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The influence of clinical course after lung transplantation on rehabilitation success

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Summary

Pulmonary rehabilitation (PR) is a cornerstone of treatment following lung transplantation (LTx). The aim of this study was to observe the influence of a prolonged postsurgical clinical course on success of a 3-week inpatient PR. LTx recipients were divided according to their clinical course defined by their individual length of stay (LOS) in the transplant center (cohort 1: LOS >; cohort 2: $\leq$42 days). Peak work rate (PWR), maximum oxygen uptake (VO_{2max}), 6-min walk distance (6-MWD), vital capacity (VC), forced expiratory volume in one second (FEV1), physical activity of daily life (ADL), and health-related quality of life (HRQoL) measured using Short Form 36 questionnaire (SF36) were assessed at beginning and completion of PR. A total of 138 patients were included (LOS >42 days: 30; LOS $\leq$42 days: 108). At completion, physical functioning (VC, FEV1, PWR, VO_{2max}, 6-MWD, ADL), and HRQoL (all SF36 domains) improved in each cohort ($P < 0.05$). No differences were found in between both cohorts in VC, FEV1, and ADL (n.s.), but in PWR, 6-MWD, and the SF36 domain 'physical functioning' ($P < 0.05$). A 3-week inpatient PR improves physical functioning despite prolonged hospitalization. HRQoL is close to normal. (ClinicalTrials.gov. identifier: NCT00759538)

Introduction

Lung transplantation (LTx) is an accepted therapeutic option to improve survival and health-related quality of life (HRQoL) in selected patients with end-stage lung diseases [1,2].

Current allocation systems and increasing waiting lists may lead to selection of sicker candidates for LTx. These high-risk candidates, some of them even transplanted from extracorporeal membrane oxygenation (ECMO) or mechanical ventilation [3], consume more health care resources and have a delayed recovery after transplantation. A prolonged hospital course with increasing postoperative complications might result in profound muscle weakness and weight loss. Before transplantation, reduced activity, drug side effects (e.g., by corticosteroids), systemic inflammation, metabolic changes, oxidative stress, and respiratory acidosis have lead to skeletal muscle wasting and deconditioning [4,5]. Respiratory muscle dysfunction causes altered functional inspiratory muscle strength and endurance [6,7]. Calcineurin inhibitors and Prednisone are required to prevent graft rejection, but compromise muscle function [8,9]. Inflammatory mediators released through rejection or infection [10] and changes in cell metabolism [11] cause further impairment.

Anxiety, fear, depression, and frustration are common findings in patients suffering end-stage pulmonary diseases [12–14]. HRQoL is commonly impaired before transplantation [15–17].

Less is known how extended hospital stay following LTx might affect the outcome of a pulmonary rehabilitation (PR) that starts immediately at discharge from the transplant center. A prolonged course with increasing postoperative complications can aggravate preoperative deficiencies.

The challenge of PR following LTx is to overcome impairments organ recipients usually present.

The aim of this study was to observe the influence of a prolonged clinical course after LTx on success of a 3-week inpatient PR.

Materials and methods

This investigator-initiated prospective observational cohort study is from a single specialized rehabilitation facility in close collaboration of a university affiliated high-volume transplant program (Hannover Medical School, Germany). Inclusion criteria were: patients undergoing single, double lung, or combined (heart and lung or heart and liver) transplantation, at Hannover Medical School between July 2007 and January 2009, aged 18 years or older. Exclusion criterion: death before demission to the rehabilitation unit. Inpatient rehabilitation is mandatory for all lung transplant recipients owing to clinical practice in German transplantation centers. German public and private insurance cover a 3-week inpatient PR generally after extensive thoracic surgery. PR was prolonged because of medical reasons (complications, physical weakness) for more than 3 weeks by the physician of the rehabilitation center upon application. Patients were divided into two cohorts according to their length of stay (LOS) in the transplant center. The 42-day cutoff was chosen, because it represented the 75th percentile of overall LOS. Because of complications necessitating hospitalization (e.g., acute respiratory insufficiency, pneumothorax, sepsis, gastrointestinal bleeding, ileus), PR could be temporally interrupted and compromised patients were transferred to the transplantation center for acute care. After successful treatment, patients were discharged to the rehabilitation unit again and the 3 week+ period of PR was completed.

The study protocol was approved by the Hannover Medical Research Ethics Committee, and the trial was registered with ClinicalTrials.gov (identifier: NCT00759538).

Assessment of physical functioning and HRQoL

At baseline and completion of PR, all patients were assessed by a pulmonary function and cardiopulmonary exercise testing (cycle ergometry), walking capacity [6-min walk distance (6-MWD)], activity of daily life (ADL: Barthel's-index [18]) and questionnaires [Short Form 36 (SF36)] [19], and Hospital Anxiety and Depression Scale [20]. Spirometry, cardiopulmonary exercise testing, and 6-MWD were applied according to ATS/ERS guidelines [21,22].

Pulmonary rehabilitation program

In the transplant center, all patients received physiotherapy, including breathing therapy 7/7. When early mobilization was achieved and chest drains were removed, patients who were able to climb stairs without assistance started an endurance (cycle ergometer, peak work load 25–30 Watts) and light strength training (0.5–1.0 kg dumbbells) 5/7. Patients with muscular weakness, who were depended on a walking frame and unable to climb stairs received physiotherapy continuously without endurance training. Those with neurological disorders (palsies, dysphonia, and dysphagia) were treated by ergotherapists and logopedic therapists complementary 7/7.

At discharge from the transplant center, all transplant recipients were transferred to the rehabilitation unit directly. Inpatient center-based PR was applied for 3 weeks with close supervision and medical support 24/7 under strict hospital hygiene. Initial cardiopulmonary exercise testing was performed to assess the individual exercise capacity. Interval exercise training was targeted to a work rate equal to 70% of peak work rate (PWR) at baseline. Bicycle exercise training was applied six times a week for 25 min daily. In addition, all patients attended upper and lower limb strength exercise training (M. latissimus dorsi pull down, upright rowing, leg extension and flexion, leg press, dumbbell) five times a week with increasing work load. Respiratory physiotherapy (breathing and relaxation techniques, reflective breathing therapy, rib cage mobilization, chest wall vibration, massage) were offered in addition six times a week. Psychological support and an educational program containing medical basics, self-management, and behavioral strategies, return to work aspects, and the eligible nutrition were added. The 3-week period bases on funding from the German health insurance system.

Outcome

Primary outcome measure was exercise capacity [maximum work rate, maximum oxygen uptake (VO_{2max}), 6-MWD] at completion of PR. Secondary outcome measures were: lung function [VC, forced expiratory volume in one second (FEV1)], Activities of daily living (Barthel's index), and HRQoL (SF36 questionnaire).

Statistical analysis

Metric variables were expressed as median (interquartile range). Categorical variables are expressed as frequency with percentage. All reported *P*-values are two-sided, unless otherwise indicated. For all analyses, *P*-values <0.05 were considered statistically significant.

Assessment of normality was carried out using the Shapiro–Wilk-test. While most parameters revealed no normality, metric variables were analyzed using the Mann–Whitney *U* or the Kruskal–Wallis test. ANOVA analysis was performed after Log-transformation for functional and HRQoL-parameters. Categorical variables were compared using the

chi-squared test or the Fisher's exact test. The software SPSS version 16.0 (SPSS Inc. Chicago, IL, USA) was applied for all statistical analyses.

Results

Between July 2007 and January 2009, 146 patients aged 18 years or older were transplanted at Hannover Medical School, whereas eight patients died early after transplantation in. A total of 138 recipients (9 single, 119 bilateral lung, 7 heart and lung, 3 other combined) started inpatient PR and were included. The median LOS in the transplant center was 25 (range 15–183) days. Cohort 1 consisted of 30 patients with a hospital stay for more than 42 days, cohort 2 of 108 patients with a LOS of $\leq$42 days. Baseline demographics are displayed in Table 1. Cohort 1 contained more urgent or high urgent transplant candidates, a higher proportion of patients with pulmonary hypertension (PH), bridging by mechanical ventilation or an extra corporal support, delayed extubation or colonization with multidrug resistant pathogens. Chronic obstructive pulmonary disease (COPD) was found more often in LOS $\leq$42 days. None of the patients suffered from myopathy. Two patients suffered critical illness neuropathy: one patient acquired it because of prolonged mechanical ventilation (12 days) after LTx and with a LOS for 89 days in the transplantation center. The second one suffered from a neuropathy diagnosed 8 months before LTx, while he had to be treated because of acute respiratory insufficiency on an intensive care unit. After he had been transplanted, he stayed for only 19 days in the transplantation center. No lung transplant recipient was discharged without sequential inpatient rehabilitation, outpatient rehabilitation was not applied. Patients with a LOS >42 days started PR with significant delay in time (67 vs. 23 days, $P < 0.0001$). At baseline, patients with a LOS >42 days had a lower initial FEV1, VC, PWR, 6-MWD, and ADL (details in Table 1), and had not been enabled because of muscular weakness to take part in a regular training program (endurance and strength training) in the transplant center. HRQoL differed in the SF36 domains 'physical functioning' (13 vs. 30, $P < 0.01$) and 'bodily pain' with less pain in those with a prolonged LOS (70 vs. 57, $P = 0.01$, Table 1). Twelve patients (in cohort 1: $n = 5$, in cohort 2: $n = 7$ patients) interrupted PR because of complications, were transferred to the transplantation center and continued PR after discharge from the transplantation center. All patients completed PR. No patient died during PR or decided to terminate PR early.

Outcome variables at completion of PR

Overall, VC, FEV1, PWR, VO_{2max}, 6-MWD, and HRQoL improved at completion of PR highly significant ($P < 0.001$). On admission, one patient depended on oxygen supplementation while he did not require it at completion of PR.

In each cohort, every single functional outcome variable improved significantly (Table 2). Baseline differences between both cohorts in FEV1, VC, and ADL diminished at completion of PR (FEV1: 56% vs. 65%, $P = 0.06$, VC: 58% vs. 66% predicted, $P = 0.2$, ADL: both 100, $P = 0.08$, Table 2). The raises in 6-MWD (LOS > 42: 123 m (plus 47% baseline) vs. LOS $\leq$ 42 days: 85 m (plus 22% baseline)) and in PWR (8 Watt (plus 28% baseline) vs. 10 Watt (plus 23% baseline)) were more pronounced in patients with a LOS >42. There was no difference according VO_{2max} between both groups.

Nevertheless endpoints representing functional status [PWR ($P < 0.001$), absolute 6-MWD ($P < 0.001$), number of climbed floors ($P < 0.001$)] were still different at completion of PR with superior results in patients with LOS $\leq$42 days (see Table 2, $P < 0.001$). The risk of complications (Pearson $\chi^2 = 1.2$, $P = 0.9$) and the duration of the rehabilitation ($P = 0.05$) were equal in both cohorts.

Short Form 36 domain rose significantly during rehabilitation. Differences between both cohorts were only seen in the SF36 domain 'physical functioning' at beginning ($P < 0.001$) and at completion ($P = 0.01$) and in the domain 'bodily pain', that was less favorable at beginning ($P = 0.01$) in cohort 2 with an assimilation between both cohorts at completion of PR ($P = 0.2$, details displayed in Table 2, Fig. 1). Significant differences despite an identical median (e.g., emotional role) resulted from differences in interquartile ranges.

Discussion

This study is the first one to observe the influence of a prolonged postsurgical clinical course after LTx on an intensive and multidisciplinary inpatient PR program in a remarkable number of transplant recipients. Patients with an extended LOS (>42 days) following transplantation received more often mechanical ventilation or ECMO, took a significant prolonged time to extubation and were at higher risk to be colonized with multidrug resistance bacteria. They revealed worse physical, functional, and mental conditions than: impairment of graft function (as reflected, e.g., by need for oxygen), early acute graft rejection – and this might occur without a need for oxygen supplementation – muscular deconditioning while awaiting transplantation or suffering from a prolonged ventilation, renal dysfunction, postsurgical or infectious complications, hindered patients with a prolonged lengths of stay to be transferred to the rehabilitation and to start a medical training therapy. Patients with prolonged LOS in the transplantation center were able to take part in an adapted, less

Table 1. Baseline demographics.

	Overall (n = 138)	LOS > 42 days (n = 30)	LOS ≤ 42 days (n = 108)	intergroup (P)
Age (years)	49 (34–56)	44 (32–56)	49 (37–57)	0.3
Gender female, *n* (%)	57 (41)	16 (53)	43 (40)	0.2
Underlying disease, *n* (%)				
COPD	44 (32)	4 (13)	40 (37)	0.02
Interstitial lung disease	34 (25)	8 (27)	26 (24)	0.8
Cystic fibrosis	36 (26)	6 (20)	30 (28)	0.5
Pulmonary hypertension	10 (7)	7 (23)	3 (3)	0.001
BOS	6 (4)	2 (7)	4 (4)	0.6
Other	8 (6)	3 (10)	5 (5)	0.4
Procedure, *n* (%)				
Single lung transplantation	9 (7)	1 (3)	8 (7)	0.7
Double lung transplantation	119 (86)	23 (77)	96 (89)	0.1
Heart and lung transplantation	7 (5)	5 (17)	2 (2)	0.005
Lung-liver transplantation	3 (2)	1 (3)	2 (2)	0.5
Admission post-LTx, days	25 (21–41)	67 (49–94)	23 (20–28)	<0.0001
Time on waiting list, days	232 (81–544)	227 (36–493)	234 (88–581)	0.4
Urgent/high urgent status, *n* (%)	88 (64)	25 (83)	63 (58)	0.02
NIV use before LTx, *n* (%)	35 (25)	2 (7)	33 (24)	0.008
Pre-LTx mechanical ventilation	12 (9)	7 (23)	5 (5)	0.004
Extracorporal support before transplant	6 (4)	6 (20)	0 (0)	<0.0001
Time to extubation, days [1]	10 (0–12)	36 (22–47)	1 (0–2)	<0.001
Multiresistant organisms	30 (22)	10 (33)	20 (19)	0.004
Bodily function				
VC, ml	2235 (1760–2705)	1915 (1232–2273)	2335 (1813–2815)	0.003
VC, % predicted	53 (44–65)	45 (36–65)	56 (45–65)	0.01
FEV1, ml	2060 (1595–2640)	1565 (1155–1933)	1850 (1433–2328)	0.007
FEV1, % predicted	54 (44–65)	49 (39–60)	55 (46–68)	0.009
Peak work rate, Watt	40 (30–50)	29 (13–37)	43 (34–52)	<0.001
VO_{2max}, ml/min/kg	12 (10–15)	11 (10–14)	12 (11–15)	0.29
6-MWD, m	370 (240–445)	262 (115–345)	390 (282–460)	<0.001
ADL, Barthel's index [1]	100 (95–100)	91 (15)	97 (7)	0.001
Floors, no.	1 (0–1)	0 (0–1)	1 (0–2)	0.002
SF36				
Physical functioning	25 (10–45)	15 (5–31)	70 (50–85)	0.02
Role physical	0 (0–50)	0 (0–25)	0 (0–50)	0.7
Bodily pain	59 (42–82)	73 (55–100)	58 (34–71)	0.003
General health perception	47 (40–61)	47 (37–57)	47 (40–62)	0.5
Vitality	50 (35–65)	43 (25–61)	50 (35–65)	0.2
Social functioning	75 (50–100)	75 (38–88)	75 (50–100)	0.6
Role emotional	100 (0–100)	100 (0–100)	100 (0–100)	0.6
Mental health	76 (60–84)	74 (59–85)	76 (59–85)	0.8
HADS				
Anxiety	4 (2–7)	3 (1–9)	5 (3–9)	0.1
Depression	3 (1–6)	4 (2–7)	4 (2–7)	0.7

Variables (exception of age) expressed in medians and interquartile ranges (25–75th percentiles). LOS, length of stay in the transplant center; NIV, noninvasive ventilation; VC, vital capacity; FEV1, forced expired volume in one second; 6-MWD, 6-min walking distance; VO_{2max}, maximum oxygen uptake; ADL, activities of daily living.

intensive program consisting of physical therapy (mobilization, therapist- and walking-device-assisted walking on ward), breathing therapy).

Patients with PH usually have a more complicated course after LTx [23]. The proportion of PH was significantly higher in the cohort with a prolonged LOS.

This inpatient rehabilitation improved physical functioning even more impressive in patients with an extended LOS, because 6-MWD and peak work load increased more pronouncedly compared to recipients with a regular course.

Starting at low level, both cohorts were narrowed, although total compensation in physical functioning was

Table 2. Bodily function, health-related quality of life and complications: intra- and intergroup comparison at baseline, and completion of PR.

	Length of stay > 42 days (n = 30)			Length of stay ≤ 42 days (n = 108)			Intergroup comparison (P)
	Baseline	Completion	P	Baseline	Completion	P	
Body weight, kg	56 (46–69)	56 (47–67)	0.6	62 (54–72)	63 (53–72)	0.9	n.s.
BMI, kg/m²	19 (17–23)	20 (17–24)	0.4	21 (19–24)	22 (18–24)	0.8	n.s.
VC, % pred.	45 (36–65)	58 (45–79)	<0.001	56 (45–65)	66 (57–80)	<0.001	n.s.
FEV1, % pred.	49 (39–60)	56 (49–74)	<0.001	55 (46–68)	65 (52–78)	<0.001	n.s.
Peak work rate, W	29 (13–37)	37 (30–48)	<0.001	43 (34–52)	53 (39–71)	<0.001	**
VO_{2max}, ml/min/kg	11 (10–14)	13 (11–16)	0.03	12 (11–15)	14 (12–16)	<0.001	n.s.
6-MWD, m	262 (115–345)	385 (260–454)	<0.001	390 (282–460)	475 (423–540)	<0.001	**
ADL (Barthel´s index)	100 (90–100)	100 (100)	0.002	100 (100)	100 (100)	<0.001	n.s.
Floors, no.	0 (0–1)	2 (1–4)	<0.001	1 (0–2)	4 (3–5)	<0.001	**
SF36							
Physical functioning	15 (5–31)	55 (39–70)	<0.001	30 (15–50)	70 (50–85)	<0.001	*
Role physical	0 (0–25)	50 (50–100)	<0.001	0 (0–50)	75 (50–100)	<0.001	n.s.
Bodily pain	73 (55–100)	94 (67–100)	0.04	58 (34–71)	78 (62–100)	<0.001	n.s.
Gen. health perception	47 (37–57)	67 (51–72)	0.01	47 (40–62)	67 (52–72)	<0.001	n.s.
Vitality	43 (25–61)	65 (49–71)	<0.001	50 (35–65)	65 (55–75)	<0.001	n.s.
Social functioning	75 (38–88)	75 (63–100)	0.03	75 (50–100)	88 (63–100)	<0.001	n.s.
Role emotional	100 (0–100)	100 (92–100)	0.004	100 (0–100)	100 (100–100)	<0.001	n.s.
Mental health	76 (61–84)	82 (71–92)	0.002	76 (59–85)	70 (50–85)	<0.001	n.s.
HADS							
Anxiety	3 (1–9)	2 (1–6)	0.04	5 (3–7)	4 (2–6)	<0.001	n.s.
Depression	4 (2–7)	4 (2–6)	0.07	4 (2–7)	2 (1–4)	<0.001	n.s.
Complications							
Total (%)		18 (60)			62 (57)	0.9	n.s.
Acute rejection		8 (27)			32 (30)	1.0	n.s.
Infection		4 (13)			14 (13)	1.0	n.s.
Airway obstruction		2 (7)			3 (3)	0.2	n.s.
DIOS		1 (3)			4 (4)	1.0	n.s.
Other		3 (10)			9 (8)	0.7	n.s.
Duration of rehab., days		28 (21–35)			21 (21–28)		n.s.

Variables expressed in medians and interquartile ranges (25–75th percentiles). Comparison >42 vs. ≤ 42 days. at completion of PR: level of significance: *<0.05, **<0.001, n.s. – $P \geq 0.05$. LOS, length of stay in the transplant center; BMI, body mass index; VC, vital capacity; FEV1, forced expired volume in one second; 6-MWD, 6-min walking distance; VO_{2max}, maximum oxygen uptake; ADL, activities of daily living; DIOS, distal intestinal obstructive syndrome; % pred., % predicted.

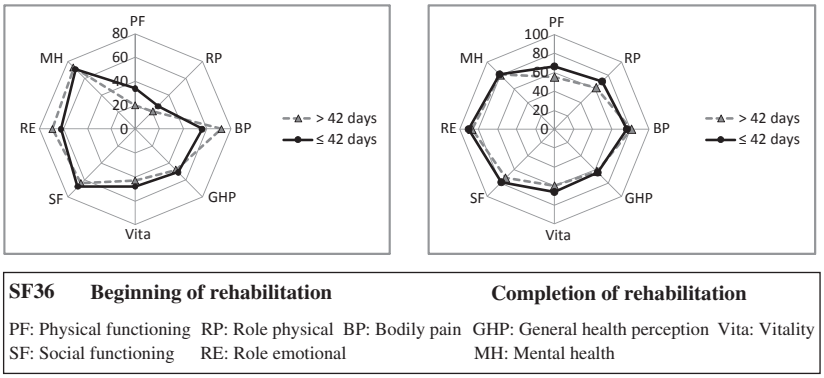

Figure 1 Health-related quality of life at beginning and completion of pulmonary rehabilitation.

not achieved. VO_{2max} usually reflects cardiovascular fitness. VO_{2max} did not differ between both cohorts anytime. At completion of PR, overall VO_{2max} reached 44% predicted.

VO_{2max} in graft recipients is usually impaired; improvement in VO_{2max} or maximal work capacity was not observed in a follow-up study for 2 years [24]. Different

authors concluded that limitations in VO_{2max} reflect muscular alteration after LTx [9,11,25,26].

Pulmonary rehabilitation following LTx has already proven its efficiency [27,28] (Table 3).

Because of the small number of published in- and outpatient rehabilitation programs, that are characterized by small sample sizes usually, start at different times in the clinical course after LTx and have different parameter sets comparisons are limited.

Nevertheless, the result of our 3 weeks lasting inpatient program according the functional parameter '6-MWD' the cohort with a LOS <42 days is similar to the 12-week outpatient programs of Munro *et al.* [28] and Maury *et al.* [29] and long-term observations by Ross *et al.* [30] 8 months or by Langer *et al.* [31] 1 year after LTx. Stiebellehner *et al.*'s [32] collective (nine patients) performed better in VO_{2max} and PWR 1 year after surgery. Tegtbur *et al.*'s [33] 136-week outpatient program started 210 days after transplantation and revealed higher PWR.

Controlled studies between in- and outpatient rehabilitation programs have not been performed until now owing to clinical practice in Germany, where no outpatient rehabilitation is applied to patients early after LTx.

Patient's self estimated HRQoLwas similar in both cohorts at beginning and improved significantly during PR. The SF36 domain 'physical functioning' mirrored the difference in functional status between both cohorts. A superior result according 'bodily pain' at beginning in the cohort with extended LOS results from the longer period between surgery and admission for PR, when wound and chest pain declined in the natural healing process. At completion of PR, the difference diminished. Reduced functional status caused by extended LOS did not severely influence perception of HRQoL, which was close to normal in most functional and all mental domains.

Patients with a LOS $\leq$42 days performed domains, that represent the physical component of the SF36 questionnaire, comparable or superior to other studies (Table 4): even patients with a LOS >42 days achieved higher scores in the domains 'bodily pain' and 'role physical' than Smeritschnig *et al.* [34] found 42 months post surgery and in 'role physical' and 'physical functioning' than Goetzman *et al.* [35] observed in his prospective study 50 months after transplantation. In the mental component of the SF36, Langer *et al.* [31] and Smeritschnik *et al.* [34] described higher scores for 'social functioning' while patient in both cohorts of our 3-week PR achieved in the domains 'vitality', 'role emotional', and 'mental health' scores that were not only superior to the results Goetzman [35], but also were in some domains superior to a healthy reference population [36]. Personal

Table 3. Rehabilitation programs in lung transplant recipients.

	Ross *et al.* [30] (n = 8)	Stiebellehner *et al.* [32] (n = 9)	Tegtbur *et al.* [27] (n = 20)	Munro *et al.* [28] (n = 36)	Maury *et al.* [29] (n = 36)	This study LOS >42 days (n = 30)	This study LOS $\leq$42 days (n = 108)
Start post-LTx (days)	251	365	210	28	37	67	23
Setting	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Inpatient	Inpatient
Training period (weeks)	6	6	140	12	12	3	3
6MWD (m)							
Start				451 ± 126	320 ± 138	233 ± 142	366 ± 131
End				543 ± 107	449 ± 128	361 ± 130	479 ± 121
VO_{2max} (ml/min/kg)							
Start	9.2 ± 0.8	18.4 ± 3.8				11.9 ± 3	12.9 ± 4
End	13.4 ± 0.8	20.3 ± 3.9				13.8 ± 4	14.4 ± 4
Peak work load (watt)							
Start		66 ± 22	64 ± 22			27 ± 17	44 ± 18
End		81 ± 22	84 ± 29			38 ± 19	56± 22

Table 4. Health-related quality of life in lung transplant recipients.

SF36 questionnaire	Langer *et al.* [31] (n = 22)	Goetzman *et al.* [35] (n = 76)	Smeritschnig *et al.* [34] (n = 94)	This study LOS >42 days (n = 30)	This study LOS $\leq$ 42 days (n = 108)	Reference value * (n = 1742)
Time since LTx, months	16 (12–24)	50 (2–131)	42 (3–117)	2.6 (1.4–4.6)	0.8 (0.5–1.4)	
Physical functioning	64 (±20)	50 (±8)	69 (±24)	55 (±20)	66 (±24)	83 (±23)
Role physical	69 (±34)	50 (±10)	59 (±42)	62 (±30)	71 (±29)	77 (±36)
Bodily pain	69 (±23)	53 (±10)	72 (±28)	81 (±23)	76 (±20)	75 (±23)
General health perception	59 (±24)	46 (±9)	59 (±20)	63 (±17)	64 (±14)	71 (±21)
Vitality	64 (±18)	52 (±9)	60 (±22)	60 (±15)	66 (±15)	69 (±19)
Social functioning	84 (±20)	52 (±8)	83 (±23)	73 (±24)	79 (±2)	84 (±22)
Role emotional	92 (±19)	52 (±7)	68 (±44)	87 (±25)	90 (±22)	82 (±33)
Mental health	77 (±19)	52 (±9)	71 (±21)	81 (±12)	82 (±15)	77 (±17)

Mean ± SD (range).
*Dutch general population [36].

perception of HRQoL is positive anytime and quite independent from objective functional status. Similar effects were described by Kugler *et al.* [37] in a sample of 280 patients in a post-transplant follow-up 3 months to 14 years after LTx.

Limitations

First, this observational study was noncontrolled and nonrandomized. In German transplant centers, all lung transplant recipients achieve inpatient rehabilitation in a specialized unit when they are discharged from the transplant center. While no outpatient programs are implemented, a randomized controlled design was impossible to create and therefore this study had a selection bias. Secondly, the distribution of underlying lung diseases was not balanced between both groups with a significant higher proportion of COPD patients in the cohort LOS $\leq$ 42 days and more patients with PH in the cohort with a prolonged LOS >42 days. A prospective randomized controlled study comparing in- and outpatient rehabilitation early after transplantation might answer this question.

Conclusion

Patients with a prolonged clinical course after transplantation in the transplant center for more than 42 days revealed worse functional conditions than those with a regular course. This 3-week inpatient rehabilitation program enhanced graft function, physical functioning and mental condition significantly despite prolonged hospitalization. It could not overcome all impacts of extended LOS in the transplant center, but improvement in graft function, oxygen uptake, and ADL were equal to patients with a regular postsurgical clinical course. HRQoL was close to normal overall.

Authorship

MD and JG: participated in research design, statistical analysis, data acquisition, analysis and interpretation, and writing of the manuscript. AT and TF: participated in data acquisition, analysis and interpretation, and writing of the manuscript. UT and AH: participated in research design, data analysis, and interpretation. TW and GW: participated in data analysis and interpretation, and critical revision of the manuscript.

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