Long-Term Effects of a 12-Week Exercise Training Program on Clinical Outcomes in Idiopathic Pulmonary Fibrosis

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Abstract

Purpose Idiopathic pulmonary fibrosis (IPF) is a chronic, devastating, lung disease, with few therapeutic options. Data are limited with respect to the long-term effect of exercise training (ET) in IPF. This study sought to evaluate the long-term effects of a 12-week ET program on clinical outcomes in IPF patients.

Methods Thirty-four IPF patients were randomly allocated to ET or control groups. ET group participated in a 12-week supervised exercise program, while the control group continued with regular medical treatment alone. Exercise capacity, 30 s-chair-stand test for leg strength, dyspnea, and Saint George’s Respiratory Questionnaire (SGRQ) for quality of life (QOL) were assessed at baseline and re-evaluated at 11 months from baseline. In addition, at 30-month time point from baseline, the impact of the 12-week intervention was analyzed with respect to survival and cardio-respiratory-related hospitalizations.

Results Thirty-two patients completed the 12-week intervention and 28 patients (14 in each group) were re-evaluated. At 11-month follow-up, no significant differences between the groups and time effect were demonstrated for most outcomes. ET group showed preserved values at the baseline level while the control group showed a trend of deterioration. Only the 30 s-chair-stand test (mean difference 3 stands, \( p = 0.01 \)) and SGRQ (mean difference -6 units, \( p = 0.037 \)) were significantly different between the groups. At 30 months, the survival analysis showed three deaths, eight hospitalizations occurred in the control group versus one death, one lung transplantation and seven hospitalizations in the ET group, with no significant differences between groups.

Conclusions At 11-month follow-up, the 12-week ET program showed clinical outcomes were preserved at baseline levels with some maintenance of improvements in leg strength and QOL in the ET group. The control group showed a trend of deterioration. At 30 months, the 12-week ET program did not show benefits in prognosis although the study was underpowered to detect such differences. We suggest including ET as a long-term continued treatment and as a core component of pulmonary rehabilitation programs for IPF patients.

Keywords 6 Min walking test · Peak oxygen consumption · Survival · Hospitalizations · Leg strength · Quality of life

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal interstitial lung disease (ILD) with unknown
etiology occurring primarily in older adults [1]. IPF has an unpredictable clinical course, associated with a poor prognosis. Five to ten percentage of patients experience an acute exacerbation of IPF each year, and cardiac events also have significant impact on morbidity and mortality [1]. Median survival ranges from 2 to 5 years from time of diagnosis [1, 2]. Long-term effective treatment, apart from lung transplantation, is still limited for most IPF patients despite some encouraging recent findings with pharmacotherapy [1, 3–5]. IPF is characterized by progressive worsening of dyspnea and lung function, impaired gas exchange, hypoxemia, exercise intolerance, skeletal muscle dysfunction, reduced functional capacity, and poor quality of life (QOL) [1, 6–9].

Exercise training (ET) is a cornerstone component of pulmonary rehabilitation programs with strong evidence of improvement in clinical outcomes such as exercise and functional capacities, level of dyspnea, and QOL among chronic obstructive pulmonary disease (COPD) patients [8, 10, 11]. Our team and others have demonstrated short-term benefits of ET among IPF patients [8, 12–15]. However, only two studies examined the long-term effects (at 6-months follow-up) of an 8-week exercise program with some conflicting results regarding outcomes preservation, and lack of assessment the long-term prognostic impact of these interventions [16, 17]. Considering the inconsistency of the long-term effect of ET in IPF in the existing studies, the gaps in the prognostic impact of ET in IPF and the clinical significance of maintenance of improved outcomes, we aimed to examine the long-term effect of a 12-week supervised ET program on clinical outcomes in patients with IPF.

Methods

Patient Recruitment and Selection

A randomized controlled study was conducted at the Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel. The study was approved by the local ethics committee and was registered in www.Clinicaltrials.gov (NCT01499745). Patients were included if diagnosed with IPF according to accepted clinico-radiological criteria according to the current established guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS) and were clinically stable in the previous 3–6 months [1]. Exclusion criteria were: severe co-morbid illnesses; unstable cardiac disease; any neurological or orthopedic contraindications for ET; exacerbation of IPF; and participation in a pulmonary rehabilitation program in the 12 months prior to recruitment. Patients treated in the Pulmonary Institute were recruited by invitation and volunteered to take part in the study. During patients’ visit at the clinic, randomization was performed by a study coordinator uninvolved in patients’ assessment or treatment. Sealed envelopes containing the patient’s intervention allocation were randomly opened, and the patient was assigned to the chosen arm. Written informed consent was obtained from all patients prior to participation.

The ET group participated in a 12-week, twice-weekly 60-min supervised group ET as well as continued care in the pulmonary unit, while the control group continued with regular medical care alone. At baseline and at 11-month follow-up from baseline, participants were assessed as described below. In addition, at the 30-month time point from baseline survival analysis was conducted, and the number of cardio-respiratory complication events was compared between the groups to evaluate the impact of the 12-week ET on prognosis. All subjects were informed regarding the study’s purposes and patients from the control group were allowed to participate in the ET program after the 12-week intervention. Due to lack of experienced staff in exercise testing evaluation, this assessment was conducted un-blinded.

Pulmonary Function Tests

Pulmonary function tests including spirometry total lung capacity, maximal voluntary ventilation, and diffusion capacity for carbon monoxide were performed according to standard techniques and ATS/ERS guidelines (Zan 530 Oberthulba, Germany) by experience respiratory technicians uninvolved in the study [18–20]. All the measured parameters were presented as percent of predicted (% predicted) values of the European Community for Coal and Steel [21].

Cardiopulmonary Exercise Test (CPET)

CPET was performed according to established guidelines on an electromagnetically braked cycle ergometer (Ergoline-800S) using breath-by-breath respiratory gas exchange (ZAN 600, Oberthulba, Germany) [22–25]. All peak cardio-pulmonary data were calculated, analysis was based on average of the last 30 s of the test. The anaerobic threshold (AT) was determined by the dual methods approach, using the V-slope method combining ventilatory equivalents ($V_{\text{E}}/V_{\text{O2}}$ and $V_{\text{E}}/V_{\text{CO2}}$) [22].

6-Min Walk Test (6MWT)

All patients were well familiar with the 6MWT from their previous visits in the pulmonary institute. The 6MWT was conducted according to ATS guidelines in a 35-m corridor at the pulmonary unit within the hospital [26]. Borg
30-S Chair-Stand to Test Leg Strength

At least 20–30 min of rest were allowed after completing the 6MWT and before performing a test according to the “senior fitness tests” guidelines [27]. The subject was encouraged to complete as many full stands as possible from the sitting position on the chair (43 cm height) within the 30 s [27].

Dyspnea and Health-Related Quality of Life

All patients fulfilled the modified Medical Research Council (mMRC) scale for dyspnea evaluation [28, 29]. In addition, a validated Saint George’s Respiratory Questionnaire (SGRQ) for IPF was also completed for QOL evaluation [30, 31].

Exercise Training Program

The program was conducted according to general ET recommendations for respiratory disease patients [23, 32]. The training program included aerobic, resistance, and flexibility exercise modes as well as deep breathing exercises in each session. The program continued for 12 weeks, twice-weekly with 60-min group ET in the pulmonary unit. The program was divided into two 6-week exercise progressive blocks, in which the overall load was gradually increased according to patient’s tolerance. In the first block, interval training was used for the aerobic component and a single set system for the resistance and flexibility components. In the second block, aerobic endurance and a multiple set system was implemented. More detailed description of the exercise program can be found in our previous report [13]. The exercise sessions were instructed by a clinical exercise physiologist, a physiotherapist and supervised by a respiratory nurse and study physician.

Primary and Secondary Outcomes

The primary outcomes were changes in: 6 min walking distance (6MWD) and peak oxygen consumption (VO2peak). The secondary outcomes were changes in pulmonary function, dyspnea, leg strength, QOL, mortality, and incidence of cardio-respiratory complication events during the follow-up. A power analysis was performed, prior to baseline recruitment, with respect to pre-post ET intervention, in order to calculate the sample size with 95 % probability and 80 % power for detecting mean difference ≥50 m in one primary outcome (6MWD) between the groups and time effect based on previous data of longitudinal changes and minimal clinical important difference in IPF patients [33, 34].

Statistical Analysis

The clinical and physiological parameters were presented as mean ± standard deviations, number and % of the group, and mean difference (with confidence interval). Patients’ baseline characteristics, including all primary and secondary parameters were compared between the ET and control groups by independent two samples t test and χ2 test for non-parametric variables. Two-way analysis of variance (ANOVA) for repeated measures was performed to compare baseline and 11-month follow-up data between the groups and the time effect [35]. Spearman’s correlation for changes in SGRQ and 6MWD was performed in the ET group [36]. Cox regression analysis of 32 patients who completed the 12-week intervention was performed at the 30-month time point using log-rank test to assess the prognostic impact of the 12-week exercise program by determining the differences in survival and time-to-event between the groups during the follow-up [37, 38]. Lung transplantation was calculated in three different analyses considered as; (1) death event, (2) censored (alive), and (3) excluded from the analysis [39]. A composed variable of number of hospitalizations for any cardio-respiratory reasons during the follow-up was compared between the groups by χ2 test. The statistical analyses were conducted using SPSS v.17 software (Chicago, IL, USA). The significance level was set at p < 0.05.

Results

The study was conducted between January 2012 and July 2014. Thirty-eight IPF patients were screened and 34 were recruited in an ongoing process during a 6-month period and randomly assigned to the ET group (n = 16) or control group (n = 18) for a 12-week intervention. During the 12-week intervention, one patient in the ET group dropped out due to exacerbation and was excluded from the analysis. In the control group, one patient withdrew consent. Thirty-two patients completed the 12-week intervention with baseline and post measurements, and 28 patients (14 in each group) were reassessed at the 11-month time point from baseline (8 months from the end of 12-week intervention) for follow-up (Fig. 1).

At baseline, there were no differences between the groups in terms of patients’ characteristics, co-morbidities, physiological and clinical parameters, and medications. During the follow-up, five patients in the control group and three patients in the ET group were treated with Pirfenidone without differences between the groups (χ2 = 0.376,
p = 0.539); there were no other changes in medications. Patients’ baseline and follow-up characteristics are shown in Table 1.

In our previous report following a short-term, 12-week intervention, we demonstrated a significant improvement in aerobic capacity, 6MWD, leg strength, pulmonary and ventilatory functions, dyspnea, and QOL among the ET group, while the control group showed a trend of deterioration [13]. At 11-month follow-up, there was no significant difference between the groups or a time effect in primary outcomes, although the control group showed a trend of worsening in 6MWD (Table 2; Fig. 2). Significant differences were seen in 30 s-chair-stand test (mean difference 3 stands, \( p = 0.01 \)), SGRQ-impact domain (mean difference -7 units, \( p = 0.01 \)) and SGRQ-total score (mean difference -6 units, \( p = 0.037 \)) between the groups (Fig. 3; Table 2). In addition, among the ET group, changes in QOL (SGRQ-total score) were significantly associated with changes in walking capacity 6MWD \( (r = -0.82, p < 0.001) \).

At the 30-month time point from baseline [median 22.7 months CI 95% (19.2–23.1) from the end of the 12 week intervention], a survival analysis showed three patients died in the control and one patient died and one was lung transplanted in the ET group (Fig. 4). Survival analyses considering lung transplantation as a death event, censored (alive) or exclusion from the analysis showed no significant difference between the groups in all these comparisons (Table 3). Eight patients (47%) from the control group and seven patients (47%) from the ET group were hospitalized due to cardio-respiratory complications \( (\chi^2 = 0, p = 0.982) \) with no statistical differences between the groups.

**Discussion**

In the present study, we examined the long-term effects of a 12-week ET program on physiological and prognostic outcomes in IPF patients. We had previously demonstrated that a 12-week supervised ET program is clinically

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**Fig. 1** Flowchart of study design
beneficial in the short-term [13]. In the current follow-up study, we showed that at the 11-month time point from baseline there are no significant differences between the ET and the control groups in most outcomes, in comparison to baseline values. We found that the ET group preserved their baseline values in most outcomes, while the control group demonstrated a trend of deterioration (Table 2). We demonstrated that only leg strength and QOL were significantly different between the groups at 11-month follow-up showing a better preservation of these outcomes in the long term (Fig. 3; Table 2). Unfortunately, our data did not show prognostic benefits of the 12-week ET program for IPF patients, although the study was underpowered to detect these differences (Fig. 4). These results further

Table 1 Baseline and follow-up characteristics of study population (N = 32)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Control (n = 17)</th>
<th>ET (n = 15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>66 ± 9</td>
<td>68.8 ± 6</td>
<td>0.337</td>
</tr>
<tr>
<td>Male/female (n/%)</td>
<td>11/6 (65/35 %)</td>
<td>10/5 (67/33 %)</td>
<td>0.907</td>
</tr>
<tr>
<td>BMI</td>
<td>28.8 ± 3.8</td>
<td>28.3 ± 3.5</td>
<td>0.686</td>
</tr>
<tr>
<td>Time from diagnosis of IPF (year)</td>
<td>1.9 ± 3.1</td>
<td>3 ± 3.7</td>
<td>0.379</td>
</tr>
<tr>
<td>Patients with history of smoking (n/%)</td>
<td>9 (53 %)</td>
<td>10 (67 %)</td>
<td>0.430</td>
</tr>
</tbody>
</table>

Supplemental oxygen users
- Rest: 16 % (17), 2 (13 %) (p = 0.471)
- Exertion: 4 (24 %), 5 (33 %) (p = 0.538)

Co-morbidities
- Pulmonary hypertension according to echocardiography (n/%) | Control: 6 (35 %), ET: 5 (33 %) (p = 0.907)
- Coronary arterial disease (n/%) | Control: 6 (35 %), ET: 7 (47 %) (p = 0.513)
- Systemic hypertension (n/%) | Control: 11 (65 %), ET: 12 (80 %) (p = 0.337)
- Chronic obstructive pulmonary disease-emphysema (n/%) | Control: 5 (29 %), ET: 2 (13 %) (p = 0.272)
- Type 2 diabetes (n/%) | Control: 4 (24 %), ET: 7 (47 %) (p = 0.169)
- Osteoporosis (n/%) | Control: 3 (18 %), ET: 2 (13 %) (p = 0.093)

Resting cardiopulmonary parameters
- FVC % predicted | Control: 70.1 ± 17.4, ET: 66.1 ± 14.8 (p = 0.487)
- TLC % predicted | Control: 68.5 ± 14, ET: 64.3 ± 13 (p = 0.231)
- DLCO % predicted | Control: 53.2 ± 12.2, ET: 48.6 ± 17.2 (p = 0.393)
- Systolic pulmonary arterial pressure (mmHg) | Control: 32.4 ± 9.2, ET: 32.5 ± 7 (p = 0.994)
- SpO2 at rest (%) | Control: 97.1 ± 1.7, ET: 96.5 ± 2.3 (p = 0.419)

Exercise capacity, dyspnea and quality of life
- VO2 peak (mL/kg/min) | Control: 14.3 ± 3.1, ET: 13.6 ± 3.4 (p = 0.539)
- 6MWD (m) | Control: 513 ± 108, ET: 471 ± 108 (p = 0.283)
- SpO2 after 6MWT (%) | Control: 85.2 ± 8.4, ET: 83.7 ± 8 (p = 0.609)
- Modified Medical Research Council-dyspnea scale (0–4) | Control: 1.7 ± 0.9, ET: 1.9 ± 0.9 (p = 0.684)

Medications
- Corticosteroids | Control: 13 (77 %), ET: 9 (60 %) (p = 0.316)
- Pirfenidone | Control: 2 (11 %), ET: 1 (6 %) (p = 0.471)

Follow-up characteristics
- New supplemental oxygen users
  - Rest (n/%) | Control: 1 (6 %), ET: 2 (13 %) (p = 0.471)
  - Exertion (n/%) | Control: 4 (24 %), ET: 5 (33 %) (p = 0.538)
  - Continued or started pulmonary rehabilitation (n/%) | Control: 2 (13 %), ET: 3 (21 %) (p = 0.564)
  - Pirfenidone users (n/%) | Control: 5 (29 %), ET: 3 (20 %) (p = 0.539)

ET exercise training, BMI body mass index, FVC forced vital capacity, TLC total lung capacity, DLCO diffusion capacity for carbon monoxide, SpO2 oxygen saturation by pulse oximeter, 6MWD 6 min walk distance, VO2 peak peak oxygen consumption
Table 2  Mean differences of changes between the exercise training and the control groups after 11 months

<table>
<thead>
<tr>
<th>Pulmonary function test</th>
<th>Control (n = 14)</th>
<th>ET (n = 14)</th>
<th>Mean difference between the groups baseline to 11 months (CI 95 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 11 months</td>
<td>Baseline</td>
</tr>
<tr>
<td>FVC %predicted</td>
<td>69 ± 14</td>
<td>67 ± 15</td>
<td>−2 ± 7</td>
</tr>
<tr>
<td>TLC %predicted</td>
<td>68 ± 12</td>
<td>69 ± 16</td>
<td>1 ± 6.5</td>
</tr>
<tr>
<td>DLCO %predicted</td>
<td>54 ± 12</td>
<td>50 ± 12</td>
<td>−4 ± 9</td>
</tr>
<tr>
<td>MVV (L/min)</td>
<td>86 ± 26</td>
<td>86 ± 22</td>
<td>−9 ± 13</td>
</tr>
<tr>
<td>Peak work-rate (watts)</td>
<td>92 ± 29</td>
<td>81 ± 34</td>
<td>−11 ± 15</td>
</tr>
<tr>
<td>VO₂ peak (mL/kg/min)</td>
<td>14.5 ± 3.2</td>
<td>14.5 ± 4.3</td>
<td>0</td>
</tr>
<tr>
<td>Anaerobic threshold (mL/kg/min)</td>
<td>10.6 ± 2</td>
<td>10.7 ± 3</td>
<td>−0.1 ±</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>526 ± 110</td>
<td>477 ± 131</td>
<td>−49 ± 86</td>
</tr>
<tr>
<td>SpO₂ after 6MWT (%)</td>
<td>86 ± 9</td>
<td>86 ± 8</td>
<td>0</td>
</tr>
<tr>
<td>30 s chair stand (number of stands)</td>
<td>14 ± 5</td>
<td>13 ± 4</td>
<td>−1 ± 3</td>
</tr>
<tr>
<td>mMRC (0–4)</td>
<td>1.6 ± 0.9</td>
<td>1.8 ± 1</td>
<td>0.2 ± 0.7</td>
</tr>
<tr>
<td>SGRQ-total score</td>
<td>17 ± 5</td>
<td>21 ± 7</td>
<td>4 ± 8</td>
</tr>
<tr>
<td>SGRQ-symptoms</td>
<td>26 ± 17</td>
<td>42 ± 28</td>
<td>16 ± 31</td>
</tr>
<tr>
<td>SGRQ-impact</td>
<td>17 ± 4</td>
<td>20 ± 9</td>
<td>3 ± 6</td>
</tr>
<tr>
<td>SGRQ-activity</td>
<td>12 ± 2</td>
<td>12 ± 3</td>
<td>0</td>
</tr>
</tbody>
</table>

Values presented as means and standard deviations, mean difference with CI

CI confidence interval, Δ changes from baseline to 11 months, ET exercise training, FVC forced vital capacity, TLC total lung capacity, DLCO diffusion capacity for carbon monoxide, MVV maximal voluntary ventilation, VO₂ peak peak oxygen consumption, SpO₂ oxygen saturation by pulse oximeter, 6MWD 6 min walk distance, mMRC modified medical research council, SGRQ Saint George’s respiratory questionnaire

*Significant differences at p < 0.05

Table 2  Mean differences of changes between the exercise training and the control groups after 11 months

Emphasize the significance of maintaining the short-term improvements by the possibility of implementation of a continuous long-term ET program for patients with IPF.

To the best of our knowledge, this is the first randomized controlled study of ET among IPF patients examining the effect of short-term exercise intervention (12 weeks) on long-term physiological outcomes (at 11 months) and prognosis (at 30 months). Previous reports of ET programs in ILD and IPF included only a short follow-up period (at 6 months) [16, 17]. We extended previous studies by providing a wide-range physiologic and prognostic assessment with a longer follow-up period, to evaluate the long-term effect of a 12-week supervised ET program, among IPF patients. Our findings are consistent with a randomized controlled study by Holland et al. [16] who showed sustained benefits in 6MWD, dyspnea, and QOL at the 6-month time point following 8-week ET program in ILD and IPF patients. Our findings are also consistent with Ryerson’s et al. [17] data showing a preservation of 6MWD, QOL, SGRQ, depression, and physical activity levels at 6-month follow-up after a 6–8-week pulmonary rehabilitation program. There is inconsistent evidence regarding the long-term effect of short-term exercise interventions in ILD and IPF patients. Additional data are needed to resolve this issue.

In the current cohort, although our data failed to show prognostic benefits and long-term maintenance in most outcomes in ET compared to control group, these first pilot prospective results demonstrate the impact of a short-term exercise intervention on prognosis among patients with IPF. However, long-term (6–12 months) ET programs in IPF have not been published and the impact
of these interventions on prognosis is unknown. This should be addressed in future large sample-sized studies.

The mechanism that may explain these findings is most probably related to detraining effects. According to the physiological “principle of reversibility”, the chronic adaptation to training will gradually reverse as the physiological stimulus has been removed [40, 41]. We previously showed that a short-term 12-week ET program effectively improved both objective-physiological (6MWD and VO_{2peak}) and subjective-perceptual outcomes (QOL and dyspnea) in the ET group [13], however, these benefits deteriorated upon cessation of training. Furthermore, IPF disease tends to progress over time, which may also lead to worsening and have a negative impact on the outcomes [1]. Our data show that leg strength and QOL outcomes are preserved better than VO_{2peak} and 6MWD as previously supported in the elderly and in young athletes [42, 43]. Similarly, this was also demonstrated among COPD patients in which short-term (6–12 weeks) exercise interventions resulted in prolonged benefits for certain outcomes (QOL and dyspnea) up to 12–18 months after completing the program [10]. In contrast, Otsuka et al. [44] found significant deterioration in physiological responses among COPD patients, as measured by CPET at 5 months after an ET program [44]. Probably, some physiological (muscle strength) and subjective-perceptual (QOL) adaptations to ET programs among IPF patients deteriorate slower than other outcomes (aerobic capacity and dyspnea), due to the detraining effect, thus long-term preservation of these outcomes seems better. Furthermore, we revealed that changes in 6MWD was associated \( (r = -0.82, p < 0.001) \) with changes in QOL among the ET group, suggesting that walking capacity could have a clinical importance for QOL in patients with IPF. These issues too, must be ascertained in future research and maintenance of improvement strategies are warranted for IPF patients.
Our study has several limitations. Despite the relatively small sample size for each group of patients, the study was adequately powered for one primary outcome (6MWD) at baseline recruitment but was underpowered to detect differences in survival and hospitalizations. Additionally, most of our participants had moderate pulmonary restriction (mean FVC; 68 % predicted) thus generalization to other IPF severities should be done with caution. Finally, blinding in exercise assessment was not undertaken.

In conclusions, following a 12-week supervised ET program in patients with IPF, at 11-month follow-up clinical outcomes were preserved at baseline levels, however, without differences between the groups in most variables. Leg strength and QOL were better preserved in the long-term among the ET group compared to the control group. The 12-week ET program did not show benefits for prognosis in IPF. We suggest including supervised ET for long-term continuous treatment for IPF patients. Further research is warranted regarding the prognostic impact of long-term exercise programs in IPF.
References


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Conflict of interest None.

Table 3 Different survival analyses of lung transplantation in patients with idiopathic pulmonary fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Control group mean survival time (months) CI (95 %)</th>
<th>ET group mean survival time (months) CI (95 %)</th>
<th>Log-rank test ($\chi^2$) $p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung transplantation considered as death event</td>
<td>21.3 (18.2–24.3)</td>
<td>24.7 (22.3–27)</td>
<td>0.128</td>
</tr>
<tr>
<td>Lung transplantation considered as censored (alive)</td>
<td>21.3 (18.2–24.3)</td>
<td>25.4 (23.4–27.5)</td>
<td>0.876</td>
</tr>
<tr>
<td>Lung transplantation excluded from the analysis</td>
<td>21.3 (18.2–24.3)</td>
<td>25.4 (23.2–27.5)</td>
<td>0.753</td>
</tr>
</tbody>
</table>

Data presented as means with CI confidence interval, ET exercise training.