the same. This condition leads to a positive energy balance in the body for fat mass growth. This obesity-sarcopenia leads to inflammation, insulin resistance, morbidity, and functional limitations in people who have fully recovered from COVID-19 [3][4][5][17].

While concerns like having an inactive lifestyle and a poor diet can enhance the speed of sarcopenia during

quarantine and after discharge [18][19][20], the close mechanism of sarcopenia and COVID-19 discussed in the following is another concern that must be considered. For this reason, it is crucial to control this unpleasant disease, especially in COVID-19 patients, as much as other risk factors of COVID-19 patients' mortality.

The mechanism between COVID-19 and Sarcopenia

Despite the mechanisms of sarcopenia and COVID-19 following different pathways at first contact, their impact on each other can be significant. By deep exploring, many pathways in both COVID-19 and sarcopenia follow the same patterns with the same triggers (Figure 2). However, establishing a firm pathway to link COVID-19 and sarcopenia still requires more investigation. For understanding the pathways, recognising the mechanism of each disease is essential.

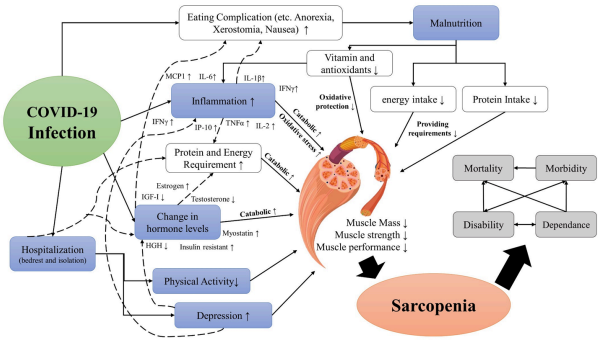

Figure 2. The mechanism of developing sarcopenia during COVID-19 infection could lead to an elevated risk of sarcopenia within patients that could lead to a higher risk of mortality, especially during hospitalisation. Blue: main factors; grey: outcomes of sarcopenia; white: factors that generally are an outcome of other factors that have an effect on sarcopenia

Mechanism of COVID-19

The mechanism of COVID-19 is still unclear, but one of the primary outcomes of its infection is the inflammatory response that can drive into inflammatory cytokine storms in a short time from the infection [14][21]. One of the first results of increasing SARS-CoV-2 infections is IL-1β, which elevates immediately after infection [14][22]. This condition subsequently releases pathogen-associated molecular patterns (PAMPs), such as viral RNA, and damage-associated molecular patterns (DAMPs), including ATP, DNA, and ASC oligomers [22]. As a result, a wave of local inflammation ensues, involving increased secretion of the pro-inflammatory cytokines and chemokines like IL-6, IFNγ, MCP1, and IP-10, which are released into the blood of afflicted patients [22]. IFNγ, TNF, and IL-2 are also increased in the next phase of defense, which leads to more inflammation in these patients [14][22].

In addition to the inflammatory response, COVID-19 infection is associated with hormone changes [23]. The considerable changes in hormones are in sex hormones, including testosterone, estrogen, and progesterone [23]. An increase in insulin resistance and estrogen during critical illness also results, as well as a decrease in testosterone, insulin-like growth factor 1 (IGF-I), and human growth hormone (HGH) in COVID-19 hospitalized patients [23][24][25]. Myostatin, an important hormone in muscle metabolism, is another hormone that effectively increases during hospitalization to inhibit muscle cell growth for saving energy and amino acids for metabolic pathways [26][27]. All these hormone changes have a trend in lowering muscle mass [23][24][25][26][27].

Malnutrition is another concern during COVID-19 infection that can result even in acute COVID-19 patients [28]. According to reports, the most common eating complications in COVID-19 patients were loss of appetite (anorexia), sore mouth (xerostomia), changes in taste, and nausea [28][29]. These eating complications can range from mild to severe, but in nearly all cases, the dietary intake of patients is significantly decreased [28][29][30]. This eating complication, in some cases, can lead to malnutrition, which explains why COVID-19 patients are one of the high-risk populations for malnutrition during hospitalisation [28][29][31]. There is also evidence that even diet patterns are associated with a higher risk of COVID-19 hospitalisation [12].

Mechanism of Sarcopenia

The mechanism of sarcopenia is simple and has a close relationship with COVID-19. Generally, increased inflammation that describes an increase in IL-6, IFNγ, TNFα, IL-2, and IL-1β is one of the most related factors to wasting [17]. On the other hand, estrogen levels, Myostatin, and insulin resistance are directly, and IGF-I, HGH, and Testosterone are negatively associated with sarcopenia [17]. Besides, malnutrition can lead to weight

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loss, muscle destruction, increased inflammation, and more severe conditions even without other pathways [30][32][33][34][35][36]. All these patterns that are directly or indirectly elevated during COVID-19 can result in wasting and sarcopenia.

The most interesting condition is related to Myostatin, which increases during this condition and elevates the sarcopenia process [27]. In addition, more dietary intake is required during hospitalisation due to an increase in total and basal energy expenditure for metabolic functions [30][37]. This increase in malnutrition puts the patients in an extra catabolic phase that worsens the disease and elevates the sarcopenia process [17][30][37].

The other pathway that can result from malnutrition is the removal of nutrients with anti-inflammatory and antioxidant protective effects on both muscle oxidation and inflammation, which can also effectively increase muscle catabolism and inflammation [17]. Other risk factors for sarcopenia are an unhealthy lifestyle, low physical activity, and depression, which occur both during and after hospitalisation [4][5][38]. Based on this evidence, COVID-19 infection can provide a suitable condition for sarcopenia growth.

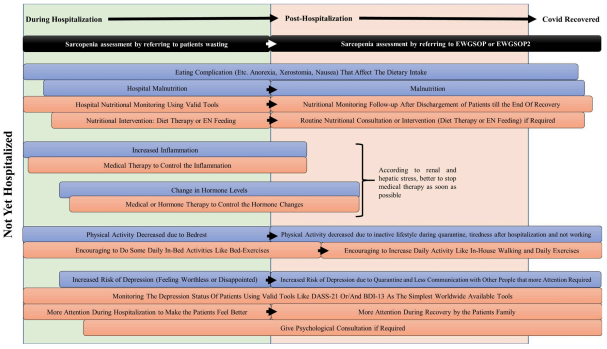

Figure 3. The stages of developing sarcopenia risk factors and required interventions during and post-hospitalisation of COVID-19 patients to stop sarcopenia development, stratified by stage of hospitalisation. During hospitalisation is shown in green, and post-hospitalisation in purple. Some interventions are suggested to continue even after full recovery for a period of time. Black: sarcopenia monitoring tools, blue: outcome of COVID-19 that elevates the risk of sarcopenia, salmon: required interventions. **Abv**: EN: Enteral Nutrition, DASS-21: Depression Anxiety Stress Scales -21, BDI-13: Beck Depression Inventory-13.

Health Care During Hospitalization

Medical and Hormone Therapy

COVID-19 patients are not hospitalised until the emergency stages, generally categorised as severe pneumonia and respiratory distress syndrome [12][14]. During this phase, patients generally have a high inflammatory response or metabolic dysfunction [12][14]. To control inflammation and inflammatory cytokine storms, medical therapy is the first line of treatment and should start as soon as possible [22]. Another intervention can be hormonotherapy, which has been reported to be helpful [23]. Nevertheless, most studies investigating the effect of hormonotherapy are ongoing [23]. However, medical therapy, due to renal and hepatic pressure, should be limited as soon as improvements in patients' clinical stages are made (Figure 3) [39][40]. Replacing alternative medical care is highly recommended [39][40].

Sarcopenia Assessment

Sarcopenia assessment is better to be started even from the first day of hospitalisation. As using dual-energy X-ray absorptiometry (DEXA) or bioelectric impedance analyser (BIA) is not possible in most cases, it is suggested to consider wasting and malnutrition indicators as important indicators of sarcopenia risk during hospitalisation [41]. To assess the risk of wasting, some criteria were provided in Table 1 that can be effective [36][41][42][43][44][45]. Monitoring tools nationally or centrally established in that region can also be useful [42][43][44][45]. However, SARC-F can be the easiest method for predicting sarcopenia in these patients [46]. Though, SARC-F is a verbal tool that may not be a practical tool in cases that are not capable of answering the questions. In this condition, clinical assessments may be more useful. In addition, we suggested considering the presence of even one sign of wasting within individuals as the risk of sarcopenia.

assessment	Consideration for Sarcopenia
SARC-F	Scored 11-20
Weight	loss of more than 10% of body weight in the last 3 months
	BMI <20.5 kg/m^2 as low risk and <18.5 kg/m^2 as high risk
mid-upper arm circumference (MUAC)	Decreases in circumference
	under 24.5 cm
Grip strength (most accurate)	<17 kg for women and <27 kg for men
Nutritional screening tools	
MST	Score ≥2
MNA	For short-form score 8-11 at risk and ≤7 high risk
	For long-form score 17-23.5 at-risk and less than 7 high risk
MUST	score 1 at risk and ≥2 high risk
NRS	Score ≥2
SNACK	score 2 at risk and ≥3 high risk
PG-SGA	scores ≥9, the higher score indicates a higher risk
Diagnosis	
Nutritional monitoring tools, because of their concentration on hospital wasting, could be used as a predictive sarcopenia assessment tool. The presence of any of the following criteria should be considered as the risk of sarcopenia, and the interventions are better to start.	

Table 1. The clinical criteria for diagnosing the Sarcopenia high-risk COVID-19 patients during hospitalisation.

Nutrition

During hospitalisation, the protein and energy requirements increase [41][43][47][48]. This is along with mild to severe malnutrition [43][47][48]. In this malnutrition, less energy and protein intake leads to wasting, more inflammation, and severity of the disease [32][33][34][35][36]. By referring to the important pathway of nutrition in critically ill patients, sarcopenia, and inflammation, controlling the patient's nutritional status can be the most effective intervention to both prevent sarcopenia and increase the survival chance of patients.

As the first line of controlling malnutrition, monitoring using available tools like the malnutrition screening tool (MST), mini nutritional assessment (MNA), malnutrition universal screening tool (MUST), nutrition risk screening (NRS), or short nutritional assessment questionnaire (SNAQ) can be very useful in both indicating the risk of malnutrition and sarcopenia [42]. These tools can be used for sarcopenia too because of their structures that concentrate on wasting criteria as part of the malnutrition assessment [42].

Despite the best setting being oral intake, using enteral feeding can be useful [41][47][49]. The intervention should be started as soon as possible. Although we do not have a firm nutritional guideline for COVID-19, we can use the same nutritional therapy that we use for infectious diseases [41][47][49].

It is expected that in COVID-19 patients, the energy requirement during hospitalisation increases by at least 10 to 30% and up to 100% [41][43][47][48]. In this condition, providing at least 25 to 30 kcal/kg body weight/day according to the clinical stage and the level

of inflammation is important [41][43][47][48]. However, the best criterion to set the energy goal is to control or stop the weight loss during hospitalisation [42][43][47].

Protein plays a vital role in maintaining muscle and tissue. The target daily protein intake is better to be at least 1.2 g/kg body weight of patients and increase up to 2 g/kg according to the clinical stage and the speed of wasting [41][43][47][48][49]. By providing sufficient protein and energy intake, a decreased risk of malnutrition, mortality, and sarcopenia can be expected.

Evidence shows that using an enriched formula with arginine (14 g/day), glutamine (14 g/day), and b-hydroxyb- methylbutyrate (3 g/day) can lead to more weight gain in muscle mass [41]. There is also evidence that dietary antioxidant elements that are partly received from a diet, like vitamin A, vitamin C, vitamin E, beta-carotene, lycopene, lutein, and selenium, can lower inflammation and muscle loss [50]. Other evidence suggests that using low Dietary Inflammatory Index (low-DII) formulas could lower the speed of sarcopenia development [51]. At the same time, an enteral formula based on low-DII is under development with antioxidant nutrients, minerals, and vitamins enrichment, which can be used in COVID-19 patients [52]. However, there is still no available data about its efficiency in critically ill patients [52]. Though enriching EN formulas with antioxidants and high-quality amino acids can be helpful.

Depression

Depression is one of the other risk factors that are not only independently associated with sarcopenia but also rise significantly during hospitalisation [38][53]. For controlling hospital depression, evaluating patients using simple, valid, comprehensive tools like the Depression Anxiety Stress Scales-21 (DASS-21) and the Beck Depression Inventory-13 (BDI-13) is important [53]. During hospitalisation, giving more attention to patients to make them feel better and performing the required psychological intervention is suggested [38][53]. However, despite the interventions for controlling depression looking simple, their impact can affect all aspects of the treatment. There is evidence that shows the importance of a good mood in the process of treatment [54].

Physical Activity

In addition to clinical and biochemical factors, bedrest lowers physical activity to nearly none, which is one of the main risk factors for sarcopenia [4][5]. Previous studies have shown that a program of hospital-supervised physical training in patients with cystic fibrosis could be useful, but the work on this subject is limited [55]. Encouraging patients to do some daily in-bed activities like bed exercises can be useful to at least lower the risk of muscle wasting in the hands and legs and elevate their spiritual wellness [55][56]. This exercise can at least lower the risk of hospital depression, as previously, the relation between physical activity and depression was established [56].

HealthCare After Hospitalization

Even after COVID-19 hospital discharge with the disease under control, the risk of sarcopenia still exists. The main reasons are the acquired risk factors of sarcopenia that are illustrated in Figure 1. For this reason, it is highly suggested to continue sarcopenia assessments for months after hospitalisation using the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) guideline (Table 2) [45]. In addition, some strategies are better to be considered even after recovery.

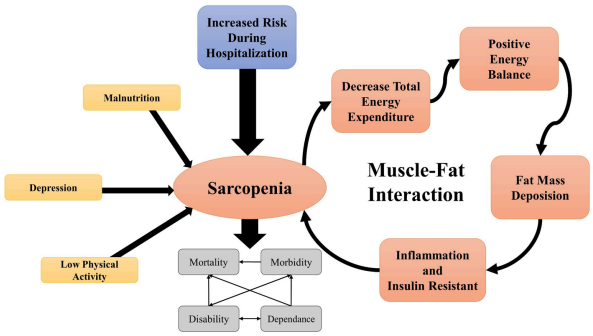

Figure 1. The related factors that could elevate the post-COVID-19 hospitalisation sarcopenia risk and the muscle-fat interaction self-generator process of sarcopenia that could lead to a severe condition of sarcopenia over time.

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assessment	Consideration for Sarcopenia	
	men	women
Screening		
SARC-F	Scored 11-20	
complementary tests		
low strength		
Grip strength	<27 kg	<16 kg
Chair stand	>15 s for five rises	
low muscle quantity		
ASM	<20 kg	<15 kg
ASM/height^2	<7.0 kg/m^2	<5.5 kg/m^2
low performance		
Gait speed	≤0.8 m/s	
Diagnosis		
Pre sarcopenia	Only low strength	
Sarcopenia	low strength and low muscle quantity	
Severe Sarcopenia	low strength, low muscle quantity and low performance	

Table 2: The clinical criteria for diagnosing Sarcopenia in COVID-19 patients after hospitalisation using EWGSOP2 sarcopenia cut-off points.

Nutrition

Nutritional interventions are not as vital as hospitalisation but still are one of the important risk factors for sarcopenia. There is evidence that some eating complications can continue from weeks to months after COVID-19 recovery and affect patients' diet [19][28][29]. It is suggested that the required nutritional intervention be made as well as during hospitalisation [49]. An intervention like diet therapy or EN feeding can be made too. At this stage, providing at least 1 to 1.2 g/kg of protein and a positive energy balance can be useful [41][43][47][48][49]. However, due to the importance of nutritional consultation and the impact of a routine follow-up, nutritional monitoring of recovered COVID-19 patients is vital [18][19].

Physical Activity

The bedrest condition is less concerning, but COVID-19 drove the worldwide population into an inactive, sedentary lifestyle [20]. Different studies reported a significant decrease in recorded daily steps during quarantine from about 10,000 to 1,500 steps/day [20][57]. This inactivity can impact insulin sensitivity, which is another associated mechanism of sarcopenia development, as much as low physical activity [20][57]. This is while COVID-19 patients still experience hospital fatigue as well as a sedentary lifestyle that can lead to more weight loss and more severe sarcopenia [58].

Several studies suggest that having sports activities can be significantly helpful in preventing or treating sarcopenia [3][4][59]. In this condition, designing specific physical training during quarantine to increase the daily physical activities of individuals is vital; however, to our knowledge, still no published study concentrates on this strategy. Nevertheless, Liu et al. showed that an

intervention by a physical activity program featuring aerobic, strength, balance, and flexibility training could be useful for muscle improvement in a high sarcopenia risk population [60].

Depression

Depression is also another sarcopenia risk factor that can continue after hospitalization and worsen during home quarantine isolation (Figure 3) [38][61][62]. In this case, continuing depression monitoring and psychological interventions is suggested. In addition to this monitoring, the role of the family can be very effective in controlling depression during the quarantine [63]. The medical team should involve the patients' families in providing a relaxing, pleasurable environment.

Limitations and strengths

To our knowledge, this is the first review that considers and provides methods to control the risk of developing sarcopenia in both hospitalization and post-hospitalization in COVID-19 patients. The strengths of the current study are its comprehensive point of view. The main limitation is the exploration phase of COVID-19, which is still unclear. Nevertheless, controlling sarcopenia is vital because the world population is aging.

Conclusion

Sarcopenia and COVID-19 have a close pathway that can cause more severe diseases. Monitoring sarcopenia and required interventions are better to be made in COVID-19 patients as soon as possible. These interventions can trigger medical therapy, nutrition, psychological health, and physical activity. All the interventions are better to continue until the removal of sarcopenia risk even after hospitalization; otherwise, high morbidity and disability will be expected in surviving COVID-19 patients.

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