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Discharge frailty following lung transplantation

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Abstract

Introduction: Frailty at listing for lung transplant has been associated with waitlist and post-transplant mortality. Frailty trajectories following transplant, however, have been less well characterized, including whether recipient frailty improves. The objective of this study was to identify prevalence and risk factors for frailty at discharge and to evaluate changes in frail recipients enrolled in an outpatient physical therapy program.

Methods: This was a single-center prospective cohort study of lung transplant recipients. Enrollees completed a Short Physical Performance Battery (SPPB) to assess frailty at listing and at initial hospital discharge.

Results: Of the 111 enrolled recipients, none were frail at listing and 18 (16.2%) were pre-frail. At discharge, however, 60 (54.1%) patients were frail. Discharge frailty was associated with pre-frailty at listing, acute kidney injury post-transplant, and longer intensive care unit stay. Among the 35 patients who were frail at discharge and who were enrolled in an outpatient PT program, the median improvement in SPPB was 6 points (IQR=5–7 points), and 85.7% became not frail over a median of 6 weeks.

Conclusion: Discharge frailty is common following lung transplantation. In most frail patients, an intensive outpatient physical therapy program is associated with improvement in frailty, as assessed by the SPPB.

Introduction

Frailty is a concept developed in the geriatric literature to capture aging-related deficits across physiologic systems that result in decreased capacity to cope with daily and acute stressors.[1,2] Frailty has been expanded from a geriatric focus to describe a clinically recognizable state of diminished energy balance, sarcopenia, and reduced strength/exertional

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tolerance leading to increased vulnerability, regardless of age.[3] There are many instruments for measuring frailty, ranging from the Rockwood Clinical Frailty Scale, which assess a number of accumulate deficits and disabilities to capture physiologic reserve across disease states, to the Fried Frailty index, which utilizes a combination of self-reported symptoms and physical performance, to the Short Performance Physical Battery (SPPB), which primarily focus on physical performance tests such as gait speed. Regardless of measurement approach, frailty has been identified as a risk factor for poor clinical outcomes, including mortality, in several surgical populations, and has been an area of increased focus in solid organ transplantation, including new consensus guidelines[4–8]

Frailty at listing has been associated with waitlist mortality in liver transplant and day-of-transplant frailty has been associated with post-transplant mortality in kidney transplant as well as increased length of stay.[9–12] Among lung transplant candidates, listing frailty, as measured by the SPPB, has been associated with increased waitlist mortality and death following transplantation.[13,14] There are, however, limited data in lung transplant on frailty trajectories from listing to post-transplant hospitalization discharge, including what fraction of recipients leave the hospital frail. Because it is unclear whether and to what extent frailty is a reversible state once it develops, identifying non-frail candidates who are at risk for leaving the hospital frail is essential for targeted “pre-habilitation” and rehabilitation efforts to reverse or stabilize frailty trajectories.

Similarly, although there is an emerging literature suggesting that frailty in patients with advanced lung disease may be reversible, there are few studies reporting on programs designed to improve frailty in transplant recipients.[15–17]. Understanding the extent to which frail recipients can be rehabilitated is an important starting point in evaluating whether improving frailty ameliorates the associated adverse outcomes. The primary objective of this study was to identify prevalence and risk factors for frailty at transplant hospitalization discharge. The secondary objective was to report subsequent changes in frail recipients enrolled in an intensive outpatient physical therapy (PT) program.

Methods

Study Design and Patient Population

This was a prospective cohort study at the Hospital of the University of Pennsylvania (HUP) from March 1st 2016 through July 1st 2017. Lung transplant recipients, including multi-organ patients, who survived to initial discharge were eligible to participate and those who provided informed consent were enrolled. HUP does not have a specific six-minute walk distance required for listing or maintenance of transplant candidacy. With very rare exceptions, however, our transplant program does not list candidates who are frail (which we define as a SPPB ≤7), requiring instead that they enroll in a rehabilitation program and demonstrate sustained improvement in their SPPB to at least the pre-frail threshold. Candidates who are pre-frail at the time of evaluation are often referred to a local supervised pulmonary rehabilitation program, as are those who are perceived to be at risk for functional decline.

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Listed transplant candidates who acutely worsen and require hospitalization are seen three to five times a week by the inpatient physical therapy service. During these treatment sessions, patients are expected to complete targeted strengthening exercises that focus on their impairments, including improving upper and lower extremity proximal muscle strength (shoulder and pelvic girdle musculature). Interventions include monitored walks (if able), intra-bed cycling, stair and/or stepper training, and lower and upper extremity resistance training with appropriate supplemental oxygen. Alert and interactive patients who require further support such as mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) utilize the MOVEO exercise platform (DJO Global, Dallas, Texas) and/or the MOTOmed Letto II ergometer (RECK-Technik GmbH & Co. KG Medizintechnik, Betzenweiler, Germany). If the candidate can ambulate while on ECMO support, a supervised walking program is initiated.

Following transplantation, patients with prolonged intensive care unit (ICU) stays utilize the MOVEO exercise platform in addition to ambulation with appropriate medical and supplemental oxygen support. Recipients who transition from the ICU to the hospital wards are seen three to five times a week by an inpatient physical therapy team who emphasize progressive functional mobility training, ambulation (including with portable chest tubes), and stair training, with the goal of progressing to a functionally independent level and transitioning to an outpatient pulmonary rehabilitation and PT program. Upon discharge from their index hospitalizations, recipients who are not transferred to an inpatient rehabilitation or long-term acute care (LTAC) facility begin an outpatient post-transplant rehabilitation program at our center. The goal is to begin within 3 days of discharge and all transplant candidates have agreed in advance to reside locally for the duration of the rehabilitation program. Patients typically complete three sessions per week for four to six weeks, customized to meet individual needs.

A licensed physical therapist completes an initial evaluation of strength, range of motion, balance, and flexibility and incorporates any specific patient and family goals. In the first session, resisted manual muscle testing is performed on all major upper and lower extremity muscle groups and hand held dynamometry is assessed in a seated position using the dominant hand. Patients are expected to tolerate 15 minutes of continuous aerobic activity and 30 minutes of intermittent upper and lower extremity resistance and balance training on the first day. Each subsequent visit is closely supervised by a physical therapist and typically lasts between 60 and 75 minutes. Treatment sessions consist of specific muscle strengthening, static and dynamic balance exercises, postural retraining, surgical precaution education, and chest expansion exercises to optimize efficient breathing patterns and facilitate productive coughing. In addition, a respiratory therapist introduces a graded aerobic exercise program, including arm pedals, recumbent or upright bicycle, and treadmill, as appropriate.

Patients use free weights or exercise equipment for strength training. The method of progression is based on the patient's hemodynamic response to activity as well as their perceived exertion. The activity must elicit an aerobic training effect that is 60 to 80% greater than their resting heart rate. The goal level is a moderate level of exercise or a 3/10 on the modified Borg scale. The patient maintains this workload until the activity no longer achieves the desired training effect and the rating of perceived exertion falls below 3/10. At this point, the number of repetitions is increased followed by an increase in the amount of resistance. As the patient nears discharge, education about home exercise frequency, duration, intensity, and safety begins. At the time of discharge from outpatient rehabilitation, each patient receives a personalized home exercise program.

Variable collection

We recorded pre-transplant data including age, sex, native lung disease (pulmonary fibrosis or non-pulmonary fibrosis), most recent six minute walk test distance before transplant, waitlist time, and lung allocation score (LAS) at transplantation. We collected additional variables including whether the patient was hospitalized at transplant, use of ECMO bridge to transplant, procedure type (bilateral or single), the presence of grade 3 primary graft dysfunction at any time point, acute kidney injury (defined as rise in creatinine >20% from baseline), or stroke during the initial hospitalization, the length of ICU and total index hospitalization, and discharge destination, categorized as home or an acute rehabilitation or LTAC facility.

Outcome Measure

During transplant evaluation and shortly before or after discharge, enrolled patients completed a SPPB, a three-component assessment that includes chair stands, gait speed, and balance. The SPPB was chosen as our assessment of frailty because it is used in our program for clinical decisions about transplant candidacy and because it has previously been validated among lung transplant recipients.[13] For research purposes, gait speed was assessed as part of a six minute walk test performed as part of the study protocol. Clinically, patients undergo separate six minute walk tests as part of their transplant evaluation and during post-transplant physical therapy, which are also reported here. The SPPB is scored on a 12 point scale that can be treated ordinally (≤7 points = frail, 8–9 points = pre-frail, 10–12 = not frail) or continuously. These cutoffs were chosen as they are used clinically at our center to define frail and pre-frail patients. The primary study outcome was discharge SPPB≤7. The secondary study outcome was change in SPPB from frail to pre-frail or not frail following outpatient physical therapy.

Statistical analysis

We used simple descriptive statistics to identify percentages, medians, and quartiles for demographic and clinical variables. We used bivariate logistic regression to compare selected demographic and clinical characteristics for patients with and without discharge SPPB≤7. We included all variables with p value < 0.20 in a multivariate logistic regression model to identify predictors discharge SPPB≤7 and reported those that reach statistical significance (p<0.05). Because the SPPB can also be assessed as an ordinal variable, we also constructed a multivariate linear regression model with SPPB treated continuously as the outcome variable. We included all predictors on bivariate linear regression with p value < 0.20 and reported those that reach statistical significance (p<0.05).

All analyses were performed using Stata (Version 15, Stata Corp, College Station, Texas). Study data were collected and managed using Research Electronic Data Capture, an

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electronic data capture tool hosted at HUP.[18] The HUP institutional review board approved this study.

Results

Overall study cohort

Between March 1st 2016 and July 1st 2017 there were 113 patients eligible for study participation, 111 of whom consented to study enrollment. Demographic and clinical characteristics of this cohort are listed in Table 1. None of the patients had a listing SPPB≤7 and only 18 (16.2%) had a SPPB in the pre-frail range (median SPPB of the entire cohort = 11, interquartile range (IQR)=10–12). The median time between listing and transplantation was 44 days and the median LAS at the time of transplant was 42.1. Only 12 (10.8%) patients were on ECMO prior to transplant, although 20 (18.0%) were hospitalized at the time of transplant. The median length of ICU stay was 6 days and the median total length of hospitalization was 18 days. Among recipients whose SPPB was not measured on the day of discharge, the median time to measurement was 3 days (IQR=1–4). The median SPPB at discharge was 7 (IQR 4–9) and 60 (54.1%) patients had a SPPB≤7 at discharge.

Characteristics of patients with discharge SPPB≤7

Comparison of characteristics of patients with and without SPPB≤7 is shown in Table 2. On bivariate analysis, female sex, pulmonary fibrosis native lung disease, shorter six minute walk distance, pre-frail SPPB at listing, LAS, ECMO bridge to transplant, PGD 3, AKI, post-transplant stroke, age, and length of ICU and total hospital stay were associated with discharge SPPB≤7. On multivariate logistic regression, female sex, AKI, length of ICU stay, and pre-frail listing SPPB were associated with discharge SPPB≤7. The same factors were still significant on multivariate linear regression, treating SPPB as a continuous variable (Table 3). On this analysis, length of total hospitalization rather than length of ICU stay was associated with lower SPPB scores at discharge.

Outpatient Physical Therapy Program

Of the study cohort, 83 patients enrolled in the outpatient PT program immediately following discharge (median time to enrollment, 3 days (IQR=1–6) and 28 were discharged to an acute rehabilitation or LTAC facility (Table 1). Among the latter group, 25 (89.3%) were frail with a median SPPB of 3 (IQR=2–5). Discharge frailty was an independent risk factor for discharge to an acute rehabilitation or LTAC facility (odds ratio (OR)=11.4, 95% confidence interval (CI)=3.2–40.9, p<0.001). The majority (82.3%) of recipients discharged to an acute rehabilitation facility, however, went on to the outpatient PT program. Overall, 100 patients (90.1%) completed the PT program. Among those who did not, the most common reason was readmission to the hospital with subsequent medical complications that prevented re-enrollment. The median time to completion of the outpatient program was 5.4 weeks (IQR=4.1–7.0). The median six minute walk distance at the start of the program was 808 feet (IQR 577–1015) compared to 1429 feet (IQR=1179–1600) at completion (p<0.001)

Among the 35 patients who were frail at discharge but who were not discharged to an acute rehabilitation or LTAC facility, the median SPPB was 6 (IQR 4–6). The median time to completion of the outpatient program for these patients was 6.0 weeks (IQR=5.1–7.1). At the time of discharge from outpatient PT, their median SPPB was 12 (IQR=11–12). The median improvement in SPPB was 6 points (IQR=5–7 points) and 85.7% were not frail at completion.

Discussion

In this prospective cohort study of listing and discharge frailty, defined by the Short Performance Physical Battery, we found that 1) more than half of lung transplant recipients who survive to discharge are frail; 2) that female sex, pre-frail SPPB score at listing, acute kidney injury post-transplant, and longer hospital and ICU stay are associated with discharge frailty; 3) that the majority of frail patients who are enrolled in an intensive outpatient physical therapy program become not frail.

A growing body of research has identified frailty as a risk factor for worse outcomes in solid organ transplant, including waitlist and post-transplant mortality, delayed graft function, unplanned readmission, and need for reduced immunosuppression.[9–14,19,20] Our study adds to this literature in two respects. First, we report frailty trajectories among lung transplant recipients who survived to discharge and risk factors for becoming frail during the time from listing to discharge. Second, we demonstrate that frailty, as defined by SPPB, can be reversed in lung transplant recipients following discharge, an area of increased focus given the impact of frailty on adverse post-transplant outcomes.[21]

Because we focused on recipients who survived to discharge, we cannot directly compare the prevalence of frailty in our cohort with other studies in solid organ transplant. Among older adult survivors of a medical ICU admission, almost 80% were frail at discharge, higher than 54.1% of recipients who were frail in our cohort, likely reflecting population and disease differences.[22,23] As with the broader transplant literature, however, we found that frailty was independent of other commonly used measures of functional impairment, including age and six minute walk test.[9–12] Unsurprisingly, patients who were pre-frail at listing were at risk for being frail at discharge, suggesting that there may be role for "pre-habilitation" in preventing discharge frailty.[16] Because we did not assess SPPB on the day of transplantation, however, we do not know whether frailty develops after evaluation but prior to listing, while on the waitlist, or during hospitalization. Although waitlist time was not associated with discharge frailty, periodic SPPB measures for patients awaiting transplant may help identify at-risk patients prior to transplant.

Other factors associated with discharge frailty include female sex, which has been reported in elderly patients but not consistently in solid organ transplant cohorts.[11,12,24–26]. Recipient pulmonary fibrosis was also associated with discharge frailty although this relationship did not persist after adjusting for age.[13] The post-transplant factors associated with frailty were AKI and length of ICU and overall hospitalization. AKI has been associated with worse health related quality of life scores among hospital survivors in multiple populations, although these differences typically resolve at 6 months.[27–29] It may be that AKI is a more general marker of illness and debility. Alternatively, although only three patients in the cohort were discharged on dialysis, impairment in renal function have been associated with

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inflammatory markers such as interleukin 6, which, in turn, have been hypothesized to mediated frailty.[13,30,31] Finally, length of ICU stay was a cumulative risk factor for discharge frailty, with increased risk with increasing days in the ICU.[22] Consistent utilization of inpatient PT, including cycle ergometry and tilt table exercise platforms in non-ambulatory recipients with prolonged ICU stays, may stabilize or improve frailty scores.[32–34]

We found that SPPB improved significantly for most frail recipients during an intensive outpatient program with a median time to completion of 6 weeks. Since enrollment in the outpatient PT program is required at our institution, regardless of degree of frailty, we do not know whether and to what extent frailty scores would improve with less intense PT or simply improve over time without intervention.[35] For example, Venado et al recently reported a median 5 point SPPB improvement among patients who were frail before transplant within the first 6 months after transplant without the use of an intensive outpatient program.[36] Because none of the patients in our cohort were frail at the time of listing, our results are not directly comparable.

Overall, improvements in frailty were similar to those noted in kidney transplant recipients, although occurred in a shorter period of time (5.4 weeks versus 3 months).[37] This may be because of a utilization of a targeted outpatient program or because no frail patients were transplanted in this cohort. We also do not know to what extent outpatient PT simply improved muscle strength (and, thereby, SPPB) without addressing other accumulated deficits that are captured in broader frailty models.[38] While it is important to demonstrate that frailty scores are reversible with a targeted program in lung transplant recipients, we do not know whether improving frailty ameliorates poorer outcomes in this population. For example, many of the frail patients were readmitted to the hospital during their outpatient PT program and were discharged back to the program to complete it. Among the patients whose frailty scores did not improve, the majority were readmitted and eventually discharged to an acute rehabilitation or skilled nursing facility because of ongoing functional impairment and/or medical needs.

Our study has several limitations. First, because this is a single center population, our results may not be generalizable to other centers with a different mix of native lung diseases, different six minute walk requirements for listing and maintenance of candidacy, or different post-transplant PT requirements. In particular, because we only list frail patients only under exceptional circumstances, our cohort may have been more robust than at other centers where the fraction of frail candidates has been reported between 10–28%.[13] Second, we relied on the SPPB for our frailty measure. Although this has been utilized in other solid organ transplant contexts, it is not certain whether other frailty instruments such as the Fried Frailty Index, which we did not utilize, or frailty constructs such as body composition may be more appropriate.[1,39,40] We are currently collecting data on knee extensor strength using a hand-held dynamometer as well as ultrasound assessments of muscle quantity and quality to add information on changes in leg muscle weakness in relationship to SPPB score changes. Third, because our focus was on frailty scores at discharge, we did not report outcomes among patients who were frail at the time of transplant. Additional data are necessary to evaluate how frailty at the time of listing should be considered in lung allocation and in candidacy decisions.

Conclusions

Discharge frailty is common following lung transplantation. In select frail patients, an intensive outpatient PT program is associated with improvement in frailty and frailty scores, as assessed by the SPPB.

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Table 1.

Characteristics of study cohort (n=111).

Age, median (IQR) yr	57 (44–64)
Age>60, n(%)	40 (36.0%)
Male, n(%)	64 (57.7%)
Pulmonary fibrosis, n(%)	65 (58.6%)
Time from frailty assessment to listing, median (IQR) d	57 (35–122)
Waitlist time, median (IQR) d	44 (14–112)
Most recent 6 minute walk before transplant, median (IQR) ft	1030 (745–1273)
LAS, median (IQR)	42.1 (36.3–56.0)
Hospitalized at transplant, n(%)	20 (18.0%)
ECMO bridge to transplant, n(%)	12 (10.8%)
Bilateral, n(%)	88 (79.3%)
PGD grade 3, n(%)	16 (14.4%)
Acute kidney injury post-transplantation, n(%)	53 (47.7%)
ICU length of stay, median (IQR) d	6 (3–13)
Post-transplant stroke, n(%)	8 (7.2%)
Length of hospitalization, median (IQR) d	18 (13–26)
SPPB on transplant assessment, median (IQR)	11 (10–12)
SPPB in pre-frail range on listing, n(%)	18 (16.2)
SPPB at discharge, median (IQR)	7 (4–9)
Tandem balance score, median (IQR)	3 (2–3)
Sit to stand score, median (IQR)	2 (1–3)
Gait speed score, median (IQR)	2 (1–4)
Discharge SPPB ≤7, n(%)	60 (54.1%)
Initial discharge to acute rehabilitation or LTAC facility, n(%)	28 (25.2%)

ECMO=extracorporeal membrane oxygenation; ICU=intensive care unit; IQR=interquartile range; ft=feet; LAS=lung allocation score; LTAC=long term acute care; PGD=primary graft dysfunction; SPPB=short performance physical battery

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Table 2.

Predictors of discharge frailty, as defined by Short Performance Physical Battery score≤7 (n=111)

	Bivariate					Multivariate				
Variable	**OR**	**95% CI**	**95% CI**	**p**		**OR**	**95% CI**	**95% CI**	**p**	
Female sex	3.23	1.45	7.17	0.004		8.65	1.42	52.80	0.02	
Pulmonary fibrosis	3.33	1.51	7.34	0.003						
Pre-frail SPPB at listing	9.2	3.21	26.36	<0.001		12.51	1.07	167.03	0.04	
6MW prior to transplant, per 100 feet	0.78	0.69	0.88	<0.001						
LAS at transplant	1.03	1.01	1.05	0.01						
ECMO bridge to transplant	2.82	0.72	11.05	0.14						
PGD 3	16.33	2.07	128.70	0.008						
AKI	4.77	2.12	10.78	<0.001		7.88	1.45	42.95	0.02	
Post-transplant stroke	6.60	0.78	55.60	0.08						
Length of ICU stay	1.21	1.10	1.34	<0.001		1.29	1.01	1.64	0.04	
Length of hospitalization	1.15	1.07	1.24	<0.001		1.12	1.00	1.26	0.05	
Age	1.02	1.00	1.06	0.04						
Age>60	1.24	0.57	2.71	0.58						
Waitlist time, per month	0.99	0.94	1.04	0.65						
Hospitalized at transplant	1.73	0.63	4.76	0.28						
Bilateral transplant	1.10	0.44	2.76	0.84						

6MW=six minute walk; AKI=acute kidney injury; ECMO=extracorporeal membrane oxygenation; ICU=intensive care unit; LAS=lung allocation score; PGD=primary graft dysfunction

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Table 3.

Predictors of discharge frailty, as defined by Short Performance Physical Battery score, treated continuously (n=111)

	Bivariate					Multivariate				
	Exp Coeff	95% CI	95% CI	p		Exp Coeff	95% CI	95% CI	p	
Female	5.39	1.67	17.36	0.005		3.48	1.32	9.16	0.01	
Pulmonary Fibrosis	6.16	1.92	19.79	0.003						
Pre-frail SPPB at listing	22.00	6.98	69.36	<0.001		4.81	1.07	21.62	0.04	
6MW prior to transplant, per 100 feet	0.73	0.64	0.84	<0.001						
LAS at transplant	1.06	1.04	1.10	<0.001						
Hospitalized at transplant	7.78	1.71	35.15	0.008						
ECMO bridge to transplant	15.84	2.47	101.5	0.004						
PGD 3	23.03	4.62	114.78	<0.001						
AKI	11.37	3.72	34.74	<0.001		3.61	1.42	9.19	0.007	
Post-transplant stroke	14.88	1.55	142.57	0.02						
Length of ICU stay	1.04	1.02	1.06	<0.001						
Length of hospitalization	1.05	1.03	1.06	<0.001		1.06	1.01	1.12	0.02	
Age	1.05	1.01	1.09	0.02		1.04	1.00	1.09	0.05	
Age>60	1.17	0.34	4.11	0.79						
Waitlist time, per month	0.99	0.91	1.07	0.75						
Bilateral transplant	1.43	0.33	6.25	0.63						

6MW=six minute walk; AKI=acute kidney injury; ECMO=extracorporeal membrane oxygenation; ICU=intensive care unit; LAS=lung allocation score; PGD=primary graft dysfunction