What predicts the success of functional recovery after lung transplantation – a retrospective cohort study

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Name student:	J.W.M. (Juul) van Grootel
Student number:	6174000
Date:	June 12, 2020
Internship supervisor(s):	Dr. K. (Karin) Valkenet, Prof. Dr. C. (Cindy) Veenhof
Internship institute:	Department of Rehabilitation, Physical Therapy Science & Sports, University Medical Center Utrecht, Utrecht, the Netherlands
Lecturer/supervisor Utrecht University:	Dr. J. (JanJaap) van der Net

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Examiner
Dr. M.F. (Martijn) Pisters

Assessors:
Dr. K. (Karin) Valkenet
Dr. J. (JanJaap) van der Net

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What predicts the success of functional recovery after lung transplantation – a retrospective cohort study

J.W.M. van Grootel[1], PTI, Karin Valkenet[1], PT, PhD, G.A. Ruigrok, MD[2] and Cindy Veenhof[1], PT, PhD

1. *Department of Rehabilitation, Physical Therapy Science & Sports, University Medical Center Utrecht, Utrecht, the Netherlands.*
2. *Heart Lung Center Utrecht, University Medical Center Utrecht, Utrecht, The Netherlands*

ABSTRACT

Background: Lung transplantation (LTx) is an intensive medical treatment with a high risk of complications, decreased physical functioning and mortality. Functional recovery in the early phase after LTx differs greatly between patients and can influence hospital length of stay and long term physical functioning.

Aim: The aim of this study was to investigate if preoperative physical function parameters predict the functional recovery after LTx.

Patients and Methods: Patients who underwent screening and LTx at the University Medical Centre of Utrecht between January 2001 and February 2020 were included. Preoperative physical function parameters and conventional risk factors were entered in a Cox Proportional Hazards model. The primary outcome was the time to walk in the hospital room for the first time after LTx.

Results: A total of 225 patients were included for data analysis. Preoperative physical function parameters were not significant in multivariate analysis. A hazard ratio of 1.663 (p=0.024) and 0.983 (p=0.039) was found for bilateral LTx and age, respectively.

Conclusion and key findings: We found preoperative physical function parameters not to be associated with functional recovery after LTx, measured as the time to walk in the hospital room for the first time after LTx. At this moment it is too early to change the physiotherapeutic screening of LTx candidates. Functional recovery needs to be reinvestigated and defined differently in further research, to determine the role of preoperative physical function parameters in screening LTx candidates.

KEYWORDS: lung transplantation, LTx, functional recovery, lung disease, survival

Address correspondence to: J.W.M. van Grootel, Department of Rehabilitation, Physical Therapy Science & Sports, University Medical Center Utrecht, Utrecht, the Netherlands. Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. E-mail: j.w.m.vangrootel@umcutrecht.nl
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INTRODUCTION

Lung transplantation (LTx) is a viable treatment option for patients with end-stage lung disease. Main important indications for LTx are chronic obstructive pulmonary disease/emphysema, interstitial lung disease/idiopathic pulmonary fibrosis, cystic fibrosis and pulmonary arterial hypertension.[1] Initially, morbidity and mortality post-LTx were high.[2] Between 1992 and 2017, the median survival time increased to 6.7 years. Currently, every year over 4,500 LTxs are performed worldwide and the median survival time for patients who survived the first year increased to 8.8 years.[3]

Before patients are placed on the waiting list for LTx, an extensive screening is performed. The primary focus of this screening is to determine contra-indications for LTx and consequently, whether acceptance to the waiting list is feasible. To obtain insight in the LTx candidate's physical state, physiotherapists measure exercise capacity using the six-minute walking test (6MWT).[4] The results of this test will be added to other clinical information to determine the ranking order of patients waiting for a LTx.

Extensive research has shown that LTx candidates show deterioration of their physical functioning such as reduced muscle mass, muscle strength and fat free mass index (FFMI).[5,6] Frailty, defined by Fried et al., includes one or more of these aspects of deterioration and is significantly associated with mortality and increased hospital length of stay after LTx.[7,8] Other known factors associated with post-LTx outcomes are age, gender, lung diagnosis, use and duration of preoperative extracorporeal life support (ECLS) and unilateral or bilateral LTx.[9,11,12]

In the Netherlands, 172 patients were on the waiting list for LTx in 2019.[10] Given the known morbidity and scarcity of donor lungs, it is fundamental to predict the course of physical recovery after LTx and improve survival benefit. Currently, candidate selection and waiting list measurements are mainly based on presumed survival. Remarkably, functional recovery after LTx is not taken into account during screening for LTx, while physical functioning is related to the ability to live independently or perform daily activities.[11,12] For this reason, physical recovery after LTx may be a valuable addition as outcome parameter in screening LTx candidates.

This study hypothesized that six-minute walking distance (6MWD), handgrip strength, quadriceps strength and FFMI, could predict functional recovery after LTx. Functional recovery was defined as the time to walk in the hospital room independently or with a walking aid for the first time after LTx. This outcome was chosen because a primary focus for hospital-based physical therapists is evaluating a patient's mobility and self-care abilities, particularly in terms of understanding the level of assistance that patients may require to safely perform daily activities. Therefore, the aim of this study was to investigate if preoperative physical function parameters predict the functional recovery after LTx.

PATIENTS AND METHODS

Design

A retrospective cohort study was performed at the University Medical Centre of Utrecht (UMCU), (see appendix 1). Data were extracted from medical records between January and March 2020. This study was approved by the Quality Committee of UMCU (19-753-C).

Participants

All participants who were screened, underwent LTx and received postoperative care at UMCU between January 2001 and March 2020 were included in this study. Candidate selection for LTx was in accordance with the International Society for Heart and Lung Transplantation guidelines and local criteria of UMCU.[3,13] Patients screened at Hospital Antonius Ziekenhuis Nieuwegein (AZN) or of whom the medical record could not be retrieved were excluded. In patients undergoing re-transplantation, medical records of the second transplantation were excluded.

Primary outcome

The primary outcome, namely the time to walk in the hospital room independently for the first time after LTx, was derived from the Activity Measure for Post-Acute Care '6-clicks'-questionnaire.[14] This parameter was reached if the patient did not require any help and performed this activity independently; use of assistive devices was allowed. Reaching this outcome was registered in the patient's medical record by nurses or physical therapists.

Secondary outcomes

Secondary outcomes were time to first extubation, including auto-extubation[15,16](days), time to hospital discharge (days) and survival (years). All parameters were extracted from the patient's medical record and dates of outcomes were counted from the date of LTx.

Demographics

Based on clinical expertise and previous research, conventional risk factors as age at time of LTx, gender, lung diagnosis, unilateral or bilateral LTx and use and duration of preoperative ECLS were obtained from medical records.[9-12,17]

Preoperative physical function parameters

Preoperative physical function parameters that were measured by a physical therapist and dietician were also obtained from medical records. The 6MWT was performed on a 35 m rectangular walking track, following the American Thoracic Society protocol.[18] The 6MWT has a reported intra-observer reliability of ICC=0.99 in patients with end-stage lung disease.[19] Results of the 6MWT were reported per 30 meter, which is the minimal clinical important difference for the 6MWT.[20] Handgrip strength was measured using a hand-held dynamometer (Jamar, USA),

following the American Society of Hand Therapists protocol.[21] The dynamometer has a reported intra-observer reliability of ICC=0.98.[22] Quadriceps strength was measured using a hand-held MicroFet2 dynamometer (Hoggan Health Industries, USA), following the 'make method' and the protocol of Andrews et al.[23] The MicroFet2 has a reported intra-observer reliability of ICC=0.81 for knee extensors.[24] Handgrip and quadriceps strength were reported per 10 N, following reporting guidelines.[25] FFMI was calculated by a person's fat mass, divided by their height squared and was measured by bioelectrical impendance analysis (BIA) (BIA, Bodystat 1500; Bodystat Ltd, Douglas, UK) expressed in percentages. The BIA has a reported intra-observer reliability of ICC=0.98.[26] All measurements were performed during screening for LTx and subsequently repeated every 6 months, the most recent available measurement was used in the analysis.

Sample size

According to the rule of thumb, there should be at least 10 'events' per variable.[27] In the current study there were twelve independent variables selected, therefore the sample size needed to be at least 120.[28]

Statistical analysis

Data was checked for normality using the Shapiro-Wilk test, histograms and QQ-plots. Demographics were presented as exact numbers, means and standard deviation (SD) were presented for normal distributed data, medians and ranges were presented for non-normal distributed data. To check for multicollinearity, Pearson Correlations (R) were calculated for all covariates, covariates with R>0.8 were excluded for further analysis, as suggested they were strongly intercorrelated. Missing value analysis was performed by Little's Missing Completely At Random (MCAR)-test.[29] When MCAR, a multiple imputation of five datasets will be used, these datasets were pooled to ensure usability of all cases in further analysis.

The Kaplan-Meier method was used to estimate the time-to-event for all variables with either an empirical or theoretical association to LTx. Patients who were deceased before they reached the 'event', were censored at the date of death. All variables were first entered in an univariate Cox model following an enter selection. P-values, hazard ratios (HR) and 95% confidence intervals were computed to estimate strength of associations.

After that, all variables were entered in a multivariate Cox model following an enter selection. To investigate the preoperative physical function parameters in further detail, a post hoc analysis was performed. For ease of interpretation preoperative physical function parameters were dichotomized by cut-off values primarily based on literature. When evidence was lacking, the median was used. The cut-off value for 6MWD was <50m, for handgrip strength <20.0 kg for females and <30.0 kg for males, for quadriceps strength <median and FFMI used a cut-off value of <15.0 for females and <16.0 for males.[18,30,31] These dichotomized variables and conventional

risk factors were added in an univariate and multivariate Cox model following an enter selection. Survival plots were obtained for dichotomized preoperative physical function parameters with $p<0.05$ in multivariate analysis.
A C-statistic was calculated for all models to obtain the discrimination of the model.[32] This C-statistic is equal to the area under the receiver operating characteristic for regression models. A value of C=0.5 corresponds to a non-informative prediction rule whereas C=1.0 corresponds to a perfect association. C often ranges between 0.6 and 0.75, a C between 0.7 and 0.8 is considered acceptable.[33,34] All analysis was performed using IBM Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Mac, Version 25.0. Armonk, NY: IBM Corp).

RESULTS

Descriptive statistics

During the study period, 441 patients underwent LTx at UMCU. In total, 211 patients were excluded because they were assessed for LTx at AZN, physical function parameters were not available for these patients. Five other patients were excluded due to other reasons (Figure 1).

Figure 1 should be here

A total of 225 patients were included for data analysis. Of these 225 patients, there was a slight majority of women and about half of the patients had cystic fibrosis (Table 1). Functional recovery after LTx followed a right skewed distribution. Of all included patients, 79.6% reached the primary outcome within the first month after LTx. The median time to walk in the hospital room independently for the first time after LTx was thirteen days. Of all included patients, 81.3% were extubated within the first week after LTx. One month after LTx, 60.4% of all included patients were discharged from hospital. Of all included patients, 45.3% survived the first five years after LTx.

Table 1 should be here

Primary outcome analyses

The R-correlation matrix showed no multicollinearity between the variables. Little's MCAR-test showed $p<0.000$, indicating missing values were missing at random. A HR of 1.031 per 30 meter ($p=0.028$) was found for 6MWD in univariate analysis. A HR of 1.663 ($p=0.024$) was found for bilateral LTx in multivariate analysis. HRs of 0.988 ($p=0.016$) and 0.983 ($p=0.039$) for age were found in univariate and multivariate analysis, respectively (see Table 2). The C-statistic was 0.650 for the model containing all variables, indicating the model's ability to predict the time to event was classified as 'nearly acceptable'.[32]

Table 2 should be here

Secondary outcome analyses

Firstly, for time to first extubation, HRs of 1.138 (p=0.031) and 1.017 (p=0.027) were found for handgrip- and quadriceps strength per 10 N in univariate analysis. HRs of 1.308 (p=0.007) and 1.787 (p=0.011) were found for bilateral LTx in univariate and multivariate analysis, respectively. Secondly, for time to hospital discharge, a HR of 1.629 (p=0.032) was found for bilateral LTx in multivariate analysis. HRs of 0.989 (p=0.020) and 0.980 (p=0.022) were found for age in univariate and multivariate analysis. Thirdly, for survival, a HR of 1.018 (p=0.024) was found for age in univariate analysis. See appendix 2 and 3 for tables with HRs and calculated C-statistics on secondary outcomes.

Post hoc analyses

HRs of 1.567 (p=0.002) and 1.697 (p=0.004) were found for quadriceps strength <267.0 N in univariate and multivariate analysis, respectively (see Table 3). The C-statistic for this model containing all variables was 0.628, this was classified as 'nearly acceptable'.[32] See figure 2 for a survival plot for time to walk independently in the hospital room divided by a quadriceps strength of <267.0 N or >267.0 N.

Table 3 should be here

Figure 2 should be here

DISCUSSION

In this retrospective cohort analysis we found preoperative physical function parameters not to be associated with functional recovery after LTx, measured as the time to walk in the hospital room independently for the first time after LTx. There were several possible explanations why this study found no associations in analysis of the primary outcome. LTx candidates are mostly in high need of a LTx which results in a poor physical state, this caused little variability in data of preoperative physical function parameters. In addition, our primary outcome was extremely right skewed, as is often the case in survival data, demonstrating significant associations was therefore challenging.[35,36] The cross-sectional character of this study avoided inter-rater reliability errors but caused the failure to measure changes of physical functioning during the preoperative time course on the other hand. This could be a reason why this study found no significant associations as well.

The time to walk independently in the hospital room after LTx had not been investigated before, but was possibly not be the best reflection of functional recovery after LTx. Registration

of the primary outcome was part of usual care and was performed by various physical therapists or nurses, which could have influenced the registrations' accuracy. Another issue related to the primary outcome was the timespan, which included only the inpatient phase. Including the outpatient phase in functional recovery could contribute to more variability in the data and would therefore be informative.

To our knowledge, this is the only study using a survival analysis to evaluate possible predictors for functional recovery after LTx. In previous research investigating associations between preoperative physical function parameters and survival after LTx, functional recovery was not taken into account. Castleberry et al. and Osho et al. showed in studies with 9,526 and 16,497 patients that 6MWD was significantly associated with survival after LTx.[7,35] These studies extracted large numbers of patients from a database, which contributed to increased power in the analysis to demonstrate significant associations. The incidence of preoperative ECLS and unilateral LTx in our study was low compared to Grimm et al., who found significant associations between age, bilateral LTx, use of preoperative ECLS and survival after LTx.[36] The use of preoperative ECLS only occurs in patients who are admitted to the intensive care unit in a very high need of a LTx, this could have influenced the preoperative physical function parameters and postoperative functional recovery. Unilateral LTx only occurs in patients with chronic obstructive pulmonary disease, the majority of patients in our study had cystic fibrosis. This was not comparable to worldwide numbers, indicating there were discrepancies between baseline characteristics of patients in Grimm et al. and our study, which could have contributed to contrary results.

Terms, conditions and ethical considerations in LTx differ greatly per region in the world. To illustrate this, populations in studies conducted in the United States of Castleberry et al. and Osho et al. consisted of mostly males, were older of age and had a higher body mass index than the Dutch population in our study.[7,35] Gender, age, body mass index and preoperative physical functioning are interrelated and differ worldwide, it could be suggested that preoperative physical functioning in our population was better compared to populations in other studies.[37] Results of studies performed in other countries should therefore be interpreted with some caution.

There were some strengths and limitations in this study. Firstly, the 15-year follow up of LTx recipients is quite unique and this question has not been addressed before. Secondly, it is important that deaths were censored, allowing for an accurate estimation of the time to reach the event alive. Time to first extubation or time to hospital discharge may have a complete different meaning depending on whether the patient was alive or not. Thirdly, to outweigh uncertainties regarding checking for all assumptions in survival analysis, C-statistics were calculated to obtain the models discrimination.[32] Unfortunately, 50% of our patients were excluded because of unavailable measurements in other centers, which led to reduced power in the analysis. Clinical experience has taught us that predicting functional recovery after LTx is not

possible on the basis of statistical significance only. In our opinion, it is questionable whether telling a patient his HR is equal to 1.0 with high probability is clinically more relevant, than telling his HR is three times higher with low probability. This expressively shows the importance of a thorough observation of all HRs in univariate and multivariate analysis and not only the HRs with significant p-values.

In conclusion, despite the fact this study showed preoperative physical function parameters not to be associated with functional recovery after LTx we would recommend some implications. More research is needed to determine the role of preoperative physical function parameters in predicting functional recovery after LTx, using other more optimal parameters and outcome measures in a prospective analysis over a longer timespan. For example, using a questionnaire or an activity monitor could offer a more contemporary and accurate measurement reflecting functional recovery. Another suggestion would be to measure preoperative physical functioning repeatedly, to detect changes in physical functioning during the preoperative time course. This might contribute to an early advice in screening LTx candidates and predicting their functional recovery after LTx. Determining the role of preoperative physical function parameters on functional recovery after LTx is needed before adjustments in screening of LTx candidates are made.

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TABLES AND FIGURES

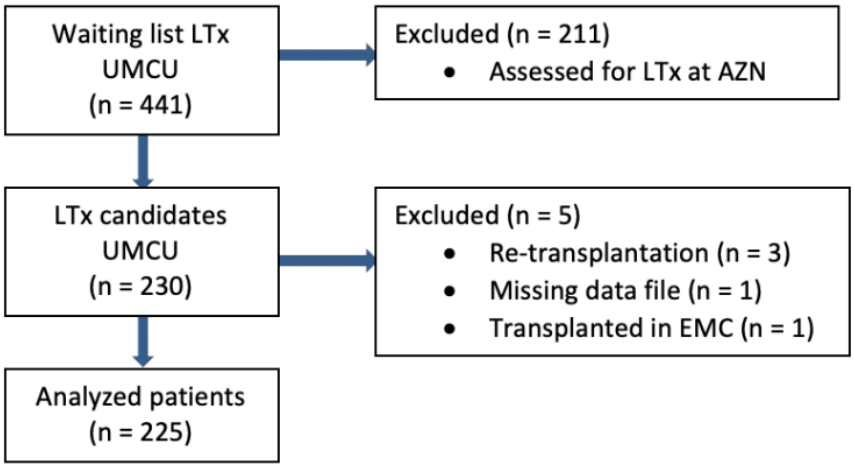


Figure 1 Flowchart of inclusion
Abbreviations: UMCU: Universitair Medisch Centrum Utrecht, AZN: Antonius Ziekenhuis Nieuwegein, EMC: Erasmus Medisch Centrum, LTx: lung transplantation

Table 1. Patient characteristics

Characteristic	N	Value
Sex, female (%)	225	116 (51.6%)
Age, median (y)	225	48 (16-66)
Lung disease (%)	225	
COPD/emphysema/A1AT		65 (28.9%)
IPF/ILD/sarcoidosis		25 (11.1%)
CF		104 (46.2%)
Other		31 (13.8%)
Transplantation type (%)	225	
Bilateral		195 (86.7%)
Body composition* (Kg/m2)		
BMI	206	20.8 (16-32)
FFMI	148	15.3 (11-29)
Use of preoperative ECLS (d)	225	0 (0-40)
Exercise capacity*		
6MWD (m)	210	250.5 (10-653)
Muscle strength*		
Handgrip strength (kg)	171	33.0 (11-75)
Quadriceps strength (N)	187	267.0 (118-584)
Functional recovery after LTx		
Time to walk independently in the hospital room (d)	212	13 (4-162)
Time to first extubation (d)	220	2 (0-87)
Time to hospital discharge (d)	221	28 (12-268)
Survival (y)	225	5 (0-18)

Abbreviations: COPD: chronic obstructive pulmonary disease, A1AT: Alpha-1 antitrypsin deficiency, IPF: idiopathic pulmonary fibrosis, ILD: interstitial lung disease, CF: cystic fibrosis, BMI: body mass index, FFMI: fat free mass index, ECLS: extracorporeal life support, 6MWD: six-minute walking distance, SD: standard deviation, y: years, d: days, kg: kilograms, m: meters, N: Newton
*Variables were measured during screening for LTx and repeated every 6 months

Table 2. HR for time to walk independently in the hospital room

	Univariate regression				Multivariate regression		
Variable	N	HR	95% CI	P value	HR	95% CI	P value
Age (y)	225	**0.988**	**0.979-0.998**	**.016**	**0.983**	**0.968-0.999**	**.039***
Male	108	0.977	0.741-1.290	.873	1.132	0.769-1.666	.531
Lung disease	225						
COPD/emphysema/A1AT	65	ref		.261	ref		.428
IPF/ILD/sarcoidosis	24	0.967	0.585-1.597	.900	0.909	0.541-1.530	.721
CF	104	1.056	0.759-1.468	.751	0.860	0.508-1.454	.573
Other	31	0.697	0.449-1.082	.698	0.677	0.426-1.075	.098
Bilateral LTx	195	1.203	0.985-1.468	.069	**1.663**	**1.068-2.588**	**.024**
Preoperative ECLS (d)	11	0.986	0.954-1.019	.399	0.999	0.964-1.034	.934
6MWD (per 30 m)	225	**1.031**	**1.003-1.059**	**.028**	1.018	0.986-1.050	.273
Handgrip strength (per 10 kg)	225	1.078	0.964-1.206	.190	1.086	0.878-1.343	.446
Quadriceps strength (per 10 N)	225	1.008	0.994-1.022	.254	1.008	0.982-1.034	.568
FFMI (Kg/m2)	225	1.002	0.949-1.057	.961	0.982	0.906-1.065	.662

*p<.05 in both univariate and multivariate analysis

Abbreviations: COPD: chronic obstructive pulmonary disease, A1AT: Alpha-1 antitrypsin deficiency, IPF: idiopathic pulmonary fibrosis, ILD: interstitial lung disease, CF: cystic fibrosis, FFMI: fat free mass index, LTx: lung transplantation, ECLS: extracorporeal life support, 6MWD: six-minute walking distance, HR: hazard ratio, CI: confidence interval, ref: reference category, y: years, d: days, m: meters, kg: kilograms, N: Newton

Table 3. Post hoc analysis for time to walk independently in the hospital room

	Univariate regression				Multivariate regression		
Variable	N	HR	95% CI	P value	HR	95% CI	P value
Age (y)	225	**0.988**	**0.979-0.998**	**.016**	**0.983**	**0.967-0.998**	**.030***
Male	108	0.977	0.741-1.290	.873	1.340	0.909-1.975	.140
Lung disease	225						
COPD/emphysema/A1AT	65	ref		.261			.288
IPF/ILD/sarcoidosis	24	0.967	0.585-1.597	.901	0.954	0.567-1.604	.862
CF	104	1.056	0.759-1.468	.753	0.904	0.535-1.528	.711
Other	31	0.697	0.449-1.082	.699	0.643	0.399-1.036	.070
Bilateral LTx	195	1.203	0.985-1.468	.069	**1.545**	**0.994-2.404**	**.015**
Preoperative ECLS (d)	11	0.986	0.954-1.019	.401	0.997	0.961-1.034	.881
6MWD <50 m	35	1.318	0.902-1.927	.153	1.075	0.681-1.697	.762
Handgrip strength f=<20.0 kg, m=<30.0 kg	114	1.249	0.947-1.646	.115	1.235	0.801-1.903	.339
Quadriceps strength <267.0 N	112	**1.567**	**1.185-2.072**	**.002**	**1.697**	**1.183-2.433**	**.004***
FFMI f=<15.0%, m=<16.0% (Kg/m2)	110	1.023	0.776-1.349	.871	0.962	0.698-1.328	.824

*p<.05 in both univariate and multivariate analysis

Abbreviations: COPD: chronic obstructive pulmonary disease, A1AT: Alpha-1 antitrypsin deficiency, IPF: idiopathic pulmonary fibrosis, ILD: interstitial lung disease, CF: cystic fibrosis, FFMI: fat free mass index, LTx: lung transplantation, ECLS: extracorporeal life support, 6MWD: six-minute walking distance, HR: hazard ratio, CI: confidence interval, ref: reference category, y: years, d: days, m: meters, kg: kilograms, N: Newton

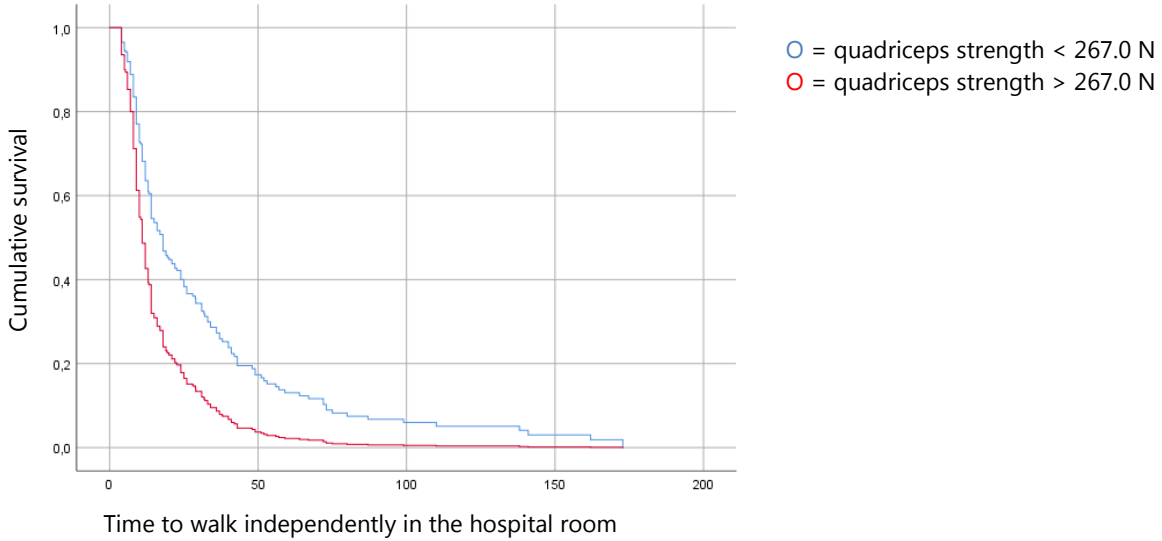
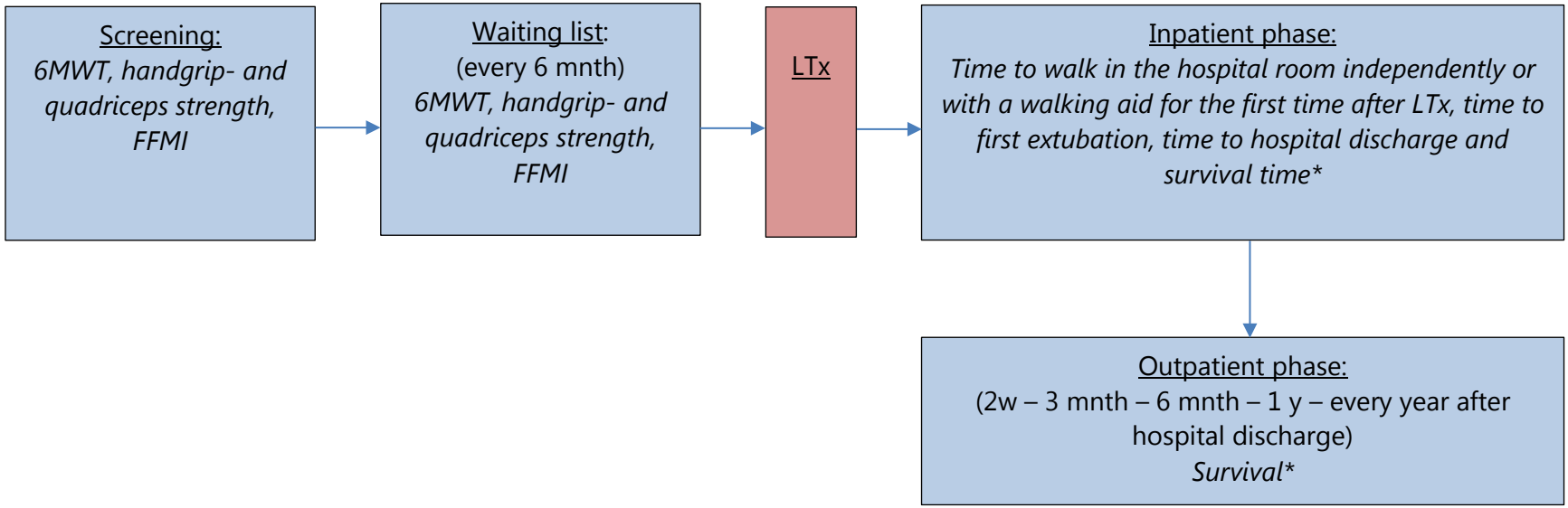


Figure 2. Cox proportional hazards estimates of time to walk independently in the hospital room for the first time after LTx, divided in subgroups by quadriceps strength on the basis of the median. Higher quadriceps strength represented a higher probability of walking independently at a certain time point ($p<0.001$).

APPENDIX

Appendix 1 Flowchart of data collection



Abbreviations: LTx: lung transplantation, 6MWT: six-minute walking test, FFMI: fat free mass index, w: weeks, mnth: months, y: year
*survival is monitored continuously, not only during in- or outpatient measurements.

Appendix 2 HRs for secondary outcomes

HR for time to first extubation							
	Univariate regression				Multivariate regression		
Variable	N	HR	95% CI	P value	HR	95% CI	P value
Age (y)	225	0.998	0.989-1.008	.692	0.993	0.977-1.009	.401
Male	108	1.261	0.952-1.670	.105	0.900	0.609-1.330	.596
Lung disease	225						
COPD/emphysema/A1AT	65	ref		.541	ref		.576
IPF/ILD/sarcoidosis	24	0.804	0.491-1.315	.385	0.798	0.483-1.319	.378
CF	104	0.867	0.625-1.202	.391	0.855	0.495-1.479	.576
Other	31	0.733	0.473-1.136	.164	0.737	0.465-1.166	.192
Bilateral LTx	195	**1.308**	**1.075-1.592**	**.007**	**1.787**	**1.141-2.797**	**.011***
Preoperative ECLS (d)	11	0.986	0.955-1.017	.365	0.997	0.964-1.031	.846
6MWD (per 30 m)	225	1.027	0.995-1.059	.095	1.013	0.997-1.053	.445
Handgrip strength (per 10 kg)	225	**1.138**	**1.012-1.281**	**.031**	0.998	0.812-1.225	.982
Quadriceps strength (per 10 N)	225	**1.017**	**1.002-1.032**	**.027**	1.012	0.986-1.038	.380
FFMI (Kg/m2)	225	1.057	0.997-1.120	.063	1.016	0.934-1.106	.704

*p<.05 in both univariate and multivariate analysis

Abbreviations: COPD: chronic obstructive pulmonary disease, A1AT: Alpha-1 antitrypsin deficiency, IPF: idiopathic pulmonary fibrosis, ILD: interstitial lung disease, CF: cystic fibrosis, FFMI: fat free mass index, LTx: lung transplantation, ECLS: extracorporeal life support, 6MWD: six-minute walking distance, HR: hazard ratio, CI: confidence interval, ref: reference category, y: years, d: days, m: meters, kg: kilograms, N: Newton

HR for time to hospital discharge							
	Univariate regression				Multivariate regression		
Variable	N	HR	95% CI	P value	HR	95% CI	P value
Age (y)	225	**0.989**	**0.979-0.998**	**.020**	**0.980**	**0.964-0.997**	**.022***
Male	108	0.990	0.862-1.137	.891	1.140	0.768-1.691	.515
Lung disease	225						
COPD/emphysema/A1AT	65	ref		.293	ref		.413
IPF/ILD/sarcoidosis	24	1.011	0.912-1.672	.972	0.953	0.566-1.605	.856
CF	104	1.039	0.746-1.446	.823	0.768	0.446-1.319	.338
Other	31	0.702	0.452-1.090	.115	0.680	0.427-1.083	.105
Bilateral LTx	195	1.193	0.978-1.455	.081	**1.629**	**1.044-2.542**	**.032**
Preoperative ECLS (d)	11	0.993	0.961-1.026	.691	1.004	0.969-1.040	.831
6MWD (per 30 m)	225	1.001	1.000-1.002	.139	1.007	0.971-1.046	.670
Handgrip strength (per 10 kg)	225	1.172	0.803-1.712	.411	1.074	0.875-1.317	.496
Quadriceps strength (per 10 N)	225	1.006	0.995-1.017	.321	1.010	0.984-1.036	.455
FFMI (Kg/m2)	225	1.233	0.928-1.613	.153	.980	0.899-1.068	.644

*p<.05 in both univariate and multivariate analysis

Abbreviations: COPD: chronic obstructive pulmonary disease, A1AT: Alpha-1 antitrypsin deficiency, IPF: idiopathic pulmonary fibrosis, ILD: interstitial lung disease, CF: cystic fibrosis, FFMI: fat free mass index, LTx: lung transplantation, ECLS: extracorporeal life support, 6MWD: six-minute walking distance, HR: hazard ratio, CI: confidence interval, ref: reference category, y: years, d: days, m: meters, kg: kilograms, N: Newton

HR for survival time							
	Univariate regression				Multivariate regression		
Variable	N	HR	95% CI	P value	HR	95% CI	P value
Age (y)	225	**1.018**	**1.002-1.033**	**.024**	1.010	0.985-1.036	.442
Male	108	0.997	0.811-1.226	.982	0.783	0.438-1.400	.409
Lung disease	225						
COPD/emphysema/A1AT	65	ref		.039	ref		.206
IPF/ILD/sarcoidosis	24	0.911	0.445-1.868	.801	1.004	0.477-2.111	.992
CF	104	0.668	0.409-1.092	.107	0.911	0.404-2.058	.823
Other	31	1.605	0.868-2.966	.131	1.862	0.979-3.541	.058
Bilateral LTx	195	1.170	0.893-1.533	.256	1.108	0.803-1.530	.531
Preoperative ECLS (d)	11	0.954	0.859-1.059	.372	0.949	0.852-1.057	.344
6MWD (per 30 m)	225	1.000	0.998-1.001	.541	0.996	0.942-1.052	.867
Handgrip strength (per 10 kg)	225	1.058	0.543-2.060	.872	1.000	0.734-1.361	.998
Quadriceps strength (per 10 N)	225	1.001	0.983-1.020	.891	0.989	0.950-1.030	.603
FFMI (Kg/m2)	225	0.923	0.609-1.397	.701	0.953	0.844-1.076	.438

Abbreviations: COPD: chronic obstructive pulmonary disease, A1AT: Alpha-1 antitrypsin deficiency, IPF: idiopathic pulmonary fibrosis, ILD: interstitial lung disease, CF: cystic fibrosis, FFMI: fat free mass index, LTx: lung transplantation, ECLS: extracorporeal life support, 6MWD: six-minute walking distance, HR: hazard ratio, CI: confidence interval, ref: reference category, y: years, d: days, m: meters, kg: kilograms, N: Newton

Appendix 3 C-statistics

C-statistics of multivariate models	
Outcome	Value
Time to walk independently in the hospital room	0.650
Time to first extubation	0.635
Time to hospital discharge	0.642
Survival	0.597