Pneumologia

Pulmonary rehabilitation following the 2019 novel Coronavirus infection

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Abstract

English:

The treatment of an infectious disease is only one step to a cure and, in many cases, infectious diseases can lead to short- and long-term impairments, including physical, cognitive and psycho-emotional complications. In this paper, we perform a literature review to identify the appropriate rehabilitation interventions for responding to COVID-19 consequences, taking into consideration the current standards for pulmonary rehabilitation and the COVID-19 literature which has been developed during the pandemic's evolution. Pulmonary, neurological, cardiac, musculoskeletal, nutritional, cognitive and psychological disabilities, as well as dysphasia, have been observed among patients who recovered after needing time in the intensive care unit (ICU), related either directly to COVID-19 or critical care treatments. Some have also been reported in patients who were asymptomatic or recovered from a mild or moderate form of the disease. Patients who still have dyspnea, exercise intolerance and fatigue, are unable to conduct activities of daily living and/or have difficulty in managing or coping with their disease, despite optimised pharmacological therapy, are most likely to benefit from pulmonary rehabilitation. Contraindications should be considered during patient selection. Rehabilitation prescription should be individually tailored, based on patient assessment and outcome measurements. Pulmonary rehabilitation interventions may involve airway clearance therapy, breathing exercises, mobilisation and strength training, flexibility training, balance training, neuromuscular electrical stimulation (NMES), activities of daily living, aerobic training, dysphagia management, nutrition therapy, cognitive training and psychological support. Medical management of comorbidities and patient-family education are key factors for achieving optimal gains from pulmonary rehabilitation.

Keywords

SARS-CoV-2 • COVID-19 • pulmonary rehabilitation • assessment

Reabilitare pulmonară în urma infecției cu noul coronavirus 2019

Rezumat

Romanian:

Tratamentul unei boli infecțioase este la un pas departare de vindecare și, în multe cazuri, bolile infecțioase pot duce la afectări pe termen scurt și lung, inclusiv complicații fizice, cognitive și psiho-emoționale. În această lucrare, efectuăm o revizuire a literaturii pentru a identifica intervențiile adecvate de reabilitare care să abordeze consecințele COVID-19, luând în considerare standardele actuale pentru reabilitarea pulmonară și literatura COVID-19 care a fost dezvoltată pe parcursul evoluției pandemiei. Au fost observate dizabilități pulmonare, neurologice, cardiace, musculo-scheletice, nutriționale, cognitive și psihologice, precum și disfație, în rândul pacienților care și-au revenit după ce au statonat în unitatea de terapie intensivă, legate fie direct de COVID-19, fie de tratamentele de îngrijire critică. Unele au fost raportate și la pacienții asimptomatici sau recuperați de la o formă ușoară sau moderată a bolii. Pacienții care încă au dispnee, intoleranță la efort și oboseală, sunt incapabili să desfășoare activități din viața de zi cu zi și / sau au dificultăți în gestionarea bolii lor, în ciuda terapiei farmacologice optimizate, sunt cei care vor beneficia cel mai probabil de reabilitarea pulmonară. Contraindicațiile trebuie luate în considerare în timpul selecției pacientului. Programul de reabilitare trebuie adaptat individual, pe baza evaluării pacienților și a măsurătorilor rezultatului. Intervențiile de reabilitare pulmonară pot implica terapie de drenaj a căilor respiratorii, exerciții de respirație, mobilizare și antrenament de forță, antrenament de flexibilitate, antrenament de echilibru, stimulare electrică neuromusculară, activități de viață de zi cu zi, antrenament aerobic, management al disfagiei, terapie nutrițională, antrenament cognitiv și sprijin psihologic. Managementul medical al comorbidităților și educația pacient-familie sunt factori cheie pentru obținerea câștigurilor optime din reabilitarea pulmonară.

Cuvinte-cheie

SARS-CoV-2 • COVID-19 • Reabilitarea Pulmonară • Evaluare

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Introduction

In late December 2019, a novel Coronavirus was identified after the Chinese health system in Wuhan declared a continuously increasing number of patients with common viral pneumonia (1, 2). Shortly afterwards, the World Health Organization (WHO) recognised the new coronavirus disease as COVID-19 (3). On 11 March 2020, COVID-19 became a pandemic and caused a major global public health issue (4, 5). At the time of writing this paper, more than 29 million positive cases have been registered and over 9,00,000 deaths have been reported according to the WHO (6).

The angiotensin-converting enzyme 2 (ACE2) was found to be a key host receptor for SARS-CoV-2 (2). Organ cells that have a significant ACE2 expression level are the main targeted cells, including the lung alveolar epithelial cells, enterocytes of the small intestine, heart and kidney, which explain the respiratory and non-respiratory clinical features in patients (7, 8). The human-to-human transmission occurs essentially by means of the respiratory tract via droplets from sneezing, coughing or rhinorrhoea within 2 m of the infected person (2, 9).

Several forms of COVID-19 have been characterised based on symptoms and the degree of severity. The first form refers to asymptomatic patients. The second form refers that the patients may present as symptomatic with mild or moderate symptoms which commonly include fatigue, fever, dry cough, headache, sore throat, nasal congestion, myalgia and arthralgia (10), though some patients have experienced particular symptoms such as keratoconjunctivitis (11), anosmia and ageusia (12). The third form includes severe-to-critical cases, usually associated with people of advanced age or patients with comorbidities such as diabetes, hypertension, cardiac and cerebrovascular diseases (10), as well as hepatic and renal dysfunction (13). In this form, a cytokine storm eventually occurs and results in a prolonged and excessive inflammatory response to SARS-CoV-2, causing multiple-organ dysfunction or acute respiratory distress syndrome (ARDS) which can lead to physiological deterioration and death (14).

To date, there is no specific treatment for COVID-19. Optimised supportive care remains the current mainstay of treatment (15). However, some antiviral agents such as hydroxychloroquine, chloroquine, remdesivir, favipiravir and lopinavir/ritonavir are being used (15). Corticosteroid and anticoagulant agents have also been utilised when the need was justified (10).

Cases evolving into acute pneumonia, ARDS, severe cardiovascular complications, acute kidney injury, sepsis and septic shock are indications for intensive care unit (ICU) admission (10, 16, 17). At this stage, the management guidelines for these patients encompasses using lung-protective ventilation, neuromuscular blocking agents to

optimise ventilator synchrony, conservative fluid strategies, empirical antibiotics for a potential bacterial superinfection with aggressive de-escalation, prone positioning as appropriate, and extracorporeal membrane oxygenation is considered in the cases of refractory hypoxemia (16).

Based on the past experiences in patients with SARS (18), functional, radiological and psychological impairments of different degrees have been reported in recovered patients, mainly characterised by dyspnea and general weakness, including physical limitations and reduced aerobic capacity over 1 month following hospital discharge. Computerised tomography (CT) of the chest showed some patchy changes indicating pulmonary fibrosis. These patients also manifested symptoms of psychological trauma about 1 month from the onset of illness. Furthermore, in the cases of severe SARS (19), survivors continued to experience long-term effects of physical dysfunction 1 year after survival; this included an impact on their occupational and social participation, in addition to the manifestation of high degrees of stress, anxiety and depression. Given these results, Landry et al. (20) concluded that the infectious disease treatment is only one step and that, in many cases, infectious diseases may result in lasting impairments, mainly activity limitations and participation restrictions. Moreover, several reports (21, 22) stated that the median length of COVID-19 patients' stay in ICU is 2–3 weeks, which is relatively long (22, 23). Stam et al. (24) indicated that the risk for physical, cognition and psycho-emotional complications, respectively, increases with the patient's length of stay (LOS) in the ICU. Additionally, there is growing evidence in the literature that patients recovering from COVID-19 can experience short- and long-term consequences resulting from either the disease itself or ICU hospitalisation (22, 23, 24). On the other hand, rehabilitation has shown promising results in reducing disability and improving clinical outcomes in survivors during disasters (25). Consequently, incorporation of rehabilitation following COVID-19 is essential. Therefore, we have performed this literature review, to identify the appropriate rehabilitation interventions to effectively respond to a wide spectrum of COVID-19 issues, taking into consideration the pulmonary rehabilitation (PR) standards and the COVID-19 literature developed along with the pandemic evolution.

COVID-19 consequences

In addition to asymptomatic patients, COVID-19 has a different clinical spectrum. In a report by Carda et al. (23), COVID-19 degrees of severity are divided into four forms: (1) Mild: normal blood oxygen saturation (SatO_2) and no dyspnea; (2) Moderate: SatO_2 94–98%, dyspnea and radiological signs of pneumonia; (3) Severe: respiratory rate (RR) >30/min,

SatO₂ ≤93%, radiological progression of lesions, dyspnea and oxygen therapy with non-invasive ventilation might be needed and (4) Critical: patients require mechanical ventilation. Furthermore, the consequences of COVID-19 resulting from each form can range from a transitory impact to a long-lasting impact. Addressing these consequences by PR based on a multidisciplinary rehabilitation team finds indication evidence in the literature.

In asymptomatic COVID-19

Patients usually recover without any CT findings, nor any residual dysfunctions (23, 26). However, based on the results of a retrospective study (27) on the radiological findings from 81 patients with COVID-19 in Wuhan, 15 asymptomatic patients were found with evolving lung lesions which persisted until after a short period of treatment. CT imaging showed a rapid progression, within 1–3 weeks, from focal unilateral to diffuse bilateral ground-glass opacities (GGO) that coexisted with or developed into consolidations. These findings indicate interstitial changes and suggest substantial fibrotic consequences following COVID-19 infection. These patients may also develop psychological problems such as anxiety and depression due to experiencing loneliness, insomnia and fear during quarantine (28).

In mild-to-moderate COVID-19

CT imaging revealed various lung lesions, mostly characterised by GGO that could evolve into consolidation and fibrosis (26). These findings were presented more in male and older patients (26). Following the SARS-CoV-2 infection, a randomised controlled study (29) demonstrated that a 6-week respiratory rehabilitation period was deemed to be effective in improving the prognosis for respiratory function, mobility, psychological function and quality of life (QoL).

In severe and critical COVID-19

An acute systemic inflammatory response to SARS-CoV-2 can result in acute pneumonia, ARDS (17), severe cardiac complications (16), sepsis and septic shock (17), which can also lead to death (30). These patients are admitted to the ICU for supportive therapy (31). They are usually older patients (>60 years) with impaired immunity and/or a medical history of comorbidity, including diabetes, hypertension, coronary artery disease, ischemic disease of the central nervous system, Parkinson's disease and bronchitis (17). After 2–3 weeks, ICU survivors may be discharged with multiple impairments,

varying between respiratory dysfunction, extrapulmonary disorders and post-intensive care syndrome (PICS), resulting in either from COVID-19 complications or the consequences of ICU treatment (22, 23, 24).

Respiratory impairments

Due to diffuse lung injury occurring in severe COVID-19 patients (30), some patients present with persistent dyspnea after the acute phase. This is usually associated with low SatO₂, which may manifest at rest and/or on exertion (23). Spirometry and pulmonary diffusion capacity tests in discharged severe COVID-19 patients showed an impaired diffusion capacity, followed by restrictive ventilatory defects (32). In critical COVID-19 patients, as described in the pre-existing literature, ARDS survivors may also have abnormal lung function and reduced exercise endurance, which, despite being generally minor, may persist for up to several years after the acute illness (33). Herridge et al (34) conducted a prospective cohort study of 109 ARDS survivors to evaluate lung function and exercise capacity 1 year after surviving intensive care. They found that patients had mild restrictive disease and decreased diffusion capacity up to 3 months after discharge. Spirometric measurements and lung volume were almost normal, though with a persistent minor reduction in diffusion capacity associated with dyspnea and sputum production at 6 months and 12 months. At 12 months, the distance walked in 6 min was significantly increased but remained below the predicted value. Exercise limitation was attributed to global muscle wasting (patients lost 18% of their baseline body weight) and weakness. Persistent dyspnea at 12 months after the onset of the illness was most likely the result of diaphragmatic dysfunction rather than a specific lung problem (35). These findings suggest the role of a global assessment in order to determine the functional limitations contributing to health-related quality of life (HRQL) decrements in ARDS survivors, and consequently in those surviving COVID-19. PR, likely associated with oxygen therapy, would be also crucial in patients who have been through severe and critical stages of COVID-19 (22, 36).

Post-extubation dysphagia (PED)

Although the prevalence of PED in COVID-19 patients was not reported, the significant prevalence of critical COVID-19 patients requiring invasive mechanical ventilation (according to the *New England Journal of Medicine* study (37), almost 60% of ICU patients needed mechanical ventilation) suggests the presence of PED in a large number of patients after extubation. PED can delay the return to normal oral feeding and increase the risk of morbidity and mortality related to aspiration pneumonia. Speech-language pathology (SLP) or physiotherapy intervention can be very effective in reducing these effects (38, 39).

Cardiac impairments

The association between COVID-19 and cardiovascular disease is continually outlined. Cardiac arrhythmias and myocardial ischemia are the most reported cardiac events in patients with severe COVID-19 (16). Various aetiologies have been explored, including unstable pre-existing chronic cardiac diseases, respiratory dysfunction and hypoxemia, viral myocardial injury, ACE2-receptor down-regulation, accentuated inflammatory response and corticosteroids use in COVID-19 patients with cardiac context (40). The Stanford Hall consensus recommends that patients recovering from COVID-19 with new or worsening cardiovascular events should undergo a comprehensive cardiac assessment, followed by a period of rest before integrating any rehabilitation programme to reduce the risk of post-infection cardiac failure secondary to myocarditis (41).

Neurological impairments

Several cases with severe COVID-19 have been identified with variable neurological disorders. The potential 'Neuroinvasion' of SARS-CoV-2 appears to be the result of a haematogenous spread through the central and peripheral nerve pathways (39). The neurological signs of the central nervous system involvement include consciousness alterations, acute cerebrovascular disease, dizziness, headache, seizure and ataxia (42). Peripheral impairments include peripheral axonal neuropathy, Guillain-Barré syndrome (43) and sensory disability comprising of a loss of taste, smell and vision (23). Mild neurological disorders showed to be transient, while the severe ones seem to persist longer and cause difficulties with daily tasks (41, 44).

Post intensive care syndrome (PICS)

This is related to ICU-acquired weakness (ICU-AW), cognitive and mental impairments manifested during ICU stay, and following ICU/hospital discharge, including the long-term prognosis of ICU survivors (45). Severe COVID-19 patients who undergo ICU treatment are at increased risk of developing short- and long-term problems associated with PICS (22, 46).

- 1) **ICU-AW:** All four limbs and respiratory muscles are affected by weakness, the diaphragm is often involved (47). ICU-AW is likely to be multifactorial and may result from prolonged proning, duration of mechanical ventilation, treatment modalities, systemic inflammatory response syndrome, multiorgan failure and sepsis (22, 45). An early report (21) stated that 30% of severe COVID-19 patients were diagnosed with ICU-AW at ICU discharge. Similarly, the early experience from the field (22) reported that many functional issues were diagnosed in COVID-19

patients following ICU discharge. For example, severe muscle weakness, fatigue, neck and shoulder pain, joint stiffness, difficulty in verticalisation, impaired balance and gait, reduced mobility, limitations in activities of daily living and work were indicated. Persistent respiratory muscle weakness and limb weakness at ICU discharge predict poor clinical outcomes and an increased risk of death or readmission to hospital or ICU (48).

- 2) **Cognitive impairments:** These include dementia, impaired attention, language deficits, diminished executive function and reduced visual-spatial abilities (45). Patients with delirium in the ICU are at significant risk for long-term consequences of cognitive dysfunction (45). Potential aetiology is direct CNS viral involvement and/or hypoxemia (49). A systematic review (50) on psychiatric and neuropsychiatric presentations associated with severe Coronavirus infections found that 65% of ICU patients with severe COVID-19 developed delirium (confusion) and 21% of patients who subsequently died had altered consciousness. At discharge, 33% had dysexecutive syndrome with symptoms such as disorientation, inattention or poorly organised responding movements to commands. Similar findings were reported in a different study (21), where mild to moderate delirium was present in all COVID-19 patients who were discharged from ICU.
- 3) **Mental impairments:** This issue might result from direct effects of a viral brain infection, the context of a procoagulant state, hypoxia, an immunological response, medical intervention and environmental factors like social isolation and/or stigma (50, 45). A report (21), including a small cohort with severe and critical COVID-19, found that anxiety or post-traumatic stress was present in 50% of patients after being discharged from ICU. The long-term mental health effects of COVID-19 are yet to be examined. However, the past epidemics with the SARS and MERS infections provide early insights into the mental outcomes of COVID-19. A meta-analysis (50) including 1,203 patients on a post severe illness stage of SARS and MERS revealed that 32.2% of cases developed post-traumatic stress disorder (PTSD), 14.9% had depression and 14.8% suffered from anxiety disorders. Additionally, the study suggests that if COVID-19 has the same infection course as SARS and MERS, possible long-term neuropsychiatric consequences should be expected in severe COVID-19 survivors.

The prevention of PICS from time in ICU is showed to be more effective than the intensive treatment of PICS upon ICU discharge (51). Early rehabilitation during ICU time may reduce ICU-AW (52) but has not shown significant improvement on PICS-related delirium and mental issues (53). Cuthbertson et

al. (54) studied the effects of an ICU follow-up programme on the HRQL of 192 ARDS survivors and the results indicated no improvement on Short Form-36 (SF-36) physical or mental component scores at 12 months post-discharge. Additionally, the programme was considerably expensive compared with the standard care. However, a series of studies have reported positive results of PR outcomes in ARDS survivors. In a case report (55), 1 month of respiratory rehabilitation followed by daily regular physical activity showed regression of alveolar condensation at about 1 month, increased activity tolerance at 3 months and alleviation of dyspnea at 6 months. In another study, Hsieh et al. (56) assessed recovery of pulmonary functions, exercise capacity and QoL upon a 2-month PR programme following ARDS caused by severe influenza A (H1N1) pneumonitis. The results revealed improvement in pulmonary functions and exercise capacity, as well as continuous progress in the total lung capacity and QoL, respectively, 1–3 months and 6 months after ICU discharge. The effect of a multicomponent rehabilitation programme on the cognitive functions following ICU discharge was investigated by Jackson et al. (57). The 3-month rehabilitation programme based on the cognitive, physical and functional training demonstrated a significant improvement in the cognitive executive functioning in ICU survivors. On the other hand, although the lack of studies evaluating the effectiveness of PR on psychiatric disorders in ICU survivors, a systematic review and meta-analysis (58) comprising 11 studies reported the PR's significant benefits on anxiety and depression symptoms in patients with chronic obstructive pulmonary disease (COPD). Furthermore, Panagioti et al. (59) concluded that PR interventions either with or without psychological component ameliorate symptoms of anxiety and depression in COPD. Subsequently, PR can confer beneficial effects in COVID-19 survivors, as well as in those at risk of PICS after ICU discharge.

PR following the acute stages of COVID-19

Referral to PR

Based on multiple outcomes resulting from COVID-19 infection, a comprehensive multidisciplinary team intervention comprising of the physician, physiotherapist, nurse, dietician, social worker, occupational therapist, pharmacist and speech therapist, alongside the psychologist will be necessary (39, 41, 60). The patient's awareness of his disability and full motivation for improvement is a valuable contribution to the treatment effectiveness and their recovery (60). Patients who have recovered from COVID-19 infection, but still have dyspnea, exercise intolerance and fatigue are unable to conduct activities of daily living and have difficulty in managing or coping with their disease, despite optimised pharmacological therapy, are most likely to

benefit from PR (41, 61). PR is feasible within all rehabilitation settings. This involves hospital inpatient, hospital outpatient, the community and the home. Patients with pulmonary sequelae such as breathlessness, bronchiectasis or pulmonary fibrosis can safely benefit from tailored PR programmes (60). Patients with significant cardiac disease, locomotor problems or severe cognitive impairments will be limited in their ability to exercise or comprehend (60, 41). COVID-19 patients with mild-to-moderate outcomes may be therefore able to undergo outpatient or home-based rehabilitation, while older adults with comorbidities and severe COVID-19 survivors who have been discharged from the ICU are at risk of deteriorating and should first be stabilised before undergoing a long rehabilitation process within the inpatient, outpatient and home settings (28, 36). Rehabilitation prescription has to be individually tailored, based on the patient assessment and outcome measurements (61). The PR programme can be adjusted to meet certain patient dysfunctions and their pre-existing or new comorbidities (60, 22, 46, 61).

Patient assessment, outcome measurements and monitoring

The referral of COVID-19 patients to PR should consider the main contraindications to PR described in Figure 1 (61, 62). The patient must show evidence of COVID-19-free status with documentation of two consecutive negative real-time reverse transcription polymerase chain reaction (RT-PCR) results at 24-h intervals (62). To ensure the patient's eligibility and safety to be enrolled in a PR programme, PR program staff should review the patient's formal medical assessment, including their medical history, physical examination, chest imaging, review of laboratory tests such as complete blood count, chemistries, electrocardiogram (ECG) and pulmonary function testing, as well as blood gas, oximetry testing and ECG stress testing if available. Patient comorbidities should be assessed before and monitored during PR (61). It is important to consider cardiopulmonary exercise testing for exercise intolerance assessment and/or 6-min walk test (6MWT) at the start of PR to formulate the exercise prescription (28, 63). Outcome measurements should be considered to assess and monitor the patient's progress, exercise safety and the PR programme's effectiveness (61). Figure 2 (28, 64, 65) summarises the common

Absolute contraindications	Relative contraindications
<ul style="list-style-type: none"> • Transmissible infectious diseases including active COVID-19 infection • Unstable arrhythmia or angina • Unstable fracture • Unstable psychiatric disorder 	<ul style="list-style-type: none"> • Demotivation • Severe cognitive disability • Progressive neuromuscular disorder • Severe uncontrolled anaemia • Intense and disabling fatigue (e.g. in relation to chemotherapy or advanced congestive heart failure, etc.) • Limited life expectancy (e.g. less than 6 months) • Severe visual impairment

Figure 1. Contraindications to pulmonary rehabilitation.

Dyspnoea	<ul style="list-style-type: none"> • Medical Research Council (MRC) dyspnoea scale • Borg Scale
Exercise capacity	<ul style="list-style-type: none"> • Six-Minute Walk Test (6MWT) • Timed Up and Go (TUG) • Shuttle Walk Test (SWT)
Balance	<ul style="list-style-type: none"> • Activities and Balance Confidence scale • The Activities-Specific Balance Confidence (ABC) scale • Berg Balance Score
ICU-AW	<ul style="list-style-type: none"> • Medical Research Council (MRC) sum score of less than 48/60 or mean MRC score of 4 in all testable muscle groups • Dominant-hand handgrip dynamometry scores of less than 11 kg (interquartile range in males and less than 7 kg in females)
Diaphragmatic weakness	<ul style="list-style-type: none"> • Endotracheal tube pressures less than 11 cm H₂O after bilateral phrenic nerve magnetic stimulation during airway occlusion • Diaphragm excursion at muscle ultrasound less than 11 mm during tidal breathing • Diaphragm thickening fraction at muscle ultrasound less than 20%
Nutritional status	<ul style="list-style-type: none"> • Subjective Global Assessment (SGA)
Post-extubation dysphagia	<ul style="list-style-type: none"> • Water swallow test • Bedside Swallow Evaluation (BSE) • Videofluoroscopic Swallow Study (VFSS)
Activities of daily living	<ul style="list-style-type: none"> • Barthel Index of Activities of Daily Living (ADL) • Functional Independence Measure (FIM)
Physical activity	<ul style="list-style-type: none"> • International Physical Activity Questionnaire (IPAQ)
Psychological function	<ul style="list-style-type: none"> • Hospital Anxiety and Depression Scale (HADS) • Impact of Events Scale – Revised (IES–R) • Post-Traumatic Stress Disorder Checklist (PCL) – Civilian • Kessler – 10 Psychological Distress (K10)
Cognitive function	<ul style="list-style-type: none"> • Montreal Cognitive Assessment Test (MCAT) • Mini-Mental State Examination (MMSE)
Quality of Life	<ul style="list-style-type: none"> • Medical Outcomes Study 36-Item Short Form (SF-36) • EuroQol (EQ) 5D
Social function	<ul style="list-style-type: none"> • Multidimensional Scale of Perceived Social Support (MSPSS)

Figure 2. Common instruments for outcome measurements potentially used after COVID-19. ADL, Barthel index of activities of daily living; BSE, bedside swallow evaluation; EQ, EuroQol; FIM, functional independence measure; HADS, hospital anxiety and depression scale; IES-R, impact of events scale-revised; ICU-AW, ICU-acquired weakness; IPAQ, International physical activity questionnaire; K10, Kessler-10 psychological distress; MRC, Medical Research Council; MCAT, Montreal cognitive assessment test; MMSE, mini-mental state examination; MSPSS, multidimensional scale of perceived social support; PCL, post-traumatic stress disorder checklist; 6MWT, Six-minute walk test; SWT, shuttle walk test; SGA, subjective global assessment; SF-36, medical outcomes study 36-item short form; TUG, timed up and go; VFSS, videofluoroscopic swallow study.

instruments for measuring COVID-19-related outcomes. When there are multiple outcomes to be evaluated, the assessment could be an exhausting process, especially for critical care survivors at the early stage of recovery. Therefore, it may be judicious to select the outcomes of most interest for the treatment guidance. Exercise capacity, dyspnea and QOL are usually key areas for demonstrating the benefits of PR for patients (61). During exercise sessions, the patient should be monitored. The session should be discontinued if the following signs are identified: blood pressure <90/60 or >140/90, decreased SaO₂ (<95%), heart rate >100, temperature >37.2, chest pain, dizziness, loss of balance, heart palpitations, excessive fatigue, severe cough, blurred vision, headache or profuse sweating (66, 28).

Management of comorbidities

Severe COVID-19 is recognised to be associated with comorbidities such as cardiovascular diseases (heart failure, coronary artery disease or cardiomyopathies), metabolic diseases (diabetes, hypertension, obesity) and COPD (67). Poor PR outcomes can relate to the presence of comorbidities. Maintaining these comorbidities in balance before beginning PR may increase the patient's chances of achieving the optimal gains from PR (68, 61).

PR interventions

Airway clearance therapy

Sputum rarely occurs in patients who experienced a mild or moderate form of COVID-19 infection. However, in severe COVID-19 cases that required ICU treatment, bronchial secretions should be controlled (22). An augmented amount of sputum may result from lung abnormalities and complications such as bronchiectasis, secondary bacterial infection and aspiration pneumonia (69). Expectoration deficiency is usually associated with an ineffective cough, indicating a reduction in expiratory flow and respiratory muscle weakness (70). Accumulated bronchial secretions can worsen dyspnea, potentiating the risk of atelectasis, reductions in lung compliance and secondary infections (71). Respiratory secretion management will aim to increase mucociliary clearance, moving the secretions to the upper airways, promoting expectoration and improving cough effectiveness (70). The choice of techniques or devices to promote expectoration and improve mucus clearance should consider the initial and ongoing pulmonary function assessment, the patient's cognitive ability, comorbidities and respiratory muscle strength (72). Cough effectiveness can be improved by activating the expiratory muscles, achieved by either an external stimulus (e.g. functional electrical stimulation) or expiratory muscle training (70).

Breathing exercises

Inspiratory muscles and diaphragmatic weakness are mainly reported in COVID-19 patients who required a considerable duration of mechanical ventilation and subsequently lose spontaneous breathing ability (28). After a successful spontaneous breathing trial, applying well-controlled breathing exercises may relieve dyspnea, improve the respiratory muscle function, ventilation and gas exchange, exercise tolerance and QoL. These exercises comprise body positions such as leaning forward, relaxation therapy and inspiratory and expiratory muscle training (66). Exercise should include non-threshold load training for inspiratory muscles, with intensity starting from 30% of the maximal inspiratory pressure, for a duration of 10–15 min/day, with

a goal of gradually increasing to 30 min/day (36). During diaphragmatic breathing, the patient is taught to intentionally move the abdominal wall during inspiration while reducing the upper ribcage motion. Then they exhale deeply and slowly against pursed lips while contracting the abdominal muscles. The exercise should be performed for 10 min, three times per day. It includes four respiratory progression positions: supine, proning, sitting and walking (36, 73).

Mobilisation and strength training

Ideally, mobilisation is most effective when addressed early during ICU. However, COVID-19 patients who present with unsatisfactory mobility after ICU discharge would also benefit from mobility exercises to achieve recovery (46). Mobilisation may improve short- and long-term functional status, cognitive faculties (but not delirium) and respiratory conditions. It could also prevent thromboembolism risk and reduce hospital LOS (74, 45). It comprises passive, active-assisted, active mobilisation (against resistance) of upper and lower limbs, and activities such as sitting, standing and ambulation (45, 62). Resistance training should be individualised and progressive. The chosen resistance for each muscle group should be at 70–80% of the person's one-repetition maximum (46), with at least 48 h of recovery between sessions of the same muscle group, during 4–6 weeks (63, 75). A recommended programme suggests 8–12 repetitions maximum for the training load of each muscle group, for 1–3 sets, with a 2-min recovery period between sets, for 2–3 sessions/week, lasting for 6 weeks, with 5–10% of training load progression per week (28).

Flexibility training

Due to prolonged immobility, muscle weakness and joints stiffness can lead to an abnormal body posture. As a result, reduced pulmonary function, shallow respiration, altered body mechanics and back pain are potential problems in COVID-19 survivors (23). Flexibility exercises may significantly improve the vital capacity, exercise tolerance and pain level. Training includes stretching exercises of the main upper and lower limb muscle groups, as well as the shoulders, trunk and neck motion exercises and thoracic expansion. Training can last for 5 min, once a day, for at least 2–3 days/week (36, 63).

Balance training

The balance should be based on an assessment to identify the area of dysfunction. Exercises have to be individually tailored and developed according to the patient's ability (51). Training may include static, dynamic, hands-free balance and using balance training instruments (28, 36, 46). Patients should be supervised by the rehabilitation therapist who must be careful to avoid the potential of risky patient falls, especially in those who are on anticoagulants treatment (63).

Neuromuscular electrical stimulation (NMES)

This has the advantage of improving muscle contraction strength without involving the cognitive, psychological and motivational aspects, otherwise required in conventional muscle training (63). In just 4 weeks of treatment, NMES has been shown to be effective in treating severely disabled patients with COPD and a poor baseline exercise tolerance. Improvement comprised of an increase in limb muscle strength, exercise capacity and dyspnea (63). These improvements would also be beneficial for COVID-19 survivors with acute deconditioning. NMES stimulus frequencies up to 10 Hz and 30 Hz are optimal for activating slow-twitch fibres (endurance function) and fast-twitch muscle fibres (power function), respectively (63). It is generally safe and well-tolerated and can be applied in inpatient, outpatient and home settings. However, there are several contraindications for use regarding patients with implanted pacemakers or defibrillators, patients with uncontrolled cardiac arrhythmias, recent myocardial infarction, unstable angina, intracranial clips and/or total knee or hip replacement (63).

Activities of daily life

Occupational therapy support is important in disabled COVID-19 patients, since it likely contributes to faster recovery, improved patient functional independence and reduced hospital LOS. The interventions should be targeted based on the assessment of patient's ability to perform or adapt to their ADLs (39, 66).

Aerobic (endurance) training

These include walking, bicycle training, slow jogging, swimming, ergometer and so on. At the beginning of training, intensity should be low to less than three metabolic equivalents of task, for a session of 20–30 min, which can be repeated 3–5 times/week, before gradually increasing in intensity and duration (28, 66). Aerobic exercises should be individually tailored and take into consideration the patient's comorbidities (28). Hornikx et al. (68) concluded that endurance exercise should be reformed so as to be adapted to the patient's underlying chronic disease and that this category of patients could get the most benefit of rehabilitation. Figure 3 (68) summarises the outpatient endurance training intensity based on the patient-specific comorbidity.

PED management

Compensatory manoeuvres aim to reduce the risk of aspiration and improve chewing and swallowing. They consist of modifying dietary textures (preferably thick liquids and chopped solid food), the patient attempting to swallow small amounts, swallowing several times, coughing each time after swallowing, or using the Mendelsohn manoeuvre

COPD

- Training lasts for 8–12 weeks, four times per week, at an intensity of 60–80% of maximal workload, for 20–30 minutes sessions.

Cardiovascular Disease (Heart Failure and Ischemic Heart Disease)

- Intensity choice depends on the preserved ejection fraction and the exercise capacity of the patient during the pretraining period, measured by a cardiopulmonary exercise test. Training sessions may range from:
 - Light: 25–44% peak VO_2 , continuous training.
 - Moderate: 45–59% peak VO_2 , continuous training.
 - High: 60–84% peak VO_2 , interval training.
 - Very High Intensity: starting from 85% peak VO_2 , interval training.

Arterial Hypertension

- Patients have to perform 30 minutes of training at moderate intensity (40–60% HRR), 5 times a week or 20 minutes at vigorous intensity (60–84% HRR), 3 times a week.

Metabolic Disease

- Patients are instructed to train for 150 minutes of aerobic exercise, 3 times a week at moderate to vigorous intensity (40–60% $\text{VO}_{2\text{max}}$).

Anxiety and Depression

- Patients are advised to train for 8–14 weeks, 3–4 times a week at moderate intensity (40% $\text{VO}_{2\text{max}}$), during sessions of 20–30 minutes.

Figure 3. Outpatient endurance training intensity regarding the patient comorbidity. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HF, heart failure; IHD, ischemic heart disease.

(voluntary prolongation of hyolaryngeal elevation at the peak of the swallow). During rehabilitative techniques, the speech-language pathologist educates the patient in adopting new postures such as turning the head to one side or placing the chin down while swallowing. They also initiate therapeutic exercises comprising of progressive strengthening and coordination of swallowing muscles, which are also involved in voice recovery (38, 76).

Nutrition therapy

Nutritional status is an important factor in recovery from critical illness. Upon discharge from the ICU, patients usually present with a condition of malnutrition associated with poorer functional outcomes including severe skeletal muscle loss (45). Therefore, severe COVID-19 survivors should be screened for malnutrition risk. Several studies (64, 77, 78) have reported that nutrition therapy based on protein delivery, combined with appropriate rehabilitation, can maximise muscle protein synthesis and reduce ICU-AW.

Cognitive training

Severe COVID-19 survivors are most likely to develop cognitive problems after a long LOS in ICU. The treatment of ICU-acquired delirium is challenging, generally based on a range of preventive measures that must be considered at the earliest stage of ICU treatment (62). These measures aim at using – when possible – short-acting sedatives, light sedation

protocols, patient's reorientation, sleep hygiene, hypoxemia management, minimising pathologic changes in blood pressure, daily spontaneous awakening trials and spontaneous breathing trials, early mobilisation, and family engagement and empowerment (79). A cognitive rehabilitation approach comprises of techniques to remediate the loss of attention, memory (visual imagery exercise, notebooks or computerised activities), problem-solving ability (learn to monitor, manage and regulate the orderly 'execution' of goal-directed ADLs), as well as comprehension (paraphrasing exercises, repeating messages back to the therapist or using adapted handouts to ensure the patient's understanding) (46, 80).

Psychological support

An aspect of great value in the management of all COVID-19 patients, it should be considered at all stages of the course of disease and recovery. Physicians and nursing staff should try to build an empathic, compassionate therapeutic alliance with the patient and family, either during the isolation period or the acute phase of the disease (45). Regular video conferencing or telephone communication is required to establish and maintain the connection between the patient and their family, as well as between healthcare providers and the family (22). Early rehabilitation during ICU in patients with critical illness did not show a significant improvement in the long-term mental outcomes, whereas ICU diaries were written or recorded by a patient or a medical person may have prevented PICS by alleviating anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms (45). After hospital discharge, intentional follow-up of the patient's health status via telephone would provide a needed emotional security for the patient who may feel abandoned or distressed (22). Counselling sessions may also be considered (39).

Patient–family education

- Recovering from COVID-19 is an opportunity to offer smoking cessation advice for active smokers (62).
- Patients with remained impaired bronchopulmonary secretion clearance should be taught techniques favouring secretion removal (39).
- Dietary advice should be addressed to patients who are obese or have a low body mass index (62).
- Patients should be encouraged to continue general exercise between supervised outpatient sessions and after completing rehabilitation in order to sustain the beneficial effects of PR (75).
- Patients should improve their quality of sleep by taking regular rest and ensuring sufficient time for sleep (28).
- Survivors of severe COVID-19 and their families should be informed about the features of PICS and its effects on the patient and their family, the long process of recovery,

the importance of caregiver involvement in treatment and the potential therapeutic strategies that may reduce PICS's impact (46).

- The educational approach must consider the cultural and educational backgrounds of the subjects, and any physical (e.g. hearing or sight impairment) and/or cognitive barriers (75).

Conclusion

Varying disabilities including pulmonary, neurological, cardiac, musculoskeletal, cognitive and psychological, as well as dysphasia have been observed among patients who survived critical care, related either directly to COVID-19 or ICU treatment. Some of these disabilities have also been reported in patients who recovered from mild or moderate forms of the disease, as well as in those who were asymptomatic. PR is deemed to be mandatory to prevent or improve these impairments, whether in the short- or long-term course of recovery. A comprehensive assessment is essential in order to first prescribe an individualised rehabilitation treatment and, second, to identify the appropriate care setting for rehabilitation referral.

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