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Effects of full-body exercise-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease characterised by progressive and irreversible fibrosis of the lung parenchyma, resulting in reduced lung function. Since conventional medicines can be associated with low effective rates and adverse events, pulmonary rehabilitation may be a promising non-pharmacological therapy for IPF. Thus, we aimed to evaluate the effects of full-body exercise-based pulmonary rehabilitation on patients with IPF by conducting a systematic review and meta-analysis of randomised controlled trials (RCTs).

Methods and analysis This systematic review and meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO). From inception to 31 August 2022, electronic databases in English and Chinese were searched, including PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials among the English databases. China National Knowledge Infrastructure, Chinese Biomedical Literature, VIP Chinese Science and Technology Periodical, and Wan Fang Data were among the Chinese databases. Two independent reviewers then screened the potential RCT studies, which were analysed according to the Cochrane Handbook criteria. The efficacy and safety of full-body exercise pulmonary rehabilitation for IPF were evaluated based on outcomes, including exercise capacity measured by 6 min walking distance and quality of life measured by St. George’s Respiratory Questionnaire. Lung function was measured based on the forced vital capacity, total lung capacity, diffusing capacity of the lungs for carbon monoxide and dyspnoea assessed by the modified Medical Research Council scale.

Ethics and dissemination Ethical approval was not required for this systematic review and meta-analysis. Results will be published in a peer-reviewed journal and presented at conferences.

PROSPERO registration number CRD42021284293.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our best knowledge, this is the first review that systematically analysed the effect of full-body exercise-based pulmonary rehabilitation on patients with idiopathic pulmonary fibrosis.

⇒ This systematic review protocol was drafted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement and has been registered in International Prospective Register of Systematic Reviews.

⇒ To minimise bias, at least two well-trained reviewers independently screened studies, extracted data and assessed risk of bias of the included studies.

⇒ We used accurate, broad search strategies of the electronic databases to minimise any potential publication bias.

⇒ The limitation of this research might be that non-English and non-Chinese studies were excluded.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a prototype of chronic, progressive and fibrotic lung disease. Although the cause of its pathogenesis remains unclear, it is understood that healthy lung tissue is replaced by altered extracellular matrix. Furthermore, the alveolar architecture is destroyed, leading to decreased lung compliance; disrupted gas exchange; and, ultimately, respiratory failure and death.1–2 Currently, the available treatment of IPF comprises antifibrotic drugs, which can slow down its progress without improving lung function.3 Unfortunately, approximately 60% of patients eventually die of respiratory failure due to disease progression, with a median survival time of 2–5 years if left untreated.1

Pulmonary rehabilitation is a comprehensive intervention based on thorough patient assessments followed by patient-tailored therapies,5 including exercise training, health education and behavioural changes. It plays an important role in the non-pharmacological treatment of lung diseases. The goals of pulmonary rehabilitation...
include reduction in patient symptoms, improvement in physical and psychological condition, and reduction in healthcare costs. Therefore, respiratory rehabilitation has a wide range of applications and is mainly suitable in all patients with chronic respiratory disease.6

Exercise rehabilitation is the core content of pulmonary rehabilitation,7 which is included in 76%-100% of pulmonary rehabilitation programmes.8-10 Regarding the pulmonary rehabilitation guidelines issued by the American College of Chest Physicians and American Association of Cardiovascular and Pulmonary Rehabilitation in 2007, upper and lower limb functional exercises and muscle strength training were mentioned as A-level recommendations.11 Studies have also shown that training improved dyspnoea symptoms, muscular strength and activities of daily living in patients with chronic obstructive pulmonary disease (COPD).12 13 Furthermore, pulmonary rehabilitation in patients after an acute exacerbation14 15 or in their stable phase of lung disease has been shown to be safe and effective.16 17 In terms of comorbidities, exercise could affect other body systems and functions, such as improving cardiovascular function,18 19 reducing mood disturbance,20 21 and improving skeletal muscle function.22 23

An official statement published by the American Thoracic Society/European Respiratory Society (ATS/ERS) in 20135 divided exercise pulmonary rehabilitation into three aspects: full-body exercise training, neuromuscular electrical stimulation (NMES) and inspiratory muscle training (IMT). The full-body exercise methods summarised in the official ATS/ERS statement of pulmonary rehabilitation include endurance, interval, resistance/strength, upper limb and flexibility training. However, this article only discussed the role of full-body exercise training in patients with IPF, whereas the effects of NMES and IMT on pulmonary rehabilitation remain controversial. Some studies have shown that NMES and IMT were adjuncts to full-body exercise training improved inspiratory muscle strength and endurance. However, they showed no effects on dyspnoea or maximal exercise capacity.24 25 Currently, there is an increasing amount of attention in the role of traditional Chinese exercise in pulmonary rehabilitation.26 27 Of note, an expert consensus and operational guidelines on exercise rehabilitation for COPD integrating traditional Chinese medicine and Western medicine was formed by an expert group on respiratory rehabilitation and a professional committee on respiratory rehabilitation from the China Medical Education Association. Since they determined that traditional Chinese exercise rehabilitation was extremely beneficial,28 this study also included traditional Chinese exercise in the scope of discussion. The pulmonary rehabilitation referred to in this paper included all forms of full-body exercise training. This included anaerobic and aerobic training classified according to the form of energy metabolism of exercise, high-intensity interval training that combines aerobic and anaerobic exercise, resistance training, endurance training, and strength training. In addition, other training methods classified according to the purpose of exercise, as well as limb training and traditional Chinese exercises were also included.

At present, the application and research on pulmonary rehabilitation mainly focuses on COPD. Since there is no clear conclusion regarding the efficacy of pulmonary rehabilitation on chronic respiratory diseases other than COPD, a consensus has yet to be reached on the efficacy of full-body exercise-based pulmonary rehabilitation in treatment of IPF. Thus, we conducted a systematic review and meta-analysis to evaluate the effectiveness of full-body exercise-based pulmonary rehabilitation in patients with IPF.

**METHODS AND ANALYSIS**

**Registration**

This systematic review and meta-analysis protocol followed the guidelines of the Cochrane Back Review Group, Cochrane Handbook, and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.29-31 This study has been registered in PROSPERO (registration number: CRD42021284293).

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**Table 1** Search strategy in PubMed

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<td>“randomized controlled trial”(Pt) OR “controlled clinical trial”(Pt)</td>
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Population
The population included male and female patients of any age who were diagnosed with IPF. The diagnosis of IPF was based on the 2011 international evidence-based guidelines for IPF diagnosis and treatment jointly published by the ATS/ERS/Japanese Respiratory Society/Latin ATS.4

Patient and public involvement
Neither the patients nor the public were involved in the design of this protocol.

Database and search strategy
Information sources were searched from inception to 31 August 2022. The following databases were used for searching in English: PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials. Similarly, the following medical databases were searched for in Chinese: China National Knowledge Infrastructure Database, Chinese Biomedical Literature Database, VIP Chinese Science and Technology Periodical Database, and Wan Fang Data. Two authors independently searched all information sources and removed all duplicate studies. Detailed information on the full search strategies for all databases is presented in tables 1–8.

Eligibility criteria
Randomised controlled trials (RCTs) that assessed the efficacy of full-body exercise training in patients with IPF were included, regardless of whether blinding was used.
Interventions
The experimental groups underwent exercise therapy only or combined with other interventions. However, the control groups underwent conventional therapy, including conventional medication, health guidance or in combination with other treatment methods.

Outcomes
The primary outcomes of interest included exercise capacity measured via 6min walking distance (6MWD) and quality of life measured via St. George’s Respiratory Questionnaire (SGRQ).

The secondary outcomes included lung function measured by forced vital capacity, total lung capacity, diffusing capacity of the lungs for carbon monoxide and dyspnoea measured by the modified Medical Research Council scale.

Study selection
The results of the literature search, including the citations and abstracts for each relevant study, were imported into the document management software NoteExpress3.2.0.7629 (Beijing Aegean Hailezhi Technology, Beijing, China). Duplicate studies were identified and removed prior to the screening process. Two researchers (YP and YX) independently searched the studies and selected articles for the screening process. If agreement could not be reached, a third author (YC) made the decision. If necessary to resolve disagreement, the authors of the study for the original data may be contacted. The process of study selection is shown in figure 1.

Data extraction
Data extracted from the studies included the following methodology information (design, number of arms, random sequence generation, allocation concealment and blinding) and patient characteristics (number of participants, sex, age, diagnostic criteria, inclusion criteria and exclusion criteria). The study characteristics (author, title, publication status and year, country and funding) and interventions (exercise type and treatment method) were also included in the extracted data.

Quality assessment of the included studies
The Cochrane risk-of-bias tool was used to assess the quality of the included RCTs. Two researchers categorised the risk of bias into high, low and unknown based on the following six items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other biases.

Data synthesis
The Review Manager V.5.4.1 (Cochrane Collaboration, London, UK) and R V.4.1.2 (R Foundation, Vienna, Austria) programs were used to analyse and synthesise the data. The mean difference (MD) or standardised MD with 95% CI was used to calculate continuous variables. If one outcome was considered inappropriate for data synthesis, we presented this result in a narrative overview.

Assessment of heterogeneity
Heterogeneity was assessed using $I^2$ statistics, as recommended by the Cochrane Collaboration. Specifically, $I^2 > 25\%$ indicated mild heterogeneity, $I^2 > 50\%$ indicated moderate heterogeneity and $I^2 > 75\%$ indicated strong heterogeneity. Moreover, a fixed effect model was used if $I^2 < 50\%$, a random effects model was used if $I^2 > 50\%$, and the source of heterogeneity was explored. In addition, sensitivity and subgroup analyses were performed.

Subgroup and sensitivity analyses
If there was significant clinical heterogeneity in the included studies, the cause of heterogeneity was explored. Subgroup analyses were performed according to the different types of study characteristics, including different interventions, duration of treatment and symptom severity at baseline. A sensitivity analysis was performed.

**Table 5** Search strategy in China National Knowledge Infrastructure Database

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**Table 6** Search strategy in Wan Fang Data

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**Table 7** Search strategy in VIP Chinese Science and Technology Periodical Database

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**Table 8** Search strategy in Chinese Biomedical Literature Database

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performed by eliminating low-quality trials one by one, thereby ensuring the robustness of results.

**Publication bias**
Publication bias was analysed using the funnel plot method if more than 10 studies would be included. If less than 10 studies would be included, the Egger test was applied.

**Quality of evidence**
This study evaluated the evidence based on the Grading of Recommendations Assessment, Development and Evaluation guidelines. Outcomes were graded into the following levels: very low, low, moderate or high.

**Ethics and dissemination**
This study was a compilation of previously published literature and did not involve participants for a clinical trial. Thus, ethical approval was not required. On completing the systematic review and meta-analysis, the results will be published in a peer-reviewed journal and presented at conferences.

**DISCUSSION**
This study aimed to evaluate the effects of all forms of full-body exercise training on patients with IPF. Compared with a published systematic review about exercise-based pulmonary rehabilitation in patients with IPF, this study only focused on full-body exercise training and included more comprehensive forms of exercise. Although pulmonary rehabilitation has been recommended as a non-pharmacological treatment of other chronic lung diseases such as COPD, the ATS/ERS guidelines indicated the use of pulmonary rehabilitation for IPF as a ‘weak recommendation’ (low-quality evidence). Two RCTs have also shown that full-body, exercise-based, pulmonary rehabilitation for IPF led to short-term (6 months) improvements in functional exercise tolerance, quality of life and dyspnoea. However, these improvements were not maintained or even declined after 6 months. Moreover, the magnitude of these improvements was smaller compared with that in patients with COPD. This suggests that full-body exercise-based pulmonary rehabilitation might not be effective in rapidly progressive diseases such as IPF. However, data collected from a cohort study by Ryerson et al showed that patients achieved a 50 m gain in the 6MWD from baseline to the 6-month follow-up after 6–9 weeks of full-body exercise-based pulmonary rehabilitation. Furthermore, Perez-Bogerd et al showed that the 6MWD, health-related quality of life (SGRQ) and quadricep strength could be maintained for up to 6 months after 6 months of full-body exercise-based pulmonary rehabilitation. Based on these findings, the role of full-body exercise-based pulmonary rehabilitation in patients with IPF has mixed conclusions, making it insufficient evidence of the benefits of pulmonary rehabilitation for IPF. To that end, this systematic review and meta-analysis of RCTs aimed to provide a comprehensive summary of results for the effects of full-body, exercise-based, pulmonary rehabilitation on patients with IPF.

**Correction notice** The article has been corrected since it was published online. The affiliation of the corresponding author (Han Yang) has been updated to “Hospital of Chengdu University of Traditional Chinese Medicine, School of...
Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, China. Contributors. YP and HY conceived and designed the study, which was revised by LQ and SW. YP made the search strategy of databases. YP and YX will search studies included, conduct data collection and analyse independently. YC will be the third reviewer for study selection and data extraction. All authors have approved the publication of this protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES