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Frailty Trajectories in Adult Lung Transplantation: A Cohort Study

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Abstract

Background: Frailty is common in adults with end-stage lung disease and is associated with death before and after lung transplantation. We aimed to determine whether frailty changes from before to after lung transplant.

Methods: In a single-center prospective cohort study among adults undergoing lung transplantation from 2010–2017, we assessed frailty by the Short Physical Performance Battery (SPPB) (higher scores reflect less frailty) and Fried Frailty Phenotype (FFP) (higher scores reflect greater frailty) before and repeatedly up to 36 months after transplant. We tested for changes in frailty scores over time using segmented mixed effects models, adjusting for age, sex, and diagnosis. We quantified the proportion of subjects transitioning between frailty states (frail versus not frail) from before to after transplant.

Results: In 246 subjects, changes in frailty occurred within the first 6 post-operative months and remained stable thereafter. The overall change in frailty was attributable to improvements amongst those subjects who were frail before transplant. They experienced a 5.1-point improvement in SPPB (95% confidence interval [CI]: 4.6, 5.7) and a 1.8-point improvement in FFP (95% CI: −2.1, −1.6) during the early period. Frailty by SPPB and FFP did not change in those who were not frail

before transplant. Approximately 84% of survivors who were frail before transplant became not frail after transplant.

Conclusions: Pre-operative frailty resolves in many patients after lung transplantation. Because a large proportion of frailty may be attributable to end-stage lung disease, frailty alone should not be an absolute contraindication to transplant.

Keywords

Frailty; lung transplant; Short Physical Performance Battery; Fried Frailty Phenotype

Introduction

Lung transplant has become an established treatment for advanced chronic lower respiratory diseases, conditions that comprise the third leading cause of mortality in the United States[1]. Lung transplant aims to extend survival[2], improve health-related quality of life (HRQL)[3] and relieve disability in patients with end-stage lung disease. These patients can be extremely ill by the time of transplant consistent with Lung Allocation Score (LAS) prioritization of candidates with the highest risk of waitlist mortality[4].

Frailty, which is particularly relevant to persons with advanced disease awaiting transplant, is a syndrome of decreased reserve and resistance to stressors, resulting from an accumulation of physiologic deficits and leading to increased vulnerability to adverse outcomes[5]. The syndrome of frailty was initially defined in community-dwelling older populations in the late 1990s[6] and early 2000s[5]. Since then, frailty has been found to be prevalent and associated with mortality in solid-organ transplant populations, including lung transplant[7][8,9].

Recently, investigators showed that pre-operative frailty scores are dynamic following kidney and liver transplantation[10,11]. The dynamics of change in frailty following lung transplantation, however, remain unknown, and may differ from that of other solid organ transplants. Conceptually, if advancing lung disease contributes disproportionately to physical frailty, frailty could be expected to improve, at least partially, after transplant. On the other hand, persons with end-stage lung disease may have other major contributors to frailty, such as sarcopenia, and thus could be particularly vulnerable to the stress of surgery, which may worsen frailty after transplant. Moreover, there is active debate as to whether or not pre-operative frailty constitutes a contraindication to lung transplantation. The purpose of our study was to determine the trajectory of frailty after lung transplant and identify specific pre-operative characteristics that impact changes in frailty.

Methods

Study design, participants, and setting

We studied participants in the "Breathe Again" study, a prospective cohort of adults undergoing first-time lung transplantation between 2010 and 2017 at the University of California, San Francisco[12] assessing the impact of lung transplant on functional status, disability, and HRQL. We assessed measures of physical frailty at the time of transplant

listing and repeatedly up to three years after transplant on the same days as routinely scheduled clinical visits (at 3-, 6-, 12-, 18-, 24-, 30-, and 36-months post-transplant). This analysis is limited to Breathe Again participants who had frailty assessed before transplant and at least one time after transplant (Table 1).

Frailty measures and assessments of change from before to after transplant

We measured physical frailty in two ways. Since the start of Breathe Again in 2010, we quantified frailty by the Short Physical Performance Battery (SPPB)[6], an aggregate score of three components of lower extremity function: gait speed, balance, and standing up from a seated position. Each component is scored on a 0–4 point range, summing to 0–12 point range. Lower values reflect worse frailty. A 1-point change in the score is clinically meaningful[13]. Consistent with other research, we defined a score 7 as frail and a score of 8–12 as "not frail"[6,14].

In 2012, we added the Fried Frailty Phenotype (FFP)[5] as a second frailty measure to the Breathe Again protocol. The FFP evaluates five components: weakness, slowness, exhaustion, shrinking, and low activity level. One point is assigned to each component present, yielding a summary range of 0–5 points. Higher scores reflect worse frailty. We defined a score 3 as frail and a score of 0–3 as "not frail"[5,14].

Since frailty can be evaluated on numeric scale or dichotomized as a binary classification (frail versus not frail), we evaluated change in frailty from before to after transplant in two different ways. First, we evaluated absolute change on a numeric scale. Next, we evaluated transitions between frailty states. Subjects who were frail before transplant either could remain so or could become not frail after transplant. Similarly, subjects who were not frail before transplant could remain so or become frail after transplant.

Analytic Approach

We tested differences in selected characteristics by baseline frailty state (frail vs. not frail) using the Student's t-test (accounting for unequal variance), chi-square, or Fisher's exact test, as appropriate. To avoid the assumption of a linear change in frailty from before to after transplant, we used cubic splines to visualize the changes in frailty scores over time. For both the SPPB and FFP, the cubic spline plots showed that the changes were not linear. The plots suggested an inflection point at six months after transplant that defined two distinct time frames: an "early period" from before transplant to six months after transplant in which frailty scores changed substantially, and a "late period" from six months through 36-months after transplant, a period during which frailty scores remained stable (Figure 2). To confirm the "cutpoint" at 6 months after transplant versus other possibilities (*e.g.*, 12 or 18 months), we fit linear mixed effects models considering subject and study visit as random effects, followed by contrast of SPPB and FFP scores between different study visits. There was a statistically significant change in SPPB and FFP scores during the early period and not during the late period. (Supplement Table 1).

To assess the magnitude of the change in frailty scores from before to after transplant, we used mixed effects models considering individual subjects and time as random effects, using an unstructured correlation. Given the non-linearity of frailty change noted above, we fit

segmented regressions for the early and late periods, and compared the slopes of frailty score change in the two periods. Since the maximum likelihood methods to fit mixed effects models provide protection against bias due to missing values, we did not impute values for missing frailty scores[15]. We subsequently adjusted the models for diagnosis group as is standard in lung transplant registry data: A=obstructive lung disease, e.g., chronic obstructive pulmonary disease (COPD); B=pulmonary vascular disease, e.g., pulmonary arterial hypertension (PAH); C=cystic fibrosis (CF) and immunodeficiency disorders; and D=restrictive lung disease, e.g., interstitial lung disease (ILD)[16]. We also included in the models age at transplant and sex[17].

Based on prior literature and biologic plausibility[5,14,18,19], we tested for interactions between change in frailty with pre-operative frailty state, diagnosis, sex, and age. Testing for an interaction between change in frailty with pre-operative frailty state (frail vs not frail) was important to account for a potential ceiling effect in which non-frail subjects may have little room for improvement. Where there was a statistically significant test for interaction for a pre-operative characterize, we carried out relevant stratified analyses.

Finally, we assessed the proportion of subjects who transitioned between frailty states from before to six months after transplant. Recognizing that one year post-transplant survival is an important metric[16,20], we also quantified the proportion transitioning frailty states from before up to one year after transplant. As a second sensitivity analysis, we also retained fatalities who were not frail prior to death by assigning those persons a transition to a frail state.

Results

Among the 276 subjects who underwent lung transplant, 246 (89%) underwent baseline pre-transplant frailty assessments and formed the cohort for analysis (244 subjects with SPPB, 162 with FFP, and 160 with both). Fewer subjects had FFP because this measure was introduced two years after study initiation [Table 1 and Figure 1]). The mean time from baseline SPPB assessment to transplant was 76 days (range 0 to 441 days) with median of 53 days (IQR: 21 to 107 days). The mean time from baseline FFP assessment to transplant was 95 days (range 0 to 769 days) with median of 68 days (IQR: 31 to 115 days). Demographic and clinical characteristics of the study population are detailed in Table 2. The median age at transplant was 59 years (Interquartile Range [IQR]: 49–66); median LAS was 45 (IQR, 37–65); and 56% were male. The most common indication for transplant was restrictive (72%) followed by obstructive (15%) lung disease. Median follow-up was 2.4 years post-transplant (IQR: 1.0–3.4). Before transplant, the prevalence of being frail by SPPB was 23% (n=55) and by FFP, 43% (n=69).

Change in Short Physical Performance Battery

During the early period (before transplant up to six months after transplant), SPPB frailty improved by 1.2 points in unadjusted and adjusted analyses (95% CI: 0.9 to 1.6; and 0.9 to 1.6, respectively). There were statistically significant interactions between change in SPPB and pre-operative frailty (p <0.0001) and a diagnosis of PAH (p =0.03). SPPB improved 5.1-points in SPPB (95%CI: 4.6, 5.7) in subjects who were frail before transplant, whereas it

remained stable among those who were not frail (change 0.2, 95%CI: -0.2, 0.5) (Table 3, Figure 3A, Supplement figure 1A). SPPB did not change in subjects with PAH (−0.4 points, 95%CI: −2.0, 1.2), whereas it improved in subjects with ILD by 1.5 points (95%CI: 1.1, 1.8), and demonstrated a trend towards improvement in subjects with COPD and CF (0.7 points, 95%CI: −0.1, 1.6; and 0.8 points, 95%CI: −0.4, 2.0, respectively) (Table 3, Supplement figure 2A).

During the late period (six through 36-months post-transplant), SPPB frailty generally remained stable and without statistically significant change (unadjusted change 0.2, 95%CI: −0.2 to 0.6; and adjusted change 0.2, 95%CI: −0.2 to 0.6). The change was similar among subjects who were frail versus not frail before transplant (change 0.2, 95% CI: −1.0, 0.6; and 0.3, 95% CI: −0.1, 0.7, respectively) (Table 3, Figure 3A, Supplement Figure 1A). There was a statistically significant interaction between SPPB change in the late period and a diagnosis of PAH (p=0.008). SPPB improved by 2.5 points in subjects with PAH (95% CI: 0.5, 4.5), whereas it remained stable in those with other diagnoses (Table 3, Supplement figure 2A). Notably, our cohort had only 11 subjects with World Health Organization group I PAH: four associated with connective tissue disease, two idiopathic, two associated with congenital heart disease with Eisenmenger's syndrome, one with pulmonary veno-oclusive disease, one with hereditary hemorrhagic telangiectasia, and one induced by drugs. Of the 11 subjects, one was frail before transplant, improved (SPPB 1 to 10) by three months and subsequently dropped out of the study. The other subject who was frail before transplant improved (SPPB 5 to 8) by six months. Among the nine subjects who were not frail before transplant, six -including those with Eisenmenger's syndrome- remained stable. Two of the subjects who were not frail before transplant declined (SPPB 10 to 0, and 12 to 9) by six months after transplant but then improved by 18 months (SPPB 0 to 11, and 9 to 10). The study period ended before the last of the nine subjects who were not frail before transplant could be reassessed.

Finally, we determined the proportion of subjects transitioning between frailty states. Of the 37 subjects who were frail by SPPB before transplant, 31 (84%) became not frail by six months after transplant. Among the 155 subjects who were not frail before transplant, 148 (95%) remained not frail (Figure 4A). Six subjects missed the six-month frailty assessment due to intervening mortality. Reanalysis treating death as equivalent to being frail yielded similar results. The proportions in such transitions were similar one year after transplant (supplement figure 3A).

Change in Fried Frailty Phenotype

During the early period (up to six months), FFP frailty declined (i.e., less frail) by an average of 0.9 points (95%CI: −1.0 to −0.7, and 95%CI: −1.0 to −0.7, in unadjusted and adjusted analysis, respectively). There were statistically significant interactions between pre-operative frailty (p<0.0001) and a diagnosis of PAH (p=0.031) with the change in FFP. FFP improved by 1.8-points (95%CI: −2.1, −1.6) in subjects who were frail before transplant, whereas it remained stable (change −0.2, 95%CI: −0.4, 0.1) in those who were not frail before transplant (Table 3, Figure 3B, Supplement Figure 1B). FFP did not change in subjects with PAH (change −0.03, 95%CI: −0.8, 0.8), whereas it improved to a similar

degree in subjects with ILD (change −0.9, 95%CI: −1.1, −0.7), COPD (change −0.8, 95%CI: −1.3, −0.3), and CF (change −1.2, 95%CI: −1.9, −0.4) (Table 3, Supplement figure 2B).

During the late period (later than 6 months), FFP frailty remained stable (change −0.1; 95% CI: −0.4 to 0.1 in unadjusted analysis and change −0.1, 95%CI: −0.4 to 0.1 in adjusted analysis). There was no statistically significant change in FFP among subjects who were frail and not frail before transplant (change −0.3, 95% CI: −0.5 to 0.01, and −0.1, 95% CI: −0.4 to 0.2, respectively) (Table 3, Figure 3B, Supplement Figure 1B). There was no statistically significant change in FFP among subjects with any specific diagnoses (Table 3, Supplement figure 2B).

Finally, of the 51 recipients who were frail before transplant, 43 (84%) transitioned to not frail 6 months after transplant. Among the 61 recipients who were not frail before transplant, 57 (93%) remained not frail (Figure 4B). Three subjects missed the six-month frailty assessment due to death. Treating death as equivalent to being frail yielded similar results. These proportions were similar at 1-year after transplant (Supplement Figure 3B).

Discussion

In this longitudinal cohort study of frailty trajectories in lung transplantation, we found that frailty, defined by both the Short Physical Performance Battery (SPPB) and the Fried Frailty Phenotype (FFP), improved to a clinically meaningful extent early after transplant and remained stable thereafter. Most notably, the majority of subjects who were frail before lung transplantation no longer met frailty criteria by either measure six months after transplantation. Our study suggests that, for the majority of subjects undergoing lung transplantation, a substantial proportion of pre-transplant frailty may be attributable to end-stage lung disease, although there may be interactions between frailty and selected sub-groups of disease. Our work adds to the growing body of evidence that frailty attributable to end-stage organ disease may be reversible once the function of the failing organ is restored. [10,21].

The reasons for the improvement in frailty measures following lung transplantation are unclear. Possible mechanisms–some speculative and others better characterized–reflect the many pathobiological processes leading to frailty that could plausibly improve after lung transplantation. For example, systemic inflammation, characterized by higher serum biomarker levels of IL-6, IL-8, TNF-α, C-reactive protein (CRP) and fibrinogen is one putative cause of frailty in community dwelling older adults[22–25]. COPD is also a systemic inflammatory disease, characterized by these same elevated biomarkers[26,27], and is also associated with decreased muscle strength[28], sarcopenia[29–31], and malnutrition[29]. In lung transplant candidates, we showed that those who are frail have higher levels of IL-6 and TNF-receptor 1, and cachexia (lower levels of leptin) when compared to candidates who are not frail[14]. Sarcopenia, defined as pathologically low muscle mass and function[32], is another component of frailty among community dwelling older adults[33]. Sarcopenia reflects age-related loss of muscle mass, reduced muscle quality and loss of functional strength[34]. Aging induces a state of anabolic resistance characterized by altered mTOR signaling, leading to reduced muscle protein synthesis in response to nutrition and exercise[35–37]. Disuse atrophy,

the unloading of muscles that leads to an imbalance between protein synthesis and degradation[38,39], is another cause of frailty, particularly in older individuals[40]. One of the mechanisms by which exercise, the opposite of disuse, prevents muscle atrophy is by inhibiting the expression of myostatin, a member of the transforming growth factor-β superfamily that suppresses muscle growth[41]. Inactivity, chronic hypoxia and cigarette smoke exposure, prevalent in many patients with end-stage lung disease, are known inducers of myostatin[42] that could cease after transplantation. Patients hospitalized for pulmonary exacerbations often have negative nitrogen balance that could result from unmet high energy or protein requirements and/or steroids, leading to loss of lean tissue and energy[43]. The catabolic state associated with pulmonary exacerbations could also improve after lung transplant. While currently speculative, investigation into these potential mechanisms and others (*i.e.*, malnutrition[44], cognition[45] and endocrine dysregulation[46]) are ongoing.

Our observation that SPPB frailty does not change in the early period and improves in the late period late in subjects transplanted for PAH should be interpreted cautiously due to the small sample size. Two subjects who were frail prior to transplantation had clinically and statistically significant improvement in SPPB during the early period. Two other subjects who were not frail had a similarly significant worsening in SPPB during the early period that subsequently recovered. These latter two subjects experienced complicated perioperative courses, including primary graft dysfunction. It is possible that post-operative critical illness led to the development of frailty[47,48]. Further studies are needed to determine whether patients with PAH truly are at risk for delayed improvement in frailty. If the risk for delayed improvement is true, one potential—albeit speculative-- mechanism could be ongoing recovery of maladaptive cardiac remodeling after lung transplantation. The increased pulmonary vascular resistance in PAH exposes the right ventricle (RV) to chronic pressure overload resulting in myocardial stiffening and fibrosis[49]. In patients undergoing lung transplantation for PAH with RV dysfunction and inadequate ventricular-vascular coupling, cardiac magnetic resonance imaging has demonstrated RV function and morphology recovery can take years[50]. Further, in patients with heart failure undergoing Ventricular Assist Device placement or heart transplantation, improvement in FFP frailty occurred over a span of 88–457 days[21].

We found no significant interaction between age and change in frailty after lung transplantation. This finding challenges a common clinical concern that transplanting older individuals will inevitably result in frailer recipients. Further, our findings need to be considered within the context of emerging literature showing that pre-operative frailty is associated with death before[14,51] and after[52,53] lung transplantation, and that frailty at the time of discharge following lung transplant surgery is associated with increased risk of unplanned rehospitalization[54].

Notably, a national survey of solid-organ transplant physicians, surgeons, and allied health professionals sponsored by the American Society of Transplantation in 2017 found that 93% of the respondents believe that frailty should be incorporated into the selection process for transplant candidates. Over 95% of respondents consider frailty useful in evaluating transplant candidacy, 23–44% routinely perform a standardized frailty assessment as part of the transplant candidacy evaluation, and 67–91% think frailty should be used to influence

decisions regarding the timing of transplantation[55]. These data suggest that frailty is already being incorporated into clinical decision making. Our findings argue that until we are better able to distinguish frailty that results in increased mortality risk from frailty attributable to advanced lung disease that will reverse after transplantation, frailty in and of itself should not be considered an absolute contraindication to transplant. Rather, our findings lend some support to the practice of carefully listing for transplant those–even older–candidates who are mostly not frail or for whom the reversal of frailty might be possible for transplant.

That pre-operative frailty reverses in the majority of subjects undergoing lung transplantation underscores the importance of distinguishing frailty that is attributable to lung disease and will improve with transplant from frailty that will identify candidates at high risk of death[14,51–53]. Doing so, either through clinical, biomarker, or imaging-based measures of non-pulmonary attributable frailty, is critical to improving risk-stratification of lung transplant candidates without denying transplant to those who will benefit[56]. In addition, whether pre-operative frailty can be improved with targeted rehabilitation and nutrition interventions is an area of active investigation[57]. Additional work is also needed to differentiate why frailty did not improve and even worsened in some lung transplant recipients.

Our study has several limitations. Most notably, we only studied patients already listed for lung transplantation. As such, our cohort represents a selected sub-group of patients with advanced lung disease. We cannot take into account the complex clinical decision making involved placing a patient on the waitlist in the first place. Thus, caution is warranted when extrapolating our findings to all patients with advanced lung disease presenting for evaluation for lung transplantation. Our study was conducted in a single center with a relatively limited number of persons who underwent transplant for condition groups other than restrictive disease. This limits the robustness of the effect estimates and study power for stratified analyses and may limit the generalizability of our findings to clinical populations with a different diagnostic mix. Further, although we repeatedly measured frailty after transplant, estimates of the changes in frailty might have been different with different sampling time frames.

Despite these limitations, our study has several strengths. Our prospective, longitudinal cohort had repeated measures of frailty over years of follow-up in a moderately large sample size. This allowed us to investigate how frailty changes from before to after lung transplantation within individuals and across clinically relevant strata. Also, we used two, well-established measures of physical frailty that have been validated in community-dwelling older adults as well as solid-organ transplant populations. That our findings were generally consistent across both measures supports the finding that frailty improves in the majority of adults undergoing lung transplantation.

In conclusion, we found that frailty rapidly improves following lung transplantation for most patients. Therefore, despite the known association between pre-operative frailty and mortality, frailty alone should not be an absolute contraindication for transplant. Work is needed to distinguish frailty that can be attributed to be lung disease and that will improve from frailty that is extra-pulmonary and may identify patients at high risk for poor outcomes.

Addressing frailty before transplantation represents a major opportunity to improve outcomes in lung transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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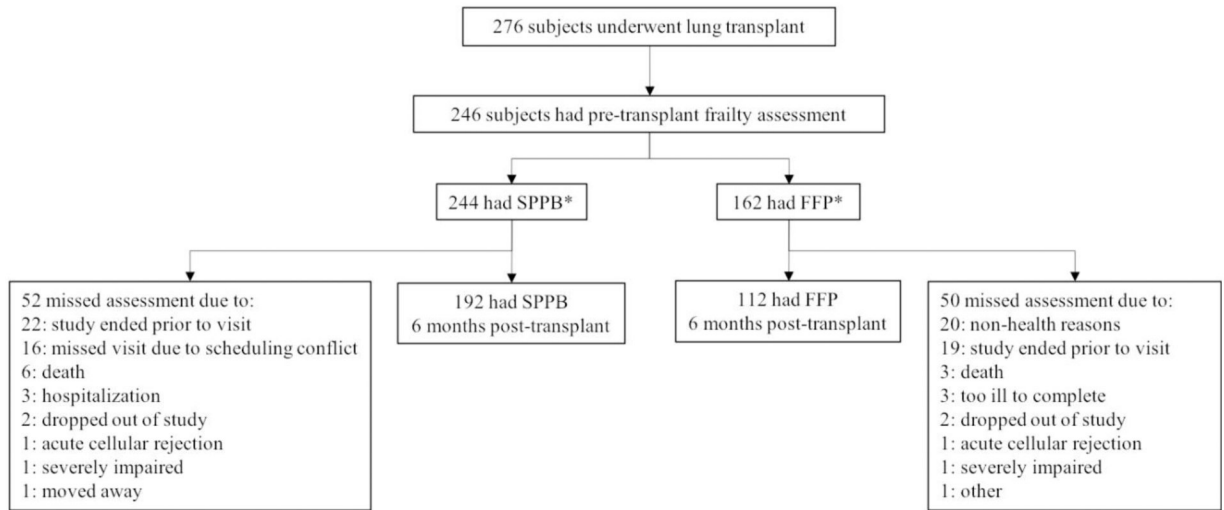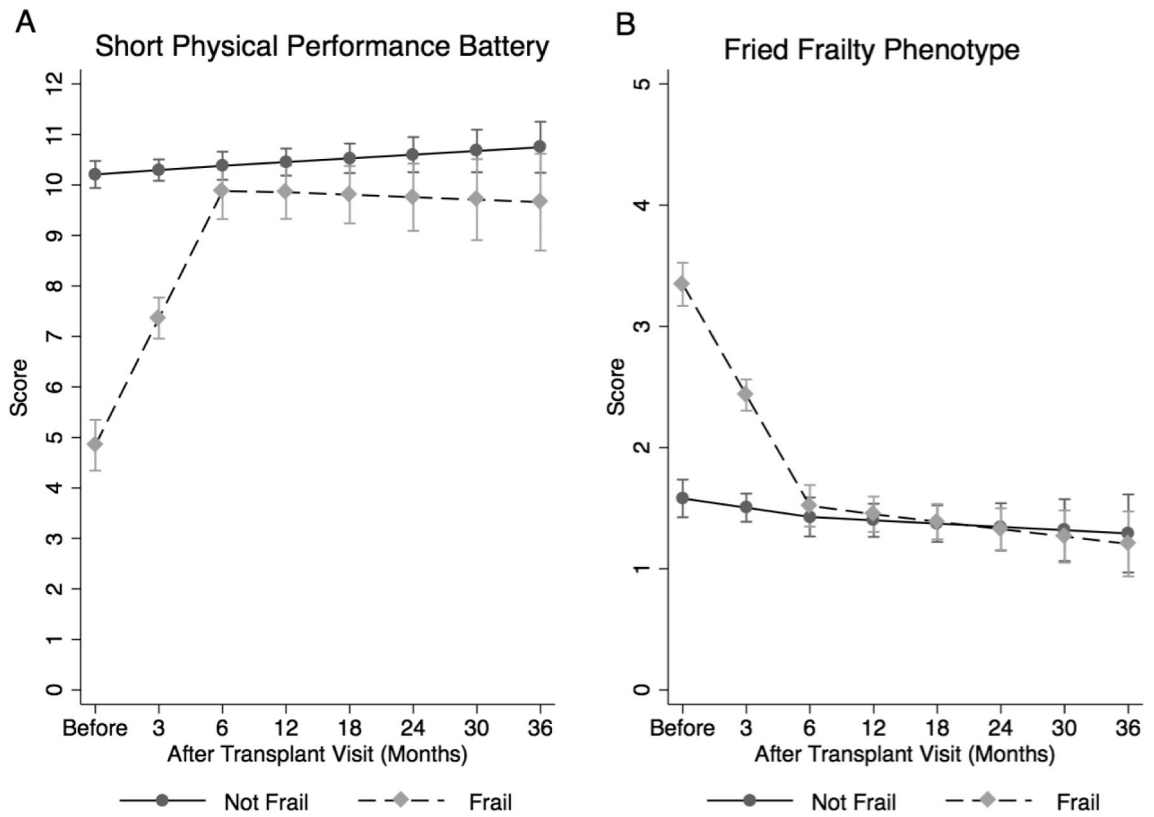
Figure 1.
Participants with frailty assessments before and six months after lung transplant. The Short Physical Performance Battery (SPPB) was collected from the start of the study in 2010. The Fried Frailty Phenotype (FFP) was added to the study protocol in 2012. * Some subjects had both frailty measures performed; the numbers are not mutually exclusive.
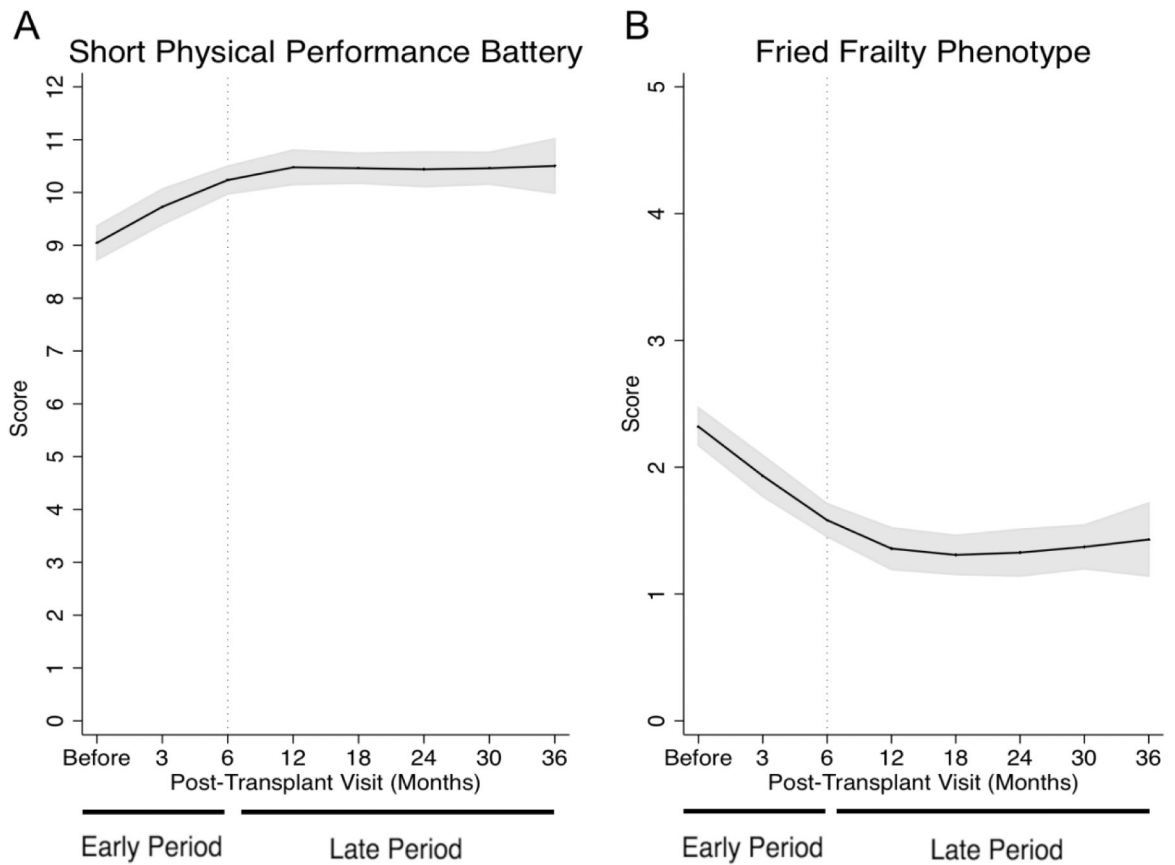
Figure 2.
Frailty Change After Lung Transplant. Cubic spline plots of the change in Short Physical Performance Battery (A) and Fried Frailty Phenotype (B) from before to after lung transplant. There is an inflection point at 6 months after transplant that defines an "early period" of frailty change followed by a "late period" of stability. The shaded bands represent the 95% confidence intervals.

The SPPB ranges from 0 to 12, a score ⩽ 7 is considered frail. The FFP ranges from 0–5, a score ⩾ 3 is considered frail.

Figure 3.
Change After Lung Transplant by Pre-transplant Frailty State. Change in Short Physical Performance Battery (SPPB) (A) and Fried Frailty Phenotype (FFP) (B) in segmented regressions for the "early period" (before transplant to six months after transplant) and "late period" (six months to 36 months after transplant). The model is adjusted for pre-transplant frailty state (not frail vs frail), pre-transplant frailty state by time period (early vs late), diagnosis, age, and sex. The estimated scores with 95% confidence intervals are shown. The SPPB ranges from 0 to 12, a score 7 is considered frail. The FFP ranges from 0–5, a score 3 is considered frail.
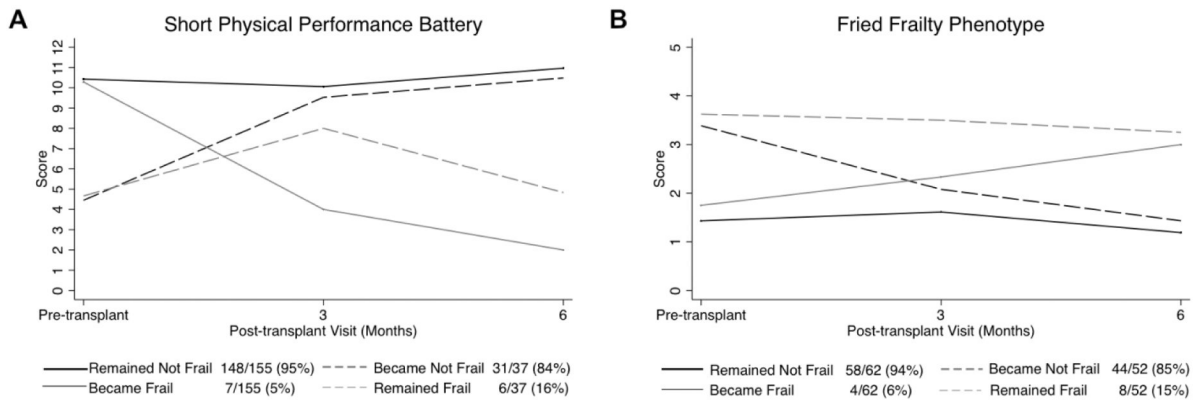
Figure 4.
Transitions of Frailty State from Before to After Lung Transplant.
Proportion of subjects who transitioned between frailty state from before to six months after lung transplant when assessed by Short Physical Performance Battery (SPPB) (A) and Fried Frailty Phenotype (FFP) (B). The SPPB ranges from 0 to 12, a score ≤ 7 is considered frail. The FFP ranges from 0–5, a score ≥ 3 is considered frail.

Table 1.

Participants with frailty assessments before and after lung transplantation

Assessment time point	SPPB only	FFP only	SPPB and FFP	Total SPPB	Total FFP
Pre-transplant	84	2	160	244	162
3 mo post-transplant	63	4	98	161	102
6 mo post-transplant	85	5	107	192	112
12 mo post-transplant	78	4	89	167	93
18 mo post-transplant	67	6	68	135	74
24 mo post-transplant	73	1	49	122	50
30 mo post-transplant	50	0	32	82	32
36 mo post-transplant	42	0	36	78	36

The Short Physical Performance Battery (SPPB) was collected from the start of the study in 2010. The Fried Frailty Phenotype (FFP) was added to the study protocol in 2012.

Table 2

Comparison of Baseline Pre-Transplant Characteristics by Frailty Status

	Short Physical Performance Battery (N = 244)			Fried Frailty Phenotype (N = 162)		
	Not Frail	Frail	P value	Not Frail	Frail	P value
No. of subjects	189 (77%)	55 (23%)		93 (57%)	69 (43%)	
Male	113 (60%)	26 (47%)	0.09	65 (70%)	36 (52%)	0.02
Age			0.61			0.87
< 35 years	13 (7%)	5 (9%)		4 (4%)	5 (7%)	
35–49 years	34 (18%)	9 (16%)		18 (19%)	12 (17%)	
50–64 years	86 (46%)	29 (53%)		42 (45%)	31 (45%)	
65 years	56 (30%)	12 (22%)		29 (31%)	21 (30%)	
Diagnosis			0.96			0.74
A (e.g. COPD)	29 (15%)	7 (13%)		11 (12%)	10 (14%)	
B (e.g. PAH)	9 (5%)	2 (4%)		6 (6%)	3 (4%)	
C (e.g. CF)	16 (8%)	4 (7%)		5 (5%)	6 (9%)	
D (e.g. IPF)	135 (71%)	42 (76%)		71 (76%)	50 (72%)	
BMI (kg/m^2)	26 ± 4	25 ± 4	0.65	27 ± 4	25 ± 4	<0.01
FEV1 % predicted	47 ± 20	49 ± 23	0.53	49 ± 20	48 ± 21	0.82
6 MWD (m)	286 ± 124	126 ± 127	<0.01	286 ± 137	244 ± 120	0.04
LAS at transplant	48 ± 17	69 ± 23	<0.01	47 ± 17	59 ± 22	<0.01
Transplant type			0.89			0.36
Bilateral	174 (92%)	51 (93%)		84 (90%)	61 (88%)	
Single	12 (6%)	4 (7%)		9 (10%)	6 (9%)	
Heart/Lung	3 (2%)	0 (0%)		0 (0%)	2 (3%)	
Inpatient at transplant	40 (21%)	37 (67%)	<0.01	18 (19%)	27 (39%)	<0.01
Ventilator at transplant	12 (6%)	7 (13%)	0.15	4 (4%)	6 (9%)	0.33
ECMO at transplant	8 (4%)	8 (15%)	0.01	3 (3%)	4 (6%)	0.46

Results presented as number of patients (percentage) or mean ± standard deviation.

COPD=Chronic Obstructive Pulmonary Disease, PAH=Pulmonary Arterial Hypertension, CF=Cystic Fibrosis, IPF=Idiopathic Pulmonary Fibrosis, BMI=Body Mass Index, FEV1=Forced Expiratory Volume in the first second, 6 MWD=Six Minute Walk Distance, LAS=Lung Allocation Score, ECMO=Extracorporeal Membrane Oxygenation.

Of the eleven subjects in whom SPPB assessments were done prior to initiation of ECMO support, seven were not frail (SPPB range 8–12) and four were frail (SPPB range 0–7). Of the five subjects in whom SPPB assessments were done on ECMO support, one was not frail (SPPB = 8) and four were frail (SPPB range 0–6). Of the six subjects in whom FFP assessments were done prior to initiation of ECMO support, three were not frail (FFP range 1–2) and three were frail (FFP range 3–4). In one subject FFP assessment was done on ECMO support; the subject was deemed frail by both measures (FFP = 3 and SPPB = 6).

Table 3.

Frailty Change from Before to After Lung Transplant by Pre-Transplant Characteristics

Model by Pre-transplant Characteristics		N	Short Physical Performance Battery (N=244)			N	Fried Frailty Phenotype (N=162)		
			Pre-transplant Score	Change during Early Period	Change during Late Period		Pre-transplant Score	Change during Early Period	Change during Late Period
1	Frail	55	5.1 (4.6, 5.7)	5.0 (4.4, 5.7)	−0.2 (−1.0, 0.6)	69	3.2 (2.9, 3.4)	−1.8 (−2.1, −1.6)	−0.3 (−0.5, 0.01)
	Not frail	189	10.5 (10.1, 10.9)	0.2 (−0.2, 0.5)	0.3 (−0.1, 0.7)	93	1.4 (1.2, 1.6)	−0.2 (−0.4, 0.1)	−0.1 (−0.4, 0.2)
2	Group A (COPD)	36	9.4 (8.6, 10.3)	0.7 (−0.1, 1.6)	−0.5 (−1.5, 0.6)	21	2.4 (1.9, 2.8)	−0.8 (−1.3, −0.3)	−0.3 (−1.0, 0.4)
	Group B (PAH)	11	9.9 (8.3, 11.4)	−0.4 (−2.0, 1.2)	2.5 (0.5, 4.5)	9	1.9 (1.2, 2.6)	−0.03 (−0.8, 0.8)	−0.6 (−1.8, 0.6)
	Group C (CF)	20	10.7 (9.2, 12.2)	0.8 (−0.4, 2.0)	0.3 (−1.2, 1.8)	11	2.1 (1.4, 2.8)	−1.2 (−1.9, −0.4)	−0.4 (−1.5, 0.6)
	Group D (ILD)	177	9.2 (8.7, 9.6)	1.5 (1.1, 1.8)	0.2 (−0.3, 0.7)	121	2.2 (1.9, 2.4)	−0.9 (−1.1, −0.7)	−0.1 (−0.3, 0.2)

Early period = 0 to 6 months post-transplant; late period = 6 to 36 months post-transplant.

COPD = Chronic Obstructive Pulmonary Disease, PAH= Pulmonary Arterial Hypertension, CF = Cystic fibrosis, ILD = Interstitial Lung Disease.

Improvement of frailty is defined as increasing Short Physical Performance Battery (range 0–12) and decreasing Fried Frailty Phenotype (range 0–5).

Estimates are mean pre-transplant frailty score and mean change in frailty score with 95% confidence intervals.

Model 1: Mixed effects model adjusted for pre-transplant frailty state (not frail vs frail), pre-transplant frailty state by time period (early vs late), diagnosis, age, and sex

Model 2: Mixed effects model adjusted for diagnosis group, diagnosis group by time period (early vs late), age, and sex