

# Sarcopenia and COVID-19 Outcomes

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**Abstract:** Coronavirus disease 2019 (COVID-19) spread rapidly and became a severe global public health threat. Older adults have a high risk of COVID-19 and its associated mortality. Sarcopenia has emerged as a predictor of poor outcomes in COVID-19 patients, including lengthy hospital stays, mortality, intensive care unit admission, need for invasive mechanical ventilation, and poor rehabilitation outcomes. Chronic inflammation, immune dysfunction, respiratory muscle dysfunction, and swallowing dysfunction may underlie the association between sarcopenia and the poor outcomes of COVID-19 patients. Interleukin 6 receptor blockers (tocilizumab or sarilumab) are recommended for treating patients with severe COVID-19, and their therapeutic effects on sarcopenia are of great interest. This review aimed to analyze the current reports on the association between sarcopenia and COVID-19 and provide an update on the contribution of sarcopenia to the severity and adverse outcomes of COVID-19 and its underlying mechanisms. We also aimed to explore the different screening tools for sarcopenia concurrent with COVID-19, and advocate for early diagnosis and treatment of sarcopenia. Given that the fight against the COVID-19 pandemic may be long-term, further research into understanding the effects of sarcopenia in patients infected with the Omicron variant is necessary.

**Keywords:** COVID-19, sarcopenia, skeletal muscle, inflammation, IL-6

## Introduction

Coronavirus disease 2019 (COVID-19) spread rapidly and became a severe global public health threat.<sup>1</sup> As of February 28, 2023, COVID-19 had been confirmed in 758,390,564 persons globally and had accounted for 6,859,093 deaths.<sup>2</sup> The COVID-19 pandemic has heavily burdened health-care systems and the economies of most countries.<sup>3,4</sup> The rapid spread of COVID-19 is currently relatively under control; however, several countries are still battling with waves of COVID-19.<sup>5,6</sup> The majority of patients with COVID-19 have mild to moderate symptoms; however, 10–20% develop severe conditions and require hospitalization and intensive care treatment. The fatality rate is higher for older people and is reported to be approximately 20% for patients aged  $\geq 80$  years.<sup>7</sup> The established risk factors for worse prognoses of COVID-19 are old age, male sex, obesity, and comorbidities such as chronic lung diseases, diabetes, and cardiovascular diseases.<sup>8–11</sup>

Sarcopenia is defined as low muscle mass with low muscle function (grip strength or physical performance)<sup>12</sup> and was formally recognized as a disease entity with the assignment of an International Classification of Diseases, Tenth Revision, Clinical Modification code (M62.84) in 2016.<sup>13</sup> The definitions by the European Working Group on Sarcopenia in Older People 2 (2019), Asian Working Group for Sarcopenia (2019), International Working Group on Sarcopenia, and Foundation for the National Institute of Health are the most used. All definitions include at least two parameters, but the use of different cutoff values leads to a lack of standardization in clinical practice. Several techniques including CT, MRI, dual-energy X-ray absorptiometry, and bioimpedance analysis (BIA) are used to estimate muscle mass; dual-energy X-ray absorptiometry and BIA are recommended in clinical practice. Muscle strength, which is usually measured as grip strength, is a well-validated parameter for determining sarcopenia. The measures of physical performance include the gait speed test, 400-m timed walk, the Short Physical Performance Battery, and the Timed Up and Go test.<sup>16</sup> Sarcopenia is commonly considered an age-related process in older adults, with a prevalence of 10–27% for older adults aged  $\geq 60$

years<sup>14</sup> and 41% for older nursing home residents.<sup>15</sup> Sarcopenia may also be secondary to diseases, malnutrition, and physical inactivity.<sup>12,16</sup>

Previous studies have demonstrated that sarcopenia increases vulnerability to adverse outcomes, such as poorer quality of life, falls, and fractures, in older adults;<sup>17</sup> increased hospitalization and mortality rates in patients with chronic diseases;<sup>18,19</sup> and poorer overall survival of patients with cancer.<sup>20</sup> Sarcopenia is predictive of a higher risk of community-acquired pneumonia in older adults,<sup>21</sup> as well as 90-day mortality in patients with aspiration pneumonia.<sup>22</sup> In addition, sarcopenia is associated with unfavorable outcomes in critically ill patients, including a greater likelihood of the use of invasive mechanical ventilation (IMV), difficult weaning, and mortality.<sup>23–25</sup>

Currently, increased attention has been paid to sarcopenia in patients with COVID-19 due to its potential effects. However, the associations between sarcopenia and COVID-19 outcomes have not been fully elucidated. This review aimed to provide an update on the contribution of sarcopenia to the severity and adverse outcomes of COVID-19 and its potential mechanism. We explored the available screening tools for sarcopenia concurrent with COVID-19 and advocate for its early diagnosis and management.

## Clinical Evidence Linking Sarcopenia to Poor Outcomes in Patients with COVID-19

### Methods

The PubMed database was searched for articles published from the beginning of publication on COVID-19 until September 2022. The following search terms were used: “sarcopenia”, “low skeletal muscle”, “muscle mass”, “grip strength”, “muscle quality”, “intramuscular adipose tissue”, “myosteatosis” and “COVID-19”. The search was restricted to human studies, and the language was limited to English. We included publications reporting data on the association between sarcopenia and poor outcomes in patients with COVID-19. We screened out non-relevant articles by reviewing the titles and abstracts. Subsequently, the full texts of the remaining articles were analyzed to determine the final inclusion. We retrieved 266 articles manually, of which 19 were the most relevant (Table 1).

### Results

The included studies investigated the associations between strength, assistance in walking, rising from a chair, climbing stairs, falls (SARC-F) score, grip strength, muscle mass or quality, and poor outcomes in patients with COVID-19. Various tools, such as BIA, CT, and ultrasonography, have been used to assess muscle mass and/or quality among COVID-19 patients in the literature (Table 1).

### SARC-F

SARC-F is a 5-item self-reported questionnaire for assessing strength, walking assistance, rising from a chair, climbing stairs, and falls.<sup>26</sup> It has a low sensitivity but high specificity and can be a convenient and inexpensive tool for sarcopenia risk screening in clinical practice.<sup>12,27,28</sup> In the same vein, SARC-F may be a simple and feasible tool for early detection of the high risk of sarcopenia in patients with COVID-19. In two studies,<sup>29,30</sup> a total score of  $\geq 4$  was indicative of a high risk of sarcopenia in patients with COVID-19. A prospective cohort study of 114 patients hospitalized for COVID-19 (age  $\geq 60$  years) from China showed that a higher sarcopenia risk was associated with more severe COVID-19.<sup>30</sup> In a cross-sectional study involving 337 consecutively hospitalized patients with COVID-19 (age  $\geq 65$  years), a higher risk of sarcopenia was associated with a high risk of mortality.<sup>29</sup>

### Grip Strength

Muscle strength is among the main indicators of muscle function in sarcopenia.<sup>12</sup> Grip strength is recommended as a good measure of muscle strength and can be measured using a hand dynamometer.<sup>31</sup> Being simple and inexpensive, the measurement of grip strength in patients with COVID-19 is noteworthy.<sup>32</sup> Kara et al<sup>33</sup> and Tuzun et al<sup>34</sup> reported that low grip strength was a predictor of the disease severity in hospitalized patients with COVID-19. A study by Gil et al showed that increased grip strength was associated with a shorter hospital stay for patients with moderate to severe COVID-19.<sup>35</sup>

**Table 1** Summary of the Association Between SARC-F, Grip Strength, Muscle Mass or Quality, and Outcomes in Patients with COVID-19

| Reference, First Author, Years, Country    | Study Design    | Participants  |                          | Sarcopenia Assessment                                      | Cut Off values  | Outcomes                             |
|--|-----------------|---|--------------------------|--|---|--------------------------------------|
|  |                 | Sex (M/F)   | Age (Years)              |  |   |                                      |
| Riesgo et al, 2021, <sup>29</sup> Spain    | Cross-sectional | ICU or COVID-19 nursing wards patients. All: 337 (167/170) Total score < 4: 33; ≥ 4: 304  | 86.1 ± 8.7               | SARC-F   | Total score ≥ 4   | Mortality                            |
| Ma et al, 2021, <sup>30</sup> China        | Prospective     | ICU or COVID-19 nursing wards patients. All: 114 (57/57) Total score < 4: 76; ≥ 4: 38   | 69.52 ± 7.25             | SARC-F   | Total score ≥ 4   | Severe illness                       |
| Kara et al, 2021, <sup>33</sup> Turkey     | Cross-sectional | COVID-19 nursing wards patients. All: 312 (172/140) Low grip strength: 40; Normal grip strength: 272                                  | 46.1 ± 14.8              | Grip strength  | Low grip strength was defined as <32 kg in males and <19 kg in females                              | Severe illness                       |
| Tuzun et al, 2021, <sup>34</sup> Turkey    | Cross-sectional | ICU or COVID-19 nursing wards patients. All: 150 (77/73) Low grip strength: 82; Normal grip strength: 68                              | 53.17 ± 15.49            | Grip strength  | Low grip strength: according to age and gender-related normative grip strength data                 | Disease severity                     |
| Gil et al, 2021, <sup>35</sup> Brazil      | Prospective     | ICU or COVID-19 nursing wards patients. All: 186 (93/93) Low grip strength: NR; Normal grip strength: NR; Low CSA: NR; normal CSA: NR | 59 ± 15                  | Grip strength, CSA of vastus lateralis (B-mode ultrasound) | According to handgrip strength and vastus lateralis CSA into sex-specific tertiles                  | LOS                                  |
| Gobbi et al, 2021, <sup>36</sup> Italy     | Retrospective   | ICU or COVID-19 nursing wards patients. All: 34 (18/16) Sarcopenia: 20 (11/9) Non-sarcopenia: 14 (5/9)                                | 71.5 ± 17.0; 68.0 ± 16.5 | Grip strength, appendicular skeletal muscle mass (BIA)     | Sarcopenia was defined according to EWGSOP2 criteria  | Rehabilitation outcomes              |
| McGovern et al, 2021, <sup>40</sup> UK     | Retrospective   | ICU or COVID-19 nursing wards patients. All: 63 (30/33) Sarcopenia: 39; Non-sarcopenia: 24  | NA                       | SMA at the L3 level (abdominal CT)                         | SMI <43 for men, <41 for women when BMI <25, or SMI <53 for men, <41 for women                      | 30-day mortality                     |
| Osuna et al, 2022, <sup>41</sup> Mexico    | Prospective     | ICU patients. All: 86 (23/63) Sarcopenia: 41; Non-sarcopenia: 45  | 48.6 ± 12.9              | SMA at the L3 level (abdominal CT)                         | BMI <30: SMI ≤ 52.3 for men and ≤ 38.6 for women; BMI ≥ 30: SMI ≤ 54.3 for men and ≤ 46.6 for women | Tracheostomy, ICU stay, hospital LOS |
| Damanti et al, 2021, <sup>42</sup> Italy   | Cross-sectional | ICU patients. All: 81 (10/71) Sarcopenia: 53; Non-sarcopenia: 28  | 59.3 ± 11.9              | SMA at the L1, 2, 3 level (abdominal CT)                   | According to vertebra levels and literature data  | Extubation, ICU stay, mortality      |
| Kim et al, 2021, <sup>45</sup> South Korea | Retrospective   | ICU or COVID-19 nursing wards patients. All: 121 (43/77) Sarcopenia: 29; Non-sarcopenia: 92   | 62 (49–75)               | SMM at the T12 level (chest CT)                            | SMI ≤ 24 for men and ≤ 20 for women   | Hospital stays                       |

(Continued)

Table I (Continued).

| Reference, First Author, Years, Country     | Study Design  | Participants   |                                      | Sarcopenia Assessment                         | Cut Off values   | Outcomes  |
|---|---------------|--|--------------------------------------|---|--|---|
|   |               | Sex (M/F)  | Age (Years)                          |   |  |   |
| Schiaffino et al, 2021, <sup>46</sup> Italy | Retrospective | ICU or COVID-19 nursing wards patients. All: 552 (364/188) Sarcopenia: NR Non-sarcopenia: NR   | 65 (54–75)                           | PMM at the T5 or T12 level (chest CT)         | Under the median value of each variable distribution   | ICU admission, hospital mortality               |
| Giraud et al, 2021, <sup>47</sup> Italy     | Retrospective | ICU or COVID-19 nursing wards patients. All: 150 (46/104) Low SMM: 43; Normal SMM: 107   | 61.3 ± 15                            | The right PMM at the T12 level                | Low muscle mass: Hu values < 30  | ICU hospitalization                             |
| Moctezuma et al, 2021, <sup>48</sup> Mexico | Retrospective | ICU or COVID-19 nursing wards patients. All: 519 (332/187) Sarcopenia: 115 Non-sarcopenia: 404                                       | 51 (42–61)                           | SMA at the T12 level (chest CT)               | SMI (cm <sup>2</sup> /m <sup>2</sup> ) < 42.6 in men and < 30.6 in women                       | Mortality, ICU admission, IMV need <sup>a</sup> |
| Ufuk et al, 2020, <sup>49</sup> Turkey      | Retrospective | ICU or COVID-19 nursing wards patients. All: 130 (76/54) Low PMI: 44; Normal PMI: 86   | 48 (36–64)                           | Pectoralis muscle area (chest CT)             | Low PMI: first tertile of PMI, < 12.73 for men and < 9 for women                               | LOS, intubation, death                          |
| Viddeleer et al, 2021, <sup>51</sup> Italy  | Prospective   | ICU or COVID-19 nursing wards patients. All: 215 (86/129) IMAT index > 2.35: NR; ≤ 2.35: NR  | 61.1 ± 14.3                          | CSA of IMAT at the T12 level (chest CT)       | IMAT index (cm <sup>2</sup> /m <sup>2</sup> ) > 2.35   | Survival  |
| Yang et al, 2020, <sup>52</sup> China       | Retrospective | ICU or COVID-19 nursing wards patients. All: 143 (70/73) High IMF deposition: 71 No high IMF deposition: 72                          | 66 (56–73.5)                         | IMF deposition at the L3 level (abdominal CT) | Low SMD: high IMF deposition with the cutoff values of 32.7 Hu in males and 28.9 Hu in females | Severe illness                                  |
| Feng et al, 2021, <sup>53</sup> China       | Retrospective | ICU patients. All: 116 (63/53) Low PMI: 58, normal PMI: 58; Low PMD: 59, normal PMD: 57  | 57 (Range, 29–84)                    | PMA and PMD at the T12 level (chest CT)       | Low PMI and PMD: corresponding sex-specific medians  | Disease deterioration, viral shedding           |
| Yi et al, 2021, <sup>54</sup> China         | Retrospective | ICU or COVID-19 nursing wards patients. All: 234 (133/101) Sarcopenia: 78; Non-sarcopenia: 156; Myosteatosi: 77; Non-myosteatosi: 77 | 44.5 (2–81)                          | SM-RA and SMA at the T12 level (chest CT)     | Cut-off values were set at the lowest tertile of SMI and SM-RA                                 | Disease severity                                |
| Kremer et al, 2022, <sup>55</sup> Germany   | Retrospective | ICU or COVID-19 nursing wards patients. Cohort I: All: 58 (31/27) Cohort II: All: 55 (38/17) Low PMAI: NR; Normal PMAI: NR           | Cohort I: 67 (54–79); II: 70 (57–79) | Psoas muscle area (B-mode ultrasound)         | PMAI (mm <sup>2</sup> /m <sup>2</sup> ) < 291.1 in male and < 260.6 in female                  | 30-day mortality                                |

**Notes:** <sup>a</sup>SMI at the level of T12 on CT was not associated with mortality, ICU admission, or IMV need in hospitalized patients with COVID-19.

**Abbreviations:** BIA, bioelectrical impedance analysis; BMI, body mass index; COVID-19, Coronavirus Disease 2019; CSA, cross-sectional area; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; Hu, Hounsfield unit; ICU, intensive care unit; IMAT, intramuscular adipose tissue; IMF, intramuscular fat; IMV, invasive mechanical ventilation; LOS, hospital length of stay; PMA, paraspinal muscle area; PMAI, pectoralis muscle area index; PMI, pectoralis muscle index;<sup>49</sup> paraspinal muscle index;<sup>53</sup> PMD, paraspinal muscle density; PMM, paravertebral muscle mass; SARC-F, strength, assistance in walking, rise from a chair, climb stairs, and falls; SMA, skeletal muscle area; SMD, skeletal muscle density; SMI, skeletal muscle mass index; SMM, skeletal muscle mass; SM-RA, skeletal muscle-radiation attenuation.

In a retrospective study from Italy, grip strength was a key predictor of the rehabilitation outcomes of post-acute COVID-19 patients.<sup>36</sup>

## BIA

BIA is recommended as an affordable, easy-to-use, and portable measurement of muscle mass in routine clinical practice.<sup>12,37</sup> BIA does not directly measure muscle mass, but it estimates muscle mass by sending a low electrical current into the body.<sup>12</sup> In a retrospective study from Italy, skeletal muscle mass measured by BIA appeared to be a key predictor of rehabilitation outcomes in patients with post-acute COVID-19.<sup>36</sup> However, the reliability of BIA may reduce when patients have abnormal hydration.<sup>38</sup> Additionally, it may not be suitable for evaluating critically ill patients in the ICU; these patients are usually edematous due to fluid overload, and muscle mass can be overestimated.<sup>39</sup>

## CT

CT is considered the gold standard for non-invasive measurements of muscle mass and is routinely performed with no additional radiation burden for patients with COVID-19. Conventionally, cutoffs for skeletal muscle measurements are evaluated at the level of the third lumbar (L3) vertebra on abdominal CT, because skeletal muscle mass in this region correlates well with total body skeletal muscle mass. The skeletal muscle mass index (SMI) was calculated as the division of the skeletal muscle area by the square of the height. A study by McGovern et al showed that low SMI at the level of the L3 vertebra was associated with a higher 30-day mortality rate among patients with COVID-19.<sup>40</sup> In patients with COVID-19 admitted to the ICU, low SMI at the L3 level was associated with a high likelihood of tracheostomy, prolonged ICU stays, and longer durations of hospital stay;<sup>41</sup> Damanti et al also showed that low muscle mass at the L1, L2, or L3 level was associated with extubation failure, prolonged ICU stay, and higher hospital mortality rate.<sup>42</sup>

Chest CT has been used to assess the presence and severity of pneumonia in patients with COVID-19, and it can also be used to identify patients with lower muscle mass who have a high risk of worse outcomes; it is, therefore, useful for both diagnostic and prognostic assessments. Skeletal muscle mass at the level of the twelfth thoracic vertebra (T12) on chest CT is significantly associated with the skeletal muscle mass at L3.<sup>43,44</sup> A study of 121 patients with COVID-19 from South Korea showed that lower SMI at the T12 level on chest CT was independently associated with prolonged hospital stay but not mortality.<sup>45</sup> In a retrospective study conducted in Italy, lower muscle mass at the T5 or T12 level on chest CT was independently associated with ICU admission and increased hospital mortality among patients with COVID-19.<sup>46</sup> Giraudo et al also showed that reduced muscle mass at the T12 level was a predictor of ICU hospitalization of patients with COVID-19.<sup>47</sup> However, in a retrospective cohort study involving 519 hospitalized patients with COVID-19 from Mexico, the SMI on CT at the T12 level was not associated with mortality, ICU admission, or IMV need.<sup>48</sup> The pectoralis muscle area is calculated as the sum of the bilateral pectoralis major and minor muscle areas. Ufuk et al reported that the pectoralis muscle area and pectoralis muscle index on chest CT were associated with prolonged hospital stays, intubation, and death of adult patients with COVID-19.<sup>49</sup>

CT has also been used to evaluate muscle quality using fat infiltration into the muscle and attenuation of the skeletal muscle.<sup>12</sup> Muscle quality refers to changes in muscle architecture and composition, as well as muscle function delivered per unit of muscle mass.<sup>12</sup> When the capacity of subcutaneous and visceral tissue for fat storage is exceeded, lipids can be stored within the skeletal muscle as intramuscular adipose tissue (IMAT).<sup>50</sup> Viddeleer et al showed that a larger cross-sectional area of IMAT at the T12 level on chest CT was a risk factor for poor survival among patients with COVID-19.<sup>51</sup> Yang et al found that high IMAT at the L3 level on abdominal CT was associated with disease severity and increased need for mechanical ventilation and risk of death.<sup>52</sup> Higher paraspinal muscle radiodensity is a proxy measure of muscle fat deposition. Feng et al reported that higher paraspinal muscle radiodensity at the T12 level on chest CT was associated with a reduced risk of disease aggravation and a decreased likelihood of prolonged viral shedding in female patients with COVID-19 admitted to the ICU.<sup>53</sup> Skeletal muscle radiation attenuation may be a reflection of myosteatorsis. In a retrospective study conducted in China, lower skeletal muscle radiation attenuation at the T12 level on chest CT was associated with an increased risk of progression to severe illness in patients with COVID-19.<sup>54</sup>

## Ultrasonography

Ultrasonography may be an innovative tool for assessing muscle mass and quality in patients with COVID-19.<sup>12</sup> It is valid and reliable and can be performed at the bedside by trained clinicians.<sup>12</sup> It ensures longitudinal monitoring of muscle loss, reduces the risks of contamination associated with mobilization to the radiology unit, and reduces radiation exposure of patients. Gil et al reported that low muscle mass assessed in the vastus lateralis cross-sectional area on B-mode ultrasound was predictive of prolonged hospital stay of patients with moderate to severe COVID-19.<sup>35</sup> Muscle indices derived from the psoas muscle were also predictors of poor outcomes. A study by Kremer et al showed that the low psoas muscle area index was associated with a higher 30-day mortality rate of patients with COVID-19.<sup>55</sup> The clinical studies on the relationships between muscle mass and quality assessed by ultrasonography and the adverse outcomes of COVID-19 are limited, and further large-scale prospective studies are needed to establish the prognostic roles of muscle mass and quality assessed by ultrasonography in patients with COVID-19.

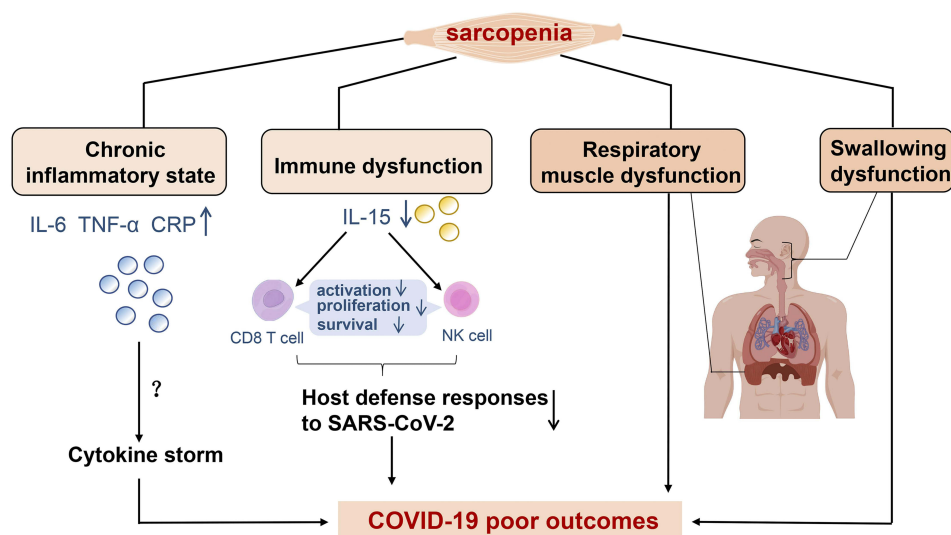
In summary, these data suggest that sarcopenia is an important risk factor for disease exacerbation and poor outcomes in patients with COVID-19. Therefore, patients with COVID-19 should be routinely screened for sarcopenia in clinical practice using available methods. Early diagnosis of sarcopenia appears to be of marked importance for identifying patients with COVID-19 at risk of unfavorable outcomes. However, different screening tools and diagnostic cut-off points for sarcopenia have been used in the above studies. Further large-scale prospective studies for exploring the relationships between sarcopenia and COVID-19 outcomes are warranted.

## Potential Mechanisms Underlying the Relationship Between Sarcopenia and COVID-19 Poor Outcomes

Sarcopenia has emerged as a predictor of poor outcomes in patients with COVID-19. Chronic inflammation, immune dysfunction, respiratory muscle dysfunction, and swallowing dysfunction may underlie the association between sarcopenia and the poor outcomes of COVID-19 (Figure 1).

### Chronic Inflammatory State

“Inflammaging” is characterized as an age-related, chronic, low-grade inflammatory state with slightly elevated plasma concentrations of pro-inflammatory factors, such as interleukin 6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and C-reactive



**Figure 1** The potential mechanisms underlying the association between sarcopenia and poor COVID-19 outcomes are chronic inflammation, immune dysfunction, respiratory muscle dysfunction, and swallowing dysfunction. A low-grade chronic inflammatory state (elevated concentrations of IL-6, TNF- $\alpha$ , and CRP) related to sarcopenia may be associated with an increased risk of a cytokine storm in patients with severe COVID-19. A key mechanism underlying impaired immunity in sarcopenic individuals is the abnormal expression of IL-15. IL-15 can regulate the activation, proliferation, and survival of CD8 T and NK cells. A lack of IL-15 signaling may lead to poor immune responses against COVID-19.

protein, contributing to the pathogenesis of age-related sarcopenia.<sup>56,57</sup> Chronic low-grade inflammation affects both muscle protein anabolism and catabolism through direct or indirect mechanisms.<sup>57</sup> Higher IL-6 and TNF- $\alpha$  serum concentrations were observed in sarcopenic older adults than in their non-sarcopenic counterparts.<sup>58</sup> Elevated concentrations of TNF- $\alpha$  were associated with an increased risk of sarcopenia in older people.<sup>59</sup> A prospective cohort study showed that high concentrations of IL-6 and C-reactive protein were associated with the loss of total appendicular skeletal muscle mass in non-sarcopenic older adults.<sup>60</sup> A meta-analysis also showed that elevated concentrations of circulating inflammatory markers were significantly correlated with lower skeletal muscle mass and muscle strength.<sup>61</sup> Taken together, skeletal muscle may be a potential central integrator between inflammation and sarcopenia during the biological process of aging.<sup>62</sup>

Cytokine storm is an uncontrolled systemic inflammatory condition characterized by high production of pro-inflammatory cytokines and chemokines, including IL-6, IL-8, TNF- $\alpha$ , and interferon, resulting from an overreaction of the immune system.<sup>63</sup> Cytokine storm may rapidly lead to acute respiratory distress syndrome, multiple organ failure, and death in patients with severe COVID-19.<sup>64</sup> Previous studies have reported significantly higher serum concentrations of proinflammatory cytokines in the majority of patients with severe COVID-19, suggesting that cytokine storms are associated with disease severity.<sup>65,66</sup> A low-grade chronic inflammatory state may be associated with an increased risk of a cytokine storm in patients with severe COVID-19.<sup>67</sup> Therefore, sarcopenic patients with COVID-19 may be more likely to develop unfavorable outcomes because of a low-grade chronic inflammatory state.

## Immune Dysfunction

Skeletal muscle is currently also regarded as a secretory organ that can produce and release various soluble factors referred to as “myokines”, in addition to being a locomotor unit.<sup>68,69</sup> Several of these myokines are secreted when the skeletal muscle contracts. Myokines can induce muscle regeneration, regulate whole-body homeostasis, and maintain immune function.<sup>68</sup> Therefore, skeletal muscle serves as a potent regulator of immune function. A key mechanism underlying impaired immunity in sarcopenic individuals is the abnormal expression of myokines, such as IL-15 and IL-6.<sup>70</sup>

IL-15 is highly expressed in skeletal muscle<sup>71</sup> and declines in aging rats.<sup>72</sup> In animal and in vitro studies, IL-15 has been demonstrated to have positive effects on skeletal muscle. IL-15 has been considered an anabolic factor in muscle protein metabolism,<sup>73</sup> and it promotes human myotube development and mitigates the deleterious effects of TNF- $\alpha$  on myogenesis.<sup>74</sup> Beneficial metabolic effects of IL-15 on skeletal muscle have been reported.<sup>75–78</sup> IL-15 increases glucose uptake through the Janus kinase 3/signal transducers and activators of transcription 3 pathway<sup>75</sup> or the Adenosine monophosphate (AMP)-activated protein kinase pathway,<sup>76</sup> regulates lipid oxidation via peroxisome proliferation activated receptor  $\delta$ ,<sup>77</sup> and mediates mitochondrial activity through the induction of peroxisome proliferation activated receptor  $\delta$ <sup>78</sup> in the skeletal muscle. The role of IL-15 in muscle physiology suggests that it may be used as a potential sarcopenia biomarker.<sup>62</sup> A cross-sectional study showed that lower plasma IL-15 concentrations were associated with sarcopenia in older adults.<sup>79</sup> However, further prospective studies are necessary to determine the association between decreased IL-15 concentrations and reduced muscle mass and strength.

IL-15 is characterized as a critical immunomodulator with anti-viral properties.<sup>80</sup> NK and CD8 T cells are required for effective viral clearance. These cells should be activated, and they should migrate to sites of infection and survive and proliferate, and IL-15 can regulate each of these processes.<sup>80</sup> In IL-15-deficient mice, defects in CD8 T and NK cells and compromised host defense responses to viral pathogens are observed,<sup>81</sup> indicating that a lack of IL-15 signaling may lead to poor immune responses against COVID-19. Thus, we speculate that the interaction between skeletal muscle and the immune system may justify the association between sarcopenia and the poor outcomes of patients with COVID-19. Reductions in IL-15 concentrations in patients with sarcopenia may affect the host defense system against COVID-19.

## Respiratory Muscle Dysfunction

The diaphragm is the main inspiratory muscle. Greising et al demonstrated that diaphragmatic sarcopenia was represented by reductions in diaphragm force and fiber size (diaphragm weakness and fiber atrophy) in aging rats.<sup>82</sup> In the diaphragm, sarcopenia affects the cross-sectional areas of type IIx and/or IIb muscle fibers.<sup>83,84</sup> The functional impact of

diaphragmatic sarcopenia is a reduction in the maximum transdiaphragmatic pressure, resulting in an impaired ability to perform expulsive, high-force non-ventilatory behaviors (coughing and sneezing).<sup>85</sup> The performance of expulsive and non-ventilatory activities is critical for airway clearance. Therefore, diaphragmatic sarcopenia may increase the risk of developing pneumonia and other respiratory system infections.<sup>86</sup>

Transdiaphragmatic pressure is the gold standard measurement of diaphragm function. However, measuring transdiaphragmatic pressure requires nasogastric catheterization, considerable expertise, and patient cooperation, which make it impossible for critically ill patients.<sup>87,89</sup> Alternatively, diaphragm function can be noninvasively evaluated using ultrasound. Diaphragm thickness, diaphragm thickening fraction, and diaphragmatic excursion measured by ultrasound are putative estimators of diaphragm function.<sup>88</sup> Sonographic measurements of diaphragm thickness provide a useful tool for assessing and monitoring for diaphragm atrophy and inactivity during mechanical ventilation.<sup>89</sup> Diaphragm thickening fraction may guide clinicians in assessing diaphragm function.<sup>90</sup> Despite its extensive use in the ICU,<sup>91,92</sup> few studies have reported on the relationship between transdiaphragmatic pressure and diaphragm thickening fraction,<sup>89,93</sup> and further investigations are required. Corradi et al reported that low diaphragmatic thickening fraction was a predictor of continuous positive airway pressure failure and the need for invasive ventilation in critically ill patients with COVID-19.<sup>94</sup> The same author reported that reduced diaphragm thickness measured by ultrasonography increased the invasive mechanical ventilation need or risk of death of hospitalized patients with COVID-19.<sup>95</sup> The observed association between reduced diaphragm thickness and poor clinical outcomes may be attributed to the limitation of the inspiratory pump strength, which promotes the progression from mild to severe respiratory failure, necessitating the need for IMV for cases of worsening pneumonia where the respiratory system becomes less compliant.<sup>95</sup> In summary, we speculate that respiratory muscle dysfunction induced by diaphragmatic sarcopenia increases the chances of contraction and the risk of poor outcomes in patients with COVID-19. Future studies are needed to further elucidate the relationships between respiratory muscle dysfunction and COVID-19 outcomes.

## Swallowing Dysfunction

Dysphagia is characterized by difficulty swallowing<sup>96</sup> and is a common problem in frail older adults.<sup>97</sup> “Sarcopenic dysphagia” refers to a swallowing disorder caused by sarcopenia of the entire body and swallowing muscles.<sup>98,99</sup> A study by Campo et al showed that sarcopenic dysphagia was associated with increased mortality rates among hospitalized older adults.<sup>100</sup> An international expert panel on dysphagia proposed that several patients with COVID-19 may have pre-existing dysphagia. In older hospitalized patients with COVID-19, sarcopenia may also contribute to dysphagia symptoms.<sup>101</sup> Sarcopenic dysphagia has attracted increasing interest in recent years; however, the association between pre-existing sarcopenic dysphagia and poor prognosis in patients with COVID-19 has not been thoroughly explored. Additionally, it has been estimated that approximately 30% of critically ill patients with COVID-19 experience post-extubation dysphagia,<sup>102,103</sup> which is associated with higher disease severity scores and longer duration of mechanical ventilation.<sup>103</sup> Thus, we speculate that pre-existing sarcopenic dysphagia may be associated with poor outcomes in patients with COVID-19. Future studies are required to further elucidate the relationships between pre-existing sarcopenic dysphagia and COVID-19 outcomes.

## Nutritional Supplementation and Physical Exercise of Sarcopenia in COVID-19 Patients

No specific drugs have been approved for sarcopenia. However, nutritional therapy and physical exercise are the mainstays of sarcopenia treatment in patients with COVID-19. Protein supplements combined with physical exercise may be effective for treating sarcopenia and COVID-19. Further prospective studies exploring whether these and other interventions can improve the outcomes of patients with COVID-19 are needed.

## Nutritional Supplementation

The ingestion of dietary protein is necessary for muscle protein synthesis.<sup>104</sup> Protein supplementation increased skeletal muscle mass during 24 weeks of resistance-type exercise training in a study.<sup>105</sup> Dietary protein supplementation also



improved physical performance in frail older adults in another study.<sup>106</sup> The International Conference on Sarcopenia and Frailty Research recommends protein supplementation or a protein-rich diet for older adults with sarcopenia.<sup>107</sup> According to the recommendation of the Society of Sarcopenia, Cachexia, and Wasting Disorders, protein intake of 1–1.5 g/kg/day combined with physical exercise appears to be reasonable for patients with sarcopenia.<sup>108</sup> In patients with injury or severe illness, or evidence of a catabolic/pro-inflammatory state, protein doses of up to 2 g/kg/day may be appropriate.<sup>108</sup> A high protein diet may be beneficial for patients with COVID-19, as proteins may prevent further muscle protein breakdown for gluconeogenesis and protect patients from progressing to a further catabolic state.<sup>109</sup> Patients with COVID-19 admitted to the ICU often have higher protein requirements, and nutritional recommendations may vary between 1.2 and 2.5 g/kg/day of protein.<sup>110,111</sup>

Vitamin D is essential for the maintenance of skeletal muscle health. There is accumulating evidence that vitamin D may play an important role in muscle regeneration and damage.<sup>112</sup> Although a meta-analysis of twenty-nine studies revealed that vitamin D supplementation improved muscle strength in individuals with low vitamin D concentrations,<sup>113</sup> there is insufficient evidence to recommend vitamin D supplementation for sarcopenia according to the International Conference on Sarcopenia and Frailty Research and Society of Sarcopenia, Cachexia, and Wasting Disorders.<sup>107,108</sup> Vitamin D may play a role in modulating the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>114</sup> A meta-analysis showed that vitamin D deficiency increased susceptibility to COVID-19 and the risk of developing severe COVID-19.<sup>115</sup> Several randomized controlled trials have reported that a high dose of vitamin D may have benefits for the treatment of COVID-19, including reducing inflammatory markers<sup>116</sup> and the need for ICU treatment.<sup>117</sup> However, a randomized controlled trial by Murai et al reported that a single high dose of vitamin D did not significantly reduce the length of hospital stay for patients with COVID-19.<sup>114</sup> The National Institute for Health and Care Excellence has recommended that there is limited evidence to support taking vitamin D supplements to prevent or treat COVID-19.<sup>118</sup> Further randomized control trials evaluating the administration of high doses of vitamin D for COVID-19 are needed.

## Physical Exercise

Evidence-based clinical practice guidelines have recommended physical exercise as a treatment for sarcopenia.<sup>107</sup> Evidence from studies shows that resistance exercise improves muscle mass, muscle strength, and physical performance in patients with sarcopenia.<sup>105,119,120</sup> Physical exercises strengthen the immune system and may provide benefits against viral communicable diseases. Active mobilization interventions are recommended for hospitalized patients with COVID-19, including bed mobility activities and active range of motion exercises.<sup>121</sup> Notably, physical exercise should be introduced gradually to patients with severe COVID-19, particularly those requiring intensive care. Exercises with assistants or auxiliary appliances should begin at low intensity and gradually increase to appropriate intensities under the supervision of physicians.<sup>122</sup> Regular exercise of adequate intensity is considered auxiliary for improving the host immune response against COVID-19.<sup>123</sup>

## Are IL-6 Receptor Blockers Promising for the Treatment of Sarcopenia in Severe COVID-19 Patients?

Elevated concentrations of pro-inflammatory cytokines (notably IL-6, IL-18, interferon, and TNF- $\alpha$ ) have been commonly reported for patients with severe COVID-19. These cytokines are often considered part of a dysregulated host immune response to SARS-CoV-2 that worsens disease severity.<sup>124</sup> IL-6 receptor blockers engage the membrane-bound and soluble IL-6 receptor,<sup>125</sup> blocking cytokine activation and regulating the host immune response to SARS-CoV-2.<sup>124</sup> Tocilizumab and sarilumab, as IL-6 receptor blockers, have been approved for the treatment of rheumatoid arthritis.<sup>126</sup> A network meta-analysis including 30 randomized clinical trials with 10,618 patients hospitalized for COVID-19 showed that the administration of IL-6 receptor blockers, compared with placebo or usual care, was associated with lower 28-day all-cause mortality rates and delayed progression to the need for invasive mechanical ventilation or death, cardiovascular support or death, and kidney replacement therapy or death of patients not receiving support for the corresponding organ

at randomization.<sup>127</sup> Currently, the World Health Organization strongly recommends tocilizumab or sarilumab for treating patients with severe COVID-19.<sup>128</sup>

Prolonged exposure to IL-6 promotes muscle atrophy and wasting by disrupting muscle anabolism and energy homeostasis.<sup>129</sup> The concomitant activities of other pro-inflammatory cytokines, such as TNF- $\alpha$ , may create the physiological environment, leading to muscle catabolism.<sup>70</sup> However, in the absence of proinflammatory cytokines, exercise-induced pulsatile IL-6 stimulates anabolic pathways associated with muscle growth and myogenesis.<sup>129</sup> A recent review concluded that for sarcopenia, IL-6 signaling may shift towards the pro-inflammatory profile as skeletal muscle function declines with age.<sup>70</sup> These findings suggest that IL-6 receptor blockers may have the potential to treat sarcopenia. Several preclinical studies have reported that IL-6 receptor blockers attenuate muscular atrophy and facilitated muscle regeneration.<sup>130,131</sup> In IL-6 transgenic mice, treatment with anti-mouse IL-6 receptor antibody blocked the activation of proteolytic systems associated with muscle atrophy in the gastrocnemius muscles.<sup>130</sup> Additionally, the acceleration of muscle regeneration was observed on day 7 after the anti-mouse IL-6 receptor antibody treatment of mice with cardiotoxin-induced muscle damage. The anti-mouse IL-6 receptor antibody, which was primarily found in infiltrated macrophages in the damaged muscle may facilitate muscle regeneration through immune modulation.<sup>131</sup> However, the administration of a monoclonal antibody against the IL-6 receptor in mice for five weeks led to increased muscle inflammation, with no significant change in muscle regeneration and muscle function.<sup>132</sup> A prospective cohort study showed that IL-6 receptor blockers may be effective for treating sarcopenia with concomitant rheumatoid arthritis. A significant increase in the appendicular lean mass was observed after treatment with tocilizumab (an IL-6 receptor blocker) for one year. However, data on muscle strength and function were not provided by this study.<sup>133</sup> Therefore, the effects of IL-6 receptor blockers on skeletal muscle remain controversial, and whether targeting IL-6 will be a useful therapeutic strategy to treat sarcopenia in patients with severe COVID-19 has not been established. The administration of IL-6 receptor blockers (tocilizumab or sarilumab) is promising for patients with severe or critical COVID-19. Future studies on the roles of IL-6 in skeletal muscle will provide a new basis for therapeutic approaches to treat sarcopenia in patients with severe COVID-19.

## Conclusion

The COVID-19 outbreak presented significant challenges in communities and for health-care systems globally. The established risk factors for worse prognoses of COVID-19 patients are older age, male sex, obesity, and comorbidities including chronic lung diseases, diabetes, and cardiovascular diseases. Sarcopenia may be an emerging risk factor. The potential mechanisms underlying the association between sarcopenia and poor COVID-19 outcomes are chronic inflammatory state, immune dysfunction, respiratory muscle dysfunction, and swallowing dysfunction. Previous studies have indicated that sarcopenia is associated with poor prognoses such as prolonged hospital stay, mortality, ICU admission, or IMV need in COVID-19 patients. Therefore, sarcopenia should be routinely screened in clinical practice using available methods for these patients. In the meantime, the prevention and treatment of sarcopenia may prevent the worsening of COVID-19. Treatments should be holistic and focused on both physical exercise and nutritional interventions. The administration of IL-6 receptor blockers (tocilizumab or sarilumab) is promising for patients with severe COVID-19. However, reports on the effects of IL-6 receptor blockers on the skeletal muscle are controversial, and whether targeting IL-6 will be a useful therapeutic strategy for treating sarcopenia in patients with severe COVID-19 is not known. Omicron is becoming the dominant strain in most countries,<sup>134,135</sup> and it seems to be less pathogenic than the earlier SARS-CoV-2 strains and four other variants of concern.<sup>134</sup> With the emergence of SARS-CoV-2 variants, the association between sarcopenia and COVID-19 may also have changed. The association of sarcopenia with poor outcomes in patients infected with the Omicron variant has not yet been studied. Given that the fight against the COVID-19 pandemic may be long-term, further research into understanding the effects of sarcopenia in patients infected with the Omicron variant is necessary.

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## Disclosure

The authors report no conflicts of interest in this work.

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