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Refining Low Physical Activity Measurement Improves Frailty Assessment in Advanced Lung Disease and Survivors of Critical Illness

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Abstract

Rationale: The frail phenotype has gained popularity as a clinically relevant measure in adults with advanced lung disease and in critical illness survivors. Because respiratory disease and chronic illness can greatly limit physical activity, the measurement of participation in traditional leisure time activities as a frailty component may lead to substantial misclassification of frailty in pulmonary and critical care patients.

Objectives: To test and validate substituting the Duke Activity Status Index (DASI), a simple 12-item questionnaire, for the Minnesota Leisure Time Physical Activity (MLTA) questionnaire, a detailed questionnaire covering 18 leisure time activities, as the measure of low activity in the Fried frailty phenotype (FFP) instrument.

Methods: In separate multicenter prospective cohort studies of adults with advanced lung disease who were candidates for lung transplant and older survivors of acute respiratory failure, we assessed the FFP using either the MLTA or the DASI. For both the DASI and MLTA, we evaluated content validity by testing floor effects and construct validity through comparisons with conceptually related factors. We tested the predictive validity of substituting the DASI for the MLTA in the FFP assessment using Cox models to

estimate associations between the FFP and delisting/death before transplant in those with advanced lung disease and 6-month mortality in older intensive care unit (ICU) survivors.

Results: Among 618 adults with advanced lung disease and 130 older ICU survivors, the MLTA had a substantially greater floor effect than the DASI (42% vs. 1%, and 49% vs. 12%, respectively). The DASI correlated more strongly with strength and function measures than did the MLTA in both cohorts. In models adjusting for age, sex, comorbidities, and illness severity, substitution of the DASI for the MLTA led to stronger associations of the FFP with delisting/death in lung transplant candidates (FFP-MLTA hazard ratio [HR], 1.42; 95% confidence interval [CI], 0.55–3.65; FFP-DASI HR, 2.99; 95% CI, 1.03–8.65) and with mortality in older ICU survivors (FFP-MLTA HR, 2.68; 95% CI, 0.62–11.6; FFP-DASI HR, 5.71; 95% CI, 1.34–24.3).

Conclusions: The DASI improves the construct and predictive validity of frailty assessment in adults with advanced lung disease or recent critical illness. This simple questionnaire should replace the more complex MLTA in assessing the frailty phenotype in these populations.

Keywords: frailty; motor activity; disability; lung transplantation; critical illness

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Frailty, defined conceptually as an increased susceptibility to stressors, has long been considered a consequence of aging and disease (1, 2). Clinical markers of physical frailty include low muscle mass, physical weakness, slow locomotion, easy fatigability, and a low degree of physical activity. In 2001, Fried operationalized frailty measurement in community-dwelling older adults using an aggregate score that encompasses each of these five conceptual domains (3). The Fried frailty phenotype (FFP) has repeatedly identified older adults at risk for disability, illness, surgical complications, and mortality (4–6).

In recent years, frailty has gained attention as a potentially important phenotype in adults with pulmonary diseases and among those facing or surviving critical illness (7–14). Although it is the most well-known instrument, the FFP is not the only operational measure of frailty, and no gold standard exists (15, 16). In our recent work, the FFP was outperformed by the Short Physical Performance Battery—another frailty measure—in identifying risk for poor outcomes for adults with advanced lung disease (11). This unexpected finding might result from mismeasurement of frailty-attributable limitations in physical activity in the context of a high prevalence of functional impairment in our study population.

Operationally, “low activity” in the FFP is quantified by the Minnesota Leisure Time Physical Activity (MLTA) questionnaire (17). The MLTA estimates kilocalories expended during several leisure activities relevant to older adults such as swimming, tennis, and racquetball. Participation in these activities, however, may be limited by the effects of advanced lung disease or may be subject to a floor effect when assessed in older survivors of acute respiratory failure, potentially resulting in misclassification of frailty.

The Duke Activity Status Index (DASI) is an alternative measure of physical activity that is validated in cardiopulmonary disease and that might better reflect activity

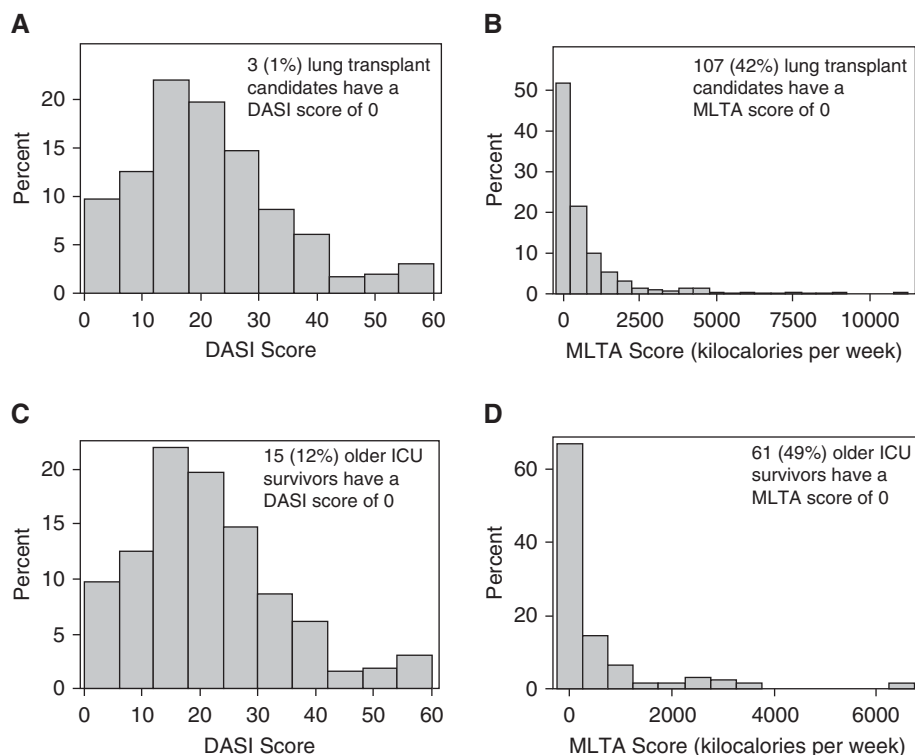


Figure 1. Assessment of content validity. Histograms of Duke Activity Status Index (DASI) scores and Minnesota Leisure Time Physical Activity (MLTA) questionnaire kilocalories expended per week for lung transplant candidates with both DASI and MLTA measured ($n = 360$) (A and B) and for older intensive care unit (ICU) survivors with both DASI and MLTA measured ($n = 124$) (C and D), respectively.

in adults with advanced pulmonary disease or older adults who become critically ill (18–20). We hypothesized that the DASI would better quantify frailty-attributable low activity than the MLTA. We examined two ongoing prospective cohort studies to test whether replacing the MLTA with the DASI would provide a more accurate and predictive measure of the FFP frailty in candidates for lung transplant and older survivors of critical illness.

Methods

Study Overview

Our overarching goal was to test whether replacing the MLTA with the DASI

questionnaire for the assessment of the low-activity component of frailty improved the measurement of the FFP in adults with advanced lung disease who were candidates for lung transplant (the derivation cohort) and older intensive care unit (ICU) survivors of acute respiratory failure (the validation cohort). We began by evaluating the content and construct validity of the MLTA and DASI as estimates of physical activity in lung-transplant candidates and older survivors of acute respiratory failure, and finished by testing the validity of substituting the DASI for the MLTA in the FFP measure of frailty. For this last step, we defined sex-specific low-activity thresholds in the derivation cohort of lung transplant candidates, and

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externally validated the thresholds in the validation cohort of older survivors of acute respiratory failure.

Study Design and Participants

We examined adults with advanced lung disease enrolled in the Lung Transplant Body Composition (LTBC) study, a prospective cohort study of candidates for lung transplant aged 18 years or older at four U.S. centers (*see METHODS* section in the online supplement for details). We also examined older survivors of acute respiratory failure enrolled in the Frailty and Outcomes in older Critical Illness Survivors (FOCIS) study, an ongoing prospective cohort study of adults aged 65 years or older who required more than 24 hours of invasive or noninvasive mechanical ventilation for acute respiratory failure and survived to hospital discharge at Columbia University Medical Center and the Allen Pavilion, a Columbia University Medical Center–affiliated New York City community hospital (*see METHODS* section in the online supplement for enrollment criteria). LTBC and FOCIS participants and/or surrogates provided informed consent for participation. Institutional review boards at all participating centers approved the studies.

Measurements of Low Activity: MLTA and DASI

FFP measurement includes an estimation of weekly activity level ascertained using the MLTA, which estimates kilocalories expended per week on the basis of self-report of the frequency and duration of participation in 18 leisure time activities that include jogging, biking, dancing, golfing, swimming, racquetball, and others (*see Figure E1* in the online supplement) (17). We defined low activity with the MLTA using the previously established FFP thresholds (3).

The DASI is a 12-item yes/no questionnaire about the ability to accomplish routine daily activities that was developed and validated in adults with cardiopulmonary disease (Figure E2) (18, 20). It assesses the ability to care for oneself, walk, climb a flight of stairs, run a short distance, do different types of housework and yard work, have sexual relations, participate in recreational activities, and others. Based

on the metabolic cost of each activity, a unit-less score between 0 and 58.2 is generated.

In LTBC, we assessed physical activity with the MLTA and DASI on the basis of participants' self-report of activities performed in the month prior to enrollment. In FOCIS, we assessed physical activity with the MLTA and DASI on the basis of report of activities performed 1 month prior to hospitalization with critical illness (*see METHODS* section in the online supplement for details).

Defining Frailty

In addition to low activity, the FFP quantifies deficits in four other conceptual domains: weakness, exhaustion, shrinking, and slowness. These constructs were

measured in LTBC using the Cardiovascular Health Study (CHS) methodology. In FOCIS, some modifications to these constructs to address measurement challenges in the hospitalized ICU survivor population were made as previously reported and as detailed in Table E1 (21). Each frailty domain was assigned 1 point if present or 0 if absent (range, 0–5). Subjects frail in at least three domains were deemed frail. Similarly to the CHS, we considered subjects evaluable for frailty if they had at least three measurements of the five potential domains (3).

Other Measurements

Demographic and clinical variables were collected from participants or electronic

Table 1. Comparison of the Duke Activity Status Index and Minnesota Leisure Time Physical Activity questionnaire with conceptually related demographic, physiologic, and functional factors in adults with advanced lung disease and older intensive care unit survivors

Characteristics	Number with Data	Duke Activity Status Index Spearman's Rho	Minnesota Leisure Time Physical Activities Spearman's Rho
Lung transplant candidate			
Age*	360	−0.08	0.08
FVC, % predicted*	351	0.16 [†]	0.08
Lung allocation score*	287	−0.37 [†]	0.06
Lean muscle mass* (ASMI)	70	0.27 [†]	0.27 [†]
BMI [‡]	360	0.07	0.12 [†]
Grip strength*	353	0.21 [†]	0.1
Gait speed*	333	0.40 [†]	0.08
6-minute walk distance*	352	0.48 [†]	0.11
Chair stand score*	234	0.30 [†]	0.11
Tandem stand score*	237	0.21 [†]	0.02
LT-VLA disability*	242	−0.66 [†]	−0.17 [†]
Older ICU survivors			
Age*	124	−0.33 [†]	−0.22 [†]
Prehospitalization Katz Basic Activities of Daily Living dependencies*	124	−0.64 [†]	−0.46 [†]
Charlson comorbidity index [‡]	124	−0.09	−0.01
BMI [‡]	124	−0.02	−0.1
Predischarge grip strength*	124	0.32 [†]	0.15
Predischarge gait speed*	118	0.4 [†]	0.27 [†]
Predischarge Katz Basic Activities of Daily Living dependencies*	124	−0.27 [†]	−0.3 [†]

Definition of abbreviations: ASMI = appendicular skeletal mass index; BMI = body mass index; ICU = intensive care unit; LT-VLA = Lung Transplant Valued Life Activities.

*Clinical characteristics and measures of function conceptually related to physical activity used to assess convergent validity.

[†]Significant after controlling for false discovery with the Benjamini-Hochberg procedure.

[‡]Clinical characteristics conceptually unrelated to physical activity used to assess discriminant validity.

medical records (*see* METHODS section in the online supplement for details).

Outcome Measures

Disability. In LTBC, disability was quantified at the time of frailty assessment using the Lung Transplant Valued Life Activities Scale (LT-VLA; range 0–3, with 0.3 reflecting a clinically meaningful difference) (22). In FOCIS, disability was assessed as the number of dependencies in the Katz basic Activities of Daily Living (ADLs) recalled from 1 month prior to hospitalization using a validated method of querying the participant and/or surrogate (23) and assessed with information from participants and their nurses just prior to hospital discharge (24).

Mortality. In LTBC, mortality was assessed at the University of California, San

Francisco. We treated removal from the waitlist for becoming too ill for transplant (i.e., delisting) or death as a composite outcome (11). Time was calculated as the number of days from frailty assessment until the date of delisting or death. Participants were censored if they underwent lung transplant. In FOCIS, we evaluated mortality within 6 months after discharge. Time was calculated as the number of days from hospital discharge until death with right censoring for follow-up at 6 months.

Analytic Approach

We evaluated content validity by examining MLTA and DASI score distributions, calculating their floor effects, and for DASI, its ceiling effect (MLTA has no upper limit). We then evaluated construct validity by testing Spearman

correlations between MLTA or DASI scores with clinical characteristics and other measures of function. We used the Benjamini-Hochberg procedure to control the false discovery rate at 0.05 (25). Next, we used fractional polynomials to plot the nonlinear, unadjusted associations between DASI scores and concurrent disability (i.e., LT-VLA scores in LTBC prehospitalization and ADL dependencies in FOCIS).

To test the validity of DASI as a frailty criterion, we first defined the DASI low-activity threshold as the lowest sex-specific quintile of scores in the LTBC cohort using methodology identical to that of the CHS. We then compared differences in demographic and clinical characteristics in those classified as frail in the “low-activity” domain by MLTA or DASI using χ^2 tests, unpaired *t* tests, or Wilcoxon rank-sum

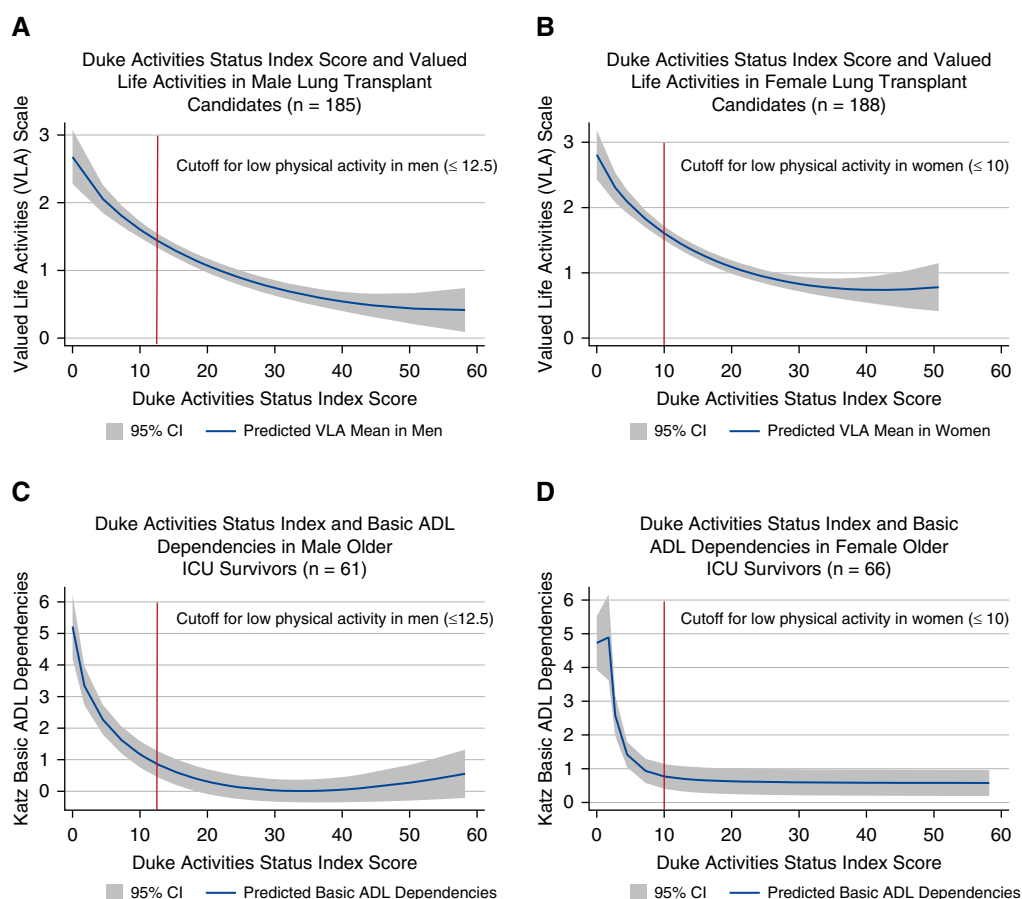


Figure 2. Unadjusted fractional polynomial prediction plots of the associations between Duke Activity Status Index scores and concurrent disability scores in male and female lung transplant candidates (A and B) and male and female older intensive care unit (ICU) survivors (C and D), respectively. The red line represents the sex-specific lowest quintile of activity observed in the Lung Transplant Body Composition cohort. ADL = activities of daily living; CI = confidence interval; VLA = valued life activities.

tests. Last, we evaluated whether replacing the MLTA (FFP-MLTA) with the DASI (FFP-DASI) strengthened the associations between frailty and disability and subsequent mortality in LTBC using multivariable linear regression and Cox models (see METHODS section in the online supplement for details). We controlled for age, sex, diagnosis, and transplant center in LTBC, and also for age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score, invasive versus noninvasive mechanical ventilation, and Charlson comorbidity index score in FOCIS. We compared the discriminant functions of the FFP-DASI and FFP-MLTA using the Harrell's C-statistics of the unadjusted models. These analyses were then repeated in the FOCIS cohort using the same low-activity threshold derived in the LTBC cohort. Analyses were performed using Stata 14.0 (StataCorp, College Station, TX) and SAS version 9.3 (SAS Institute, Cary, NC) software.

Results

Among 618 LTBC participants, 605 had MLTA measured, 373 had DASI measured, and 360 had both. Among the 373 with DASI, the median age was 59 years (interquartile range [IQR], 48–64), and the median lung allocation score (LAS) was 37 (IQR, 34–43). The most common indication for lung transplant was interstitial lung disease (64%). A total of 40 (20%) from the University of California, San Francisco, died or were delisted during the study period.

Among 130 FOCIS participants, 124 had both MLTA and DASI measured and complete follow-up (Figure E3). The median age was 73 years (IQR, 68–81); 87% were admitted from home; and the median APACHE II score was 28 (IQR, 23–34). A total of 31 (24%) died within 6 months after hospital discharge.

Content, Construct, and Predictive Validity in the LTBC Cohort

Among LTBC participants, the median DASI score was 19.0 (IQR, 12.5–26.7; range, 0–58.2). The median MLTA was 63.3 kcal/wk (IQR, 0–603.8; range, 0–10,908). The MLTA exhibited a substantially greater floor effect than DASI (42% vs. 1%) (Figures 1A and 1B), and the

DASI ceiling effect was 3%. DASI scores also exhibited a more normal distribution than MLTA. Sixty-five percent met the CHS MLTA low-activity frailty definition, and (by definition) 20% had DASI low activity (men, ≤ 12.5 ; women, ≤ 10). Higher DASI scores, but not MLTA kilocalories per week, correlated with greater FVC percent predicted, grip strength, gait speed, 6-minute walk distance (6MWD), chair stands, and tandem stands (Table 1). Furthermore, higher DASI scores more strongly correlated with lower LT-VLA disability than did the MLTA kilocalories per week (Spearman's rho, -0.66 vs. -0.17 , respectively; both $P < 0.05$). Sex-stratified fractional polynomial plots showed that lower DASI scores, particularly below the low-activity threshold, were more strongly associated with LT-VLA disability than higher scores (Figures 2A and 2B). Low activity by MLTA was not associated with

FVC, 6MWD, or the LAS (Table E2), whereas low activity by DASI was associated with lower FVC, shorter 6MWD, and higher LAS (Table 2).

Although the effect estimates of the adjusted association between FFP-DASI or FFP-MLTA and LT-VLA disability were similar (FFP-DASI β , 0.69; 95% confidence interval [CI], 0.53–0.85; and FFP-MLTA β , 0.50; 95% CI, 0.36–0.64; both $P < 0.001$), FFP-DASI was more strongly associated with disability than was the FFP-MLTA, as evidenced by the larger χ^2 value (FFP-DASI $\chi^2 = 71.2$ vs. FFP-MLTA $\chi^2 = 47.4$) (Table 3). Frailty was associated with death/delisting in LTBC only after substituting DASI for MLTA (Table 4, Figure 3). After adjusting for covariates, FFP-MLTA was not associated with lung transplant candidate death/delisting (hazard ratio [HR], 1.42; 95% CI, 0.55–3.65). In contrast, after adjusting for covariates, FFP-DASI was independently associated with a

Table 2. Characteristics of subjects with advanced lung disease by low-activity frailty criteria based on the Duke Activity Status Index

Characteristics	Normal Activity by DASI Score	Low Activity by DASI Score*	P Value
Number of participants, %	294 (79%)	79 (21%)	
Age, yr, median (IQR)	59 (48–64)	60 (49–66)	0.576
Sex, n (%)			0.764
Female	147 (50.0%)	41 (51.9%)	
Male	147 (50.0%)	38 (48.1%)	
Race, n (%)			0.324
White	248 (84.9%)	61 (78.2%)	
Black	26 (8.9%)	9 (11.5%)	
Other	18 (6.2%)	8 (10.3%)	
Diagnosis group, n (%)			0.299
COPD	74 (25.4%)	21 (27.3%)	
PAH	13 (4.5%)	0 (0.0%)	
CF	21 (7.2%)	5 (6.5%)	
ILD	183 (62.9%)	51 (66.2%)	
BMI, kg/m ² , median (IQR)	25.4 (22.0–29.5)	26.1 (21.7–29.1)	0.927
FVC	2.0 (1.5–2.6)	1.8 (1.3–2.4)	0.013
FVC, % predicted, median (IQR)	53 (42–64)	46 (38–59)	0.033
6MWD, m, median (IQR)	328 (243–411)	212 (129–315)	<0.001
Lung allocation score, median (IQR)	36.3 (33.7–40.7)	43.6 (36.7–52.9)	<0.001
Center, n (%)			0.062
UCSF	67 (22.8%)	25 (31.6%)	
CUMC	148 (50.3%)	43 (54.4%)	
PENN	43 (14.6%)	4 (5.1%)	
PITT	36 (12.2%)	7 (8.9%)	

Definition of abbreviations: 6MWD = 6-minute walk distance; BMI = body mass index; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; CUMC = Columbia University Medical Center; DASI = Duke Activity Status Index; ILD = interstitial lung disease; IQR = interquartile range; PAH = pulmonary arterial hypertension; PENN = University of Pennsylvania; PITT = University of Pittsburgh; UCSF = University of California, San Francisco.

*Cutoff for frailty criterion of low activity is the lowest sex-specific quintile of DASI score in the Lung Transplant Body Composition study cohort: less than or equal to 12.5 for men and less than or equal to 10 for women.

Table 3. Associations between frailty and concurrent Lung Transplant Valued Life Activities disability in adults with advanced lung disease and between frailty and concurrent Katz Basic Activities of Daily Living dependencies at hospital discharge in older intensive care unit survivors

	Lung Transplant Candidates			Older ICU Survivors		
	(n = 378 with MLTA, n = 358 with DASI)			(n = 130)		
	β* (95% CI)	χ ² Statistic	P Value	β [†] (95% CI)	χ ² Statistic	P Value
Frail using MLTA (FFP-MLTA)	0.50 (0.36–0.64)	47.4	<0.001	3.17 (2.12–4.22)	35.8	<0.001
Frail using DASI (FFP-DASI)	0.69 (0.53–0.85)	71.2	<0.001	2.50 (1.67–3.35)	34.6	<0.001

Definition of abbreviations: CI = confidence interval; DASI = Duke Activity Status Index; FFP = Fried frailty phenotype; ICU = intensive care unit; MLTA = Minnesota Leisure Time Physical Activity questionnaire.

*Estimate reflects average increase in concurrent Lung Transplant Valued Life Activities–rated disability in frail adults with advanced lung disease compared with those who were not frail. The Lung Transplant Valued Life Activities score ranges from 0 to 3; higher scores indicate worse disability, and 0.3 reflects a clinically meaningful difference. Models are adjusted for age, sex, diagnosis, and center.

[†]Estimate reflects average increase in concurrent basic activities of daily living dependencies in frail older ICU survivors compared with those who were not frail. Models are adjusted for age, sex, Charlson comorbidity index score, Acute Physiology and Chronic Health Evaluation II score, and invasive versus noninvasive mechanical ventilation.

threefold increased risk of death/delisting (HR, 2.99; 95% CI, 1.03–8.65).

Content, Construct, and Predictive Validity in the FOCIS Cohort

Among FOCIS participants, the median DASI score was 15.5 (IQR, 7.25–34.7; range, 0–58.2). The median MLTA was 15.4 kcal/wk (IQR, 0–395; range, 0–6,675). Similarly to LTBC, the MLTA had a greater floor effect than DASI (49% vs. 12%) (Figures 1C and 1D), and the DASI ceiling effect was 6%. Seventy-three percent met the CHS MLTA low-activity definition, and 35% met the DASI low-activity definition.

Compared with the MLTA, higher DASI scores correlated more strongly with younger age, greater grip strength, faster gait speed, and fewer prehospitalization and pre-discharge ADL dependencies (Table 1).

As expected, DASI was not correlated with body mass index or with the Charlson comorbidity index (Table 1).

Sex-stratified fractional polynomial plots revealed little to no association with ADL dependencies above DASI scores of 20, but we observed a strong association with low DASI scores with an inflection point in the curve just below LTBC-defined thresholds (Figures 2C and 2D). Low activity by both DASI and MLTA were associated with older age and more ADL dependencies both prior to hospitalization and at hospital discharge (Table 3 and Table E3). Low activity by DASI, but not MLTA, was also associated with admission from a skilled-care facility.

The strength of the associations of FFP-DASI and FFP-MLTA with concurrent ADL dependencies were similar (β, 3.17; 95% CI,

2.12–4.22; χ² = 35.8; P < 0.001; and β, 2.50; 95% CI, 1.67–3.35; χ² = 34.6; P < 0.001, respectively) (Table 3). Notably, frailty was associated with 6-month mortality only after substituting DASI for MLTA (Table 4, Figure 3). After adjusting for covariates, FFP-MLTA was not associated with 6-month mortality in older survivors of acute respiratory failure (HR, 2.68; 95% CI, 0.62–11.6). In contrast, after adjusting for covariates, FFP-DASI was independently associated with a greater than fivefold increased risk of 6-month mortality (HR, 5.71; 95% CI, 1.34–24.3).

Discussion

In both advanced lung disease and older survivors of acute respiratory failure, we

Table 4. Associations between frailty and death or delisting in adults with advanced lung disease and between frailty and 6-month survival after hospital discharge in older intensive care unit survivors

	Death/Delisting Hazard Ratio (95% CI) in Lung Transplant Candidates	Harrell’s C-Statistic	6-Mo Mortality Rate Ratio (95% CI) in Older ICU Survivors	Harrell’s C-Statistic
Number of participants	203		130	
Frail using MLTA (FFP-MLTA)	1.58 (0.65–3.82)	0.60	2.75 (0.66–11.5)	0.55
Frail using DASI (FFP-DASI)	2.85 (1.12–7.30)	0.61	5.34 (1.27–22.4)	0.61
Adjusted associations*				
Number of participants	201		130	
Frail using MLTA (FFP-MLTA)	1.42 (0.55–3.65)		2.68 (0.62–11.6)	
Frail using DASI (FFP-DASI)	2.99 (1.03–8.65)		5.71 (1.34–24.3)	

Definition of abbreviations: CI = confidence interval; DASI = Duke Activity Status Index; FFP = Fried frailty phenotype; ICU = intensive care unit; MLTA = Minnesota Leisure Time Physical Activity questionnaire.

*For the Lung Transplant Body Composition study cohort, models are adjusted for age, sex, and diagnosis. For the Frailty and Outcomes in older Critical Illness Survivors study cohort, models are adjusted for age, sex, Charlson comorbidity index score, Acute Physiology and Chronic Health Evaluation II score, and invasive versus noninvasive mechanical ventilation.

Table 5. Older intensive care unit survivor characteristics by low-activity frailty criteria based on the Duke Activity Status Index

Characteristics	Normal Activity by DASI Score	Low Activity by DASI Score*	P Value
Number of participants, %	84 (66)	43 (34)	
Age, yr, median (IQR)	71 (67–80)	79 (71–86)	0.0006
Female sex, n (%)	39 (46)	27 (63)	0.081
Race/ethnicity, n (%)			0.426
Non-Hispanic white	25 (30)	17 (40)	
Black	11 (13)	7 (16)	
Hispanic	47 (56)	18 (42)	
Indian	1 (1.2)	1 (2.3)	
Residence 1 mo prior to hospitalization, n (%)			0.002
Home	79 (94)	32 (74)	
Skilled-care facility	5 (6)	11 (26)	
Katz Basic Activities of Daily Living dependencies 1 mo prior to hospitalization, median (IQR)	0 (0–0)	2 (1–5)	<0.0001
BMI, kg/m ² , median (IQR)	25.9 (22.6–30.2)	26.2 (21.2–32.3)	0.691
APACHE II score, mean (SD)	29 (24–34)	26 (22–33)	0.08
Charlson comorbidity index score, median (IQR)	2 (1–4)	2 (1–3)	0.86
Type of respiratory support, n (%)			0.1
Mechanical ventilation	71 (84)	31 (72)	
Noninvasive ventilation only	13 (16)	12 (28)	
ICU stay, d, median (IQR)	4 (3–8)	4 (3–9)	0.82
Total hospital stay, d, median (IQR)	13 (8–23)	12 (9–27)	0.853
DNR status during hospitalization	9 (26)	15 (17)	0.249
Disposition at hospital discharge, n (%)			0.017
Home	50 (59)	16 (37)	
Skilled-care facility	34 (41)	27 (63)	
Katz Basic Activities of Daily Living dependencies prior to hospital discharge, median (IQR)	2 (0–5)	5 (2–6)	0.0009

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; DASI = Duke Activity Status Index; DNR = do not resuscitate; ICU = intensive care unit; IQR = interquartile range.

*Cutoff for low-activity frailty criterion is the lowest sex-specific quintile of Duke Activity Status Index score in the Lung Transplant Body Composition study cohort: less than or equal to 12.5 for men and less than or equal to 10 for women. Participants were asked about DASI activities they could perform 1 month prior to the hospitalization for critical illness.

found that the DASI is a more valid measure of physical activity than the MLTA. We also found that an FFP assessment that uses the DASI identifies a frail phenotype at increased risk of death independent of age, sex, and severity of illness in the LTBC cohort, as well as age, sex, comorbidities, mechanical ventilation, and severity of illness in the FOCIS cohort, whereas the FFP using the MLTA did not.

Conceptually, frailty instruments should be comprised of operational measures of frailty domains that are not attributable to other diseases and that are discriminative within the population of interest. The FFP was derived in suburban community-dwelling older adults who perhaps had fewer activity limitations

than adults with advanced lung disease or older survivors of acute respiratory failure. Indeed, applying the CHS-based 20th-percentile frailty cutoff for MLTA-defined low activity classified 65% of lung transplant candidates and 73% of older ICU survivors as frail. There may be several explanations for this finding. The MLTA may capture low activity that is attributable to both frailty and functional limitations caused by a high burden of comorbidities such as advanced lung disease. Alternatively, the items comprising the MLTA (e.g., gardening, golf, tennis) may not be relevant to urban-dwelling adults or accessible for those of a lower socioeconomic class, and they may underestimate the energy expended in those with severe acute or chronic disease (26). For each activity that is not

performed, a score of 0 is assigned without distinguishing whether activities are not performed because of inability or lack of interest.

The DASI differs from the MLTA by assessing both basic and independent ADLs, sexual relations, and recreational activities that cross socioeconomic classes and that may be less affected by the built environment (18). By demonstrating improved content and construct validity compared with the MLTA, our findings show that the DASI queries activities more relevant to adults with advanced lung disease or survivors of critical illness. Importantly, operationalizing the low-activity domain by DASI strengthens the associations of frailty with disability and mortality in those with advanced lung disease and older survivors of acute respiratory failure. Using the DASI may minimize misclassification of frailty-attributable low activity and better discriminate between levels of activity relevant in the fields of pulmonary and critical care medicine. Also, the MLTA questionnaire has proven to be particularly challenging to complete in several FFP studies of older adults because it takes a substantial amount of time to administer (17). To address this, investigators have applied *ad hoc* modified definitions of low physical activity (4, 27, 28) or have even excluded the criterion altogether (29). Replacing the MLTA with the DASI should make the FFP assessment easier and faster to administer because the DASI is a simple 12-item yes/no questionnaire that takes less than 5 minutes to complete (18).

Our study has notable strengths. To date, existing frailty measures, including the FFP, have been developed in community-dwelling older adults and applied to other populations without their validity being tested. We performed relatively large concurrent prospective cohort studies to refine and validate an operational measure of frailty for use in pulmonary and critical care medicine. By prospectively collecting measures of frailty and other clinical assessments, we were able to demonstrate the improved validity of using an alternative measure of physical activity to the MLTA. In addition to finding stronger associations of frailty with disability and mortality, our refined FFP-DASI instrument is actually easier to administer, making it more feasible for use in future studies. This refined

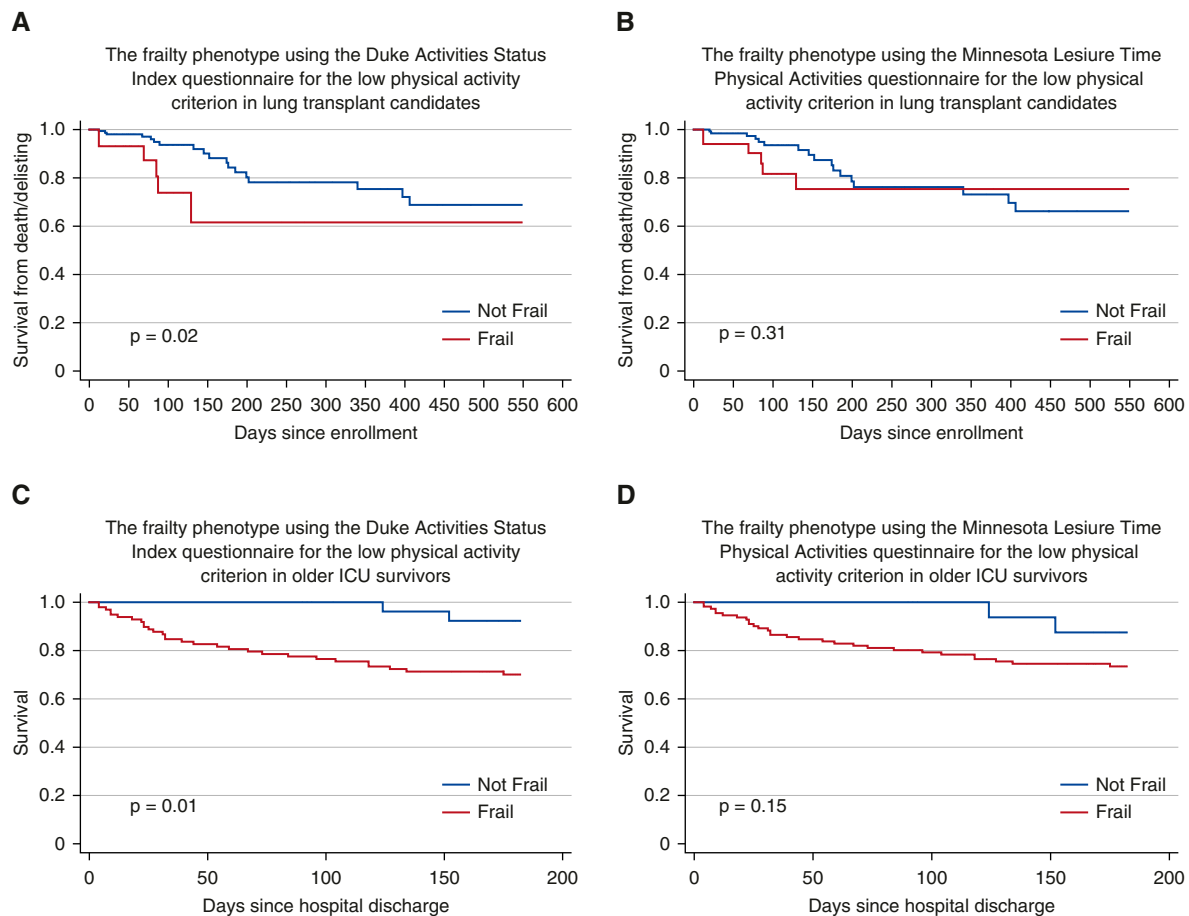


Figure 3. Kaplan-Meier survival curves for frail (score, ≥ 3) and nonfrail (score, 0–2) lung transplant candidates (A and B) and older intensive care unit (ICU) survivors (C and D) using the Duke Activity Status Index scores and Minnesota Leisure Time Physical Activity questionnaire kilocalories per week expended for the low-activity criterion, respectively. *P* values are for the log-rank test.

assessment of the frailty phenotype may also be useful for mechanistic studies that seek to understand the pathobiology of frailty in pulmonary disease or critical illness and may be a useful endpoint in trials designed to prevent or treat frailty in these populations. Whereas prior studies have demonstrated that prehospitalization frailty measured with the Rockwood Clinical Frailty Scale predicts short- and long-term adverse outcomes on ICU admission (12–14, 30), FOCIS is the first to measure post-ICU frailty as the cumulative effects of physical deficits that were present prior to critical illness and those acquired during critical illness. Being able to risk stratify and identify older ICU survivors during the week prior to hospital discharge with frailty measurements will arguably facilitate prognostic and predictive enrichment of sampling older ICU survivors for future clinical trials

aimed at improving critical illness survivorship with interventions that cross the care continuum from post-ICU acute care to either post-acute facility care or home care after hospital discharge.

Despite these strengths, our study has several limitations. We refined only the low physical activity criterion of the FFP. Quantifying frailty in the fields of pulmonary and critical care medicine might be further improved by refining the other criteria of the FFP, including the domains from other operational measures of frailty and adding imaging or biomarker assessments of frailty. In the field of geriatrics, consensus statements and opinion leaders recognize that measurements of frailty will evolve and suggest that biomarkers and anthropomorphic measures (e.g., sarcopenia) that reflect the underlying pathobiology of frailty could further

improve measure validity (15, 31–37). Although we developed the low-activity threshold for DASI in a multicenter cohort (LTBC) using the CHS paradigm of lowest quintile cutoff, it is possible that a threshold developed by other methods or derived from FOCIS would perform even better in survivors of critical illness. However, our fractional polynomial plots (Figure 2) support the generalizability of the LTBC cohort cutoff to survivors of critical illness. These plots show that number of concurrent ADL dependencies in FOCIS increases drastically below the LTBC-defined low physical activity threshold.

The assessment of DASI and MLTA activities 1 month prior to hospitalization in FOCIS participants and/or surrogates may be subject to recall bias. Although this is possible, we believe, for several reasons, that such recall bias may be minimal and

does not undermine the validity or relevance of our work. Others have demonstrated that retrospective patient and proxy reports of physical function prior to hospitalization are similar and have predictive validity (23, 38, 39). In studies that have identified differences between patient and proxy reports of pre-morbid health-related quality of life, those differences were limited primarily to mental health and symptom domains but not physical functioning domains (40, 41). Our approach is consistent with prior studies that involved retrospective and proxy reports of prehospitalization frailty

based on the Rockwood Clinical Frailty Scale (which involves querying about prehospitalization independence in basic and instrumental ADLs, mobility, comorbidities, and cognition) (12–14, 30). These studies, like ours, demonstrated strong construct and predictive validity. With regard to our study and its potential application to future cohort studies and clinical trials, despite the potential for recall bias, our findings that the DASI improves the predictive validity of the FFP supports the internal validity of our approach. Clinically, our approach also reflects how we obtained information

about our patients, which makes our method of assessment both feasible and generalizable to clinical practice.

In summary, we have developed and validated a refined and streamlined measure of frailty for use in pulmonary and critical care medicine. Future studies are needed to further refine the measurement of frailty and to develop interventions aimed at reducing frailty-attributable morbidity and mortality in these vulnerable populations. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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