

BMJ Open Effects of pulmonary rehabilitation in lung transplant candidates: a systematic review

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ABSTRACT

Objectives: The aim of this systematic review of randomised controlled trials (RCTs), and quasi-experimental and retrospective studies is to investigate the effects of pulmonary rehabilitation (PR) in patients with advanced chronic disease on the waiting list for lung transplantation.

Setting: PR performed for inpatient or outpatient lung transplant candidates.

Intervention: PR programme including aerobic exercise training and/or resistance exercise training.

Primary and secondary outcomes: Quality of life and exercise capacity (primary outcomes). Survival rate after transplant surgery; pulmonary function; respiratory muscle strength; psychological aspects; upper and lower extremity muscle strength and adverse effects (secondary outcomes). Two review authors independently selected the studies, assessed study quality and extracted data. Studies in any language were included.

Results: This was a systematic review and studies were searched on the Cochrane Library, MEDLINE, EMBASE, CINAHL and PEDro. Experimental and retrospective studies evaluating the effects of PR in candidates for lung transplantation (>18 years old) with any lung diseases were included. 2 RCTs, and two quasi-experimental and two retrospective studies, involving 1305 participants were included in the review. 5 studies included an enhancement reported in quality of life using the Short Form 36 questionnaire and showed improvements in some domains. All studies included exercise capacity evaluated through 6 min walk test and in five of them, there were improvements in this outcome after PR. Owing to the different characteristics of the studies, it was not possible to perform a meta-analysis.

Conclusions: Studies included in this review showed that PR is an effective treatment option for patients on the waiting list for lung transplantation and can improve quality of life and exercise capacity in those patients. Although individual studies reported positive effects of PR, this review shows that there is a need for more studies of a high methodological quality addressing PR effects in lung transplant candidates.

Trial registration number: PROSPERO
CDR42015025110.

Strengths and limitations of this study

- This was the first systematic review focused on pulmonary rehabilitation (PR) before lung transplantation.
- The results of this review show that the literature does not adequately address the effects of PR in patients on a waiting list for lung transplantation. It is known that PR has been considered standard care for patients with pulmonary chronic diseases who might be included on a transplant list.
- Only a few studies could be included in this systematic review, which shows a need for more studies designed to evaluate the objectives of the study.
- A meta-analysis could not be performed due to the insufficient number of studies included.

INTRODUCTION

Rationale

Patients with different pulmonary conditions such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, idiopathic pulmonary fibrosis and pulmonary arterial hypertension can progress to advanced lung disease that causes a pronounced impact on life. Usually patients with advanced lung disease have a higher degree of ventilatory limitation and disability, and a greater risk of complications.¹ They also have reduced exercise tolerance, which is associated with dyspnoea and fatigue.^{2 3} Lung transplantation is a well-accepted therapy designated for a range of severe lung conditions, and evidence supports its success in improving survival and quality of life. It is known that the number of organ donors is much lower than the number of patients with severe lung conditions. Therefore, a patient selected to undergo transplantation must be a candidate with expectations for a good long-term outcome.⁴

Access to lung transplantation, a complex procedure, is becoming a more reasonable

option for patients with advanced lung disease, especially those patients with chronic respiratory failure, cardiovascular risk factors, and muscular and nutritional conditions, factors that can influence the prognosis for a successful lung transplantation.⁵ Therefore, pulmonary rehabilitation (PR) is an important process that focuses on avoiding comorbidities and complications.⁵

Most PR programmes are in accordance with the American College of Sports Medicine (ACSM), which recommends that patients with chronic diseases participate in aerobic exercise, resistance training, flexibility training and muscular fitness activities. In general, PR exercises follow the principles of exercise prescription guidelines from the ACSM, which is a methodology based on frequency, intensity, time and type of activity. Usually there is no consensus on the optimal exercise intensity for patients with chronic respiratory disease.⁶ However, intensity is based on a rated perceived exertion or 60% to 80% of peak work rate if results from an exercise test are available.⁶

The PR programme must be individualised and the modality and intensity of training must be selected individually for each patient. The duration of the training can vary from 6 weeks to 6 months and it is conducted by multidisciplinary teams.⁷ In 2013, the American Thoracic Society and the European Respiratory Society defined PR as “an evidence-based, multidisciplinary, and comprehensive intervention for symptomatic patients with chronic respiratory disease that present decreased activities of daily living. PR aims to reduce symptoms, optimise functional status, increase participation, and reduce healthcare costs making the manifestations of the disease stable or reversible”.²

Many rehabilitation centres incite the enrolment of patients with advanced lung disease in PR before lung transplantation. The role of PR in preoperative patients is essential to restore them to independent functioning, relieve symptoms, decrease disability and increase quality of life by increasing their participation in social and physical activities.⁸ It has been proven that exercise capacity (6 min walking distance) and resting carbon dioxide in arterial blood values are directly related to the rate of success in lung transplantation.⁸ Szelkely *et al*⁹ evidenced that those parameters can predict hospital stay after surgery and mortality and PR can decrease intensive care unit days, mechanical ventilation days and chest tube days.⁹ Costache *et al*¹⁰ showed that improvements in post-transplant survival might have been originated from pretransplant PR along with other factors that enhanced during surgery better immunosuppressive regimens and antibiotic protocols and decreased blood needs. PR plays an important role for the maintenance of exercise tolerance and physical functioning before and especially after lung transplantation as common extrapulmonary manifestations could be persistent in this period.¹¹ In a systematic review Wickerson *et al*¹² demonstrated that exercise should be included in the regular management of patients for lung transplant before and after

transplantation. Although there is an absence of specific PR protocol for patients for lung transplant it seems that it could enhance positive effects on maximal and functional exercise capacity, quality of life and skeletal muscle function.¹²

As mentioned previously, patients for lung transplant usually have a very challenging and advanced disease and face a greater limitation in activity and restriction in participation in PR programme. Nevertheless, the clinical benefits of PR for patients with COPD and other forms of advanced lung disease make the engagement in a PR programme required for patients for lung transplant in the preoperative time period.¹ It is important to synthesise the evidence obtained from a PR programme in order to improve this service in rehabilitation centres considering its benefits to patients with advanced lung disease and improving their adherence.

Objectives

To gather evidence on the effects of PR in people with advanced chronic disease who are on the waiting list for lung transplantation.

METHODS

Protocol and registration

The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO CDR42015025110) on 7 August 2015 before titles were investigated and studies selected for search results. This review is reported in accordance with PRISMA guidelines.¹³

Eligibility criteria

Types of studies

Experimental studies and retrospective studies were included.

Types of participants

Candidates for lung transplantation (>18 years old) with any lung diseases.

Types of interventions

We included studies evaluating the effects of PR before lung transplantation.

Types of outcome measures

The primary outcomes this review proposed to look for were: quality of life measured by any respiratory disease-specific or generic instrument and exercise capacity measured by the usual tests applied in clinical settings such as the 6 min walk test (6MWT), incremental shuttle walk test, as well as other maximal or submaximal cardiopulmonary tests.

The secondary outcomes were: survival rate after transplant surgery; pulmonary function that could be measured by spirometry, body plethysmography or diffusion capacity for carbon monoxide; respiratory muscle

strength measured by maximal inspiratory and expiratory pressure; psychological aspects assessed using questionnaires; upper and lower extremity muscle strength measured by one maximal repetition or other manual or non-manual muscle test, and adverse effects.

Language

We included articles reported in any language.

Information sources

The literature search strategies were developed using medical subject headings (MeSH) related to PR and lung transplant candidates.

Studies were identified from searches of the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), latest issue (the Cochrane Library); MEDLINE (Ovid) 1946 to date; EMBASE (Ovid) 1974 to date; CINAHL Plus (Ebsco) 1937 to date, and trials registries (ClinicalTrials.gov and the WHO trials portal).

Search strategy

The proposed MEDLINE strategy is listed in online supplementary appendix 1. This strategy was adapted for use in the other databases.

All databases were searched from their inception to the present, and there was no restriction on publication language.

The reference lists of all primary studies were checked and review articles were checked for additional references.

Study records

Two review authors (MH and GC) independently screened the titles and abstracts of all potential studies identified in the search. The studies were coded as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'.

We retrieved the full-text study report/publication, and the two review authors (MH and GC) independently screened the full text, identified studies eligible for inclusion and identified and recorded the reasons for exclusion of ineligible studies. Disagreement was resolved through discussion, or, if required, a third review author was consulted (VFP).

Data items

A data collection form was used for the study characteristics and outcome data was pilot-tested on at least one study in the review. Two review authors (MH and GC) extracted the study characteristics from the included studies. The following study characteristics were extracted:

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung

function, smoking history, inclusion criteria and exclusion criteria.

3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time periods reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (MH and GC) independently extracted outcome data from the included studies. The 'Characteristics of included studies' table notes whether outcome data were reported in a usable way. Disagreements were resolved by consensus or by involving a third review author (VFP).

Risk of bias individual studies

Two review authors (GC and GAR-S) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.¹⁴ Any disagreements were resolved by discussion or by involving another author (RRB). The risk of bias was assessed according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

Each potential source of bias was graded as high, low or unclear, and a quote was provided from the study report together with a justification for our judgement in the 'Risk of bias' table. The risk of bias judgements across different studies for each of the domains was summarised.

The review was conducted according to the Cochrane Collaboration tool for assessing the risk of bias (table 8.5.a in the Cochrane Handbook for Systematic Reviews of Interventions).¹⁴

Dealing with missing data

We contacted investigators in order to verify key study characteristics and obtain missing numerical outcome data where possible (eg, when a study was identified as an abstract only).

Data synthesis

As a meta-analysis could not be undertaken, we have provided a narrative synthesis of the available data.

RESULTS

Results of the search

In November 2015, we identified a total of 1413 studies including duplicates. This total was composed of 165 hits from MEDLINE, 1172 from EMBASE, 60 from CENTRAL and 16 from CINAHL. We did not find any

ongoing studies suitable for the review in clinicaltrials.gov or in the WHO ICTRP. After screening the titles and abstracts, we identified 13 studies as potentially relevant. We obtained the full text for those studies with ambiguous titles and abstracts so we could determine whether to include them from the review. Six studies met the inclusion criteria.^{15–20} See figure 1 for full details on the results of the search. No further studies were included in this review.

Included studies

Two RCTs,^{18 20} two quasi-experimental studies^{16 17} and two retrospective studies^{15 19} were included in this review.

One included study was conducted in Canada,¹⁵ one in Brazil,¹⁶ one in Poland,¹⁷ two in Germany^{18 19} and one in the US.²⁰ All studies were published in English.

Participants

The studies varied in size from 9 to 811 participants. All participants in the studies included were older than 18 years of age. The patients were on lung transplant waiting lists in all the studies.

Intervention and control groups

Table 1 shows the six studies included^{15–20} where patients performed aerobic exercises on a treadmill, cycle ergometer or Nordic walking.

In the Li *et al*¹⁵ study, data from candidates for lung transplant who received PR at a hospital consisting of stretching, aerobic exercises and resistance training

three times per week for 1.5 to 2 hours for a mean of 47 ±59 sessions was analysed. In the Florian *et al*¹⁶ study, all participants in the intervention group underwent training for 36 sessions for 90 min per session. In the Jastrzebski *et al*¹⁷ study, patients performed Nordic walking exercise training with ski poles at ~75% of their maximum heart rate for 12 weeks (two cycles of 2-week hospital-based supervised rehabilitation and 4-week home-based rehabilitation). In the Gloeckl *et al*¹⁸ study, patients followed a multidisciplinary 3-week inpatient rehabilitation programme that included exercise units for 5–6 days/week, but during the second and third week, exercise training was split into two sessions per day. The total amount of exercise time per session increased from 10 to 30 min for continuous training and from 12 to 36 min for interval training, yielding an isocaloric total work in both groups. In the Kenn *et al*¹⁹ study, data were evaluated from 811 patients referred for lung transplantation who were enrolled in PR 5–6 days per week for supervised sessions of endurance training of 10–20 min at 60% of peak work rate and graduated from a cycle test plus 30–45 min of strength exercises. In the Manzetti *et al*²⁰ study, sessions were offered three times a week for 6 weeks. The education plus exercise group attended an exercise programme twice a week for 6 weeks with 30 min of aerobic training, and the participants in the education group were not recommended for exercise.

Outcomes

The six studies included^{15–20} evaluated exercise capacity through the 6MWT. Five studies^{15–19} evaluated health-related quality of life (HRQL) through the Short Form 36 questionnaire (SF-36 questionnaire). The study by Li *et al*¹⁵ also evaluated HRQL using the Saint George Respiratory Questionnaire (SGRQ), the Standard Gamble, the Visual Analogue Scale and the EuroQol five dimensions questionnaire (EQ-5D). Two studies (refs. 17 18) assessed lung function measured with either a MasterScreen Body plethysmograph or spirometry. The study by Manzetti *et al*²⁰ also evaluated exercise tolerance through cardiopulmonary exercise testing and quality of life with different scales (Quality of Well-being scale (QWB), Quality of Life Index (QLI) and Symptom Frequency/Symptom Distress scale (SFSD)) and the Li *et al*¹⁵ study assessed exercise tolerance by measuring training volumes and calorie expenditure from the start of PR until the transplant.

Risk of bias

Assessment of the risk of bias was performed in both RCTs. Full details for the risk of bias judgements can be found in figure 2.

Allocation

One study reported adequate sequence generation and allocation concealment and was judged to have a low risk of bias.¹⁸ One study was judged to have a high risk

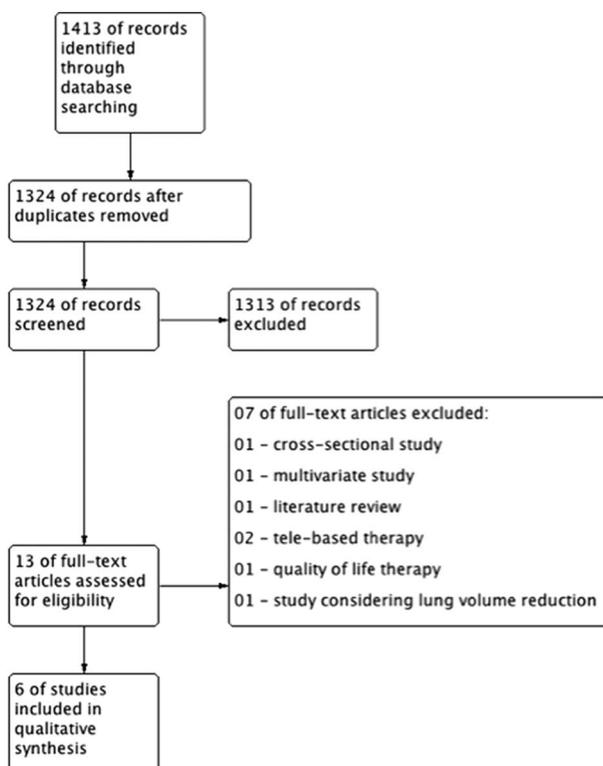


Figure 1 Study flow diagram.

Table 1 Study characteristics of the studies included

	Design	Country	Participants	Interventions	Outcomes
Li <i>et al</i> ¹⁵	Retrospective cohort study	Canada	345 patients Mean age: 51±14 years	Duration: 1.5 to 2 hours per session 3 times per week; 47±59 sessions. Interventions: Stretching aerobic exercise and resistance training. Aerobic exercise: arm ergometer, cycle ergometer, treadmill training. Duration increased up to 20 min of treadmill. Resistance and stretching: biceps, triceps, quadriceps, hamstrings and hip muscles.	- Exercise capacity: 6MWT - Quality of life: SF-36; SGRQ, Visual Analogue Scale, Standard Gamble and EQ-5D.
Florian <i>et al</i> ¹⁶	Prospective study	Brazil	58 patients Mean age: 46±14 years	Duration: 90 min, 3 times/week (36 meetings). Intervention: Warming-up: breathing exercises associated with arm raising. Muscle strengthening: arm and leg exercises with an initial load of 30% of one repetition maximum testing and with one set of 10 repetitions per exercise (the load was increased by 0.5 kg every 7 sessions according to the patient tolerance). Aerobic exercises: performed on a treadmill, beginning at 60% of the speed of the 6MWT (progressive protocol every 6 min until reaching 30 min). The speed was increased by 0.3 km/h every 7 sessions.	- Exercise capacity: 6MWT. - Health-related quality of life: SF-36.
Jastrzebski <i>et al</i> ¹⁷	Quasi-experimental study	Poland	22 male patients Mean age: 50.4 years	Duration: Two 6-week cycles: 2-week hospital-based rehabilitation and 4-week home-based rehabilitation. Interventions: Nordic walking at 75% of maximal heart rate-monitored heart rate and oxygen saturation at first session at hospital. Distance according to 6MWT.	- Quality of life: SF-36. - Dyspnoea: MRC questionnaire. - Exercise capacity: 6MWT. - Pulmonary function: spirometry.
Gloeckl <i>et al</i> ¹⁸	Randomised control trial	Germany	60 patients Mean age: 53±6 years	Duration: 3 weeks inpatient rehabilitation programme (5 to 6 days/week). Interventions: Interval training: cycling at 100% peak work rate for 30 s alternating with 30 s of rest. Continuous training: cycling at 60% of peak work rate.	- Exercise capacity: 6MWT. - Lung function: MasterScreen Body Plethysmograph. - Health-related quality of life: SF-36.
Kenn <i>et al</i> ¹⁹	Retrospective study	Germany	811 patients -COPD(n=360) 54±7.6 years -AATD(n=127) 51±6.3 years -ILD(n=195) 54±8.7 years -CF(n=69) 31±7.4 years -Other(n=60) 45±12.9 years	Duration: 5 to 6 days per week yielding 25 to 30 sessions. Interventions: Supervised sessions of endurance training 10–20 min at 60% of peak work rate, elaborated from an incremental cycle test; 30–45 min training sessions, including individual strength training (four to six exercises with 3×20 repetitions at the maximum tolerated load), specialised breathing techniques and controlled coughing exercises along with active physiotherapy. Twice per week (for 1 hour), all patients participated in educational sessions addressing self-management, coping strategies, nutritional interventions and structured lessons developed for candidates for LTx: postoperative drug management, living with the new organ, and psychosocial aspects after LTx.	- Exercise capacity: 6MWT. - Quality of life: SF36. - Lung function and blood gas analyses: spirometry and body plethysmography.

Continued

Table 1 Continued

	Design	Country	Participants	Interventions	Outcomes
Manzetti <i>et al</i> ²⁰	Randomised control trial	USA	9 patients Mean age: 40±10 years	Duration: 3 times/week for 6 weeks (education classes); 2 times/week (exercise classes). Interventions: Education+exercise: the same educational programme plus exercise programme that included treadmill, bicycle ergometer, light aerobic exercises and light upper extremity weight training within the participant's physical capacity. Education alone: classes in anatomy, physiology and pathophysiology, home oxygen systems, stress reduction techniques and alternative sexual techniques taught by a multidisciplinary team of healthcare providers.	- Exercise tolerance: 6MWT and cardiopulmonary exercise testing. - Quality of life: QWB, QLI and SFSD.

6MWT, 6 min walk test; AATD, α -1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; EQ-5D, EuroQol five dimensions questionnaire; ILD, interstitial lung disease; LTx, lung transplantation; MRC, medical research council questionnaire; QWB, quality of well-being scale; QLI, quality of life index; SF-36, Short Form 36 questionnaire; SFSD, symptom frequency/symptom distress scale; SGRQ, Saint George respiratory questionnaire.

Figure 2 Risk of bias judgements.

	Manzetti 1994	Gloeckl 2012	
	⊖	⊕	Random sequence generation (selection bias)
	?	⊕	Allocation concealment (selection bias)
	?	⊖	Blinding of participants and personnel (performance bias)
	?	⊕	Blinding of outcome assessment (detection bias)
	⊖	⊕	Incomplete outcome data (attrition bias)
	⊖	⊕	Selective reporting (reporting bias)
	⊖	⊖	Other bias

of bias once the randomisation described was determined to be inappropriate.²⁰

Blinding

The Gloeckl *et al*¹⁸ study described the blinding of participants and personnel as not possible and was judged to have a high risk of bias because the outcomes could have been influenced by this shortcoming. Another study²⁰ did not describe blinding of participants and personnel, so it was judged to have an unclear risk of bias.

Blinding of outcome assessors was described in Gloeckl *et al*,¹⁸ which was judged to have low risk of bias. The Manzetti *et al*²⁰ study did not provide sufficient data to permit judgement, so it was judged to have an unclear risk of bias.

Incomplete outcome data

The Gloeckl *et al*¹⁸ study informed the missing outcome data as numbers balanced across the intervention groups, with similar reasons allowed for missing data across groups and it performed an intention-to-treat analysis. The Manzetti *et al*²⁰ study was judged to have a high risk of bias because it did not assess whether the groups were similar at the baseline, although it described the reasons for drop-outs.

Selective reporting

The Gloeckl *et al*¹⁸ study was registered on clinicaltrials.gov, and all of the prespecified primary and secondary outcomes were reported in a prespecified way. The Manzetti *et al*²⁰ study failed to include results for a key outcome that should have been reported.

Other potential sources of bias

We identified other potential sources of bias in two studies. In the Gloeckl *et al*¹⁸ study some patients in the continuous training group also presented interval-training characteristics due to the high number of unintended breaks. In the Manzetti *et al*²⁰ study the sample size was small and the participants in the education group had diagnoses that resulted in physiological limitations that may have been more likely to respond to interventions included in an exercise programme and this study also showed inappropriate statistical analysis.

Effects of interventions

Primary outcomes: quality of life

Five of the six studies included a reported enhancement in quality of life using the SF-36 questionnaire showing improvements in some domains over time. In the Li *et al*¹⁵ study, the mental health component also significantly decreased after PR (47±11 to 45±12, $p<0.05$). In this study, all components of the SGRQ showed significant decline after the PR programme (65±14 to 69±11, $p<0.05$) and in the EQ-5D scores (0.55±0.24 to 0.47±0.27, $p<0.05$), revealing an improvement in health-related quality of life after completing the PR. In the Florian *et al*¹⁶ study, participants improved in physical functioning ($p=0.001$), role-physical ($p=0.045$); vitality ($p<0.001$); social functioning ($p=0.001$); and mental health ($p=0.001$). In the Jastrzebski *et al*¹⁷ study quality of life showed improvement through an increase in the physical cumulative score from the SF-36 (27.2±8.2 to 29.9±9.1, $p<0.05$) after 6 weeks of PR. In the Gloeckl *et al*¹⁸ study although all sum scores of the SF-36 improved, only the physical health summary score in the control group (4.3±6.9 points) and the mental health summary score (9.7±13.0 points) in the intervention group increased significantly. In the Kenn *et al* study,¹⁹ the retrospective analysis of data from the SF-36 showed improvements in the physical health summary after the PR programme (mean δ : 1.9, SD δ : 8.5, $p<0.001$) and in the mental component summary (mean δ : 8.7, SD δ : 13.5, $p<0.001$). The Manzetti *et al*²⁰ study used three different questionnaires: results showed that the QWB scores improved significantly over time ($p=0.005$), with both groups demonstrating higher scores at the completion of the study. However, there were no significant differences between the groups or interaction. For the QLI and SFSD scores, there were no significant differences between the groups, over time or interaction.

Primary outcomes: exercise capacity

All studies included in this review evaluated exercise capacity through the 6MWT. The study by Li *et al*¹⁵ showed that patients walked an average of 320±119 m in the beginning and 314±116 m in the final 6MWT prior to transplantation, presenting an average of 15 m less after an average of 47 sessions ($p=0.002$). In the Florian *et al* study,¹⁶ after completion of the programme, there was a

mean increase of 72 m in the 6MWT ($p=0.001$), whereas a significant decrease in perceived dyspnoea was described ($p=0.001$).¹⁶ A significant increase in the 6MWT distance was found in the study by Jastrzebski *et al*,¹⁷ from 310.2±130.2 to 361.9±131.5 m, which means an average increase of 51.6 m ($p<0.005$). In the Gloeckl *et al* study,¹⁸ the exercise programme was effective in both groups (a significant increase in the 6MWT of 35±28 m for the interval group and 36±42 m for the continuous group, $p<0.05$). Similar to the Jastrzebski *et al*¹⁷ study, a significant increase in the 6MWT distance was found in the study by Kenn *et al*¹⁹ with a mean different pre-PR to post-PR of 55.9±58.5 m ($p<0.001$). In the Manzetti *et al*²⁰ study, the 6MWT improved significantly over time ($p<0.03$). However, no significant differences between groups were found. Manzetti *et al*²⁰ evaluated exercise tolerance through cardiopulmonary exercise in nine participants and showed that there were no significant differences in workload between the groups, over time or in interaction.

Secondary outcomes: pulmonary function

Jastrzebski *et al*¹⁷ assessed lung function by spirometry and showed a significant increase in the mean value of forced vital capacity after 12 weeks of PR (44% to 53% of predicted values; $p<0.05$). Gloeckl *et al*¹⁸ assessed lung function measured by plethysmograph in 60 participants and showed that at discharge, none of the lung function parameters were significantly different from baseline values.

Secondary outcomes: adverse effects

The study by Jastrzebski *et al*¹⁷ evaluated the effects of PR on the dyspnoea ratings using the Medical Research Council (MRC) questionnaire, the baseline dyspnoea index and the oxygen cost diagram and although there were improvements in those measurements, they did not achieve statistical significance.

Secondary outcomes: survival rate after transplant surgery; respiratory muscle strength; psychological aspects and upper and lower extremity muscle strength.

None of the studies that were included specifically evaluated any of these outcomes.

DISCUSSION

Summary of main results

This systematic review assessed the effects of PR in patients with lung disease on a waiting list for lung transplantation. Six studies were included with a total of 1305 patients who had the following conditions: COPD, idiopathic pulmonary fibrosis, pulmonary emphysema, interstitial idiopathic pneumonia, non-specific interstitial pneumonia or other types of advanced lung disease. Although these studies met the inclusion criteria, they differed significantly in terms of intervention characteristics and methods. Since the included studies employed different interventions by using different methodologies,

a meta-analysis for lung function was not possible due to the high heterogeneity.

None of the articles addressed the effects of PR on the survival rate after transplant surgery or on the respiratory muscle strength. Overall, PR was applied as physical exercise, which in only one study was divided into two groups: continuous training or interval training, and its effects were observed in different outcomes.

Overall completeness and applicability of the evidence

Two randomised controlled trials, two quasi-experimental studies and two retrospective studies were included and although they had a different design, all the studies defined PR as a therapeutic option for patients for lung transplant that was capable of reducing dyspnoea, increasing exercise capacity and improving quality of life.

All studies included patients with similar age ranges on a waiting list for lung transplantation; however, there was heterogeneity in the types of disease included in each study. Gloeckl *et al*¹⁸ included only patients with COPD stage IV in accordance with the GOLD assessment,²¹ while Florian *et al*,¹⁶ Manzetti *et al*,²⁰ Jastrzebski *et al*,¹⁷ Kenn *et al*¹⁹ and Li *et al*¹⁵ included any patient on a waiting list for lung transplantation regardless of the health condition. While some could argue that this heterogeneity renders the results of this review less significant, it is the positive results from PR raised in the six studies that suggest how important this therapy is to this population irrespective of the underlying disease.

With regard to exercise capacity, four of the six studies that were included reported an increase in the 6MWT after participation in PR.^{16–18 20} The 6MWT evaluates exercise capacity and it is an important tool to identify benefits derived from different therapeutic interventions such as PR.²² It is known that there is a minimal clinically important difference (MCID) in the 6MWT that ranges from 25 to 35 m for lung diseases, which is related to an increase in survival.^{22–24} The four studies mentioned above^{16–18 20} showed an improvement in the MCID reinforcing the importance of PR for patients with lung disease.

The literature indicates that a significant relationship exists between the baseline 6MWT for patients on the waiting list for a lung transplant and survival, and that the results from the 6MWT—as a continuous variable—are related to patient mortality.^{25 26} A reduction of more than 50% in mortality for every 500-foot increment in the baseline 6MWT was indicated by Martinu *et al*²⁵ and a cut-off of 207 m in the test to predict survival was shown by Lederer *et al*.²⁷ Although there is a strong correlation between the 6MWT and the rate of post-transplant survival, Castleberry *et al*²⁶ showed a low accuracy in dichotomisation in predicting 1-year mortality. Thus, the ability of a single value to predict mortality is limited and it should be used carefully.

Quality of life was assessed by five studies using the SF-36 questionnaire. Florian *et al*¹⁵ and Kenn *et al*¹⁹ found an increase in the domains of physical

functioning and mental health, while Gloeckl *et al*¹⁸ only found an increase in the mental health component and Jastrzebski *et al*¹⁷ found an increase only in the physical functioning component. Li *et al*¹⁵ found a decrease in the mental health component of the SF-36 questionnaire, but reported a good result after the application of the SGRQ with a significant decrease in the total score and in all domains. Manzetti *et al*²⁰ also evaluated the patient's quality of life using a QWB that showed a significant improvement after PR.

Health-related quality of life is an important component to determine the impact of chronic diseases in patients' perceptions about their own health.²⁸ Gilbert and Smith²⁸ showed that PR is recommended for patients with advanced lung disease because of increases in quality of life scores and decreases in sensations of dyspnoea. Similar results were found in a recent systematic review of patients with COPD that showed significant improvements in quality of life after PR.²⁹ However, the same study showed that after a follow-up, no clinically relevant difference was found in this outcome.²⁹ Furthermore, it was demonstrated in a systematic review that there is an association between specific comorbidity in COPD and worse quality of life.³⁰

Only two of the six studies that were included evaluated some of the secondary outcomes considered in this review, but none of them evaluated upper and lower extremity muscle strength. Nonetheless, rehabilitation has been proven to also improve limb muscle function in patients with lung disease such as COPD.³¹ A statement from American Thoracic Society (ATS) and European Respiratory Society (ERS) highlighted that quadriceps muscle strength, endurance and fatigability improved significantly after exercise training in patients with COPD.³¹ Moreover, a relationship between quadriceps muscle function and exercise capacity has been found in patients with COPD and in patients with interstitial lung disease (ILD) that presented weakness in the knee extensors.³² Considering the importance of skeletal muscle dysfunction, Liao *et al*³³ in a systematic review, proved that resistance training significantly improved knee extension strength and that this could be related to better exercise capacity and reduced dyspnoea.

Quality of the evidence

This review is limited due to a lack of studies in the literature addressing the topic that was chosen. In addition, the studies that were included had different intervention protocols and different designs, which made comparisons between them more difficult.

From the two RCTs included in the review, only one described the random sequence generation method and allocation concealment so it was classified as having a low risk of bias. According to Savović *et al*,³⁴ inadequate reporting of trial methods can severely compromise the assessment of study quality and the risk of bias in the study results. Furthermore, ineffectively reported randomisation has been associated with bias in estimating

the effectiveness of interventions.³⁵ The study by Gloeckl *et al*¹⁸ reported that researchers were blinded regarding the allocation of patients. In a randomised controlled trial that involves exercises, it is not possible for the participants and the personnel to be blinded to the intervention and the lack of double blinding or its unclearness can be associated with intervention effects overestimation.

Potential biases in the review process

A systematic process for the inclusion of studies and pre-specified criteria for the methods were implemented in order to minimise the risk of bias in this review.

Incomplete outcome data and selective reporting were considered potential sources of bias in this review. These issues had limited analytical value once the data from the two RCTs could not be entered into a meta-analysis. Additionally, subgroup and sensitivity analyses were not possible due to the insufficient data.

Subgroup analysis could have showed possible differences in disease pathophysiology, age groups and duration of PR. Furthermore, sensitivity analysis could have identified the influence of trial quality and trial size on the results, therefore revealing a source of the substantial heterogeneity found among studies.

Agreements with other studies

PR has been defined as a component of the management of pulmonary diseases according to the ATS and the ERS.² The studies included in this review are in agreement with an extensive number of studies on the benefits of PR in other lung conditions.²⁻⁷ Nonetheless, to the best of our knowledge this is the first review to assess the effectiveness of PR in patients on a waiting list for lung transplantation.

In 2013 the ATS and the ERS incorporated the concepts of PR for patients with different chronic respiratory diseases other than COPD and the PR scope to reduce symptoms, increase participation, optimise functional status and reduce healthcare costs.²

Dowman *et al*³⁶ studied PR in ILD and found its benefits in improving functional exercise capacity, dyspnoea and quality of life in these patients. Troosters *et al*³⁷ on the other hand, studied PR in patients with COPD and, as Dowman *et al*,³⁶ found benefits in functional capacity, health-related quality of life besides improvement in activity, daily function and restoration of independent function. The study by Mereles *et al*³⁸ shows the same benefits of PR in patients with pulmonary hypertension. Regarding patients with severe chronic respiratory disease preparing for lung transplantation or lung volume reduction surgery, Rochester *et al*.¹ present in a review study the function of PR in the care of these patients. This review supports that although it is not known whether PR increases survival to surgery, increases patient tolerance for surgery or reduces postoperative complications, it is clear that it improves exercise tolerance, health status, dyspnoea and quality of life.¹

Although there are RCTs and other studies regarding PR in different lung conditions, pretransplantation PR reports have been few and uncontrolled, and RCTs are lacking and they were discussed in this review.

AUTHOR'S CONCLUSIONS

Although this review could not perform a meta-analysis, the studies that were included indicate that PR can improve exercise capacity and quality of life over time, regardless of the type of exercise that is conducted and the disease background of the patient. The most important topic arising from the studies assessed in this review is that PR can be a beneficial and efficient treatment for patients with advanced lung disease on the waiting list for lung transplantation.

Well-conducted studies are needed to assess the benefits of PR in lung transplant candidates. In addition, more attention needs to be paid to good reporting and high-quality study design, including items such as adequate random sequence generation and allocation concealment, blinding and determination of trial sample size before a study is initiated.

Contributors MH and GC were the main systematic reviewers and worked across all stages of the review from inception to completed draft. GAR-S is the statistical expert and provided advice on data analysis and commented on the final document content. RRB provided advice on data analysis and commented on the final document content. VFP provided advice throughout the project, and was involved in screening, selection and commenting on the analysis and the final document content.

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