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Meta-analysis

Effect of pulmonary rehabilitation for patients with long COVID-19: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Pulmonary rehabilitation (PR) has demonstrated efficacy in managing long COVID-19, underscoring the need to refine and tailor PR strategies for optimal patient outcomes.

Objectives: To evaluate the impact of PR on patients with long COVID-19 and to compare the efficacy of different types and durations of PR interventions.

Design: Systematic review and meta-analysis.

Data sources and methods: We systematically searched randomized controlled trials (RCTs) of the effectiveness of PR in long COVID-19 patients published before April 2024. The primary outcomes were physical capacity assessed by the 6-minute walking test (6MWT), lung function measured by forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC), health-related quality of life (HRQoL), and fatigue. Secondary outcomes were thirty-second sit-to-stand test (30STST), handgrip strength tests, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), dyspnea, depression, anxiety, perceived effort, and adverse events.

Results: A total of 37 studies with 3363 patients were included. Compared to controls, PR improved physical capacity (6MWT, 30STST, handgrip), lung function (FEV1, FVC, MIP, MEP), HRQoL, fatigue, dyspnea, and anxiety but did not reach statistical significance for depression. Subgroup analyses of PR duration indicated that programs of ⩽4 weeks improved 6MWT; those between 4 and 8 weeks significantly improved 6MWT, lung function (FEV1, FVC), HRQoL, and reduced fatigue; and programs over 8 weeks improved HRQoL and reduced fatigue. Exercise type analysis revealed that breathing exercises improved 6MWT, lung function (FEV1, FVC), and HRQoL; multicomponent exercises enhanced 6MWT performance and reduced fatigue; the combination of both types improved 6MWT, FEV1 (L), FVC (%pred), HRQoL, and reduced fatigue.

Conclusion: PR improves physical capacity, lung function, and quality of life and alleviates dyspnea, fatigue, and anxiety in long COVID-19 patients. A 4- to 8-week PR program and a combination of both breath exercises and multicomponent training is most effective for managing long-term COVID-19 syndromes.

Trial registration: PROSPERO ID: CRD42024455008.

Keywords: exercise, long COVID-19, pulmonary rehabilitation

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Introduction

The World Health Organization (WHO) defines long COVID-19 symptoms as new symptoms that occur beyond 3 months after infection or more severe symptoms than those experienced before COVID-19, and which persist for at least 2 months with no other explanation.[1] Over 200 symptoms of long COVID-19 have been identified, with the most commonly reported being fatigue, shortness of breath, and cognitive dysfunction.[2,3] These affect daily life and quality of life,[4] impacting 10%–30% of nonhospitalized, 50%–70% of hospitalized, and 10%–12% of vaccinated individuals since the start of the COVID-19 pandemic.[5] Despite WHO has declared the end of the "emergency" phase, we are still in the midst of a pandemic that is demonstrating a lasting impact on public health.[6,7]

Pulmonary rehabilitation (PR), initially developed to manage chronic obstructive pulmonary disease (COPD), is now recognized as a core management practice for various chronic cardiopulmonary conditions.[8] WHO and European Respiratory Society/American Thoracic Society[9,10] guidelines also recommended PR for the management of long COVID-19 symptoms primarily based on expert opinion and observational data. Subsequently, several reviews[11–20] have reported that PR interventions are effective and safe for improving physical capacity, lung function, exertional dyspnea, psychological well-being, and QoL. However, the association between rehabilitation interventions and some outcomes, such as lung function, fatigue, and QoL, has been inconsistent across the reviews. Moreover, the efficacy of various PR modalities and their duration on patients' physical functioning remains an area of uncertainty for these patients. A meta-analysis[18] found that the duration of PR—whether 4–8 weeks or more than 8 weeks—did not significantly influence outcomes for patients with long COVID-19. However, this conclusion is based on a limited number of studies, underscoring the necessity for further research to delineate the impact of PR duration and modalities on physical functioning and symptom alleviation.

As several new RCTs[21–26] have been published, it is essential to update the available scientific evidence on this topic, to evaluate the effect of PR on symptoms and physical function in long COVID-19 patients, and to identify the most effective delivery modality and duration of PR. Accordingly, the objective of this review was to comprehensively assess the effects of PR in patients with long COVID-19 symptoms. Specifically, the impacts of the duration of PR delivery and exercise training type were explored to identify the optimal regimen for long COVID-19 patients.

Materials and methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta Analysis Protocols checklist (PRISMA-P)[27] (Table S1) and the Cochrane Handbook's standards for intervention reviews.[28,29] Our protocol was preregistered with PROSPERO (CRD42024455008).

Search strategy

Two authors conducted independent searches in PubMed, Embase, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials databases for eligible studies up to April 2024. The mean search terms were ("COVID-19" OR "SARS CoV 2") AND ("Pulmonary Rehabilitation" OR "Lung Rehabilitation" OR "physical treatment"); the detailed search strategy was in Table S2. Reference lists of all relevant studies and reviews were also reviewed for additional studies.

Inclusion and exclusion criteria

The inclusion criteria were RCTs; adult patients (⩾18 years old) with laboratory-confirmed COVID-19; and those that included PR treatment compared to a control group that received usual care, no treatment, educational brochure, sham device, or unsupervised PR.[14] The exclusion criteria included patients who did not meet the screening requirements; laboratory or animal studies; and studies not published in English. Additionally, commentaries, reviews, editorials, conference abstracts, letters, statements, case reports, short surveys, study protocols, and duplicate publications from the same study were excluded. Furthermore, studies with data that could not be extracted through the reported statistical methods or lacked targeted outcomes were also excluded. The final decision to include or exclude any study was based on a full-text review by two investigators, focusing on publication

date, study type, study design, and results. Discrepancies were resolved by the other authors.

Outcomes

The primary outcomes were functional exercise capacity measured using the 6-minute walking test (6MWT), lung function measured via forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC), health-related QoL (HRQoL), and fatigue levels. Secondary outcomes were physical and functional capacities measured via the 30 s sit-to-stand test (30STST); handgrip strength; respiratory muscle function based on the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP); the statuses of dyspnea, depression, and anxiety; perceived effort measured via the modified Borg Scale; and adverse events.

In the included studies, HRQoL was measured with different scales including the Short Form Health Survey-12 (SF-12), Saint George's Respiratory Questionnaire score (SGRQ), King's Brief Interstitial Lung Disease questionnaire (K-BILD), the Euro Quality-5 Dimensions-3 Levels questionnaire (EQ-5D-5L), the Short Form-36 Health Survey Questionnaire (SF-36), the 26-item World Health Organization Quality of Life (WHO-26 items) questionnaire, or the Barthel Index. To correct for differences in the direction of scales for HRQoL, data on SGRQ were inverted.[30] Dyspnea was measured using the Multidimensional Dyspnea-12 (MD12), the modified Medical Research Council Dyspnea Scale (mMRC), the Baseline Dyspnea Index-Transition Dyspnea Index (BDI-TDI), the Barthel Dyspnea Index, the Patient Reported Outcomes Measurement Information System (PROMIS), the Dyspnea Severity Short Form, or the Borg Dyspnea Scale. Fatigue was measured using the Visual Analog Scale-Fatigue (VAS-F), Fatigue Scale-14 (FS-14), the Fatigue Severity Scale, the Chalder Fatigue Scale (CFQ11), the 10-point Borg Scale (fatigue), or the Modified Fatigue Impact Scale. Depression was measured using the Beck Depression Inventory (BDI), Patient Health Questionnaire-9 (PHQ-9), the Self-rating Depression Scale, or the Hospital Anxiety and Depression Scale (HADS). Anxiety was measured using the General Anxiety Disorder Questionnaire-7 (GAD-7), the Self-rating Anxiety Scale, or HADS. Perceived effort was measured using the modified Borg Scale, which measures the entire range of activities that the individual perceives when exercising.

Subgroup analyses were conducted to explore the impact of various factors on primary outcomes. The factors included exercise training duration ($\leqslant$4, 4–8, $>$8 weeks) and exercise training types, including breathing exercises (exercises to strengthen respiratory muscles, breathing control exercises, airway clearance techniques, thoracic expansion, or Liu-zi-jue exercises, etc.), multicomponent exercises (integrated of aerobic, strength, resistance, or endurance exercises, etc.), and a combination of both (both breathing exercises and multicomponent exercises).

Data extraction

Two authors independently extracted information from the included studies based on the Cochrane recommendations.[28] Recorded details included the first author, publication year, setting, country, sample size, age, sex, body mass index, patient demographics, illness characteristics, intervention protocols, and study outcomes. Data were verified by other authors (B.D. and W.T.) before analysis. Categorical outcomes were noted as the number of patients with each outcome compared to the total in each group. Continuous outcomes included sample size and mean (SD) or median (IQR), with medians converted to estimated means (SD).[31] Discrepancies were resolved through discussions with other authors.

Study quality, certainty of evidence, and trial sequential analysis

The quality of RCTs was assessed using Cochrane Collaboration's tool (RoB-2 tool)[29] for risk of bias. This tool includes five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain was rated as "low," "some concerns," or "high."

GRADEpro GDT was used to assess the certainty of the results[32,33] according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria. The evaluation included five domains: risk of bias in individual studies, inconsistency, indirectness, imprecision, and publication bias. The overall

certainty of the evidence was rated as high, moderate, low, or very low.

Trial sequential analysis (TSA)[34,35] version 0.9.5.10 (beta software) was used to evaluate the effect of PR, reduce random error, assess conclusion reliability, and estimate the sample size needed for meta-analysis. TSA aimed for a 5% risk for type I error and a 20% risk for type II error (80% power) in this study. If the cumulative *Z*-curve surpasses the trial sequential monitoring boundary or reaches the required information size (RIS), the evidence is sufficiently strong. If the *Z*-curve does not cross any boundaries and the RIS is not reached, it indicates insufficient evidence for a conclusion, necessitating more studies.

Data synthesis and analysis

Meta-analysis was conducted using available data from primary studies with RevMan Review Manager (version 5.4.1). Continuous outcomes were reported as mean differences (MDs) with 95% confidence interval (95% CI). Mean (SD) were estimated from median IQRs for further comparison. For different scales (e.g., SGRQ and EQ-5D-5L) measuring the same outcome, the standardized MD (SMD) was used. The I^2 statistical index (0%–100%) measured heterogeneity, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. A fixed effects model was applied if I^2 was less than 50%, otherwise, a random effects model was used.[36] Publication bias was assessed with a funnel plot. The significance threshold for p values was set at 0.05.

Results

Search results

A total of 19,718 relevant studies were obtained from databases, with 6211 duplicate records removed. After screening titles and abstracts, 73 studies were selected for full-text review. Based on selection criteria, 36 studies were further excluded, resulting in 37 eligible RCTs.[21–26,37–67] The search and screening process was detailed in Figure 1.

Characteristics of the included studies

Table 1 displayed the main characteristics of the studies included in the meta-analysis, while Tables S3–S5 provided further demographic details. A total of 37 RCTs with 3363 participants)[21–26,37–67] was included in the meta-analysis. Face-to-face PR was conducted in a hospital or clinic in 10 RCTs,[24,37,38,42,46–48,52,58,61] telerehabilitation PR (e.g., via telerehabilitation tools, videoconference, or phone call) was conducted in 25 RCTs,[21–23,25,26,39–41,44,45,49,50,53–57,59,60,62–67] and a combination of both was conducted in 2 RCTs.[43,51] In total, 22 RCTs[22,25,26,37–39,42,43,45–47,49–53,56,58,61,62,66,67] included patients previously hospitalized due to COVID-19 infection. Nine RCTs[21,24,40,44,48,59,60,63,65] included patients who had not been hospitalized following COVID-19 infection. Six RCTs[23,41,54,55,57,64] included a mixed population of both patients.

The interventions and controls were shown in Table 1, with further details provided in Table S6. The duration of PR ranged from 3 days to 16 weeks, 8 RCTs[26,38,44,45,47,52,59,60] had a duration ⩽4 weeks, 20 RCTs[21,22,24,25,37,40,41,43,48,49-51,54–57,62,64–66] had a duration with 4–8 weeks, 8 RCTs[23,39,42,46,53,61,63,67] had a duration of >8 weeks; 1 RCT[58] only mentioned the duration of PR ranged from admission to discharge. Breathing exercises were performed in 13 RCTs,[38,41,44,47,49,51,52,54,55,57,58,60,65] multicomponent exercises were performed in 9 RCTs,[26,46,48,53,59–61,66,67] and a combination of both exercises were performed in 15 RCTs.[21–25,37,39,42,43,45,50,56,62–64] PR programs varied in the number of sessions and intervention approaches employed. Only two studies mentioned the exercise intensities: one with "Low-intensity pulmonary rehabilitation"[40] and the other with "Moderate/Low-intensity aerobic exercises."[46] The control group received usual care, no treatment, was given an educational brochure explaining breathing exercises and self-management guidelines, or used a sham device.

Literature quality and bias assessment

The quality evaluation results of the RCTs are shown in Figure S1. Overall, 10 RCTs (27.0%)[37,38,40,43,49,52,62,63,66,67] showed a high risk of bias, 19 (51.4%)[21–24,26,39,42,44,45,48,51,54,56–60,64,65] showed some concern, and 8 (21.6%)[25,41,46,47,50,53,55,61] had a low risk of bias. Among the included RCTs, 6[41,44,46,59,60,64] were performed with double blinding, and the others were performed with single blinding, no blinding, or had an unclear design; only 3 RCTs[38,40,49] were inadequate for randomization; and 6

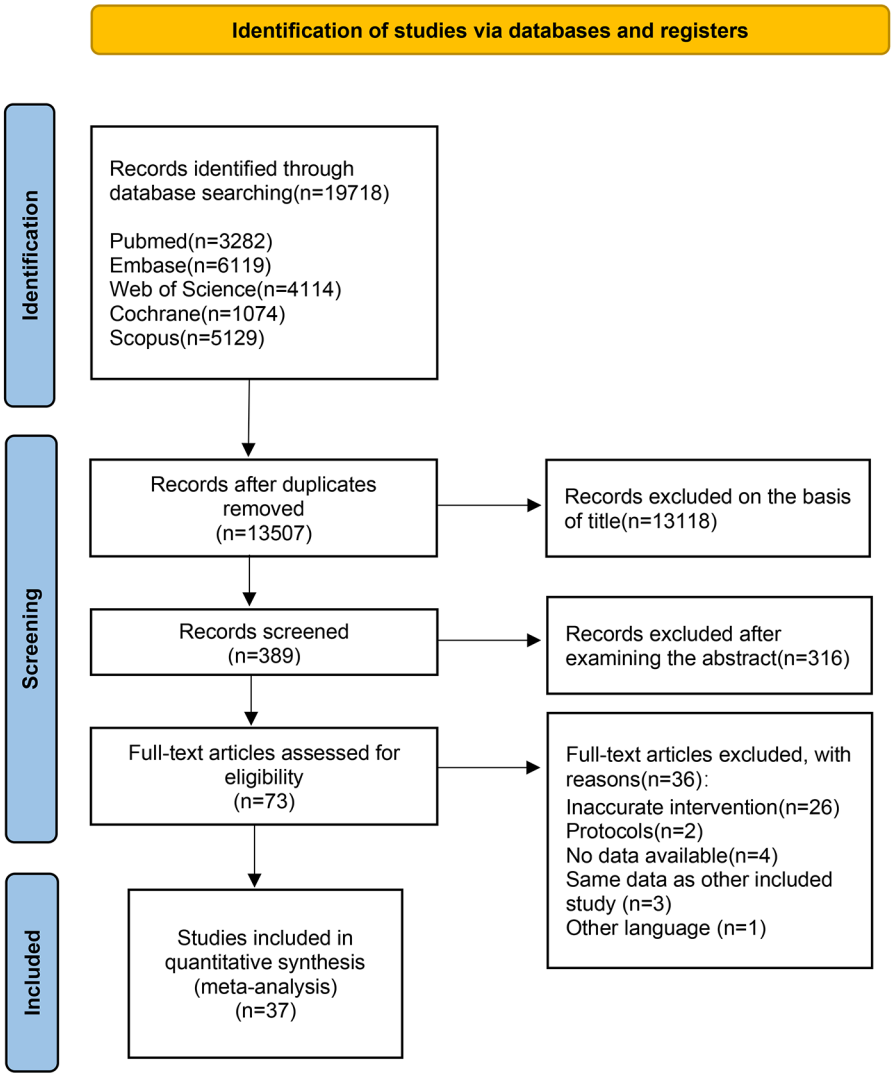

Figure 1. Flow diagram of the study.

RCTs[25,41,47,50,53,54] included the intention to treat analyses of missing data, while the others did not.

Clinical outcomes

Physical capacity. Fourteen RCTs[23,24,43–46,50,51,55,59,60,62,64,67] reported physical capacity outcomes in the 6MWT, showing significant improvement after PR compared to controls. TSA confirmed this finding: the *z*-curve reached the optimal information size and crossed the significance boundary. Statistically significant improvements were also observed in the 30STST[40,44,53,59,60,63,64] and handgrip strength[41,42,48,64,67] following rehabilitation intervention (Figure 2 and Figures S3–S5).

Lung function

The meta-analysis also indicated that PR improved FEV1 (L,[37,41,45,48,50,51,53,55,65,67] %pred[26,41,48,55,62,67]), FVC (L,[41,48,50,51,53,55,65,67] %pred[26,41,43,48,55,62,67]), MIP (cmH_2O,[26,38,41,54,67] %pred[41,54,67]), MEP (cmH_2O,[26,41,67] %pred[41,67]), while also reducing dyspnea[21,24–26,44,47–49,52,54–57,60–62,64,66] compared to controls. TSA showed that *z*-curves reached the optimal information size and crossed the significance boundary for FEV1 (L and %pred) and MIP (cmH_2O and %pred). However, the optimal information size was not reached or the significance boundary was not crossed for FVC (L, %pred) and MEP (cmH_2O, %pred; Figure 2 and Figures S6–S14).

Table 1. Demographic details of the included RCTs.

Author (year)	Country	Study design (RCT: M/S)	Participants characters	Sample size (intervention/control)	Intervention (A/B/C)*	Control	Duration of intervention (weeks)	Outcomes#
Bagherzadeh-Rahmani (2022)[37]	Iran	S	ICU COVID-19	30/15	[C]Pilates training	No intervention	8	④⑨
Bento (2023)[38]	US	S	Hospitalized patients recovered from COVID-19	30/30	[A]IMT and PT	Standard medical and PT	3	⑥
Bileviciute-Ljungar, (2024)[21]	Sweden	S	Nonhospitalized long-COVID-19	60/56	[C]Breathing and muscle strength exercises	Waiting list	8	⑧
Capin (2022)[39]	US	S	COVID-19 survivors	29/15	[C]Breathing, strength, aerobic, and balance exercises	Educational handout	12	⑧⑨
da Silva (2023)[22]	Brazil	S	Discharged COVID-19	33/34	[C]Breathing, aerobic, and muscle strength exercises, etc.	Usual care	8	⑨
De Souza (2021)[40]	Brazil	S	Nonhospitalized patients	104/92	Low-intensity pulmonary rehabilitation	No non-drug intervention	6	②⑩
Del Corral (2022)[41]	Spain	S	Long-COVID-19 symptoms (32% hospitalized)	44/44	[A]Respiratory muscles training	The placebo device	8	③④⑤⑥⑦⑨⑪⑫
Elhamrawy (2023)[42]	Jordan	S	Older hospitalized long-COVID-19 patients	18+18/18	[C]Tai chi exercise/ [B] Aerobic training	No intervention	12	③⑩
Elyazed (2024)[23]	Egypt	S	Long-COVID-19 (hospitalized or home, no ICU)	34/34	[C]Respiratory muscle, resisted, and walking exercises	No exercise program	12	①⑧⑨⑩

(Continued)

Table 1. (Continued)

Author (year)	Country	Study design (RCT: M/S)	Participants characters	Sample size (intervention/control)	Intervention (A/B/C)*	Control	Duration of intervention (weeks)	Outcomes#
Fares (2023)[43]	Egypt	S	Post hospitalization severe COVID-19	50/50	[C]Breathing, circuit, and walking exercise	Continued medications	6	①⑤
Gomes (2024)[24]	Brazil	S	With long-COVID-19 syndrome	18/16	[C]Lung expansion, IMT, strength, and aerobic exercises	Educational lectures	6	①⑧⑩
Gonzalez-Gerez (2021)[44]	Spain	S	Nonhospitalized COVID-19 in the acute phase	21/21	[A]Breathing exercises	No intervention	1	①②⑧⑬
Hashemi (2023)[45]	Iran	S	Discharged COVID-19	38/38	[C]Breathing, strength, and endurance exercises	Routine post-discharge care	4	①④
Ibrahim (2023)[46]	Saudi Arabia	S	Post-discharge older COVID-19	24+25/24	[B]Moderate / Low-intensity aerobic exercises	Medical care and advice	10	①⑨⑪⑫
Javaherian (2023)[47]	Iran	S	Hospitalized severe COVID-19	20/20	[A]Breathing exercises	Basic care	3 days	⑧
Jimeno-Almazán (2022)[48]	Spain	S	Nonhospitalized long-COVID-19 (mild acute infection)	19/20	[B]Resistance and intensity exercises	Follow the WHO guidelines	8	③④⑤⑧⑨⑩⑪⑫
Kalantari (2021)[49]	Iran	S	ICU COVID-19	30/30	[A]Breathing exercises	Routine hospital care	8	⑧⑨⑩
Li (2022)[50]	China	M	Post-discharge COVID-19	59/61	[C]Breathing, aerobic, and LMS exercises.	Education	6	①④⑤⑧⑨
Liu (2020)[51]	China	M	Elderly hospitalized COVID-19	38/38	[A]Breathing exercises	No intervention	6	①④⑤⑨⑪⑫

(Continued)

Table 1. (Continued)

Author (year)	Country	Study design (RCT: M/S)	Participants characters	Sample size (intervention/control)	Intervention (A/B/C)*	Control	Duration of intervention (weeks)	Outcomes#
Liu (2021)[52]	China	S	Hospitalized severe COVID-19	64/64	[A]Qigong exercise (Liu Zi Jue) and acupressure therapy	Conventional treatment	3	⑧⑩⑪
Longobardi (2023)[53]	Brazil	S	COVID19 patients discharged from ICU	25/25	[B]Aerobic and strengthening exercises	General advice	16	②③④⑤⑨⑩⑪⑫
McGregor (2024)[25]	UK	M	Discharged long-COVID-19	298/287	[C]Breathing, aerobic, Pilates, and yoga	Best practice usual care	8	⑧⑨⑪⑫
McNarry (2022)[54]	UK	S	Long-COVID-19 (discharged or home)	224/57	[A]Inspiratory muscle exercises	Usual care	8	⑧⑥⑨
Okan (2022)[55]	Turkey	S	Long-COVID-19 (presented to clinic with dyspnea)	26/26	[A]Breathing exercises	Exercises brochure	5	①④⑤⑧⑨
Paneroni (2024)[26]	Italy	M	Residual disability after hospitalization for COVID-19	40/39	[B]Aerobic and muscle-strengthening exercises	Not receive exercise program	4	①④⑤⑥⑦⑧⑨⑩
Pehlivan (2022)[56]	Turkey	S	COVID-19 discharged within 4 weeks	20/20	[C]Breathing and aerobic exercises	Exercise brochure	6	⑧⑨⑩⑪
Philip (2022)[57]	UK	S	Long COVID-19 (17% hospitalized)	74/76	[A]English National Opera breathe exercises	Usual care	6	⑧⑨⑫
Qingguang (2022)[58]	China	S	Hospitalized COVID-19 patients	52/52	[A]Liu-zi-jue exercise	Conventional treatment	To discharge	⑧⑩⑪
Rodriguez-Blanco (2021)[59]	Spain	S	Nonhospitalized COVID-19 in the acute phase	20/20	[B]Resistance and strength exercises	No intervention	1	①②⑬

(Continued)

Table 1. (Continued)

Author (year)	Country	Study design (RCT: M/S)	Participants characters	Sample size (intervention/ control)	Intervention (A/B/C)*	Control	Duration of intervention (weeks)	Outcomes#
Rodríguez-Blanco (2022)[60]	Spain	S	Nonhospitalized COVID-19 in the acute phase	34+29/ 25	[A]Breathing / [B]Strength exercise	No intervention	2	①②⑧⑩⑬
Romanet (2023)[61]	France	M	Hospitalized long-CARDS	27/33	[B]Endurance training rehabilitation	Standard physiotherapy	13	⑧⑨
Şahın (2023)[62]	Turkey	S	COVID-19 survivors (ward or ICU >10 days)	24/24	[C]Breathing, strength exercises, and regular walking	No tele-coaching	8	①④⑤⑧⑨⑪⑫
Samper-Pardo (2023)[63]	Spain	S	Nonhospitalized long COVID-19	52/48	[C]Respiratory physiotherapy and physical exercise; etc.	Usual treatment	12	②⑨
Sari (2022)[64]	Turkey	S	Long-COVID-19 (83% hospitalized)	13/13	[C]Breathing, resistance, and inspiratory muscle exercises	Breathing, resistance exercises	6	①②③⑧⑨⑩⑪⑫
Sedaghati (2023)[65]	Iran	S	Older adults COVID-19	15/15	[A]Breathing exercises	Necessary treatments	8	④⑤
Simpson (2023)[66]	UK	S	Hospitalized COVID-19	20/20	[B]Strength-based movements	Wait-list	6	⑧⑨⑩⑪⑫
Teixeira (2022)[67]	Brazil	S	Discharged COVID-19	32/32	[B]Resistance and aerobic exercises	No intervention	12	①③④⑤⑥⑦

M/S, multi-center/single-center; RCT, randomized control trial; Intervention*, more details in Table S6, [A]breathing exercises (exercises to strengthen respiratory muscles, breathing control exercises, airway clearance techniques, thoracic expansion, Liu-zi-jue exercises, etc.), [B]multicomponent exercises (integrated of aerobic, strength, resistance, endurance exercises, etc.), [C]combination of both; ICU, intensive care unit; CARDS, COVID-19-related acute respiratory distress syndrome; IMT, inspiratory muscle training; PT, physical therapy; LMS, lower limb muscle strength; Outcomes#: ① 6MWT, ② 30STST, ③ Handgrip, ④ FEV1 (L,%pred), ⑤ FVC (L,%pred), ⑥ MIP (cmH_2O, %pred), ⑦ MEP (cmH_2O,%pred), ⑧ Dyspnea, ⑨ HRQoL, ⑩ Fatigue, ⑪ Depression, ⑫ Anxiety, ⑬ Brog Scale.

Outcomes	No. of Studies	No. of Participants (Intervention/Control)	MD/SMD (95%CI)	Favors control	Favors intervention	P-value	I^2
Physical and functional capacities							
6MWT	14	406/388	77.95 [50.91, 104.99]			<0.001	93%
30STST	7	253/229	2.65 [0.87, 4.44]			0.004	85%
Handgrip	5	106/113	0.50 [-0.00, 1.00]			0.05	66%
Respiratory function							
FEV1	10	293/292	0.38 [0.14, 0.63]			0.002	89%
FVC	8	228/242	0.21 [0.08, 0.34]			0.001	35%
FEV1(%pred)	6	159/168	4.30 [1.94, 6.67]			0.0004	0%
FVC(%pred)	7	209/218	6.94 [5.12, 8.76]			<0.001	30%
MIP	5	223/160	14.08 [8.09, 20.07]			<0.001	0%
MEP	3	93/101	11.05 [0.58, 21.51]			0.04	2%
MIP(%pred)	3	167/101	17.07 [10.24, 23.91]			<0.001	42%
MEP(%pred)	2	56/64	12.31 [5.23, 19.39]			0.0007	36%
Dyspnea	18	809/725	-0.70 [-1.04, -0.37]			<0.001	88%
HRQoL	19	910/832	0.84 [0.44, 1.25]			<0.001	93%
Physical health	11	401/388	0.80 [0.30, 1.30]			0.002	91%
Mental health	10	373/359	0.49 [0.09, 0.88]			0.02	85%
Fatigue	12	403/382	-0.58 [-1.04, -0.13]			0.01	89%
Depression	10	483/468	-0.35 [-0.73, 0.03]			0.07	84%
Anxiety	9	466/456	-0.60 [-1.01, -0.18]			0.005	86%
Perceived effort							
Borg Scale	3	66/59	-1.80 [-2.32, -1.29]			<0.001	14%

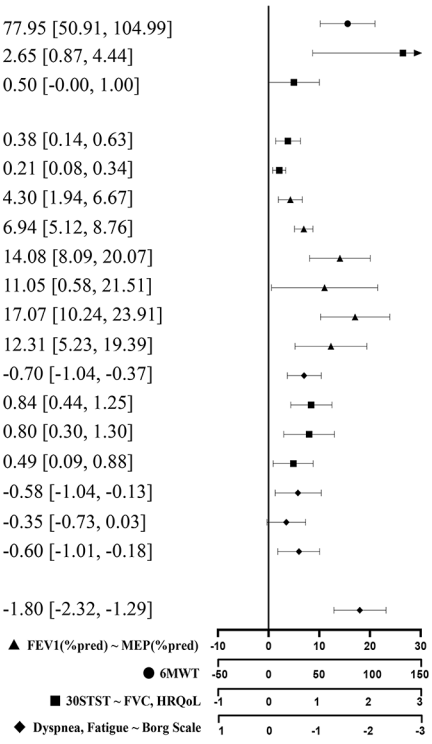

Figure 2. Treatment outcomes of rehabilitation interventions versus control group.

HRQoL, fatigue, anxiety, depression, and modified Borg Scale

Nineteen RCTs[22,23,25,26,37,41,46,48–51,54–57,61–63,66] reported overall QoL, and the pooled estimate showed that PR effectively improved HRQoL, in both the physiological and mental health dimension. The meta-analysis demonstrated that PR reduced fatigue[23,24,26,40,42,48,49,52,53,56,60,64] and anxiety,[25,41,46,48,51,57,62,64,66] decreasing the score on the modified Borg Scale[44,59,60] compared to controls. However, no effect on depression[25,41,46,48,51,52,56,62,64,66] was detected (Figure 2 and Figures S15–S19).

Subgroup analysis

A prespecified subgroup analysis based on exercise duration of PR indicated that when PR duration ⩽4 weeks, rehabilitation led to improvements in the 6MWT but did not improve FEV1 (L, %pred), FVC (%pred), HRQoL, or fatigue. When PR duration was between 4 and 8 weeks, significant improvements were observed in 6MWT, FEV1 (L, %pred), FVC (L, %pred), HRQoL, and fatigue relief. When PR duration >8 weeks, rehabilitation led to further improvements in the HRQoL and fatigue, but no additional improvements in the 6MWT, FEV1 (L), and FVC (L) were observed. An analysis based on exercise training types of PR revealed that breathing exercises improved 6MWT, lung function (FEV1 (L, %pred), FVC (L, %pred)), and HRQoL, but had no effect on fatigue; multicomponent exercises enhanced 6MWT performance and reduced fatigue without impacting lung function or HRQoL; the combination of both types improved 6MWT, FEV1 (L), FVC (%pred), HRQoL, and reduced fatigue (Figure 3 and Figures S3, S6–S9, S15, S16).

Adverse events

Adverse events were reported in 16 RCTs. Nine of these[21,26,39,47,48,53,55,56,66] showed no adverse events in either group, two studies[25,50] reported persistent/significant disability, hospitalization/

Outcomes	No. of studies	No. of Participants (Intervention/Control)	MD/SMD (95%CI)	Favors control	Favors intervention	P-value	I^2
Exercise duration							
≤ 4 weeks							
6MWT	4	101/94	116.80 [95.04, 138.56]			<0.001	0%
FEV1	2	79/79	0.51 [-0.59, 1.62]			0.36	97%
FVC	1	44/44	0.00 [-0.36, 0.36]			1.00	-
FEV1(%pred)	2	81/81	1.78 [-3.90, 7.46]			0.54	47%
FVC(%pred)	2	81/81	3.64 [-7.50, 14.77]			0.52	65%
HRQoL	3	111/111	0.17 [-0.27, 0.62]			0.45	64%
Fatigue	4	160/153	-0.14 [-0.70, 0.43]			0.64	83%
4-8 weeks							
6MWT	7	215/220	68.84 [56.24, 81.44]			<0.001	15%
FEV1	7	221/212	0.38 [0.11, 0.64]			0.005	89%
FVC	6	191/197	0.24 [0.11, 0.38]			0.0005	45%
FEV1(%pred)	4	110/111	5.12 [2.63, 7.61]			<0.001	0%
FVC(%pred)	5	160/161	7.46 [5.58, 9.33]			<0.001	0%
HRQoL	14	723/666	0.69 [0.31, 1.06]			0.0003	89%
Fatigue	6	200/186	-0.77 [-1.34, -0.20]			0.008	83%
> 8 weeks							
6MWT	3	90/74	52.27 [-14.37, 118.90]			0.12	98%
FEV1	2	37/45	-0.03 [-0.36, 0.31]			0.88	0%
FVC	2	37/45	-0.01 [-0.37, 0.36]			0.98	0%
FEV1(%pred)	1	12/20	-2.52 [-14.20, 9.16]			0.67	-
FVC(%pred)	1	12/20	0.00 [-10.06, 10.06]			1.00	-
HRQoL	4	150/129	1.89 [-0.00, 3.78]			0.05	98%
Fatigue	3	73/73	-0.99 [-1.56, -0.42]			0.0007	62%
Exercise training types							
Breathing exercises							
6MWT	4	110/103	63.79 [41.44, 86.13]			<0.001	0%
FEV1	4	121/121	0.36 [0.05, 0.67]			0.02	78%
FVC	4	121/121	0.32 [0.04, 0.60]			0.02	57%
FEV1(%pred)	2	70/70	5.56 [0.71, 10.42]			0.02	0%
FVC(%pred)	2	70/70	5.54 [0.92, 10.17]			0.02	0%
HRQoL	6	305/244	0.99 [0.22, 1.77]			0.01	94%
Fatigue	3	123/116	-0.17 [-0.98, 0.63]			0.68	88%
Multicomponent exercises							
6MWT	4	104/84	76.43 [5.50, 147.37]			0.03	83%
FEV1	3	56/65	0.05 [-0.25, 0.34]			0.76	0%
FVC	3	56/ 65	0.04 [-0.28, 0.36]			0.81	0%
FEV1(%pred)	3	68/77	-0.67 [-6.96, 5.63]			0.84	0%
FVC(%pred)	3	68/77	1.60 [-3.78, 6.98]			0.56	0%
HRQoL	5	146/129	0.63 [-0.13, 1.39]			0.11	89%
Fatigue	5	125/122	-0.86 [-1.45, -0.28]			0.004	79%
Combination of both							
6MWT	7	218/223	87.51 [68.79, 106.24]			<0.001	71%
FEV1	3	116/106	0.62 [0.18, 1.06]			0.006	92%
FVC	1	51/56	0.04 [-0.27, 0.35]			0.80	-
FEV1(%pred)	1	21/21	4.95 [1.95, 7.95]			0.001	-
FVC(%pred)	2	71/71	8.07 [5.94, 10.20]			<0.001	13%
HRQoL	8	459/459	0.90 [0.19, 1.62]			0.01	95%
Fatigue	5	95/92	-0.65 [-1.21, -0.09]			0.02	70%

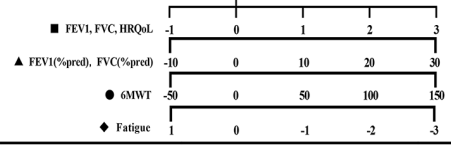

Figure 3. Subgroup analyses of the primary outcomes of rehabilitation interventions versus control group.

prolongation of hospitalization, stomach ulcer, and uncomfortable symptoms in both groups, one study[38] noted minor oxygen desaturations in the intervention group. Three studies[41,60,67] reported symptom exacerbation, hospitalization, or ICU admission in control group. One study[63] reported reinfection with COVID-19 as an adverse effect but did not specify the group affected (Table S7).

Quality of evidence

The GRADE assessment for certainty was moderate for 6MWT, 30STST, FVC (L), FVC (%pred), MIP (%pred), MEP (%pred), and fatigue; it was low for handgrip, FEV1 (L), FEV1 (%pred), MIP (cmH_2O), MEP (cmH_2O), dyspnea, HRQoL, depression, anxiety, and the modified Borg Scale. The details are summarized in the Supplemental Appendix (Figure S20).

Discussion

This systematic review synthesized evidence from 37 RCTs that examined the effects of PR in patients with long COVID-19 symptoms. Compared to the control group, PR resulted in statistically significant and clinically important improvements in physical capacity (as measured using the 6MWT, 30STST, and handgrip test), respiratory function (based on FEV1, FVC, MIP, MEP, and dyspnea), HRQoL, fatigue, and anxiety; the results did not reach statistical significance for depression. Subgroup analyses showed that PR programs ⩽4 weeks enhanced 6MWT, 4–8 weeks improved 6MWT, lung function, HRQoL, and reduced fatigue, while programs >8 weeks improved HRQoL and fatigue reduction; exercise type analysis indicated breathing exercises improved 6MWT, lung function, and HRQoL, multicomponent exercises increased 6MWT and reduced fatigue, and their combination optimized all outcomes.

Our review had several strengths. First, compared to recently published meta-analyses (Table S8), we were able to summarize and present the effect of PR through multiple dimensions with more RCTs. Second, we performed TSA with adjusted CIs to control for the risk of random error due to multiple outcomes, sparse data, and repetitive testing on accumulated data. The GRADE assessment for the certainty of evidence was also run to assess the certainty of the results. Third, we performed subgroup analyses to compare the type of PR (breathing exercises, multicomponent exercises, and a combination of both) and the duration of PR (⩽4 weeks, 4–8 weeks, and >8 weeks) on the symptoms and physical function of long COVID-19 patients.

In agreement with most previous systematic reviews (Table S8), our findings indicate that PR is associated with an improvement in the physical capacity of patients with long COVID-19. The TSA indicated that more than 80% of the RIS was accrued, and the certainty of evidence was moderate. Exercise intolerance, measured as physical capacity, is a key feature of acute and chronic lung disease. A previous study[68] reported that a minimally important difference of 20–30 m in the 6MWT could be considered a significant change in physical capacity in patients with acute respiratory distress syndrome or acute respiratory failure. Our review found that PR improved the 6MWT with a mean difference of 77.95 m with a 95% CI of 50.91–104.99 m in patients with long COVID-19. We also found that the improvement in the 6MWT following PR was larger than the effect demonstrated in similar reviews regarding COPD (43.93 m)[69] and interstitial lung disease (ILD) (40.07 m).[70] It is reasonable to assume that patients with long COVID-19 may experience improvements of larger magnitude following PR, because most patients may simply be recovering from COVID-19 and may not have had preexisting or longstanding exercise limitations as seen in patients with chronic respiratory disease.

We also found that PR significantly improved lung function, HRQoL, and fatigue. TSA showed that z-curves reached the optimal information size for some outcomes, and the certainty of evidence was low to moderate. These results are inconsistent with those of some previous reviews (Table S8). There may be many factors contributing to this difference, such as the initiation time of intervention, the exercise training duration, the exercise training types, the severity of COVID-19, and comorbidities at enrollment, among others. Therefore, we also performed subgroup analyses according to the type and duration of PR.

In subgroup analyses of different PR periods, we found that PR duration ⩽4 weeks led to improvements in the 6MWT distance, suggesting that short-term PR can enhance physical performance. The improvement in the 6MWT was greater for

PR periods ⩽ 4 weeks (116.80 m) than for 4 and 8 weeks (66.58 m), which may suggest that early initiation of PR may be more beneficial to patients with long COVID-19. When the PR duration was between 4 and 8 weeks, rehabilitation intervention may have a greater benefit in patients with long COVID-19. The improvements in 6MWT, lung function, HRQoL, and fatigue were observed in 4 and 8 weeks PR intervention. Again, patients may have simply been recovering from COVID-19 and may not have had any exercise limitations as seen in patients with chronic respiratory disease; thus, a shorter PR duration (over 4 weeks) in these populations may benefit patients[71] compared to chronic respiratory diseases (such as COPD, over 8 weeks),[72] and our results support this view. However, when PR duration > 8 weeks, rehabilitation led to further improvements in the HRQoL and fatigue, some benefits may continue to accrue with extended PR, but no additional improvements in the 6MWT and lung function were observed. This may indicate that extended programs may indeed offer additional benefits, but physical performance improvements may plateau after 4–8 weeks, and the impact of extended PR on lung function requires further investigation due to limited study numbers. While early initiation and a 4 to 8-week duration of PR for long COVID-19 syndromes are considered crucial, the optimal timing for starting rehabilitation interventions and the ideal duration of PR programs to maximize benefits for these patients still require further investigation.

In subgroup analyses of different exercise training types, we found that a combination of both breathing and multicomponent exercises was associated with better improvement in all of the primary outcomes (physical capacity, lung function, HRQoL, and fatigue). As presented in Table S6, the methods of rehabilitation intervention vary significantly across different studies. For physical training, most studies involved a combination of aerobic training (such as walking, jogging, and cycling), resistance training, balance exercises, functional activities, stretching, and biobehaviourally informed elements; besides, the intensity of the rehabilitation interventions was not clear in most studies, the number and duration of sessions across various studies were different. Thus, we categorized them as multicomponent exercises. In line with a former review,[72] multicomponent exercises, also considering both aerobic and resistance exercises, etc., were associated with improvement in fatigue, and psychological condition (6MWT). Additionally, the included studies focused on breathing exercises, which included pursed lip breathing, diaphragmatic breathing, incentive spirometer use, airway clearance techniques, and coughing training, either in isolation or combination. We observed an improvement in lung function following breathing exercises, but not with multicomponent exercises. As previous studies have mentioned,[73] breathing exercises, particularly inspiratory muscle training, may improve inspiratory muscle strength and endurance, and alleviate dyspnea, which could subsequently improve physical capacity (6MWT) and the HRQoL; however, multicomponent exercises may not improve the pressure-generating capacity of the inspiratory muscles. The majority of the included studies investigated the effectiveness of comprehensive rehabilitation interventions that included both breathing exercises and multicomponent exercises, and we found a synergistic effect when these two approaches are combined. However, the PR programs varied among the studies included in our review in terms of the number of sessions and intervention approaches employed, we are still unable to determine which specific approaches and intensities are more beneficial for patients. Thus, a careful analysis of patients presenting with functioning impairments, and an individualized rehabilitation approach included both breathing exercises and multicomponent exercises could play a crucial role in reducing the consequences of long-term COVID-19 symptoms.

In a previous study, COVID-19 patients had a markedly elevated chance of acquiring mental health issues, particularly anxiety and depression.[74] In our review, there was a significant difference in anxiety but not depression following PR compared to controls. The results are inconsistent among current reviews,[11,13,19] reasons for this discrepancy may include the limited number of publications included in previous reviews and the lack of a specific therapy established to treat symptoms. Maybe comprehensive treatment therapies, including psychotherapy, medicine, and exercise therapy, can reduce the symptoms of anxiety and depression through a variety of mechanisms.

Our findings have some implications for practice. First, as long COVID-19 has been recognized as a public health problem[1] with a heavy economic burden[75] and we are still in the midst of the

pandemic,[6,7] it is of high importance to develop a safe and effective strategy for these long COVID-19 based on high-quality evidence. Our results indicate that PR is effective and safe in patients with long COVID-19. It is applicable to a broad population and may also be valuable for future pandemics. Besides, in relation to the duration of PR, in addition to advocating for the prompt initiation of PR, it is crucial to highlight the significant benefits that a 4–8 week PR program can offer to COVID-19 patients, and prolonging the PR program beyond the initial 8 weeks may produce greater gains. Furthermore, the synergistic approach of combining exercise training with breathing training for these patients is more beneficial. It is essential to develop an exercise program that includes aerobic exercise, resistance training, and flexibility training tailored to their individual capabilities and goals to improve psychological condition. The intensity, frequency, and duration of these exercises could be adjusted based on the patient's tolerance and progress. In conjunction with this, breathing exercises—including diaphragmatic breathing, pursed lip breathing, incentive spirometer use, airway clearance techniques, and coughing training—should be integrated into the program to assist in improving lung function and overall effectiveness.

There were several limitations to our review. First, the overall evidence GRADE was low to moderate, and bias in the included studies in terms of allocation concealment, blinding, and missing data may have led to an overestimation of the treatment outcomes. Second, due to heterogeneity among the included studies in terming of the exercise training types, PR duration, intensities, session frequencies, baseline disease severity levels, disease progression, comorbidities, and other factors, further subgroup analysis is limited. Third, as there were no standard measurement tools for HRQoL, fatigue, dyspnea, depression, or anxiety, SMD analysis was used, and TSA could not be performed on these results due to the large number of rating scales used in the RCTs. This may have led to an underestimation or overestimation of the treatment outcomes.

Conclusion

This systematic review and meta-analysis found that PR significantly improves physical capacity, respiratory function, HRQoL, fatigue, and anxiety in patients with long COVID-19, with the certainty of evidence being low to moderate. Early initiation of rehabilitation and 4–8 weeks duration of PR are important in managing long COVID-19 syndromes, with longer PR durations potentially offering additional benefits. The integration of both breathing exercises and multicomponent training within PR is found to be the most beneficial for patients with long COVID-19.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

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Jian Kang: Writing – original draft; Writing – review & editing.

Wei Tan: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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Supplemental material

Supplemental material for this article is available online.

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