ORIGINAL ARTICLE

Frailty Phenotypes, Disability, and Outcomes in Adult Candidates for Lung Transplantation

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Abstract

Rationale: Frailty is associated with morbidity and mortality in abdominal organ transplantation but has not been examined in lung transplantation.

Objectives: To examine the construct and predictive validity of frailty phenotypes in lung transplant candidates.

Methods: In a multicenter prospective cohort, we measured frailty with the Fried Frailty Phenotype (FFP) and Short Physical Performance Battery (SPPB). We evaluated construct validity through comparisons with conceptually related factors. In a nested case–control study of frail and nonfrail subjects, we measured serum IL-6, tumor necrosis factor receptor 1, insulin-like growth factor I, and leptin. We estimated the association between frailty and disability using the Lung Transplant Valued Life Activities disability scale. We estimated the association between frailty and risk of delisting or death before transplant using multivariate logistic and Cox models, respectively.

Measurements and Main Results: Of 395 subjects, 354 completed FFP assessments and 262 completed SPPB assessments; 28% were frail by FFP (95% confidence interval [CI], 24–33%) and 10% based on the SPPB (95% CI, 7–14%). By either measure, frailty correlated more strongly with exercise capacity and grip strength than with lung function. Frail subjects tended to have higher plasma IL-6 and tumor necrosis factor receptor 1 and lower insulin-like growth factor I and leptin. Frailty by either measure was associated with greater disability. After adjusting for age, sex, diagnosis, and transplant center, both FFP and SPPB were associated with increased risk of delisting or death before lung transplant. For every 1-point worsening in score, hazard ratios were 1.30 (95% CI, 1.01–1.67) for FFP and 1.53 (95% CI, 1.19–1.59) for SPPB.

Conclusions: Frailty is prevalent among lung transplant candidates and is independently associated with greater disability and an increased risk of delisting or death.

Keywords: biomarker; body composition; disability; frailty; lung transplantation

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At a Glance Commentary

Scientific Knowledge on the Subject: Frailty, originally a geriatric syndrome, reflects increased vulnerability to physiologic stressors. Emerging evidence has demonstrated frailty to be associated with morbidity and mortality in abdominal organ transplant and other surgical populations, but it has not been evaluated in lung transplantation.

What This Study Adds to the Field: We found that frailty, as ascertained using either of two established measures, is prevalent among adult lung transplant candidates at four U.S. transplant centers. In addition to establishing the construct validity of frailty in lung transplant candidates, this study shows that frailty is associated with greater disability and increased rates of death or delisting before transplant.

The aim of lung transplants is to extend survival, reduce disability, and improve health-related quality of life for persons with advanced lung diseases. Despite rigorous candidacy screening practices, improvements in surgical and medical management, and iterative advancements in organ allocation policies, nearly 20% of adults awaiting lung transplants die or are removed from the waiting list owing to disease progression before receiving a suitable donor offer (1). After lung transplants, nearly the same proportion of patients die within the first postoperative year (2). Notably, serious morbidity after transplant is increasing, with resultant disability and associated decrements in health-related quality of life (3, 4). Although known risk factors for death are already incorporated into lung allocation in the United States (Lung Allocation Score [LAS]), persistently high mortality and increasing morbidity underscore the need to identify novel risk factors for poor outcomes to maximize the individual and societal benefit of lung transplants (5).

Frailty is an independent risk factor for disability, perioperative complications, and mortality in older medical (6–9) and surgical patient populations (10–13). Conceptualized first in the field of geriatrics, *frailty* is defined as a generalized vulnerability to stressors resulting from an accumulation of physiologic deficits across multiple interrelated systems (14). These deficits, in turn, deplete the body's physiologic reserves, resulting in a "state of risk" for disproportionate declines in health status following exposure to an additional stressor such as major surgery. Drawing from the geriatrics experience, frailty has become recognized more recently as a risk factor for poor outcomes in solid organ transplantation. Specifically, frailty has been found to be associated with delayed graft function and mortality in kidney transplant recipients and waitlist mortality in liver transplant candidates (15–17).

In this multicenter study, we aimed to establish the prevalence and validity of frailty in lung transplant candidates. We hypothesized that frailty would be common and independently associated with disability and an increased risk of death or delisting in lung transplant candidates. Some of the results of this study have been reported previously in the form of abstracts (18–24).

Methods

Study Design, Participants, and Settings

We analyzed participants in the Lung Transplant Body Composition Study, which is an ongoing observational prospective cohort study of the impact of preoperative body composition on outcomes after lung transplants. For this analysis, candidates for lung transplant age ⩾18 years were recruited at the University of California, San Francisco (UCSF); Columbia University Medical Center (CUMC); the University of Pennsylvania; and the University of Pittsburgh. The study period was from March 17, 2011, to October 10, 2014; however, each center began enrolling subjects at different times within that period. Participants provided written informed consent for participation. Institutional review boards at each participating center approved this study.

Frailty Assessment

Several validated measures of frailty have been developed (25). Informed by differing conceptual underpinnings (26), some measures are composed of multidimensional assessments of physical functioning, whereas others include assessment of factors such as cognition, social isolation, or counts of major comorbidities (27). Because listing for lung transplants is contingent on adequate social support, cognitive functioning, and freedom from severe comorbidity, we hypothesized frailty measures that emphasized physical functioning would perform better in lung transplant candidates.

We applied two well-validated frailty measures that emphasize physical functioning. The Fried Frailty Phenotype (FFP) is an aggregate score of five constructs: shrinking, exhaustion, low physical activity, slowness, and weakness (14). Each construct is assigned 1 point if present or 0 if absent. Thus, the FFP score ranges from 0 to 5, with higher scores reflecting increased frailty. The FFP can be evaluated as a binary (frail, FFP ⩾ 3), categorical (frail, FFP ⩾ 3; prefrail, FFP = 1–2; not frail, FFP = 0), or ordinal scale (0–5) (14). The Short Physical Performance Battery (SPPB) is a three-component battery of lower extremity performance measures that includes gait speed, chair stands, and balance (6, 7). Each measure is scored from 0 to 4, with an aggregate score ranging from 0 to 12. In contrast to the FFP, lower SPPB scores reflect increased frailty. The SPPB can also be evaluated using a binary (frail, SPPB ⩽ 7), categorical (frail, SPPB ⩽ 7; prefrail, SPPB = 8–9; not frail, SPPB ⩾ 10), or ordinal scale (0–12) (7). Details on the frailty measures and scoring are provided in Table E1 in the online supplement. Because of the timing of study initiation and related instrument introduction at each center, not all subjects underwent assessments with both the FFP and SPPB frailty measures.

Other Measurements

Sarcopenia, now defined by abnormally low lean body mass and decreased function, is a cardinal physiologic feature of frailty (28–30). Using exclusively low muscle mass thresholds, others have shown low lean muscle mass sarcopenia to be an independent risk factor for infections and mortality in liver transplant recipients (31–33). At UCSF and CUMC, lean body mass was assessed in Clinical and Translational Science Award–funded research centers using whole-body dual-energy X-ray absorptiometry (Lunar Prodigy DXA, GE Healthcare, Madison, WI, at UCSF; Discovery W, Hologic,

Bedford, MA, at CUMC). The appendicular skeletal muscle mass index (ASMI) was calculated as previously described (34). Lean mass precision error (±1 SD) is 0.8 kg (35). We defined lean muscle mass sarcopenia as an ASMI of ⩽5.45 kg/m^2 for women and ⩽7.26 kg/m^2 for men (28).

Demographic and clinical variables at study entry were abstracted from medical records. Variables included body mass index (BMI; in kilograms per meter squared), race and/or ethnicity, diagnostic indication for transplant, hemoglobin (in grams per deciliter) (27, 36), FVC (in liters), 6-minute-walk distance (6MWD; in meters), and LAS.

Construct Validity Assessment

The convergent and discriminative validity of frailty measures was tested through comparisons with theoretically related clinical factors and measures of functioning. Factors tested included age, FVC, BMI, lean body mass (ASMI), grip strength, 6MWD, hemoglobin, and LAS. We hypothesized that frailty would be more strongly correlated with grip strength and exercise capacity than with age, BMI, or lung function. We anticipated that grip strength would correlate more strongly with the FFP than with the SPPB because it is the measure by which the FFP weakness construct is determined. On similar grounds, we also hypothesized that frailty measures would be positively associated with lean body mass and negatively associated with hemoglobin.

To further evaluate construct validity, we conducted an exploratory nested case–control study of selected biomarkers that have been shown to be associated with frailty in other populations (37). We measured serum IL-6 (38–40), tumor necrosis factor receptor 1 (40), insulin-like growth factor I (41), and leptin (42) in singletons at UCSF (Wolters Laboratory) using commercially available ELISA kits (R&D Systems, Minneapolis, MN). Blood was drawn in citrated tubes at the time of frailty assessments at UCSF and CUMC, then centrifuged within 45 minutes. The serum fraction was isolated and stored at −80°C for subsequent analysis. For this analysis, we identified all frail subjects by SPPB with a diagnosis of either pulmonary fibrosis or chronic obstructive pulmonary disease (COPD) for whom we had serum (n = 12) and 26 frail subjects by FFP and randomly selected one age-, sex-, and diagnosis-matched control for each individual from the nonfrail group.

Outcome Measures for Tests of Association

Disability. Disability was assessed with the Lung Transplant Valued Life Activities scale (LT-VLA). The LT-VLA is a validated measure of disability in lung transplantation (43). It considers disability across the full spectrum of functioning beyond activities of daily living and is associated with measures of functioning and health-related quality of life. It has a range from 0 to 3. Higher scores reflect increased disability; a difference of 0.3 is considered clinically meaningful.

Delisting or death before transplant. We treated delisting or death as a composite outcome. Dates of delisting and death as well as reason for delisting were obtained through medical record review. For delisting, only delisting due to becoming too ill for transplant was considered for the outcome. Time was calculated as the number of days from frailty assessment until date of death or delisting. Subjects were censored if they underwent lung transplant.

Table 1. Comparison of Demographics and Baseline Clinical Characteristics by Frailty Status

	Short Physical Performance Battery			Fried Frailty Phenotype		
	Frail	Not Frail	*P* Value	Frail	Not Frail	*P* Value
No. of subjects	26	236		99	255	
Age, yr	59 (50–65)	59 (50–65)	0.86	58 (46–63)	59 (50–65)	0.11
Male	13 (50%)	135 (57%)	0.48	50 (51%)	142 (56%)	0.38
Female	13 (50%)	101 (43%)		49 (49%)	113 (44%)	
Race/ethnicity						
White, non-Hispanic	15 (58%)	180 (76%)	0.07	65 (66%)	210 (82%)	0.003
Black	5 (19%)	13 (6%)		5 (5%)	8 (3%)	
Asian	1 (4%)	15 (6%)		7 (7%)	8 (3%)	
Hispanic	2 (8%)	19 (8%)		7 (7%)	13 (5%)	
Other	1 (4%)	4 (2%)		14 (14%)	11 (4%)	
Diagnostic category*						
Group A (COPD)	6 (23%)	78 (33%)	0.38	25 (25%)	70 (27%)	0.85
Group B (PAH)	2 (8%)	14 (6%)		6 (6%)	14 (5%)	
Group C (CF)	0 (0%)	13 (6%)		7 (7%)	24 (9%)	
Group D (ILD)	18 (69%)	131 (56%)		61 (62%)	147 (6%)	
Body mass index, kg/m^2	26.2 ± 7.5	26.1 ± 4.5	0.93	24.1 ± 4.6	26.0 ± 4.8	0.001
Hemoglobin, g/dl	12.0 ± 1.9	13.4 ± 2.0	0.004	12.5 ± 1.8	13.3 ± 2.0	0.001
Creatinine, mg/dl	0.9 ± 0.5	0.8 ± 0.2	0.83	0.8 ± 0.3	0.8 ± 0.2	0.62
FEV_1, L	1.4 (1.1–1.7)	1.3 (0.8–1.9)	0.49	1.2 (0.8–1.7)	1.3 (0.8–1.8)	0.58
FVC, L	1.7 (1.4–2.5)	2.2 (1.6–2.7)	0.12	1.9 (1.4–2.4)	2.0 (1.5–2.6)	0.16
6-minute-walk distance, m	141 (36–213)	355 (237–485)	<0.001	208 (134–323)	333 (244–423)	<0.001
LAS	78 (62–94)	45 (36–50)	<0.001	44 (35–61)	37 (33–42)	<0.001

Definition of abbreviations: CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; LAS = Lung Allocation Score; PAH = pulmonary arterial hypertension.
Data are presented as n (%), mean ± SD, or median (interquartile range).
*Diagnostic categories used for calculation of the Lung Allocation Score (9).

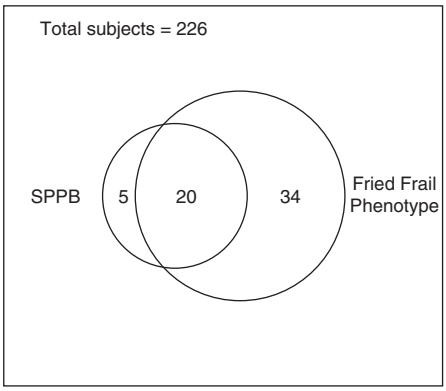

Figure 1. Comparison of the overlap of frailty diagnosis assessed by the Fried Frailty Phenotype (FFP) and Short Physical Performance Battery (SPPB). The *rectangle* represents the number of subjects with both SPPB and FFP assessments performed. Of the 25 frail subjects ascertained by SPPB, 20 were also frail by FFP (80%; 95% confidence interval, 64–96%). Of the 395 subjects in this study overall, 226 underwent both FFP and SPPB frailty assessments.

Analytical Approach

Baseline characteristics were compared by using Student's *t* test, the Wilcoxon rank-sum test, or the χ^2 test, as appropriate. We chose to perform statistical hypothesis tests of baseline characteristics between frail and nonfrail participants because these differences inform the construct validity of the frail phenotypes of interest. We used Spearman correlations to test convergent and discriminative validity. *Lower* scores on SPPB and *higher* scores on FFP indicate worse frailty. Therefore, for the correlation analyses, we reverse coded the SPPB so that the direction of the correlations would be consistent between measures. To account for multiple testing, we used the Benjamini-Hochberg procedure to control the false discovery rate at 0.05 (44). For all other analyses, we used a *P* value less than 0.05 as the threshold for statistical significance. To compare log-transformed biomarker levels in frail versus nonfrail subjects, we used the Wilcoxon rank-sum test. We used multivariate linear regression to estimate the association between both SPPB and FFP frailty and LT-VLA disability. Covariates were selected based on plausible associations with frailty and/or disability. In sequential models, all conditioned on center, we assessed unadjusted (model 1), demographic (model 2), acuity (model 3), and functioning factors (model 4). Although the covariates included in models 3 and 4 are conceptually related to frailty (e.g., BMI or 6MWD), we were interested in determining whether measures of frailty provided information above and beyond routinely collected clinical information. Our sample size required us to consider a parsimonious list of covariates.

We visually inspected the unadjusted association of frailty with delisting or death before lung transplant using Kaplan-Meier methods. We evaluated this association using established binary and categorical cutoffs for both the SPPB and FFP (7, 14). As a sensitivity analysis, we evaluated the association between SPPB and time to delisting or death across a range of binary cutoffs (45–47). To adjust for potential confounders, we used stratified Cox proportional hazards models, employing a similar approach to sequential modeling as used in examining the association between frailty and LT-VLA disability. We used individual and global tests for nonzero slope of covariates versus log survival time to evaluate the proportionality of hazards. The scales for SPPB and FFP are not directly comparable. Therefore, for both the regression and Cox model analyses, we standardized the scales by dividing each by its standard deviation.

One subject in the SPPB analyses and two subjects in the FFP analyses were missing one covariate value each relevant for model 4 (i.e., FVC or BMI). We used 10-fold multiple imputation by chained equations to account for these missing data (48). In examining the association between frailty and delisting or death, we performed an additional sensitivity analysis using competing risks analysis to estimate the association between frailty and delisting or death with lung transplant as the competing risk. Analyses were performed using Stata (version 13.1; StataCorp, College Station, TX) and SAS (version 9.3; SAS Institute, Cary, NC) software.

Results

Among the 395 subjects enrolled during the study period, 219 (55%) were male. The median age was 59 years (interquartile rage [IQR], 50–64), and the median LAS was 37.4 (IQR, 33.2–45.6). The most common indication for lung transplant was interstitial lung disease (56%), followed by COPD (30%) (Table E2). Of the cohort, 354 subjects completed FFP assessments, 262 completed SPPB assessments, and 200 underwent whole-body dual-energy X-ray absorptiometry (Table E2 and Figure E1).

We found that frailty was common: 10% were frail based on the SPPB (95% confidence interval [CI]: 7–14%) and 28% by the FFP (95% CI, 24–33%) (Table 1). There was no difference in the proportion of frail subjects by disease category. The median SPPB score was 11 (IQR, 9–11; SD, 2.1) and was skewed toward the not frail state (Figure E2A). The median FFP score was 2 (IQR, 1–3; SD, 1.2) and more normally distributed (Figure E2B). Table E3 shows the SPPB domains and the subject

Table 2. Tests of Convergent (Positive Correlation) and Divergent (Negative Correlation) Validity of Frailty Phenotypes and Conceptually Related Demographic, Physiologic, and Functional Factors

Correlation	SPPB (*n* = 262)*	FFP (*n* = 354)*
ASMI	−0.15	−0.21†
BMI	−0.03	−0.23†
Grip strength	−0.24†	−0.34†
6MWD	−0.55†	−0.34†
FVC	−0.18†	−0.15†
LAS	0.34†	0.29†
Hemoglobin	−0.28†	−0.24†
Age	0.18†	−0.11†

Definition of abbreviations: 6MWD = 6-minute-walk distance; ASMI = appendicular skeletal muscle index; BMI = body mass index; FFP = Fried Frailty Phenotype by ordinal score; LAS = Lung Allocation Score; SPPB = Short Physical Performance Battery by ordinal score.
Because lower scores on the SPPB denote increased frailty and higher scores for FFP denote increased frailty, SPPB scores were reverse coded for this analysis.
*ASMI: n = 141 for SPPB and n = 200 for FFP; hemoglobin: n = 192 for SPPB and n = 318 for FFP.
†Significant at false discovery rate of 0.05.

scores across each domain. Table E4 shows the proportion of subjects considered frail in each of the FFP domains. Although 35% of subjects had low muscle mass sarcopenia (95% CI, 28–42%), sarcopenia was not associated with frailty. Among frail subjects by SPPB, 22% had sarcopenia, whereas 34% of nonfrail subjects had sarcopenia (P = 0.47 by χ^2 test). Among frail subjects by FFP, 41% had sarcopenia, whereas 33% of nonfrail subjects had sarcopenia (P = 0.33).

Although the prevalence varied by measure, both the SPPB and FFP appeared to measure similar conceptual constructs. Figure 1 shows that among those for whom both measures were available (n = 226), 80% of the subjects who were frail by SPPB were also frail by FFP. The strength and direction of correlations between SPPB and FFP and other measures were as hypothesized (Table 2). For example, both the SPPB and FFP negatively correlated with 6MWD, lean muscle mass, and grip strength, and both positively correlated with LAS. The strength and direction of the correlations were generally unchanged when stratified by age older than 60 years,

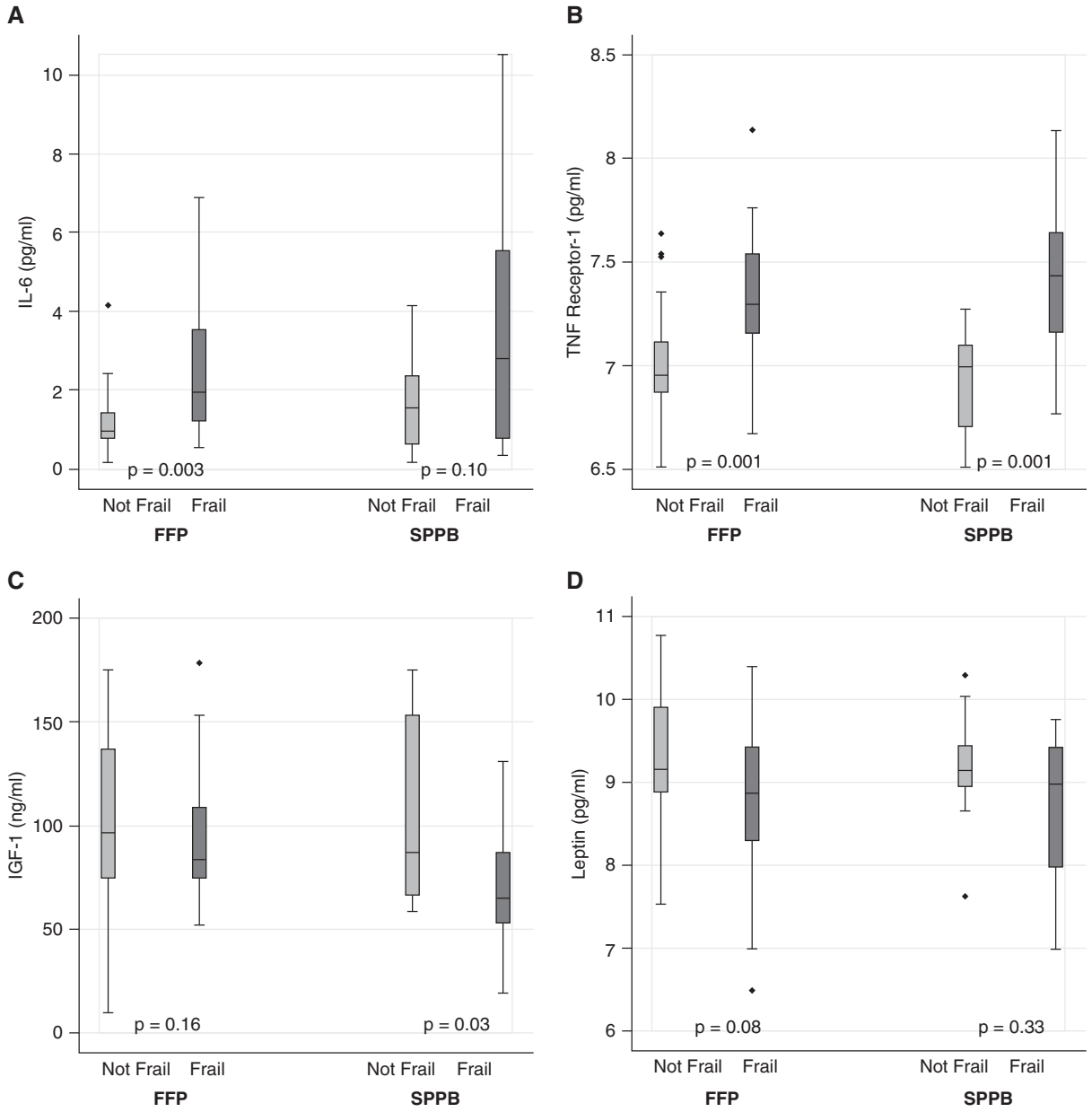

Figure 2. Box plots of (*A*) IL-6, (*B*) tumor necrosis factor (TNF) receptor 1, (*C*) insulin like growth factor (IGF)-1, and (*D*) leptin levels by frailty status. *Horizontal lines within the box plots* represent the medians, and *borders of box plots* represent the interquartile ranges (IQRs). *Whiskers* represent the highest value within 1.5 IQR of the upper quartile and lowest value within 1.5 IQR of the lower quantile. *Dots* represent outlier values. FFP = Fried Frailty Phenotype; SPPB = Short Physical Performance Battery. For FFP, comparisons are made between 26 cases and 26 age-, sex-, and diagnosis-matched controls. For SPPB, comparisons are made between 12 cases and 12 age-, sex-, and diagnosis-matched controls.

pulmonary fibrosis, COPD, and in complete case analyses (stratifications are given in Tables E5–E9). We observed differences in biomarker levels consistent with findings in other populations, although not all comparisons achieved statistical significance. Frail subjects tended to have higher levels of IL-6 (SPPB, $P = 0.10$; FFP, $P = 0.003$) and tumor necrosis factor receptor 1 (SPPB, $P = 0.001$; FFP, $P = 0.001$)) and lower levels of insulin-like growth factor I (SPPB, $P = 0.03$; FFP, $P = 0.16$) and leptin (SPPB, $P = 0.33$; FFP, $P = 0.08$) (Figure 2A–2D).

We found that frailty was strongly associated with increased disability (Table 3). After adjusting for age, sex, diagnosis, and center, each SD unit of worsening (i.e., decrease) in SPPB score was associated with a 0.25-point (95% CI, 0.17–0.34) increase in LT-VLA disability. After further adjusting for LAS, lung function, and BMI, each 1 SD unit worsening in SPPB score was associated with a 0.12-point higher LT-VLA disability (95% CI, 0.04–0.21). We observed a similar association between FFP frailty and disability. Each 1 SD unit worsening in FFP score (i.e., increase) was associated with a 0.26-point higher LT-VLA disability (95% CI, 0.19–0.34), adjusting for age, sex, diagnosis, and center, and a 0.17-point higher disability (95% CI, 0.09–0.25) after further adjusting for LAS, lung function, and BMI.

Frailty was also associated with an increased rate of delisting or death before lung transplant. In unadjusted analyses, frailty by either SPPB (score $\leqslant 7$) or FFP (score $\geqslant 3$) was associated with an increased estimated cumulative incidence of delisting or death ($P < 0.05$). The cumulative incidence of delisting or death by 1 year was 36% (95% CI, 16–68%) for subjects assessed to be frail by SPPB, compared with 16% for subjects who were not frail (95% CI, 10–25%) (Figure 3A). The cumulative incidence of delisting or death by 1 year was 27% (95% CI, 17–43%) for subjects assessed as frail based on FFP, compared with 13% for subjects who were not frail (95% CI, 8–20%) (Figure 3B). A monotonic stepup in risk was evident when we evaluated frailty as an ordinal categorical variable. For both the SPPB and FFP, estimated cumulative incidence of delisting or death was highest for frail subjects, intermediate among prefrail subjects, and lowest for the nonfrail subjects (Figures 3C, 3D). The association between frailty determined by SPPB and delisting or death was not substantively impacted by the binary cutoff used (data not shown).

Each SD unit of worsening in SPPB score was associated with a twofold relative increase in the risk of delisting or death after stratifying by center (hazard ratio [HR], 2.04; 95% CI, 1.49–2.79) (Table 4). After additionally stratifying by diagnosis and adjusting for age and sex, the risk estimate increased to threefold per 1 SD unit worsening in SPPB score (HR, 2.99; 95% CI, 1.77–5.06). Further adjusting for LAS, BMI, and 6MWD decreased the risk estimate to 2.40 (HR, 2.40; 95% CI, 1.03–5.59). We found a similar but attenuated relationship between frailty measured by the FFP and delisting or death before lung transplant. Each SD unit of worsening in the FFP score was associated with a 37% relative increase in the risk of delisting or death after stratifying by center (HR, 1.37; 95% CI, 0.98–1.91). Additional stratification by diagnosis and adjustment for age and sex did not appreciably change the risk estimate, but it did narrow the confidence interval (HR, 1.38; 95% CI, 1.01–1.89). Unlike SPPB, after further adjustment for LAS, BMI, and 6MWD, FFP-defined frailty was no longer a risk factor for delisting or death before lung transplant (HR, 0.95; 95% CI, 0.66–1.35). Results from the sensitivity analysis using competing risks demonstrated similar patterns of risk across frailty measures and models (Table E10).

Table 3. Association between Frail Phenotypes and Mean LT-VLA Disability

	SPPB (*n = 253*)	FFP (*n = 254*)
Model 1	0.27 (0.19–0.35)	0.28 (0.20–0.36)
Model 2	0.25 (0.17–0.34)	0.26 (0.19–0.34)
Model 3	0.12 (0.04–0.21)	0.18 (0.10–0.25)
Model 4	0.12 (0.04–0.21)	0.17 (0.09–0.25)

Definition of abbreviations: FFP = Fried Frailty Phenotype; LT-VLA = Lung Transplant Valued Life Activities; SPPB = Short Physical Performance Battery.
Effect estimates are increases in mean LT-VLA (95% confidence intervals) per 1 SD worsening in frailty score. Worsening is defined as a decrease in SPPB and an increase in FFP. Values greater than 0 indicate greater disability. An LT-VLA increase $\geqslant 0.3$ is clinically meaningful.
Model 1: adjusted for center.
Model 2: model 1 + age, sex, diagnosis.
Model 3: model 2 + Lung Allocation Score.
Model 4: model 3 + FVC, body mass index.

Discussion

In this multicenter cohort study of adult lung transplant candidates, we found that frailty, as assessed using two distinct measures, was common and independently associated with patient-reported disability and with subsequent delisting or death before transplant. We also found that the FFP and SPPB measures have reasonable construct validity; that is, they correlate with measures of impairment, functioning, and illness (including the LAS) and show differences in biomarker levels consistent with findings in other populations. Taken together, our findings suggest that frailty assessment might provide important morbidity and mortality risk information above and beyond typically captured clinical measures and the LAS. Our findings may be particularly relevant today, given that older and sicker patients are prioritized for lung transplants and morbidity and mortality remain persistently and unacceptably high. Frailty assessment provides a novel, objective measure that can be used to identify lung transplant candidates at increased risk before transplant for post-transplant disability and poor outcomes. Our findings also raise important questions about whether preoperative frailty might be associated with heightened risk for complications after transplant.

Our findings of the association of frailty with disability and mortality in lung transplant candidates are consistent with observations in other populations. Frailty measures operationalize what clinicians intuitively recognize as a sense that a patient may poorly tolerate a new physiologic stressor such as surgery. Fried, who was pivotal in initiating the construct, proposed

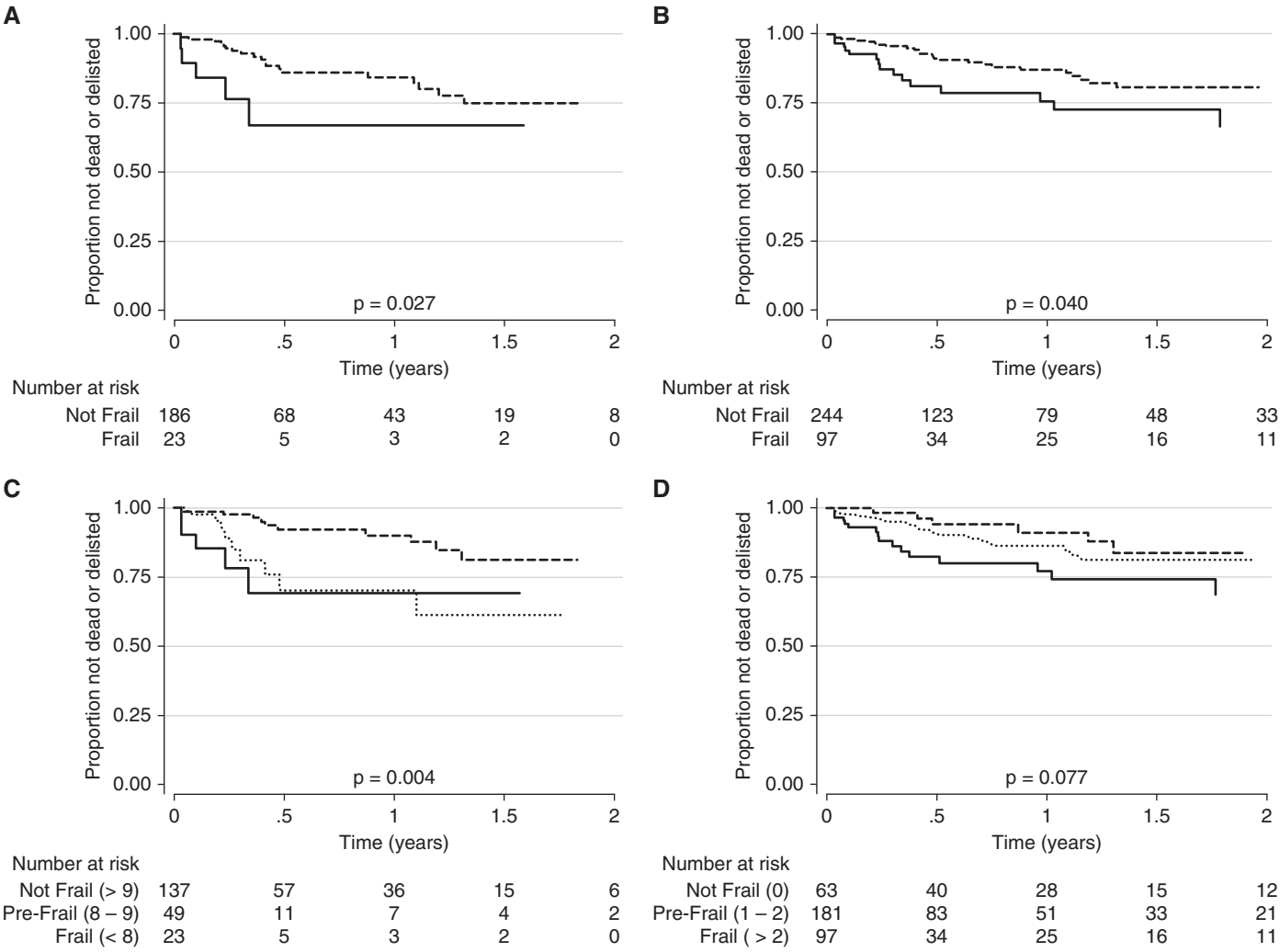

Figure 3. Time to delisting or death before lung transplant by (*A*) Short Physical Performance Battery (SPPB) binary score, (*B*) Fried Frailty Phenotype (FFP) binary score, (*C*) Short Physical Performance Battery ordinal score, and (*D*) Fried Frailty Phenotype ordinal score. *Solid lines* represent frail, *dotted lines* represent prefrail, and *dashed lines* represent not frail. For SPPB, lower scores denote increased frailty; for FFP, higher scores denote increased frailty.

that frailty could be conceptualized as an accumulation of physiologic deficits resulting in attenuated physiologic reserves (14). These reserves are required for the dynamic maintenance of homeostasis in the face of new physiologic stressors. Such attenuated reserves, or "homeostenosis" (26), result in a state of risk in which new stressors such as major surgery may exceed these reserves, resulting in catastrophic system failure. Concurrent with this conceptual definition, Fried and others developed operational measures of frailty (7, 14, 27), showing that it is associated with important outcomes in geriatric populations, including hip fracture, disability, institutionalization, poorer health-related quality of life, and mortality (6, 14, 49, 50). Following on this work, others found that preoperative frailty assessment predicted perioperative complications and mortality following cardiac and abdominal surgery above and beyond existing risk stratification tools (12, 13, 51–53). Most recently, these measures have been shown to predict death in liver transplant candidates as well as delayed graft function and death in kidney transplant recipients (15–17).

Frailty conceptually ties together a number of the previously observed risk factors for poor outcomes in patients with advanced lung disease and lung transplants. For example, low BMI and hypoalbuminemia are associated with both frailty and sarcopenia (presumably because abnormally low lean muscle mass and function is a putative driver of the frail phenotype) (29, 40, 42, 54, 55). We previously demonstrated that preoperative underweight status and hypoalbuminemia are strongly associated with mortality after lung transplant (34, 56). Also, low lean muscle mass sarcopenia is common in patients with COPD and in lung transplant candidates (34, 47). Consistent with these reports, lean muscle mass correlated with both of the frailty measures used in this study.

Protein biomarkers provide some insights into potential mechanisms driving the frailty phenotype. For example, leptin levels tended to be lower in our frail subjects. Leptin, a measure of adipose tissue mass, is

Table 4. Associations between Frail Phenotypes and the Risk of Delisting or Death before Lung Transplant

	SPPB (*n* = 209)	FFP (*n* = 341)
Model 1	2.04 (1.49–2.79)	1.37 (0.98–1.91)
Model 2	2.99 (1.77–5.06)	1.38 (1.01–1.89)
Model 3	2.20 (1.14–4.25)	1.14 (0.85–1.54)
Model 4	2.40 (1.03–5.59)	0.95 (0.66–1.35)

Definition of abbreviations: FFP = Fried Frailty Phenotype; SPPB = Short Physical Performance Battery.
Effect estimates are hazard ratios (95% confidence intervals) per 1 SD worsening in frailty score. Worsening is defined as a decrease in SPPB and an increase in FFP.
Model 1: unadjusted, stratified by center.
Model 2: adjusted for age and sex, stratified by center and diagnosis.
Model 3: adjusted for model 2 + Lung Allocation Score.
Model 4: adjusted for model 3 + body mass index, 6-minute-walk distance.

lower in patients with cachexia as well as frailty (42, 57, 58). Chronic inflammation is considered another potential cause of the frail phenotype (40, 59). Increased IL-6 and chronic cytomegalovirus infection are associated with frailty as well as with primary graft dysfunction and acute and chronic allograft rejection following lung transplant (38, 39, 60–65). Our future efforts will be focused on understanding the mechanisms underpinnings suggested by our biomarker findings. Importantly, recent work in older populations suggests that frailty may be reversible through targeted exercise- and nutrient-based interventions (66–68). Targeting at-risk, frail patients *before* lung transplant may reduce perioperative complications, reduce the risk of death, and mitigate disability and risk of poorer health-related quality of life after transplant.

Although our findings support the validity and relevance of frailty assessment in lung transplant candidates, the strength of the associations between frailty and disability and delisting or death appeared to differ by instrument. Although conceptually frailty has face validity and the instruments used in this study have reasonable construct validity, neither was developed specifically for adults with advanced lung disease. Thus, some frailty components, such as low activity or exhaustion in the FFP, may be confounded by lung disease. For example, the activity scale used in the FFP instrument includes activities that few lung transplant candidates are likely to perform, such as jogging and tennis. Supporting this possibility is the high prevalence of frailty by FFP observed in our study compared with other populations and the stronger observed association between the SPPB and disability and delisting or death compared with the FFP after controlling for relevant covariates. Alternatively, whereas the prevalence of frailty by FFP is high relative to other populations, lung disease may cause frailty, which could also explain, in part, the prevalence of frailty that we observed. Many advanced lung diseases are associated with systemic inflammation, hypoxia, chronic infections, increased resting energy expenditure, corticosteroid and other immunomodulator use, and immobility, which are all theoretical causes of frailty (69–74). Future work should focus on refining the operational measure of frailty in lung disease to improve risk prediction.

Our study has notable strengths. We performed a relatively large prospective multicenter study. We evaluated the construct validity of frailty by two different established instruments in comparison with relevant clinical measures and biomarkers that represent putative mechanistic pathways driving frailty. In estimating the association between frailty and key clinical outcomes, our study size enabled us to control for multiple relevant covariates. Despite these strengths, we did not have a sufficient number of subjects to confidently estimate the impact of frailty across clinically relevant stratified analyses, such as by age category or diagnostic subgroup. For example, our cohort included relatively few subjects with cystic fibrosis or pulmonary arterial hypertension. Also, it is possible that unmeasured covariates could explain the observed association between frailty and disability and delisting or death. Additionally, requirements for pulmonary rehabilitation before listing for lung transplant varied across the participating centers. Whereas one center requires completion of pulmonary rehabilitation at a program of the patient's choosing, others less stringently recommend regular exercise. Although our models were conditioned or stratified by center, it is possible that this methodological approach did not fully account for the potential impact of pulmonary rehabilitation. Further, because these measures were implemented at different times at the four participating centers, not all subjects underwent all measurements. Finally, and importantly, this study did not investigate the impact of preoperative frailty on outcomes after lung transplant. Further work should clarify this impact and the relevance of frailty across clinically important strata of lung transplant candidates before frailty can be used to inform patient management, determine transplant candidacy, or be considered in lung allocation schema. Indeed, if preoperative frailty is *not* associated with poorer postoperative outcomes, frail patients may benefit from prioritization, whereas if it is, frailty assessments may help identify patients unlikely to benefit from lung transplantation.

In summary, despite stringent selection criteria, frailty is common and associated with disability, delisting, and death in candidates awaiting lung transplant. This study provides support for the importance of frailty in lung transplantation and is consistent with the emerging importance of refined assessments of functioning and body composition in the lung transplant population. Multipronged efforts aimed at refining clinical assessments, understanding the mechanisms, and developing interventions targeting perturbations in body composition may provide important insights into the high morbidity and mortality in patients with advanced lung disease and lung transplants. ■

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