YALE JOURNAL OF BIOLOGY AND MEDICINE 97 (2024), pp.463-472. doi: 10.59249/NHFT4839

REVIEW

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM

Post-Acute Sequelae of SARS-CoV-2 Infections: Exercise Limitation and Rehabilitation

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Patients with prior SARS-CoV-2 infections can develop chronic symptoms; this clinical presentation has been called post-acute sequelae of SARS-CoV-2 infection, post-COVID condition, and long COVID. It can develop in both outpatient cases and in hospital cases; the frequency depends on the severity of infection and comorbidity. Many of these patients have exercise limitation when tested using cardiopulmonary exercise tests. The potential explanations for reduced exercise capacity include cardiac limitations, respiratory limitations, skeletal muscle weakness, deconditioning, and limiting symptoms out of proportion to any measured physiological limitation, and many patients have more than one explanation for the exercise limitation. Since these patients may have required prolonged hospitalization, deconditioning has been considered a potential explanation for their post-hospitalization limitations. Patients with deconditioning have a low oxygen uptake per minute (VO_2) maximum with no obvious cardiac or respiratory limitation, but some do have measurable muscle weakness. One complex study reported that these patients had a high proportion of high-fatigable glycolytic fibers, reduced mitochondrial function, atrophic fibers, and focal necrosis in skeletal muscle. Some post-COVID patients have chronic fatigue and post-exertional malaise and meet the clinical criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Most patients with post-COVID syndrome do improve with conventional cardiopulmonary rehabilitation. However, patients with post-exertional malaise need special attention to their exercise programs and careful monitoring for adverse effects. In summary, patients with long COVID can have complex presentations with a broad range of symptoms and several possible exercise limitations. Their rehabilitation program should be based on their physical capacity and their symptom profile.

INTRODUCTION

Patients with prior SARS-CoV-2 infections can develop chronic symptoms. This syndrome has been called post-acute sequelae of SARS-CoV-2 infection, post-COVID condition, and long COVID and can develop in 10% to 30% of non-hospitalized cases and 50% to 70% in hospitalized cases [1]. The frequency depends on both the severity of infection and the underlying comorbidity. Other risk factors include sex/gender, socioeconomic factors with reduced access to medical care, and certain ethnicities. This disorder has several presentations which include chronic symptoms, such as fatigue, new onset medical conditions, such as diabetes, and exacerbation of chronic disorders, such as heart failure. The etiology is unknown, and possible mechanisms include persistent

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Abbreviations: CPET, cardiopulmonary exercise test; VO_2, oxygen uptake per minute; VCO_2, CO2 excretion per minute; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity.

Keywords: Post-acute sequelae of SARS-CoV-2 infection, long COVID, exercise limitation, deconditioning, rehabilitation, myalgic encephalomyelitis/chronic fatigue syndrome

Author Contributions: JM: project development, literature review, manuscript drafting, approval of final version; KN: project development, literature review, manuscript drafting, approval of final version.

low-grade viral replication, activation of dormant viruses, such as Epstein-Barr virus, changes in the intestinal microbiota, autoimmune reactions with tissue injury, endothelial abnormalities with microclots in vessels, and neurologic dysfunction in the brainstem and/or peripheral nerves [1]. There is no definite drug treatment for these patients, and the usual approach involves treatment of specific medical disorders, counseling, and physical rehabilitation. Some patients have presentations consistent with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [1].

The following questions seem important. 1) What is the definition of post-COVID syndrome? 2) How frequent is it? 3) What are the limiting factors in these patients' exercise performance? 4) Can these patients undertake routine physical rehabilitation? 5) Is it important to try to distinguish between patients with post-COVID exercise limitation and patients with post-COVID exercise limitation and post-exertional malaise? 6) Are mental/psychological symptoms important factors that cause disability in these patients? 7) Can counseling help these patients recover mental and physical function?

This condition occurs in approximately 10% of patients recovering from COVID infection. In 2022, the World Health Organization (WHO) proposed a definition which included the presence of symptoms lasting for at least 2 months in individuals with probable or confirmed SARS-CoV-2 infection more than 3 months previously [2]. One important problem with this definition is that many patients in 2020 did not have confirmed infections due to the lack of PCR testing available throughout the world. Consequently, the number of infected but unidentified patients is likely large and could create difficulties in studies which involve control subjects who have no laboratory confirmation of infection but in fact had been infected. Cardiopulmonary rehabilitation is used in many patients who survive acute cardiopulmonary disorders or who have chronic cardiopulmonary symptoms. However, current recommendations suggest that patients with moderate to severe ME/CFS should not participate in routine rehabilitation because it can cause significant post-exertional malaise and contribute to chronic fatigue. Therefore, comparisons between long COVID and ME/CFS become important, both in terms of understanding the pathogenesis of these two disorders and designing rehabilitation programs.

Exercise limitation in post-COVID patients could involve: 1) cardiac limitation; 2) respiratory limitation; 3) skeletal muscle weakness; 4) deconditioning; 5) symptom limitation but no definite physiological limitation; or 6) a combination of limiting factors. This review considers studies that have used cardiopulmonary exercise testing to identify limits in patients with post-COVID conditions, determined the frequency of deconditioning in these patients, reported outcomes in rehabilitation studies in these patients, and made comparisons between patients with post-COVID conditions and ME/CFS and patients with post-COVID conditions. Studies analyzing the types of impairment in post-COVID patients are discussed next.

METHODS

A comprehensive literature search was conducted using the PubMed, Google Scholar, and Embase databases. Key search terms included "post exertional malaise in long covid," "pulmonary rehab + post exertional malaise," "pulmonary rehab + post exertional malaise + long covid," and "post exertional malaise in long covid studies." The search was limited to English-language publications. Preprints due to lack of peer review and case reports were excluded from the analysis.

TYPES OF IMPAIRMENT

Kersten et al. (2022) analyzed cardiopulmonary exercise testing (CPET) results in 143 symptomatic post-COVID patients [3]. Eventually, 120 patients were included in the final analysis. Seventy-eight patients (65%) had no limitation, 19 patients (15.8%) had deconditioning, 11 patients (9.2%) had pulmonary mechanical limitation, seven patients (5.8%) had pulmonary vascular limitation, and five patients (4.2%) had cardiac limitation. Patients with the deconditioning had a reduced peak oxygen uptake per minute (VO_2) (21.8 ± 5.5 mL/kg/min, 78.7 ± 4.1% of the target) with no other abnormalities in breathing pattern or respiratory gases. Patients who required hospitalization had a lower peak VO_2 than patients who did not and an increased A-a O_2 gradient.

Mancini et al. (2021) evaluated 41 post-COVID patients with unexplained dyspnea using CPET [4]. These patients had an average age of 45 and an average left ventricular ejection fraction of 59% ± 9%. Their peak VO_2 was 20.3 ± 7 mL/kg/min (77 ± 21% of predicted). Thirty-six patients had a respiratory exchange ratio greater than 1.05, indicating excellent effort during testing. Twenty-four patients had a peak VO_2 less than 80% of predicted, 22 of these patients had a low O_2 pulse, 23 had an increased VE/CO2 excretion per minute (VCO_2) ratio, and 14 had dysfunctional breathing. Seventeen patients had a VO_2 max greater than 80% predicted, and 12 of these had dysfunctional breathing. Consequently, 26 out of 41 patients had dysfunctional breathing; 25 patients had a resting end-tidal CO_2 less than 35 mmHg. Seven patients underwent invasive testing with right heart catheterization, and five patients had preload failure. Thirty-two patients met the criteria for chronic fatigue with reduced activities during the day and at least four unexplained chronic symptoms. However, after exclud-

ing patients with medical diagnoses that might cause these symptoms, only 19 had clinical presentations consistent with chronic fatigue. The authors conclude that circulatory impairment, abnormal ventilatory parameter patterns, and chronic fatigue are common in patients with post-acute sequelae of SARS-CoV-2 infections. In their discussion, they outlined the pathogenesis for persistent symptoms in these patients, which includes cardiac injury and vascular abnormality resulting in circulatory impairment, lung injury with ventilatory impairment, and muscle dysfunction resulting in reduced O_2 extraction and metabolism.

Sorensen et al. (2024) reported CPET results in 169 patients post-COVID infection who had persistent symptoms [5]. Thirty-two patients (19%) had workloads below 84% of predicted, 91 patients (54%) had VO_2/workload slopes below predicted levels, 115 patients (68%) had a peak VEs below 85% of predicted, and 26 individuals (15%) had VE/VCO_2 slopes greater than 34. These individuals did not have uniform impairments and could be classified into three groups, namely abnormal VO_2, abnormal VO_2/workload slope, and abnormal VE/VCO_2 slope. Some individuals had more than one impairment, and eight individuals, for example, had abnormalities in all three parameters. Forty-one individuals underwent repeat testing one year after their initial study, and there were no significant changes in their CPET parameters. Again, this study indicates that these patients can have several impairments that can result in exercise limitation.

Contreras et al. (2023) reviewed CPET results in 77 patients with post-COVID dyspnea and compared these results to 766 patients who underwent testing for evaluation of unexplained dyspnea [6]. Post-COVID patients reported an increased frequency of neuromuscular/orthopedic symptoms and CNS changes, but no increase in dyspnea or fatigue in comparison to other patients undergoing testing. Patients post-COVID had a lower predicted peak VO_2 and a lower maximum minute ventilation. Thirty-four individuals (44%) had chronotropic incompetence, and 16 individuals (21%) had low peak systolic blood pressures. This study demonstrates that some post-COVID patients have significant cardiovascular disorders which limit exercise.

Durstenfeld et al. (2022) analyzed 38 studies that reported CPET results in 2160 individuals 3 to 18 months after SARS-CoV-2 infection, including individuals with long COVID symptoms and individuals without these symptoms [7]. The mean peak VO_2 was -4.9 mL/kg/min (95% CI: -6.4 to -3.4) lower in patients with symptoms in comparison to individuals without symptoms. These results were attributed to deconditioning, peripheral limitations with abnormal oxygen extraction, dysfunctional breathing, and chronotropic incompetence. There was no consistent pattern to explain the limitations in these patients, and some patients likely had more than one explanation for exercise limitation. It is difficult to distinguish deconditioning from abnormal peripheral oxygen uptake and metabolism without invasive studies. In addition, the preload failure is difficult to identify and may be present even in patients with normal cardiac output.

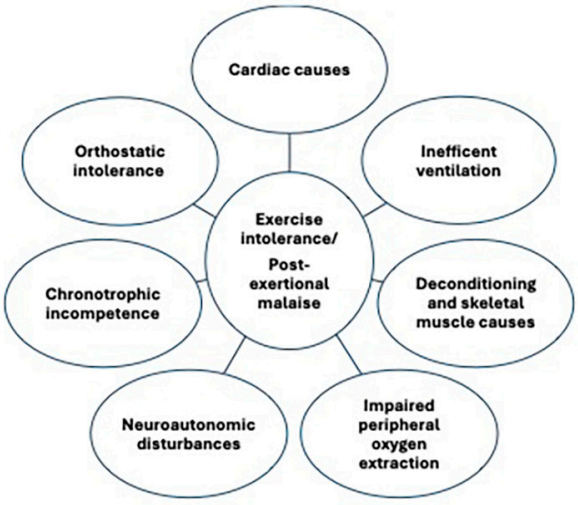

Figure 1. This figure provides an overview of the causes of exercise intolerance and post-exertional malaise in patients with long COVID.

These studies demonstrate that some but not all patients with long COVID have abnormal exercise capacity based on CPET results but do not have single cardiorespiratory abnormality to explain their exercise limitation. Potential explanations for exercise limitation include reduced cardiac output, inefficient ventilation, deconditioning and skeletal muscle injury, impaired peripheral O_2 extraction, chronotropic incompetence, and abnormal blood pressure responses to exercise. Since many patients had reduced levels of physical activity secondary to acute illness or lockdowns during the COVID pandemic, deconditioning is a reasonable explanation for reduced exercise responses in some patients, and relevant studies will be considered next.

Figure 1 illustrates the types of impairment in these patients. This classification is not straightforward and depends on multiple factors, including the infection, age, comorbidities, and complications during hospitalization, if any.

DECONDITIONING STUDIES

Chen et al. (2021) published a systematic review on hospital-associated deconditioning which is relevant to acute SARS-CoV-2 infections requiring hospitalization [8]. Risk factors for deconditioning include increased

age, poor nutritional status, reduced mobility, and reduced overall preadmission functional status. In addition, cognitive impairment and depression were associated with hospital-associated deconditioning. These risk factors are potentially important in patients admitted to the hospital with COVID infection, especially in older patients. However, in many cases there is very little information about prehospitalization status that would allow prediction of deconditioning. Hospital-based care, which typically includes sleep disruption, painful stimuli, reduced mobility, and inadequate nutrition, contributes to the development of this syndrome. Patients with reduced skeletal muscle mass are at increased risk, and patients with dysfunction of the hypothalamus-pituitary-adrenal axis are also at increased risk. Consequently, in COVID patients, as in all patients, hospitalization can result in deconditioning, and simple interventions in hospital care could reduce the frequency and severity of deconditioning.

Rinaldo et al. (2021) studied exercise limitation in 75 patients who had prior COVID-19 infections; 41 of these patients had a reduced exercise capacity [9]. These patients had a reduced peak VO_2, reduced peak workloads, and early anaerobic thresholds, and reduced VO_2/work slopes. Their O_2 pulse at the peak level was reduced, but lactate levels at the peak were similar in both groups. The VE/VCO_2 slopes were identical. These authors suggest that this reduction in exercise capacity was probably explained by muscle deconditioning.

Appelman et al. (2024) reported a complex study on healthy control subjects and long COVID patients to determine changes in muscle structure and function following exercise [10]. All of these post-COVID patients had post-exertional malaise and had a lower VO_2 max and lower peripheral O_2 extraction. Analysis of muscle biopsy specimens indicated the patient with long COVID had a higher proportion of high-fatigable glycolytic fibers and reduced mitochondrial function. Tricarboxylic acid cycle metabolites were lower in the skeletal muscle and in blood in these patients. The concentration of amyloid containing deposits was higher in the skeletal muscle for long COVID patients at baseline before exercise, and this concentration increased in both groups after exercise. In addition, skeletal muscle biopsies indicated that patients with long COVID had a higher percentage of small atrophic fibers and focal necrosis, and both these abnormalities increased after exercise patients with long COVID. These patients also had more CD68+ macrophages in skeletal muscle than healthy control subjects. Overall, these studies indicate that patients with long COVID had exercise-induced decreases in skeletal muscle mitochondrial enzyme activity, increased accumulation of amyloid fragments in skeletal muscle, and histologic evidence of severe muscle tissue damage. These findings likely explain the decreased physical activity in these patients and also demonstrate that post-exertional malaise is associated with increased muscle injury. The explanation for these changes is uncertain, but they clearly establish that muscle function is abnormal in this particular cohort of patients.

Ferreira et al. discussed the mechanisms of exercise intolerance in COVID patients in an editorial published in 2021 [11]. Possible causes of these limits include cardiac dysfunction, respiratory dysfunction, decreased peripheral extraction of O_2, and excessive symptoms in a patient with no obvious limits on CPETs. They also suggest that deconditioning should be considered in patients with decreased VO_2 without another explanation. They note that there is not necessarily a correlation between the severity of infection at the time of hospitalization and the reduction in peak VO_2. In addition, deconditioning does not explain persistent symptoms in a patient with preserved peak VO_2. In particular, it is difficult to determine which patients have reduced O_2 extraction from peripheral blood flow. Ambrosino et al. (2022) discussed the possibility that endothelial dysfunction caused deconditioning in patients who are COVID-19 survivors and had reduced exercise performance [12]. Endothelial dysfunction could develop as a consequence of microthrombosis. In addition, these patients could have a primary myopathy related to infection with mitochondrial injury and decreased cellular O_2 metabolism.

In summary, patients with SARS-CoV-2 infections can have residual involvement of their lungs, cardiovascular system, skeletal muscles, and central nervous system after they recover from the acute infection. Some patients have definite reductions in VO_2 max but do not have obvious cardiac or respiratory limitations, and this exercise limitation has been attributed to deconditioning in some cases. This may reflect impaired peripheral O_2 extraction, mitochondrial dysfunction, or loss of skeletal muscle mass. It is difficult to determine the exact abnormality in skeletal muscle in patients with deconditioning.

RESPIRATORY DISORDERS WITH NORMAL CONVENTIONAL PULMONARY TESTING

Some patients, especially those with acute respiratory failure requiring mechanical ventilation, have very definite pulmonary disease based on pulmonary function testing and radiographic images after COVID infection. However, some patients may have “subclinical” lung injury which may not be detected with routine pulmonary function testing. Alhuthail et al. (2021) studied the breathing patterns of patients with long COVID using structured light plethysmography [13]. This study included 110 hospitalized patients who had been managed either in the intensive care units requiring intubation and mechanical ventilation (N=65) or on respiratory wards

(N=45). Patients in the intensive care unit had increased respiratory rates compared to the patients in hospital wards. There was no significant difference in the respiratory rate variability between the two groups. There was no definite explanation for this result. This technique provides a simple method to evaluate the respiratory status in patients who had had COVID-19 infections, and this technique could be used to monitor results during rehabilitation.

Kjellberg et al. (2024) measured lung function in 48 individuals who had had COVID infection. The median time since the infection was 65 weeks [14]. Small airway function was measured using a multiple breath washout technique and impulse oscillometry. Twenty-one subjects stated that they had breathing difficulties, and these individuals had evidence of small airway disease based on the multiple breath washout technique. Twenty participants were classified by the predominant abnormality identified with these tests; 12 participants had reduced physical function based on 1-minute sit-to-stand tests, 12 individuals had a small airway dysfunction, and three individuals had normal results on both tests. Therefore, the study indicates that individuals with breathing difficulties post-COVID can have normal spirometry and diffusion capacity measurements, but abnormal small airway function based on multiple breath washout techniques. In addition, they can have reduced physical function based on measurement of sit-to-stand cycles. There was no correlation between changes in lung function and changes in physical function in this study.

The results in these two studies indicate that routine pulmonary function testing may not identify a residual lung injury in post-COVID patients and that weak lower extremities can be a factor in exercise limitation.

MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME

Some post-COVID patients have clinical presentations similar to ME/CFS. The diagnostic criteria for this clinical disorder include persistent severe fatigue that limits ordinary activities for at least 6 months, post-exertional malaise, sleep disorders, and either cognitive impairment or orthostatic intolerance or both. Multiple disorders including viral infection can trigger this syndrome.

Niewolik et al. (2024) analyzed the results from 2371 patients with persistent long COVID symptoms using information collected from Internet surveys [15]. The most frequent symptoms were chest pain, dizziness/vertigo, and respiratory symptoms with shortness of breath and cough. The most severe symptoms were fatigue and "brain fog." Cluster analysis identified three clusters, including cluster A with "rheumatological and neurological symptoms," cluster B with "neuro-psychological symptoms and cardiorespiratory symptoms," and cluster C with "general infection signs, dermatological and otology symptoms." A large number of participants (n=1424) had symptoms in all three clusters. These investigators concluded that some patients had symptom complexes similar to ME/CFS or rheumatologic inflammatory disorders. This study demonstrates that post-COVID symptoms can fall into multiple categories and do not involve just the cardiorespiratory systems.

Andronescu et al. (2024) analyzed the impact of COVID-19 infections in the United States military healthcare system beneficiaries using questionnaires [16]. The study group included 2383 participants; 687 had at least 1 positive SARS-CoV-2 test. The individuals with prior COVID infection were more likely to meet instrument-based criteria for depression, fatigue, impaired cognitive function, and impaired functional abilities. Overall patients with history of COVID infection were twice as likely to report cognitive impairment and fatigue. These symptoms may reflect ME/CFS, and these patients should be assessed using validated questionnaires for post-exertional malaise and for orthostatic intolerance.

Vernon et al. (2023) distributed post-exertional malaise questionnaires to 227 people who applied for care at a long COVID care center [17]. The results from 80 respondents were compared to the results from 151 ME/CFS patients which had been collected during an ongoing research study. The majority of respondents in both cohorts were women, and the majority had university level educations. Seventy-nine out of the 80 long COVID patients reported post-exertional malaise. This usually developed minutes after exertion, hours after exertion, or a day or more after exertion, and recovery required at least a day or several days. Triggers included medium physical exertion, such as shopping, stress, and insufficient sleep. Seventy-seven long COVID patients noted fatigue, and 64 noted sleepiness. Recovery often required rest, sleep, and hydration. The principal method of prevention was avoidance. The answers to this questionnaire were very similar to the answers provided by ME/CFS patients in an ongoing study at this center. In summary, this study demonstrates that the patients with long COVID who applied to a clinic for long COVID patients had typical symptoms associated with ME/CFS.

Pagen et al. (2023) analyzed the frequency of post-exertional malaise and orthostatic intolerance in people "living" with a post-COVID-19 condition [18]. This study was based on Internet surveys using the PRIME post-COVID cohort. The study groups included 955 respondents with prior COVID infection and post-COVID conditions, 2174 respondents with prior COVID infection but no post-COVID condition, and 654 respondents who never had a COVID infection. In respondents

living with post COVID conditions, 48.1% of women and 41.2% of men had post-exertional malaise and 29.3% of women and 27.9% of men had orthostatic intolerance, based on validated questionnaires. Factors associated with these two conditions included an age ≤60 years, ≥1 comorbidity, and living alone. This study would suggest that a relatively large percentage of patients with prior COVID infections who have persistent COVID-related symptoms have post-exertional malaise and or orthostatic intolerance.

Legler et al. (2022) reported results from a prospective longitudinal study of patients with post-COVID syndrome [19]. The information collected included survey information, laboratory tests, and hand grips strength testing. This study included 106 patients who were tested 3-8, 9-16, and 17-20-months post-infection. Fifty-five patients had post-COVID syndrome-like ME/CFS, and 51 patients had post-COVID syndrome; the mean age was 40 years. Patients with the ME/CFS syndrome had symptoms with higher severity that persisted longer. Lower hand grip strength at the initial evaluation correlated with symptom persistence, especially in patients with ME/CFS. This study demonstrates that post-COVID syndrome can persist for 20 months post-infection and that many patients can be classified as having postinfectious ME/CFS.

Joseph et al. (2023) reviewed exercise pathophysiology in patients with ME/CFS and patients with post-acute sequelae of COVID [20]. Approaches to this evaluation include both noninvasive CPET testing and invasive CPET testing. Potential explanations for impaired exercise performance include inadequate (failed) biventricular preload, impaired systemic oxygen extraction, deconditioning, and excessive dyspnea on exertion which limits performance. They concluded that patients with ME/CFS and patients with post-acute sequelae of COVID can have similar symptom burdens and alterations in exercise performance.

Consequently, clinicians should evaluate long COVID patients for the possibility of ME/CFS. This diagnosis will likely influence the approach to rehabilitation.

Rehabilitation Studies

Regardless of the explanation for exercise limitation in patients with long COVID, patients and clinicians want to know treatment options. Standard cardiopulmonary rehabilitation programs provide important benefits to patients with either cardiac disease or respiratory disease. Is this approach useful in patients with long COVID?

Bouteleux et al. (2021) reported the results of rehabilitation in 39 patients with COVID-19 infection with persistent dyspnea [21]. These patients had significant improvement in their levels of dyspnea but no change in their levels of fatigue. Their 6-minute walk distance increased, the frequency of hyperventilation syndrome decreased, and overall quality of life improved. However, they had persistent anxiety and depression. The rehabilitation sessions lasted 1.5 hours 3 times per week, but there was significant variability in the number of sessions completed.

Colas et al. (2023) compared the outcomes in patients with long COVID, coronary artery disease, and fibromyalgia in a 4-week exercise rehabilitation program that included three sessions per week [22]. This study included 38 patients in each group. Cardiac autonomic nervous system testing involved resting heart rate, baroreflex sensitivity, and heart rate variability. The physical rehabilitation program for long COVID patients involved three 2-hour sessions per week over 4 weeks. Two sessions of exercise included 90 minutes of aerobic exercise and 30 minutes of resistance exercise, and one therapeutic educational session involved symptom management. Persistent symptoms in the COVID patients included asthenia (100%, N=38), exertional dyspnea (84%, N=32), sleep disorder (50%, N=19), cognitive impairment (47%, N=18), diffuse pain (39%, N=15), anxiety syndrome (24%, N=9), and chest pain (18%, N=7). Each group had an increase in VO_2 at anaerobic threshold, an increase in peak VO_2, and an increase in hand grip force with rehabilitation. The COVID-19 patients had larger increases in the peak VO_2 than patients with coronary disease. There was no significant change in autonomic variables in any group.

Hausswirth et al. (2023) analyzed the effect of a 4-week neuro-meditation program on cognitive and function in 34 patients with long COVID [23]. This randomized controlled trial included 17 patients in the intervention group and 17 patients in the control group. This intervention involved ten 30-minute sessions over 5 weeks. Each session involved sound therapy with coach-guided meditation. Primary outcomes included computerized cognitive tasks and questionnaires analyzing mental and physical fatigue, perceived stress, and mood. Other outcomes included anxiety and depressive symptoms, muscular pain, joint pain, headache, and sleep quality. Patients with long COVID were significantly different from healthy subjects at baseline on all self-reported questionnaires. The meditation program improved responses on all questionnaires in the intervention group. Therefore, this study suggests that a neuro-meditation program can reduce cognitive impairment in patients with long COVID.

Pouliopoulou et al. (2023) published a systematic review and meta-analysis of rehabilitation interventions in patients with post-COVID-19 conditions [24]. This study included 14 trials with 1244 patients. Seven trials with 389 participants reported improved functional exercise

Table 1. Summary of Rehabilitation Studies

Author	Study design	Sample size	Age	Male	Rehab duration	Outcome
Bouteleux et al. (2021)	Longitudinal study over 1 year	39 patients	48 ± 15yr	17(44%)	Highly variable. However, patients were evenly distributed in sets of <6weeks, 6-12 weeks, 12-24 weeks and >24 weeks.	Statistically significant improvement in mean exertional dyspnea and functional capacity as measured by 6MWT and 3 min sit-to-stand test along with hyperventilation.
Colas et al. (2023)	Prospective comparative study over 4 weeks	38 long COVID patients versus control group of 38 coronary artery disease and 38 fibromyalgia patients	COVID group- 46.9 ± 12.7 Coronary Group- 61.4 ± 9.45 Fibromyalgia Group- 47.4 ± 9.93	COVID group- 17(45%) Coronary Group- 29(76%) Fibromyalgia Group- 3(8%)	4 weeks	The mixed (aerobic and resistance) exercise program improved cardiovascular and muscular health, but there were no significant differences between groups. Only VO_2 peak showed a slight advantage for long COVID patients compared to coronary group.
Hausswirth et al. (2023)	Parallel randomized control trial over 5 weeks	34 long COVID patients randomly assigned to an intervention group (n=17) or a control group (n=17) and normative group of 15 healthy participants	Intervention Group- 47.1 ± 8.3 Control Group- 48.7 ± 10.4 Normative Control- 45.9 ± 11.8	Intervention Group- 4(24%) Control Group- 5(29%) Normative Control- 5(33%)	5 weeks	Long COVID patients benefited from Rebalance®, showing improvements in subjective symptoms and cognitive function, particularly on reaction-based tasks.
Pouliopoulou et al. (2023)	Systematic review from Jan 2020 to Feb 2023	1244 patients	50 [47-56] years	684(55%)	Not applicable	Rehabilitation interventions improved functional capacity as measured by 6MWT but had mixed results for fatigue, muscle strength and endurance, dyspnea, and respiratory function.
Edward et al. (2023)	Literature review	Not applicable	Not applicable	Not applicable	Not applicable	Long COVID deconditioning can be addressed with patient tailored exercise protocols. Rowing is favored by the authors due to its ability to promote both concentric and eccentric muscle remodeling.

Gloeckl et al. (2024)	Literature review and online survey	Not applicable	Not applicable	Not applicable	Most studies mention 3-12 weeks	For people with long COVID, exercise programs should be tailored to their PEM severity. A personalized pacing strategy is recommended for PEM patients while a more traditional regimen could be used for patients without PEM.
Volckaerts et al. (2024)	Data analysis of randomized controlled PuRe-COVID trial	51 patients	Not mentioned	Not mentioned	Not applicable	Repeat 6MWTs in long COVID patients showed improvement in only 51% of study group. This suggests factors like PEM, overexertion, or lack of motivation may influence results. Given the variability in results, 6MWD data can help tailor treatment and inform future research.

6MWT, 6-minute walk test, 6MWD, 6-minute walk distance, PEM, Post-exertional malaise

capacity based on 6-minute walk tests, and the patients in the intervention group had an increase of 35.8 ± 6.6 meters in their 6-minute walk tests. Eight trials with 573 participants reported significant changes in dyspnea following the intervention, and five trials with 366 participants reported significant improvement in quality of life. There were no significant changes in forced expiratory volume in the first second (FEV1) or forced vital capacity (FVC). This study demonstrates that physical rehabilitation has the potential to improve functional capacity and quality of life in patients with post-COVID conditions.

Edward et al. (2023) reviewed the characteristics and treatment of exercise intolerance in patients with long COVID [25]. In their analysis, long COVID results from deconditioning, which reportedly can develop with as little as 20 hours of inactivity. They suggest that exercise protocols should include both static exercise with maximal voluntary contractions that increase blood pressure and dynamic exercise which can increase cardiac output. Their review included five trials that reported improvement in 6-minute walk distance, dyspnea, fatigue, quality of life, and lower body muscle strength. These authors concluded that exercise training can improve these patients' physical condition, but it must be based on assessment of the individual, his or her symptoms, and his or her comorbidities.

Gloeckl et al. (2024) developed practical recommendations based on a literature review and a survey of 14 experts in this field for exercise training in patients with long COVID with or without post-exertional malaise [26]. They classified patients into three groups, including no post-exertional malaise, mild/moderate post-exertional malaise, and severe post-exertional malaise. Recommendations for patients with severe post-exertional malaise include setting limits for both physical and mental activity to avoid overload. Their recommendations do not include suggestions regarding systematic counseling and other neuropsychological techniques.

The baseline assessment of post-COVID patients could use CPET, which is not available in many centers, or 6-minute walk tests to establish their activity level for rehabilitation. Volckaerts et al. (2024) analyzed the results from repeat 6-minute walk tests with a median time interval of 91 minutes between tests in 51 post-COVID patients [27]. The first 6-minute walk test had a mean distance of 548 ± 95 meters; the second walk test had a mean distance of 547 ± 94 meters. Twenty-six patients performed better on the second test than on the first test, and 25 patients had a worse performance on their second test. The explanation for these differences and test results is uncertain but does offer the possibility that post-exertional malaise contributed. Therefore, two tests on the same day can help establish the patient's baseline physical capacity and potentially can help identify patients

with post-exertional malaise who will need careful attention to the results and potential adverse effects of their rehabilitation program.

In summary, many patients with long COVID can increase their exercise tolerance and strength with aerobic and strength training (Table 1). Patients with post-exertional malaise need more assessment and more frequent monitoring to avoid adverse effects associated with physical activity.

LIMITATIONS

A significant limitation in the study of long COVID is the non-specific nature of many of the associated symptoms. This makes it challenging to definitively attribute these symptoms solely to long COVID, as they may also be explained by other conditions or factors. The Bradford Hill criteria, a widely recognized framework for evaluating causal relationships in epidemiological research, have not been fully met for long COVID syndrome. Several factors contribute to this; these include the relatively recent emergence of the virus, the challenges associated with studying its long-term consequences, and the unique yet broad characteristics of this newly recognized disease condition.

The studies used in this review had multiple formats, including randomized trials, cohort studies, and reviews. Consequently, it was not possible to provide a uniform assessment of study quality.

SUMMARY AND RECOMMENDATIONS

Patients with long COVID do not have uniform clinical presentations. Many of these patients have chronic fatigue and impaired overall physical activity levels, and some have a clinical presentation very similar to ME/CFS. Some of these patients, but not all, have abnormal CPET results and can have several types of impairment. Important abnormalities include reduced cardiac output, abnormal ventilatory responses to exercise, and reduced peripheral O_2 extraction. Patients need a comprehensive assessment to determine their symptom profile, comorbidity, and expectations with rehabilitation. In addition, they need to be screened for ME/CFS. Many patients benefit from rehabilitation that includes physical activity and counseling. Patients with ME/CFS-like presentations will need to start an exercise program with limited physical activity and short duration, and they must be evaluated to determine whether or not this is causing post-exertional malaise. Counseling should focus on positive aspects of ongoing rehabilitation and limit undue attention to current symptoms.

Acknowledgments: none.
Conflicts: none.
Financial support: none.

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