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REVIEW



Cardiorespiratory and skeletal muscle damage due to COVID-19: making the urgent case for rehabilitation

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ABSTRACT

Introduction: It has become increasingly evident that COVID-19 contributes to multiorgan pathophysiology. The systemic inflammatory response increases both pro-inflammatory cytokine and chemokine levels, leading to immune dysregulation and increasing the likelihood of incurring cardiac and pulmonary injuries.

Areas covered: Longer periods of hospitalization (~20 days) increase susceptibility to ICU-acquired muscle weakness and deconditioning, which decreases muscle function and functional capacity. These conditions affect the quality of life in the post-COVID-19 period and require multi-disciplinary approaches to rehabilitate the cardiopulmonary and musculoskeletal systems of these patients. In this context, this narrative review, which included articles published in the Embase, PEDro and PubMed databases up to December 2020, is focused on discussing the essential role of exercise and rehabilitation health professionals in the COVID-19 recovery process, from hospitalization to hospital discharge, addressing strategies for professionals to mitigate the cardiac and pulmonary impairments associated with hospitalization to home or ambulatory rehabilitation, purposing ways to conduct rehabilitation programs to restore their functional status and quality of life after the infection.

Expert opinion: In the current environment, these findings further point to the vital role of rehabilitation health professionals in the coming years and the urgent need to develop strategies to assist COVID-19 survivors.

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COVID-19; exercise; rehabilitation; respiratory therapy; cardiac rehabilitation; quality of life

1. Introduction

It has become increasingly evident that COVID-19 contributes to multiorgan pathophysiology. This is due to a systemic inflammatory response that increases both pro-inflammatory cytokine and chemokine levels, leading to immune dysregulation and increasing the likelihood of incurring cardiac and pulmonary injuries [1,2]. Additionally, neurological and kidney injuries associated with COVID-19 can trigger chronic cardiorespiratory injuries [3]. Furthermore, longer periods of hospitalization (~20 days) increase susceptibility to intensive care unit-acquired muscle weakness (ICU-AW) [4,5], which impairs muscle function and decreases functional capacity [6]. Collectively, these conditions affect the quality of life in the post-COVID-19 period and require multi-disciplinary approaches to rehabilitate the cardiopulmonary and musculoskeletal systems of these patients [7,8].

In this context, to better elucidate key aspects of COVID-19 pathophysiology, its cardiorespiratory consequences, and the essential role of exercise in the COVID-19 process, we conducted this narrative review, including supporting literature

searches from the following databases: 1) Embase (Via Capes Periodicals) Scientific Electronic Library Online (SciELO); 2) Physiotherapy Evidence Database (PEDro); and 3) PubMed. Duplicate papers were excluded and papers available up to December 2020 were considered to address strategies for professionals to mitigate the cardiac and pulmonary impairments associated with hospitalization to home or ambulatory rehabilitation. At hospital discharge, we address how to receive and manage these patients in the clinical rehabilitation setting, purposing ways to conduct pulmonary and cardiac rehabilitation to restore their functional status and quality of life after the infection, described as the post-COVID-19 phase.

2. COVID-19 epidemiology, pathophysiology and systemic damage leading to cardiorespiratory injury due to SARS-CoV-2 infection

The family of coronaviruses mainly affect the human respiratory system [9] and its infections have been reported for years. In 2020, a new pandemic spread across the world. The new

Article highlights

- COVID-19 contributes to multiorgan pathophysiology due to a systemic inflammatory response and immune dysregulation.
- The cardiorespiratory system can be directly or indirectly affected by COVID-19 and a portion of patients who survive may have limiting impairments in cardiorespiratory function.
- Exercise has anti-inflammatory properties working as a modulator of the immune system; moderate-intensity exercise is recommended to improve immune function, being related to lower incidences of upper respiratory tract infections.
- The benefits of exercise in rehabilitation programs are well recognized and highly recommended for patients with COPD, CHF and other comorbidities, especially to improve musculoskeletal function.
- Multidisciplinary approaches and rehabilitation programs are needed to restore functional status, exercise capacity, independence and quality of life, and rehabilitation specialists play a vital role in this field.

coronavirus (COVID-19), named by the World Health Organization (WHO) as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), constitutes the seventh known coronavirus able to infect humans and has potential to develop respiratory distress similar to the first severe acute respiratory syndrome (SARS) outbreak reported in 2002 (SARS-CoV) [10–12]. The pathogenic complexity of SARS-CoV-2, which involves a high transmission potential, is being globally investigated so that treatment and immunization strategies can be developed as quickly as possible to contain the outbreak.

Although COVID-19 triggers respiratory symptoms, such as cough (63.1% of patients), chest tightness (35.7%), shortness of breath (35%) and respiratory failure (19.5%), it can also develop a variety of non-respiratory symptoms, such as diarrhea (12.9%), headache (15.4%), ocular manifestations (32%), and loss of smell and taste (53%); approximately 20% of the patients with COVID-19 are completely asymptomatic [13–17].

Studies have found the genome of SARS-CoV-2 to be 79.5% to 96% similar to the genome of SARS-CoV previously described [18], and regarding the protein sequencing, these viruses share 76% similarity [19]. However, the SARS-CoV-2 outbreak has had a much greater and more severe global when compared to the other two major outbreaks due to coronaviruses (SARS-CoV and MERS-CoV) [11]; by 16 December 2020 the WHO reported that almost 72 million people have been infected and about 1,623,064 of them have died around the world [20].

Regarding cell entry mechanisms, it is already known that SARS-CoV-2, like SARS-CoV, uses the angiotensin converting enzyme-2 (ACE2) as a cell surface receptor to enter the host [21]. ACE2 is a multifunctional protein highly expressed in the heart and vessels and its primary physiological role is the enzymatic conversion of angiotensin (Ang) II to Ang1-7 and Ang-I to Ang1-9, which are protective peptides of the cardiovascular system [22]. Nevertheless, SARS-CoV-2 has a significantly higher ACE2 binding affinity compared to SARS-CoV [23].

Some studies indicate SARS-CoV-2 uses lung epithelial cells as its primary target, since ACE2 is also expressed in the lower respiratory tract [24]. On the other hand, a more recent study

found that in addition to the lungs, ACE2 seems to be expressed to higher levels in many other human tissues, such as in the small intestine, testis, kidneys, heart, thyroid, and adipose tissue. Thus, in terms of ACE2 expression, the lungs and other systems can be a target for the virus [25], although severe complications due to SARS-CoV-2 infection seems to primarily be centered on the respiratory system [9,26].

Immune responses play an important role in the pathogenic response of coronaviruses infections as these infections induce an overreaction of the immune system [27]. Like SARS-CoV and MERS-CoV, SARS-CoV-2 induces low levels of antiviral factors interferons and high levels of pro-inflammatory cytokines such as interleukins (IL – IL-1 β , IL-2, IL-6, IL-10) and tumor necrosis factor (TNF α) and high levels of chemokines, characterizing immune dysregulation. Increased cytokines and chemokines levels lead to increased inflammatory cells into lung tissue inducing lung injury [28,29].

The immune dysregulation observed in SARS-CoV-2 infection show that the cytokine storm is closely related to the development of SARS and the severity and risk of death, given that cytokine storm is considered one of the major causes of multiple-organ failure observed in critically ill patients with COVID-19 [26,30]. Therefore, immune dysregulation and the pro-inflammatory state is closely related to respiratory tissue injury. In addition, a potentially greater risk of upper respiratory tract infections due to coronavirus has been previously demonstrated in people with a compromised immune system [27].

In association to the systemic inflammatory response, endothelial cell dysfunction is an important component observed in patients with COVID-19 [31], which is related to the fact that ACE2 receptors are also produced by endothelial cells [32]. ACE2 works as a protective factor in a variety of organs acting as a regulator of blood pressure and anti-atherosclerosis mechanisms; moreover, ACE2 it is also a cell receptor to SARS-CoV-2 [33]. In this context, SARS-CoV-2 binds to ACE2 receptors, leading to reduced ACE2 expression, promoting endothelial cell dysfunction and increasing blood pressure and other cardiovascular abnormalities [34]. Infection of endothelial cells is of particular importance, as this can lead to severe microvascular and macrovascular dysfunction and hypercoagulability [35].

Endothelitis related to SARS-CoV-2 infection has already been reported and the widespread endothelial dysfunction seen in patients with COVID-19 is associated with the procoagulant state and cell apoptosis [31], damaging the cardiovascular system. Endothelitis is characterized by the decreased availability of nitric oxide (NO), which reduces vasodilation capacity and induces a pro-inflammatory and pro-thrombotic state [36].

In addition to these disorders, peripheral and central nervous systems are also affected by COVID-19 as was previously observed in other viral infections [37,38]. Due to its neurotropic characteristics, SARS-CoV-2 can invade nervous tissue, potentially leading to toxic encephalopathy and other acute cerebrovascular disorders, especially because of the increased pro-inflammatory cytokines that may be associated with cerebrobasilar disease [39].

Immune dysregulation is closely related to the capacity of the virus to invade the nervous system (NS). During a viral infection, the infected cells induce an antiviral response as an intrinsic immunity strategy, as well as initiate paracrine signaling from the infected cells to cells that remain uninfected as an innate immunity [40]. When the site of the primary infection loses local control of the infection, it can rapidly disseminate to other susceptible tissue [41], leading to virus replication and potentially an overreaction of the innate immune response. This detrimental response in the NS can lead to meningitis, encephalitis, meningoencephalitis and death [40].

The COVID-19 infection carries the aforementioned concerns, as evidenced by the fact that SARS-CoV-2 can invade the NS [42]. In patients with mild COVID-19, NS symptoms are more related to loss of smell and taste, dizziness and headache. However, neurological abnormalities have been described in approximately 30% of hospitalized patients with COVID-19, 85% of those with acute respiratory distress syndrome [43]. Cytokine dysregulation, hypoxia, and metabolic dysfunction in COVID-19 may trigger encephalopathy in some infected patients, while endothelial dysfunction and hypercoagulability seem to be related to stroke risk [42].

In addition, the development of Guillain-Barré syndrome associated with SARS-CoV-2 infection was first reported on 1 April 2020 and has since been reported in other patients [44] [45]. Neurological disorders can also compromise the respiratory system due to muscle dysfunction present in these patients [46] which can alter respiratory function by increasing central respiratory drive [47]. Respiratory muscle function can also be affected due to neuromuscular dysfunction as it occurs in acute neuromuscular respiratory disease, and Guillain-Barré syndrome has also been related to respiratory dysfunction in previous studies [46,48,49].

SARS-CoV-2 infection can also trigger acute kidney injury (AKI) as a severe complication of COVID-19. The AKI is also associated with the increased pro-inflammatory cytokine

responses that lead to interstitial kidney inflammation and a collapsing glomerulopathy disorder [50]. Discussing the pathophysiology of AKI due to COVID-19, Batlle et al. reported that the organ crosstalk between the injured kidney, heart and lungs may further propagate injury [51]. Moreover, it is already known that AKI is associated with the development of pulmonary complications such as pulmonary edema [52]. In this context, as kidney injuries are related to decreased exercise tolerance together with the impaired ventilatory function, a recent systematic review [53], including seven studies, assessed patients with chronic kidney disease, demonstrated that exercise can improve cardiopulmonary function, increasing exercise tolerance and ventilatory efficiency; greater benefits were observed in protocols that combined modes of exercise (aerobic and resistance training) [53].

3. Direct damage to the cardiorespiratory system caused by COVID-19

Discussing the variety of complications due to the SARS-CoV-2 infection leads to the observation that COVID-19 constitutes a condition of multisystem disorders (partially summarized in **Figure 1**). However, the impact of COVID-19 on the cardiorespiratory system is a primary focus given the virus' impact on both the heart and lungs, with potential chronic implications [54].

In this regard, cardiorespiratory complications are quickly emerging as a threat to patients with COVID-19 from admission to the hospital and continuing upon discharge. Patients with cardiovascular risk factors such as advanced age, diabetes, hypertension, obesity, cerebrovascular disease, and male gender are identified as factors portending increased risk, with greater levels of morbidity and mortality from COVID-19. A study with 416 patients found that, of the patients who died, 10.6% had coronary artery disease (CAD), 4.1% had heart failure (HF) and 5.3% had cerebrovascular disease [55].

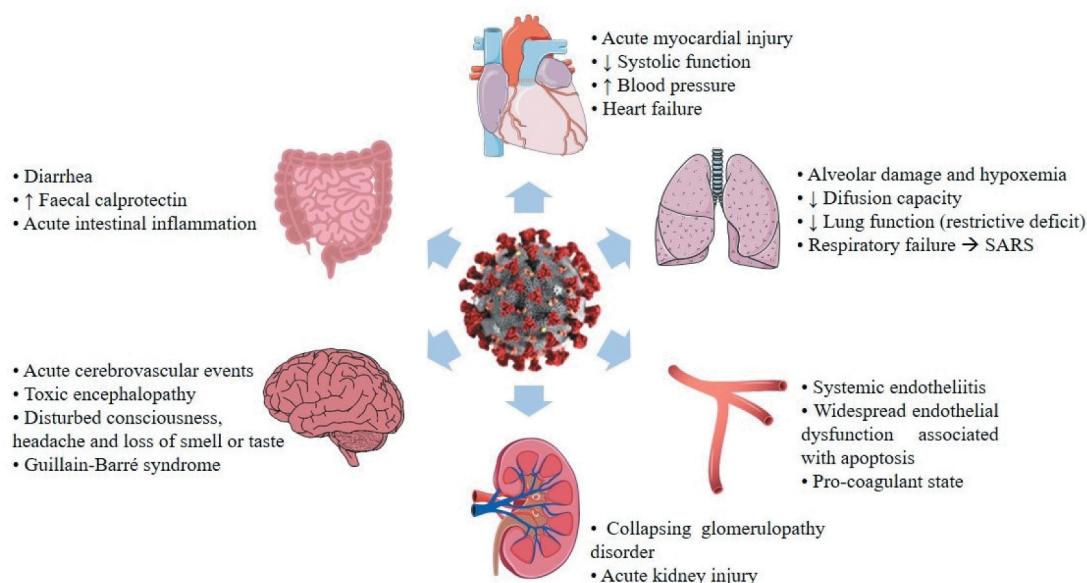


Figure 1. Multisystem disorders due to the SARS-CoV-2 infection.

In addition, some patients with COVID-19 develop heart injuries, which becomes an increased risk for in-hospital mortality [56]. Acute myocardial injury is the heart disease most described as a complication in COVID-19, present in 8% to 12% of cases [57]. Serious COVID-19 infections are also associated with cardiac arrhythmias due to infection-related myocarditis [58,59]. Zhou et al. found that 23% of all COVID-19 infected and hospitalized patients developed HF and in 52% of these cases, the development of HF was fatal, while only 12% survived [60].

According to Zhou et al., hypercoagulability was present in 19% of patients with COVID-19 [60]. From the immunological overactivity and endothelial dysfunction generated, these patients are more susceptible to deep venous thrombosis, pulmonary artery microthrombosis, and distal arterial microthrombosis, all of which can potentially destabilize atherosclerotic plaques. This may explain the development of acute coronary syndromes such as myocardial ischemia, ischemic stroke, and pulmonary embolism in patients with COVID-19 [61,62].

In addition, it is possible that other mechanisms, such as unbalanced T-cell and cytokine responses, activate macrophages that infiltrate the infected myocardium, resulting in fulminant myocarditis and severe cardiac damage [63]. Therefore, viral invasion can cause damage to cardiac myocytes, leading to myocardial dysfunction and arrhythmias [35]. Wang et al. found an incidence of arrhythmias to be 16.7% in 138 patients hospitalized with COVID-19; the incidence was higher (44.4%) in those who were admitted to the intensive care unit (ICU) compared to those who were not (8.9%) [58]. Increased creatine kinase in patients with SARS-CoV-2 indicate the potential presence of acute myocardial injury [58].

Approximately 80% of the infected COVID-19 population present with no symptoms or mild to moderate symptoms; the remaining 20% have more severe manifestations that potentially requires hospitalization [64,65]. Regarding the respiratory system, Jiang et al. found that 29% of the patients with COVID-19 who were hospitalized develop SARS, often requiring intensive care and artificial mechanical ventilation [66]. In this context, patients with a severe clinical course from COVID-19 can experience hypoxemia, diffuse alveolar damage and muscle weakness acquired in the hospital as a secondary impairment [67]. The symptoms of COVID-19 in the respiratory system are fever (reported in 83% to 99% of the patients), dry cough (59.4% to 82%), and difficulty of breathing (dyspnea – reported in approximately 55% of hospitalized patients) observed at the beginning of the disease, which presents as the main characteristic of COVID-19 [58,68]. Among hospitalized patients with dyspnea, more than 50% needed intensive care, of which 46% to 65% of these patients worsened in a short period of time and died from respiratory failure [69,70].

Regard hospitalized patients with COVID-19, Zhou et al. found that 31% developed SARS [60]. Chest computed tomography (CT) revealed that 96% of these patients showed bilateral ground-glass opacities [69]. The infiltrates are limited in extent and, initially, are characterized by a ground-glass pattern on CT that signifies interstitial and non-alveolar edema and lymphopenia [69,71]; this

manifestation may progress to SARS and necessitate the urgent need for mechanical ventilation (MV) [72].

The primary infection of the respiratory system through SARS-CoV-2, particularly in type 2 pneumocytes, is manifested by the progression of systemic inflammation and overactivation of immune cells, resulting in increased levels of proinflammatory cytokines (IL-6, IL-7, IL-22 and CXCL10) [35]. Thus, inflammation generated in the lungs is characterized through blood mediators. Zhao et al [73], suggested that the excessive immune response plays an important role in pathogenesis, where the abnormal increase in CRP, IL-6 and neutrophils contributed to acute lung damage and are associated with significant pathophysiology and fatal events. Another important process is the activation of coagulation with formation of thrombi in the lungs and other organs, indicating the damage caused by endothelial dysfunction from the interruption of pulmonary vasoregulation, generating ventilation-perfusion incompatibility [71].

Regarding pulmonary function, Mo et al [74] evaluated 110 non-critical discharged middle-aged patients diagnosed with COVID-19 and performed pulmonary function testing on the day of or one day before discharge. This group reported important abnormalities in diffusing capacity for carbon monoxide (DLCO) in 47.2% of the cases (DLCO was 64.79% of predicted for severe pneumonia cases) and total lung capacity (TLC) in 25% (TLC was 79.16% of predicted for severe pneumonia cases), followed by a lower number of patients with abnormalities in forced expiratory volume in the first second (FEV₁) in 13.6% of the cases, forced vital capacity (FVC) in 10%, FEV₁/FVC in 4.5% and small airway function in 7.3%. In addition, the percent-predicted value for total lung capacity in severe cases of pneumonia due to COVID-19 was lower than that reported for mild illness, suggesting greater lung volume impairment in severe cases. These findings indicate impairment in lung diffusion capacity is a primary abnormality in patients with COVID-19, followed by restrictive ventilatory dysfunction.

Moreover, Sheng et al. found that viral infections increase the risk of pulmonary fibrosis, which can be one of the serious complications following recovery from COVID-19; the prevention of pulmonary fibrosis due to COVID-19 is an issue that needs to be urgently addressed [75].

It is also important to emphasize that pulmonary function testing should be considered as a clinical follow-up exam for patients recovering from COVID-19, particularly given patients with impaired lung function can benefit from pulmonary rehabilitation programs, as seen in patients with COPD, asthma, and other lung diseases [76,77].

The impact of COVID-19 on the cardiorespiratory system and precipitating damage is illustrated in **Figure 2**.

4. Severe diaphragm myopathy associated with COVID-19

There is emerging evidence suggesting that the respiratory muscles may also be affected by SARS-CoV-2 infection [78,79]. A postmortem study by Shi et al. [78] examined the respiratory

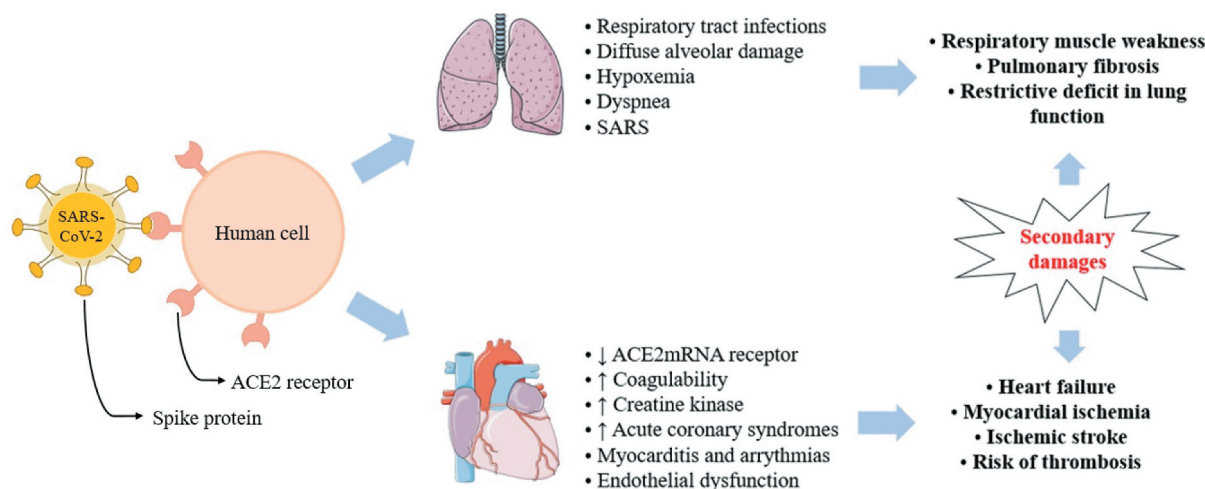


Figure 2. Cardiorespiratory damages due to COVID-19 and its possible secondary damages.

muscles of patients admitted to the ICU with COVID-19 compared to those without. They found that ACE-2 is expressed in the myofiber membrane of the human diaphragm, and evidence of viral infiltration of SARS-CoV-2 was observed in the diaphragm myofibers of patients with COVID-19. Patients with COVID-19 also demonstrated increased expression of genes associated with fibrosis, and a twofold increase in both epimysal and perimysal fibrosis compared to those without COVID-19, despite similar durations of MV and ICU stay [78].

This potential COVID-19-related acute respiratory muscle myopathy is concerning as COVID-19-related SARS may also reduce respiratory system compliance [79,80]. Those combined effects from COVID-19 infection may shift the balance between the pressure demands of breathing (alveolar ventilation) and the pressure generating capacity of the respiratory muscles increasing the risk of respiratory failure thus requiring MV. However, MV alone has been shown to induce rapid atrophy and profound weakness of the respiratory muscles [81]. Additionally, patient demographics at an increased risk of severe respiratory complications from COVID-19 requiring ICU admission and/or MV, such as older age, obesity, and lung disease, are associated with respiratory muscle weakness and difficulty weaning from MV [79]. The combination of these factors may contribute to the poorer outcomes following COVID infection especially in high risk patients [82]. They may explain the persistent dyspnea, and fatigue in patients recovering from COVID-19 [83]. Lastly, these COVID-related changes to the respiratory muscles may also explain the phenotype of patients with COVID-19-related SARS and respiratory failure without typical reductions to respiratory changes compliance [84,85].

As treatment priorities for COVID-19 rapidly evolve, rehabilitation health professionals with particular expertise in respiratory conditions (e.g., physiotherapists, exercise physiologists) are being recognized as essential members of the multidisciplinary team that cares for patients with COVID-19. As such, it is important to discuss when rehabilitation health professionals should initiate care in patients infected with SARS-CoV-2, how long this care should continue and how

treatment approaches and goals evolve as a patient transitions from acute to long-term treatment [86–88].

5. Rehabilitation health professionals and the management of hospitalized patients with COVID-19

Rehabilitation health professionals play a vital role in the care of patients with COVID-19, starting in the ICU as they work directly on respiratory care, manage ventilatory support, improve musculoskeletal disorders, functional capacity, and physical autonomy, all of which are essential to a successful discharge upon recovery [89] and illustrated in Figure 3.

Regardless of severity of viral infection, hospitalized patients should be monitored for pulmonary assessment, especially during oxygen supplementation, noninvasive mechanical ventilation (NIV) and orotracheal intubation [90]. This is accomplished by direct observation and pulse oximetry; oxygen therapy using a nasal cannula or Venturi mask should be used as indicated to maintain oxygen saturation (SpO_2) levels between 90% and 96% [91].

Use of NIV is not highly recommended due to its high association with increased respiratory failure rate [92]. On the other hand, high flow nasal oxygen is used for hypoxia associated with COVID-19 at flow rate to no more than 30 L/min due to its potential viral transmission [90]. Therefore, in some cases, it is necessary to provide strict airborne personal protective equipment (PPE) and negative pressure rooms, which are recommended to isolate patients capable of generating airborne infection. When negative pressure rooms are not available, it would be preferable to isolate the infected patients into a single room separated from areas containing non-COVID-19 infected patients [93]. In the event of ventilation failure, the criteria for MV are $FiO_2 > 60\%$ and/or tidal volume >9 ml/kg, or the inability to tolerate 2 hours without NIV [90].

In some cases, experts suggest extracorporeal membrane oxygenation (ECMO) in hospitals with sufficient medical resources, a strategy that should be initiated before injurious MV. The purpose of ECMO is to maintain sufficient

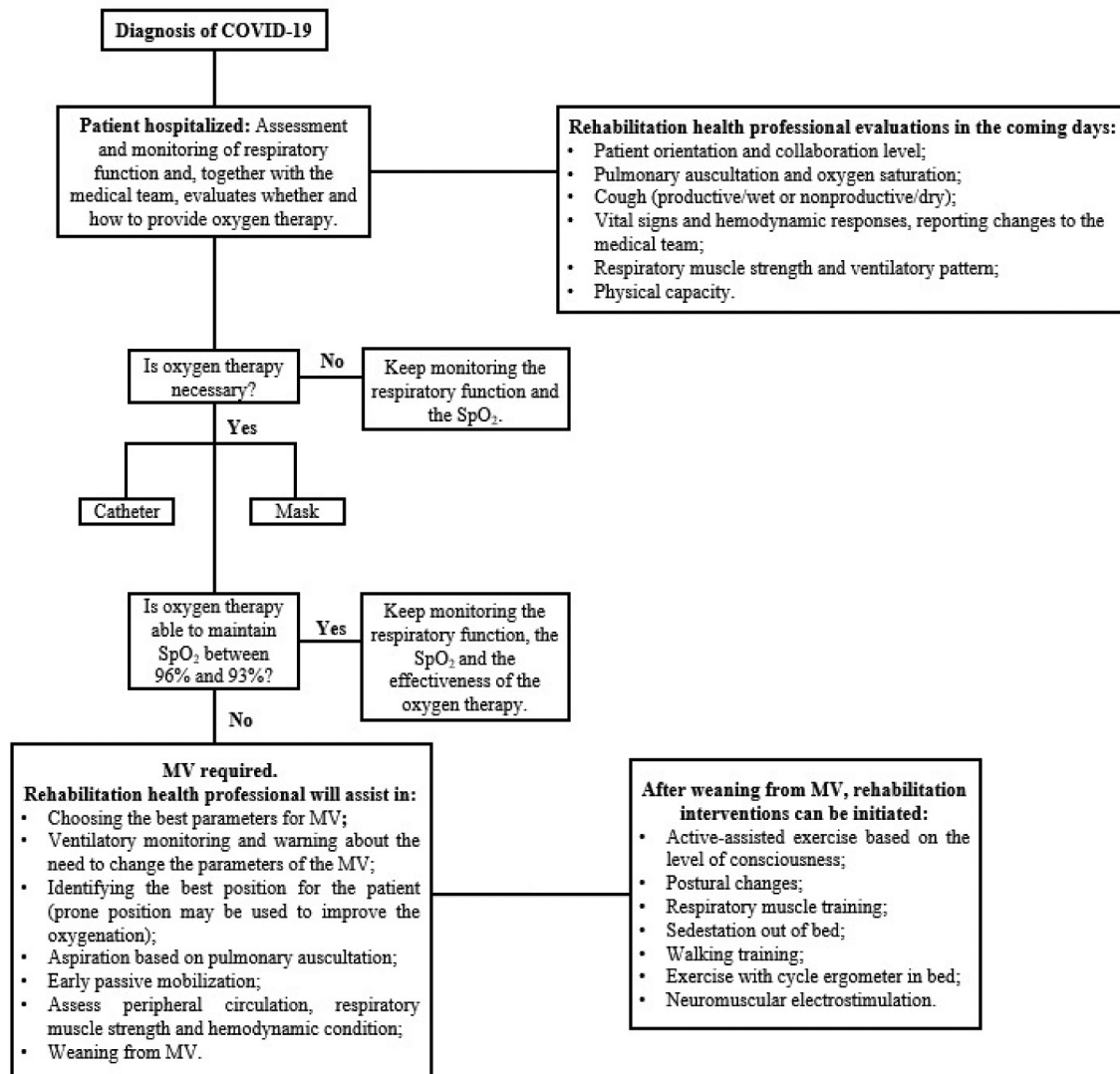


Figure 3. Rehabilitation health professional interventions in the care of patients hospitalized with COVID-19.

oxygenation and removal of carbon dioxide (CO_2) [94]. Prone positioning in moderate-to-severe COVID-19 patients, i.e. ratio of arterial oxygen partial pressure to fractional inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 150 mmHg, is also a strategy to prevent deterioration, and has been shown to have a beneficial effect on oxygenation, lung recruitment, and stress distribution. Physiotherapists, for example, can be an important part of the prone positioning team in the ICU, providing staff education and leading prone positioning, which maintained for more than 12 hours [92,94].

Based on previous studies [92,95–100], we summarize the main methods of intervention and in-hospital care in the management of patients with severe cases of COVID-19 in **Table 1**.

As patients with COVID-19 admitted in ICU are often submitted to invasive MV, sedation and neuromuscular blockers, the onset of muscle weakness and dysfunction are of great concern. The longer the patient remains in the ICU (approximately 21 days or more for COVID-19 patients), the greater the risk of developing long-term reductions in physical function, as well as cognitive and emotional complications [101,102].

Prolonged bed rest is the primary driver for a condition known as ICU-acquired muscle weakness (ICU-AW), which is characterized by decreased muscle protein synthesis, loss of muscle mass, decreased force generation, and increased muscle catabolism [103]. Frequently, discharged ICU patients report dyspnea, pain, impaired lung function, and exercise intolerance, in addition to decreased mobility, more frequent falls and quadriparesis [103]. In addition, when patients recover from the infection and are discharged from the ICU, post-intensive care syndrome (PICS) may occur as a result of secondary injuries from the intensive care treatment and the consequences of severe respiratory issues [104,105]. During the previous SARS-CoV outbreak, a review of available literature found lung function 6–8 weeks after discharge demonstrated a mild-moderate restrictive pattern indicative of respiratory muscle weakness in 6–20% of the patients assessed [106]. Additionally, in a prospective cohort study with 97 survivors of SARS, persist reductions in exercise capacity as measured by in 6-minute walk test at 12 months was apparent [107].

Considering the deleterious impact of prolonged immobilization, physiotherapy is an important component of the

Table 1. Clinical features, intervention, and care in hospital to COVID-19 patients.

Clinical features of patient COVID-19	Intervention	Care in the hospital environment
Arterial oxygen saturation (SaO ₂) <93% or signs of respiratory distress and hypoxia [95]	Oxygen (O ₂) therapy – nasal cannula with a flow rate of 3–5 L/min [95] Noninvasive ventilation (CPAP, bilevel, high-flow nasal oxygen) and nebulization	The patient must remain in a room with negative pressure with respiratory and contact isolation. Not highly recommended for patients with COVID-19. Indicated only for patients in isolated rooms, due to its high risk of aerosolization [96] and potential to expose health professionals and the hospital environment to infection. Limiting the flow rate to 30 L/min can reduce the viral transmission [92]
Necessary O ₂ flow >10 L/min [95]	Endotracheal intubation and invasive mechanical ventilation [95]	Closed airway suction is recommended to reduce the risk of viral aerosol [97]
Severe acute respiratory syndrome	Endotracheal intubation Early invasive mechanical ventilation	Rapid sequence induction (RSI) and correct cricoid pressure. The RSI may be modified in patients with very high alveolar–arterial gradient [97] Tidal volume (Severe SARS: 3–6 ml/kg; Mild and Moderate SARS: 4–8 ml/kg) Plateau pressure (<30 cmH ₂ O) Driving pressure (<15 cmH ₂ O) PaO ₂ /FiO ₂ based on patient needs [98]
	Extracorporeal membrane oxygenation	Designated areas for the placement and removal of personal protective equipment and air-purifying respirators [99]
	Prone position [100]	The response can be assessed 1-hour post placement: increase of 20 in PaO ₂ /FiO ₂ or an increase of 10 mmHg in PaO ₂ compared to baseline measurements

SaO₂: arterial oxygen saturation; O₂: oxygen; L/min: liters per minute; CPAP: continuous positive airway pressure; ml/kg: milliliters per kilogram; cmH₂O: centimeters of water; SARS: severe acute respiratory syndrome; PaO₂/FiO₂: ratio of arterial oxygen partial pressure to fractional inspired oxygen; mmHg: millimeters of mercury.

acute rehabilitation process. Candan et al [108]. discussed the ICU-AW and its long-term consequences in patients with COVID-19, highlighting the importance of physiotherapy during the recovery phase, and indicating that a lack of physiotherapy during the acute treatment process may be one of the reasons for the increased frequency of loss of physical function after discharge from ICU.

To prevent the deleterious effects of bedrest, early mobilization is encouraged when it is safe for the patient, as indicated by a stable clinical presentation, including stable respiratory and hemodynamic status. Early mobilization includes bed mobility, sitting out of bed, sitting balance, sit to stand, walking, upper/lower limb ergometry, and range of motion and muscle strengthening exercises (Figure 3)[92].

6. Recovery from the acute phase of COVID-19: entering the next phase in rehabilitation

As described previously, the multisystem effects potentially triggered by COVID-19 can drastic and long-lasting effects on one's health and physical function [3]. In particular, damage to the cardiorespiratory system has significant implications for the ability to perform activities of daily living and participate in an exercise program [29,34,47,52]. Moreover, the lasting effects of a COVID-19 infection requires further investigation; previous research into other SARS-related infections demonstrate lasting impacts on cardiorespiratory function [109].

COVID-19 survivors may also suffer from a 'post-COVID-19 syndrome,' described as the persistence of some symptoms even after the infection, as suggested by Goërtz et al. [110]. This research group analyzed the persistent symptoms 3 months after COVID-19 infection in 2113 patients, including: 1) hospitalized patients with positive a RT-PCR test for COVID-19; 2) nonhospitalized patients positive for COVID-19;

nonhospitalized patients who presented with symptoms diagnosed by physician; and 4) nonhospitalized patients suspected of COVID-19 without a symptom diagnosis by a physician. This analysis found that patients presented with a median number of 14 (range 11–17) symptoms during the infection, and dyspnea and fatigue were the most prevalent symptoms in all the four groups of patients, present in 89.5% and 94.9% of the patients, respectively. After the infection, following a mean period of 79 ± 17 days, there was a mean reduction to 7 symptoms per patient, although dyspnea and fatigue were still both highly prevalent, 71% and 87%, respectively. The authors concluded that multiple symptoms are still present 3 months after the symptoms onset, characterizing the 'post-COVID-19 syndrome'.

Recently, Ferraro et al [111]. characterized late COVID-19 consequences and investigated the role of rehabilitation in reducing COVID-19 related fatigue as a strategy to improve functional status. Seven previously hospitalized post-COVID-19 patients, mean aged 65.71 ± 11.90 years, were included and 85.7% of them showed COVID-19 related fatigue. All of the patients were admitted to a rehabilitation unit and underwent a patient-tolerated intervention (1–2 session per day, 30 minutes per session, 6 days/week). Both the six minute walk test (6MWT) and 10 minute walk test (10MWT) were used to evaluate the physical performance. Upon admission, low physical performance was observed in all patients (6MWT = 172.9 ± 64.1 m and 10MWT = 11.2 ± 4.7). Following rehabilitation, significant improvements were observed in functional status, especially in two patients (Case 2–6MWT = 306 m vs. 120 m; and Case 3–6MWT = 330 m vs. 100 m). The authors suggested that fatigue persists due to neuromotor consequences that persist after infection, and highlight the vital role of rehabilitation in the post-COVID-19 phase.

Therefore, initiation of rehabilitation following SARS-CoV-2 infection should be considered an essential component of the plan of care. In this sense, it is important to highlight the role and need for multidisciplinary approaches and the role of physical exercise in optimizing recovery from COVID-19, particular in the domains of exercise and functional capacity and quality of life (QoL) [112].

In this context, maintaining a physically active lifestyle is recommended since physical exercise plays an important role in reducing levels of systemic inflammation [113,114] and lowering the incidence of upper respiratory tract infections [115]. Because COVID-19 triggers an inflammatory state, regular exercise is recommended to improve immune function and reduce pro-inflammatory cytokine levels [114,116]. Nevertheless, the type, intensity and duration of exercise is relevant, as different intensities can trigger different systemic physiological responses [114,116] and, as such, it is important to appropriately establish the optimal exercise prescription for a given patient. As such, regular moderate-intensity exercise (40–60% heart rate reserve or 65–75% of maximal heart rate [117] or Borg dyspnea score ≤ 3 [118]) is recommended due to its beneficial effects on immune function and its relationship with increased neutrophil phagocytic activity and lower levels of circulating pro-inflammatory cytokines [114].

El-Kader et al [119]. evaluated and compared the impact of a six month aerobic exercise (AE) or resistance exercise (RE) program on immune system function in 60 sedentary elderly subjects. The AE group performed 40-minute sessions on a treadmill at different workloads 3 days/week, while the RE group performed 40 min of exercises that included chest press, biceps curl, triceps extension, lower back, abdominals, leg press, leg curl, and leg extension, all at 60% to 80% of their one maximal repetition weight, 3 days/week. In this study, the AE demonstrated a greater benefit on immune system function and reducing systemic inflammatory markers; these findings have important implications for COVID-19, as elderly individuals are at higher risk for poor outcomes [120,121].

Exercise training also plays an important role in endothelial dysfunction because of its ability to induce NO synthesis through hemodynamic forces of blood flow, which stimulates the endothelium and triggers shear stress, working as a potent up-regulator of endothelial nitric oxide (eNOS) levels [122,123]; shear stress can be activated through a single session of resistance exercise, increasing eNOS levels [124].

In 2002 Fuchsjaeger-Mayrl et al [125]. conducted a clinical trial to evaluate the effectiveness of AE to improve endothelial function and to determine if a persistent improvement can be achieved by regular physical training in 26 subjects with type-1 diabetes; the authors compared an intervention group ($n = 18$, bicycle exercise training) to a control group ($n = 8$, no intervention). Vascular function was evaluated at baseline, after 2 and 4 months of AE, and 8 months after the absence of regular exercise. The AE program increased peak oxygen consumption (VO_2) by 13% after 2 months and by 27% after 4 months in the intervention group. Moreover, flow-mediated dilation of the brachial artery significantly improved in the AE group (FMD – from $6.5 \pm 1.1\%$ to $9.8 \pm 1.1\%$). These beneficial effects were reversed after 8 months of exercise

cessation, concluding that AE improves endothelial function but must be maintained to retain the positive physiologic effects.

Recently, Pedralli et al [126]. evaluated and compared the effects of different exercise training programs (i.e., AE, RE and combined AE+RE) on endothelial function in subjects with prehypertension or hypertension. A total of 54 subjects were randomly allocated to AE, RE or AE+RE groups, each performing 40-minute exercise sessions twice a week for 8 weeks. The authors found all three training programs similarly and significantly improved endothelial function as assessed by FMD [(AE: +3.2% (95%CI 1.7, 4.6) ($p < 0.001$); RE: +4.0% (95%CI 2.1, 5.7) ($p < 0.001$); and AE+RE: +6.8% (95%CI 2.6, 11.1) ($p = 0.006$)].

Because early rehabilitation has received attention as strategy for patients that have been hospitalized with COVID-19, in the recovery phase after the severe respiratory failure or hospital stay, Curci et al [127]. proposed an early rehabilitation protocol in post-acute COVID-19 patients to reduce dyspnea and improve muscle function and the ability to perform activities of daily living. However, their findings suggest that most patients that required respiratory support, suffered from dyspnea and shortness of breath with minimal activities. In addition, the National Institute for Health and Clinical Excellence guidelines recommend safety procedures to avoid the risk of aerosol-generation, such as NIV and cough assist. Thus, pulmonary rehabilitation should continue for these patients during the recovery process.

Liu et al [128]. recently conducted a randomized controlled trial to investigate the effects of a 6-week respiratory rehabilitation training on respiratory function, QoL, mobility and psychological function in elderly patients with COVID-19. A total of 72 patients (36 for the control group and 36 for the COVID-19 group) performed 2 respiratory training sessions per week for 6 weeks; interventions included respiratory muscle training, cough exercises, diaphragmatic training, stretching exercise and home exercises. The authors found the respiratory rehabilitation program improved the respiratory function, QoL and anxiety in elderly patients with COVID-19.

Additionally, the COVID-19 pandemic facilitated the application of remote rehabilitation medicine. Due to quarantine, many patients are now required to perform home-based exercise rehabilitation, utilizing wearable devices, mobile phone APPS, and virtual reality [129]. Remotely delivered rehabilitation programs has been previously shown to be as effective as the conventional face-to-face programs in patients with COPD in terms of improving functional capacity and symptoms as well as being a safe and well-tolerated [130].

Tele-rehabilitation is a potential tool to provide exercise therapy [131,132], psychological support, and nutrition advice during the COVID-19 pandemic, allowing meaningful interactions without face-to-face contact between patients and healthcare professionals. Based on previous respiratory viral outbreaks, many discharged patients may have residual deficits affecting physical, psychological and respiratory function. Thus, tele-rehabilitation offers remotely supervised therapy by a multiprofessional team to patients within their homes or community [131].

The main advantages of tele-rehabilitation are portability and versatility, since its developed to use natural body movements with minimal use of equipment. Besides the cost-effective advantage, the use of visualization screens makes therapeutic more engaging and stimulating as it provides visual feedback [131,133].

In a systematic review, Ceravolo et al [134], discussed rehabilitation activities in patients hospitalized in the acute phase of the infection, suggesting monitoring patients' clinical conditions and passive mobilization to avoid immobilization sequelae. Home-based exercises should include aerobic, resistance, balance, coordination and mobility training for 5–7 days/week. However, tele-rehabilitation should be the first option to avoid face-to-face interaction.

In order to develop a strategy to offer rehabilitation care to patients recovering COVID-19, Salawu et al [131], proposed an innovative form of post-discharge care through tele-rehabilitation, to facilitate the monitoring of these patients by medical teams. The authors classified patients into two streams: 1) Stream 1 patients with COVID-19 who require intensive care/NIV support; and 2) Stream 2 patients with COVID-19 who did not require hospitalization in intensive care/NIV support. According to the proposed protocol, patients should initiate tele-rehabilitation through cell phones and videos 4–6 weeks after hospital discharge, which extends to the 12th week, so that patients are continuously monitored by a multidisciplinary medical team and exams, such as chest radiography and computer tomography are continued. The proposed protocol includes two patients assessment, at weeks 4–6 and 12 weeks, where the medical team contacts the patient remotely. These assessments will be used to identify suitable patients to benefit from a tele-rehabilitation program. Patients who cannot participate in this form of treatment (e.g., patients with balance deficits) need a face-to-face assessment with the appropriate infection risk management implemented. In addition, the authors propose that monitoring patients' recovery should be performed as an integral component, capable of assessing and managing the post-COVID-19 residual deficits.

Because tele-rehabilitation methods have demonstrated positive experiences, with the intention to treat the respiratory consequences in patients affected with COVID-19 and maintaining social distancing policies, Gonzalez-Gerez et al [135], developed a therapeutic pulmonary tele-rehabilitation protocol in a randomized controlled trial, separating three different groups of patients, considering randomized allocation. Patients allocated in group 1 will participate in a respiratory exercise program, consisting of 10 exercises based on the recommendations of the College of Physiotherapists of Madrid, Spain. The interventions will be based on techniques of active cycles of breathing and postural changes. Patients allocated in group 2 will realize a nonspecific toning exercise program, which will consist of 10 toning exercises based on the recommendations of the College of Physiotherapists in Andalusia, Spain. Finally, patients from group 3 will constitute the sham group. The sham program will consist of 10 sedentary exercises based on sophrology and meditation with mental exercise visualization, concentration and mental activity, not following a linear progression and without the objective to obtain benefits through meditation. In all three programs

offered, the interventions will be taught to patients telemanually during the first session, and will be carried out once a day, for 21 days, being reinforced by a physical therapist daily by videoconference. The authors reported that results will be communicated to authorities and published in a medical scientific journal.

In terms of patient assessment, Finkelstein et al [132], developed a pilot study with the aim of presenting approaches for a remote assessment of exercise capacity through an interactive platform. The authors developed a personalized remote physiotherapeutic assessment system for an exercise program, which can be adapted according to the level of functional capacity of each patient, including gait and balance limitations. The system consists of a: 1) personal computer with Zoom for the physical therapist; 2) personal computer with Zoom for the patient; and 3) wrist oximeter and arm bike for the patient. The physical therapist will be able to give the instructions and monitor the patient's condition during remote therapy. In this pilot study, the authors collected data from 15 reports of 15 different patients. Regarding the usability of remote exercise evaluation, the results revealed high general acceptance by all patients, affirming the potential benefits of patient-centered digital health. Moving forward, the authors intend to develop an interface analyzing different subgroups of patients with different socioeconomic backgrounds, different age groups, computer skills, literacy and numeracy.

As such, remotely delivered rehabilitation should be considered as a viable and effective approach. If conventional face-to-face healthcare is provided, healthcare professionals and patients must follow hygiene and social distancing rules to minimize the risk of contamination; important considerations for modifications and adaptations for face-to-face rehabilitation is described in [Table 2](#)[136].

7. Conclusions

In summary, as the world continues to address the COVID-19 pandemic, we have rapidly gained an appreciation for the deleterious multisystem effects of the virus. These effects have significant and potentially long-lasting implications for exercise and functional capacity as well as quality of life. As such, it is clear that healthcare professionals with expertise in rehabilitation are an essential component of the multidisciplinary team that is charged with the care of patients with COVID-19. Rehabilitation should be initiated in the acute phases of COVID-19 recovery and continue over the long term, particularly to address and reverse the impacts of the virus on cardiorespiratory and muscle function. Moreover, leading a healthy lifestyle, including regular exercise, is an important strategy to prevent the severity of the response to a viral infection and must be considered a vital public health strategy moving forward.

8. Expert opinion

The findings discussed in this review study highlight the crucial role of physical rehabilitation in patients recovering from COVID-19, initiated soon after acute recovery. Considering that COVID-19 increasingly show its multiorgan pathophysiology followed by systemic impairments after the infection, either by

Table 2. Guidelines to provide face-to-face rehabilitation programs avoiding the spread of the SARS-CoV-2 virus [136].

Care for the environment
<p>Encourage hygiene habits in your workplace; Keep all equipment and devices, such as stretchers, knobs, handrails, materials and tools for continuous use and others, clean after each use; Keep the rooms clean and well ventilated; Provide washbasins with liquid hand soap and paper towel and a trash that can be opened and closed without using hands (with pedal or other type of device); Provide appropriate personal protective equipment for staff's role; Provide visual alerts such as signs and posters at entrances and in strategic places providing instructions on hand hygiene, respiratory hygiene, cough etiquette and care for the prevention of COVID-19 spread. Ensure a minimum distance of 2 meters between people in waiting areas and do not keep objects that can be shared, such as books and magazines. If facilities lack waiting areas, then designated areas or waiting lines should be created by partitioning or through signage; Install barriers to limit contact with patients in screening; The residues must be packed in red bags, which must be replaced when they reach 2/3 of their capacity or at least once every 48 hours, regardless of the volume and identified by the symbol of infected substance.</p>
<p>Guidelines for healthcare professionals Keep your hands clean. In the absence of soap and water, use hand sanitizer with 70% alcohol content. Repeat this procedure before and after each activity; Wear goggles or face shield, surgical mask, and apron, and change them after each appointment; Carefully assess the need to care for patients at higher risk (elderly over 60 years old, immunosuppressed, people with cancer and other underlying diseases or comorbidities); Organize your exercise program routine so that you can avoid touching the patients, keeping indoor social distancing policies. When touching a patient is necessary, hands should be cleaned before and after the contact, with soap and water or hand sanitizer with 70% alcohol content; Avoid using cell phones during service. In case of essential use of cell phone, the device should be cleaned before and after each use. Before returning to the patient, clean your hands again with hand sanitizer with 70% alcohol content or soap and water; Meet individually and organize your schedule according to the average frequency of patients; Guide your patients and family members about measures to be taken to avoid contagion, restricting the spread of the virus as much as possible.</p>
<p>Guidelines for patients Avoid agglomerations in the means of transportation when traveling to attendance; Wash your hands before and after each visit, using water and soap or hand sanitizer with 70% alcohol content; Use non-woven fabric (TNT) or cotton fabric masks throughout the service and period you are in the establishment; Avoid the participation of family members in activities, except in situations that their support is required, and in these cases, remember that members of your family also need to wear masks throughout the service period; Inform the health professional or the establishment, prior to your attendance, if you have any symptoms of the new coronavirus (COVID-19) such as fever, dry cough, difficult of breathing and others.</p>

damage triggered directly by the infection or secondary damage caused by long-term rest and/or other therapeutic methods to manage the disease. Considering that many patients may suffer multiple consequences of the infection, mainly in the musculoskeletal and cardiorespiratory systems, therapeutic interventions can assist in maintaining/improving functional status of these patients, preventing the progression or development of other problems secondary to COVID-19 in the post-infection phase.

There is large evidence about rehabilitation programs and its beneficial effects for people with cardiac, respiratory, neurological, musculoskeletal, metabolic and other disorders. Rehabilitation health professionals are essential in the recovery process of many diseases, and exercise has been increasingly seen as medicine in terms of preventing, treating and improving several conditions. As we are gaining a better understanding of the consequences of COVID-19, we can already say, with high confidence, that a significant percentage of COVID-19 survivors will benefit from physical rehabilitation to treat secondary impairments triggered by COVID-19 and/or its treatment methods. Therefore, future studies should have the main objective of solidifying strategies and protocols to be adopted in clinical practice for COVID-19 survivors. However, it is necessary to consider that one of the great current challenges is social distance, which limits or prevents the assistance to patients, mainly those without access to the internet, a computer or cell phone, making it difficult to carry out tele-rehabilitation. In addition, learning the techniques and exercises proposed by the rehabilitation professional can also be a challenge for patients, and consequently for health-care professionals. In this sense, it will be important to

standardize rehabilitation strategies to overcome these challenges that permeate the real world, developing protocols and strategies that allow the inclusion and participation of these patients who need rehabilitation services.

As early rehabilitation is highlighted in the current scenario, mainly to treat the sequelae of COVID-19 survivors, according to the literature presented, early initiation of rehabilitation, soon after the acute phase of recovery, is warranted, on average four weeks after discharge from the hospital, considering individual needs and difficulties. It is also important to highlight the need for a specialized multidisciplinary team to monitor the various cases, since COVID-19 can have numerous presentations, many of which have not yet been fully elucidated.

Thus, monitoring health status (echocardiography, spirometry, analysis of muscle function, for example) after COVID-19 and early treatment of the sequelae caused by the disease can facilitate the diagnosis of new conditions and reduce future health costs, in addition to facilitating the search for solutions to maintain or improve the quality of life of these patients.

In addition, a recent systematic study reported the global estimates of the need to rehabilitation and found that at least one in three people worldwide needs rehabilitation services at some point in the course of some illness or injury, and also found the musculoskeletal disorders to contribute most to the increased prevalence for rehabilitation services [137].

Thus, as physical exercise works to improve skills and, mainly, to perform activities of daily living, it is a good strategy to improve functional capacity, restoring the patient's physical autonomy, which is essential to a successful discharge upon recovery.

These findings added to the current scenario further point to the vital role of rehabilitation health professionals in the

coming years and the urgent need to discuss and develop protocols and strategies to assist these patients, which presupposes the need to develop clinical trials to answer the large number of questions that surround us now, especially on how to assist COVID-19 survivors.

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