Intensive care unit-acquired weakness: A review from molecular mechanisms to its impact in COVID-2019

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Abstract

Intensive Care Unit-Acquired Weakness (ICU-AW) is a generalized and symmetric neuromuscular dysfunction associated with critical illness and its treatments. Its incidence is approximately 80% in intensive care unit patients, and it manifests as critical illness polyneuropathy, critical illness myopathy, and muscle atrophy. Intensive care unit patients can lose an elevated percentage of their muscle mass in the first days after admission, producing short- and long-term sequelae that affect patients' quality of life, physical health, and mental health. In 2019, the world was faced with coronavirus disease 2019 (COVID-19), caused by the acute respiratory syndrome coronavirus 2. COVID-19 produces severe respiratory disorders, such as acute respiratory distress syndrome, which increases the risk of developing ICU-AW. COVID-19 patients treated in intensive care units have shown early diffuse and symmetrical muscle weakness, polyneuropathy, and myalgia, coinciding with the clinical presentation of ICU-AW. Besides, these patients require prolonged intensive care unit stays, invasive mechanical ventilation, and intensive care unit pharmacological therapy, which are risk factors for ICU-AW. Thus, the purposes of this review are to discuss the features of ICU-AW and its effects on skeletal muscle. Further, we will describe the mechanisms involved in the probable development of ICU-AW in severe COVID-19 patients.

Key Words: ICU-acquired weakness (ICU-AW); coronavirus disease 2019; skeletal muscle atrophy; critical illness.

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Patients in a critical state frequently require admission to the intensive care unit (ICU), generally, for extended periods.[1] During the ICU stay, mechanical ventilation (MV) is usually an invasive treatment required to save the patient's life.[2] These patients can develop ICU-acquired weakness (ICU-AW), a neuromuscular dysfunction, generalised and symmetric disorder, without an identified etiology other than the critical illness and its treatments.[1,3,4] ICU-AW has a high impact on the length of ICU stay and the time of the patient's recovery. The adverse consequences of ICU-AW also affect patients' reinsertion to daily living activities and represent a high economic cost for the patients and the health care services.[5] In 2019, a global pandemic began due to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which led to millions of people falling ill with coronavirus disease 2019 (COVID-19), many of them in critical condition.[6] There are similarities between the clinical conditions of patients with COVID-19 and those patients who develop ICU-AW (prolonged MV, ICU interventions, myalgias, muscle loss, and inflammation),[6-8] suggesting that severe COVID-19 patients could have a high chance of developing ICU-AW during their ICU stay. Thus, the purposes of this review are to discuss the characteristic

of ICU-AW and its effects on skeletal muscle to describe the probable development of ICU-AW in severe COVID-19 patients.

ICU-acquired weakness

Muscle weakness is a frequent problem in ICU patients, and it can be induced due to primary or secondary causes. Primary causes (< 0.5% of all ICU admissions) include neuromuscular pathologies that need intensive care, such as myasthenia gravis, multiple sclerosis, amyotrophic lateral sclerosis, and Guillain–Barré Syndrome, among other neurological disorders. Secondary causes correspond to treatment for other life-threatening conditions in the ICU.[4,9]

ICU-AW affects the proximal rather than distal area of the limbs' muscles and the respiratory muscles.[1] Muscle tone become diminished, and tendon reflexes may be reduced or normal. ICU-AW does not strain the face and eyes muscles.[1,10-13]

The incidence of ICU-AW is approximately 80% in ICU patients. It is associated with a longer duration of MV and hospitalisation along with a significant functional impairment for survivors.[2] The prevalence of ICU-AW oscillates between 25 and 75%. Still, it could vary depending on the studied patient population, risk factors, timing of assessment (hospitalisation days and severity of the patients), and the methods used for diagnosis.[12,14,15]

Risk factors for ICU-acquired weakness

The risk factors for ICU-AW are classified as modifiable and non-modifiable (Figure 1).

The modifiable risk factors include hyperglycaemia and drugs used to treat critically ill patients.[4,16-18] The ICU-AW patient's hyperglycaemia is an independent risk factor for ICU-AW, which could be developed by parenteral nutrition or depending on the patients' high severity state.[10,16,17] Regarding drugs for treating ICU patients, a high risk of ICU-AW has been associated with vasoactive medication duration and doses (β-agonists mainly).[19] The use of corticosteroids has shown contradictory results: when focusing exclusively on patients with sepsis, it has been associated with the risk of ICU-AW, but in patients with hyperglycaemia, a protective effect has been suggested.[16,17] Although it is not yet clear, the use of neuromuscular blocking agents, such as cisatracurium has shown adverse effects in muscle weakness. These agents have been considered an independent risk factor for ICU-AW.[16,20] Certain antibiotics, such as aminoglycosides and vancomycin, develop muscle weakness.[21-23] Lastly, continuous sedation has a more pronounced effect on muscle atrophy and weakness than patients in a conscious state but immobilised in the absence of sedation.[24]

The non-modifiable risk factors for developing ICU-AW are the severity of critical illness and mortality prediction. The severity of disease score and mortality prediction scores are often determined by the scale Acute Physiology and Chronic Health Evaluation (APACHE) II score, which estimates ICU mortality, and Sequential Organ Failure Assessment (SOFA) score, which evaluates the overall function and dysfunction of each organ system based on the degree of dysfunction of six organ systems. Higher scores on these scales indicate greater severity of clinical evolution, including a greater risk of death.

Other non-modifiable risk factors include sepsis, inflammation (systemic inflammatory response syndrome, SIRS), multiple organ failure, longer duration of MV, and stay in the ICU.[16,19,25,26] Prolonged MV is an independent risk factor for ICU-AW.[16] MV increases the risk of ICU-AW and diaphragmatic weakness dysfunction, increasing the risk of failed ventilation and weaning, thus extending the MV and making up a vicious circle.[14,16] Other risk factors are high levels of pro-inflammatory cytokines, an elevated lactate level, being a woman and/or older person, a premorbid state, and frailty conditions that may predispose to the severity of the weakness.[16,26]

Clinical manifestations of ICU-acquired weakness

ICU-AW corresponds to nerve and muscle dysfunction due to generalized systemic inflammation and the risk factors mentioned above.[27] ICU-AW commonly manifests in three different ways: polyneuropathy, myopathy, and muscle atrophy (Figure 1).[25] These three conditions can contribute to varying proportions of this pathological condition and manifest alone or in combination.[5,12,28]

Critical illness polyneuropathy (CIP) is defined as a distal sensory-motor polyneuropathy that affects limb and respiratory muscles and autonomic nerves in symmetric form.[12,29] There is a loss of axons in CIP and reduced nerve excitability with preserved myelin sheets. [1,12] The aetiology could include loss of the blood-nerve barrier, inexcitability of the endoneurial membrane, and direct toxic effects from ICU therapies, including hyperglycaemia or lipids derived from parenteral nutrition, which would induce muscle denervation and atrophy.[12,29]

Critical illness myopathy (CIM) is a primary acute myopathy with loss of myosin filaments, loss of muscle membrane excitability, and possible necrosis.[1,12] CIM is characterised by limb and respiratory muscle weakness with retained sensory function, which is not related to denervation.[2,12] The proposed CIM aetiology includes chemokine-induced autophagy of muscle fibre, muscle membrane inexcitability, acquisition of channelopathies, or direct toxic effects of ICU care, including corticosteroids or neuromuscular blockade.[29]

Muscle atrophy is a typical feature of ICU-AW. Pronounced muscle wasting in ICU patients could be explained by mechanical unloading due to immobilisation/denervation and the catabolic state of critical illness, with reduced anabolism.[5,14] Activated proteolytic systems have been observed in type II fibres, together with myosinolysis (proteolytic degradation of

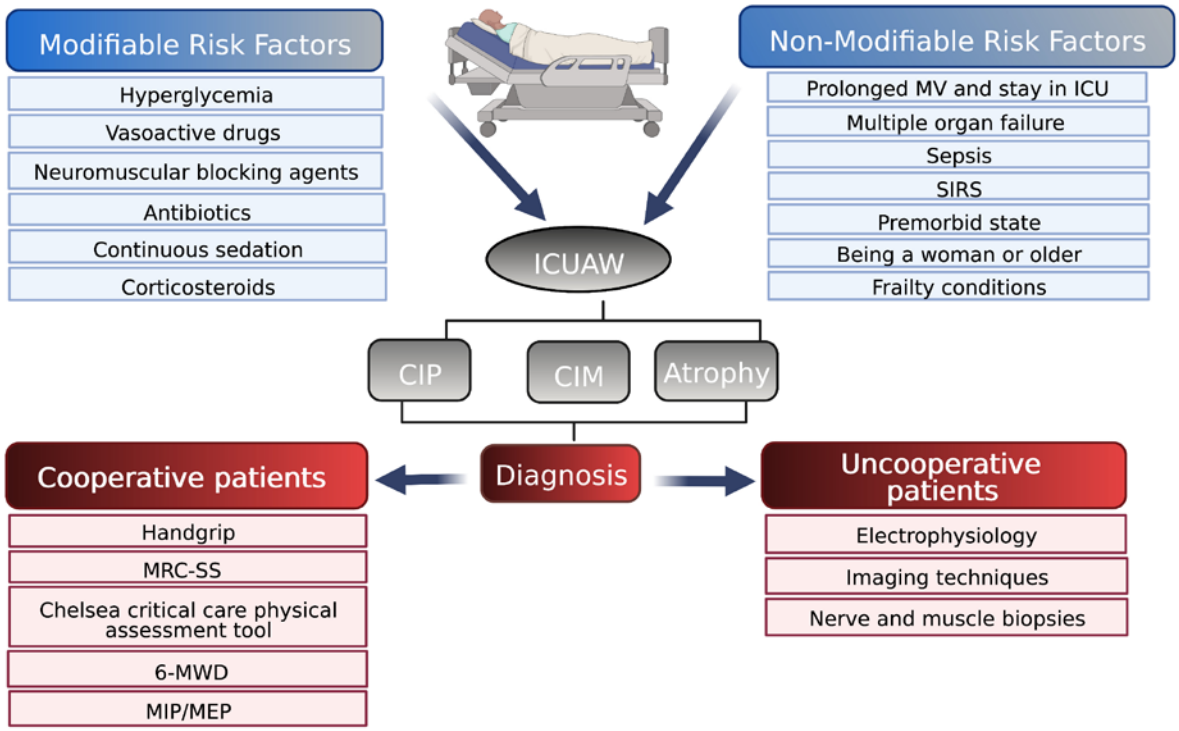

Fig 1. *Features of ICU-acquired weakness. ICU-AW commonly manifests in three different manners: Critical Illness Polyneuropathy (CIP), Critical Illness Myopathy (CIM), and muscle atrophy. The modifiable risk factors include hyperglycaemia (an independent risk factor for ICU-AW); common drugs for the treatment of intensive care unit (ICU) patients (such as vasoactive medications); neuromuscular blocking agents (such as citraturia); antibiotics (such as aminoglycosides and vancomycin); continuous sedation; and corticosteroids (with contradictory results). The non-modifiable risk factors include prolonged mechanical ventilation (MV) (an independent risk factor for ICU-AW) and stay in ICU; multiple organ failure; the presence of sepsis; the presence of Systemic Inflammatory Response Syndrome (SIRS); premorbid state: to be a woman and/or older; and frailty conditions. The diagnosis of ICU-AW will depend on whether the patient is conscious or not. In awake/cooperate patients, the evaluation tests are handgrip dynamometry and six grades MRC-SS (the gold standard for the diagnosis of ICU-AW). Also, some tests or scores provide information about the patients' functional abilities: functional status score for the ICU and Chelsea Critical Care Physical Assessment tool; 6-minute walking distance (6-MWD) (assesses functional walk capacity post ICU); and maximum inspiratory and expiratory pressure (in respiratory muscles). In unconscious/uncooperative patients, the evaluation consists of electroneurography test (to evaluate nerve conduction velocities and amplitude of nerve action potentials) and, electromyography (to evaluate activity at rest, motor unit potentials and maximal effort); imaging techniques (computed tomography (CT), ultrasonography, magnetic resonance imaging, dual-energy X-ray absorptiometry, neutron activation analysis, bioelectrical impedance); and nerve and muscle biopsies (used mainly in research).*

ICU-AW: ICU-acquired weakness; ICU: intensive care unit; SIRS: systemic inflammatory response syndrome; MV: mechanical ventilation; CIP: Critical Illness Polyneuropathy; CIM: Critical Illness Myopathy; MRC-SS: Medical Research Council sum score; 6-MWD: 6-minute walking distance; CT: computed tomography: MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure

myosin), consistent with primary myopathy and neurogenic muscle atrophy.[2,25] These pathological disorders translate clinically into loss of strength and muscle mass, weakness, and significant functional disorders in activities of daily living, which are independent predictors of mortality in critically ill patients. [2] Patients with ICU-AW have significantly decreased handgrip strength and reported worse physical performance. [29] Despite improvements in overall strength in the timeline, physical function-related quality of life remained significantly below the expected age-adjusted indicators at all time points.[29]

ICU-acquired weakness diagnosis

ICU-AW diagnosis requires both clinical assessments of muscle strength (peripheral and/or respiratory muscles) and complete electrophysiological evaluation of peripheral nerves and muscles (Figure 1).[4,12]

Diagnosis in awake/cooperative patients

The gold standard for ICU-AW diagnosis is handgrip dynamometry and the Medical Research Council sum score (MRC-SS).[12] Handgrip dynamometry evaluates the dominant hand's isometric muscle strength.[12,18] In ICU-AW, the cut-off scores are less than 11 kg (interquartile range [IQR] 10–40) in males and less than 7 kg (IQR 0–7.3) in females.[18,24,30] The handgrip is a non-invasive test with quick and easy bedside testing. Besides, it has high inter-rater reliability and increased sensitivity and specificity. Its disadvantages are that patients must be awake, cooperative, and must comprehend the assessor's instructions. In general, these conditions are difficult for ICU patients because they could be in a coma, have pain, or use sedative drugs; therefore, it is uncertain whether the outcome is representative of global muscle strength or not.[4,12,24,31]

The six-grade MRC-SS is a strength test that allows assessment of muscle strength in 12 muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and foot dorsiflexion).[4,12,31] Individual scores are combined into a total score, which allows for an estimated overall motor function. Its advantages are that it is a bedside non-invasive test with high reliability and validity. However, it requires the patient to be alert, cooperative, and motivated, which is not always possible; it may be affected by the positioning of the patient and availability of limbs for assessment (immobilisation, for example); and it has a low sensitivity to changes in muscle function. [4,12,31] There is also a modified score MRC-SS of 4-grade, but it still requires further validation.[4,24]

Other less commonly used tests are functional status score for the ICU, scored physical function in intensive care test, and Chelsea critical care physical assessment tool, which provide information about the patients' functional abilities. The 6-minute walking distance (6-MWD) assesses functional walking capacity, but it is mainly used to evaluate how patients perform at discharge and at post-ICU follow-up.[24,32-34]

In respiratory muscles, the determination of maximum inspiratory and expiratory pressure represents the strength of the general respiratory muscles. Still, they require the patient to be awake and cooperative. The measurement of transdiaphragmatic pressure or endotracheal tube pressure in response to phrenic nerve stimulation could be a good option, but it is an invasive technique that requires magnetic stimulation and qualified staff. Imaging techniques, such as chest X-rays or ultrasonography, can be used, but they have low sensitivity and specificity.[4,35-38]

Diagnosis in unconscious/uncooperative patients

The strategies applied to unconscious/uncooperative patients, such as electrophysiological and imaging techniques, have been incorporated to the diagnosis of ICU-AW. Electrophysiological studies are primarily aimed at differentiating between CIM and CIP in unconscious patients. However, they can also be used when the patient is cooperative and voluntary muscle activation is possible. Among the most used tests are electroneurography which evaluates nerve conduction velocities and amplitude of nerve action potentials, as sensory nerve action potentials and compound muscle action potentials; and electromyography (which includes activity at rest, motor unit potentials and maximal effort). These tests provide a measure of muscle function regardless of whether the patient is awake and cooperative, which allows assessment of the contractile properties of skeletal muscles without the need for voluntary muscle activation.[1,12,13,39,40]

The imaging techniques can assess muscle mass and body composition with different precision grades and costs. Among these, the skeletal muscle area at the third lumbar vertebra level measured through computed tomography (CT) on admission is more exact. It allows a better diagnosis of patients in the ICU state. Its disadvantages are that it is expensive, requires specialised staff and software, and exposes patients to a high radiation level.[4,41] Other techniques include ultrasonography, magnetic resonance imaging, dual-energy X-ray absorptiometry, neutron activation analysis, and bioelectrical impedance.[42-44] Nerve and muscle biopsies could provide essential and precise information of muscle states but are invasive, expensive, and specialised techniques, so they are used mainly in research.[39,42,45]

Skeletal muscle atrophy in ICU-acquired weakness

Skeletal muscle atrophy is characterised by decreased structural proteins essential for muscle function (such as myosin heavy chain and myosin light chain).[46,47] Some reports show that ICU patients can lose as much as 20% of their muscle mass in the first 10 days after ICU admission, depending on the disease severity.[5,48] This mass loss is caused by an increase in a catabolic state in the muscle in these first days. Beyond this specific muscle damage, ICU-AW patients show significant impairments in body structure and function. These alterations produce a critical limitation of physical activity, even offering complete immobilisation.[10,29,49,50]

In ICU-AW, several causes can produce muscle wasting. Some studies have proposed disturbed metabolism, sepsis, and/or malnutrition as inductors of muscle wasting.[48,51] It has also been attributed to immobilisation and chronic disease.[52,53] There is evidence that part of ICU patients' treatment, such as drug administration, muscle relaxants, corticosteroids, and even intravenous sedation, can exacerbate the effect produced by

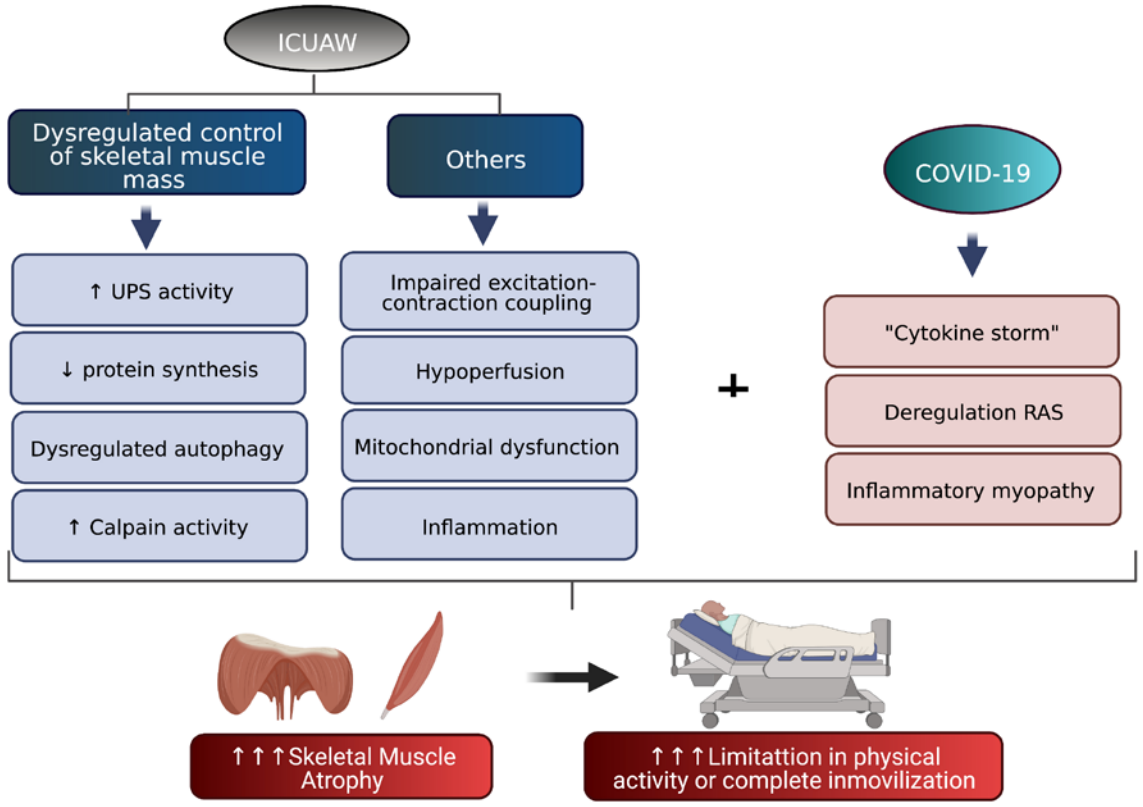

Fig 2. *Physiopathology mechanisms associated to high chance of developing ICU-acquired weakness and its severe consequences in COVID-19 patients. Dysregulated control of skeletal muscle mass and other factors induce muscle weakness and skeletal muscle atrophy in ICU-AW. There is increased ubiquitin-proteasome system (UPS) activity, dysregulated autophagy, decreased protein synthesis, and increased calpain activity. Other factors that induce muscle weakness and skeletal muscle atrophy in ICU-AW patients are impaired excitation-contraction coupling, hypoperfusion, mitochondrial dysfunction, and inflammation. In COVID-19, the possible pathophysiological mechanisms for developing ICU-AW in patients treated in ICU include the cytokine storm, deregulation of the renin-angiotensin system (RAS), and inflammatory myopathy.*

ICU-AW: ICU-acquired weakness; COVID-19: coronavirus disease 2019; UPS: ubiquitin-proteasome system; mTOR: mammalian target of rapamycin; ICU: intensive care unit; TNF-α: tumour necrosis factor-alpha; IL-1: Interleukin 1; IFN: Type I interferon; IL-6: Interleukin 6; RAS: Renin-angiotensin system; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE2: angiotensin-converting enzyme 2; MV: mechanical ventilation.

immobilisation. Thus, the same therapy for ICU patients can decrease the muscle mass.[52,53]

At the physiopathological level (Figure 2), one of the muscle wasting features in the critical illness is the loss of myosin and myosin-related proteins due to the imbalance between muscle protein synthesis and degradation.[52,54] Studies performed in animal models of ICU-AW and critically ill patients present increased ubiquitin-proteasome system (UPS) activity as the dominant regulator of muscle proteolysis.[39] UPS activation is induced by oxidative stress, energy stress, pro-inflammatory cytokines (tumour necrosis factor-alpha [TNF-α], interleukin 1 [IL-1], and interleukin 6 [IL-6]), mechanical silencing (defined as loss of external muscle strain (weight-bearing), and internal muscle strain (contraction), and sepsis conditions that could increase the gene expression of crucial UPS players.[39,52,55,56]

Moreover, dysregulated autophagy has been found in muscles from critically ill patients, contributing to the degradation of muscle fibre and inducing muscle loss.[45,57] Furthermore, in critical illness conditions with prolonged bed stay resulting in minimal mechanical load stimuli, protein synthesis is decreased, reinforcing muscle loss for reducing mTOR1 pathway activity.[39,52] Calpain, an enzyme that participates in sarcomere disassembly, could lead to Z-band disintegration and myofibrillar protein breakdown in critical illness. However, the antecedents that support this possibility are minimal.[39]

Muscular mitochondrial dysfunction has been observed in critical patients. They show a vicious cycle of macromolecules and organelle damage due to mitochondrial damage compromises energy provision and increases the production of free radicals and reactive oxygen species, which can induce proteolysis.[39,52] Regulation of mitochondrial size and morphology may play a critical role in muscle atrophy and is determined by an imbalance between mitochondrial fission and fusion.[58,59]

Furthermore, impaired excitation-contraction coupling due to altered intracellular calcium homeostasis for sodium channel inactivation has been reported in muscle of ICU-AW patients.[39] This alteration could fail to coordinate repetitive firing within the motor neurons that can precede electrical failure in axons and nerve-muscle coupling or neuromuscular junction (NMJ) degradation, as observed in aging.[60,61]

Under ICU-AW conditions, hypoperfusion, probably caused by oedema formation because of vasodilation and increased permeability, may favour axonal degeneration, neuronal injury, and a chronic membrane depolarisation of terminal motor axons in skeletal muscle.[13,39]

Inflammation is an essential factor that induces muscle atrophy in several patients. The systemic inflammatory-mediated pathology is considered the most significant risk factor for ICU-AW.[62] Inflammation has a higher impact on ICU-AW development than inactivity when evaluating patients with critical diseases.[63] A recent meta-analysis concluded that lower muscle strength and skeletal muscle mass are significantly associated with higher levels of circulating inflammatory markers.[64] In ICU patients, muscle biopsies have shown signs of inflammation, pronounced infiltration with adipose tissue, and fibrosis, which could also lead to muscle mass loss.[39,45]

Due to the early appearance of muscle atrophy and the impact of muscle dysfunction in the ICU outcome, the development of persistent post-ICU complaints, and low quality of life, research about ICU-AW has increased. The researchers have focused on studying the mechanisms and factors that influence muscle dysfunction in a patient chronically ill, which promotes the development of possible therapies or treatments for ICU patients to avoid and/or improve this muscular condition.

Therapeutic strategies in ICU-acquired weakness patients

Substantial loss in muscle mass develops in the first stage of ICU; however, its impact on muscle function is extended to the period after the patients are discharged.[48] These antecedents indicate that implementing some strategies to avoid impaired muscle structure and function in the early ICU stage is essential to prevent impaired status after ICU stay. As immobilisation is the most common feature in ICU patients, several studies have focused on finding treatments considering immobilisation as the leading cause of skeletal muscle wasting in these patients. The development of treatment for ICU-AW is based on three strategies: pharmacological, nutritional, and mechanical loads (physical therapy and/or electrostimulation).

Pharmacology treatment of ICU-acquired weakness:

There are several drugs for ICU-AW treatment: anabolic steroid oxandrolone and growth hormone (to increase muscle mass), propranolol (to decrease muscle loss), immunoglobulin (to control inflammation), and glutamine therapy (to improve nutritional status). However, the evidence is not yet sufficient to recommend their use. Insulin therapy could be a promising treatment because it has shown significant preventive effects upon CIP/CIM, but it is not yet possible to recommend it as a common strategy due to the substantial risk of hypoglycaemia.[4,65,66]

Nutrition treatment: Concerning the contribution of nutrition to the clinical outcome of ICU-AW patients, randomised controlled clinical trials have not shown an apparent effect.[48] The recommendations in the initial phase in ICU stay (1–4 days) are to deliver calories and proteins progressively, and from day five onward, to deliver a high-caloric supplementation.[67]

Few studies have assessed the impact of nutritional strategies on muscle mass or function in ICU-AW patients, and their results are inconclusive.[48,67-70] Protein supplementations in the early phases of dysfunction have been used to treat muscle mass loss, but the results are contradictory. Some authors indicate that protein administration does not improve the catabolic state during the early phase of critical illness, and protein synthesis does not change to increased protein delivery.[5,71,72] Other authors indicate that exogenous nutrients supplemented as part of the dietary protein during critical illness reach the skeletal muscle and can induce the synthesis of muscle protein and, at the same time, can inhibit proteolysis [73]

It has been demonstrated that immobilisation can induce an inflammatory condition in the muscle, altering muscle energy and nutrient metabolism. Considering this analysis, some researchers have focused on studying the effects of enhanced protein provision, specific substrate delivery, and physical exercise in the prevention of muscle mass loss in ICU patients.[48] This reaffirms that the loss of muscle mass in ICU patients in the first phase should be considered a multifactorial condition. Thus, the prevention of muscle wasting in ICU patients should be focused on the control of all the associated risk factors,[74] such as immobility or nutrient deficits that are key for avoiding protein loss and metabolic alterations.[75-77]

Mechanical loads

Physical therapy: It is well established that physical therapies can improve health in different ways, including neurological, metabolic, and morphological adaptation.[78-81] Training, exercise, and movement are essential stimuli for the induction of protein synthesis,

mainly via direct activation of the mTOR pathway and, consequently, increasing muscle mass under normal conditions.[82] Physical therapy is considered an essential field in critical care,[83] because it may improve muscle function by targeting different aspects: anti-inflammatory effects, potentially reducing local cytokine expression, and increasing the expression of anti-apoptotic factors. [84] Patients with muscle wasting are commonly referred to physical therapy when they are discharged from the ICU, but physical rehabilitation must begin early in the ICU stay.[85]

Anekwe et al. developed an analysis to evaluate the effects of rehabilitation in two subgroups of ICU patients, screened and randomised, with 49% and 36% lower odds of developing muscle wasting, respectively.[85] The sub-analysis based on the time of onset of rehabilitation suggests that in the first 72 hours after ICU admission, the rehabilitation programme is protective against ICU-AW development compared to beginning rehabilitation later (more than 72 hours). However, these beneficial effects may be explained by the preventive protocol working better or by the patients being able to participate more actively in its rehabilitation in the early stage of the disease. In this line, Hickmann et al. previously demonstrated that mobilisation attenuated the muscle atrophy induced by disuse in the early or catabolic phase of critically ill patients, maintaining the muscle fibre cross-sectional area.[86]

Electrical stimulation: Evidence suggests that beneficial effects in ICU patients are observed with neuromuscular electrical stimulation (NMES) treatments. The NMES could reduce skeletal muscle atrophy in ICU patients.[87] However, controversial results are observed on whether NMES could reduce ICU-AW risk compared to usual care in ICU.[88] NMES have been shown to improve other conditions, such as time on a mechanical ventilator, hospital length stay, and acute mortality associated with ICU-AW, but it does not enhance global muscle strength.[50,88-90] The main reasons NMES intervention are not recommended yet are the low quality of the experimental evidence due to the limited number of participants, differences in the NMES parameters, such as frequency, intensity, and duration, and limiting the pooling and interpretation of data.[88]

Potential therapies

One of the vasoactive peptides with a beneficial effect on structure and function in skeletal muscle is angiotensin-(1–7) [Ang-(1–7)] which belongs to the non-classical axis of the renin-angiotensin-system. Ang-(1–7) has anti-atrophic activity in skeletal muscle, posing a potential treatment for ICU-AW. Ang-(1–7) produces its effects through the G-protein-coupled transmembrane receptor Mas.[91] The actions of Ang-(1–7) include the inhibition of cell proliferation, vasodilation, and antihypertensive effects.[92-94] In skeletal muscle, Ang-(1–7) reportedly acts in the prevention of fibrosis and autonomic dysfunction associated with Duchenne muscular dystrophy, as well as the decrease in angiotensin II (Ang II)-induced insulin resistance and transforming growth factor (TGF)-β signaling.[95-97] Ang-(1–7) also has anti-atrophic effects in skeletal muscle, counteracting the muscle wasting induced by Ang II, immobilisation, and sepsis through a mechanism dependent on the Mas receptor and protein kinase B (PKB/Akt) activity. Furthermore, at the catabolic level, studies in mice have shown that systemic administration of Ang-(1–7) prevents the myosin heavy chain (MHC) decrease and increases atrogin-1 and MuRF-1 in skeletal muscle. Lastly, Ang-(1–7) can prevent the reduction in the diameter of muscle fibres and avoid the transition in their type.[98-101]

Thus, Ang-(1–7) could be an exciting candidate for possible future therapies to curb muscle mass loss in patients with ICU-AW.

ICU-acquired weakness and COVID-19

Since 2019, the world has faced a complex health situation due to the COVID-19 pandemic. COVID-19 is an infectious disease caused by SARS-CoV-2. The World Health Organization (WHO), in April 2022, reported 497057239 infected people and 6179104 deaths from the virus in the world.[102]

The clinical manifestation of this viral infection includes asymptomatic or symptomatic patients. The common symptoms are cough, sore throat, headache, fever, gastric discomfort, fatigue, dyspnoea, and muscle and joint pain. [103] In symptomatic patients, the condition's severity is highly variable and can be managed on an outpatient basis, requiring hospitalisation or admission to intensive care units (ICU). Severe COVID-19 patients usually need access to the ICU and, in many cases, the use of mechanical ventilation (MV) and other invasive treatments to save their lives. In this context, the risk of developing ICU-AW is high.[6]

There is still little information regarding COVID-19 patients developing ICU-AW. However, there are several similarities between patients with severe COVID-19 and CIM patients, such as prolonged MV, classical ICU interventions, myalgias, significant muscle loss, and hyper-inflammation.[7,8]

Considering that COVID-19 produces severe respiratory disorders, such as pneumonia (75%) and acute respiratory distress syndrome (ARDS) (15%), these patients have a high probability of developing ICU-AW.[104] Hence, SARS-CoV-2 could cause neuromuscular symptoms like another coronavirus previously reported such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). In these viruses, patients reportedly develop several neuromuscular alterations, such as myalgia, rhabdomyolysis, and polyneuropathy.[105-107] About 75% of COVID-19 patients admitted to the ICU require MV,[108-110] and the median length of stay in the ICU and hospital is 14 and 17 days, respectively.[111]

High probability of developing ICU-acquired weakness in COVID-19 patients

Still, not many clinical studies describe the development of ICU-AW in COVID-19 patients treated in ICU. However, the current information shows that a high percentage of these patients developed early diffuse and symmetrical muscle weakness (CIM)[112-115] or polyneuropathy (CIP)[116] with absent deep tendon reflexes,[117] and myalgia,[114] coinciding with the clinical manifestations of ICU-AW. These patients present several risk factors of ICU-AW, such as required intensive care, invasive mechanical ventilation, pharmacological therapy for ICU (corticosteroids, sedatives drugs, neuromuscular blocking agents), hyperglycaemia, and prolonged ICU stays.[118]

The ICU-AW diagnosis in patients with COVID-19 has been developed through clinical tests that show lower scores in mobility scales, decreased handgrip strength, and Barthel index. [112,118] Electrodiagnostic findings have shown normal sensory conduction, low amplitude, and increased distal latency of compound muscle action potentials (CMAP), and electromyography (EMG) showed signs of critical illness myopathy (CIM), [112,114,116,117] which would confirm the presence of ICU-AW in patients with more severe COVID-19.

Thus, when COVID-19 patients require prolonged ICU stays, it is highly probable that they develop ICU-AW. However, the impact on functional status and long-term consequences of ICU-AW in these survivors remain unclear. Despite a lack of evidence, the median and extended time consequences can have severe adverse effects on daily life activities. The rehabilitation programmes could effectively reverse muscle weakness caused by ICU-AW in COVID-19 patients.

Mechanisms for the development of ICU-acquired weakness in COVID-19 patients treated in ICU

At the pathophysiological level (Figure 2), in COVID-19 exhibits a "cytokine storm," with increases in cytokine and chemokine levels[119] and triggers coagulopathy and thrombosis.[120] The principal cytokines identified in COVID-19 patients are TNF-α, IL-1, type I interferon (IFN), and IL-6,[121] the same cytokines that are increased in critically ill patients.[39] A high correlation between the level of IL-6 in the blood and mortality and severity has been described in patients with COVID-19.[122,123] It is known that there may be an imbalance in muscle metabolic homeostasis that exacerbates the loss of muscle mass due to a systemic increase in IL-6.[124,125] Furthermore, in a Syrian hamsters model injected with SARS-CoV-2, the animals developed typical COVID-19 and weight loss signs associated with increases in interferon δ and TNF-α.[126] The IFN dysregulated release in COVID-19 could produce a maladaptive immune response with hyperactivity of innate immunity and immunosuppression.[127] This COVID-19 cytokine storm could aggravate the patient's condition and promote the development of ICU-AW.

In COVID-19 patients, deregulation of the renin-angiotensin system (RAS) can also play a role in ICU-AW development.[128] RAS can modulate skeletal muscle mass through two pathways: classical and non-classical. Angiotensin (Ang) I is converted to Ang II by angiotensin-converting enzyme (ACE) in the classical axis. If Ang II is bound to angiotensin type 1 (AT1R), the adverse effects are inflammation, vasoconstriction, atherogenesis, fibrosis, and skeletal muscle atrophy.[129] In the non-classical axis, angiotensin-converting enzyme 2 (ACE2) converts Ang II into Ang (1-7). Positive skeletal muscle consequences include anti-inflammatory, anti-atrophic, and antifibrotic effects.[130,131] The SARS-CoV-2 receptor is ACE2. When the virus binds to its receptor, it downregulates the ACE2 protein,[132] which could lead to deregulation of RAS with increased activity of the classical axis and decreased activity of the non-classical axis,[128] affecting the muscle mass balance. In coronavirus disease, post-mortem muscle samples of SARS-CoV patients showed muscle atrophy and necrosis;[132] thus, it cannot be ruled out that SARS-Cov-2 might have similar effects on skeletal muscle.

However, COVID-19 patients may develop an inflammatory myopathy called immune-mediated necrotising myopathy (IMNM) or necrotising autoimmune myopathy. The myopathy in severe COVID-19 patients may be explained by immune mechanisms (due to massive cytokine release than the direct invasion of the virus into muscle tissue), immune myositis infection with the virus, electrolyte disturbances, drugs, hypo-excitability of the membrane, necrosis, or hypoxia.[114,133] Inflammatory myopathy is characterised by proximal muscle weakness accompanied by elevated serum muscle enzyme levels, such as creatine kinase (CK), scattered necrosis of myofibers, few infiltrated lymphocytes, size variation of muscle fibres, and central nuclei.[134] This condition must necessarily be diagnosed by muscle biopsy,[134,135] but CK could be a good and more accessible alternative. CK has generally been considered an indicator of muscle damage and inflammatory response.[136] Patients with severe COVID-19 reportedly have higher CK serum levels and muscle injury than ICU patients.[105] However, it is crucial to consider that CK is nonspecific and can be elevated by prolonged bed rest and medications instead of a direct muscle injury from COVID-19.[137]

Treatment of ICU-acquired weakness in COVID-19 patients

The current treatments applied to COVID-19 patients in the ICU are: "conservative intravenous fluids, empirical intravenous antibiotics for suspected bacterial coinfection, consideration for early, invasive endotracheal intubation and ventilation to maintain adequate oxygenation and carbon dioxide elimination, lung-protective ventilation strategies, such as limiting tidal volumes and inspiratory pressures, periods of prone positioning while mechanically ventilated to decrease the

risk of mechanical lung injury and consideration of extracorporeal membrane oxygenation".[138]

After discharge from ICU, these patients could present similar long-term sequelae of ARDS, such as multiorgan impairment, pulmonary dysfunctions, dyspnoea, fatigue, reduced exercise capacity, exertional hypoxemia, reduced muscle strength, shoulder dysfunction, dysphagia, anxiety symptoms, and cognitive and mental health dysfunction.[139,140] These sequels could affect functionality in daily activities and require rehabilitation. In addition, another aspect to consider and that could have important negative effects on the subsequent functional recovery of ICU and COVID-19 patients is the lack of mobilization during hospitalization. In this regard, a study by Liu et al. (2022)[141] conducted with data from 135 ICUs, with a total of 1,229 patients in 33 countries around the world, showed that more than 90% of patients with MV (positive or negative for COVID-19) during the pandemic, remained completely immobile most of the time. These results are worrying considering the enormous number of sequelae that these patients can have and, without a doubt, it is essential to change the therapeutic approach to one where mobility is a fundamental element of the rehabilitation.[141]

Regarding post-ICU rehabilitation in COVID-19 patients, given the limited information, more research is needed.[139,142] Patients with physical function sequelae of ICU-AW and COVID-19 need physical therapy to reverse the disability associated with cardiopulmonary dysfunction and muscle atrophy. The physical treatment includes earlier mobilisation, exercise training, neuromuscular electrical stimulation, and respiratory rehabilitation, which can consist of respiratory care and respiratory training.[143-145]

Therefore, developing rehabilitation programmes for post-COVID-19 patients treated in the ICU for medium- and long-term treatments are essential. Although it is a topic that is beginning to be studied and understood, considering the relevance for patient recovery and the associated health costs, it is relevant to explore the possible factors that influence the risk of ICU-AW in COVID-19 patients.

Conclusions and perspectives

In the future, it is necessary to investigate the pathophysiological process that favours possible myopathy and the development of ICU-AW in patients with COVID-19.[133] In this regard, biopsy, despite being an invasive procedure, could be essential,[114] as well as nerve conduction and EMG studies.[116] A detailed neurological and muscular evaluation is also essential because many ICU-AW patients with COVID-19 may have early deficits.[146]

If the long-term physical consequences of COVID-19 on skeletal muscle are added to the effects of ICU-AW,[147-156] recovery is complex, along with the high health care costs that this entails.[117] It is crucial to start a nutritional intervention and preventive physical and respiratory therapy to delay the accelerated loss of skeletal muscle mass and maintain respiratory function during the ICU stay. After ICU discharge, it is essential to include multidisciplinary therapy that considers muscle function treatment from nutritional, pharmacological, and physical rehabilitation aspects. The target could be the progressive recovery of mass and general muscle strength and the function of the respiratory muscles and, with it, the generalised recovery of physical function. All these interventions that are used post-ICU-AW patients must be adapted to the needs of patients with COVID-19 exhibiting long-term persistent symptoms, such as fatigue, dyspnoea, pain, and cough.[139,145]

List of acronyms

6-MWD - 6-minute walking distance
ACE - angiotensin-converting enzyme
ACE2 - angiotensin-converting enzyme 2
Akt - protein kinase B
Ang II - angiotensin II
Ang-(1–7) - angiotensin-(1–7)
APACHE - acute physiology and chronic health evaluation
ARDS - acute respiratory distress syndrome (
AT1R - angiotensin type 1
CIM - critical illness myopathy
CIP - critical illness polyneuropathy
COVID-19 – Corona virus disease 2019
CT - computed tomography
ICU -intensive care unit
ICU-AW - intensive care unit - acquired weakness
IFN - type I interferon
IL-1 - interleukin 1
IL-6 - interleukin 6
IQR - interquartile range
MEP: maximum expiratory pressure
MIP - maximum inspiratory pressure
MRC-SS - medical research council sum score
mTOR - mechanistic target of rapamycin
MuRF-1 - muscle-specific RING finger protein 1
MV - mechanical ventilation
NMES - neuromuscular electrical stimulation
NMJ - neuromuscular junction
PKB - protein kinase B
RAS - renin-angiotensin system
SARS-CoV-2 - severe acute respiratory syndrome Coronavirus 2
SIRS - systemic inflammatory response syndrome
SOFA - sequential organ failure assessment
TNF-α - tumour necrosis factor-alpha
UPS - ubiquitin-proteasome system
WHO - world health organization
MERS-CoV - Middle East respiratory syndrome coronavirus

Contributions of Authors

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship

for this article, take responsibility for the work's integrity as a whole. Conceptualization: JA, OA, AG and CC-V; validation: JA, OA, and AG; formal analysis: JA, OA, AG, FS and CC-V; investigation: JA, OA, AG, and C C-V; original draft preparation: JA, OA, AG, and CC-V; revision and editing: C C-V and FS; supervision: C. C-V; project administration: C C-V; funding acquisition: C C-V, and FS. All authors have read and approved the final edited typescript.

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The authors declare no conflict of interests.

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