Review Article :

Pulmonary Rehabilitation for Patients Post Severe COVID-19:A Literature Review

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Received on 5.7.2021, Accepted for publication on 12.9.2021 dx.doi.org/10.5455/mjhs.2021.04.010

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Abstract

Background & Aims:

The overall understanding of the clinical outcomes and prognostic factors among patients discharged from hospitals following the acute phase of COVID-19 is still limited. Thus, there is still considerable debate regarding whether patients discharged from the hospital after a severe COVID-19 infection have fully recovered or whether they retain permanent lung damage or experience fibrotic lung changes. Many recommendations regarding respiratory rehabilitation in the post-acute phase have been published. Still, the efficacy of those published recommendations is unclear. This review has shed light on the need for more evidence of the beneficial effects of pulmonary rehabilitation programs on patients recovering from COVID-19 and their role in ensuring that this population can resume a functional life. Most of the evidence assessing the impact of pulmonary rehabilitation programs on COVID-19 survivors has been published as reports by various organizations and pulmonary rehabilitation committees, although there have been a few prospective cohort and cross-sectional studies. However, to produce findings that can be translated into practice, the challenges inherent to this

الملخص

الخلفية و الاهداف :

لايزال الاستيعاب العام لمرض كوفيد-١٩ والذي يسببه فيروس كورونا محدودا من ناحية معرفة المضاعفات الإكلينيكية المصاحبة للمرضى المتعافين منه والذين خرجوا من المستشفيات. حيث مازال هناك جدل واسع في مجال الابحاث العلمية عن احتمالية حدوث تغيرات فسيولوجية لأنسجة الجهاز التنفسي للأشخاص الذين تعافوا من الإصابة بفيروس كوفيد-١٩ الحاد والذي من الممكن ان يؤدي الى تليف في انسجة الرئة. لذلك تم نشر العديد من التوصيات من جهات مختصة تتعلق بأهمية التأهيل الرئوي للمرضى المتعافين من الإصابة بكوفيد-١٩. ومع ذلك لا توجد دراسات كافيه حول تأثير برامج التأهيل الرئوي في تحسين الوظائف التنفسية. تم في هذه الدراسة الحالية مراجعة الدراسات الوبائية المنشورة التي درست تأثير برامج التأهيل الرئوي في تحسين جودة الوظائف التنفسية للمرضى الناجين من كوفيد- ١٩. وتشير نتائج هذا التقرير الى أن اغلب الأدلة عباره عن تقارير من قبل منظمات ولجان طبية في مجال الرعاية التأهيلية مع قلة وجود ابحاث منهجية علميه في هذا المجال. وذلك يرجع الى وجود بعض التحديات في مجال الابحاث المتعلقة بالرعاية التأهيلية التي يجب أن تدرس بشكل كافي منها خطر التعرض للإصابة والحظر الوبائي والتباعد الجسدي. مثل هذه العوامل تشكل عائقا امام تنفيذ الدراسات في هذا المجال. لذلك هناك المزيد الذي من الممكن تقديمه في مجال التأهيل الرئوي لزيادة استيعاب الاثار طويلة المدى المتعلقة بفهم مرض كوفيد-١٩ وايضا في سياق أي جائحة عدوى تنفسيه في المستقبل.

line of research need to be addressed. Specifically, the extant risk of infection, quarantine times, and physical barriers rules have added more challenges to the implementation of pulmonary rehabilitation sessions. Overall, this field still has much to accomplish in the future to fully understand the long-term outcomes of COVID-19, also in the context of any future respiratory infection pandemic.

Key words:
COVID-19, pulmonary rehabilitation.

INTRODUCTION:

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic with the first outbreak in China, the relevant literature has focused on the disease's epidemiology, diagnostic testing, and treatment modalities as well as the cardiopulmonary complications of patients with COVID-19, particularly those admitted to hospital [1–3]. With the ongoing pandemic, the overall understanding of the clinical outcomes and prognostic factors among patients discharged from hospital following the acute phase of COVID-19 is still limited [4,5]. Current evidence suggests that COVID-19 patients may complain from respiratory, physiological, and psychological impairment after hospital discharge [4]. Furthermore, research has shown that around one-third of COVID-19 patients had severe respiratory failure and acute respiratory distress syndrome (ARDS), which can lead to persistent respiratory and physical impairment [6]. Thus, lung tissue alterations, such as consolidation, thickening of the vascular wall , and pleural effusion have been reported among acute COVID-19 pneumonia patients [7]. Finally, the increased risk of intensive care unit (ICU) acquired weakness has also been discussed in the literature as patients who experience severe respiratory failure end up on a mechanical ventilator and have extended ICU or hospital stays [8]. Despite this substantial body of research, there is still considerable debate regarding whether patients discharged from the hospital after a severe COVID-19 infection have fully recovered or whether they retain permanent lung damage or experience fibrotic lung changes. Studies have shown that up to 30% of patients who recover from severe COVID-19 pneumonia continue to experience breathlessness and require supplementary oxygen [9]. While there is conflicting evidence regarding the actual pathophysiological mechanism through which a COVID-19 infection can predis-

pose a patient to lung fibrosis, a meta-analysis suggested that a chronic viral infection can induce a mild and long-latency inflammatory response that contributes to the fibrotic response 10. In line with this, other studies have reported that ARDS can predispose patients to lung fibrosis; as a COVID-19 infection can cause ARDS, there is thus a risk of fibrosis, even after recovery [11].

Owing to the respiratory complications as a sequela of severe COVID-19 pneumonia, many recommendations have been published regarding respiratory rehabilitation in the post-acute phase. However, the efficacy of these recommendations is unclear. In addition, few studies have examined the effectiveness of pulmonary rehabilitation programs in the context of COVID-19, and thus, much of the published literature on this topic comprises editorial letters or recommendations from rehabilitation societies or organizations. Against this backdrop, the current report reviews published articles addressing pulmonary rehabilitation in patients with COVID-19 and highlighting the benefits of such rehabilitation for patient outcomes.

Pathophysiology mechanisms of COVID-19 infection to lung injury:

The virus that responsible for COVID-19 disease, SARS-CoV-2, is an enveloped virus. It infects the host cells through a series of viral spike proteins attached to the receptor on the host called angiotensin-converting enzyme-2 (ACE2) [12–14]. Then, endocytosis occurred in which the viral genome is released into the host cell to establish the synthesis of the viral RNA through changes in the endoplasmic reticulum of the infected cell [15]. Research has provided a list of host cells targeted by the SARS-CoV-2 virus, including type II pneumocytes, alveolar macrophages in the lungs, and basal epithelial cells in the nasal passages[5]. Many research identified different mechanism that activate proinflammatory and profibrotic pathways in the host cell after SARS-CoV-2 invasion [16,17]. Thus, a reduction in the host cell ability to balance the renin-angiotensin system (RAS) is occurred as result of reduction in the expression of ACE2 that caused by cleavage of SARS-CoV-2 spike proteins18. Therefore, when the RAS is reduced at the cellular level, an increase in the activation of interleukin (IL)-6 and tumour necrosis factor-α (TNFα) occurred as well as the increase in recruitment of neutrophils and macrophages. This series of action cause direct endothelial cell injury16,18. Biological research have listed IL-2, IL-7, IL-10, and TNFα as inflammatory cytokines which increased in COVID-19 patients[19–21].In addition , cellular injury occurs as result of viral replication and simu-

lation of the immune response of infected cell,. This results in altered cell function and demise of type II alveolar epithelial cells, which suggested to be responsible for the beginning of the development of pulmonary fibrosis[21,22].

In terms of the disease severity, different SARS-CoV-2 infection phenotypes have been identified based on clinical and radiological characteristics [23]. The first, Phenotype-1 is the most common and is characterized by mild respiratory symptoms, a normal chest radiograph, and the absence of hypoxemia; symptomatic treatment is used for such patients. Phenotype-2 is characterized by the presence of hypoxemia or multiple small ground-glass opacities on the chest radiograph. These patients require close respiratory monitoring because they may progress to Phenotype-3, which presents more significant hypoxemia, higher respiratory rates, and high IL-6 and other inflammatory marker levels [23]. This type also requires close monitoring as patients may need to be intubated. Phenotype-4 is characterized by alveolar edema and normal/low lung compliance, meaning patients have severe hypoxemia requiring intubation [23,24]. Treatment should include tidal volumes of 6 mL/kg PBW and moderate-to-high positive end-expiratory pressure (PEEP) as well as lateral or prone positioning. Phenotype-5 is characterized by an ARDS-like appearance, and management should follow standard ARDS guidelines. A protective ventilatory strategy and prone positioning are indicated [23,24].

Thus, the majority of patients with a severe manifestation of COVID-19 required respiratory support and ICU admission, where 88% of those required assisted ventilation by a mechanical ventilator25. There is a lack of consensus in the data regarding the respiratory mechanics and optimal mechanical ventilator setting in patients admitted to ICU for COVID-19 associated respiratory failure3,26. Intubated patients with severe COVID-19 disease were placed on with high PEEP, increasing barotrauma incidence [27]. Studies suggest that COVID-19 patients who progressed to ARDS have oedema and atelectasis, which cause a change in lung volumes, resulting in over distention of the lung (called volutrauma), or an increase in the strain of the ventilated alveolar space (called atelectraum). Additionally, the alteration in lung tissue due to the pathological process of severe COVID-19 causes friability of the lung parenchyma and subsequently increases the risk of lung fibrosis [27].

Pulmonary rehabilitation for post-COVID-19 infection:

Pulmonary rehabilitation, in general, considers a critical component in the manage-

ment approach to enhance the shortness of breath and exercise tolerance, and ultimately the health status of patients with chronic lung disease[28]. The primary strategy of pulmonary rehabilitation programs is exercise training, education, and behaviour changes. All those strategies improve physical and psychological well-being, therefore promoting the long-term health quality of life [29]. Different health settings utilize different approaches and structures of pulmonary rehabilitation programs; however, all programs share the key components of training include: endurance, interval, resistance/strength exercise of upper and lower limbs, walking, and self-management training. Most of those sessions usually implemented through outpatient programs 30. Since the pulmonary rehabilitation program includes many sessions for a long period, patient adherence is the major issue to achieve such a program's effectiveness [31].

The need for pulmonary rehabilitation in COVID-19:

The need for pulmonary rehabilitation for COVID-19 patients has been discussed in the literature. Specifically, during the acute phase of a severe COVID-19 infection, patients receive intensive medical management, including prolonged mechanical ventilation, sedation, and neuromuscular blocking agents. This intensive medical management is considered a risk factor for developing post-intensive care weakness [32]. Studies have shown that many patients referred to pulmonary rehabilitation programs after severe COVID-19 have symptoms common to other ICU patients, including dyspnea, anxiety, prolonged pain, and reduced physical function and quality of life [33].

Consistent with SARS infection outcomes, many studies have hypothesized that the lung tissue damage and alteration that occur in severe COVID-19 may cause various degree of physical dysfunction[34]. Therefore, experiences with pulmonary rehabilitation in post-SARS patients provide supportive evidence for the implementation of pulmonary rehabilitation programs for COVID-19 patients [35]. Therefore, COVID-19 patients tend to have the same problems as patients with chronic lung disease; however, COVID-19 patients, the need for a pulmonary rehabilitation program is critical to overcome breathlessness and fatigue, improve physical performance, and subsequently enhance the quality of life [36]. The main goal of pulmonary rehabilitation programs for COVID-19 survivors is usually endurance as these patients had a prolonged hospital stay and are thus at risk of developing ICU acquired weakness[8,28]. Moreover, as dyspnea and a high respiratory rate are known predictors of

severe disease or death, it is important to continue monitoring such patients closely. While many pulmonary rehabilitation programs focus on endurance, there is a need for more research on how to best quantify patients' endurance level as part of an outcome assessment[37]. Meanwhile, many patients with COVID-19 require supplemental O2 for post-acute rehabilitation, and thus a secondary goal in rehabilitation programs is to wean them off O2. Third, prolonged bed rest and immobility contribute to the loss of strength, and studies have indicated that patients with COVID-19 have a greater muscle mass loss compared to pathologies with similar ICU and bed rest time[38]. This may be due to specific COVID-19 loads, the impact of the prolonged lack of muscle tissue oxygenation, and the physiological reaction to longer periods of increased respiratory rate and heart rate along with decreased PaO232. Finally, there is the issue of independence: most patients are discharged as early as possible to free up ICU and hospital beds, meaning that the patients may not yet be fully independent at home[39].

With the growing body of evidence showing that COVID-19 survivors have pulmonary sequelae after the acute phase of the infection, an increasing number of studies have investigated the clinical outcomes among COVID-19 survivors, especially concerning the long-term effects [35,39,40]. In relation to the abovementioned points on the functional deficits post COVID-19, various associations and committees have published recommendations for inpatient and outpatient pulmonary rehabilitation[37,41–43]. Those recommendations have been utilized as essential clinical practice guidelines for effectively managing severe COVID-19 with ICU support. However, the main challenges for pulmonary rehabilitation, which mainly take the form of inpatient sessions, are the limited numbers of therapists compared to the number of patients as well as existing infection and hygiene measures, especially if the patients are isolated [44].

Reviewing the published research:

Most of the evidence assessing the impact of pulmonary rehabilitation programs on COVID-19 survivors has been published as reports by various organizations and pulmonary rehabilitation committees, although there have been a few prospective cohort and cross-sectional studies [36,39,40,44]. Thus, the guidelines and recommendations for implementing pulmonary rehabilitation programs in the COVID-19 era have primarily come from organizations [41–43,45,46]. Table 1 present the published studies on the effective of pulmonary rehabilitation on COVID-19 patients. At the beginning of the COVID-19 pandemic, several stud-

ies described the short-term effects of inpatient pulmonary rehabilitation for patients with severe COVID-19 infection admitted to ICU and placed on mechanical ventilation. For example, a cross-sectional survey recruited post-COVID-19 patients referred to a rehabilitation unit in Italy and assessed their pulmonary function and disability status 36. The study shared the experience of their pulmonary rehabilitation program and stressed the clinical importance of pulmonary rehabilitation programs for COVID-19 patients in the early stages of recovery [36].

In 2020, Spielmann et al. described the effect of a three-week standardized inpatient pulmonary rehabilitation program for hospitalized COVID-19 patients and compared their outcomes to the outcomes of patients who had other lung diseases and had undergone a similar pulmonary rehabilitation program in 2019 [47]. The study found improvements in physical performance, measured by Functional Independence Measure (FIM) and 6 Minute Walk Test (6-MWT), among hospitalized COVID-19 patients. This finding provides emerging evidence regarding clinical and functional improvements for severe COVID-19 and highlights the importance of post-acute pulmonary rehabilitation for COVID-19 recovery [47]. Other studies have indicated that the length of time on ventilation, level of sedation, and function after extubation are the most important indicators of long-term recovery48. Furthermore, Puchner et al., who conducted a cohort study to assess the status of COVID-19patients enrolled in a pulmonary rehabilitation program, showed that more than 50% of their sample had pathological Forced expiratory volume in 1 second (FEV1), Forced vital capacity (FVC), and Total lung capacity (TLC) below < 80%. That study also found that 83% of study participants still showed reduced diffusing capacity of the lungs for carbon monoxide(DLCO) at the end of the rehabilitation program [40].

Beyond this, many studies have reported that patients have reductions in their maximum inspiratory pressure and diffusion capacity measures within the first year following their discharge from ICU [49]. Those reductions in respiratory function manifest as increased work of breathing and an effective cough [50]. Mo et al. found that patients discharged from hospital after severe COVID-19 pneumonia had impaired lung diffusion capacity and complained of dyspnea, chest pain, and general fatigue for weeks after hospital discharge [51]. Moreover, another study reported that COVID-19 survivors who were referred to a pulmonary rehabilitation program still had residual infiltrates of the lung, which possibly progressed to fibrosis, leading to

a limitation in gas exchange [41,52]. The study further highlighted that COVID-19 survivors require close monitoring of their lung function and residual capacity to monitor changes in FEV1, FVC, FEV1/FVC%, and DLCO% 41. Additionally, respiratory and aerobic exercises has shown promise in helping to enhance endurance and quality of life of COVID-19 patients in addition to reduction in the anxiety and depression level [53].

Meanwhile, there is limited clinical trial-based evidence regarding pulmonary rehabilitation for COVID-19 survivors. One randomized-controlled trial (RCT) assessed the effectiveness of a 10-min pulmonary rehabilitation session for six weeks on respiratory function, Health-related quality of life (HRQoL), mobility, and psychological function among elderly COVID-19 survivors discharged from hospital 39. The study's findings showed an improvement in respiratory function (FEV1/FVC), HRQoL, and in level of anxiety among their patients.

Recently, a scoping review highlighted pulmonary rehabilitation in COVID-19 patients, underlining the lack of data on this topic, although the recommendations published by various societies highlight the benefits of early pulmonary rehabilitation program initiation [54]. The review strongly suggests implementing a plan for multidisciplinary rehabilitation programs to prevent the development of long-term consequences of COVID-19.

Table 1: Epidemiological studies that have been carried out to assess the impact of pulmonary rehabilitation programs on COVID-19 survivors.

Study author	Type of study	Study population	Main Finding
Curci C et al.[36]	Cross-sectional study	Post-acute COVID-19 patients in Italy	Patients suffered from dyspnea and shortness of breath for minimal activities. This caused disability, and few of the study population were able to perform 6-MWT in which they have poor results.
Spielmanns M et al.[45]	Cohort study	post-COVID-19 patients referred to pulmonary rehabilitation in 2020 compared to patients with other lung diseases in 2019	Comprehensive pulmonary rehabilitation resulted in improvement in -MWT and FT
Puchner B et al[38]	cohort study	Patienst discharged after severe to critical COVID-19 infection	83% of all study participants still reduced the DLCO at the end of the rehabilitation program
Liu K et al.[39]	Quasi-experimental study	Elderly COVID-19 survivors, weaned off from mechanical ventilation and discharged from hospitals in China	Pulmonary rehabilitation over 6 weeks reulsted in Improvement in respiratory function (FEV1/FVC), QoL, level of anxiety, physical function (SF-36).

CONCLUSION:

This review has shed light on the need for more evidence of the beneficial effects of pulmonary rehabilitation programs on patients recovering from COVID-19 and their role in ensuring that this population can resume a functional life. However, to produce findings that can be translated into practice, the challenges inherent to this line of research need to be addressed. Specifically, the extant risk of infection, quarantine times, and physical barriers rules have added more challenges to the implementation of pulmonary rehabilitation sessions. In response to this, there has been much discussion of the role of home-based telemedicine in pulmonary rehabilitation 55,56. Overall, this field still has much to accomplish in the future to fully understand the long-term outcomes of COVID-19, also in the context of any future respiratory infection pandemic.

Key Points:

• Research suggested that chronic viral infection can induce an inflammatory response that contributes to the fibrotic response.

• The is a lack of solid evidence on the impact of pulmonary rehabilitation programs on COVID-19 survivors.

• Most of the studies highlighted the challenges to the implementation of pulmonary rehabilitation sessions.

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