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Effects of Exercise on COVID-19 Patients: A Narrative Review

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Abstract

Background: Challenges concerning patient management exist worldwide, particularly in the critical care. In this review, we have summarized some studies regarding respiratory physiotherapy and exercise in COVID-19 patients.

Methods: For searching related articles, PubMed, Google Scholar, Embase, and the Web of Science databases were used. Keywords such as "respiratory physiotherapy" and "COVID-19," "exercise," "effect of exercise in COVID-19," and "respiratory physiotherapy for COVID-19 in ICU" were used to identify related papers until December 2021. The abstracts and entire texts were evaluated by 3 separate reviewers.

Results: During the symptomatic phase, individuals may benefit from brief durations of bed rest. Exercise appears to provide both emotional and physical benefits for individuals in the early stages of infection. As a result, it may lower viral load, minimize cytokine storm, shorten the acute phase, and expedite recovery. Mild exercise may also increase the autophagy pathway, which improves the immune system function in response to COVID-19 infection. Keeping this in mind, intense activity, especially without the guidance of an expert physical therapist, is not advantageous during the inflammatory period and may even be regarded a second hit phenomenon. Mild exercises during bed rest (e.g., acute phase) may reduce the risk of pulmonary capillary coagulation and deep vein thrombosis.

Conclusion: Although respiratory physiotherapy and prone positioning in hospitalized patients, particularly in critical care, can be challenging for medical staff, they are cost-effective and noninvasive approaches for COVID-19 patients. Early physiotherapy and muscle training exercise for patients in the intensive care unit (ICU) seems to be beneficial for patients and may reduce bed rest-induced weakness, improve oxygenation, and reduce length of stay. Finally, breathing exercises can improve some symptoms of COVID-19, like dyspnea and weakness.

Keywords: COVID-19, Critical Care, Physiotherapy (Techniques), Exercise, Physical Therapy

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Introduction

Because of the worldwide coronavirus outbreak, concerns have increased about the management of critically ill patients. According to some reports, most patients were classified as mild to moderate, and less than 10% of pa-

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↑What is "already known" in this topic:
Bed rest with immobility has always been recommended for patients suffering from flu-like symptoms, thus, this notion might be extended to coronavirus disease 2019 (COVID-19) infection. As a result, one may expect that bed rest might be advantageous for COVID-19 patients during the acute period. On the other hand, it is generally recommended that exercise is necessary to maintain and promote health.

→What this article adds:
Mild exercise could improve the autophagy mechanism that ameliorates the function of the immune system in response to COVID-19 infection. Respiratory physiotherapy and prone positioning in hospitalized patients, particularly in critical care, can be challenging for medical staff, however, they are cost-effective and noninvasive approaches for COVID-19 patients.

tients required hospitalization (1). Bed rest immobility has always been recommended for patients suffering from flu-like symptoms, and so this notion might be extended to coronavirus disease 2019 (COVID-19) infection. As a result, one may expect that bed rest might be advantageous for COVID-19 patients, particularly during the acute period. Our observations at the bedside revealed some findings in this respect, since the patients' health deteriorated and oxygenation levels dropped shortly after moderate exertion. On the other hand, long rests can have devastating side effects like deep vein thrombosis, sarcopenia, loss of muscle mass, and a reduction in the immune system level.

One of the complications of critically ill patients who need to be admitted to the intensive care unit is pulmonary involvement or acute respiratory distress syndrome (ARDS) (1-3). According to the Berlin definition (4), severe ARDS is based on the degree of hypoxemia, which is a common complication of COVID-19 patients. Patients with mild to moderate pulmonary involvement who require no hospitalization are advised to complete their rest at home. However, the immobility of patients, hospitalization, or home quarantine can reduce the organ's resistance to viral infections. This, in turn, can lead to adverse effects on the immune system, respiratory, cardiovascular, musculoskeletal systems, and cognition (5). Consequently, this review aims to summarize findings on the effect of respiratory physiotherapy and exercise on COVID-19 patients.

Methods

This narrative review was done with ethical consideration. Two expert reviewers independently evaluated the eligibility of articles. All articles confirmed by both reviewers entered into this study. To search related articles, PubMed, Google Scholar, Embase, and the Web of Science databases were used. Main keywords such as "respiratory physiotherapy" and "COVID-19," "exercise," "effect of exercise in COVID-19," and "respiratory physiotherapy for COVID-19 in ICU" were used to identify related papers until December 2021. The database search was done in the first week of January 2022. The abstracts and entire texts were evaluated by 3 separate reviewers. The inclusion criteria were manuscripts that assessed the effect of respiratory physiotherapy and exercise on COVID-19 patients and disease phase. The study was limited to the papers written in the English language. Exclusion criteria were non-English papers and papers related on nonhuman subjects.

Of a total of 27,300 articles (Fig. 1 & Table 1), 1100 manuscripts were entered to the screening process. Finally, 63 papers were included in the study and reviewed narratively.

Results

The characteristics of the studies and resources used in this review are summarized in Table 1.

The Critical Role and the Benefits of Respiratory Physiotherapy in COVID-19 Patients

Negative changes in pulmonary function and decreased pulmonary compliance in patients with coronavirus are life-threatening and are among the reasons for physiotherapy interventions (6). In respiratory physiotherapy, an attempt is made to improve the patient's respiratory status

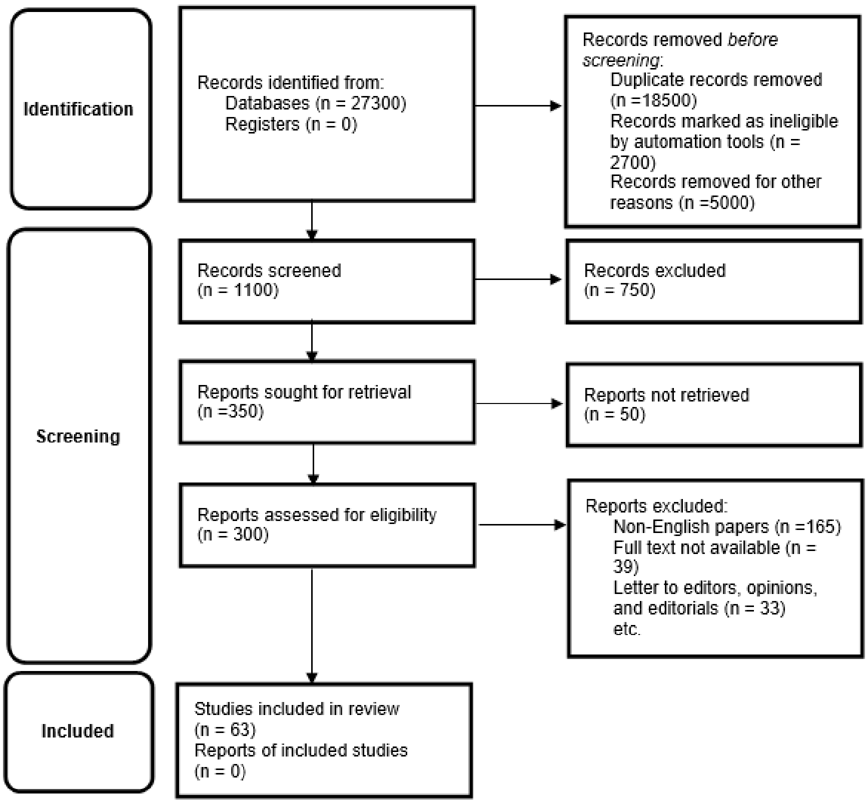

Fig. 1. The PRISMA 2020 flow diagram of the present review

Table 1. Features of studies used in this review

First Author	Year	Study Design
Dean E (6)	2020	Perspective
Silva CM da S e (7)	2021	literature review
Vitacca M (8)	2020	review
Simonelli C (9)	2020	observational
Cerqueira Neto ML de (10)	2013	prospective nonrandomized clinical trial
Kayambu G (11)	2013	systematic review
Silver JK (12)	2020	n/a
Gonzalez-Gerez JJ (13)	2021	Randomized clinical trial
Thomas M (14)	2009	Randomized controlled trial.
Gaskell DV (15)	n/a	n/a
Al Chikhanie Y (16)	2021	prospective cohort study
Carolyn L Rochester (17)	2015	Practice Guideline
Battaglini D (18)	2021	observational
Bissett B (19)	2019	review
Matthews CE (20)	2002	Observational
Wong C-M (21)	2008	Retrospective
Nieman DC (22)	1990	n/a
Kostka T (23)	2000	prospective
Jones BH (24)	1994	review
Ahmadi S (25)	2020	review
Ekblom B (26)	2006	cohort
Lasanianos NG (27)	2010	review
Halabchi F (28)	2020	Editorial
Gattinoni L (29)	2020	Editorial
Kumagai Y (30)	2007	n/a
Jewell NA (31)	2007	In vivo
Sim Y-J (32)	2009	Lab test
Wareing MD (33)	2004	In vivo
Lin KL (34)	2008	In vivo
Legge KL (35)	2003	n/a
Kohut ML (36)	2006	In vivo
Lowder T (37)	2006	In vivo
Kobayashi S (38)	2015	Review
Choi Y (39)	2018	review
Viret C (40)	2018	review
He C (41)	2012	n/a
Vainshtein A (42)	2016	review
Escobar KA (43)	2019	review
Wang L (44)	2020	review
Wu NN (45)	2019	review
Baker FL (46)	2021	n/a
Abdelbary AA (47)	2021	Case report
Calles-Escandon J (48)	1984	n/a
Damiot A (49)	2020	review
Machado CLF (50)	2020	Short report
Narici M (51)	2021	review
Peçanha T (52)	2020	Perspectives
Guadalupe-Grau A (53)	2020	Commentary
Moro T (54)	2020	review
Sun S (55)	2020	n/a
Ammar A (56)	2020	n/a
Breen L (57)	2013	Clinical trial
Alomari MA (58)	2020	n/a
Barnes GD (59)	2020	Practice guideline
Carfora V (60)	2021	narrative review
Kollias A (61)	2020	Commentary
Wittmer VL (62)	2021	narrative literature review
Mohammadi M (63)	2021	letter
Rahmati-Ahmadabad S (64)	2020	mini review
Moonen HPFX (65)	2021	retrospective cohort
Jiandani MP (66)	2020	retrospective observational
Miller C (67)	2021	retrospective
Binda F (68)	2021	Prospective

by deep breathing and cough stimulation. Physical therapists deal with respiratory distress syndrome in the intensive care unit (ICU). Besides, many efforts are made to correct the body position and posture, the sensory system, particularly proprioception sense, passive and active mobilization, and gravity exercise. These clinical goals are based on comprehensive assessments and examinations to counteract the physical and psychological negative effects of total bed rest, improve and augment gas exchange, reduce airway shunt, deconditioning, and critical illness

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complications, and optimize long-term functional outcomes (7).

The multiple-benefits of respiratory physical therapy and rehabilitation were considered for 3 phases of COVID-19 patients: (1) acute phase, presenting with critical respiratory impairment (emergency department, first aid, ICU, stepdown unit); (2) acute phase, with severe respiratory impairment (internal medicine, respiratory, infectious disease, or other wards); and (3) post-acute phase (other units, intermediate care facilities, and subacute wards) (8). The results of a study in Northern Italy provided algorithms for guidance: (1) oxygen de-escalation by decreasing the inhaled fraction of oxygen (FiO2); (2) oxygenation enhancement through the use of a Venturi mask; and (3) reconditioning and physical activity (9). The previous study suggested that physical therapy interventions enhanced significant respiratory function and also improved cardiovascular and cerebral hemodynamic function (10). Complications of bed rest can be prevented with early physical therapy and rehabilitation; therefore, it would enhance the physical function, which might result in a reduction in the time of weaning (11). Besides, some results suggest that prerehabilitation for patients awaiting surgery might enhance the surgical outcomes in various populations (12). Gonzalez-Gerez et al (13) studied the effects of 10 breathing exercises, which have been proven in previous studies (14, 15), on mild to moderate COVID-19 patients in the acute phase of disease. They performed at the patient's house once a day for 7 days, depending on the Borg assessment score (BS). A physical therapist assisted with the exercise program. It is concluded that these programs can improve physical condition and dyspnea.

Chikhanie et al (16) studied pulmonary rehabilitation (PR) and 21 severe COVID-19 patients performed the Tinetti balance test, 6-minute walking distance, respiratory exercises, muscle strengthening, cycling, and gymnastics according to current American thoracic society/European respiratory society (ATS/ERS) recommendations (17). The following multidimensional testing batteries were done at admission and discharge: pulmonary function tests, psychological assessments, muscular strength, and balance measures, and the 6-minute walking test (6MWT). All patients attended all of the scheduled sessions without any side effects or limits. All COVID-19 patients improved significantly after PR in all physical and psychological assessments. There was a significant association between 6MWT improvement and the number of days after ICU in COVID-19 patients, and a trend for a significant correlation between 6MWT improvement and the number of days in PR.

The efficacy of respiratory physiotherapy (RPT) on intubated critically ill COVID-19 patients was evaluated by blood gas analysis (BGA) and lung ultrasound (LUS) (18). After weaning and extubation with conventional oxygen therapy (COT), one experienced physiotherapist specializing in RPT for critically ill patients performed respiratory physiotherapy maneuvers (2 strategies for individuals requiring invasive mechanical ventilation or who are spontaneously breathing). RPT was initiated just after consideration for the weaning process and bed head elevation (30°) and early passive mobilization (30 minutes per day) until the day of extubation. After weaning from the ventilator, each spontaneously breathing patient receiving COT did RPT with bed head elevation (30°), early sitting posture, and vigorous activity. The results suggested that the PaO2/FiO2 ratio improved immediately after RPT compared with baseline before RPT and at 6 hours after RPT compared with the baseline. The median LUS score decreased from 24 to 20. A correlation was observed between the variation of the LUS score and the percentage of lung gas volume. They concluded that while RPT improves oxygenation in critically ill COVID-19 patients, the improvement in oxygenation is not reflected by a reduction in LUS score, the improvement in LUS score after RPT is correlated with the lung gas volume at computed tomography, and finally, chest RPT has no effect on hemodynamics in COVID-19 patients.

According to Bernie Bissett et al (19), employing a high-intensity method, inspiratory muscle training (IMT) for ICU patients is likely to increase not only the inspiratory muscle strength but also the quality of life in patients who have recently been weaned from mechanical ventilation for 7 days or longer. To maximize practicality, effective IMT necessitates a multidisciplinary approach, with all health care providers collaborating to improve circumstances for successful IMT. They recommended using a removable threshold device to perform high-intensity training (5 sets of 6 breaths at a minimum of 50% of maximum inspiratory pressure) once per day, monitored by a physiotherapist, with the intensity increasing every day so that patients can just about complete the sixth breath in each set.

Exercise and Its Role in Viral Respiratory Infections

Some studies suggest that moderate exercise might play a role in the risk reduction of infection severity (20-22). Preinfection mild-intensity exercise results in significantly lower respiratory virus-associated mortality in laboratory studies on animals (23). However, exercise can be hazardous and associated with different injuries (24), which means that if exercise is not standardized or under the supervision of an experienced trainer, it can cause damage to the body rather than benefit. Furthermore, intense exercise before or during viral infection was associated with increased morbidity and mortality (25, 26). Extensive exercise could be regarded as a second-hit phenomenon (27). It might be considered that the cytokine storm, which is regulated by the immune system in response to viral infection, is the first hit. However, the definition of extensive exercise is not yet clear, and more research is needed to shed light in this regard. Also, the effect of exercise in COVID-19 infection is highly time-dependent (28). In the first phase of infection, "viral" exercise might be beneficial. However, in the subsequent phase, "inflammation" exercise seems to be hazardous. First, it would increase the risk of viral contamination due to the high level of viruses in the expired patients. Secondly, as mentioned previously, it can be a "second hit phenomenon" and deteriorate the physiological adaptation of the body.

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It is hypothesized that COVID-9 patients might represent 2 phenotypes as follows (29): Type L (Low elastance, high compliance), better ventilation-to-perfusion ratio, low lung weight and low recruitability, and Type H (High elastance, high right-to-left shunt), high lung weight and high recruitability. At the first stage, COVID-19 pneumonia demonstrates an L-type phenotype; these patients might stay without any changes for some time, and later on, they could improve or exacerbate. As shortness of breath worsens, a shift from the L to the H type occurs as a result of high-stress ventilation. In high elastance, low tidal volume is required for ventilation, and therefore, high tidal volume and respiratory effort seem to be deleterious and hazardous. In the inflammatory phase, specifically in H-type patients (COVID-19), intensive deep breathing could cause pulmonary epithelial injury. As a result, respiratory physiotherapy is indicated for hospitalized patients, particularly those in the critical care unit. In the case of pulmonary involvement (eg, ARDS), all efforts should be directed at lowering transpulmonary pressure, pulmonary edema, and the likelihood of lung damage. To avoid shear stress, mechanically ventilated patients with limited compliance are given a low tidal volume approach. High tidal volume and high transpulmonary pressure appear to be harmful during the inflammatory phase of the disease; hence, this might be the case with spontaneous breathing. Forcing the patient to take deep breaths (like in sports) or inducing a strong cough during the inflammatory phase may aggravate the harm. As a result, it is preferable for the patient to be more relaxed at this point, and to compensate for this immobility, an anticoagulant should be provided to the patient under the supervision of a d-dimmer (prophylactic, mild dose, or moderate dose).

Discussion

Exercise: Cellular, Molecular, and Autophagy Perspective

In terms of cellular and molecular biology, the construction of type I interferons, which are regulated by plasmacytoid dendritic cells, alveolar macrophages, and infected epithelial cells, is the primary reaction to respiratory viral infections (30, 31). Interferon type I has a high potential for antiviral responses (32). The accumulation of monocytes, macrophages, and neutrophils in the lungs, which results in the production of inflammatory cytokines, may be linked to immunopathologic responses (33, 34). Pulmonary natural killer cells that can be detected within 48 hours of infection consolidate their performance by producing interferon and virus-infected cells lyse (35). Yet, the effect of exercise on each of these components of the immune system is not well known (32). Mild exercise could play a critical role in limiting or clearing viral infections by increasing the activity of several components of the immune system. Moderate exercise raises interleukin-2 and antigen-specific IFN- levels (36). In the early stages of illness, moderate exercise can diminish pulmonary cellular infiltration and shift the T-helper 1 to T-helper 2 index (37). Persistent exercise has been linked to a reduction in symptoms, inflammatory factors, viral load, and inflammatory cytokine levels. Then, during the first period of illness, acute exercise may be helpful (32).

Besides, autophagy, as a natural and intracellular mechanism, by removing unnecessary or dysfunctional components, plays an important role (38). Thus, in viral infections, autophagy controls the infection by mechanisms, such as the destruction of viruses, regulating the inflammatory responses, and ameliorating antigen presentation (39, 40). Some studies have shown that exercise can induce autophagy by several intracellular mechanisms (41-43). On the contrary, it should not be underestimated that exercise in some chronic conditions, such as cardiovascular disease, can inhibit autophagy and reduce autophagic cell apoptosis (44, 45).

In a cross-sectional study on a healthy man, Baker et al (46) concluded that acute exercises like incremental continuous cycling affect multiple SARS-CoV-2 specific T-cell mobilization to the blood vessels and elevation of neutralizing antibodies temporarily, which can be caused by increased lymphatic flow due to exercise. Furthermore, exercise increased the IFN- response to SARS-CoV-2 peptide stimulation in the blood. Infection appears to be linked to an increased metabolic demand for specific exercise workloads, which was reversed following immunization to preinfection levels.

Mild to moderate exercise induces an increase in the excretion of urea and creatinine. It is an important consideration, particularly in medications that can induce nephrotoxicity, such as Favipiravir in COVID-19 patients (47, 48). Also, COVID-19 patients, particularly those in intensive care units, are at the risk of developing acute kidney injury; thus, exercise should be done with caution. It is highly vital for patients with a history of kidney disease.

Physical and Psychological Effects of Exercise in Patients With COVID-19

Although there is no direct evidence of the effect of physical therapy on the prevention or treatment of COVID-19, it is strongly recommended that by adopting an active lifestyle, the social isolation damage because of coronavirus infection could be prevented (49), especially in the elderly population (50). Evidence from COVID-19 home confinement suggested that low/medium intensity, high volume exercise, and a 15% to 25% reduction in calorie intake could prevent the harmful effects of sedentarism (51). Evidence also showed that even short-term inactivity could affect cardiac function negatively. On the other hand, home-based physical activity programs improved the health of cardiovascular and diabetic patients (52, 53). Furthermore, these programs have the potential to prevent skeletal muscle loss following exercise by applying a low load (54).

The Dangers of Bed Rest in COVID-19 Infection

Prolonged rest in patients with coronavirus can have dire or even life-threatening consequences. According to recommendations, people should be aware of social distancing, isolation, and quarantine, which in practice could result in an extended period of social isolation at home

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(55, 56). This in turn could lead to a decline in physical activity and increases in sedentary behavior, which are associated with the loss of muscle mass (51, 57, 58). Besides, inactivity and bed rest might induce insulin resistance (51), which could result in muscle loss due to social distancing measures and even a major susceptibility to COVID-19 (52). The results of a clinical study showed that prolonged rest and intensive care unit admission were significantly associated with deep vein thrombosis (53). Recent evidence-based recommendations suggest that patients with coronavirus who are at risk for thrombosis and blood clots (venous thromboembolism and deep vein thrombosis) should be considered for anticoagulant therapy (59-61).

Exercise in Accordance With the Severity of the Disease: Intensity and Timing

Recently, the results of a narrative review by Wittmer et al (62) confirmed that mild exercise in the early stage of the disease could be prescribed for COVID-19 patients, keeping in mind the comorbidities and contraindications of patients, if any. Furthermore, Mohammadi et al (63) claimed that during the inflammatory stage of COVID-19, exercise, particularly intense exercise, cannot be beneficial and may result in disease exacerbation. It is hypothesized (64) that high-intensity exercise (conservatively) may be dangerous and help to exacerbate the COVID-19 virus, owing to the production of oxidants and immune system suppression. It should also be emphasized that COVID-19 illness might be asymptomatic for several days, making strenuous high-intensity activity riskier. It suggests that moderate-intensity physical activity (instead of high-intensity physical activity) should be advocated as a nonpharmacological, low-cost, and practical strategy to deal with the COVID-19 virus.

Patients who were discharged from the ICU are highly exposed to intensive care unit acquired weakness. Meanwhile, they are more willing to undergo physical rehabilitation in comparison to non-COVID pneumo-sepsis ICU discharged patients (65). Therefore, SARS-CoV-2 patients who are going to be discharged may take advantage of primitive intensive physical therapy. It seems that physiotherapy intervention in the acute care of COVID-19 patients can facilitate recovery and discharge (66).

One of the most important considerations for COVID-19 patients in the ICU is that some of them may receive neuromuscular blocking agents (NMBA) (total dose, intermittent dose, and continuous). Applying respiratory physiotherapy can be harsh and impossible for nurses and physiotherapists. On this occasion, an intensivist or physiotherapist may recommend some passive and active muscle-strengthening exercises (67). Some occasions in clinical settings, the prone position may be applied to COVID-19 patients with dyspnea and decreased oxygen saturation as a nonpharmacological (also non-invasive) approach aimed at improving oxygenation. It is mostly used on awake patients (sometimes in mechanically ventilated patients), but it is said to be difficult for health care providers (68) (nurses and physiotherapists), especially in mechanically ventilated patients. When mechanically ventilated patients go into the prone position, there are several risks, such as unwanted extubation, discharging intravenous catheters, and clipping the oxygen pipe.

Before concluding, it should be noted that the COVID-19 epidemic still has many unknown aspects. In particular, the assessment of the quality of care (69) provided and the role of education for staff (also medical students) and patients are not yet clear (70). Also, with the onset of global vaccination against coronavirus infection, the role of exercise in vaccination efficacy should be reexamined (71, 72).

Conclusion

A strong body of evidence is in favor of supervised physical therapy and exercise for these patients. In the symptomatic phase (ie, the first week of disease), patients might take advantage of short periods of bed rest, but not complete bed rest. As previously stated, it appears that exercise would have both mental and physical benefits for patients in the early stages of infection. As a result, it may lower viral load, minimize cytokine storm, shorten the acute phase, and expedite recovery.

Later on, in the early phase of infection (before the second week), mild exercise could improve the autophagy mechanism that ameliorates the function of the immune system in response to COVID-19 infection, particularly in the sequence inflammation phase. Keeping this in mind, intense exercise, especially without the guidance of a qualified physical therapist, is not useful at all and may even be regarded a second-hit phenomena. Mild workouts during bed rest (ie, acute phase) may minimize the likelihood of pulmonary capillary coagulation and deep vein thrombosis. Although respiratory physiotherapy and prone positioning in hospitalized patients (particularly in critical care) can be challenging for medical staff, they are cheap and noninvasive approaches for COVID-19 patients. Also, by utilizing some novel technologies, such as telemedicine, muscle training exercises, and physiotherapy, can be delivered to patients either at their home or the hospital. Early physiotherapy for patients in the ICU seems to be beneficial for patients and may optimize ICU-induced weakness due to bed rest and reduce length of stay. Finally, breathing exercises can improve some symptoms of coronavirus disease, such as dyspnea and weakness.

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Ethical Approval

This study was a narrative review and the institutional review boards were exempt from ethical approval.

Conflict of Interests

The authors declare that they have no competing interests.

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