Exercise training for lung transplant candidates and recipients: a systematic review

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Both inpatient and outpatient exercise training appears beneficial for improving exercise capacity and quality of life in lung transplant candidates and recipients. Further research investigating the effect on post-surgery clinical outcomes is required. https://bit.ly/2XD6J6S

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ABSTRACT Exercise intolerance and impaired quality of life (QoL) are characteristic of lung transplant candidates and recipients. This review investigated the effects of exercise training on exercise capacity, QoL and clinical outcomes in pre- and post-operative lung transplant patients. A systematic literature search of PubMed, Nursing and Allied Health, Cochrane (CENTRAL), Scopus and CINAHL databases was conducted from inception until February, 2020. The inclusion criteria were assessment of the impact of exercise training before or after lung transplantation on exercise capacity, QoL or clinical outcomes.

21 studies met the inclusion criteria, comprising 1488 lung transplant candidates and 1108 recipients. Studies consisted of five RCTs, two quasi-experimental and 14 single-arm cohort or pilot studies. Exercise training improved or at least maintained exercise capacity and QoL before and after lung transplantation. The impact on clinical outcomes was less clear but suggested a survival benefit. The quality of evidence ranged from fair to excellent.

Exercise training appears to be beneficial for patients before and after lung transplantation; however, the evidence for direct causation is limited by the lack of controlled trials. Well-designed RCTs are needed, as well as further research into the effect of exercise training on important post-transplant clinical outcomes, such as time to discharge, rejection, infection, survival and re-hospitalisation.

Introduction

Lung transplantation is a surgical procedure for selected patients with life-threatening, advanced lung disease that is unresponsive to other medical or surgical treatments. The most common disease entities resulting in lung transplantation include chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension [1]. Over recent years, advances in organ preservation, immunosuppressant therapies, surgical techniques and peri-operative management have led to gradual improvements in survival rates of transplantation surgery. The median

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survival rate of 5.8 years, nevertheless, still remains below that of other solid-organ transplants [2]. It is well documented that the number of patients awaiting lung transplantation exceeds the number of suitable donor organs available. As waiting list times can therefore be prolonged, averaging 326 days in the UK [3], it is important to maintain functional capacity and prevent further physical deterioration in patients awaiting lung transplantation [4].

In patients with advanced lung disease, several physiological factors negatively impact physical activity, including ventilatory limitations, metabolic and gas exchange abnormalities, cardiovascular impairment and peripheral muscle weakness [5]. Evidence indicates that functional capacity, as assessed through the 6-min walk test (6MWT), is reduced in patients awaiting lung transplantation compared to healthy age-matched individuals. The 6MWT distance, therefore, constitutes an important predictor of mortality [6, 7] and has been established as a predictor of post-transplant survival [8, 9]. A previous systematic review [10], comprising two randomised controlled trials (RCTs), two quasi-experimental studies and two retrospective studies concluded that pulmonary rehabilitation can be a beneficial treatment for improving functional capacity and quality of life (QoL) in lung transplant candidates. Studies are, however, still scarce, particularly RCTs. Notably, in the previous review [10], there were no studies looking at the effect of pulmonary rehabilitation on important outcomes, such as survival.

Following lung transplantation, there is a marked improvement in pulmonary function. However, patients still experience physical impairments, such as limited exercise capacity (40–60% of predicted normal values), early-onset of metabolic acidosis and skeletal muscle weakness, all of which persist for years after transplant surgery [11, 12]. In the early post-transplant phase, this is likely due to deconditioning from the extended intensive care and hospital stay following surgery, which can vary from 3 to 6 weeks or more if complications ensue. Additionally, immunosuppressant medications which are taken chronically following lung transplantation are accompanied by several side effects, including adverse effects on the cellular features of skeletal muscle [13]. Lung transplant patients also face a number of psychological stressors throughout the course of the transplant journey, which can significantly impact QoL, physical functioning and adherence to recovery regimes [14].

At 1 year post surgery, daily sedentary time remains significantly increased in lung transplant patients compared to healthy individuals, with daily steps, standing time and walking time all significantly reduced [15]. It has, therefore, been deemed necessary to implement therapeutic exercise protocols after lung transplantation. Such studies (RCTs, controlled trials and prospective cohorts) have been presented in a systematic review that was published in 2010 [16]. The overall quality of these studies was deemed fair to moderate and positive outcomes were indicated in areas of maximal and functional exercise capacity, skeletal muscle function and lumbar bone mineral density. Since the previous systematic reviews [10, 16], there have been several new studies investigating the effect of exercise therapy protocols before [17–21] and after [22–30] lung transplantation.

The American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation [31] highlights the need to understand the mechanisms of improvement in functional capacity and QoL following pulmonary rehabilitation interventions in lung transplant candidates and recipients. Accordingly, the aim of the present systematic review is to investigate the effects of exercise training before and after lung transplantation on exercise capacity, QoL and clinical outcomes (including survival, length of hospital or intensive care unit (ICU) stay, hospitalisations). Additionally, the safety of exercise training protocols in this patient population will be evaluated.

Methods

Protocol and registration

This systematic review was conducted in accordance with the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [32]. The review protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42020166322).

Search strategy

PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Nursing and Allied Health, Scopus, and CINAHL databases were searched from inception until February 2020. These six databases were chosen due to their relevance in clinical research and use in related systematic reviews [10, 16]. Database-specific search strategies, developed and pilot tested in consultation with a senior librarian, were based on keywords and MeSH terms related to “lung transplantation”, “exercise”, “rehabilitation”, “exercise capacity”, “quality of life” and “survival”. Full details of the PubMed search strategy are detailed in supplementary material. The reference lists of all relevant systematic reviews identified in the search were also screened for additional studies. The search was restricted to peer-reviewed studies written in English, as access to a translator was not available. All search results were collated using EndNote software (Thomson Reuters, New York, NY,

USA) and duplicates removed. Remaining references were exported to the systematic review management software program Rayyan (Qatar Computing Research Institute, Doha, Qatar).

Inclusion criteria

The titles and abstracts were reviewed independently by two authors (E. Hume and J. Manifield) to determine if the studies met the pre-determined PICOS (population, intervention, comparators, outcomes and study design) criteria as follows. Population: lung transplant candidates or recipients (>18 years old) with any lung disease; intervention: studies evaluating the effects of an exercise training intervention. This was defined as all planned, structured and repetitive physical activity that had a final or an intermediate objective of improving or maintaining physical fitness [33]; comparator: no exercise control group, an active control group or a different dose/mode/setting of exercise training were considered acceptable controls in RCTs; outcomes: exercise capacity (assessed through 6MWT, incremental shuttle walk test (ISWT), endurance shuttle walk test (ESWT) or cardiopulmonary exercise testing (CPET)), QoL (including health-related QoL (HRQoL)) and psychological health, assessed through generic or respiratory-specific questionnaires), clinical outcomes (survival, hospitalisations, length of hospital or ICU stay); design: studies of all design type were included, as evidence suggests that non-randomised intervention studies, including observational study designs, are key to many areas of healthcare evaluation and can provide complementary evidence to RCTs [34].

Screening of full texts was performed by two independent reviewers (E. Hume and J. Manifield) and the reasons for exclusion of ineligible studies was recorded. Any disagreements were resolved through consultation with a third reviewer (I. Vogiatzis).

Data extraction and synthesis

Data extraction was performed by a single author (E. Hume) using a predesigned, standardised Excel (Microsoft, Redmond, WA, USA) form. The following study characteristics were extracted: author information (including name of first author and year of publication), participant characteristics (number, mean age, sex, baseline lung function), study design, setting (country, inpatient, outpatient or home based) interventions details, outcome measures (exercise capacity, QoL and clinical outcomes) and effect sizes for post-intervention differences between intervention and control/comparison groups (RCT and non-randomised controlled trials), or pre- to post-intervention differences (cohort and pilot studies). Effect size was expressed as Cohen's d using the mean difference and pooled standard deviation [35]. Meta-analyses were planned if three or more studies with clinical and methodological homogeneity were identified [36]. For questionnaires with subscales, only those reporting composite scores were extracted, to give a clearer picture of the efficacy of one therapeutic approach *versus* another [37].

Quality assessment

The methodological quality of the studies was evaluated using the Downs and Black checklist [38], designed to assess both randomised and non-randomised study designs. The checklist comprises 27 questions under four sub-scales of reporting, external validity, internal validity (bias and confounding) and power. Each question was scored out of 1, except for question five, which was scored out of 2, with a maximum total score of 28. Scoring of the last item (study power) was modified from a 0–5 scale to a 0–1 scale, where 1 was scored if a sample size/power calculation was present, while 0 was scored if there was no power/sample size calculation or explanation whether the number of subjects was appropriate [38, 39]. A score of 24–28 points was considered excellent, 19–23 good, 14–18 fair and <14 poor, in terms of methodological quality [40]. Each study was scored independently by two authors (E. Hume and J. Manifield), with discrepancies resolved through consensus.

Results

A total of 1962 articles were yielded from the six database searches, of which, 393 records were duplicates. Following screening of titles and abstracts, 47 articles remained for full text screening. On completion of full text screening, 21 studies met the eligibility criteria and were included in the review. A PRISMA flow diagram of the screening process is presented in figure 1. Due to heterogeneity in study designs, interventions, comparison groups and outcome measures, quantitative synthesis *via* meta-analysis was not performed, as pooling the data would have led to misleading results that were not clinically meaningful [41].

Study characteristics and interventions

The characteristics of the included studies are presented in table 1.

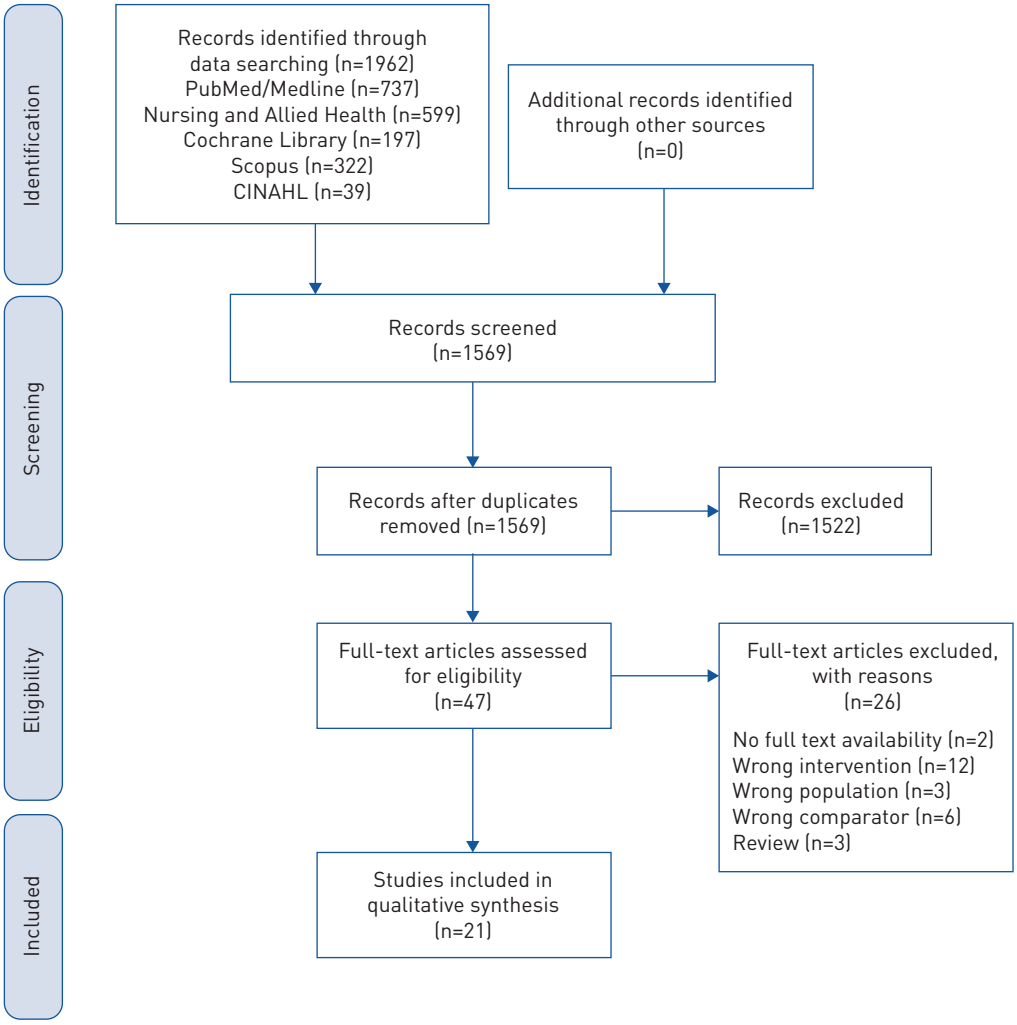

FIGURE 1 PRISMA flow diagram for database search and study selection process.

Pre-transplant

Nine of the 21 studies involved pre-transplant patients (n=1488), with a mean age of 52 years (range 37–63 years) and average forced expiratory volume in 1 s (FEV_1) % predicted range of 26 to 54%. Between 43 and 95% (median=58%) of participants in each study were male. Of the pre-transplant studies, there was one RCT [42], two quasi-experimental [17, 18], five cohort studies [19, 20, 43–45] and one single-arm pilot study [21]. Eight of the nine studies implemented both aerobic and resistance exercise [17, 19–21, 42–45] and one study included Nordic walking only [18]. Two studies were conducted as inpatient programmes [42, 44], four were outpatient exercise programmes [17, 19, 43, 45], two combined outpatient and home-based training [18, 20], and one was home-based using an online application [21]. The length of exercise training ranged from 3 to 16 weeks, with exercise session frequency ranging from two to six exercise sessions per week.

Post-transplant

Twelve studies involved exercise training with post-transplant populations. These studies included 1108 recipients of either single or bilateral lung transplant, with a mean age of 52 years (range 44–59 years), and average FEV_1 % predicted ranging from 64 to 75%. Between 47 and 98% (median=56%) of participants in each study were male. Included studies comprised four RCTs [22–24, 30], five cohort studies [25, 26, 46–48] and two single-arm pilot studies [27, 29]. A further, controlled trial by Vivodtzev *et al.* [28] used healthy individuals as a control group; therefore, only the outcomes reported for lung transplant recipients were included in this review. One RCT compared the effect of exercise training to an active control group (physical activity counselling) [22], one compared an inpatient programme with outpatient physiotherapy [23], one compared different durations of supervised exercise training [24] and one compared exercise

TABLE 1 Characteristics of included studies

First author [ref.]	Setting	Sample	Study design	Duration and frequency	Intervention	Comparison	Outcomes 1) **Exercise capacity** 2) **QoL** 3) **Clinical outcomes**
Pre-transplant							
Gloeckl *et al.* [42]	Germany: supervised inpatient programme	Sample size: 60 Mean age years: 53±6 Sex: 47% male FEV_1 % pred: 25±8	RCT	3 weeks 5–6× per week	Exercise programme. Interval training: 30 s cycling alternating with 30 s rest. Resistance exercises.	Exercise programme. Continuous training: cycling (60% PWR). Resistance exercises.	1) 6MWT, PWR 2) SF-36 3) Not assessed
Florian *et al.* [17]	Brazil: supervised outpatient programme	Sample size: 89 Mean age years: 56±11 Sex: 64% male FEV_1 % pred: 46±15	Quasi-experimental	12 weeks (36 sessions) 3× per week	Exercise programme. Aerobic exercises: treadmill walking. Resistance: arm and leg exercises. Breathing exercises associated with arm raising.	Patients not completing 36 sessions	1) 6MWT 2) SF-36 3) Survival rate, LOS in hospital and ICU, IMV
Ochman *et al.* [18]	Poland: outpatient and home-based programme	Sample size: 40 Mean age years: Intervention: 50±8 Control: 54±9 Sex: 95% male FEV_1 % pred: Intervention: 39±20.5 Control: 43±22.2	Quasi-experimental	12 weeks	Exercise programme. Nordic walking	No treatment control group	1) 6MWT 2) SF-36 3) Not assessed
Florian *et al.* [43]	Brazil: supervised outpatient programme	Sample size: 58 Mean age years: 46±14 Sex: 48% male FEV_1 % pred: 33±16	Cohort study	12 weeks 3× per week (36 sessions)	Exercise programme. Aerobic exercises: treadmill walking. Resistance: arm and leg exercises. Breathing exercises associated with arm raising. Stretching: major muscle groups.	None	1) 6MWT 2) SF-36 3) Not assessed
Da Fontoura *et al.* [19]	Brazil: supervised outpatient programme	Sample size: 31 Mean age years: 57±10 Sex: 58% male FEV_1 % pred: 54±16	Cohort study	12 weeks 3× per week	Exercise programme. Aerobic exercise: treadmill. Resistance exercise: upper and lower body (light weights and resistance bands).	None	1) 6MWT 2) SF-36 3) Not assessed

Continued

TABLE 1 Continued

First author [ref.]	Setting	Sample	Study design	Duration and frequency	Intervention	Comparison	Outcomes 1) **Exercise capacity** 2) **QoL** 3) **Clinical outcomes**
Kenn *et al.* [44]	Germany: supervised inpatient programme	Sample size: 811 Mean age years: COPD male: 54±7.6 COPD female: 54±7.4 AATD male: 51±6.3 AATD female: 52±8.2 ILD male: 54±8.7 ILD female: 53±7.9 CF male: 31±7.4 CF female: 31±8.6 Other male: 45±12.9 Other female: 45±11.3 Sex: 43% male FEV_1 % pred: COPD male: 25.2±12.6 COPD female: 25.5±7.6 AATD male: 25.6±9.2 AATD female: 27.2±8.9 ILD male: 49.2±19.5 ILD female: 43.5±16.4 CF male: 23.8±7.8 CF female: 26.2±7.7 Other male: 33.5±15.2 Other female: 33.2±20.5	Cohort study	5–6 weeks 5–6× per week (25–30 sessions)	Exercise programme. Aerobic exercise: cycle ergometer. Resistance training. Breathing exercises. Controlled coughing exercises.	None	1) 6MWT 2) SF-36 3) Not assessed
Li *et al.* [45]	Canada: supervised outpatient programme	Sample size: 345 Mean age years: 51±14 Gender: 55% male FEV_1 % pred: Not stated	Cohort study	47±59 sessions 3× per week	Exercise programme. Aerobic exercise: arm ergometer, cycle ergometer and treadmill; Stretching and resistance training: biceps, triceps, quadriceps, hamstrings and hip muscles.	None	1) 6MWT 2) SF-36, SGRQ, VAS, Standard Gamble, EQ5Q 3) Discharge disposition, hospital and ICU LOS, intubation days

Continued

TABLE 1 Continued

First author [ref.]	Setting	Sample	Study design	Duration and frequency	Intervention	Comparison	Outcomes 1) **Exercise capacity** 2) **QoL** 3) **Clinical outcomes**
Pehlivan *et al.* [20]	Turkey: supervised outpatient and home-based programme	Sample size: 39 Mean age: 37±13 Sex: 64% male FEV_1 % pred: 26±11	Cohort study	8 weeks (minimum) 5× per week (2 supervised, 3 at home)	Exercise programme. Aerobic exercise: cycle ergometer, treadmill walking, arm ergometer. Resistance exercises. Home exercises: breathing exercises, strengthening exercises using Thera-bands, walking.	None	1) 6MWT 2) SF-36, BDI 3) Not assessed
Singer *et al.* [21]	USA: home-based programme using app	Sample size: 15 Mean age years: 63±6 Sex: 67% male FEV_1 % pred: 42±26	Pilot Study	8 weeks	Exercise programme. Home-based exercise using Aidcube App. Aerobic exercise: treadmill or ground walking. Resistance exercises: Thera-bands.	None	1) 6MWT 2) Not assessed 3) Not assessed
Post-transplant							
Langer *et al.* [22]	Belgium: supervised outpatient programme	Sample size: 36 Mean age years: 59±6 Sex: 50% male FEV_1 % pred: Intervention: 79±18 Control: 69±17	RCT	12 weeks 3× per week	Exercise programme. Aerobic exercises: cycling, walking, stair climbing. Resistance exercises: leg press equipment.	Physical activity counselling. 6 sessions, 15–30 mins	1) 6MWT (% pred), V_{O_2peak} (% pred), PWR (% pred) 2) SF-36 and HADS 3) Not assessed
Ihle *et al.* [23]	Germany: supervised inpatient programme	Sample size: 60 Mean age years: Intervention=49±14 Control=50±12 Sex: 57% male FEV_1 % pred: Not reported	RCT	23±5 days	Inpatient exercise programme. Endurance training. Resistance training: upper and lower limb. Stretching: major muscle groups. Range-of-motion exercises: neck, shoulders and trunk.	Outpatient physiotherapy. Cardiovascular exercise, airway clearance and breathing exercises.	1) 6MWT, PWR, V_{O_2peak} 2) SF-36, SGRQ 3) Not assessed

Continued

TABLE 1 Continued

First author [ref.]	Setting	Sample	Study design	Duration and frequency	Intervention	Comparison	Outcomes 1) **Exercise capacity** 2) **QoL** 3) **Clinical outcomes**
Fuller *et al.* [24]	Australia: supervised outpatient programme and home-based unsupervised programme	Sample size: 66 Mean age years: 51±13 Sex: 50% male FEV_1 % pred: Intervention: 70±21 Control: 69±23	RCT	14 weeks 3× per week	Exercise programme. 14 weeks supervised. Aerobic training: treadmill and cycle ergometer. Resistance training: upper and lower limb. Functional exercises and core stability.	Exercise programme. 7 weeks supervised 7 weeks home-based. Aerobic training: treadmill and cycle ergometer. Resistance training: upper and lower limb. Functional exercises and core stability.	1) 6MWT 2) SF-36 3) Not assessed
Gloeckl *et al.* [30]	Germany: inpatient programme	Sample size: 80 Mean age years: 56±7 Sex: 53% male FEV_1 % pred: 68±20	RCT	4 weeks 5–6× per week	Exercise programme with WBVT. Aerobic exercise: cycle ergometer. Resistance exercises: major muscle groups +WBVT squats.	Exercise programme. Aerobic exercise: cycle ergometer. Resistance exercises: major muscle groups.	1) 6MWT, PWR 2) HADS, CRQ 3) Not assessed
Candemir *et al.* [25]	Turkey: outpatient programme (two sessions supervised, one unsupervised)	Sample size: 23 Mean age years: 47±10 Sex: 88% male FEV_1 % pred: 75±15	Cohort study	12 weeks	Exercise programme. Aerobic exercise: treadmill, cycle ergometer. Resistance exercise: lower and upper extremities	None	1) ISWT and ESWT 2) SGRQ, CRQ and HADS 3) Not assessed
Munro *et al.* [46]	Australia: supervised outpatient programme	Sample size: 36 Mean age years: 46±14 Sex: 50% male FEV_1 % pred: 71±18	Cohort study	12 weeks 3× per week	Exercise programme. Aerobic exercises: cycling, treadmill walking. Resistance training: upper and lower limb. Stretching: major muscle groups	None	1) 6MWT 2) SF-36 3) Not assessed
Maury *et al.* [47]	Belgium: supervised outpatient programme	Sample size: 36 Mean age years: 57±4 Sex: 47% male FEV_1 % pred: 70±21	Cohort study	12 weeks 3× per week	Exercise programme. Aerobic exercises: cycling, walking, stair climbing. Resistance exercises: quadriceps muscle.	None	1) 6MWT 2) Not assessed 3) Not assessed

Continued

TABLE 1 Continued

First author [ref.]	Setting	Sample	Study design	Duration and frequency	Intervention	Comparison	Outcomes 1) **Exercise capacity** 2) **QoL** 3) **Clinical outcomes**
Stiebellehner *et al.* [48]	Austria: supervised outpatient programme	Sample size: 9 Mean age years: 44±6 Sex: 67% male FEV_1 % pred: 65±17	Cohort study	6 weeks 3–5× per week	Exercise programme. Aerobic exercise: cycle ergometer	None	1) V_{O_2}peak 2) Not assessed 3) Not assessed
Schneeberger *et al.* [26]	Germany: supervised inpatient programme	Sample size: 722 Mean age years: COPD SLTx: 59±5 COPD DLTx 54±7 ILD SLTx: 58±7 ILD DLTx: 54±9 Sex: 55% male FEV_1 % pred: COPD SLTx: 51.1±16.6 COPD DLTx: 73.7±20.1 ILD SLTx: 60.2±18.9 ILD DLTx: 65.6±18.1	Cohort study	6 weeks 5–6× per week	Exercise programme. Aerobic training: cycle ergometer. Resistance training: lower extremities. Breathing exercises. Activities of daily living: stair climbing.	None	1) 6MWT 2) SF-36 3) Not assessed
Andrianopoulos *et al.* [27]	Germany: supervised inpatient programme	Sample size: 24 Mean age years: 58±6 Sex: 58% male FEV_1 % pred: 75.4±22	Pilot study	3 weeks 5–6× per week (15 sessions minimum)	Exercise programme. Aerobic training: cycle ergometer. Resistance training: upper and lower limb. Activities of daily living training: walking and/or calisthenics exercises.	None	1) 6MWT 2) Not assessed 3) Not assessed
Choi *et al.* [29]	USA: home programme using computer program	Sample size: 4 Mean age years: 55±17 Sex: 75% male FEV_1 % pred: 71.3±25.2	Pilot study	8 weeks 8 sessions	Exercise programme. Aerobic exercise: walking. Resistance exercises: cuff weights. Balance exercises.	None	1) 6MWT 2) Not assessed 3) Not assessed
Vivodtzev *et al.* [28]	France: home programme (supervised *via* phone)	Sample size: 12 Mean age years: 47±13 Sex: 83% male FEV_1 % pred: 74±24	Controlled trial (healthy controls)	12 weeks 3× per week	Exercise programme. Aerobic exercise: cycle ergometer.	None	1) V_{O_2}peak, endurance time 2) Not assessed 3) Not assessed

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CF: cystic fibrosis; AATD: α_1-antitrypsin deficiency; SLTx: single lung transplant; DLTx: double lung transplant; RCT: randomised controlled trial; QoL: quality of life; 6MWT: 6-min walk test; V_{O_2peak}: peak oxygen uptake; PWR: peak work rate; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; SF-36: Short Form 36 Questionnaire; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; VAS: Visual Analogue Scale; BDI: Beck Depression Inventory; Hospital LOS: hospital length of stay; ICU LOS: intensive care unit length of stay; IMV: invasive mechanical ventilation; WBVT: whole body vibration training.

training with whole body vibration training (WBVT) to exercise training alone [30]. Ten of the 12 studies implemented exercise programmes comprising both aerobic and resistance exercise [22–27, 29, 30, 46, 47] and two comprised aerobic training only [28, 48]. Four studies implemented inpatient programmes [23, 26, 27, 30], five were outpatient programmes [22, 25, 46–48] and two were home based [28, 29]. The length of training varied from 3 to 14 weeks, with session frequency ranging from three to six times a week.

Quality assessment

Quality assessment ratings, using Downs and Black, are presented in table 2. The mean score for the 21 included studies was 18 out of a possible 28 (range 14 to 25), indicating fair to excellent methodological quality. The RCTs scored highest for methodological quality. Across studies, scoring was low for item 8 (reporting of adverse events), item 12 (representative sample), item 14 (blinding of subjects), item 15 (blinding of assessors) and item 27 (sample size). Poor scoring for item 14 was expected, as it is difficult to blind patients from the condition they are receiving, due to the nature of the intervention. The methodological quality of the non-randomised and cohort studies was limited because of non-random allocation and lack of control for confounding variables.

Exercise capacity outcomes

The measures of exercise capacity pre- and post-exercise intervention are presented in table 3.

Pre-transplant

All nine pre-transplant studies in the review assessed functional exercise capacity using the 6MWT, with seven of the nine studies reporting a significant improvement in this outcome after exercise training. In addition to the 6MWT, Gloeckl *et al.* [42] also assessed peak work rate (PWR) during an incremental test, and found that both interval and continuous training significantly improved both measures of exercise capacity, with no difference in the magnitude of improvement between groups. Florian *et al.* [17] reported a significant increase in 6MWT distance in the exercise training group; however, no 6MWT data were presented for the control group. Nordic walking elicited a significant improvement in 6MWT distance compared with a control group after 12 weeks [18]. Of the five cohort studies, four showed significant improvements in 6MWT distance following combined aerobic and resistance training [19, 20, 43, 44].

TABLE 2 Downs and Black Methodological Quality Assessment

First author [ref.]	Reporting (out of 11)	External validity (out of 3)	Internal validity: bias (out of 7)	Internal validity: confounding (out of 6)	Power (out of 1)	Total score (out of 28)
Pre-transplant						
Gloeckl *et al.* [42]	11	2	5	6	1	**25**
Florian *et al.* [17]	8	2	5	4	0	**19**
Ochman *et al.* [18]	7	1	4	3	0	**15**
Florian *et al.* [43]	8	3	5	3	0	**19**
Da Fontoura *et al.* [19]	8	2	5	2	0	**17**
Kenn *et al.* [44]	8	2	5	3	0	**18**
Li *et al.* [45]	7	2	3	3	0	**15**
Pehlivan *et al.* [20]	8	1	5	3	0	**17**
Singer *et al.* [21]	9	3	5	3	0	**20**
Post-transplant						
Langer *et al.* [22]	9	2	6	6	1	**24**
Ihle *et al.* [23]	9	2	5	5	0	**21**
Fuller *et al.* [24]	11	2	6	5	1	**25**
Gloeckl *et al.* [30]	10	2	6	4	1	**23**
Candemir *et al.* [25]	8	1	5	3	0	**17**
Munro *et al.* [46]	7	3	4	3	0	**17**
Maury *et al.* [47]	7	2	4	3	0	**16**
Stiebellehner *et al.* [48]	7	1	5	2	0	**15**
Schneeberger *et al.* [26]	9	1	5	2	0	**17**
Andrianopoulos *et al.* [27]	8	1	5	2	0	**16**
Choi *et al.* [29]	7	1	4	2	0	**14**
Vivodtzev *et al.* [28]	7	1	5	1	0	**14**

Cut-off points of the summative score are: excellent (24–28), good, (19–23), fair (14–18), and poor (<14).

TABLE 3 Effects of pre- and post-transplant exercise training interventions on measures of exercise capacity

First author [ref.]	N	Duration	Measure	Intervention/comparison	Δ (mean±SD where reported)	Pre–post p-value	Between group p-value	Effect size
Pre-transplant								
Gloeckl *et al.* [42]	60	3 weeks	6MWT (m)	Interval ET	35.4±28.9	p<0.05	p=0.89	INT<CON; 0.0008
				Continuous ET	35.7±42.2	p<0.05		
			PWR (W)	Interval ET	12.0±8.5	p<0.05	p=0.38	INT>CON; 0.29
				Continuous ET	9.3±10.1	p<0.05		
Florian *et al.* [17]	89	12 weeks	6MWT (m)	ET	43±86	p=0.005	-	PRE<POST; 0.5
				Control	NR	NR	-	-
Ochman *et al.* [18]	40	12 weeks	6MWT (m)	Nordic walking ET	64	p=0.0378	p=0.034	UTC
				Control	−57	p=0.0059		
Pehlivan *et al.* [20]	39	8 weeks	6MWT (m)	ET	54.3	p=0.001	-	PRE<POST; 0.49
Florian *et al.* [43]	58	12 weeks	6MWT (m)	ET	72	p=0.001	-	PRE<POST; 0.57
Da Fontoura *et al.* [19]	31	12 weeks	6MWT (m)	ET	58±63	p<0.001	-	PRE<POST; 0.92
Kenn *et al.* [44]	811	5–6 weeks	6MWT (m)	ET	55.9±58.5	p<0.001	-	PRE<POST; 0.96
Li *et al.* [45]	345	47±59 sessions	6MWT (m)	ET	−6	p=0.002	-	PRE>POST; −0.05
Singer *et al.* [21]	15	8 weeks	6MWT (m)	Tele-rehabilitation	−7.8	p=0.73	-	PRE>POST; −0.10
Post-transplant								
Ihle *et al.* [23]	60	23±5 days	6MWT (m)	ET (inpatient)	45	p<0.001	p=0.214	INT>CON; 0.24
				Control (outpatient physiotherapy)	24	p<0.001		
			V_{O_2}peak (mL·min^{-1}·kg^{-1})	ET (inpatient)	1.3	p=0.039	p=0.293	INT<CON; −0.19
				Control (outpatient physiotherapy)	2.2	p=0.005		
			PWR (W)	ET (inpatient)	7.3	p=0 022	p=0.600	INT>CON; 0.09
				Control (outpatient physiotherapy)	4.7	p=0.070		
Langer *et al.* [22]	36	12 weeks	6MWT (% pred)	ET	23	-	p=0.008	INT>CON; 0.37
				Control (PA counselling)	19	-		
			V_{O_2}peak (% pred)	ET	16	-	p=0.149	INT>CON; 0.20
				Control (PA counselling)	12	-		
			PWR (% pred)	ET	16	-	p=0.093	INT>CON; 0.26
				Control (PA counselling)	11	-		
Fuller *et al.* [24]	66	14 weeks	6MWT (m)	14 weeks supervised ET	149±169	-	p=0.36	INT<CON; −0.44
				7 weeks supervised ET	202±72	-		
Gloeckl *et al.* [30]	80	4 weeks	6MWT (m)	ET+WBVT	83.5	p<0.001	p=0.029	INT>CON; 0.54
				ET	55.2	p<0.001		
			PWR	ET+WBVT	16.8	p<0.001	p=0.042	INT>CON; 0.38
				ET	12.6	p<0.001		

Continued

TABLE 3 Continued

First author [ref.]	N	Duration	Measure	Intervention/comparison	Δ (mean±SD where reported)	Pre–post p-value	Between group p-value	Effect size
Candemir *et al.* [25]	23	12 weeks	ISWT (m)	ET	103	p<0.001	-	PRE<POST; 0.87
			ESWT (min)		8	p<0.01	-	PRE<POST; 1.33
Munro *et al.* [46]	36	12 weeks	6MWT (m)	ET	92	p<0.001	-	PRE<POST; 0.79
Maury *et al.* [47]	36	12 weeks	6MWT (m)	ET	129	p<0.05	-	PRE<POST; 0.97
Stiebellehner *et al.* [48]	9	6 weeks	V_{O_2}peak (mL·min^{-1}·kg^{-1})	ET	1.9	p<0.05	-	PRE<POST; 0.49
Schneeberger *et al.* [26]	722	6 weeks	6MWT (m)	ET in COPD SLTx	109±68	p<0.001	-	PRE<POST; 1.60
				ET in COPD DLTx	117±82	p<0.001	-	PRE<POST; 1.43
				ET in ILD SLTx	115±79	p<0.001	-	PRE<POST; 1.46
				ET in ILD DLTx	132±77	p<0.001	-	PRE<POST; 1.71
Andrianopoulos *et al.* [27]	24	3 weeks	6MWT (m)	ET	86±77	p<0.001	-	PRE<POST; 0.73
Choi *et al.* [29]	4	8 weeks	6MWT (m)	ET Tele-rehabilitation	71	-	-	PRE<POST; 0.62
Vivodtzev *et al.* [28]	12	12 weeks	V_{O_2}peak (L·min^{-1})	Home-based ET	0.13±0.22	p=0.059	-	PRE<POST; 0.59
			Endurance time (65% PWR) (min)		9±12	p<0.05	-	PRE<POST; 0.75

ET: exercise training; WBVT: whole body vibration training; 6MWT: 6 min walk test; ISWT: Incremental Shuttle Walk Test; ESWT: Endurance Shuttle Walk Test; V_{O_2peak}: peak oxygen uptake; PWR: Peak Work Rate: SLTx: single lung transplant; DLTx: double lung transplant; COPD: Chronic Obstructive Pulmonary Disease; INT: intervention; CON: control; PRE: Pre-intervention; POST: Post-intervention; UTC: unable to calculate; (Δ): change from baseline.

However, the cohort study by Li *et al.* [45] found a small decrease in 6MWT distance from the time of waiting list enrolment to the final 6MWT conducted before transplantation, after an average of 47 sessions of pulmonary rehabilitation. Home-based exercise training demonstrated no significant change in 6MWT distance in a pilot study [21].

Post-transplant

Six different measures of exercise capacity were used across the 12 post-transplant studies: 6MWT distance [22–24, 26, 27, 29, 30, 46, 47], ISWT, ESWT [25], peak oxygen uptake (V_{O_2peak}) [22, 23, 28, 48], peak work rate (PWR) [22, 23, 30], and endurance time (sustained at 65% PWR) [28]. Langer *et al.* [22] found a significant increase in 6MWT distance (% predicted) following exercise training compared to a control group; however, there were no significant differences in V_{O_2peak} (% predicted) nor PWR (% predicted). Ihle *et al.* [23] found no significant difference in the improvement of 6MWT distance, V_{O_2peak} or PWR when inpatient rehabilitation was compared with outpatient physiotherapy. Furthermore, improvements in 6MWT distance were not significantly different between 7 and 14 weeks of supervised exercise training [24]. Gloeckl *et al.* [30] showed significantly greater improvements in 6MWT distance and PWR, with the addition of WBVT to exercise training. Four cohort studies implementing aerobic and resistance training found statistically significant increases in either 6MWT distance [26, 46, 47] or ISWT distance [25]. Stiebellehner *et al.* [48] showed significant gains in V_{O_2peak} after an aerobic exercise programme. Furthermore, a pilot study [27] found a significant increase in 6MWT distance after exercise based pulmonary rehabilitation. However, the pilot study by Choi *et al.* [29] showed a 71-m improvement in 6MWT distance in four patients with either IPF or CF, but failed to conduct any statistical analysis.

QoL outcomes

The measures of QoL are presented in table 4. For the purpose of this review, QoL was operationalised as measures encompassing HRQoL and/or psychological health.

Pre-transplant

QoL was assessed in eight of the nine pre-transplant studies using the Short Form (SF)-36 questionnaire, which generates eight sub-scale and two summary scores (physical component summary (PCS) and mental component summary (MCS)). Only the four studies reporting the summary scores were included in the review. Other QOL measures included St Georges Respiratory Questionnaire (SGRQ) [45], EQ-5D [45], Standard Gamble [45] and Beck Depression Inventory (BDI) [20]. Of the studies using the SF-36 questionnaire, Gloeckl *et al.* [42] found significant improvements in SF-36 PCS scores in the continuous training but not the interval training group, whereas enhancements SF-36 MCS scores were found only with interval training. da Fontoura *et al.* [19] found significant improvements in SF-36 PCS scores, but no significant change in SF-36 MCS scores. Whereas, Kenn *et al.* [44] found significant increases in both SF-36 PCS and MCS scores overall for all disease entities. In contrast, Li *et al.* [45] revealed a significant decline in SF-36 MCS, SGRQ and EQ-5D scores, along with no change in SF-36 PCS and Standard Gamble scores from listing to immediately prior to lung transplantation.

Post-transplant

QoL was assessed in seven of the 12 post-transplant studies. Several measures were used including the SF-36 questionnaire [23, 24, 26, 46], Hospital Anxiety and Depression Score (HADs) [22, 25, 30], SGRQ [23, 25] and Chronic Respiratory Questionnaire (CRQ) [25, 30]. Data from three studies were excluded from the results, as summary score data were not provided for the SF-36 [23, 46], SGRQ [23], CRQ [30] and QoL Profile for Chronic Diseases [23] sub-scale questionnaires. Langer *et al.* [22] found no significant benefit of 12 weeks exercise training on anxiety and depression scores with a control group. Fuller *et al.* [24] concluded that both 7 and 14 weeks of supervised training enhanced SF-36 PCS and MCS scores at 14 weeks, with no significant difference found between the two groups. Gloeckl *et al.* [30] found no significant difference in the improvement of HADS scores between WBVT and exercise training compared to exercise training alone. Schneeberger *et al.* [26] showed improvements in SF-36 PCS and MCS scores in COPD and interstitial lung disease (ILD) patients, with no significant differences found in scores between transplant procedures for either disease entity. Candemir *et al.* [25] demonstrated significant increases in HADs, SGRQ and CRQ scores following a comprehensive outpatient programme.

Clinical outcomes

Clinical outcome measures after surgery were reported in two pre-transplant studies [17, 45]. Florian *et al.* [17] concluded that patients with IPF who underwent exercise-based pulmonary rehabilitation had a higher survival rate 5 years after transplant (89.9% *versus* 60.9%; p<0.001), a shorter length of stay in the ICU (5 days *versus* 7 days; p=0.004) and hospital (20 days *versus* 25 days; p=0.046), along with a lower requirement for more than 24 h invasive mechanical ventilation (IMV) (9% *versus* 41.6%; p<0.001),

TABLE 4 Effects of pre- and post-transplant exercise training interventions on measures of QoL

First author [ref.]	N	Duration	Measure	Intervention/ comparison	Pre–post p-value	Between group p-value	Effect size
Pre-transplant							
Gloeckl *et al.* [42]	60	3 weeks	SF-36	Interval ET	PCS: p>0.05 MCS: p<0.05	PCS: p=0.43 MCS: p=0.066	PCS: INT<CON; −0.24 MCS: INT>CON; 0.57
				Continuous ET	PCS: p<0.05 MCS: p>0.05		
Pehlivan *et al.* [20]	39	8 weeks (minimum)	BDI	ET	p=0.004	-	PRE<POST; 0.28
Da Fontoura *et al.* [19]	31	12 weeks	SF-36	ET	PCS: p=0.004 MCS: p=0.113	-	PCS: PRE<POST; 0.43 MCS: PRE<POST; 0.15
Kenn *et al.* [44]	811	5–6 weeks	SF-36	ET	PCS: p<0.001 MCS: p<0.001	-	PCS: PRE<POST; 0.22 MCS: PRE<POST; 0.64
Li *et al.* [45]	345	~16 weeks (47 ±59 sessions)	SF-36	ET	PCS: p=0.11 MCS: p<0.05	-	PCS: PRE>POST; −0.125 MCS: PRE>POST; −0.47
			SGRQ		p<0.05	-	PRE>POST; −0.52
			SG		p=0.050	-	PRE>POST; −0.08
			EQ-5D		p<0.05	-	PRE>POST; −0.48
Post-transplant							
Langer *et al.* [22]	36	12 weeks	HADs	ET	-	Anxiety: p=0.812	Anxiety: INT<CON; −0.36
				Control (PA counselling)	-	Depression: p=0.899	Depression: INT<CON; −0.09
Fuller *et al.* [24]	66	14 weeks	SF-36	14 wks supervised ET	-	PCS: p=0.32 MCS: p=0.74	PCS: INT>CON; 0.11 MCS: INT<CON; −0.18
				7 wks supervised ET	-		
Gloeckl *et al.* [30]	80	4 weeks	HADs	ET+WBVT	Anxiety: p=0.180 Depression: 0.247	Anxiety: p=0.174 Depression: p=0.533	Anxiety: INT<CON; 0.33 Depression: UTC
				ET	Anxiety: p=0.001 Depression: 0.038		
Candemir *et al.* [25]	23	12 weeks	HADs	ET	Anxiety: p=0.001 Depression: p<0.01	-	Anxiety: PRE<POST; 3.00 Depression: PRE<POST; 2.00
			SGRQ		p<0.01	-	PRE<POST; 1.36
			CRQ		p<0.001		PRE<POST; 1.52
Schneeberger *et al.* [26]	722	6 weeks	SF-36	ET (COPD SLTx)	PCS: P⩽0.001 MCS: P⩽0.01	-	PCS: PRE<POST; 1.00 MCS: PRE<POST; 0.53
				ET (COPD DLTx)	PCS: P⩽0.001 MCS: P⩽0.001		PCS: PRE<POST; 0.78 MCS: PRE<POST; 0.47
				ET (ILD SLTx)	PCS: P⩽0.001 MCS: P⩽0.001		PCS: PRE<POST; 0.67 MCS: PRE<POST; 0.83
				ET (ILD DLTx)	PCS: P⩽0.001 MCS: P⩽0.001		PCS: PRE<POST; 1.00 MCS: PRE<POST; 0.67

ET: exercise training; WBVT: whole body vibration training; SLTx: single lung transplant; DLTx: double lung transplant; INT: intervention; CON: control; SF-36: Short Form 36 Questionnaire; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; VAS: Visual Analogue Scale; BDI: Beck Depression Inventory; SG: Standard Gamble; PCS: Physical Component Summary; MCS: Mental Component Summary.

compared with control subjects. Cox regression models revealed that patients who completed the 12- week exercise programme had a reduced 54% risk of death (hazard ratio0.464, 95% CI 0.222–0.970; p=0.041). In the single-arm cohort study by Li *et al.* [45], the absence of control data meant it was not possible to interpret the effect of the intervention on clinical outcome measures; however, data showed that, at the end of hospital admission for transplantation, 79% were discharged home, 13% to inpatient rehabilitation and 8% died. The median hospital length of stay was 18 days (range 7 to 313 days).

Safety

Adverse event reporting was poor, with only 38% of studies (four pre-transplant studies [18, 21, 42, 44] and four post-transplant studies [24, 26, 29, 30]) mentioning adverse events. Of those, no adverse events related to exercise training were reported over the study period.

Discussion

In this systematic review, evidence from 21 studies including 2596 patients was synthesised to examine the effect of exercise training on exercise capacity, QoL and clinical outcomes before or after lung transplantation. While there is evidence suggesting positive effects of exercise training interventions on these outcomes, the current evidence is predominantly limited to non-randomised and observational studies and is therefore of lower quality. Prior to and following transplantation, the evidence suggests that exercise training can maintain or improve functional exercise capacity, with effects for improvements ranging from small to large. Furthermore, the enhancements in 6MWT distance tend to exceed the minimal clinically important difference (MCID) defined for chronic lung diseases [49–51]. Most studies demonstrate a beneficial impact of exercise training on QoL outcomes. Data on clinical outcomes is sparse; however, it indicates a survival benefit of exercise training, accompanied with favourable post-operative outcomes.

Exercise capacity: pre-transplant

Seven of the nine studies reported improvements in exercise capacity following completion of an exercise programme prior to lung transplantation. Of these studies, two were inpatient (3–6 weeks) and five were outpatient programmes (8–12 weeks), with no observable benefit of one approach over the other. The 6MWT is commonly used in pre- and post-operative evaluation and has proven beneficial in determining the effect of therapeutic interventions, due to its prognostic value [6, 52]. It has also been found to correlate with V_{O_2peak} in candidates for lung transplantation [53]. The improvements presented in the seven studies all exceeded the MCID for 6MWT distance for patients with chronic lung disease, which have been reported as >30 m for COPD [49], >22–37 m for ILD [50], and 33 m for pulmonary hypertension [51]. Currently, evidence for the MCID in cystic fibrosis is lacking. Despite this, direct causation cannot be confirmed, due to the lack of a no-treatment control group in eight of the nine studies.

The RCT comparing interval and continuous training did not confer any benefit of one approach over the other, in terms of functional or maximal exercise capacity [42]. This finding agrees with that of Beauchamp *et al.* [54], where interval and continuous training were deemed comparable in patients with COPD. However, interval training was associated with lower training symptoms and therefore may be used as alternative, more tolerable method of training [42]. Of the two studies showing no improvement in 6MWT distance, the intervention implemented by Li *et al.* [45] was significantly longer (~16 weeks) compared to other pre-transplant studies (3–12 weeks) in this review [18–20, 42–44]. Therefore, this longer time period may have resulted in greater disease progression and risk for exacerbation. It is also important to note that a criterion for lung transplant listing is a survival prognosis of less than 2 years, therefore maintenance of 6MWT distance pre-transplantation could be considered a positive finding, as functional deterioration can occur rapidly during the waiting period. Indeed, the pilot study by Singer *et al.* [21] was the first to introduce home-based tele-rehabilitation prior to lung transplantation, and demonstrated maintenance of 6MWT distance, although this could also be due to the small sample size (n=15). Overall, the intervention [21] was well received and safe, hence, further investigation in the form of an RCT should be conducted to determine the true effect of this novel intervention, that could confer similar benefits to supervised exercise training, but without the financial and logistical demands.

The above findings confirm and expand those reported in the review by Hoffman *et al.* [10], in which a significant improvement in 6MWT distance was found in four of the six studies included. Since the review by Hoffman *et al.* [10], more observational studies have added to the evidence base; however, RCTs are still lacking. A possible reason for the lack of RCTs in this population is that as exercise-based pulmonary rehabilitation has become a well-recognised treatment in patients with chronic respiratory diseases [55–57], obtaining a non-exercising control group is difficult and potentially unethical.

Exercise capacity: post-transplant

All 12 studies conducted post-transplantation reported an improvement in at least one measure of exercise capacity. However as only one study compared exercise training to a non-exercising control group [22], it is difficult to draw definite conclusions. Nevertheless, in this study [22] the improvement in 6MWT distance was significantly higher in the intervention group than the control group, both at 12 weeks and 1 year. This study scored well on the quality assessment, providing robust evidence that exercise training has a beneficial effect on functional exercise capacity, which reflects the capacity required to undertake activities of daily living [58]. However, this evidence is restricted to the participant age range of 40–65 years highlighting a need for future RCT's in younger lung transplant recipients [22]. It should be highlighted that the control group in the study by Langer *et al.* [22] demonstrated an improvement of 132 m over the 12-week intervention period. Thus, the natural course of recovery from lung transplantation can result in clinically significant increases in 6MWT distance, even when additional exercise training is not undertaken. This supports the fact that although all single-arm studies showed significant enhancements in 6MWT distance, definite cause and effect cannot be determined.

Langer *et al.* [22] found no significant improvement in maximal exercise capacity (V_{O_2peak} (% predicted) or PWR (% predicted)) immediately post-intervention. Despite this, V_{O_2peak} (% predicted) was 71% in the exercise training group at 12 weeks and 78% at 1 year, which exceeds the values commonly reported in the first year following lung transplant of 40–60% of predicted normal values [59, 60]. The higher V_{O_2peak} (% predicted) values shown in this study may be due to only patients with an uncomplicated post-operative period being included. Therefore, this does not represent patients having a prolonged hospital stay, who are likely to exhibit lower exercise capacity as a result of prolonged deconditioning. In recipients 12–18 months post-transplant, Stiebellehner *et al.* [48] demonstrated significant improvements in V_{O_2peak} after aerobic training; however, these values were still limited to 65% predicted. It is noted that prior to initiating the exercise programme, patients were followed for 6 weeks and showed no significant change in V_{O_2peak} and PWR. The comparison between the control and intervention period improves the internal validity of this cohort study, by attempting to differentiate the effect of the training intervention from natural recovery.

Both inpatient and outpatient exercise training significantly improved V_{O_2peak} in recipients 4.5±3.2 years following transplant [23]. Thus, exercise training is beneficial in the long-term and short-term management of lung transplant recipients. It is known that chronic exercise limitation following lung transplant is predominantly due to impaired oxidative capacity of skeletal muscle which is exacerbated by immunosuppressive medications [11], thus optimising peripheral muscle function is an important goal of exercise training [61]. Gloeckl *et al.* [30] concluded that WBVT may be used as a complimentary therapy to exercise training, demonstrating further enhancements in exercise capacity. This is thought to be due to the mechanical vibration eliciting neuromuscular adaptations.

The previous systematic review looking at exercise training interventions post-transplantation [16] showed a positive effect on exercise capacity (maximal or functional) in four studies. This review expands significantly on those findings, with 12 studies exhibiting improvements in at least one measure of exercise capacity. In addition to strengthening the evidence base, this review includes studies examining the effect of different modes, doses and settings of exercise training on exercise capacity.

Quality of life: pre- and post-transplant

The most common measure of QoL was the SF-36 questionnaire, which is a global measure of HRQoL [62]. Prior to transplantation, improvements in SF-36 PCS scores ranged from 2 to 4 points and MCS from 2 to 10 points. Currently, the interpretation of changes in SF-36 scores is challenging, as the MCID for lung transplant candidates has not yet been defined. General recommendations for the tool suggest a MCID of four points [2], and a study conducted in IPF patients proposed a MCID of >2–4 units for PCS and MCS scores [63].

Notably, interval training was associated with a significant improvement in SF-36 MCS scores over time, which may be partly attributed to the lower training symptoms (dyspnoea and leg fatigue) associated with this mode of training [42, 64]. Although Li *et al.* [45] found no improvement in QoL scores, measures reflecting physical function (SF-36 PCS, SGRQ activity domain) were better preserved than other HRQoL measures (*e.g.* SF-36 MCS). Comparison of HRQoL in lung transplant candidates to normative populations has typically shown greatest impairment in physical function rather than mental health domains [37], highlighting the importance of maintaining or improving this aspect.

After transplant, Langer *et al.* [22] found no significant difference in HADS scores between the exercise training and control group. This may be related to low baseline scores indicative of sub-clinical levels of anxiety (intervention=5.0±3.4 *versus* control=7.1±4.1) and depression (3.8±3.4 *versus* 4.5±3.5) [65]. As such, there was little scope for improvement in this outcome domain, particularly in the intervention group. This is supported by the significant improvement in HADS scores reported by Candemir *et al.* [25], in which baseline scores were 10±1 and 9±1 for anxiety and depression, respectively.

The improvements in the SF-36 PCS and MCS scores following exercise training [24, 26] well exceeded the estimated MCID (>2–3 units) proposed for lung transplant recipients [66]. A multi-centre study [67] exploring the trajectory of QoL from pre-transplant to 1 year post-transplant without exercise training, reported significant gains in PCS score (+10.9), demonstrating a natural course of physical QoL improvement. This is likely due to marked improvements in pulmonary function, resulting in reduced symptom burden and enhancing the ability to complete everyday activities. However, in this observational study MCS remained unchanged. This indicates that exercise training has a beneficial impact on this QoL component, as improvements in this domain were evident in studies implementing exercise training [24, 26]. Since the review by Wickerson *et al.* [16] which incorporated one study evaluating QoL, further studies have shown a beneficial impact of exercise training on QoL [22, 24–26, 30], adding to this preliminary evidence. Besides survival, improving QoL is one of the key objectives of lung transplantation, hence interventions that can enhance QoL following the procedure are of great importance.

Clinical outcomes

The evidence pertaining to exercise training and post-transplant clinical outcomes is sparse. Since the last systematic review [10] however, a quasi-experimental study has concluded that pulmonary rehabilitation conducted before lung transplantation halved the risk of mortality and reduced the risk of prolonged ICU and hospital stay [17]. This study [17] is limited by its design, as lack of randomisation may have led to potential selection bias. Additionally, the study [17] only included those with IPF, so findings cannot be extrapolated to all transplant patients.

Safety of exercise training

Limited studies (38%) report data on safety; however, in those that did, no adverse events related to exercise training were reported. This highlights the inconsistent and inadequate reporting of safety in exercise training trials in lung transplant patients, a population that has an increased risk for complications and comorbidities.

Strengths and weaknesses of this review

To our knowledge, this is the first systematic review to synthesise the effects of exercise training in both lung transplant candidates and post-transplant recipients. The review was conducted in a rigorous manner in accordance with PRISMA guidelines [32]. Specific search terms were used to identify appropriate articles and bias was minimised through independent screening by two investigators, using pre-defined criteria. Limitations to this review include the lack of RCTs (five out of 21 studies) and absence of a comparator group or *a priori* sample size calculations in most studies. As such, it was not possible to perform a meta-analysis due to multiple sources of heterogeneity, including type of exercise training intervention, study design and outcome measures. Additionally, participants across studies varied in underlying respiratory disease and age. Currently, there is little evidence on the effect of exercise training on clinical outcomes; however, the single study included does show a survival benefit [17]. Additional research is needed to establish the efficacy of home-based exercise training interventions. Future studies implementing exercise training should ensure consistent reporting of safety outcomes (*e.g.* adverse events), as this information is important for decision making by regulators, policy makers and health-care professionals. Findings should be interpreted with caution due to the single-arm study designs implemented in most studies, limiting the ability to establish definite cause and effect. Nevertheless, the review represents the best available overview of the current evidence base for exercise training pre- and post-lung transplantation.

Conclusions

Both inpatient and outpatient exercise training appears to be beneficial for patients before and after lung transplantation. In general, most studies indicated exercise training interventions to be effective in improving exercise capacity and QoL. Accordingly, exercise training appears valuable in the management of patients both listed for transplantation and following lung transplant surgery.

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