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Systematic Review

Impact of Rehabilitation on Fatigue in Post-COVID-19 Patients: A Systematic Review and Meta-Analysis

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Abstract: The post-COVID-19 syndrome may affect patients after the COVID-19 post-acute phase. In particular, the 69% of patients reported persistent fatigue at the discharge. To date, no clear data are available regarding the most effective rehabilitative approaches for the treatment of this condition. Thus, this systematic review aimed to evaluate the rehabilitation treatment's efficacy on fatigue in post-COVID-19 patients. We systematically searched PubMed, Scopus, and Web of Science databases to find longitudinal study designs presenting: post-COVID-19 patients as participants; a rehabilitative approach aimed to reduce post-COVID-19 syndrome as intervention; and fatigue intensity assessed through an evaluation tool that quantified the perceived exertion (i.e., fatigue severity scale, FSS; Borg Scale (BS); Borg Category Ratio 10, CR10; Checklist Individual Strength (CIS) fatigue scale; FACIT (Functional Assessment of Chronic Illness Therapy) fatigue scale). The present systematic review protocol was registered on PROSPERO (registration number CRD42021284058). Out of 704 articles, 6 studies were included. Nearly all patients showed COVID-19-related fatigue, and after the rehabilitation treatment, only 17% of subjects reported the persistency of symptoms. The overall effect size reported a −1.40 decrease in Borg Category Ratio 10 with a SE of 0.05 and a 95% CI between −1.50 and −1.30 ($p < 0.001$). The present systematic review and meta-analysis underlines the rehabilitation role in the fatigue reduction in patients affected by post-COVID-19 syndrome.

Keywords: fatigue; COVID-19; rehabilitation; telerehabilitation; post-COVID-19; long COVID; post-COVID-19 syndrome; exercise

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1. Introduction

Coronavirus disease 2019 (COVID-19) is spread via infectious droplets due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which might result in a bilateral interstitial pneumonia that could lead to long-term respiratory, physical, and psychological dysfunctions [1–3]. The most severe cases are commonly referred to intensive care units (ICUs); in this context, the patients are intensely monitored and treated with oxygen therapy, non-invasive ventilation such as continuous positive airway pressure, and even invasive ventilation [4,5]. Furthermore, the long immobilization and prone positioning may lead to several complications in patients hospitalized in ICUs, with a weak tolerance of early rehabilitation and rapid desaturation [1]. Thus, respiratory dysfunction, muscle weakness, joint stiffness, motor deconditioning, balance and postural impairment, and pain might be frequently present in the acute phase, with a huge impact on the patient's general conditions [6–8]. However, rehabilitation is crucial not only during the ICU stay but even in the post-acute phase when the patients are transferred to post-acute specialized COVID-19 rehabilitation units or other hospital settings [9–16].

A post-intensive care syndrome (PICS) is a new or worsening impairment of a subject's physical, cognitive, or mental health status arising during the ICU hospitalization and persisting after the discharge, may be often described in patients discharged from ICUs [17]. Several degrees of respiratory, physical, and psychological distress characterized the PICS, and lead to the need to customize any rehabilitative intervention to each patient's specific condition [18]. As reported by the Cochrane Rehabilitation REH-COVER action [11–13], the functional outcomes in post-ICU hospitalized COVID-19 patients may be improved by a patient-tailored neuromuscular and respiratory rehabilitation. However, COVID-19 might have detrimental sequelae even after the post-acute phase, depicting a new pathological condition: the "post-COVID-19 syndrome (PCS)" or "long COVID" [19]. This disorder is defined by the main International Guidelines as a complex of signs and symptoms that could not be explained by other diagnoses that last more than 12 weeks after COVID-19 [20,21] and may be divided in subacute or ongoing symptomatic COVID-19, including symptoms and impairments present from 4–12 weeks after acute COVID-19, and chronic or PCS, with symptoms and impairments persisting more than 12 weeks from the onset of COVID-19 [22]. A severe disability might be caused by long COVID in subjects even at the end of the disease that will need to be adequately investigated and treated [20]. PCS was reported in the 10% of people testing positive for COVID-19 by symptom surveillance surveys [23], and due to the huge numbers of individuals worldwide who have been, or will be, affected by COVID-19, this condition presents a relevant societal impact that would be long lasting [22].

PCS presents a similarity with the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), including persistent fatigue, systemic myalgia, depressive symptoms, and non-restorative sleep, even if any association or causation between these conditions is yet to be determined [24]. A persistent breathlessness was reported by 53% of patients after discharge, persistent cough by 34%, and persistent fatigue by 69% [19]. In an Italian study, fatigue, a multidimensional health problem, was identified as one of the most common and disabling consequences of COVID-19, with an incidence of 53% of 143 individuals seven weeks post discharge [25]. Moderate or severe fatigue was reported more frequently in female subjects, and no marked difference through ethnicity or body mass index (BMI) was noticed [15]. Alhumayn et al. [26], in a relevant systematic review of systematic reviews, pointed out that fatigue might result from many factors, including respiratory muscle weakness, post-viral fatigue syndromes, and possible general deconditioning. The authors also defined how fatigue significantly impacts the health-related quality of life (HRQoL) and general health status of post-COVID-19 subjects, with a decrease in up to 69% of patients from 14 days to 3 months post infection and a reduction in the performance of activities of daily living (ADL) [27,28].

The prevalence of fatigue in COVID-19 patients during follow-up and after rehabilitation treatment was investigated by several studies [23,29–36]. To date, no clear data are available in the scientific literature regarding the most effective rehabilitative approaches for the treatment of fatigue, a widespread complication that affects ADLs in post-COVID-19 subjects.

In this context, this systematic review and meta-analysis intended to assess the efficacy of rehabilitation in fatigue treatment in post-COVID-19 patients.

2. Materials and Methods

2.1. Search Strategy

We systematically searched PubMed, Scopus, and Web of Science databases for articles published from the inception until 20 June 2022, according to each specific thesaurus, following the strategy depicted in Table 1. We performed the systematic review according to the guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for systematic reviews (PRISMA-ScR) guidelines [37] and the Cochrane Handbook for Systematic Reviews of Interventions [38]. Systematic review protocol is available in the International Prospective Register of Systematic Reviews (PROSPERO) with the following number: CRD42021284058.

Table 1. Search strategy.

PubMed
("coronavirus" OR "COVID-19" OR "post-COVID" or "long COVID") AND ("rehabilitation" OR "exercise" OR "physical therapy" OR "telemedicine" OR "telerehabilitation") AND ("fatigue" OR "Borg" OR "fatigue severity scale" OR "FSS" OR "FACIT" OR "CIS")
Scopus
TITLE-ABS-KEY ((("coronavirus" OR "COVID-19" OR "post-COVID" or "long COVID") AND ("rehabilitation" OR "exercise" OR "physical therapy" OR "telemedicine" OR "telerehabilitation") AND ("fatigue" OR "Borg" OR "fatigue severity scale" OR "FSS" OR "FACIT" OR "CIS")))
Web of Science
(("coronavirus" OR "COVID-19" OR "post-COVID" or "long COVID") AND ("rehabilitation" OR "exercise" OR "physical therapy" OR "telemedicine" OR "telerehabilitation") AND ("fatigue" OR "Borg" OR "fatigue severity scale" OR "FSS" OR "FACIT" OR "CIS"))

2.2. Selection Criteria

Two reviewers, after duplication removal, independently screened all potential papers for eligibility, and any disagreement was solved by a third reviewer's consultation.

The following PICO model was used to evaluate the study eligibility:

- (P) Participants: patients affected by PCS;
- (I) Intervention: rehabilitative interventions;
- (C) Comparator: not applicable;
- (O) Outcome measure: fatigue evaluation through an evaluation tool that quantified the perceived exertion (i.e., fatigue severity scale (FSS); Borg Scale (BS); Borg Category Ratio 10 (CR10); Checklist Individual Strength (CIS) fatigue scale; FACIT (Functional Assessment of Chronic Illness Therapy) fatigue scale).

We included only observational studies with a longitudinal study. We excluded: (1) studies without assessment of fatigue through specific evaluation tools; (2) studies on children (age < 18 years); (3) studies on patients with previous psychological disorders; (4) studies written in a language different from English; (5) full-text unavailability (i.e., posters and conference abstracts). The 2020 PRISMA flow diagram is depicted in Figure 1.

2.3. Data Extraction

Two reviewers independently extracted data from included studies using a customized data extraction on a Microsoft Excel sheet; in case of disagreement, the consensus was achieved through a third reviewer.

We extracted the following data: (1) First author; (2) Journal; (3) Publication year; (4) Nationality; (5) Study design; (6) Age of study participants; (7) Sex of study participants; (8) Anamnestic characteristics of study participants; (9) Comorbidities of study participants; (10) Length of stay (LOS) in intensive care unit (ICU); (11) LOS in Rehabilitation Units; (12) COVID-19 clinical manifestations; (13) Rehabilitative intervention; (14) Fatigue assessment at the baseline and the end of treatment (T1); (15) Other clinical functional assessments.

2.4. Quality Assessment

We applied the risk of bias of the Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies) checklist [39], according to PRISMA-ScR, to evaluate the included studies' methodological quality [40,41]. Each article was separately evaluated by two authors, and any disagreements were solved involving a third author. The JBI-QES tool consists of nine domains that allow us to identify any bias in a study. Options for each judgment are low risk of bias, moderate risk of bias/some concerns, serious risk of bias, critical risk of bias, and no information. The basis for an overall risk-of-bias judgment was provided by the domain-level reports.

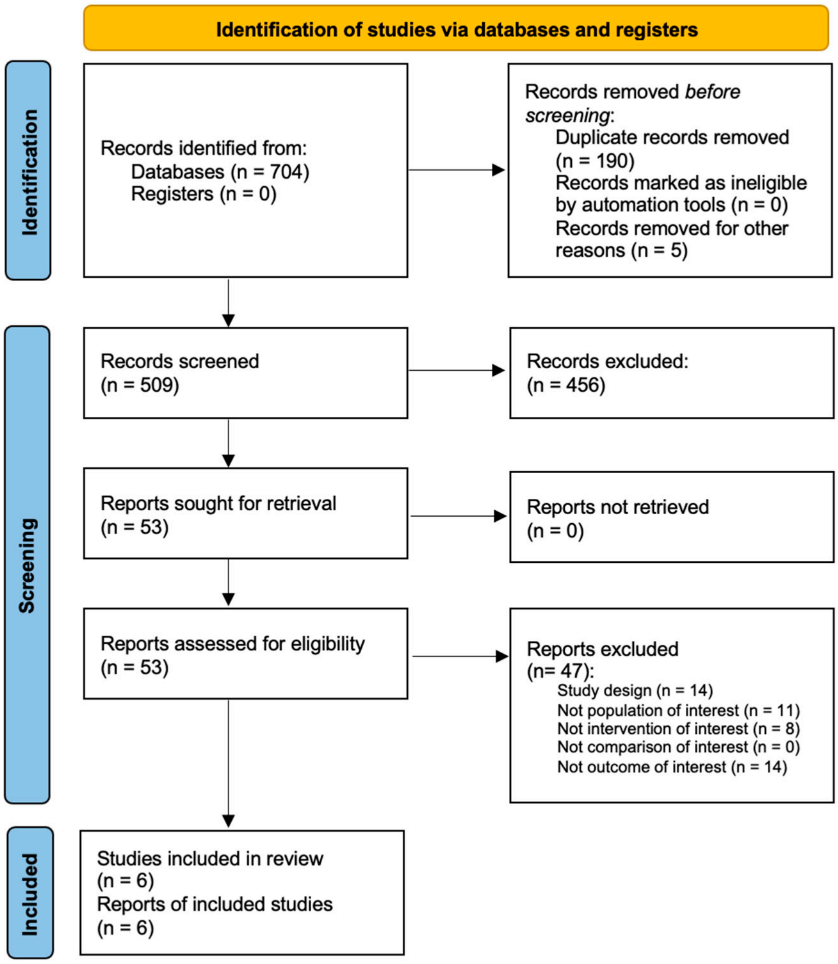

Figure 1. Flow chart of the included studies.

2.5. Statistical Analysis

We mainly conducted the statistical analysis using R version 4.0.0 software, and $p < 0.05$ was considered a statistical significance. Mean Borg CR10 scores and corresponding standard deviations (SD) were inserted into a proportional meta-analysis to identify an overall Borg CR10 in rehabilitation from post-COVID-19 fatigue. The mean Borg CR10 scores and standard deviations from studies were entered into a random-effects meta-analysis to obtain standardized differences in means between the two-time points. We included data from both longitudinal and cross-sectional studies; however, for the analyzes used to identify a mean Borg CR10 score, we followed the formulae for calculating the mean difference and its standard error (SE). We applied the I2 index to measure the heterogeneity present between the point estimates; I2 is a ratio, from 0 to 100, variating among point estimates that is attributable to heterogeneity, and its values lie on a scale [42,43]. Large I2 values suggest that the point estimates are not drawn from the same population, and a threshold of 75% is considered an index for high heterogeneity. We subsequently analyzed Funnel plots to assess publication bias with rank-order correlations reported.

3. Results

3.1. Study Characteristics

At the end of the search, we identify 704 studies, 509 of which were considered suitable after the title and abstract screening, and after the removal of duplicates. Then, 456 were excluded after the title and abstract screening, according to the PICO model. Thus, we assessed 53 articles for eligibility, and we excluded 47 of them for various reasons (see Table 2 for further details).

Table 2. Reasons for article exclusion by the present systematic review.

*Articles excluded after title and abstract screening phase (n = 456) **	
Study design	139 (31%)
Not population of interest	173 (38%)
Not intervention of interest	132 (29%)
Not comparison of interest	0 (0%)
Not outcome of interest	12 (3%)
Articles excluded after full-text screening phase (n = 47)	
Study design	14 (30%)
Not population of interest	11 (24%)
Not intervention of interest	8 (17%)
Not comparison of interest	0 (0%)
Not outcome of interest	14 (30%)

The exclusion of the articles followed the PICO model defined in the Methods Section. Data are expressed as counts (percentages). * = Papers were excluded also for more than one reason during the title and abstract screening phase and the full-text screening phase.

Therefore, we included six studies [44–49] in this systematic review (see Figure 1 for further details). Three studies were case series [44–46], one was a prospective interventional study [47], one was a cohort study [48], and one was a case report [49]. The studies' main characteristics are described in detail in Tables 3 and 4.

A total of 65 subjects were analyzed. Study cohorts ranged from 30 [48] to 1 [49] patients, with ages ranging from 23 years [47] to 80 years [46]. Twenty-nine subjects (45%) needed intensive care. LOS in ICU ranged from 0 days [44–46,49] to 45 days [45], LOS in COVID-19 unit ranged from 7 days [45] to 39 days [44], and LOS in rehabilitation ranged from 21 days [49] to 90 days [45], but in two studies [46,49], the rehabilitation program was conducted at home. During COVID-19 disease, all subjects were affected by bilateral pneumonia [44–46,49], while pulmonary embolism was diagnosed in two (3%) subjects [44], stroke in two subjects [44,48], peripheral neuropathy in three (5%) subjects [44], flu-like symptoms in seven (11%) subjects [45,46], low oxygen level in six (3%) subjects [45,46], dyspnea in seven (11%) subjects [45–47], gastrointestinal disorders in three subjects [45,46] (5%), and cardiological and neurological symptoms in one subject (2%) [45]. Concerning the fatigue measure, one study applied the Borg Scale [46], two studies [44,45] used the CR10, one study [46] the FSS, one study [49] the CIS fatigue scale, and one the FACIT fatigue scale [48]. Regarding intervention: one study [44] adopted increased intensity physical exercise; one study administered [45] a combination of aerobic and resistance exercise; one study [42] applied aerobic exercise, strength training of upper and lower limbs, and educational discussions program; one study used posture changes, passive mobilization of the limbs, breathing control exercises, and passive muscle stretching and pumping exercises; one study provided [47] aerobic training and breathing exercise training; and three studies [46,49] performed an individual telerehabilitation program. No studies provided a follow-up after the end of the rehabilitative intervention.

3.2. Main Findings of the Included Studies

A cohort of seven subjects was analyzed by Ferraro et al. [44] after two consecutive negative SARS-CoV2 swabs. All post-COVID-19 patients experienced a patient-tailored rehabilitation intervention (30 min sessions, 1–2 sessions/day for 6 days/week), consisting of a progressively increased intensity of physical exercise. In this case series, COVID-19-related fatigue was showed by almost all patients (86%), but only Case 2, needing ICU during the acute phase, presented a severe perceived exertion (CR10 = 7). After the rehabilitation treatment, 71% did not show fatigue, while the other two cases described only a very light perception of effort.

Table 3. Main findings of the included studies (case report and case series).

Article	Nationality	Study Design	Study Group	Intervention	Outcome	Main Findings
Ferraro et al. [44] Journal of Medical Virology 2020	Italy	Case series	n tot = 7 male/female = 5/2 mean age = 43.8 years LOS in ICU = 4.7 days LOS in COVID-19 Unit = 16.57 days LOS in Rehabilitation Unit = nr	Increased-intensity physical exercises 1/2 sessions per day of 30 min each for 6 days/week	Borg CR10	At baseline, 86% of patients presented COVID-19-related fatigue, but after rehabilitation treatment, 71% did not show any fatigue.
Tozato et al. [45] Revista Brasileira de Terapia Intensiva, 2020	Brazil	Case series	n tot = 4 male/female = 2/2 mean age = 56 years LOS in ICU = 15 days LOS in COVID-19 Unit = 19.75 days LOS in Rehabilitation Unit = 90 days	Aerobic exercise 3 times/week, 30 min, resistance exercise 3 times/week, 3 series of 10 repetitions each	Borg CR10	At the end of the treatment, CR10-associated dyspnea variables were reduced for all cases.
Wootton et al. [46] Respirology Case Reports, 2020.	Australia	Case series	n tot = 3 male/female = 3/0 mean age = 70.6 years LOS in ICU = 1.33 days LOS in COVID-19 Unit = 12 days LOS in Rehabilitation Unit = 42 days	Individual telerehabilitation program, including education and progressive exercise sessions (15–30 min each) featuring breathing, aerobic, and strength training	5 STS, 1 min STS, FSS, mMRC	Fatigue score on the FSS worsened at the six-week time-point in two cases. Patients demonstrated improvements from commencement of rehabilitation to the six-week time-point on the 5 STS and 1 min STS.
Bickton et al. [49] American Journal of Medicine & Rehabilitation, 2021	Malawi	Case report	n tot = 1 male/female = 1/0 mean age = 46 years LOS in ICU = 0 days LOS in COVID-19 Unit = 10 days LOS in Rehabilitation Unit = 21 days	Individual telerehabilitation program, using a treatable traits approach, with weekly contact by a physiotherapist with multidisciplinary team (MDT) input	mMRC, CIS-Fatigue	At the end of the treatment, the CIS fatigue scale score was 11, indicating normal fatigue.

Legend: 1 min STS = 1 min Sit to Stand Test; 5 STS = 5 repetitions Sit to Stand test; BI = Barthel Index; Borg RPE = Borg Rating of Perceived Exertion; CIS-Fatigue = Checklist Individual Strength Fatigue questionnaire; FSS = Fatigue Severity Scale; mMRC = Modified Medical Research Council; nr = not reported.

Table 4. Main findings of the included studies (observational studies).

Article	Nationality	Study Design	Study Group	Intervention	Outcome	Main Findings
Ahmed et al. [47] European Journal of Physiotherapy, 2021	Pakistan	Prospective interventional study	n tot = 20 male/female = 13/7 mean age = 39.6 years LOS in ICU = 3–5 days LOS in COVID-19 Unit = 5–8 days LOS in Rehabilitation Unit = nr	5 weeks (3 session/week) of aerobic training (20–60 min/session) and breathing exercise training (10 min/session)	6 MWT, Modified Borg dyspnea scale evaluated before and after treatment.	At the end of the treatment, there was a statistically significant improvement in performance at the 6 MWT (635.3 ± 11.6 vs. 560.3 ± 11.3; $p < 0.001$) and at the Borg Dyspnea Scale (3.1 ± 0.1 vs. 4.5 ± 0.2; $p < 0.001$)
Daynes et al. [48] Chronic Respiratory Disease, 2021	United Kingdom	Observational study	n tot = 30 male/female = 16/14 mean age = 58 years LOS in ICU = nr LOS in COVID-19 Unit = 10 days LOS in Rehabilitation Unit = nr	6 weeks (2 session/week) of aerobic exercise, strength training of upper and lower limbs and educational discussions	ISWT, ESWT, FACIT evaluated before and after treatment.	At the end of the treatment there was significant improvements in clinical outcomes of walking capacity as ISWT (413 [229] vs. 300 [198] m; $p < 0.01$) and ESWT (837 [406] vs. 292 [260]; $p < 0.01$). Moreover, there was a statistically significant increase in FACIT values (34 [13] vs. 29 [14]; $p < 0.01$)

Legend: 6 MWT = 6 minutes Walking Test; ESWT = Endurance Shuttle Walking Test; FACIT = Functional Assessment of Chronic Illness Therapy (fatigue score); ISWT = Incremental Shuttle Walking Test; nr = not reported.

Tozato et al. [45] recruited four post-COVID-19 patients with several degrees of severity. During the rehabilitation program, based on cardiovascular and pulmonary rehabilitation principles, all patients reported dyspnea (CR10 ranged from 2 to 7). CR10 values were reduced for all cases at the end of the treatment, showing increased functional capacity and improved prognosis (CR10 ranged from 0 to 5).

Wotton et al. [46] analyzed three males who underwent a telehealth rehabilitation program: patients were trained to exercise four days per week at first and then, progressively, six days a week. Primarily, a mode of aerobic exercise training ground-based walking training with a low starting intensity was administered. At the six-week time-point, fatigue score on the FSS deteriorated in two cases and, when interrogated, both patients described feeling the burden of returning to normal daily duties, work, and career roles whilst still recovering from COVID-19, which contributed to their feelings of amplified fatigue and low mood.

Ahmed et al. [47] performed a prospective interventional study at the outpatient department of the Bin-Inam Rehabilitation Centre in Pakistan. Twenty participants discharged from the hospital (negative PCR report) at least two weeks before were recruited and underwent a five-week (3 sessions/week) program of aerobic training and Buteyko Breathing Technique breathing exercise on-site under the supervision of a physiotherapist. The Borg dyspnea score improved from 4.5 (0.2) to 3.1 (0.1) with a $p < 0.001$ after five weeks of exercise training. Sub-group 1 was composed of patients who did not need ventilatory support during their acute phase of the disease, and they demonstrated a more remarkable improvement in dyspnea than sub-group 2, composed of patients who underwent non-invasive ventilation or mechanical ventilation support during their acute care setting (33% reduction in perception of dyspnea in group 1 compared to 31% in group 2).

In the Daynes et al. [48] study, 30 individuals completed the COVID-19 rehabilitation program, consisting of two supervised sessions per week, for 6 weeks, of training composed by aerobic exercises, upper and lower limbs strength training, and educational discussions including breathlessness, cough, fatigue, fear and anxiety, memory and concentration, taste and smell, eating well, getting moving again, sleeping well, managing daily activities, and returning to work. The FACIT improved by 5 points ($p < 0.01$), from 29 to 34 points.

In this case, report [49], a 46-year-old man, successfully discharged after ten days of hospital admission due to severe COVID-19, performed a pulmonary telerehabilitation program; at the beginning, his CIS fatigue scale score of 43 exceeded the threshold for "severe fatigue". Specifically, the rehabilitation program, designed by Bickton, consisted of a qualified physiotherapist's supervision via WhatsApp text messaging, video, and audio calls for 3 weeks. At the end, the CIS fatigue scale score was 11, indicating normal fatigue.

3.3. Meta-Analysis

The meta-analysis presented random effect model performed with a heterogeneity of 74% ($p = 0.67$). The overall effect size (ES) reported a statically significant decrease in Borg Scale (−1.40) with an ES of 0.05 (95%CI: −1.50–−1.30; $p < 0.001$) (see Figure 2 for further details).

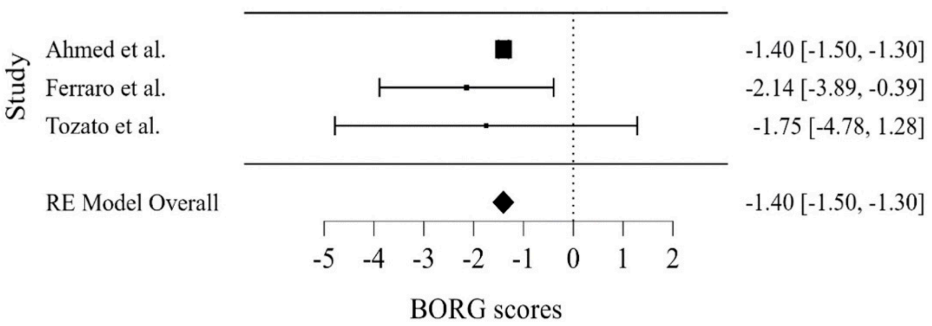

Figure 2. Forest plot of Borg Scale [44,45,47].

The funnel plot, reported in Figure 3, appeared fairly symmetrical. The values flatten symmetrically without outliners, resulting in a low expression of publication bias, despite the small sample.

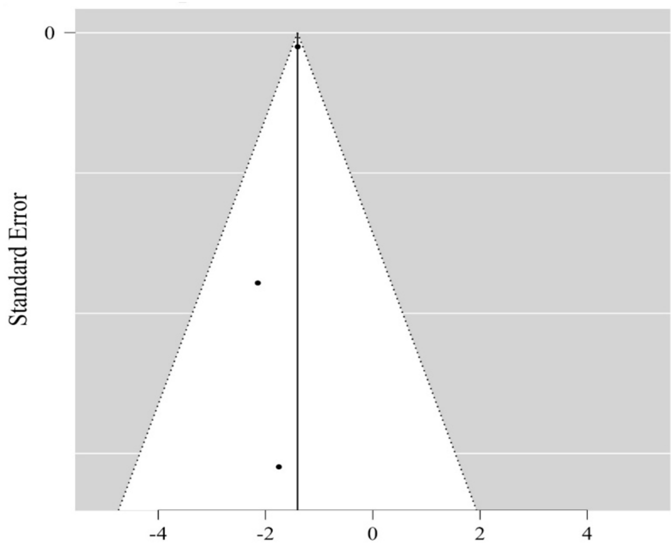

Figure 3. Funnel plot of the included studies.

3.4. Risk of Bias

To evaluate the quality of evidence included in this review, we applied the Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies). We assessed the nine-question risk-of-bias domains, as depicted in Table 5.

Table 5. Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies).

Author and Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Ferraro et al. [44]	N/A	N/A	Y	N	Y	Y	Y	Y	Y
Tozato et al. [45]	N/A	N/A	Y	N	Y	Y	N	Y	Y
Wootton et al. [46]	N/A	N/A	Y	N	Y	Y	Y	Y	Y
Ahmed et al. [47]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Daynes et al. [48]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bickton et al. [49]	N/A	N/A	Y	N	Y	Y	N	Y	N/A

Legend: Q1 = Is it clear in the study what is the 'cause' and what is the 'effect' (i.e., there is no confusion about which variable comes first)?; Q2 = Were the participants included in any comparisons similar?; Q3 = Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?; Q4 = Was there a control group?; Q5 = Were there multiple measurements of the outcome both pre and post the intervention/exposure?; Q6 = Was follow-up complete, and if not, were differences between groups in terms of their follow up adequately described and analyzed?; Q7 = Were the outcomes of participants included in any comparisons measured in the same way?; Q8 = Were outcomes measured in a reliable way?; Q9 = Was appropriate statistical analysis used?; N = no, Y = yes; N/A = not applicable.

All included articles presented full-text availability, and at least one serious risk of bias was identified, resulting into an overall serious risk of bias for that study. A lack of data on baseline characteristics of participants, non-random sampling approaches (convenience samples), missing data, lack of a reliable tool to estimate and report outcomes were reported in the included studies.

4. Discussion

The present systematic review described the state of the art regarding the rehabilitation efficacy in the fatigue treatment in people affected by PCS. The findings underlined that nearly all patients showed COVID-19-related fatigue, with a mean hospital LOS of

15.6 days (in two studies [46,49], the rehabilitation program was conducted at home). Specifically, after the rehabilitation treatment, only 17% of subjects stated the symptoms persistency, with a significant reduction in their severity. The studies included in our review performed different rehabilitation interventions: high-intensity exercise was administered in one study [44]; a combination of aerobic and resistance exercise was performed in one study [45]; one study [47] administered aerobic training and breathing exercise training; in one study [48], patients underwent a program with aerobic exercise, strength training of upper and lower limbs, and educational discussions; in one study, patients underwent a program with posture changes, passive mobilization of the limbs, breathing control exercises, and passive muscle stretching and pumping exercises; finally, in two studies [46,47], an individual telerehabilitation program was applied. In this scenario, telerehabilitation was applied successfully during the first wave of the epidemic [50]. Moreover, it may also be a valid support for the management over time of patients suffering from PCS.

The biological mechanisms of chronic fatigue occurrence in COVID-19 patients are still unclear, with a recent review hypothesizing inflammatory overregulation, increased resistance to cerebrospinal fluid drainage, and even impaired metabolism in the cerebellum and frontal lobe [51,52]. Our meta-analysis showed a statistically significant decrease in Borg Scale ($p < 0.001$), though the high heterogeneity (74%; $p = 0.67$) of the included studies should be considered [44–49]. The statistical methodology applied in our paper, the proportional meta-analysis, was recently introduced in the literature and only allowed the evaluation of the Borg Scale variation. However, as demonstrated in the funnel plot, the studies are homogenous concerning publication bias. Despite the lack of evidence in the literature concerning the COVID-19-related fatigue treatment, several studies confirmed that physical exercise might be effective in the reduction in this symptom in chronic and immune-mediated diseases (e.g., osteoarthritis, rheumatoid arthritis, Parkinson's disease, and multiple sclerosis) [53–59]. At the same time, Tew et al. [60], in a pilot randomized controlled trial, reported that a specific moderate/high-intensity exercise program is feasible in patients affected by quiescent or mildly active IBD.

Furthermore, aerobic capacity and muscle strength without adverse effects on disease progression are enhanced thank to the rehabilitative approach [61].

Our systematic review showed that a specific rehabilitation program might improve symptoms and HRQoL in post-COVID-19 patients [44,62], thus testifying to the need for a careful analysis of patients presenting functioning impairments related to PCS. We retain that an individualized rehabilitation approach could play a crucial role in the reduction in the disabling consequences of COVID-19, with particular attention to fatigue. A recent paper by Fugazzaro et al. [22] evaluates 5 RCTs that administer several rehabilitation treatments to 512 subjects affected by PCS, comparing them with no or minimal rehabilitation or active rehabilitation interventions. The authors analyzed the effectiveness of experimental rehabilitation approaches in the improvement of different outcomes, such as dyspnea and fatigue, pulmonary function tests, muscle mass and strength, functional exercise capacity, quality of life, and independence. In the conclusion, the working group underlined the need to overcome the literature gap regarding the rehabilitation approach in patients affected by such a disabling COVID-19 consequence. A naturalistic qualitative study by Schiavi et al. [63], part of a single-center mixed-method cross-sectional study (RE-ACT) conducted in Italy during the first peak of the SARS-CoV-2 pandemic, investigated the symptoms, activities, and participation of individuals who had been hospitalized for COVID-19 through the main research question, "Tell me, how has it been going since you were discharged?". The authors concluded that persistent symptoms, isolation feelings, fear and stigma, emotional distress, a fatalistic attitude, and return to life were the key aspects of participants' experience after hospital discharge. Alhumayn et al. [26] stated that given the impossibility to correlate acute symptoms with the onset of chronic sequelae and the PCS manifestation variability, a multidisciplinary team is mandatory to depict each patient's needs. Sanchez-Sanchez-Ramirez et al. [64], in a systematic review of the literature and meta-analysis, intended to explore post-COVID-19 effects on patients' chest computed tomography, lung function, respiratory symptoms, fatigue, functional capacity, HRQoL, and the ability to return to work after three months post-infection through the analysis of 24 papers that presented information on a total of 5323 adults, with a prevalence of fatigue of 38%. This condition showed an HRQoL impact up to 6 months after infection, with a not significant correlation with the respiratory symptoms' severity during the acute phase [65]. Nevertheless, fatigue is the most frequent manifestation reported in post-COVID-19 subjects (around one-third of patients) and could be considered a consequence of muscle weakness, respiratory symptoms, and general deconditioning. They also suggested that the SARS-CoV2 infection might trigger post-viral fatigue syndromes [66]. Bickton et al. [49] confirmed these results in a case report included in our systematic review: fatigue, assessed by the CIS fatigue scale, decreased from 43 to 11 after rehabilitation.

Paneroni et al. [66] analyzed the performance of patients without comorbidities after COVID-19 pneumonia using Borg Scale to assess fatigue. This cross-sectional study concluded that patients recovering from moderate-to-severe pneumonia presented a high prevalence of muscle weakness and impaired physical performance, suggesting the need for appropriate rehabilitation programs.

There has been debate about possible long-term sequelae such as myalgic encephalomyelitis in COVID-19 patients. Describing the mechanisms underlying "post-COVID-19 fatigue syndrome" is crucial for the development of preventive and early treatment methods for this syndrome [52].

Mendelson et al. [67] addressed the problem of post-COVID-19 fatigue, and, referring to the Stanford Hall consensus statement [68], the users defined it necessary to start the treatment with low-intensity exercises, to be increased according to the patient's tolerance. In a cross-sectional study, Halpin et al. [15] analyzed the prevalence of fatigue in a population in the United Kingdom: 72% of the subjects admitted to the ICU and 60% of ward patients presented fatigue. Therefore, the authors underline the need to administer adequate rehabilitation treatment in consideration of this symptom impact on HRQoL. The same conclusions were reported by Humphreys et al. [23], whose findings highlight the importance of a tailored physical activity for post-COVID-19 people and improvement of support to resume activities significant to individual well-being.

This systematic review presents study limitations that should be underlined. First, the total number of study participants included is very small, considering that the studies are all case series and case reports; indeed, it did not allow us to draw strong conclusions. Second, the small amount of time in which the included articles were analyzed made it impossible to include subjects with long-term follow-up. Second, the study design of the selected articles did not provide control data. Third, we did not include studies on COVID-19 patients who might also present fatigue among their symptoms. Lastly, the heterogeneity of the scales utilized to measure fatigue could lead to bias.

As stated before, PCS shows a relevant long-lasting societal and economic impact resulting from the great numbers of individuals worldwide who have been or will be affected by COVID-19, considering that 10% of people testing positive for COVID-19 develop this condition. Furthermore, long COVID may cause a severe disability that significantly affects the patients' functioning and HRQoL. In this context, it is essential to identify and treat this disabling condition, and rehabilitation could play a key role in reducing post-COVID-19 fatigue.

5. Conclusions

The present systematic review with meta-analysis analyzed the effectiveness of post-COVID-19 rehabilitation in reducing fatigue based on multiple case reports and cohort studies with non-double-blind interventions. Taken together, the findings suggested that rehabilitation might play a key role in post-COVID-19 patients, especially regarding its impact on fatigue, a disabling consequence of the SARS-CoV-2 infection. The proportional meta-analysis and the overall ES identified a statically significant Borg Scale decrease, but further studies are still needed to provide a stronger conclusion and further clinical evidence to highlight the effects of rehabilitation in these subjects.

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