EVIDENCE SUMMARY

RESEARCH QUESTION: **Among long COVID-19 patients with residual pulmonary symptoms, should pulmonary rehabilitation be done to improve pulmonary function and quality of life?**

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RECOMMENDATION

Recommendation	Certainty of Evidence	Strength of Recommendation
We suggest individualized pulmonary rehabilitation with pre-intervention medical clearance for patients with long COVID syndrome who show residual pulmonary symptoms to improve pulmonary function and quality of life.	Very Low	Weak

Consensus Issues
Pulmonary rehabilitation is a multi-component and a multi-disciplinary process which aims to improve functionality and quality of life. This non-pharmacologic intervention, however, may not be available in all centers especially in smaller institutions. Despite this, and although the included studies had small sample sizes and there was high heterogeneity in intervention strategies, the documented harms are very low and the balance of effects favors the perceived benefits (both in respiratory and non-respiratory outcomes).

KEY FINDINGS

- A total of five randomized controlled clinical trials were evaluated which investigated the effect of pulmonary rehabilitation on the pulmonary function and quality of life among long COVID patients with residual pulmonary symptoms.
- Pooled results showed significant benefit on pulmonary function test (FEV, FVC, and FEV1/FVC) as well as an increase in exercise capacity and physical fitness score after PR as shown by a higher 6MWT and VO_2max in those who underwent pulmonary rehabilitation (PR).
- Other than this, participants in the PR group showed significant improvement in health-related QoL scores across all domains after the intervention and a significantly lower post-intervention self-rated anxiety score compared to the control group.
- Lastly, with regards to safety outcomes, the most common symptoms experienced ranged from chest tightness, cough, and weakness with chest tightness occurring more in the PR group.
- Certainty of evidence was very low because of serious risk of bias and imprecision in most of the critical outcomes.

PREVIOUS RECOMMENDATION
As of 19 February 2021

We recommend individualized pulmonary rehabilitation with pre-PR medical clearance for long COVID patients who show residual respiratory symptoms. *(Moderate certainty of evidence; Strong recommendation)*

Consensus Issues
The panel recommends that the start and duration of pulmonary rehabilitation for each patient should be individualized depending on the assessment of the pulmonologist. Studies showed that the assessment of pulmonary rehabilitation should start at least 6months after their hospital admission and last as long as 6 weeks. **However, recommendation on when the pulmonary rehabilitation should start differs across professional medical societies**. An international task force from the European Respiratory Society and American Thoracic society recommends that the assessment should be done 6-8 weeks after hospital discharge in order to identify patients who will have residual symptoms, In addition, pulmonary rehabilitation for other conditions last for 6-9 weeks.

INTRODUCTION

Long-COVID, also called post-acute COVID-19 syndrome (PACS), is an umbrella term for a complex multisystem secondary condition that follows COVID-19, irrespective of its severity [1,2]. The World Health Organization (WHO) defines post-COVID-19 condition as persistent symptoms and/or signs, developing during or after an acute COVID-19 illness and lasting for at least 2 months and persisting beyond 12 weeks from the acute disease, that cannot be explained by an alternative diagnosis [3]. Although the magnitude of this new health condition is still unknown, its prevalence has been estimated to be about 20% of the individuals who have recovered from the acute phase of SARS-CoV-2 infection [4]. The most commonly reported symptoms among long COVID patients are muscular weakness, fatigue, and breathlessness [5,6]. A systematic review on respiratory function in 380 patients with post-COVID-19 demonstrated that altered respiratory function and impaired diffusion capacity was observed in about 40% of patients at 1 to 3 months after hospital discharge [7].

Pulmonary rehabilitation (PR) is one of the most effective management strategies to improve shortness of breath, health status, and exercise tolerance of patients with COPD. It also leads to a reduction in symptoms of anxiety and depression [7]. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) statement concluded that PR could reduce dyspnea, increase exercise capacity, and improve QoL in individuals with chronic obstructive pulmonary disease (COPD) and may also result in meaningful short-term benefits in patients with interstitial lung diseases (ILD) and other lung conditions with similar pathophysiology like COVID-19 infection [8,9]. A review suggested that a comprehensive rehabilitative approach comprising a multidisciplinary team offering cardiorespiratory, neuromuscular, and psychological interventions should be offered for patients with post-COVID-19 [10].

REVIEW METHODS

According to the research question, we have included only randomized controlled trials (RCTs) which have determined the effect of “pulmonary rehabilitation” on dyspnea, exercise capacity, lung functions, fatigue, and quality of life (QoL) in patients (of any age and of both gender) with long COVID as defined by WHO [3]. Trials conducted on hospitalized COVID-19 patients and trials whose experimental intervention was limited to drugs or dietary supplements, non-randomized study designs, observational studies, case series, and case reports were excluded. Based on the criteria above, a comprehensive and systematic literature search to identify relevant studies in PubMed, Cochrane Library, WHO trial Registry, and ClinicalTrial.gov databases were done up to January 03, 2023. A preprint search was also done in medRxiv and bioRxiv. Our search strategy combined concepts related “post-COVID-19,” “lungs,” “respiratory impairment,” “long COVID,” “rehabilitation,” “randomized controlled trial,” “pulmonary rehabilitation,” “pulmonary function,” and “quality of life;” (See Appendix 2: Search Strategy). MeSH and free text search were also performed. Secondary searches were made by manually screening the bibliographies of identified articles and tracking the citing articles to determine the studies that were not identified by the database search (See Appendix 3: PRISMA Flow Diagram).

RESULTS

Four new RCTs were added to the existing data from the previous review, all of which were evaluated to have low to high-risk of selection and detection biases. All of the included studies [11-15] have full text prints available.

Characteristics of included studies

Of the five RCTs included, two were judged to have "low risk of bias" [12,14] and three had "some concerns" [11,13,14]. All trials reported utilization of randomization albeit detailed procedures regarding the allocation process were only described in one study [12]. Given the kind of intervention being studied (PR), blinding of both participants and professionals are difficult, if not impossible. Still, all of the included studies described that the functional outcomes were collected by blind assessors, while subjective data such as dyspnea, fatigue, and quality of life were personally reported by the participants mostly by answering validated questionnaires and follow-up surveys.

The five RCTs included in this review investigated a total of 414 participants, ages 18 years old and above, who met the criteria for PACS as per WHO definition. In all of the studies, patients were assessed at baseline and at the scheduled follow-up, the time frame of which ranges from 6 weeks to 28 weeks. One of the trials provided for multiple follow-ups to observe short term and long-term effects of PR [12].

Two of the included trials [11,12] assessed the effect of the experimental intervention in comparison to no rehabilitation / drug-only intervention or minimal rehabilitation intervention. While the study by Srinivasan et al. [15] compared the combination of pursed lip breathing exercises together with bhastrika pranayama to the breathing exercises performed with incentive spirometry alone. The two other remaining studies [13,14] randomly assigned subjects to receive either a 12-week Inspiratory Muscle Training (IMT) or usual care, the latter of which is based on the leaflets and recommendations by WHO. The delivery modality of the interventions was equally distributed between "with" and "without" monitoring and supervision. Intervention settings were mostly performed and administered at home due to the limitations set about by the pandemic.

With regards to the results, only one RCT sufficiently imputed data for drop-outs and also analyzed the data of the participants using the intention-to-treat analysis [12]. The remaining studies [11,13-15] did not provide data regarding this which makes them vulnerable to attrition bias (See Appendix 4: Characteristics of Included Studies)

Efficacy outcomes

Pulmonary Function Test

Pulmonary function, commonly measured through spirometry in terms of FEV1, FVC, FEV1/FVC ratio, and their percent predicted values, and lung volumes among others was designed as a primary outcome in three studies [11,12,15]. Pooled data showed significant improvement in FEV1 (MD 0.15, 95% CI 0.05-0.26; I^2=0%; moderate certainty) in the PR group (intervention) compared to the control group after intervention. This is supported by the study done by Liu et al. which measured the FEV1/FVC ratio between groups which presented significant improvement at 6 weeks from baseline on FEV1/FVC within the intervention group but not in the control group (MD 6.96%; 95% CI 4.08-9.84%; moderate certainty). On the other hand, with regards to changes in FVC, no significant difference was found (MD 0.14, 95% CI -0.11 to 0.4; I^2=75%; very low certainty).

Exercise Capacity and Physical Fitness

Only two studies [11,12] reported results for six-minute walking test (6-WMT) to demonstrate improvement on functional exercise capacity. This is measured in accordance with guidelines from the European Respiratory Society and American Respiratory Society and recorded as 6 min walking distance (6MWD) in meters. Pooled estimate of the effect of PR on 6-MWT (MD 58.77 meters, 95% CI 37.7-79.85; I^2=0%; moderate certainty) was in favor of those in the PR group. With regards the physical fitness, VO_2 max was measured in two of the included studies [13,14]. VO_2 max refers to how much oxygen your body can absorb

and use during exercise and is a method to determine cardiorespiratory fitness in an individual [16]. Pooled results showed higher mean change from baseline in the mean VO_2 max among patients in the PR group (MD 4.58, 95% CI 3.44-5.72; I^2=0%; moderate certainty).

Quality of Life (QoL) Assessment and Activities of Daily Living

The study by Liu and colleagues [11] used the eight-domain SF-36 QoL scale to measure the effect of PR on health-related QoL among patients with long COVID syndrome. No significant difference on SF-36 health-related QoL scores across all eight domains were found at baseline between participants who underwent PR (intervention) and those who did not (control). Only participants in the PR group showed significant improvement in health-related QoL scores across all domains after the intervention. On the other hand, no significant improvement was observed in the control group. In terms of difference in mean health-related QoL scores, patients who underwent PR when compared to controls showed a significant overall improvement in health-related QoL; thus, favoring PR (See Table 1).

Table 1. Pre and post-intervention assessments using SF-36 in both pulmonary rehabilitation (intervention) and (medication/non-rehabilitation) control groups.

QoL SF 36 Domains	PULMONARY REHABILITATION (n=36)			CONTROL (n=36)			MD of QoL Scores at Baseline (PR versus Control)	MD of QoL Scores Post-Intervention (PR versus Control)
	BASELINE	POST	PRE & POST DIFFERENCE	BASELINE	After 6 weeks	PRE & POST DIFFERENCE		
Physical health	52±6.2	71.6±7.6	**19.60** (95% CI 16.40, 22.80)	53.2±7.7	54.1±7.5	**0.9** (95% CI -2.61, 4.41)	**-1.20** (95% CI -4.43, 2.03)	**17.50** (95% CI 14.01, 20.99)
Body role function	61.2±6.6	75.9±7.9	**14.70** (95% CI 11.42, 17.98)	61.3±7.2	62.0±7.3	**0.7** (95% CI -2.65, 4.05)	**-0.10** (95% CI -3.29, 3.09)	**13.90** (95% CI 10.39, 17.41)
Physical pain	63.5±7.4	78.3±7.8	**14.80** (95% CI 11.29, 18.31)	63.5±8.1	62.9±7.9	**-0.60** (95% CI -4.30, 3.10)	**0** (95% CI -3.58, 3.58)	**15.40** (95% CI 11.77, 19.03)
General health	61.8±7.7	74.2±7.9	**12.40** (95% CI 8.80, 16.00)	61.8±8.4	61.4±6.9	**-0.40** (95% CI -3.95, 3.15)	**0** (95% CI -3.72, 3.72)	**12.80** (95% CI 9.37, 16.23)
Energy	60.6±6.9	75.6±7.1	**15.00** (95% CI 11.77, 18.23)	60.5±7.1	61.2±6.3	**0.70** (95% CI -2.40, 3.80)	**0.10** (95% CI -3.13, 3.33)	**14.40** (95% CI 11.30, 17.50)
Social function	59.4±7.2	69.8±6.4	**10.4** (95% CI 7.33, 13.47)	59.5±7.0	58.9±6.6	**-0.6** (95% CI -3.74, 2.54)	**-0.10** (95% CI -3.38, 3.18)	**10.90** (95% CI 7.90, 13.90)
Emotional role function	61.4±6.9	75.7±7.0	**14.30** (95% CI 11.09, 17.51)	61.4±7.3	60.8±7.3	**-0.6** (95% CI -3.97, 2.77)	**0** (95% CI -3.28, 3.28)	**14.90** (95% CI 11.60, 18.20)
Mental health	61.5±6.5	73.7±7.6	**12.2** (95% CI 8.93, 15.47)	61.6±7.2	62.1±7.6	**0.50** (95% CI -2.92, 3.92)	**-0.10** (95% CI -3.27, 3.07)	**11.60** (95% CI 8.09, 15.11)
INTERPRETATION							**No significant difference in QoL scores between PR and control groups at baseline**	**Significantly higher difference in mean QoL scores in PR group post-intervention (FAVORS PR)**

Abbreviations: MD, Mean Difference; PR, Pulmonary Rehabilitation; QOL; Quality of Life

On the other hand, the Short Form Health Survey-12 (SF-12) was used in the study of Li et al. [12] to measure the physical and mental status of the included subjects. Results showed that the mean difference was significant on the score of physical components between groups (MD 3.79 points, 95% CI 1.24-6.35) at 6 weeks from baseline, but not significant on the score of mental components (MD 2.18 points, 95% CI 0.54-4.90).

Anxiety and Depression

One study assessed anxiety and depression status of patients using self-rating anxiety scale (SAS) and self-rating depression scale (SDS) [11]. No significant difference SAS and SDS scores were found at baseline between participants who underwent PR (intervention) and those who did not (control). Post-intervention self-rated anxiety score was significantly lower in the PR group than the control group (MD -7.50; 95% CI -10.65 to -4.35; low certainty). While self-rated depression score was lower in the PR group compared to controls, difference in mean scores was not statistically significant (MD -1.30; 95% CI -4.32 to 1.72; very low certainty).

Table 2. Pre and post-intervention assessments using SF-36 in both pulmonary rehabilitation (intervention) and (medication/non-rehabilitation) control groups.

QoL SF 36 Domains	PULMONARY REHABILITATION (n=36)			CONTROL (n=36)			MD of SAS/SDS Scores at Baseline (PR versus Control)	MD of SAS/SDS Scores Post-Intervention (PR versus Control)
	BASELINE	POST	PRE & POST DIFFERENCE	BASELINE	After 6 weeks	PRE & POST DIFFERENCE		
Self-rated anxiety	56.3 ± 8.1	47.4 ± 6.3	**-8.90** (95% CI -12.25, -5.55)	55.8 ± 7.4	54.9 ± 7.3	**0.90** (95% CI -2.50, 4.30)	**0.50** (95% CI -3.08, 4.08)	**-7.50** (95% CI -10.65, -4.35)
Self-rated depression	56.4 ± 7.9	54.5 ± 5.9	**-1.90** (95% CI -5.12, 1.32)	55.9 ± 7.3	55.8 ± 7.1	**0.10** (95% CI -3.23, 3.43)	**-0.10** (95% CI -3.29, 3.09)	**-1.30** (95% CI -4.32, -1.72)
INTERPRETATION							**No significant difference in SAS/SDS scores between PR and control groups at baseline**	**Significantly lower difference in mean SAS scores in PR group post-intervention (FAVORS PR FOR ANXIETY)**

Safety Outcomes

Adverse Events

Only Li et al. [12] reported the adverse events associated with the interventions done. The most common symptoms experienced ranged from chest tightness, cough, and weakness. Other symptoms also described were sputum discharge, dizziness, and back pain among others. No serious adverse event occurred during the study period. Overall, no significant difference in the occurrence of adverse events during the whole study period is seen between the control group and PR group (RR 0.93; 95% CI -0.7 to 1.2; low certainty).

Table 3. Summary of Findings

Critical Outcomes	Basis (Number and Type of Studies, Total Participants)	Effect Size	95% Confidence Interval	Interpretation	Certainty of Evidence
FEV1	2 RCT (n=192)	MD 0.15	0.05, 0.26	Benefit	Moderate
FVC	2 RCT (n=192)	MD 0.14	-0.11,0.40	Inconclusive	Very Low
FEV/FVC	1 RCT (n=72)	MD 6.96	4.08, 9.84	Benefit	Low
Six-minute Walk Test	2 RCT (n=191)	MD 58.77 meters	37.70, 79.85	Benefit	Moderate
Peak VO2	2 RCT (n=174)	MD 4.58	3.44, 5.72	Benefit	Moderate
QOL: Physical Health	1 RCT (n=72)	MD 17.50 points	14.01, 20.99	Benefit	Low
QOL: Body Role Function	1 RCT (n=72)	MD 13.90 points	10.39, 17.41	Benefit	Low
QOL: Physical Pain	1 RCT (n=72)	MD 15.40 points	11.77, 19.03	Benefit	Low
QOL: General Health	1 RCT (n=72)	MD 12.80 points	9.37, 16.23	Benefit	Low

QOL: Energy	1 RCT (n=72)	MD 14.40 points	11.30, 17.50	Benefit	Low
QOL: Social Function	1 RCT (n=72)	MD 10.90 points	7.90, 13.90	Benefit	Low
QOL: Emotional Role Function	1 RCT (n=72)	MD 14.90 points	11.60, 18.20	Benefit	Low
QOL: Mental Health	1 RCT (n=72)	MD 11.6 points	8.09, 15.11	Benefit	Low
Self-rated anxiety	1 RCT (n=72)	MD -7.50 points	-10.65, -4.35	Benefit	Low
Self-rate depression	1 RCT (n=72)	MD -1.30 points	-4.32, 1.72	Inconclusive	Very Low
Adverse Events	1 RCT (n=119)	RR 0.93	-0.70, 1.2	Inconclusive	Low

Certainty of evidence

The overall certainty of evidence was rated very low due to the presence of risk of bias, inconsistency, and imprecision. The studies included in this meta-analysis used heterogenous outcome measures which made it difficult to draw comparisons among presented results. Similarly, all included studies are open-label trials and lacked the possibility of blinding, which may affect the assessment of outcomes. In addition, the sample size of some of the included trials were relatively small and therefore, making it difficult to generalize the results from the pooled outcomes since minor variations in the number of events may render treatment effect on some of the primary outcomes as non-significant. Lastly, most of the subjects included were those with mild and moderate PACS with the majority leaning towards the older age group which may undermine applicability to the younger age group and those with severe PACS.

RECOMMENDATIONS FROM OTHER GROUPS

As of 05 January 2023, there are five (5) guidelines on pulmonary rehabilitation on individuals with post-acute COVID syndrome or long COVID.

Group / Society / Network	Year	Recommendations	Certainty of Evidence / Strength of Recommendation
Turkish Society of Physical Medicine and Rehabilitation [17]	2021	Comprehensive PR is indicated for individuals with ongoing fatigue, respiratory symptoms, diminished activities of daily living, reduced exercise tolerance, and limited functionality 6 to 8 weeks following discharge. Comprehensive PR should be applied in a well-apalpha-lowered PR setting. After the assessment and program prescription by the PMR physician, an approach can be made with a core rehabilitation team consisting of PMR physician, nurse, physiotherapist and occupational therapist, as well as with a wider rehabilitation team including psychologist, nutritionist, speech and swallowing therapist, etc. according to the identified deficits and problems of the patient. The PR setting for the post-COVID-19 patients should be chosen based on the clinical status, existing impairments and characteristics of the patients.	None stated; Consensus of expert
Swiss Society for Pulmonologists (SSP) [18] Funke-Chambour (2021)	2021	SSP Recommendation: Patients after COVID-19 who present with persistent respiratory symptoms are recommended to undergo a rehabilitation program.	Strong Recommendation; Consensus reached
World Health Organization [20]	2022	A workforce for the rehabilitation of adults with post COVID-19 condition may include but is not limited to physiotherapists, occupational therapists, nurses, psychologists, speech and language therapists, physicians and social workers. Community health care workers may be required based on local needs. (Conditional recommendation for) For the clinical rehabilitation management of breathing impairment in adults with post COVID-19 condition we suggest using a combination of education and skills training on self-management strategies such as nasal breathing and pacing approaches and, in the absence of PESE, physical exercise training. Breathing control techniques could be offered to those presenting with a suboptimal breathing pattern, and psychological support may be useful to address contributing factors such as anxiety. (Conditional recommendation for)	Conditional Recommendation
British Thoracic Society [21] Singh (2020)	2020	Adapt and improve PR models to accommodate post-COVID patients: Timing: Survivors of COVID-19 who were either managed in the community or admitted to hospital and who require rehabilitation should be referred to their local PR service at least 6-8 weeks after recovery from COVID-19. Exercise: consider existing principles of exercise prescription for post-COVID patients with significant deconditioning and breathlessness. In addition, those with fatigue may benefit from graded exercise therapy. Other adaptations should be considered in the presence of post COVID fatigue, mood disturbances, and cognitive issues.	None stated; Consensus of expert

ONGOING STUDIES AND RESEARCH GAPS

As of 05 January 2023, there are 8 ongoing trials studying the effect of pulmonary rehabilitation to patients with post-COVID syndrome (See Appendix 8: Characteristics of Ongoing Trial). With the increasing burden of COVID-19 and its sequelae in the foreseeable future, more high-quality large studies with adequate power are required in order to confirm and further elucidate the findings above. In addition to this, upcoming trials should explore other outcomes such as cost-effectiveness, feasibility, and safety. Also, a common assessment strategy and outcome measure is highly suggested in order to be able to pool and compare the results of different trials in the future which in turn, can aid in formulating cohesive, generalizable, and evidence-based recommendations regarding the effect of pulmonary rehabilitation in patients with post COVID symptoms.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=4/10)

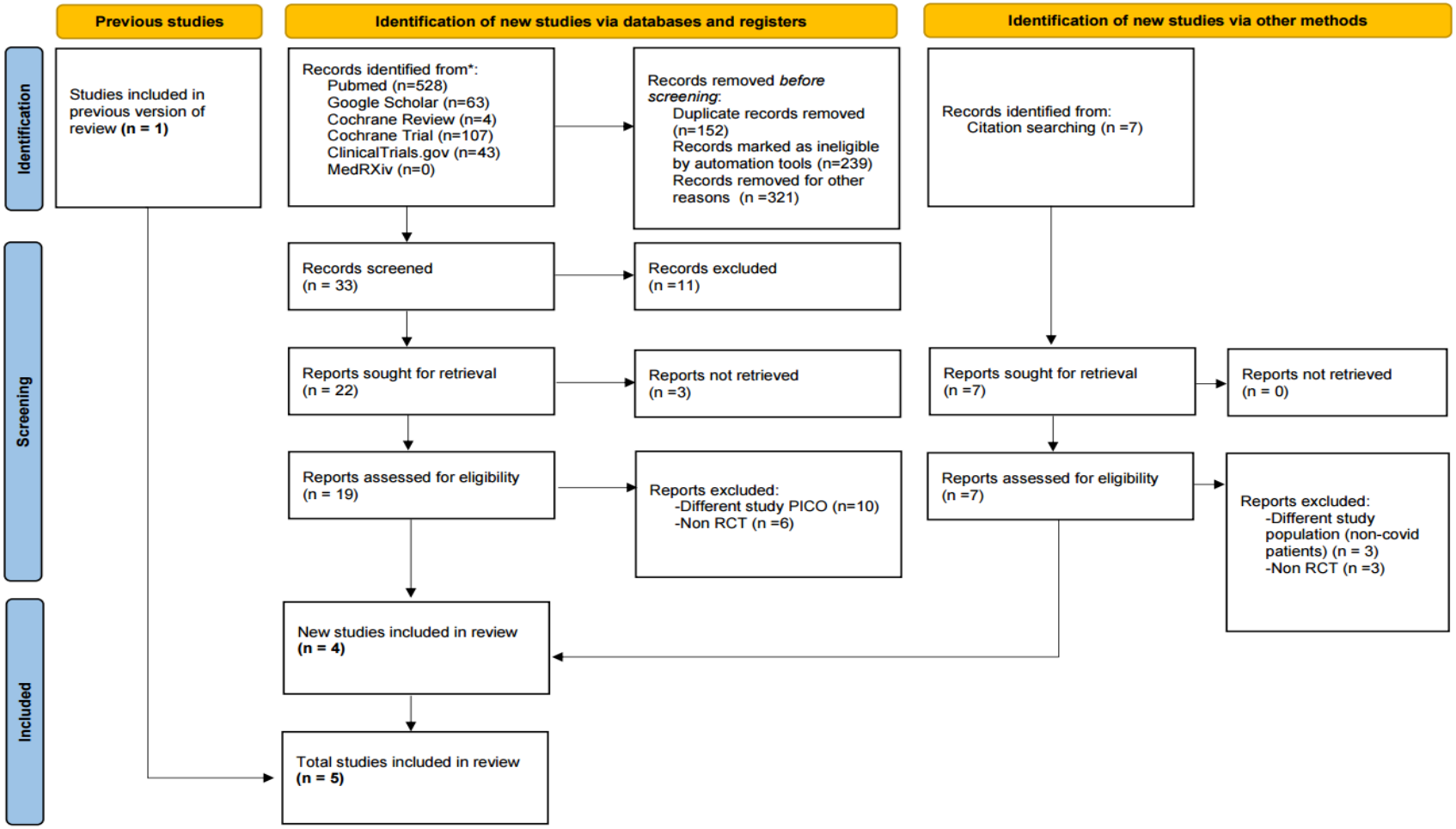
FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (4)					Globally, 7.5% of adults are experiencing persistent symptoms three or more months after their initial COVID-19 diagnosis. Nearly one in five American adults who have had COVID-19 still have "Long COVID" [22].
Benefits	Large (1)	Moderate (3)	Small	Varies			Observed **significant improvements** across secondary endpoints including presence of **dyspnea (p < 0.001)**, **fatigue (p < 0.001)**, and **quality of life (p < 0.001)**. **Pulmonary function parameters (forced expiratory volume in 1s, lung diffusion capacity, inspiratory muscle pressure) significantly increased during rehabilitation.** [24]
Harm	Large	Moderate (1)	Small (2)	Trivial (1)			**No serious adverse events** occurred during the study period. Eight patients were hospitalized, all for non-life-threatening reasons unrelated to COVID-19 or the intervention and all in the follow-up period. Most common adverse events are: chest tightness, weakness, cough. [12]
Certainty of Evidence	High	Moderate	Low (1)	Very low (3)			VERY LOW
Balance of effects	Favors intervention	Probably favors intervention (3)	Does not favor intervention	Probably favors no intervention (1)	Favors no intervention	Varies	There is a **paucity of studies reporting adverse events in long COVID undergoing PR**. However, with the limited available data, it shows that there is **low incidence of adverse events with PR in long COVID**. Other than this, the study by Gloecki (2021) concluded that pulmonary rehabilitation is a feasible, safe and effective therapeutic option in COVID-19 patients independent of disease severity. [25]
Values	Important uncertainty or variability	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			

Resources Required	Uncertain	Varies (1)	Large cost (1)	Moderate cost (1)	Negligible cost (1)	Moderate savings	Large savings	**No studies available with regards to cost-effectiveness of PR in patients with long COVID.** However, feasibility and cost effectiveness studies done on COPD found that the cost per QALY was below £17000, below the willingness to pay threshold suggested by the NICE. Evidence from the studies suggests that PR is cost-effective with savings for the healthcare provider involved.[26] No local data or studies available.
Certainty of evidence of required resources	No included studies (2)		Very low	Low (2)	Moderate	High		
Cost effectiveness	No included studies (1)		Probably / Favors the comparison (1)	Probably favors the intervention (1)	Favors the intervention	Varies (1)		
Equity	Varies (1)		Reduced	Probably reduced (1)	Probably no impact (1)	Probably increased (1)	Increased	
Acceptability	Varies (1)		No Probably no	Yes	Probably yes (3)			For the use: 4 (weak) Against the use:
Feasibility	Varies (1)		No Probably no	Yes (1)	Probably yes (2)			

Appendix 2: Search Strategy

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Pubmed	Search: ((Long Covid Syndrome) OR (Post Acute Covid Syndrome)) AND (Pulmonary Rehabilitation) ((("post acute covid 19 syndrome"[MeSH Terms] OR ("post acute"[All Fields] AND "covid 19"[All Fields] AND "syndrome"[All Fields]) OR "post acute covid 19 syndrome"[All Fields] OR ("long"[All Fields] AND "covid"[All Fields]) OR "long covid"[All Fields]) AND ("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "syndrome"[MeSH Terms] OR "syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields])) OR ("Post"[All Fields] AND ("acute"[All Fields] OR "acutely"[All Fields] OR "acutes"[All Fields]) AND ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "covid"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19"[All Fields]) AND ("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "syndrome"[MeSH Terms] OR "syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]))) AND (("lung"[MeSH Terms] OR "lung"[All Fields] OR "pulmonary"[All Fields]) AND ("rehabilitant"[All Fields] OR "rehabilitants"[All Fields] OR "rehabilitate"[All Fields] OR "rehabilitated"[All Fields] OR "rehabilitates"[All Fields] OR "rehabilitating"[All Fields] OR "rehabilitation"[MeSH Terms] OR "rehabilitation"[All Fields] OR "rehabilitations"[All Fields] OR "rehabilitative"[All Fields] OR "rehabilitation"[MeSH Subheading] OR "rehabilitation s"[All Fields] OR "rehabilitational"[All Fields] OR "rehabilitator"[All Fields] OR "rehabilitators"[All Fields]))	02-Jan-2023 02:45PM	528	2
CENTRAL	“Long Covid” OR “Post Acute Covid Syndrome” AND “Pulmonary Rehabilitation” AND “Randomized Controlled Trial”	03-Jan-2023 10:15 AM	111	0
Google Scholar	“Long Covid” OR “Post Acute Covid Syndrome” AND “Pulmonary Rehabilitation” AND “Randomized Controlled Trial”	03-Jan-2023 01:18 PM	63	1
ClinicalTrials.gov	“Long Covid” OR “Post Acute Covid Syndrome” AND “Pulmonary Rehabilitation” AND “Randomized Controlled Trial”	03-Jan-2023 04:22 PM	43	0
Bibliographic Search	N/A	05-Jan-2023 12:45PM	7	1

Appendix 3: PRISMA Flow Diagram

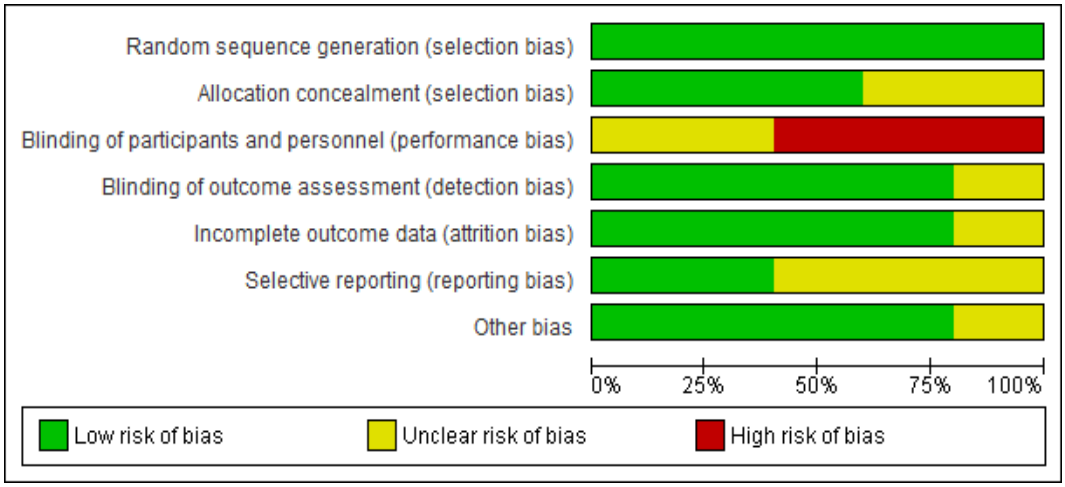


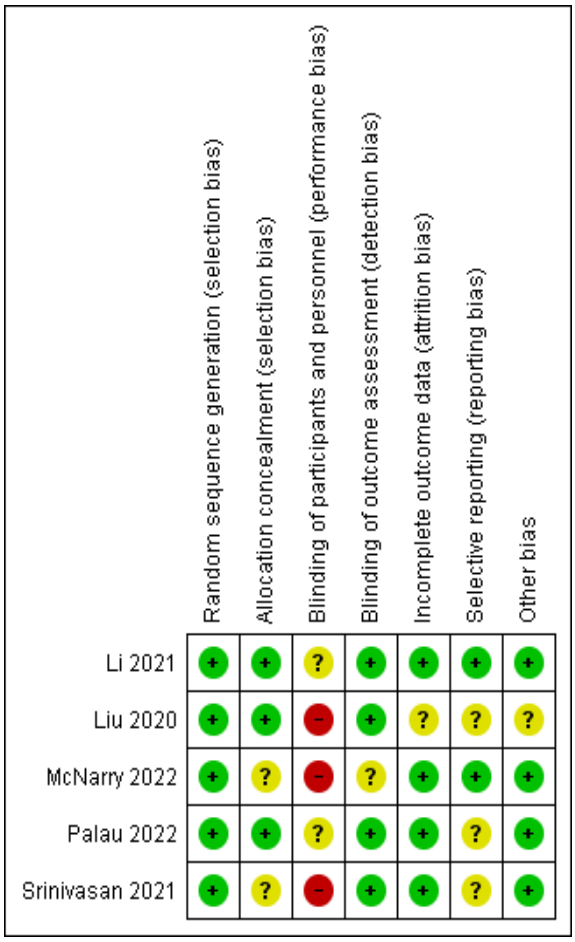
Appendix 4: Characteristics of Included Studies

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Respiratory Rehabilitation in elderly patients with Covid-19: A randomized controlled study Liu et. al. (2020) PMID: 32379637	Open, randomized controlled trial	China	N=72 I: 36 C: 36	1. A definite diagnosis of COVID-19; 2. Aged ≥ 65 years; 3. 6 months after the onset of other acute diseases; 4. MMSE score > 21; 5. No COPD or any other respiratory disease; 6. FEV1 in 1s ≥70%.	Respiratory rehabilitation (2 sessions per week for 6 weeks), once a day for 10 minutes: 1. Respiratory muscle training 2. Cough exercise 3. Diaphragmatic training 4. Stretching exercise 5. Home exercise Follow-up: 6 weeks	No Respiratory Rehabilitation	1. Pulmonary function (FEV1, FVC, FEV1/FVC, DLCO) 2. Exercise capacity (6- MWT) 3. QoL (SF-36) 4. Activities of daily living (FIM scale) 5. Anxiety and depression assessment (SDS, SAS)
A telerehabilitation program in post-discharge Covid-19 patients (TERECO): a randomized controlled trial Li et. al. (2021) PMID: 34312316	Parallel group, randomized controlled trial	China	N= 120 I:59 C:61	1. Aged 18–75 years, discharged from one of the participating hospitals after inpatient treatment for COVID-19 2. Had modified British Medical Research Council (mMRC) dyspnoea15 score of 2–3	Participants took part in an unsupervised 6-week home exercise program delivered through a smartphone application called RehabApp and monitored with a chest-worn heart rate (HR) telemetry device. Teleconsultations with therapists were carried out once per week. The exercise program involved 3–4 sessions per week. It included: (i) breathing control and thoracic expansion, (ii) aerobic exercise and (iii) LMS exercises specified in a three-tiered exercise plan with difficulty and intensity scheduled to increase over time. Follow-up: 6 weeks and 28 weeks	Short educational instructions at baseline.	Primary outcome: 1. 6 min walking distance (6MWD) in meters. Secondary outcomes: 1. squat time in seconds; 2. pulmonary function assessed by spirometry; 3.HRQOL measured with Short Form Health Survey-12 (SF-12) and mMRC-dyspnea. Outcomes were assessed at 6 weeks (post-treatment) and 28 weeks (follow-up).
Efficacy of pursed lip breathing with bhastrika pranayama vs incentive spirometry in rehabilitating post covid 19 follow up-a randomized control study Srinivasan et. al. (2021)	randomized controlled trial	India	N=48 I: 24 C: 24	1. Patients at post COVID-19 follow up clinic 2. Aged 18–60	The experimental group received Pursed lip breathing along with Bhastrika Pranayama. Follow-up: 6 weeks	Control group received breathing exercises via incentive spirometry	The Pulmonary Function Testing with the FVC & FEV1 was used as an outcome evaluation.

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Effect of a home-based inspiratory muscle training programme on functional capacity in post discharged patients with long COVID: the InsCOVID trial Palau et. al. (2022)	randomized controlled trial	Spain	N=26 I: 13 C: 13	1. Symptomatic adult >18 years old with a previous admission due to SARS-CoV-2 Pneumonia 2. At least 3months after discharge 3.With informed consent.	Home-based 12-week program of IMT Follow-up: 12 weeks	Usual Care	Primary outcome 1. Change in peak oxygen consumption Secondary outcome: 1. Changes in QoL, ventilatory efficiency, and chronotropic response during exercise
Inspiratory muscle training enhances recovery post-COVID-19: a randomised controlled trial McNarry et. al. (2022)	randomized controlled trial	UK	N=148 I: 111 C: 37	1. prior self-reported COVID-19 infection, 2. primary symptom of breathlessness 3. age ⩾18 years	The PrO2 (PrO2Fit Health, Smithfield, RI, USA), a handheld inspiratory flow resistive device that wirelessly syncs to a computer, smartphone or tablet via an app to provide users with graphical biofeedback during and following each inspiratory effort, was used. Participants were trained on its set-up and use during the first session Follow-up: 8 weeks	Usual Care	Primary outcome 1. Health-related quality of life, as estimated by the 15-item King's Brief Interstitial Lung Disease (K-BILD) Secondary outcome: 1. Perceived breathlessness was assessed by the Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) 2. Inspiratory muscle strength was assessed using the PrO2 device

Appendix 5: Risk of Bias Assessment of Included Studies





Appendix 6: GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulmonary Rehabilitation	Usual Care/No intervention	Relative (95% CI)	Absolute (95% CI)		
FEV1												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	95	97	-	MD **0.15 higher** (0.05 higher to 0.26 higher)	⨁⨁⨁◯ Moderate	CRITICAL
FVC												
2	randomised trials	serious[a]	serious[b]	not serious	serious[c]	none	95	97	-	MD **0.14 higher** (0.11 lower to 0.4 higher)	⨁◯◯◯ Very low	CRITICAL
FEV1/FVC												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	36	36	-	MD **6.96 higher** (4.08 higher to 9.84 higher)	⨁⨁◯◯ Low	CRITICAL
6MWT												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	95	96	-	MD **58.77 meters higher** (37.7 higher to 79.85 higher)	⨁⨁⨁◯ Moderate	CRITICAL
peakVO2												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	124	50	-	MD **4.58 ml/kg/min higher** (3.44 higher to 5.72 higher)	⨁⨁⨁◯ Moderate	CRITICAL
QoL: Physical Health												
	randomised trials	serious[a]	not serious	not serious	serious[d]	none	36	36	-	MD **17.5 points higher** (14.01 higher to 20.99 higher)	⨁⨁◯◯ Low	CRITICAL
QoL: Body Role Function												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	36	36	-	MD **13.9 points higher** (10.39 higher to 17.41 higher)	⨁⨁◯◯ Low	CRITICAL
QoL: Physical Pain												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none			-	MD **15.4 points higher** (11.77 higher to 19.03 higher)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulmonary Rehabilitation	Usual Care/No intervention	Relative (95% CI)	Absolute (95% CI)		
QoL: General Health												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none			-	MD **12.8 points higher** (9.37 higher to 16.23 higher)	⨁⨁◯◯ Low	CRITICAL
QoL: Energy												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none			-	MD **14.4 points higher** (11.3 higher to 17.5 higher)	⨁⨁◯◯ Low	CRITICAL
QoL: Social Function												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none			-	MD **10.9 points higher** (7.9 higher to 13.9 higher)	⨁⨁◯◯ Low	CRITICAL
QoL: Emotional Role												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none			-	MD **14.9 points higher** (11.6 higher to 18.2 higher)	⨁⨁◯◯ Low	CRITICAL
QoL: Mental Health												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none			-	MD **11.6 points higher** (8.09 higher to 15.11 higher)	⨁⨁◯◯ Low	CRITICAL
Self-rated anxiety												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none			-	MD **7.5 points lower** (10.65 lower to 4.35 lower)	⨁⨁◯◯ Low	CRITICAL
Self-rate depression												
1	randomised trials	serious[a]	not serious	not serious	very serious[d,e]	none			-	MD **1.3 points lower** (4.32 lower to 1.72 higher)	⨁◯◯◯ Very Low	CRITICAL
Adverse Effects												
1	randomised trials	not serious	not serious	not serious	very serious[d,e]	none	35/59 (59.3%)	38/60 (63.3%)	**RR 0.93** (0.70 to 1.20)	**44 fewer per 1,000** (from 190 fewer to 127 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Studies included have moderate to high risk of bias due to lack of data on allocation concealment and lack of blinding

b. substantial heterogeneity present (I2=75%) which may be due to variation in the treatment effect and differences in the features of the population included.

c. Mean difference estimates cross line of no difference

d. small sample size/optimal sample size possibly not reached

e. Risk estimate cross line of no effect

Appendix 7: Forest Plots

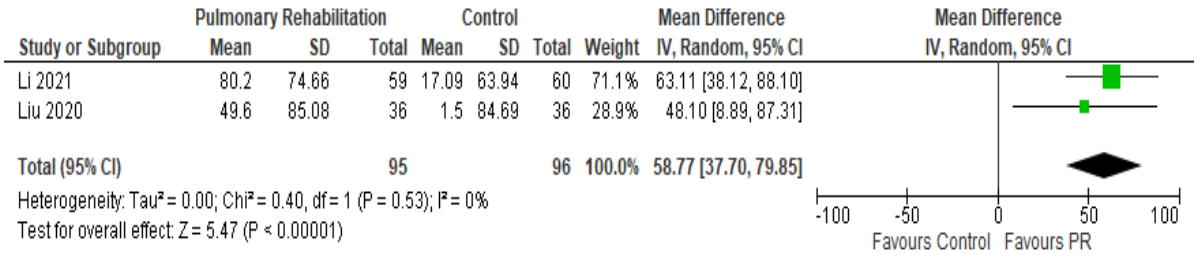


Figure 1. Forest plot for change in 6MWT after intervention from baseline

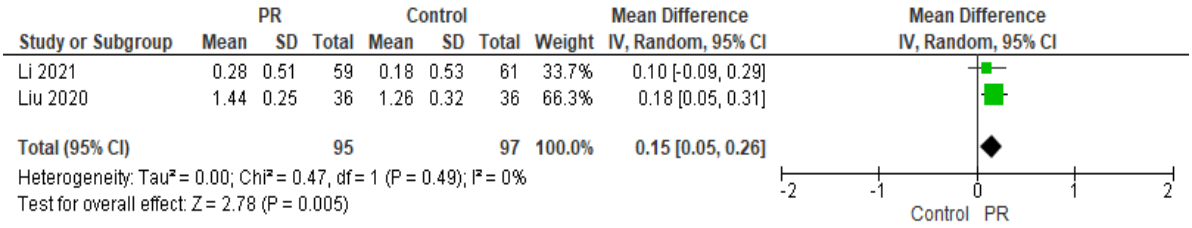


Figure 2. Forest plot for change in FEV1 after intervention from baseline

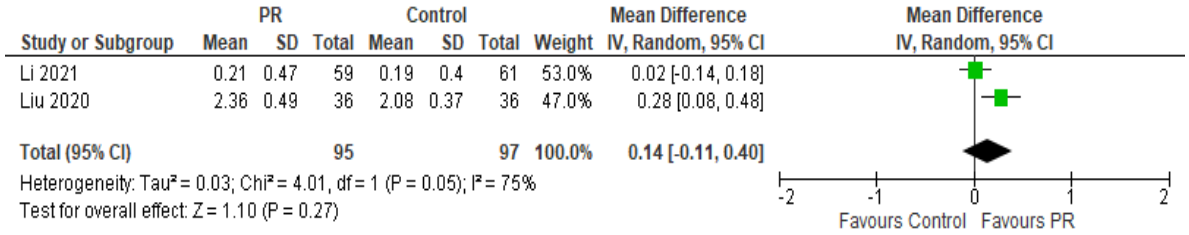


Figure 3. Forest plot for change in FVC after intervention from baseline

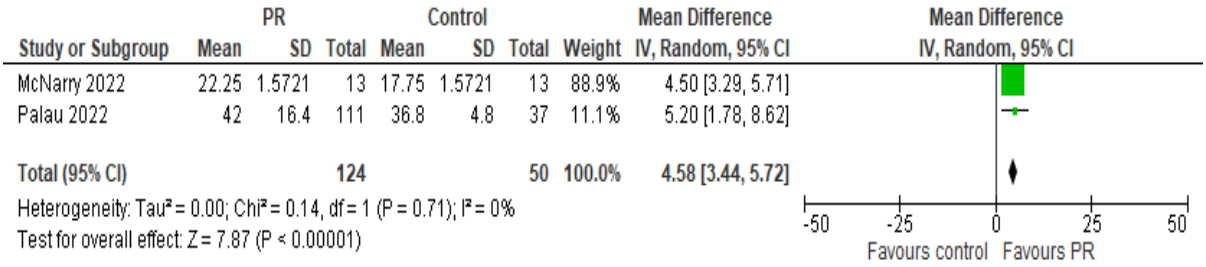


Figure 4. Forest plot for change in peakVO2 after intervention from baseline

Appendix 8: Ongoing Studies

Title	Conditions	Interventions	Characteristics	Population	Outcome Measures
Pulmonary Rehabilitation for Long COVID (Post COVID-19 Condition) NCT05244044 Still Recruiting Study Start: April 19, 2022 Study Completion: February 1, 2024	• COVID-19 • Long COVID • Post COVID-19 Condition	• Other: Pulmonary rehabilitation in primary care	Study Type: Interventional Study Design: • Allocation: Randomized • Intervention Model: ParallelAssignment • Masking: Single (Outcomes Assessor) • Primary Purpose: Treatment Locations: Belgium	Enrollment: 134 Age: 18 Years and older (Adult, Older Adult) Sex All	• Exercise capacity • Change in physical activity • Change in COVID-19 related symptoms • Change in quality of life • Change in fatigue • Change in dyspnea • Change in functional status • Change in work productivity and activity impairment. • Change in anxiety and depression symptoms. • Change in dysfunctional breathing
Post COVID-19 Pulmonary Rehabilitation Program Other names: COVID-19 PULMONARYREHAB NCT04982042 Completed but no results yet Study Start: March 1, 2021 Study Completion:July 30, 2022	• Covid19 • COVID-19 Respiratory Infection • Lung Diseases • Respiratory Insufficiency • Muscle Weakness Anxiety Disorder; Mixed with Depression (Mild)	Other: Pulmonary Rehabilitation	Study Type: Interventional Study Design: • Allocation: Non-Randomized • Intervention Model: ParallelAssignment • Masking: Single (Outcomes Assessor) • Primary Purpose: Treatment Locations: Brazil	Enrollment: 40 Age: 16 Years and older (Child, Adult, Older Adult) Sex All	• Functional status after Pulmonary Rehabilitation Program (COVID-19REHAB) • Exercise capacity after Pulmonary Rehabilitation Program (COVID-19REHAB) • Forced Vital Capacity after Pulmonary Rehabilitation Program (COVID-19REHAB) • Forced Expiratory Volume infirst second after PulmonaryRehabilitation Program (COVID-19REHAB) • Inspiratory muscle strength after Pulmonary RehabilitationProgram (COVID-19REHAB) • Peripheral muscle strength after Pulmonary RehabilitationProgram (COVID-19REHAB) • Levels of anxiety and depression after PulmonaryRehabilitation Program (COVID-19REHAB) • Quality of Life after Pulmonary Rehabilitation Program (COVID-19REHAB) • Health costs after COVID -19.

Pulmonary Rehabilitation Implemented with Virtual Realityfor Post-COVID-19 Patients NCT05244135 Completed but no results yet Study Start: February 28, 2022 Study Completion: September 30, 2022	COVID-19	Procedure: Pulmonary rehabilitation	Study Type: Interventional Study Design: • Allocation: Randomized • Intervention Model: ParallelAssignment • Masking: Single (Outcomes Assessor) • Primary Purpose: Treatment Location: Poland	Enrollment: 66 Age: 40 Years to 60 Years (Adult) Sex All	• Lung function • Dyspnea • Stress • Anxiety and depression • Individual's perception ofquality of life • Heart Rate Variability • Impact of technology
Effect of Pulmonary Rehabilitation Program on PostHospitalization Severe COVID-19 Patients NCT05476835 Completed but no results yet Study Start: May 15, 2021 Study Completion: May 15, 2022	Post COVID-19 Condition	• Combination Product: respiratory exercises - incentive spirometer - walking	Study Type: Interventional Study Design: • Allocation: Randomized • Intervention Model: ParallelAssignment • Masking: None (Open Label) • Primary Purpose: SupportiveCare Location: Egypt	Enrollment: 100 Age: 50 Years to 70 Years (Adult, Older Adult) Sex All	• improvement in dyspneascale • improvement in spirometrymeasures • improvement in oxygen saturation and 6-minute walktest
Pulmonary Rehabilitation Implemented with VR for Post-COVID-19 Patients NCT05242094 Recruiting Study Start: January 1, 2021 Study completion: September 1, 2022	COVID-19	Procedure: Pulmonary Rehabilitation Program	Study Type: Interventional Study Design: • Allocation: Randomized • Intervention Model: ParallelAssignment • Masking: Single (Outcomes Assessor) • Primary Purpose: Treatment Location: Poland	Enrollment: 2000 Age: 30 Years to 80 Years (Adult, Older Adult) Sex All	• Hospital Anxiety and Depression Scale • Functional Capacity

Pulmonary Rehabilitation Program With Pulsed Electromagnetic Field Therapyin Patients With Post-covid Sequelae. NCT05379517 Not yet recruiting Study Start: September 15, 2022 Study Completion: December 30, 2022	COVID-19	• Device: Pulsed electromagnetic fieldtherapy Other: Pulmonary rehabilitation program (PRP)	Study Type: Interventional Study Design: • Allocation: Randomized • Intervention Model: ParallelAssignment • Masking: Single (Outcomes Assessor) • Primary Purpose: Treatment Location: Spain	Enrollment: 33 Age: 45 Years to 65 Years (Adult, Older Adult) Sex All	• Changes in Forced expiratoryvolume in the first second of expiration (FEV#). • Changes in Forced vitalcapacity (FVC). • Changes in FEV# / FVCindex. • Changes in Maximal inspiratory pressures (MIP)and maximal expiratory pressures (MEP)
Effects of Cardiopulmonary Rehabilitation in Participants With Post-COVID 19 Syndrome. NCT05402007 Recruiting Study Start: March 30, 2022 Study Completion: December 30, 2022	• Post-COVID-19 Syndrome • Exercises • Pulmonary Rehabilitation • COVID-19 Randomized ClinicalTrial	• Other: Pulmonary rehabilitation exercises at the Rehabilitation Center Other: Home Intervention	Study Type: Interventional Study Design: • Allocation: Randomized • Intervention Model: ParallelAssignment • Masking: Single (Investigator) • Primary Purpose: Treatment Location: Brazil	Enrollment: 90 Age: 18 Years to 65 Years (Adult, Older Adult) Sex All	• Peripheral muscle function I • Peripheral muscle function II • Peripheral muscle function III • Daily living activity • Quality of life improvement
Pulmonary Rehabilitation Post-COVID-19 NCT05003271 Recruiting Study Start: April 4, 2022 Study Completion: August 2022	COVID-19	Other: Exercise program (virtual/ remote)	Study Type: Interventional Study Design: • Allocation: Non-Randomized • Intervention Model: ParallelAssignment • Masking: None (Open Label) • Primary Purpose: Treatment Location: Canada	Enrollment: 24 Age: 18 Years and older (Adult, Older Adult) Sex All	• Change in lung capacity • Change in dyspnea • Change in fatigue • Change in exercise capacity • Change in post-exercisesaturation • Change in physical function • Change in activitiesparticipation • Changes in health-related quality of life (HRQoL) assessed with the EQ-5D-5L • Changes in health-related quality of life (HRQoL) assessed with the Short form(SF)-36 questionnaire • Symptoms change • Patient satisfaction with thestudy