Medical Research Archives

ESMED European Society of Medicine

OPEN ACCESS

Published: May 31, 2022

Citation Kortianou EA, Mavronasou A, et al., 2022. Practicalities for Exercise Prescription in Long-COVID-19 Rehabilitation. A Narrative Review, Medical Research Archives, [online] 10(5).

https://doi.org/10.18103/mra.v10i5.2801

Copyright: © 2022 European Society of Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: https://doi.org/10.18103/mra.v10i5.2801

ISSN: 2375-1924

REVIEW ARTICLE

Practicalities for Exercise Prescription in Long-COVID-19 Rehabilitation. A Narrative Review

Eleni A. Kortianou[1], Aspasia Mavronasou[1,2], Vaia Sapouna[1]

[1] Clinical Exercise Physiology & Rehabilitation Research Laboratory, Physiotherapy Department, School of Health Sciences, University of Thessaly, Greece.

[2] 1st Department of Critical Care and Pulmonary Medicine, Pulmonary Rehabilitation Unit, National and Kapodistrian University of Athens, Evangelismos General Hospital, Greece

* ekortianou@uth.gr

ABSTRACT

Many COVID-19 survivors worldwide suffer from persistent symptoms, impaired functional capacity and quality of life. Rehabilitation exercise interventions for the long-term physical consequences of coronavirus disease 2019 (COVID-19) are currently being reported. As a result, the clinical practice and research focus on interventions that support recovery from ongoing symptomatology, independently to hospitalization. To date, the outpatient rehabilitation programs offer various exercise modes and training intensities for people recovering from long-term symptomatology of COVID-19.

This narrative review summarizes previous studies that used exercise training protocols at the outpatient rehabilitation setting, presents the effectiveness of training on the functional outcomes and provides practical issues of the application of exercise training which overcome possible respiratory and peripheral muscle limiting factors of exercise and functional capacity for patients with Long-COVID-19. To this end we make recommendations on how better to implement exercise training in future studies so as to maximize training effects.

Due to lack of randomized trials, more research is needed in the field of the exercise training modalities that are more effective and in parallel more tolerable for patients with persistent post-COVID-19 symptoms. In this context, interval training mode with short exercise periods can prevent high lactate accumulation and allow more intense exercise stimuli to the deconditioned peripheral muscles with minimal cardiac strain and exercise-induced hyperventilation, thus improving exercise capacity in this patients' population.

Keywords: COVID-19, post-COVID-19, exercise training, rehabilitation, physiotherapy

1. Introduction

The announcement of the pandemic by the World Health Organization (WHO) for the coronavirus disease 2019 (COVID-19) there was straightaway followed by great interest of the clinicians on the impact of the disease on patients' physical and functional capacity. Therefore, the first rehabilitation instructions for inpatients and outpatients survivors were published[1]. To date, there is a considerable body of recommendations on the rehabilitative strategies that are needed for managing physical and cognitive limitations and psychological effects in people who were infected from SARS-Cov-2 and mainly to those who present an ongoing symptomatology after hospitalization[2.3]. The WHO suggested the definition of "post-COVID conditions" in order to describe the symptomatology that usually occurs 3 months from the onset of COVID-19 and cannot be explained by an alternative diagnosis[4]. Furthermore, the National Institute for Health and Care Excellence (NICE) suggested the term "Long-COVID-19" to describe the signs and symptoms that continue or develop after acute COVID-19 and it includes both the ongoing symptomatic COVID-19 (for signs and symptoms lasting 4-12 weeks after infection) and the Post-COVID-19 syndrome (for symptoms lasting more than 12 weeks from the onset of COVID-19)[5]. Although the majority of patients recovers almost in one month after infection, some patients are diagnosed with COVID-19 related complications for longer than 6 months after acute illness and they experience from 1 up to a mean of 14 symptoms[6]. Furthermore, relapse of symptoms occur in irregular patterns up to 7-9 months from acute illness. Physical activity limitations were profound at 71% and inability to exercise at 55%. Moderate to severe problems on daily physical activities are reported at 6 months follow up, while 22% of unrecovered individuals are not working due to their physical inability at 7 months follow up[5]. Post-COVID symptomatology may be presented in people with mild disease through to those hospitalized with severe critical disease[7]. Symptoms may be persistent from the time of the initial infection or may be presented later and can be fluctuating or remitting over time[8]. Post-COVID symptomatology can have an impact on daily living and physical activities[9]. Common symptoms that influence patients' physical capacity include fatigue, dyspnea, cardiac and respiratory abnormalities (e.g. chest pain, autonomic dysfunction, myocarditis), post-traumatic stress disorders, muscle pain and headache[10,11]. Specially designed COVID-19 clinics and outpatients rehabilitative services may support feasible and effective interventions to those individuals who are in need of follow-up care[12-24]. Despite the limited published evidence on what exercise interventions will benefit people who present post-covid-19 symptomatology, it is recommended that physiotherapists, as members of a broad multidisciplinary team, should encourage physical activity and support healthy lifestyles programs for people recovering from COVID-19[25]. To this aim, a Covid-19 rehabilitation prospective surveillance model for detecting any physical and psychological impairments in patients with post-Covid-19 syndrome has been recently published by experts in the cardiorespiratory, neuromuscular, mental health and functional disability,[26] in order to implement effective rehabilitative interventions. Until solid evidence will suggest the best practice management for symptomatology of long-COVID-19 syndrome,[27] the exercise training approaches follow the structure of the basic rehabilitation programs designed for chronic respiratory and cardiac patients[29,30].

Therefore, the main purpose of this review article is to summarize the current stage of practice on the basic structure and outcomes of an outpatient rehabilitation program for adult patients with long-Covid-19 syndrome. To this end, we make recommendations on how better to implement exercise training in this patient population for mitigating possible respiratory and peripheral muscle limiting factors to exercise capacity.

2. Rationale for exercise for long-COVID-19 patients

According to the available evidence, the most frequent self-reported symptoms during follow-up at 3 months after symptom onset, even in the middle-aged population (mean age of 50 years) mostly without serious comorbidities and normal physical examination, are fatigue and dyspnea, described by 60-87% and 60-71% of patients, respectively[30,31]. The modified Medical Research Council scale (mMRC) and the New York Heart Association (NYHA) functional scale are used to assess dyspnea during daily activities in patients with long-COVID-19.

Irrespectively of hospital admission, cured infection and normalization of inflammatory markers, persistent dyspnea is more profound in daily activities[7] and it is translated to lower functional capacity, as assessed by the total distance covered during the 6-Minute Walk Test (6-MWT)[32,33]. It is debated if persistent dyspnea is always associated with abnormal lung function[30,33]. For instance, some studies have shown that patients with persistent dyspnea reveal normal pulmonary function (normal spirometry and lung diffusion capacity values) 3 months after hospital discharge[33,34] and other findings show that at a period between 30 to 90 days after the onset of acute COVID-19 symptoms, patients with persistent dyspnea present low spirometry and lung diffusion capacity (DLco) values, similarly with low functional capacity (low % predicted distance covered at 6-MWT) and exercise-induced desaturation[30]. Some authors attribute the dyspnea to the ventilatory inefficiency, mainly due to a potential ventilation/perfusion mismatch[30]. Others, suggest that enhanced chemoreflex sensitivity and/or increased dead space[35] mainly account for the hyperventilation syndrome[36] and cause dyspnea in daily activities. In the study of Barrato et al.,[35] patients with COVID-19 presented increased dead space ventilation at rest (VD/VT= 0.63) compared to that measured at the peak of exercise (VD/VT= 0.38) during a cardiopulmonary exercise test (CPET), indicating that resting hyperventilation contributes mainly at breath discomfort.

Given the potential impact that the virus has on the cardiac, pulmonary and skeletal muscle systems, it is evident that the cardiorespiratory fitness can be compromised following SARS-Cov-2 infection. Therefore, any circulatory impairment, ventilatory inefficiency or peripheral muscle deconditioning could explain some of the limitations in exercise capacity in patients with long-covid-19 syndrome symptomatology[34,37,38]. In this context, CPET remains the gold-standard to provide the most comprehensive and accurate assessment of all limiting physiological factors of exercise capacity, either on hospital discharge[32,35] or at a period longer than the 3 months from the onset of infection[33,34,38,39]. Several studies explored limitations in exercise capacity during CPET implementation, at 3 months post-discharge (mean age 55 years) and revealed that those who report mainly dyspnea during activities of daily living (mMRC: 1 to 4, or NYHA ≥ II) have a percent-predicted peak oxygen consumption (VO_2peak, % predicted) less than 80-85% ranging from 13 to 24 ml O_2/kg/min[33,34,38,39]. Those patients who reported persistent dyspnea, revealed an impaired ventilatory efficiency (quantified by higher ventilation/carbon dioxide production, VE/VCO_2 slope) compared to asymptomatic subjects who had previously hospitalized for COVID-19, suggesting a potential ventilation/perfusion mismatch[33,34].

The pulmonary vascular response to exercise does not present major pathological change at a 3-month or at a 6-month follow-up, and may not be responsible for exercise limitation, in symptomatic or non-symptomatic patients, as the pulmonary vascular pressure (indicated from the Right Venus Systolic Pressure) remains in relative low levels (15-24 mmHg)[33,35]. Interestingly, even for hospitalized patients in ICUs, 6 months after discharge, the pulmonary vasculature (as assessed by $P(A-a)O_2$ and arterial blood gases at exhaustion) was not the major causes of physical limitations to exercise[37].

The inflammatory load of the initial SARS-CoV-2 infection ensuing cytokine storm and the hypothesis of sustained and prolonged systemic inflammation in COVID-19 survivors potentially explains the persistent systemic complaints such as body weakness, fatigue and myalgia[32]. Fatigue may be due to either systematic inflammation, in anemia or in muscle deconditioning[32,35].

Notably, in the study of Aparisi et al.,[33] there were no significant differences in hemoglobin (median value for both groups 14 g/dL) and in all the inflammatory indices (CRP, IL-6, ferritin and D-dimer) in patients with persistent daily fatigue, compared with asymptomatic patients at a follow-up of 3 months after hospital discharge. Additionally, there were no significant differences in lung diffusion capacity (DLco), neither desaturation nor differences in breathing reserve were detected during the CPET, suggesting that the lower aerobic capacity in symptomatic patients attributed to peripheral muscle factors.

Similarly, at the time of hospital discharge, impaired exercise capacity (as assessed by a CPET) was mainly related to peripheral muscle factors (oxygen extraction) rather than respiratory or cardiac limitations[35]. Furthermore, at the peak of exercise, the exercise-induced hyperventilation was due to enhanced chemoreflex sensitivity (lactate at peak exercise: 3.5 versus 1.0 mmol/L at rest), rather than the increased VD/VT at rest (VD/VT=0.38)[35]. At the same post-discharge period, the 50% of patients of a large cohort of 200 Covid-19 survivors (median age 58.8 years) showed limitation in exercise capacity (percentage predicted VO_2<85%) and the vast majority (82.5%) declared leg fatigue as the reason for interrupting the CPET. Furthermore, authors reported a modest positive correlation ($r=0.36$, $p<0.001$) between peak VO_2 and maximal strength of the lower limb muscles, suggesting that to some degree the muscle deconditioning might be responsible for the most of the exercise limitations[38]. The muscle deconditioning is evident even at 6 months following hospitalization in ICU for COVID-19[37] and it is the major cause of mid-term impairment in physical fitness[33,34].

3. Candidates for exercise rehabilitation

It is recommended by the consensus of the NHS, the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP) that a proactive follow-up at 6 weeks after discharge should be provided for checking new or ongoing symptoms and complications[5,16]. Although conclusive evidence is not yet available, candidates for inclusion in an outpatient rehabilitation program are all patients recovering from COVID-19 disease and suffering from limitations of physical capacity and associated symptoms[6,8]. Actually, in this context, all the rehabilitation programs were applied for patients with post-covid-19 symptomatology starting between weeks 4 to 8 after hospital discharge[13,15,16,18,19,21,24]. To the best of our knowledge only one study implemented physical conditioning exercise for non-hospitalized patients via videoconferences[40].

The proposed by Postigo-Martin et al.,[26] prospective surveillance model for detecting any rehabilitative need in patients with post-covid-19 syndrome, includes reliable tools for making necessary assessments and suggests cut-off points as inclusion criteria for rehabilitation. Particularly, patients are suggested to start a rehabilitative exercise program when they present low aerobic capacity ($VO_2 \leq 15$ ml/kg/min as evaluated at the CPET) and limited functional capacity (<350 meters distance covered at the 6-MWT). Additionally, respiratory muscle training is suggested when respiratory muscle weakness is profound (Maximum Inspiratory Pressure - Maximum Expiratory Pressure <65-80% of the predicted values).

Practically, the Post-COVID-19 Functional Status Scale (PCFSS ≥2) and the modified British Medical Research Council dyspnea score (mMRC ≥2) are useful tools for the health professionals to identifying those patients who might be in need and consequently might benefit from an exercise rehabilitation program[12]. Patients with sarcopenia (skeletal muscle loss) are also candidates for exercise training[22]. Patients with active COVID-19 should not be included for exercise training. Additionally, patients with uncontrolled hypertension, severe lung and heart disease, myocarditis, cardiac chest pain, history of severe cognitive or mental disorder, any musculoskeletal disability or injury, recent surgery of lower extremities, neurological conditions that cause disability, end-stage diseases (e.g. end-stage cancer) should be excluded or directed to other forms of interventions[25]. For unsupervised interventions, patients with mMRC dyspnoea over 3 it is considered to be excluded for safety reasons[19].

4. Baseline Assessment of physical capacity

In order to exclude all contraindications of exercise, a comprehensive physical assessment is needed before entering an either supervised or unsupervised rehabilitation program. As most post-COVID-19 patients have not reached full recovery at three months,[38] a clinical history assessment and an appropriate physical examination which includes assessment of physical, as well as functional capacity should be done. Before referral, all individuals are suggested to have pulmonary function tests combined with dyspnea (mMRC) and echocardiogram. Spirometry and diffusing lung capacity for carbon monoxide abnormalities encountered more profoundly among patients who were hospitalized with severe/critical disease[41] or among non-critically ill, non-hospitalized patients who tested positive for SARS-CoV-2[30]. Therefore, it seems reasonable to investigate DL_{CO} at the baseline to exclude the cause of exercise-induced hypoxemia. An echocardiography at rest or during exercise testing may exclude possibly increased pulmonary pressure or a silent heart disease, mainly presented in patients who were treated with noninvasive ventilation during hospitalization[35].

Blood test is carried out to rule out anemia that may limit patients' exercise capacity[42]. C-reactive protein, Interleukin-6, D-dimer, ferritin and B-type natriuretic peptide (BNP) are suggested to be measured for an integrated clinical assessment[43].

The symptom-limited cardiopulmonary exercise testing, using a treadmill or a cycle ergometer, is proposed as the gold standard for the assessment of the physiological limitations (ventilatory, cardiac, and metabolic) during exercise and therefore, facilitates decision making for participation in a rehabilitation exercise program[16].

An important observation in all studies was that, after a 3-month post-covid-19 onset, all the patients were able to complete the CPET on a cycle ergometer with increased intensity without any complications. Although CPET may give extended useful information on exercise limiting factors, wherever this is not possible, the 6-min walk test (6-MWT) may also be considered a good indicator for physical function in patients with post-covid-19 symptomatology,[41] such as it is in other diseases[44]. The assessment of physical capacity using submaximal tests (e.g. the 6-MWT) may be more representative, since fatigue and dyspnea are reported as persistent symptoms in daily life activities,[6] which are usually activities at submaximal movement intensities.

A recent mapping review on the measures of physical performance, identified 31 studies and addressed the most commonly tests used in COVID-19 patients in outpatient rehabilitation settings[45]. Functional impairment can be assessed at 4-6 weeks post-discharge with appropriate tools, such as the six-minute walk test (6MWT), the 2-minute walk test (2-MWT), the 1-minute sit-to-stand test (1-min STS) and the Short Physical Performance Battery (SPPB). In all the aforementioned tests, lower values were reported in post-COVID-19 patients compared to normal reference values[45]. The 6-MWT is the most used test at a period of the follow-up (1 to 6 months post-discharge) probably because it may indicate accurately any functional limitations[45] and exercise-induced desaturation in post-covid-19 population[24,41]. In a study it was the main functional parameter as an inclusion criterion for rehabilitation entry (e.g., the distance covered was below 70% of the predicted value)[16]. A cut-off value of 350 meters of walking distance is proposed for entry in an outpatient rehabilitation program,[26] however, in some rehabilitation studies the functional ability (as measured by the distance covered at the 6-MWTs) was lower (e.g., <250 meters)[17,23]. By using the distance covered on the 6-MWT, an estimation of the peak oxygen uptake can be made[24] as well as a guidance for the exercise training intensity that can be followed[23].

Another submaximal exercise test, suited to the post-COVID-19 patients' functional performance, is the 1-minute sit to stand test. Either assessed face-to-face[11,13,20] or remotely[18] it gives information regarding hemodynamic and subjective responses and therefore, it serves as a basis of prescription and evaluation of improved exercise capacity. During all functional tests the exercise-induced level of breathlessness and fatigue are assessed using the Borg scale (0-10). It is also crucial that heart rate and oxygen saturation are measured, since the exercise-induced desaturation has been associated with exercise limitation[24,41].

Respiratory muscle assessment using the maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) is suggested, as values lower to 65-80% of the predicted are considered pathological[46]. Survivors with persistent dyspnea (mMRC ≤2) 6 months after discharge, present MIP values ranged from 30-97% of the predicted values,[37] with those patients who were treated in the ICUs presenting more profound weakness. However, only in one rehabilitation program the MIP and MEP values were assessed at baseline and at a 3-month follow-up of a tele-supervised home-based exercise training program, indicating improvement following a general, non-specified to the respiratory muscle, training program[15].

Quadriceps muscle strength assessment is also suggested as its strength is associated with functional performance in post-COVID-19[11]. Additionally, postural symptoms assessment such as palpitations or dizziness on standing, lying and standing heart rate and blood pressure should be carried out (using the 3-minute active stand test for orthostatic hypotension)[47]. Nutritional evaluation, body mass index (BMI) and free fat mass index (FFMI) could also be assessed for indicating further needs for special exercise training (e.g., adding more resistance training exercises)[1].

Collectively, given that pulmonary function abnormalities may be present even in asymptomatic individuals, it seems reasonable that all patients who are referred to exercise training should have a baseline respiratory as well as cardiopulmonary and functional screening. The assessment of patient-reported outcomes using Borg and modified Medical Research Council (mMRC) dyspnea scales, as well as health-related questionnaires should be also pursued.

5. Safety precautions

For safety purposes, each outpatient rehabilitation unit follows a protocol set by the infection prevention and control department of the hospital. Before entering the rehabilitation unit patients must present a negative rapid antigen detection (Rapid test) for SARS-CoV-2, done within the last 24 hours. Symptoms and thermometry check should take place before each session and patients with active symptoms (such as fever, cough or snuffles) should be excluded from any exercise session. All the medical staff should use appropriate personal protection equipment (gloves, KN95/FFP2 face masks) during the entire training session. Each device of the equipment should be disinfected with alcohol before every use, as per guidelines[48]. It is recommended that patients and staff should have access to soap and napkins for proper hand washing.

When groups of patients exercise together, it is suggested that the training equipment (e.g. cycle ergometer, treadmill) should be surrounded by Plexiglas, making a distance of at least 2 meters between the equipment, allowing patients to be exercise without a facial mask. When the rehabilitation program is provided individually (e.g. in case of the production of aerosols from patients) patients are suggested to wear protective masks, wherever it's feasible and to keep social distancing (>2 m).

To the best of our knowledge, contraindications for exercise session initiation have not been published for patients with post-covid-19 symptomatology. However, on the beginning of an exercise session, some of the following signs are considered important to be measured, since hypertension and diabetes are common comorbidities: resting heart rate >100 beats per minute or <50 beats per minute, blood pressure ≥160/100 mmHg or ≤90/60 mmHg, SpO2 ≤94%. Blood glucose should be monitored before and after each session if insulin or oral medications are been prescribed, since exercise-induced hypoglycemia can occur up to 6 hours after the cessation of the exercise session[49].

During the whole exercise session all patients should be monitored for exercise-induced hypoxemia using pulse oximetry. Criteria for stopping or reducing exercise intensity are an oxygen saturation (SpO_2) < 90% and dyspnea symptoms (Borg ≥ 6). Whether a drop ≥ 3% in SpO_2 is observed, oxygen should be added with a maximum of 6–8 L per minute via nasal cannula to maintain the SpO_2 > 90% [12,15].

Termination of exercise session is indicated if any of the following occur: difficulty or shortness of breath with no relief after resting, chest pain or tightness, dizziness, headache, blurred vision, palpitation, unable to maintain balance.

6. Exercise Prescription

The main features of an outpatient rehabilitation program has been previously presented[2]. Rehabilitation programs are being evaluated in ongoing clinical studies and being validated for both their safety and effectiveness. To date, several studies engaged small (10<n<40)[12,14-16,18,20,21,24,40] or large (50<n<140)[13,19,22] cohorts of post-covid-19 patients in exercise rehabilitation interventions, based on the principles of pulmonary, cardiac, neurological and musculoskeletal rehabilitation (Figure 1). The mean age of the participants ranged from 39 to 64 years. Practically, in those studies,[12,13,16,18-22,40] a structured approach to exercise prescription described by the American College of Sports Medicine (ACSM) was used[50]. This involves recommendations regarding the frequency (F), the intensity (I), the exercise duration or time (T) and the exercise type or mode (T), often known as the FITT components. A variety of the aforementioned parameters were used.

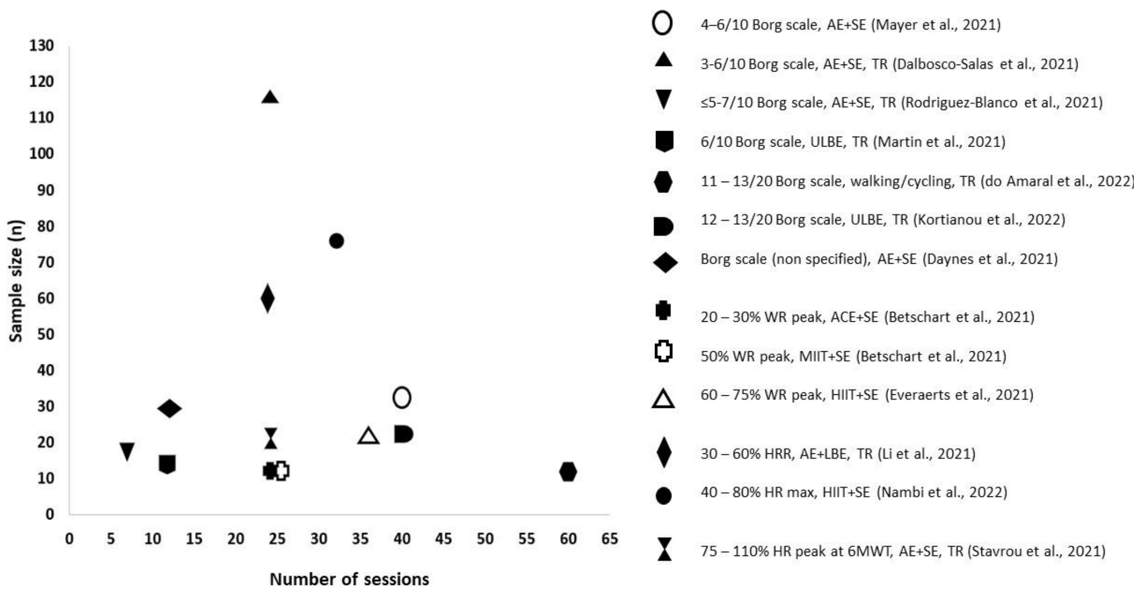

Figure 1. Number of exercise training sessions and sample size (n) for the rehabilitation studies in outpatients with post-COVID-19 symptomatology. Each symbol represents one study. Exercise intensity training was based on: Borg Scale, peak work rate (WRpeak), heart rate reserve (HRR), estimated maximum heart rate (HRmax), heart rate peak at the 6-MWT. AE: aerobic exercise; SE: strengthening exercise; TR: telerehabilitation; ULBE: upper and lower body exercise; ACE: aerobic continuous exercise; MIIT: moderate intensity interval training; HIIT: high intensity interval training; LBE: lower body exercise.

In all the aforementioned studies it was emphasized that exercise programs were widely accepted by all the patients. Usually, the exercise programs consisted of performing moderate strength and endurance exercise for 10–30 min duration or included recreational gymnastics, stationary bicycle and arm ergometer.

The mode of exercise: The majority, used a combination of aerobic and resistance exercise training. The type aerobic exercise was either continuous[13,21] or interval[16,22] or a combination of both[12]. Treadmill, cycle ergometer, arm ergometer and stair climbing or steps, or aerobic exercises for upper and lower limbs were performed, along with resistance training of lower and upper limbs (Figure 1). Usually, when patients were not able to perform continuous training for more than 10 min, on a standard intensity (e.g. 70-80% of their maximum work load), an interval training mode was implemented[12,16]. Resistance training was preferred because of its low risk for cardiorespiratory complications[51]. The optimum resistance required for the muscle groups were decided based on ten-repetition maximum (10 RM) and the muscles were mainly trained according to the DeLorme method[23].

The intensity of exercise: In all studies and for the whole exercise prescription process the following variables were used for describing the exercise intensity: the Borg scales (0-10 or 6-20),[13,15,16] the percentage of heart rate reserve (% HRR), the peak work rate (WRpeak),[12] the oxygen uptake reserve or the percentage of the maximum heart rate (% HRmax) (Figure 1)[22]. For those subjects with post-COVID-19 symptomatology who had low exercise capacity (VO_2peak <85% predicted)[12] or low functional capacity (baseline 6-MWT distance <200 m), the intensity of exercise training was equal or less than the intensity corresponding to anaerobic threshold (AT) and an aerobic low-intensity interval program was chosen[22]. Exercise intensity close to AT (<60% VO_2peak, exercise HR intensity around 100 beats/minute) are well tolerated by the patients for a training session duration of 30 min[12,19] and could be applied with safety in this patients' population either at face-to-face[12] rehabilitation or at telerehabilitation[18,19]. Low-intensity (40%–60% of HRmax) or high-intensity (60-80% of HRmax) aerobic exercise combined by resistance training were also used in COVID-19 patients with sarcopenia (aged over 60 years old, Fat Free Mass Index < 7 kg/m^2) with comparable results in lower limb muscle cross-sectional area improvement (measured by a magnetic resonance) in both groups[22]. The results suggest that either low or high-intensity aerobic training combined with resistance training improves the physiological characteristics of the lower limb muscles at the end of the training period (8th week) and at a 6-month follow-up.

In some studies, when patients were not able to sustain exercising for more than 10 minutes of continuous training at high intensity (e.g. 80% of the maximal work load during CPET), an interval mode was preferred (starting at intensities 60-75% of peak work load) aiming to increase the benefits of exercise training[16]. In a population of post-covid-19 patients (n=12) with a wide range of age (26-84 years), a mixed exercise program consisting of 2 sessions of low intensity (20-30% of peak Work Rate) continuous mode followed by two sessions of higher intensity interval mode (alternating 3 min at 20-30% WRpeak to 4 min at 50% of WRpeak) was tolerable for the requested training duration of 30 min[12]. Authors claimed that the progressive increase in the training intensity (as adjusted to reach a perceived exertion of 4-6/10 on the Borg scale) was achieved in 9 out of the 12 patients and they demonstrated significant improvement in their functional capacity (80-170 meters improvement from baseline to post-training assessment at the walking distance of the 6-MWT).

For the resistance training, exercise intensity started at 50-85% of 1 repetition maximum (1-RM) and it was adjusted progressively up to reaching a perceived exertion of fatigue between 3-6 on the Borg Scale (0-10). Total resistance training duration ranged from 20-40 minutes[12,13,15] and included multi-joint exercises using bodyweight, rubber bands, dumbbells, plastic bottles, for 1-3 sets of 8-12 or 15 repetitions per session.

Exercise duration at each session: When training consisted of a combination of aerobic endurance training followed by resistance training, one hour sessions was equally divided between modes[16].

In all studies a progressive overload for the aerobic training was obtained by increasing both exercise intensity and duration, based on perceived symptoms exertion scores (target dyspnoea / fatigue scores between 4–6 on the Borg scale, 0-10)[12,16]. No study used vigorous-intensity exercise (>85% of the peak HR achieved at the CPET) greater than 5 days per week, as this might increase the incidence of musculoskeletal injury and oxidative stress[52].

Frequency of exercise (i.e., the number of days per week) ranged from 2 to 6 days, with total number of exercise training sessions from 10 to 60 (Figure 1) at a training period of 2 to 3 months for supervised, face-to-face training[12,14,16,17,21,22] or unsupervised,[18,19,24] or, telerehabilitation training[13,18,19,24,20,40]. In some studies[13,14,20] two sessions per week were applied, with the frequency varying with the intensity of exercise.

7. The main functional benefits from exercise training

A recent systematic review analyzed 6 studies with total 264 patients with post-COVID-19 symptomatology (58 of them non-hospitalized), aged from 20 to 84 years, for detecting the effects of aerobic and resistance training on functional capacity[53]. Only, four functional tests were reported, the 6-MWT (in 3 studies), the SPPB (in 2 studies), the Timed Up and Go test and the 1-minute sit to stand test (in 1 study). Although a clinically significant improvement demonstrated in 6-MWT (>30 m), in 1-min STST (>2.5 repetitions) and in SPPB (>1 points), the normal predicted values of functional capacity were not achieved in all studies[53]. Figure 2 shows the improvement (Delta) at the distance covered at the 6-MWT after the exercise training programs. The normal predicted values in 6 minute walking distance were achieved only when high-intensity training was followed for a 3-month training period, indicating that the total exercise load is fundamental for better functional adaptations[12,16]. Future high-quality randomized controlled trials are required to investigate whether more intense exercise training and/or longer training period or a most appropriate time point of implementation of exercise are needed to achieve better functional outcomes. Remotely supervised home-based exercise programs have been recommended and supported by several studies as an innovative strategy for implementing therapeutic exercise[13,15,20,21,40] with comparable functional results with the face-to-face rehabilitation[21] and better results than non-rehabilitation[15,40].

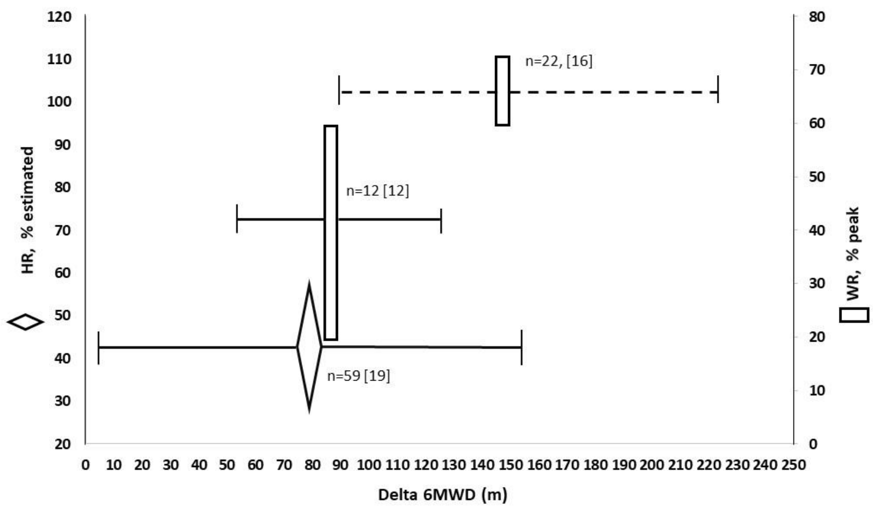

Figure 2. The improvement [Delta: post-pre rehabilitation] for the distance (6MWD) covered at the 6-Minute Walking Test, after the exercise training programs as given by each study [reference number is in brackets]. Rhombus: the exercise intensity was based on heart rate reserve determined by Karvonen's formula (HR, % estimated). Rectangles: the exercise intensity was based on % peak work rate at a cardiopulmonary exercise test (WR, % peak). Solid lines represent standard deviations of the mean values [refs 12 and 19]. Dashed line represents the 25-75 interquartiles of the median value [ref 16]

8. Practical Issues and Recommendations

Exercise training in patients with post-COVID-19 symptomatology aims to increase the aerobic capacity with a relative tolerable muscle effort and low demand on respiratory and circulatory system. So, researchers are encouraged to identify effective rehabilitation interventions tailored to the heterogeneous and multi complex patients' phenotype. Given that the intensity and the duration of exercise are important determinants of the physiologic adaptations that occur in response to training[54] and the fact that in patients with chronic respiratory and/or cardiac diseases there are indications that greater physiological benefits can be obtained through high-intensity compared to moderate-intensity training,[55] it could argued that in the rehabilitation setting, exercise strategies at high-intensity training could be more effective for some functional and physiological outcomes also, in post-covid-19 patients. In support of the above argument, the study of Everaerts et al.,[16] used high-intensity interval exercise (>75% WRpeak), 3 times per week, 1.5 hours per session for 3 months, in patients (n=22) who were discharged from hospital (15 patients were treated in the ICU). Patients achieved much improvement in the distance covered during the 6-MWT (90-221 meters, 76-91% of the predicted) and in the quadriceps muscle strength (post-rehabilitation values ranged between 71-87% of the predicted) (Figure 2). Interval training mode with short exercise periods (<30 sec), in healthy elderly[56] or patient populations[57,58] has shown that it can improve exercise capacity, prevent high lactate accumulation and allow more intense exercise stimuli to the peripheral muscles with minimal cardiac strain[58] and exercise-induced hyperventilation[57]. Practical recommendations for implementation of such high-intensity interval training on a cycle ergometer, in chronically ill patients has been previously reported[59].

Before establishing specialized exercise programs in post-COVID-19 patients, there is a need to test the exercise type that patients could be able to sustain without any risks of medical health complication and ensure that this will be adapted to the physical limitations of each participant.

Therefore, physiotherapists who develop an exercise plan should consider that the heavier the work rate, the shorter should be the exercise periods (~30 seconds) and also, the longer the rest intervals (~30-60 seconds) ought to be. Exercise training bouts as short as 30 to 60 seconds do not exacerbate the ventilatory requirement, as lactic acid concentration and its effect on arterial blood pH are significantly lower compared to moderate intensity constant-load exercise[57]. Consequently, patients may complete the total work in moderate exertion (less leg fatigue) and relatively stable metabolic (arterial lactate concentration less than 4 mmol/L) and ventilatory response[57]. As it was followed in some previous studies,[12,16] we believe that the implementation of interval exercise training should be based on the intensity of the leg discomfort (e.g. using the Borg Scale 0-10) up to the limits of heavy perception (5-6/10) and the exercise duration for each session should be kept similar to previous studies (e.g. 30-40 minutes)[12-24]. However, the amount of the targeted training work to be achieved is greater than that of continuous exercise by alternating the exercise and the rest periods. Additionally, the magnitude of peripheral muscle adaptations to interval training might be superior to those achieved with continuous exercise training. The training load can be increased 5-8 watts for the next few sessions when perceived exertion of leg fatigue scores at 4-5/10 at the Borg Scale and heart rate is monitored as safe (a limit of 75% of the predicted maximum heart rate)[12]. During the 30-second breaks, when patients focus on breathing techniques without being interfered by cycling exercise, physiotherapists can teach them to adopt pursed-lips breathing to promote improvements in tidal volume, arterial saturation and decrease end-expiratory lung volume, thus reducing breathlessness during exercise[60]. Breathing control techniques were implemented in some studies[16,23] as a main component of the exercise program aiming to decrease breathing frequency and increase tidal volume. Pursed-lips breathing and breathing control exercises (diaphragmatic breathing), should be demonstrated comprehensively at the beginning of the training period and their performance should be checked regularly in order to improve hemodynamic status[61] and to avoid possible exercise-induced hyperventilation[62]. As, resistance training is prescribed to all the patients, the optimum resistance required for the major muscle groups (shoulder flexors, extensors and abductors, elbow flexors and extensors, hip flexors and extensors, knee flexors and extensors) are decided based on ten-repetition maximum (10 RM) and the muscles are trained progressively according to the DeLorme method[23]. To avoid any inflammatory reaction related to exercise[62] and mitigate any inflammatory load that further compromise functional capacity and exercise tolerance, patients can be regularly checked (e.g. every week) for body discomfort and the magnitude of fatigue symptoms, using the Fatigue Severity Scale (FSS)[63]. Scores ≤ 36 units are considered safe regarding the imposed exercise load[63].

9. Research Recommendations

From our point of view, two topics are considered interesting and we recommend for future research, possibly designed for randomized control trials (RCTs).

Firstly, as tele-rehabilitation gains pathway, remote assessment using digital communication technologies offers a quick and promising option for assessing rehabilitation needs as well as patients' physical capacity. Therefore, various assessment tools such as functional tests (walking, balance, step, performance tests) should be validated for remote use. Under the current pandemic-related circumstances, few studies[18] have used some performance tests for assessing remotely patients' capacity, however the validity of the remote use has not been previously examined. Therefore, when functional tests can be reliably performed remotely, using digital communication technologies, the delivery of an integrated tele-rehabilitation approach will help therapy in situations such as this. In this context future validity studies are needed.

Some recommendations for future RCTs on exercise-based treatments for post-COVID-19 syndrome may give practical insights about the type of exercise that should be prescribed with emphasis on exercise intensity and load management.

Intermittent exercise with short exercise periods (e.g. 30-60 sec) is shown to be effective in people with chronic disease entities characterized by peripheral muscle wasting[57,58]. Consequently, the research that focus on continuous versus interval exercise training is a challenging approach in patients with post-COVID-19 symptomatology and low aerobic capacity. Interval training may be superior to other training modalities since it enables patients to tolerate high-intensity exercise for sufficiently long periods of time with less symptoms of dyspnea and leg fatigue, as this type can endure higher rates of exercise aerobically thereby yielding very little lactate production[57]. Interval training may be followed by physically limited post-COVID-19 patients (with PCFSS>2), as it is easily tolerated by other chronic physically limited patients[57,58].

Considering the FITT components: frequency, intensity, duration or time of exercise and interval type, a cycle ergometer training might be as follows:

- Frequency: 2-3 times weekly.
- Intensity: initially patients are familiarized on the cycle ergometer at an intensity equivalent to 80% of the maximal work load achieved at the CPET, for 15-20 minutes for the first 3-4 sessions. If the 10-point Borg scale is used to describe exercise intensity, most exercise should be performed between 5 to 6 intensity for rating the leg fatigue and 3 to 4 for perceived breath discomfort (dyspnea). Training work load may be increased by 5% of peak capacity when patients rate their perceived dyspnea as moderate.
- Interval type (mode): 30 seconds exercise period with 30 seconds rest or even 30 seconds exercise – 60 seconds rest (for more physically limited individuals).
- Duration: Time may be increased from 30 to 40 minutes per session (including rest periods), at intensities that progressively reach 120% of the baseline maximum work load. Such a training program (adding the rest periods) lasts longer per session than one using continuous exercise, however the total exercise time may be equal to that at the continuous training.
- Pursed-lip breathing during rest periods is suggested to increase tidal volume and reduce breathing frequency.

When the CPET is not included at the baseline assessment, the 6MWT can be used as an alternative exercise test that can help to address the exercise protocol. In this case the exercise intensity may be equivalent to 80-110% of the maximal heart rate achieved at the 6MWT, for 15-20 minutes for the first 3-4 sessions. Furthermore, the training work load may be increased progressively until patients rate their perceived fatigue and dyspnea as moderate (up to 5 at the Borg scale 0-10).

In any control trials researchers should keep in mind that a tailored exercise program stands as an effective therapy for mitigating the related to body weakness post-COVID-19 symptomatology. The interval training, by alternating the exercise and the rest periods, may be a good option to prevent high lactate accumulation allowing more intense exercise stimuli to the peripheral muscles with minimal cardiorespiratory straining.

10. Limitations of this review

This is not a systematic review or meta-analysis that can determine and document the evidence of the exercise principles used in patients with post-covid-19 symptomatology. This was beyond the scope of this narrative review. Our aim was to look at the studies that have been done, so far and to summarize the characteristics of the exercise training programs that have been implemented, aiming to give ideas for future studies on modes of exercise training that may be more tolerable and probably effective to this patient population. Two years after the first reported cases of COVID-19, the number of randomized control trials (RCTs) and quasi RCTs regarding post-COVID-19 rehabilitation remains low. To date, studies with high levels of evidence on the effectiveness of such programs on COVID-19 survivors' functional capacity are lacking[27]. Further studies should explore the full potential of different exercise training programs in the recovery of COVID-19 survivors.

11. Conclusion

To date, there is sufficient evidence suggesting that an individualized and comprehensive exercise training should be provided according to physical limitations of each patient with post-covid-19 symptomatology. However, evidence from high-quality trials on the exercise training components and the effectiveness of different exercise programs in COVID-19 survivors is lacking. Suggestions on exercise prescription regarding practical issues may facilitate future research giving practical insights about the most efficient type of exercise, with emphasis on intensity and load management, may enable a complete functional recovery and a return to the pre-infection functional status.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare

Acknowledgements

Authors would like to acknowledge Ms Maria Siafaka, PT, MSc for participating in editing of the manuscript

References

1. Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: Interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society and American Thoracic Society-coordinated international task force. *Eur Respir J*. 2020;56(6):2002197. doi: 10.1183/13993003.02197-2020
2. Boutou AK, Asimakos A, Kortianou E, Vogiatzis I, Tzouvelekis A. Long COVID-19 Pulmonary Sequelae and Management Considerations. *J Pers Med*. 2021;11(9):838. doi: 10.3390/jpm11090838
3. Lugo-Agudelo LH, Cruz Sarmiento KM, Spir Brunal MA, et al. Adaptations for rehabilitation services during the COVID-19 pandemic proposed by scientific organizations and rehabilitation professionals. *J Rehabil Med*. 2021;53(9):jrm00228. doi: 10.2340/16501977-2865
4. World Health Organization (WHO). A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
5. National Institute for Health and Care Excellence (NICE): Clinical Guidelines. In COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19; National Institute for Health and Care Excellence: London, UK, 2020. Available online https://www.nice.org.uk/guidance/ng188 (accessed on 3 March 2022).
6. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4): 601–615. doi: 10.1038/s41591-021-01283-z
7. Bell ML, Catalfamo CJ, Farland LV, et al. Post-acute sequelae of COVID-19 in a non-hospitalized cohort: Results from the Arizona CoVHORT. *PLoS One*. 2021;16(8):e0254347. doi: 10.1371/journal.pone.0254347
8. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 Long term effects of COVID-19: A systematic review and meta-analysis. doi: 10.1101/2021.01.27.27.21250617
9. Belli S, Balbi B, Prince I, et al. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived hospitalization. *Eur Respir J*. 2020;56(4):2002096. doi: 10.1183/13993003.02096-2020
10. Fernández-de-Las-Peñas—C, Martin-Guerrero JD, Navarro-Pardo E, Rodriguez-Jimenez J, Pellicer-Valero OJ. Post-COVID functional limitations on daily living activities are associated with symptoms experience at the acute phase of SARS-CoV-2 infection and internal care unit admission: A multicenter study. *J Infect*. 2022;84(2):248-288. doi: 10.1016/j.jinf.2021.08.009
11. Paneroni M, Simonelli C, Saleri M, et al. Muscle strength and physical performance in patients without previous disabilities recovering from COVID-19 pneumonia. *Am J Phys Med Rehabil*. 2021;100(2):105-109. doi: 10.1097/PHM.0000000000001641
12. Betschart M, Rezek S, Unger I, et al. Feasibility of an Outpatient Training Program after COVID-19. *Int J Environ Res Public Health*. 2021;18(8):3978. doi: 10.3390/ijerph18083978
13. Dalbosco-Salas M, Torres-Castro R, Rojas Leyton A, et al. Effectiveness of a Primary Care Telerehabilitation Program for Post-COVID-19 Patients: A Feasibility Study. *J Clin Med*. 2021;10(19):4428. doi: 10.3390/jcm10194428
14. Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for individuals post-COVID to improve fatigue,

breathlessness exercise capacity and cognition - A cohort study. *Chron Respir Dis*. 2021;18:14799731211015691. doi: 10.1177/14799731211015691

15. do Amaral VT, Viana AA, Heubel AD, et al. Cardiovascular, respiratory and functional effects of tele-supervised home-based exercise training in individuals recovering from COVID-19 hospitalization: A randomized clinical trial. doi: 10.1101/2022.01.24.22269745
16. Everaerts S, Heyns A, Langer D, et al. COVID-19 recovery: benefits of multidisciplinary respiratory rehabilitation. *BMJ Open Respir Res*. 2021;8(1):e000837. doi: 10.1136/bmjresp-2020-000837
17. Hermann M, Pekacka-Egli AM, Witassek F, Baumgaertner R, Schoendorf S, Spielmanns M. Feasibility and Efficacy of Cardiopulmonary Rehabilitation After COVID-19. *Am J Phys Med Rehabil*. 2020;99(10):865-869. doi: 10.1097/PHM.0000000000001549
18. Kortianou EA, Tsimouris D, Mavronasou A, et al. Pilot application of a home-based exercise program combined with tele-rehabilitation in previously hospitalized patients with COVID-19. A prospective observational study. *Pneumon*. 2022;35(2). doi: 10.18332/pne/146521.
19. Li J, Xia W, Zhan C, et al. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomized controlled trial. *Thorax*. 2021;thorax jnl-2021-217382. doi: 10.1136/thoraxjnl-2021-217382
20. Martin I, Braem F, Baudet L, et al. Follow-up of functional exercise capacity in patients with COVID-19: It is improved by telerehabilitation. *Respir Med*. 2021;183:106438. doi: 10.1016/j.rmed.2021.106438
21. Mayer KP, Parry SM, Kalema AG, et al. Safety and Feasibility of an Interdisciplinary Treatment Approach to Optimize Recovery From Critical Coronavirus Disease 2019. *Crit Care Explor*. 2021;3(8):e0516. doi: 10.1097/CCE.0000000000000516
22. Nambi G, Abdelbasset WK, Alrawaili SM, et al. Comparative effectiveness study of low versus high-intensity aerobic training with resistance training in community-dwelling older men with post-COVID 19 sarcopenia: A randomized controlled trial. *Clin Rehabil*. 2022;36(1):59-68. doi: 10.1177/02692155211036956
23. Spielmanns M, Pekacka-Egli AM, Schoendorf S, Windisch W, Hermann M. Effects of a Comprehensive Pulmonary Rehabilitation in Severe Post-COVID-19 Patients. *Int J Environ Res Public Health*. 2021;18(5):2695. doi: 10.3390/ijerph18052695
24. Stavrou VT, Tourlakopoulos KN, Vavougios GD, et al. Eight Weeks Unsupervised Pulmonary Rehabilitation in Previously Hospitalized of SARS-CoV-2 Infection. *J Pers Med*. 2021;11(8):806. doi: 10.3390/jpm11080806
25. Thomas P, Baldwin C, Beach L, et al. Physiotherapy management for COVID-19 in the acute hospital setting and beyond: an update to clinical practice recommendations. *J Physiother*. 2022;68(1):8-25. doi: 10.1016/j.jphys.2021.12.012
26. Postigo-Martin P, Cantarero-Villanueva I, Lista-Paz A, Castro-Martín E, Arroyo-Morales M, Seco-Calvo J. A COVID-19 Rehabilitation Prospective Surveillance Model for Use by Physiotherapists. *J Clin Med*. 2021;10(8):1691. doi: 10.3390/jcm10081691
27. Negrini F, de Sire A, Andrenelli E, Lazzarini SG, Patrini M, Ceravolo MG. Rehabilitation and COVID-19: a rapid living systematic review 2020 by Cochrane Rehabilitation Field. Update as of October 31st, 2020. *Eur J Phys Rehabil Med*. 2021;57(1):166–170. doi: 10.23736/S1973-9087.20.06723-4
28. Randal JT, Beatty AL, Beckie TM, et al. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association and the American College of Cardiology. *Circulation* 2019; 140(1):e69-e89. doi: 10.1161/CIR.0000000000000663
29. Rochester CL, Vogiatzis I, Holland AE, et al. An official American Thoracic Society/European Respiratory Society Statement: Enhancing Implementation, Use and Delivery of Pulmonary Rehabilitation. *Am J Respir Crit Care Med* 2015;192(11):1373-1386. doi: 10.1164/rccm.201309-1634ST
30. Cortés-Telles A, López-Romero S, Figueroa-Hurtado E, et al. Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea. *Respir Physiol Neurobiol*. 2021;288:103644. doi: 10.1016/j.resp.2021.103644
31. Goërtz YM, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res*. 2020;6(4):00542–2020. doi: 10.1183/23120541.00542-2020

32. Raman B, Cassar MP, Tunnicliffe EM, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine*. 2021;31:100683. doi: 10.1016/j.eclinm.2020.100683
33. Aparisi A, Ybarra-Falcón C, García-Gómez M, et al. Exercise Ventilatory Inefficiency in Post-COVID-19 Syndrome: Insights from a Prospective Evaluation. *J Clin Med*. 2021;10(12):2591. doi: 10.3390/jcm10122591
34. Rinaldo RF, Mondoni M, Parazzini EM, et al. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. *Eur Respir J*. 2021;58(2):2100870. doi: 10.1183/13993003.00870-2021
35. Baratto C, Caravita S, Faini A, et al. Impact of COVID-19 on exercise pathophysiology: a combined cardiopulmonary and echocardiographic exercise study. *J Appl Physiol (1985)*. 2021;130(5):1470-1478. doi: 10.1152/japplphysiol.00710.2020
36. Motiejunaite J, Balagny P, Arnoult F, et al. Hyperventilation: A Possible Explanation for Long-Lasting Exercise Intolerance in Mild COVID-19 Survivors. *Front Physiol*. 2021;11:614590. doi: 10.3389/fphys.2020.614590
37. Debeaumont D, Boujibar F, Ferrand-Devouge E, et al. Cardiopulmonary exercise testing to assess persistent symptoms at 6 Months in people with COVID-19 who survived hospitalization: A pilot study. *Phys Ther*. 2021;101(6):pzab099. doi: 10.1093/ptj/pzab099
38. Clavario P, De Marzo V, Lotti R, et al. Cardiopulmonary exercise testing in COVID-19 patients at 3 months follow-up. *Int J Cardiol*. 2021;340:113-118. doi: 10.1016/j.ijcard.2021.07.033
39. Skjørten I, Wathne Ankerstjerne OA, Trebinjac D, et al. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. *Eur Respir J*. 2021;58(2):2100996. doi: 10.1183/13993003.00996-2021
40. Rodriguez-Blanco C, Gonzalez-Gerez JJ, Bernal-Utrera C, Anarte-Lazo E, Perez-Ale M, Saavedra-Hernandez M. Short-Term Effects of a Conditioning Telerehabilitation Program in Confined Patients Affected by COVID-19 in the Acute Phase. A Pilot Randomized Controlled Trial. *Medicina (Kaunas)*. 2021;57(7):684. doi: 10.3390/medicina57070684
41. Guler SA, Ebner L, Aubry-Beigelman C, et al. Pulmonary function and radiological features 4 months after COVID-19: First results from the national prospective observational Swiss COVID-19 lung study. *Eur Respir J*. 2021;57(4):2003690. doi: 10.1183/13993003.03690-2020
42. Connes P, Machado R, Hue O, Reid H. Exercise limitation, exercise testing and exercise recommendations in sickle cell anemia. *Clin Hemorheol Microcirc*. 2011;49(1-4):151-163. doi: 10.3233/CH-2011-1465
43. Daher A, Balfanz P, Cornelissen C, et al. Follow up of patients with severe coronavirus disease 2019 (COVID-19): pulmonary and extrapulmonary disease sequelae. *Respir Med*. 2020;174:106197. doi: 10.1016/j.rmed.2020.106197
44. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: Field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44(6):1428–1446. doi: 10.1183/09031936.00150314
45. Simonelli C, Paneroni M, Vitacca M, et al. Measures of physical performance in COVID-19 patients: a mapping review. *Pulmonology*. 2021;27(6):518-528. doi: 10.1016/j.pulmoe.2021.06.005
46. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005, 26, 948–968. doi: 10.1183/09031936.05.00035205
47. Finucane C, van Wijnen VK, Fan CW, et al. A practical guide to activate stand testing and analysis using continuous beat-to-beat non-invasive blood pressure monitoring. *Clin Auton Res*. 2019; 29:427-441. doi: 10.1007/s10286-019-00606-y
48. Verbeek JH, Rajamaki B, Ijaz S, et al. Personal protective equipment for preventing highly infectious diseases due to exposure to contaminated body fluids in healthcare staff. *Cochrane Database Syst Rev*. 2020;4(4):CD011621. doi: 10.1002/14651858.CD011621.pub4
49. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: A scientific statement from the American Heart Association. *Circulation*. 2013;128(8): 873–934. doi: 10.1161/CIR.0b013e31829b5b44

50. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine. Position Stand: quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011;43(7):1334–1359. doi: 10.1249/MSS.0b013e318213fefb
51. Williams MA, Haskell WL, Ades PA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* 2007;116(5):572–584. doi: 10.1161/CIRCULATIONAHA.107.185214
52. Filgueira TO, Castoldi A, Santos LE, et al. The relevance of a physical active lifestyle and physical fitness on immune defense: mitigating disease burden, with focus on COVID-19 consequences. *Front Immunol.* 2021;12:587146. doi: https://doi.org/10.3389/fimmu.2021.587146
53. Ahmadi Hekmatikar AH, Ferreira Junior JB, Shahrbanian S, Suzuki K. Functional and Psychological changes after exercise training in post-COVID-19 patients discharged from the hospital: A PRISMA-Compliant Systematic Review. *Int J Environ Res Public Health.* 2022;19(4):2290. doi: 10.3390/ijerph19042290
54. Rees K, Taylor RS, Singh S, Coats AJS, Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev.* 2004;(3):CD003331. doi: 10.1002/14651858.CD003331.pub2
55. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1997;155(5):1541-1551. doi: 10.1164/ajrccm.155.5.9154855
56. Ahmaidi S, Masse-Biron J, Adam B, et al. Effects of interval training at the ventilatory threshold on clinical and cardiorespiratory responses in elderly humans. *Eur J Appl Physiol and Occup Physiol.* 1998;78(2):170-176. doi: 10.1007/s004210050403
57. Vogiatzis I, Nanas S, Kastanakis E, Georgiadou O, Papazahou O, Roussos C. Dynamic hyperinflation and tolerance to interval exercise in patients with advanced COPD. *Eur Respir J.* 2004;24(3):385-390. doi: 10.1183/09031936.04.00128903
58. Meyer K, Samek L, Schwaibold M, et al. Physical responses to different modes of interval exercise in patients with chronic heart failure-application to exercise training. *Eur Heart J.* 1996;17(7):1040-1047. doi: 10.1093/oxfordjournals.eurheartj.a015000
59. Kortianou EA, Nasis IG, Spetsioti ST, Daskalakis AM, Vogiatzis I. Effectiveness of interval exercise training in patients with COPD. *Cardiopulm Phys Ther J.* 2010;21(3):12-19. PMCID: PMC2941353
60. Spahija J, de Marchie M, Grassino A. Effects of imposed pursed-lips breathing on respiratory mechanics and dyspnoea at rest and during exercise in COPD. *Chest.* 2005;128(2):640-650. doi: 10.1378/chest.128.2.640
61. Sakhaei S, Sadagheyani HE, Zinalpoor S, Markani AK, Motaarefi H. The impact of pursed-lips breathing maneuver on cardiac, respiratory and oxygenation parameters in COPD. *Open Access Maced J Med Sci.* 2018; 6(10):1851-1856. doi: 10.3889/oamjms.2018.407
62. Fregonezi GA, Resqueti VR, Güell Rous G. Pursed lips breathing. *Arch Bronconeumol.* 2004;40(6):279-282. doi: 10.1016/s1579-2129(06)70099-4
63. Krupp LB, LaRocca NG, Muir-Nash, Steinberg AD. The fatigue severity scale. *Arch Neurol.* 1989;46(10):1121-1123. doi:10.1001/archneur.1989.00520460115022