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REVIEW ARTICLE (META-ANALYSIS)

Effectiveness of Pulmonary Rehabilitation in Interstitial Lung Disease, Including Coronavirus Diseases: A Systematic Review and Meta-analysis

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Objective: A meta-analysis of randomized controlled trials (RCTs) was conducted to determine the effect of pulmonary rehabilitation on functional capacity and quality of life in interstitial lung diseases, including those caused by coronaviruses.
Data Sources: MEDLINE, EMBASE, SPORTDiscus, Cochrane Library, Web of Science, and MedRxiv from inception to November 2020 were searched to identify documents.
Study Selection: Publications investigating the effect of pulmonary rehabilitation on lung function (forced vital capacity [FVC]), exercise capacity (6-minute walk distance [6MWD]), health related quality of life (HRQOL), and dyspnea were searched.
Data Extraction: The data were extracted into predesigned data extraction tables. Risk of bias was evaluated with the Cochrane Risk of Bias tool (RoB 2.0).
Data Synthesis: A total of 11 RCTs with 637 interstitial lung disease patients were eligible for analyses. The pooled effect sizes of the association for pulmonary rehabilitation were 0.37 (95% confidence interval [CI], 0.02-0.71) for FVC, 44.55 (95% CI, 32.46-56.64) for 6MWD, 0.52 (95% CI, 0.22-0.82) for HRQOL, and 0.39 (95% CI, −0.08 to 0.87) for dyspnea. After translating these findings considering clinical improvements, pulmonary rehabilitation intervention increased predicted FVC by 5.5%, the 6MWD test improved by 44.55 m, and HRQOL improved by 3.9 points compared with baseline values. Results remained similar in sensitivity analyses.
Conclusions: Although specific evidence for pulmonary rehabilitation of coronavirus disease 2019 patients has emerged, our data support that interstitial lung disease rehabilitation could be considered as an effective therapeutic strategy to improve the functional capacity and quality of life in this group of patients.
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Interstitial lung diseases (ILDs), also known as diffuse parenchymal lung diseases, are a set of chronic lung conditions characterized by exercise limitation and dyspnea.[1] Pathologic features dominated by diffuse alveolar damage have also been reported in severe acute respiratory syndrome (SARS)[2,3] and coronavirus disease 2019 (COVID-19), both diseases result from infection by viruses in the coronavirus (CoV) family. CoVs are a family of enveloped, single-stranded−RNA viruses[4] responsible for the 2 large epidemics in the past 2 decades, SARS and the Middle East Respiratory Syndrome.[5-7] Toward the end of 2019, COVID-19 was identified as the cause of a severe respiratory illness, which was declared a global pandemic and is still spreading across the world with a growing number of confirmed cases.[8]

Although most individuals with COVID-19 develop mild or asymptomatic disease, approximately 14% experience severe disease and 6% become critically ill.[9] In the acute phase, severely affected patients may develop pneumonia characterized by

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bilateral interstitial infiltrate, acute respiratory distress syndrome,[10] and related pulmonary fibrosis that is even susceptible to lung transplantation.[11] Moreover, an increased risk of encephalopathy has been described in hospitalized patients with acute respiratory symptoms.[12,13] The evolution of COVID-19 in the medium- and long-term is still uncertain; however, it appears to be similar to SARS regarding its clinical features.[14] Epidemic data of previous CoV infections show that pulmonary fibrosis may develop early in patients with SARS,[15] which has shown a functional disability associated with the degree of lung function impairment that might be related to residual lung fibrosis, muscle weakness, and systemic effects of the viral illness.[4,16] Additionally, research has shown an important decrease in lung function, physical fitness, and health related quality of life (HRQOL) among patients recovering from CoV infections.[17,18]

Recent clinical guidelines recommend pulmonary rehabilitation for the management of the long-term effects of critical illness associated with severe acute respiratory syndrome coronavirus 2 infection.[19] Pulmonary rehabilitation is an evidence-based standard of care designed to improve the physical and psychological condition for patients with lung disease that include but are not limited to exercise training, education, and behavior change.[20] Previous research reports have shown the effectiveness of pulmonary rehabilitation in improving fitness and HRQOL in patients with CoV or diseases with similar respiratory consequences.[21,22]

As COVID-19 is a new disease, there is a lack of data in the literature about the recovery pathway on sequelae of severely affected patients, and an optimal treatment is extremely urgent. Pulmonary rehabilitation might have an important role in improving functional capacity and the quality of life of survivors of this disease. Thus, the aim of this systematic review and meta-analysis was to synthetize the evidence about the effectiveness of pulmonary rehabilitation in health outcomes of ILDs, including those caused by CoVs.

Methods

This systematic review and meta-analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[23] The Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines were used as a reporting structure for this systematic review.[24] This meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration no.: CRD42020178937).

List of abbreviations:

6MWD	**6-minute walk distance**
CI	**confidence interval**
CoV	**coronavirus**
COVID-19	**coronavirus disease 2019**
ES	**effect size**
FVC	**forced vital capacity**
HRQOL	**health-related quality of life**
ILD	**interstitial lung disease**
RCT	**randomized controlled trial**
SARS	**severe acute respiratory syndrome**

Search strategy

Two reviewers (S.R.-G, S.N.A.-A.) independently searched the MEDLINE (via PubMed), EMBASE (via Scopus), SPORTDiscus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science, and MedRxiv databases from inception to November 2020. Disagreements were solved by consensus or involving a third researcher (V.M.-V.). The search strategy used was: (covid OR coronavirus OR "Middle East Respiratory Syndrome Coronavirus" OR "Severe Acute Respiratory Syndrome" OR SARS-CoV OR "Acute Respiratory Distress Syndrome" OR ARDS OR "acute hypoxemic respiratory failure" OR "pulmonary fibrosis" OR "lung fibrosis" OR "interstitial lung disease" OR "interstitial pneumonia") AND ("physical therapy" OR "respiratory muscle training" OR "respiratory rehabilitation" OR "pulmonary rehabilitation" OR exercise OR exercises). The reference lists of the articles included in this review, as well as the list of references of studies included in previous systematic reviews and meta-analyses, were reviewed for any additional relevant studies.

Study selection

Studies concerning the effectiveness of different pulmonary rehabilitation programs in ILD or patients with CoV were included in this systematic review. Inclusion criteria were: (1) randomized controlled trials (RCT); (2) participants who had ILD (including pulmonary fibrosis) or postacute CoV; (3) physical exercise or pulmonary rehabilitation as the intervention; (4) comparison with controls undergoing usual care or activities without physical demand; and (5) outcomes of lung function, exercise capacity, HRQOL, and dyspnea.

The exclusion criteria were: (1) patients with mild-moderate severity of COVID-19 as they were not at risk of developing pulmonary fibrosis[25]; (2) studies comparing the same modality of exercise with different doses of time, frequency, or duration; (3) conference abstracts without a full published article; (4) studies with inconsistencies or that did not provide enough data to calculate the effect size (ES); and (5) studies published in languages other than English or Spanish.

When more than 1 report provided data from the same sample, only the publication with the most detailed results or providing data for the largest sample size was included. Regarding HRQOL, only studies reporting a total score of a HRQOL scale were selected.

Search and data extraction

The main characteristics of the selected studies were summarized in an ad hoc table including information about (1) study characteristics such as year of publication, country, and sample size; (2) population characteristics such as type of respiratory disease, mean age, and time from diagnosis; (3) intervention characteristics such as duration, frequency, type, and exercise regime training; and (4) outcomes such as lung function, exercise capacity, HRQOL, and dyspnea. Disagreements in data collection were settled by consensus.

Classification of the outcome

Pulmonary rehabilitation program outcomes were classified according to 4 main areas: lung function, measured using forced vital capacity (FVC); exercise capacity measured using the 6-minute walk distance (6MWD); HRQOL, measured using a quality of life scale; and dyspnea measured at baseline using a dyspnea scale.

Risk of bias assessment

The quality of RCTs was assessed using Cochrane Collaboration's tool for assessing risk of bias.[26,a] This tool evaluates the risk of bias according to 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall bias was considered as "low risk of bias" if the study was classified as low risk in all domains, "some concerns" if there was at least 1 domain rated as having some concerns, and "high risk of bias" if there was at least 1 domain rated as high risk or several domains rated as having some concerns that could affect the validity of the results.

Data extraction and quality assessment were independently performed by 2 reviewers (S.N.A.-A., S.R.-G.), and inconsistencies were solved by consensus or involving a third researcher (V.M.-V.).

Statistical analysis

We calculated a pooled ES of the mean differences for 6MWD using a random effects model based on the DerSimonian and Laird method.[27] A pooled ES of the standardized mean differences was necessary to use for FVC, HRQOL, and dyspnea outcomes because different measures or scales were reported by studies. A combined estimate was calculated when studies applied more than 1 questionnaire for reporting the dyspnea grade. Additionally, statistical heterogeneity was analyzed using the I^2 statistic. Heterogeneity was considered as not important (I^2, 0%-40%), moderate (I^2, 30%-60%), substantial (I^2, 50%-90%), or considerable (I^2, 75%-100%); the corresponding P values were also considered.[28]

Following the Cochrane Handbook recommendations, when data on the SDof change on outcomes from baseline were lacking, the estimates relied on standard errors, 95% confidence intervals (CI), and P values to calculate the SD. Finally, when studies were scaled inversely (ie, lower values indicated worse outcomes), the mean in each group was multiplied by −1.

Random effects metaregression analyses were conducted to assess whether baseline age influenced the association of pulmonary rehabilitation and outcome related variables. Sensitivity analyses were performed by removing studies one by one to assess the robustness of the summary estimates and to detect whether any particular study accounted for a large proportion of heterogeneity among pulmonary rehabilitation ES pooled estimates.

Finally, we used Egger's regression asymmetry test to assess publication bias.[29] A level of <0.10 was used to determine whether publication bias might be present. Statistical analyses were performed using Stata Statistical software, version 16.0.[b]

Results

The literature search retrieved 12,214 articles, which were reviewed based on the title and abstract after discarding duplicates. Finally, 11 RCTs[21,30-39] met the inclusion criteria and were selected for this systematic review and meta-analysis (fig 1), including a total sample of 637 participants. Excluded studies with reasons for exclusion are available in supplementary table S1 (available online only at http://www.archives-pmr.org/).

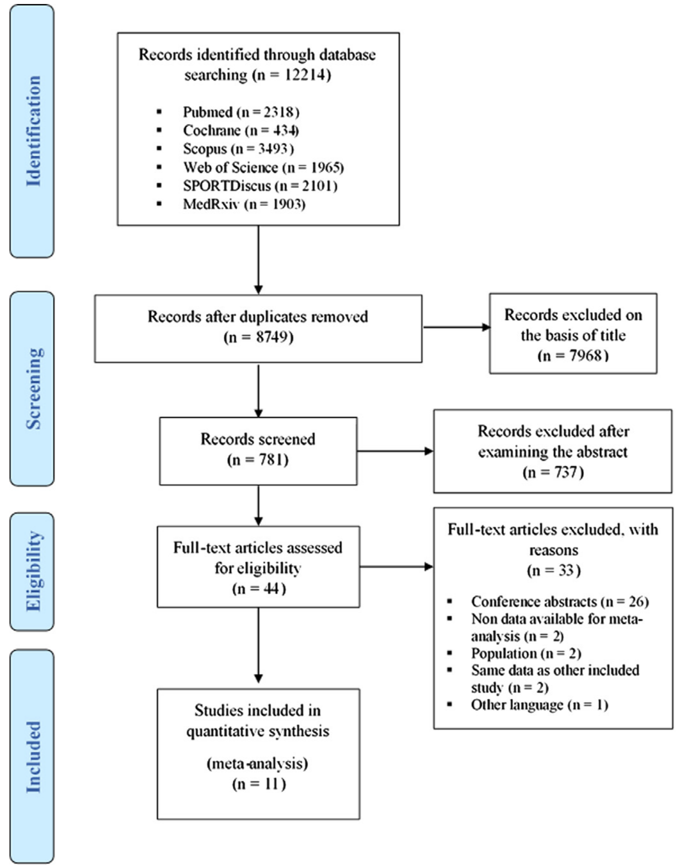

Fig 1 Flow chart for identification of trials for inclusion in the meta-analysis.

Table 1 presents descriptive information for the 11 studies included in the review. The study data were obtained in samples from Europe,[34,37] North America,[31,33,39] Asia,[21,35,36,38] and Australia.[30,32] The age of included participants in the systematic review ranged between 35.9-72.2 years. Different pulmonary clinical entities were analyzed in the included studies: ILD was examined in 3 studies,[30,32,37] idiopathic pulmonary fibrosis in 6 studies,[31,33,34,36,38,39] and postrespiratory CoV disease in 2 studies.[21,35] Additionally, different pulmonary rehabilitation interventions were examined in the studies selected, including combined exercise (aerobic with strength), combine exercise with specific respiratory exercises, and aerobic exercise with specific respiratory muscle training.

Risk of bias

As evaluated by Cochrane Collaboration's tool for RCTs, 18.2% of the studies showed a high risk of bias,[31,37] 72.7% showed some concerns,[21,32-36,38,39] and 9.1% had a low risk of bias.[30] When studies were analyzed by individual domains, 91% had shortcomings in the selection of the reported results domain[21,31-39] (supplementary fig S1, available online only at httP://www.archives-pmr.org).

Meta-analysis

The pooled ES estimates for pulmonary rehabilitation were 44.55 (95% CI, 32.46-56.64) for 6MWD, 0.52 (95% CI, 0.22-0.82) for HRQOL, and 0.39 (95% CI, −0.08 to 0.87) for dyspnea.

Table 1 Characteristics of the RCTs included in the meta-analysis

Study Characteristics		Population Characteristics			Intervention					
Study	Country	Respiratory Disease	Age (y)	Time From Diagnosis	Min/Session	Frequency (Times/wk)	Weeks	Experimental Group	Control Group	Outcomes
Dowman et al[30]	Australia	ILD	EG: 69±11 CG: 70±11	NR	NR	2	8	30 min of aerobic exercise (cycling and walking) Upper and lower limb resistance training (10-12 RM)	Weekly telephone support	6MWD, SGRQ-I, UCSD SOBQ, mMRC
Gaunaurd et al[31]	United States	Idiopathic pulmonary fibrosis	EG: 71±6 CG: 66±7	NR	90	2	12	10 educational lectures, 30 min of endurance training, 20 min of flexibility exercises (3 sets/30s), 25 min of strength training (2-3 sets/10-15 repetitions)	Handouts about the educational lectures	SGRQ-I
Holland et al[32]	Australia	ILD	EG: 70±8 CG: 67±13	NR	NR	2	8	30 min of endurance training (cycling and walking) Upper limb endurance training Functional strength for lower limbs	Weekly telephone support	6MWD, mMRC
Jackson et al[33]	United States	Idiopathic pulmonary fibrosis	EG: 71±6 CG: 66±7	3-48 mo before screening	120	2	12	15 min of educational lectures, 30 min of endurance training (cycling and walking), 15 min of flexibility exercises (3 sets/30s), 15-30 min of strength training (3 sets/15 repetitions)	Normal activities	6MWD, Borg Dyspnea Index
Jarosh et al[34]	Germany	Idiopathic pulmonary fibrosis	EG: 68±9 CG: 65±10	NR	NR	5-6	3	Medical care, psychological support, breathing therapy, education. Endurance or interval cycle training (60% or 100% peak work rate) Resistance training for major muscle groups (3 sets/15-20 repetitions maximum)	Usual care	6MWD, CRDQ
Lau et al[21]	China	Recovering from SARS	EG: 35.9±9.3 CG: 38.3±11.2	NR	60-90	4-5	6	30-45 min of endurance training (limbs ergometer, stepper, or treadmill) Upper and lower limbs resistance training (3 sets/10-15 repetitions at maximum load)	Educational session about exercise rehabilitation	6MWD
Liu et al[35]	China	COVID-19	EG: 69.4±8.0 CG: 68.9±7.6	NR	10	2	6	Respiratory muscle training (3 sets/10 breaths/ 60% MEP) and diaphragm muscle (30 contractions, placing a weight on the anterior abdominal wall) Stretching and cough exercise Home exercise (pursed-lip breathing and coughing training)	Usual care	FVC, 6MWD
Nishiyama et al[36]	Japan	Idiopathic pulmonary fibrosis	EG: 68.1±8.9 CG: 64.5±9.1	>3 mo	NR	2	10	Educational lectures Treadmill 20 min of strength training for the limbs	Usual care	FVC, 6MWD, SGRQ, BDI
Perez-Bogerd et al[37]	Belgium	ILD	EG: 64±13 CG: 64±8	NR	90	3-2	12-12	Endurance training (cycling, treadmill, arm cranking and stair climbing) and peripheral muscle training (3 sets/8 repetitions) 30 min of multidisciplinary treatment Medical care and medical follow-up	Medical care and identical medical follow-up as EG	6MWD, SGRQ
Vainshelboim et al[38]	Israel	Idiopathic pulmonary fibrosis	EG: 68.8±6 CG: 66±9	EG: 3±3.7 y CG: 1.9±3.1y	60	2	12	Regular medical care and exercise training: calisthenic and deep breathing exercises, 30 min of aerobic training (treadmill walking, leg cycling, step climbing) Resistance training (1-2 sets/12-15 repetitions)	Regular medical care	FVC, 6MWD, SGRQ, mMRC

(*continued on next page*)

Table 1 (*Continued*)

Study Characteristics		Population Characteristics			Intervention					Outcomes
Study	Country	Respiratory Disease	Age (y)	Time From Diagnosis	Min/Session	Frequency (Times/wk)	Weeks	Experimental Group	Control Group	
								5 min of flexibility exercises Encourage PA levels on other days		
Yuen et al[39]	United States	Idiopathic pulmonary fibrosis	EG: 67.4±7.4 CG: 72.2±8.4	EG: 3.5±3.4 y CG: 3.0±4.2 y	30 for Wii games and 30 for physical activity	3	12	Wii Fit exergames with an exercise protocol similar to that reported by Gaunaurd[31] and Vainshelboim[38] Additional physical activity	Control Wii video game not requiring movement Additional physical activity	6MWD, SGRQ, Borg Dyspnea Index

NOTE. Values are presented as mean ± SD.
Abbreviations: BDI, baseline dyspnea index; CG, control group; CRDQ, Chronic Respiratory Disease Questionnaire; EG, experimental group; MEP, maximal expiratory pressure; mMRC, Modified Medical Research Council dyspnea scale; NR, not reported; PA, physical activity; RM, repetition maximum; SGRQ, St. George's Respiratory Questionnaire; SGRQ-I, St. George's Respiratory Questionnaire specific for idiopathic pulmonary fibrosis; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire.

Heterogeneity among studies was rated as not important for 6MWD (I^2, 0.0%), moderate for HRQOL (I^2, 50.1%), and substantial for dyspnea (I^2, 71.3%) (figs 2-4). FVC data were available in 3 studies, which showed a significant effect of treatment (ES, 0.37; 95% CI, 0.02-0.71) (not shown).

The random effects metaregression models indicated that age (=0.3499, P=.489 for FVC; =−0.4345, P=.499 for 6MWD; =0.0913, P=.413 for HRQOL; and =0.4196, P=.117 for dyspnea) was not related to the association between the intervention and outcome-related variables (supplementary table S2, available online only at http://www.archives-pmr.org/).

Sensitivity analysis

The pooled ES estimates for the association between pulmonary rehabilitation and all outcome related variables were not significantly modified in magnitude or direction when individual study data were removed from the analysis one at a time. Extra sensitivity analysis was performed excluding the 2 CoV studies showing a pooled ES estimate of 42.00 (95% CI, 27.08-56.92) for 6MWD.

Publication bias

Egger's test revealed no significant publication bias for any pooled analyses. Funnel plots are shown in supplementary figures S2-S4 (available online only at http://www.archives-pmr.org/).

Discussion

This systematic review and meta-analysis provides a synthesis of evidence supporting the effectiveness of pulmonary rehabilitation to improve lung function (measured by FVC), exercise capacity (measured by 6MWD), and HRQOL in patients with ILD, including patients with CoV. Meta-regression analysis did not find an association between the magnitude of the effect and the age of patients in the studies.

Among nonpharmacologic interventions to treat these clinical entities, regular exercise is known to be a low-cost solution to improve health, wellbeing, and economic productivity of patients with chronic lung disease,[40] especially for those with ILD, in whom conventional pharmacologic treatment has shown a limited response.[41]

Previous Cochrane reviews support positive effects and no adverse events of pulmonary rehabilitation in patients with ILD, showing improvements of 38.61-44.34 m for 6MWD, 0.58-0.59 for HRQOL, or −0.47 to −0.68 for dyspnea.[42,43] Our meta-analysis, in line with the results of previous studies, confirms consistent clinical benefits for exercise capacity (6MWD), HRQOL, and dyspnea in patients with ILD, adding beneficial effects respect to lung function (FCV). Also, our data were similar with regard to the magnitude of change in 6MWD in patients post-CoV, probably because similar respiratory improvements have been reported in both patients with ILD and those post-CoV who are severely respiratory affected because they have interstitial pneumonia, fibrosis, or diffuse alveolar damage in common.[44,45]

Translating our research effect estimates to clinical improvements by using methods endorsed by the Cochrane Collaboration,[46] a pulmonary rehabilitation intervention increased the predicted FVC by 5.47%, and HRQOL improved 3.9 points with respect to baseline values. The 6MWD test improved by 44.55 m compared with baseline values.

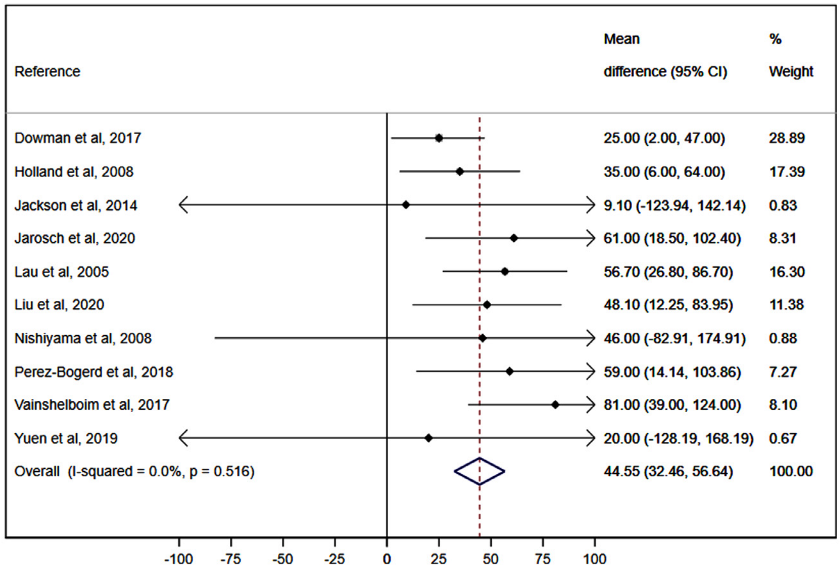

Fig 2 Mean difference (95% CI) of effect of pulmonary rehabilitation vs usual care on exercise capacity (measured by 6MWD) inmediately after intervention (n= 616).

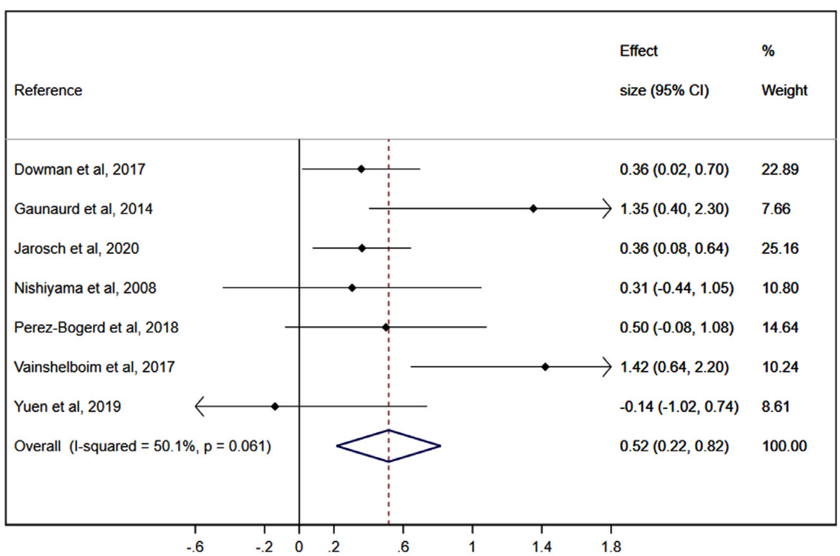

Fig 3 Standardized mean difference (95% CI) of effect of pulmonary rehabilitation vs usual care on health related quality of life inmediately after intervention (n= 354).

Functional status is extremely important for people with diffuse parenchymal lung disease, and the 6MWD test is widely recognized as a valid and reliable measuring tool.[47] Additionally, the distance achieved for these patients is closely related with disease severity and mortality risk.[48] Recent studies have reported severe disability in postacute patients with COVID-19 with poor results in this test because walk distances are below those expected for their age.[49,50] In patients with diffuse parenchymal lung disease, Holland et al[47] concluded that changes between 29-34 m may be clinically significant; thus, an increase of 44.55 m is significant for improving functional capacity in this population. Previous studies have reported similar clinical changes compared with our data, with results ranging between 38.38-48.6 m.[22,51,52] Regarding FVC, the other major clinical outcome for pulmonary rehabilitation, differences between 2%-6% are suggested to be clinically relevant.[53] Our pooled ES (5.47%) falls within this range of improvement.

The HRQOL scales used in our study are considered an instrument whose validity, reliability, and responsiveness is sufficiently proven.[54] Additionally, they are considered appropriate to measure HRQOL that may have a predictive value for mortality in patients with ILD.[55] Although a 3.9-point improvement vs baseline assessment resulted in a moderate ES, this change remains under the recognized minimal clinical important difference for this value,[56] which is in line with previous findings.[22]

Our data also show a positive, but not statistically significant, effect of pulmonary rehabilitation on dyspnea. In this sense, the direction of the association was not homogeneous between studies, probably owing to the different tools used to assess this outcome

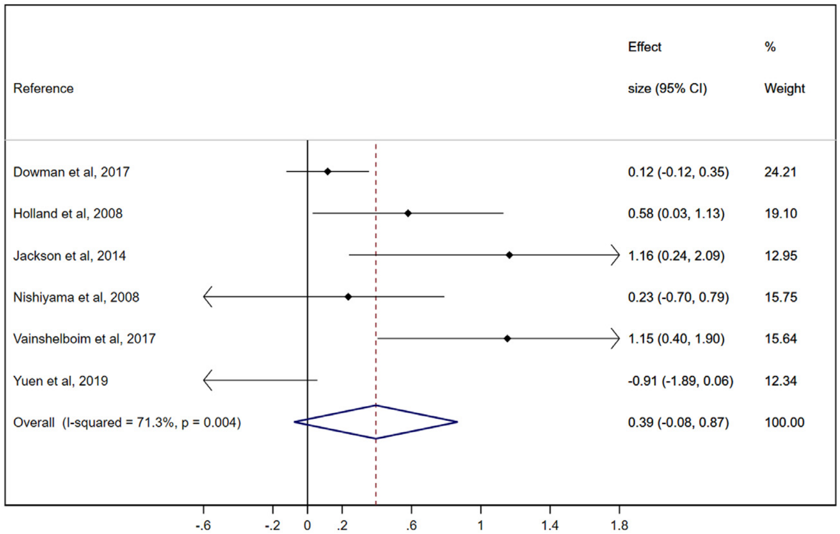

Fig 4 Standardized mean difference (95% CI) of effect of pulmonary rehabilitation vs usual care on dyspnea inmediately after intervention (n= 300).

and the lack of responsiveness of some of the dyspnea measurement tools.[57,58]

Study limitations

This study has some limitations that should be acknowledged. First, our study focused on rehabilitation of pulmonary involvement in patients with COVID-19. However, because this is a systemic disease,[59] along with the lung damage, other comorbidities such as myopathy of femoral head necrosis[60] might have an important effect in the functional capacity of these patients. Thus, the rehabilitation treatment plan should be carried out according to the framework of the International Classification of Functioning, Disability and Health.[61] Second, because of the scarcity of studies, it was not possible to conduct a subgroup analysis separating those interventions that uniquely included an exercise modality from those that included a modality combining 2. Additionally, it was not possible to examine the pulmonary rehabilitation regime (intensity, duration, frequency of the exercise) because information was lacking or was presented in a heterogeneous manner across studies. Nevertheless, most studies showed the same exercise training modality, which may help the generalizability of our findings. Also, although the overall methodological quality of included trials was satisfactory, most trials lacked information regarding the selection of the reported results domain from the Cochrane Collaboration's tool for assessing risk of bias and the risk of bias was rated as "some concerns" in most. Third, the pooled estimates of this meta-analysis were calculated from studies that, in addition to pulmonary fibrosis, included other ILD-related entities, which might have influenced our findings. In this sense, disease severity may have influenced the effect of the intervention, but it was not available in most studies. Nevertheless, with respect to participants with CoV, all were hospitalized with lung lesions, and participants with mild-moderate severity symptoms were excluded. Fourth, to assess the effect of pulmonary rehabilitation on patients' HRQOL, we only analyzed studies that provided a total score of the scale used. However, physical or mental domains provided by other scales may potentially act as confounders or mediators in this association. To overcome some of these limitations, we conducted several sensitivity analyses to provide evidence regarding the robustness of the results.

Conclusions

This meta-analysis revealed a positive association between pulmonary rehabilitation and lung function, exercise capacity, and quality of life in patients with ILD, including severely affected patients with CoV. We are aware that further studies are necessary to confirm the role of pulmonary rehabilitation in the management of respiratory disabilities caused by COVID-19; however, although specific evidence of the effect of pulmonary rehabilitation in patients who have survived the severe acute respiratory syndrome coronavirus 2 infection appears contradictory, our data support that this intervention improves their functional capacity and their quality of life.

Suppliers

a RoB 2: a revised tool for assessing risk of bias in randomised trials; Cochrane Collaboration
b Stata statistical software, version 16.0; Stata Corp.

Keywords

Coronavirus; COVID-19; Pulmonary fibrosis; Rehabilitation; SARS virus

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Table S1 Studies excluded after full text read with the reason for exclusion.

Reference (Author and Year)	Reason for Exclusion
Barbier et al, 2014	Conference abstract
Bogerd et al, 2011	Conference abstract
Cohen et al, 2013	Conference abstract
De Las Heras et al, 2019	Conference abstract
Dowman et al, 2015	Conference abstract
Gaunaurd et al, 2011	Conference abstract
Gaunaurd et al, 2013	Conference abstract
Gaunaurd et al, 2014	Conference abstract
Gomez et al, 2012	Conference abstract
Gomez et al, 2013	Conference abstract
Jackson et al, 2012	Conference abstract
Jackson et al, 2014	Conference abstract
Jarosch et al, 2016	Conference abstract
Jastrzebski et al, 2017	Conference abstract
Koulopoulou et al, 2016	Conference abstract
Kramer et al, 2013	Conference abstract
Lanza et al, 2019	Conference abstract
Menon et al, 2011	Conference abstract
Nykvist et al, 2016	Conference abstract
Schneeberger et al, 2016	Conference abstract
Shen et al, 2016	Conference abstract
Stessel et al, 2015	Conference abstract
Vainshelboim et al, 2013	Conference abstract
Vainshelboim et al, 2013	Conference abstract
Vainshelboim et al, 2014	Conference abstract
Vainshelboim et al, 2015	Conference abstract
Parisien-La Salle et al, 2019	Non data available for meta-analysis
Cockcroft et al, 1981	Population
Greening et al, 2014	Population
Vainshelboim et al, 2014	Same data as other included study
Vainshelboim et al, 2016	Same data as other included study
Liu et al, 2017	Other language
Wapenaar et al, 2020	Non data available for meta-analysis

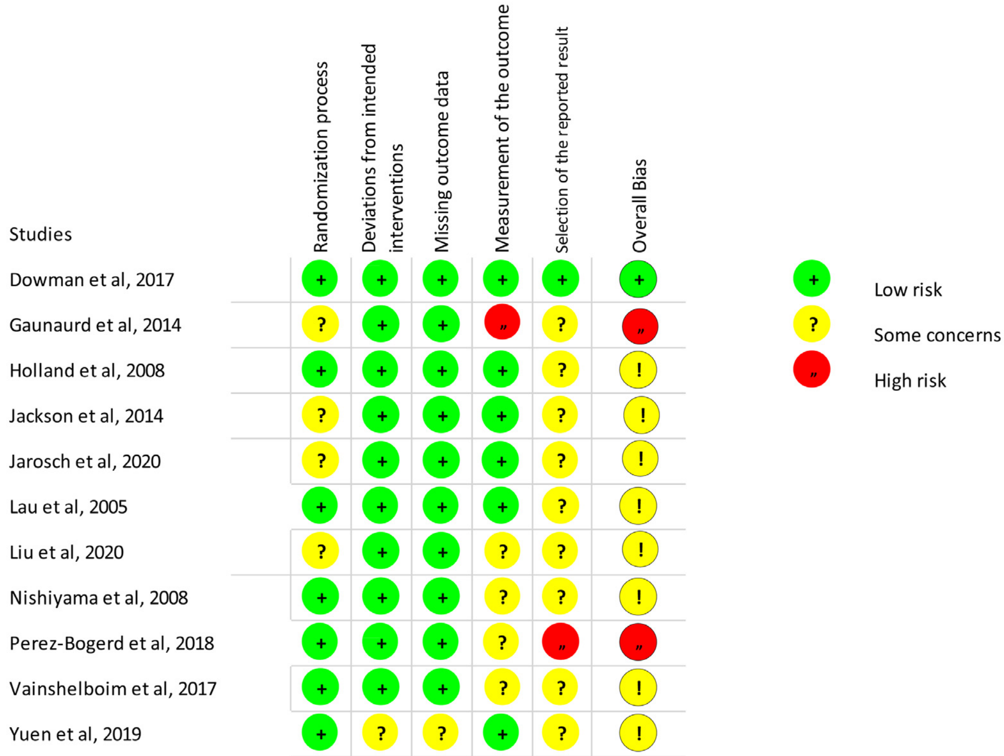

Figure S1 Risk of bias for included studies.

Table S2 Meta-regressions analyses based on age.

	Age		
Outcome	n	β	p
Lung function (FVC)	3	0.3499	0.489
Exercise capacity (6MWD)	10	-0.4345	0.499
Health related quality of life	7	0.0913	0.413
Dyspnoea	6	0.4196	0.117

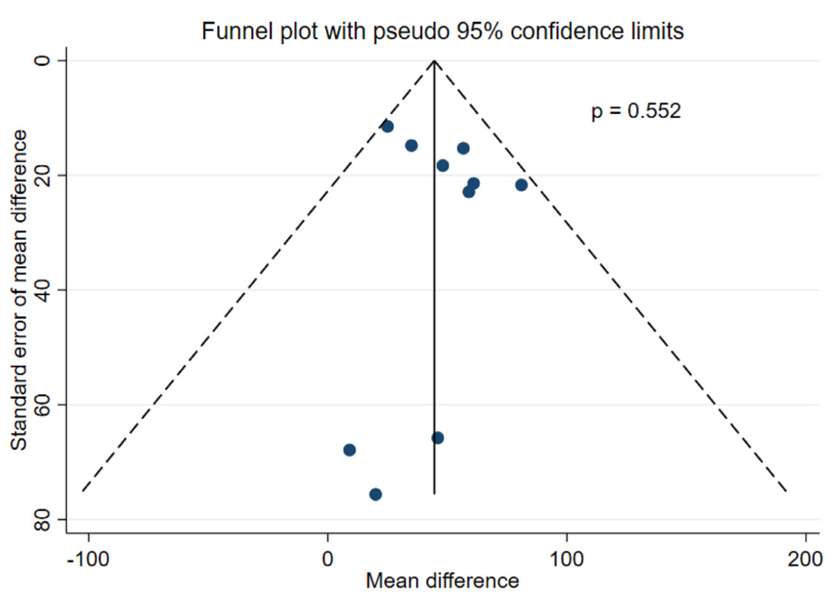

Figure S2 Funnel plot showing publication bias results for exercise capacity outcome (measured by 6-MWD).

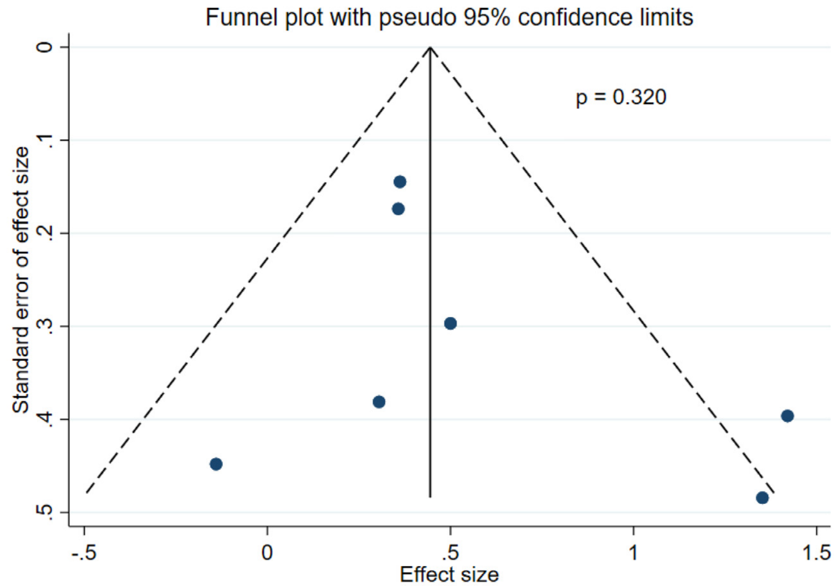

Figure S3 Funnel plot showing publication bias results for quality of life outcome (measured by St. George Respiratory Questionnaire (SGRQ) or SGRQ-1 (SGRQ specific for idiopathic pulmonary fibrosis)).

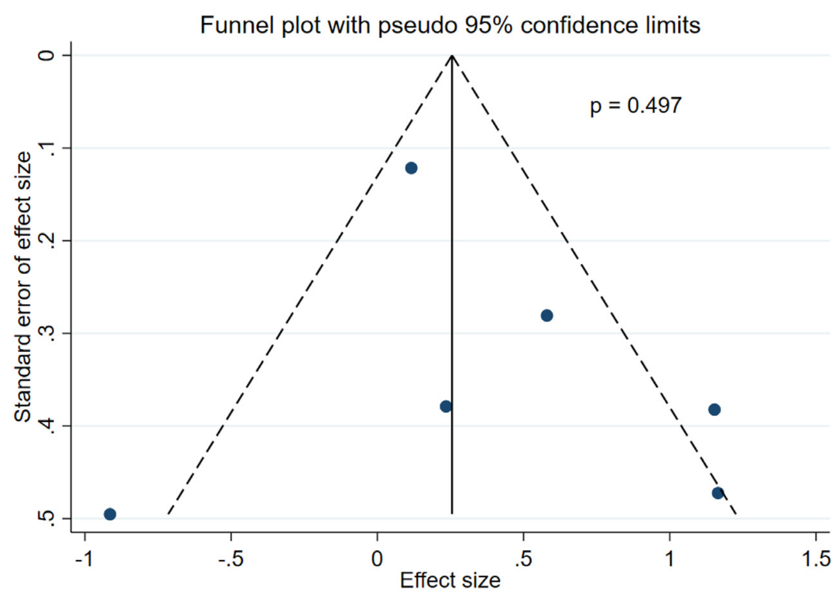

Figure S4 Funnel plot showing publication bias results for dyspnoea outcome.