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Construct and Predictive Validity of Sarcopenia in Lung Transplant Candidates

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Abstract

Rationale: Sarcopenia is associated with disability and death. The optimal definition and clinical relevance of sarcopenia in lung transplantation remain unknown.

Objectives: To assess the construct and predictive validity of sarcopenia definitions in lung transplant candidates.

Methods: In a multicenter prospective cohort of 424 lung transplant candidates, we evaluated limited (muscle mass only) and expanded (muscle mass and quality) sarcopenia definitions from the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), the Foundation for the National Institutes of Health (FNIH), and a cohort-specific distribution-based lowest quartile definition. We assessed construct validity using associations with conceptually related factors. We evaluated the relationship between sarcopenia and frailty using generalized additive models. We also evaluated associations between sarcopenia definitions and key pretransplant outcomes, including disability (quantified by the Lung Transplant Valued Life Activities scale [range, 0–3; higher scores = worse disability; minimally important difference, 0.3]) and waitlist delisting/death, by multivariate linear and Cox regression, respectively.

Results: Sarcopenia prevalence ranged from 6% to 13% by definition used. The limited EWGSOP2 definition demonstrated

the highest construct validity, followed by the expanded EWGSOP2 definition and both limited and expanded FNIH and lowest quartile definitions. Sarcopenia exhibited a linear association with the risk of frailty. The EWGSOP2 and expanded lowest quartile definitions were associated with disability, ranging from 0.20 to 0.25 higher Lung Transplant Valued Life Activities scores. Sarcopenia was associated with increased risk of waitlist delisting or death by the limited and expanded lowest quartile definitions (hazard ratio [HR], 3.8; 95% confidence interval [CI], 1.4–9.9 and HR, 3.5; 95% CI, 1.1–11.0, respectively) and the EWGSOP2 limited definition (HR, 2.8; 95% CI, 0.9–8.6) but not with the three other candidate definitions.

Conclusions: The prevalence and validity of sarcopenia vary by definition; the EWGSOP2 limited definition exhibited the broadest validity in lung transplant candidates. The linear relationship between low muscle mass and frailty highlights sarcopenia's contribution to frailty and also questions the clinical utility of a sarcopenia cut-point in advanced lung disease. The associations between sarcopenia and important pretransplant outcomes support further investigation into using body composition for candidate risk stratification.

Keywords: sarcopenia; frailty; lung transplantation

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The number of patients aged 65 years or older with end-stage lung disease undergoing lung transplantation is rising dramatically (1, 2). Worldwide, the proportion of patients within this age group at the time of lung transplantation increased from 3.3% in 2005 to almost 17% in 2017 (1). Growth has been even more dramatic in the United States, where this population represented only 4% of new lung transplant recipients in 2002 compared with 32% in 2017 (2).

Concurrent to this shift toward transplant in older individuals, postoperative morbidity and resource use have also increased, with some studies also showing a rise in post-transplant mortality (3, 4). Older age is an independent risk factor for discharge to an inpatient rehabilitation facility after lung transplantation (3, 5), unplanned 30-day readmission after transplant surgery (2), and less health-related quality of life (HRQL) benefit derived from transplant compared with younger recipients (6). These findings are particularly relevant given the expected median survival of only 3 years for lung transplant recipients aged 65 years and older (7).

In light of these trends, lung transplant centers worldwide are struggling to identify which older patients will have improved functional status, HRQL, or prolonged survival after transplantation. Measures of physiologic age, rather than chronologic age, may help to identify patients at increased risk of morbidity and mortality in lung transplantation. Efforts to test concepts from geriatric medicine in this population have shown that frailty—a state of low physiologic reserve—is associated with increased risks of disability, readmission after lung transplant surgery, and mortality before and after lung transplantation (8–10). Although these findings have identified a novel risk factor for poor transplant outcomes, pathobiological causes underlying these associations are unknown. This knowledge deficit hinders our understanding of frailty in advanced lung disease and impedes the development of targeted interventions to improve outcomes in lung transplantation.

Sarcopenia, defined as low skeletal muscle mass combined with poor muscle

quality, may represent one factor underlying these associations. Believed to be a key physical component of frailty (11), sarcopenia is associated with physical disability, falls, and death in older adults (12, 13). It is associated with morbidity and mortality before and after other solid organ transplants (14–16).

Decreased skeletal muscle mass and poor muscle quality have been observed in lung transplant candidates (17, 18) and are associated with mortality in patients with chronic obstructive pulmonary disease (COPD) (19, 20). Weak grip strength is also associated with longer length of stay after lung transplant surgery (21). Thus, sarcopenia may serve as a driver of poor outcomes in lung transplantation.

Although sarcopenia is conceptually straightforward, operationalizing its measurement is not. Like frailty, numerous operational definitions of sarcopenia have been proposed. None, however, have been validated in advanced lung disease. Identifying a valid operational definition of sarcopenia in lung transplant candidates could provide consistency in reporting prevalence across future studies, enable testing of the association between sarcopenia and transplant outcomes, and allow for evaluation of interventions to improve sarcopenia. In this prospective cohort study of patients with advanced lung disease awaiting lung transplantation, we aimed to establish the prevalence of sarcopenia in lung transplant candidates, test the construct validity of existing definitions of sarcopenia, examine sarcopenia's relationship with frailty, and evaluate associations between sarcopenia and clinical outcomes such as pretransplant disability and waitlist delisting or death.

Methods

Study Design, Setting, and Participants

This study analyzed participants in the Lung Transplant Body Composition Study, a multicenter prospective cohort study examining the impact of preoperative body composition on lung transplant outcomes. Adult lung transplant candidates aged 18 years or older are being recruited at the University of California, San Francisco; the University of

Pennsylvania; and Columbia University Medical Center. The study period began in June 2017 and is ongoing. Institutional review boards at each center approved this study. Study participants provided written informed consent.

Sarcopenia Definitions and Measurement

Originally described as an age-related decline in skeletal muscle mass, recent operational definitions of sarcopenia have expanded to require the simultaneous presence of decreased skeletal muscle mass and poor muscle quality (either weak muscle strength or functional limitation) (22). These broadened definitions reflect increasing recognition of contributions from both mass and quality in determining maximal force generated by skeletal muscle. Several operational definitions have been proposed by consensus statements. Little evidence exists, however, regarding the validity of applying these in advanced lung disease or whether one definition is superior to the rest. As a result, we elected to test the most promising candidate definitions.

A priori, three pairs of sarcopenia definitions (six total) were evaluated. Each pair included a “limited” definition of sarcopenia that consisted of low muscle mass alone as well as an “expanded” definition that included both low muscle mass and poor muscle quality. The pairs included definitions from the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, and a distribution-based definition derived from our study cohort (22–24). The EWGSOP2 definition proposed cut-points derived from normative references of healthy adults age 18 to 90 years (23). The cut-point for appendicular skeletal muscle mass was set at two standard deviations (SDs) below the mean reference value (25), the cut-point for grip strength was set at 2.5 SDs below the mean reference value (26), and the gait speed cut-point of ≤ 0.8 m/s was derived from studies demonstrating an association between a gait speed of ≤ 0.8 m/s and increased mortality in adults age ≥ 65 (27). The FNIH Sarcopenia Project pooled nine existing data sources to identify diagnostic thresholds for

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sarcopenia (24). Because the EWGSOP2 and FNIH definitions were derived in community-dwelling older populations, the proposed cutoffs may not be generalizable to patients with advanced lung disease. Thus, we elected to test a third distribution-based definition derived from our study cohort, using the lowest quartile of each sarcopenia component. The six sarcopenia definitions evaluated are described in Table 1.

Skeletal muscle mass was quantified by bioelectrical impedance analysis (InBody S10 [InBody]). InBody S10 quantifies the skeletal muscle mass of the bilateral upper and lower extremities, which are summed to generate a measure of appendicular skeletal muscle mass. InBody S10 measurements demonstrate test–retest reliability (intraclass correlation coefficient, 0.96) (28) and strong correlation with whole-body dual energy X-ray absorptiometry ($r = 0.94$) (29). For lowest quartile and EWGSOP2 definitions, muscle mass is expressed as appendicular skeletal muscle mass (ASM) divided by height squared (ASM/ht^2). For the FNIH definition, muscle mass is expressed as ASM divided by body mass index (BMI) (ASM_{BMI}). Measures of muscle quality included grip strength and gait speed. The average of three isometric grip strength attempts was used, quantified using a hydraulic handheld dynamometer (Jamar [Patterson Medical/Performance Health]) with the participant seated, shoulder adducted, and neutrally rotated and elbow flexed at 90° . The average of two gait speed attempts was used, which were measured while the participant walked 4.57 m on a flat surface. Frailty (by Short Physical Performance Battery [SPPB] and Fried Frailty Phenotype [FFP]), grip strength, gait speed, and measures of body

composition were measured by research coordinators at each site. Research staff adhered to defined study protocols detailed in a manual of operating procedures. New coordinators underwent rigorous training on the performance of these measures under observation by an experienced coordinator until deemed proficient. Regular quality control checks were performed to minimize the potential for measurement differences attributable to study staff across sites.

Measures of Construct Validity

Because a gold-standard definition of sarcopenia in advanced lung disease is lacking, we undertook a multistep process to identify the most valid definition. We first assessed construct validity, the degree to which a definition effectively measures its intended entity. For construct validity, we evaluated the convergent and discriminant validity of the six sarcopenia definitions described above. Convergent validity assesses correlations with conceptually related variables. Discriminant validity examines correlations (or anticipated lack thereof) with conceptually unrelated variables. The following components were examined: 6-minute walk distance (6MWD), physical frailty (SPPB), and Short Form 12 (SF12) Physical and Mental Health Component Summary scores (SF12-PCS and SF12-MCS, respectively), measures that focus on HRQL (SF12 range, 0–100; higher scores indicate better HRQL; minimally important difference [MID], 5) (30, 31). Because sarcopenia is believed to represent a physical component of frailty, a frailty domain unrelated to physical fitness (the Trails B Test, an assessment of cognitive limitation) was tested as a variable for discriminant validity

(32). We hypothesized that skeletal muscle mass would positively correlate with 6MWD, SPPB frailty score, and SF12-PCS and would not correlate with Trails B Test score or SF12-MCS.

Participants completed study visits upon study enrollment and subsequently at 3-month intervals. These visits included measures of body composition, grip strength, gait speed, 6MWD, frailty, cognition, and survey measures of disability and HRQL. Forty-seven patients were on either mechanical ventilation or extracorporeal membrane oxygenation before transplant. Frailty was measured in 40 of these patients during their most recent visit before transplant; frailty assessment was not able to be performed for the seven patients who were hospitalized at the time of their last scheduled clinic visit before transplant. Because the instrument used to measure body composition is portable and the measurements can be performed even when a patient is hospitalized, body composition assessment was performed on all 47 patients. For patients who underwent transplantation, the most proximal values before transplant surgery were used. For patients who did not undergo transplantation, the most proximal values at the time of dataset analysis were used.

Frailty

We evaluated the association between sarcopenia and two operational physical frailty measures (SPPB and FFP). SPPB was used in binary ($SPPB \leq 7$ is frail) and continuous (range, 0–12; lower scores reflect increased frailty) forms (33). FFP was used in binary ($FFP \geq 3$ is frail) and continuous (range, 0–5; higher scores reflect increased frailty) forms

Table 1. Description of sarcopenia definitions

	Muscle Mass (Men)	Muscle Mass (Women)	Grip Strength (Men)	Grip Strength (Women)	Gait Speed
EWGSOP2					
Limited*	$ASM/ht^2 < 7.0 \text{ kg/m}^2$	$ASM/ht^2 < 5.5 \text{ kg/m}^2$	—	—	—
Expanded†			and	<27 kg	or
FNIH					
Limited	$ASM_{BMI} < 0.8$	$ASM_{BMI} < 0.512$	—	—	—
Expanded			and	<26 kg	or
Lowest Quartile					
Limited	$ASM/ht^2 < 7.4 \text{ kg/m}^2$	$ASM/ht^2 < 5.8 \text{ kg/m}^2$	—	—	—
Expanded			and	<27 kg	or
				<14 kg	or
					$\leq 0.8 \text{ m/s}$

Definition of abbreviations: ASM = appendicular skeletal muscle mass; BMI = body mass index; EWGSOP2 = European Working Group on Sarcopenia in Older People 2; FNIH = Foundation for the National Institutes of Health; Lowest Quartile = distribution-based lowest quartile of sarcopenic study participants.

*Limited definitions require *only* appendicular skeletal muscle mass below specified cut-point for diagnosis of sarcopenia.

†Expanded definitions require *both* appendicular skeletal muscle mass *and either* grip strength or gait speed below specified cut-points for diagnosis of sarcopenia.

(34). The FFP physical activity domain was assessed using the Duke Activity Status Index rather than Minnesota Leisure Time Activity scale, a modification shown to improve FFP construct and predictive validity in advanced lung disease (35).

Outcome Variables

Physical disability was quantified using the Lung Transplant Valued Life Activities (LT-VLA) scale, a 15-item measure of disability validated for use in advanced lung disease and lung transplantation (range, 0–3; higher scores reflect greater disability; a change of 0.3 is considered clinically meaningful). The LT-VLA scale measures disability across a broad spectrum of daily activities, including obligatory (required for survival), committed (focused on social roles such as working or caring for others), and discretionary (activities of leisure) categories (36).

Frailty and sarcopenia measures were not provided to the clinical team and thus were not factored into clinical decision-making regarding removal from the lung transplant waitlist. Dates of waitlist death or delisting because of being deemed too ill for transplantation were abstracted from the medical record at the time the dataset was analyzed.

Analytical Approach

To evaluate construct validity, we used Pearson correlation coefficients to measure the magnitude and direction of association between ASM/ht^2 or ASM_{BMI} and our variables of interest. Next, we assessed “known-groups” construct validity by Student’s *t* test for SPPB, SF12-PCS, and SF12-MCS and Hodge-Lehman tests for 6MWD and Trails B Test. Known-groups testing allows for comparison of the relative construct validity of each definition. Using this method, the proportion of hypotheses met by each definition can be compared. Construct validity is considered to be strong if at least 75% of hypotheses are met (37). We hypothesized that sarcopenia would be associated with shorter 6MWD and worse SF12-PCS and SPPB frailty score and would not be associated with Trails B Test score or SF12-MCS. We tested agreement between the candidate sarcopenia definitions using Cohen’s κ .

Next, we evaluated the association between appendicular skeletal muscle mass index (ASM/ht^2) and frailty by SPPB and FFP using generalized additive models adjusted for age, sex, and diagnosis. Although prior literature has demonstrated that sarcopenia is

associated with frailty, most studies have tested this relationship using dichotomous definitions of sarcopenia, imposing a potentially artificial threshold on sarcopenia as “present” or “absent.” Whether a clear threshold or a more graded relationship exists between muscle mass and risk of frailty has not previously been established in advanced lung disease. Generalized additive models allowed us to model the relationship between muscle mass and frailty and to model whether that relationship was linear or nonlinear.

Sarcopenia is a well-established risk factor for physical disability in other populations. As a limited proxy for sarcopenia, low BMI has been associated with increased risk of waitlist death but is prone to misclassification. Identifying associations between sarcopenia and clinical outcomes would begin to elucidate sarcopenia’s clinical relevance in advanced lung disease and transplantation. Thus, to assess the relationship between sarcopenia and waitlist disability and death, we tested associations between our candidate sarcopenia definitions and these outcomes by linear regression and Cox proportional hazard modeling, respectively. All models were adjusted for age, sex, race, and diagnosis. There were no significant interactions between candidate sarcopenia definitions and covariates included in the models.

For our primary models of predictive validity, we aimed to estimate the total effect of regressing sarcopenia on disability or waitlist delisting/death. In these models, we adjusted for age, sex, race, and diagnosis but did not adjust for other markers of disease severity and transplant urgency that may lie on the causal pathway between sarcopenia and disability and waitlist delisting/death. For example, some of these markers, such as weight loss (low BMI), low albumin, exercise intolerance (6MWD), or the Lung Allocation Score itself likely reflect both sarcopenia (causal pathway) and advanced lung disease (Figure E2 in the online supplement).

We recognized that some may be interested in the relationship between sarcopenia and disability and waitlist delisting/death independent of a measure of disease severity. Thus, in secondary models, we also adjusted for the Lung Allocation Score, calculated at the time of body composition measurement (Table E4).

For death, we employed a composite outcome of waitlist delisting because of being too ill or death, as we have done previously (9). We compared cumulative probabilities of death/delisting between sarcopenic and

nonsarcopenic groups using Kaplan-Meier methods. For Cox models, nonproportionality was tested using martingale residuals.

Not all subjects completed their pretransplant visits. Overall, the rate of missing data was small (21/424 [=5%] for the frailty assessment and 60/424 [=14%] for the survey on pretransplant disability and HRQL). We imputed missing values based on reasons for missingness. Missing data were considered missing at random (MAR) if a subject did not complete the frailty assessment or the survey for reasons other than health (for example, he/she missed the clinic appointment because of inclement weather, left the clinic before completing the frailty assessment or survey because of traffic, refused assessment for non-health-related reasons, or was unable to answer the survey because of limited English proficiency). A frailty assessment or survey was categorized as missing not at random if the subject was hospitalized or too ill to complete it. For data MAR, we performed 20-fold multiple imputation. Because the distribution of missing data was not balanced across centers, an indicator for centers was included in the multiple imputation model. The assumption of missing completely at random (MCAR) is stronger than MAR and is relatively rare. Because multiple imputation can be applied on data both MAR and MCAR, we did not test whether our data was MAR or MCAR specifically. For data missing not at random, we imputed with the median of the worst quartile of observed values, as we have done previously (38). Patients lacking both grip strength and gait speed ($n = 26$) were included only in the analyses involving the limited definitions of sarcopenia. Analyses were performed using R (version 3.6.1, R Foundation) and SAS (version 9.4, SAS Institute).

Results

Of 424 adult lung transplant candidates, 197 (46%) were female, with a median age of 57 years (interquartile range [IQR], 52–66); 326 (77%) were White, 35 (8%) were Asian, 29 (7%) were Black/African American, 34 (8%) identified as another race, and 66 (16%) were Hispanic. Most participants had interstitial lung disease ($n = 283$; 67%), followed by COPD ($n = 85$; 20%) (Table 2). The median follow-up time was 10.7 months (IQR, 5.2–15.3).

Depending on the definition used, the prevalence of sarcopenia varied. For example, 12% of participants had sarcopenia by the

Table 2. Demographics and baseline characteristics by sarcopenia status

Variable	Limited Definitions					
	EWGSOP2		FNIH		Lowest Quartile	
	Nonsarcopenic	Sarcopenic	Nonsarcopenic	Sarcopenic	Nonsarcopenic	Sarcopenic
Number of subjects	366	58	372	52	320	104
Age, yr	57.9 (11.9)	53.7 (14.2)	57.1 (12.5)	59.1 (10.2)	58.2 (11.9)	54.7 (12.9)
Sex, F	170 (46.4)	27 (46.6)	181 (48.7)	16 (30.8)	150 (46.9)	47 (45.2)
Race						
White	292 (79.8)	34 (58.6)	293 (78.8)	33 (63.5)	261 (81.6)	65 (62.5)
Black	27 (7.4)	2 (3.4)	29 (7.8)	0 (0)	24 (7.5)	5 (4.8)
Asian	21 (5.7)	14 (24.1)	26 (7.0)	9 (17.3)	18 (5.6)	17 (16.3)
Other	26 (7.1)	8 (13.8)	24 (6.5)	10 (19.2)	17 (5.3)	17 (16.3)
Hispanic	51 (13.9)	15 (25.9)	46 (12.4)	20 (38.5)	37 (11.6)	29 (27.9)
Disease diagnosis*						
COPD	73 (19.9)	12 (20.7)	80 (21.5)	5 (9.6)	64 (20.0)	21 (20.2)
PAH	22 (6.0)	2 (3.4)	21 (5.6)	3 (5.8)	18 (5.6)	6 (5.8)
CF	24 (6.6)	8 (13.8)	32 (8.6)	0 (0)	19 (5.9)	13 (12.5)
IPF	247 (67.5)	36 (62.1)	239 (64.2)	44 (84.6)	219 (68.4)	64 (61.5)
BMI, kg/m ²	26.8 (4.2)	21.4 (3.5)	25.7 (4.5)	28.1 (3.6)	27.2 (4.1)	22.4 (3.6)
SF12-PCS	27.2 (9.3)	26.0 (9.3)	27.1 (9.5)	26.4 (8.4)	27.1 (9.3)	27.0 (9.4)
6MWD, m	280 [175–366]	203 [109–298]	279 [175–366]	200 [110–298]	278 [179–366]	246 [127–324]
LAS	42.8 (13.9)	48.5 (18.8)	42.9 (14.5)	48.3 (16.1)	42.4 (13.1)	47.1 (18.5)
SPPB score	9.9 (2.7)	8.3 (3.9)	9.8 (2.9)	9.3 (3.1)	10.0 (2.6)	8.9 (3.6)
Trails B Test score	92 [69–119]	104 [76–139]	92 [69–119]	109 [76–141]	88 [68–115]	106 [77–142]
SF12-MCS	48.1 (10.7)	48.8 (13.4)	47.9 (11.0)	50.2 (11.5)	48.1 (10.7)	48.2 (12.1)
Variable	Expanded Definitions					
	EWGSOP2		FNIH		Lowest Quartile	
	Nonsarcopenic	Sarcopenic	Nonsarcopenic	Sarcopenic	Nonsarcopenic	Sarcopenic
Number of subjects	367	36	378	25	353	50
Age, yr	57.5 (12.1)	56.6 (12.2)	57.2 (12.4)	61.0 (6.8)	57.4 (12.1)	57.5 (12.6)
Sex, F	169 (46.0)	19 (52.8)	177 (46.8)	11 (44.0)	166 (47.0)	22 (44.0)
Race						
White	292 (79.6)	19 (52.8)	297 (78.6)	14 (56.0)	282 (79.9)	29 (58.0)
Black	24 (6.5)	2 (5.6)	26 (6.9)	0 (0)	25 (7.1)	1 (2.0)
Asian	25 (6.8)	7 (19.4)	27 (7.1)	5 (20.8)	23 (6.5)	9 (18.0)
Other	26 (7.1)	8 (22.2)	28 (7.4)	6 (24.0)	23 (6.5)	11 (22.0)
Hispanic	53 (14.4)	11 (30.6)	54 (14.4)	8 (33.3)	48 (13.6)	16 (32.0)
Disease diagnosis*						
COPD	76 (20.7)	7 (19.4)	80 (21.2)	3 (12.0)	75 (21.2)	8 (16.0)
PAH	23 (6.3)	1 (2.8)	23 (6.1)	1 (4.0)	22 (6.2)	2 (4.0)
CF	27 (7.4)	3 (8.3)	30 (7.9)	0 (0)	27 (7.6)	3 (6.0)
IPF	241 (65.7)	25 (69.4)	245 (64.8)	21 (84.0)	229 (64.9)	37 (74.0)
BMI, kg/m ²	26.5 (4.4)	21.6 (3.6)	25.9 (4.5)	27.5 (4.2)	26.5 (4.4)	22.6 (3.8)
SF12-PCS	27.3 (9.4)	25.8 (9.0)	27.2 (9.5)	26.8 (8.2)	27.4 (9.5)	26.0 (8.3)
6MWD, m	283 [183–367]	185 [100–276]	282 [182–366]	175 [93–226]	282 [183–366]	198 [119–312]
LAS	41.7 (12.3)	48.2 (16.7)	41.7 (12.4)	50.9 (16.4)	41.5 (11.9)	48.2 (17.5)
SPPB score	10.0 (2.7)	7.8 (3.8)	9.9 (2.8)	8.4 (3.4)	10.1 (2.7)	8.1 (3.6)
Trails B Test score	92 [69–119]	105 [85–144]	92 [69–118]	117 [95–157]	90 [69–117]	110 [81–150]
SF12-MCS	48.2 (10.8)	47.6 (12.7)	48.2 (11.0)	47.8 (11.8)	48.2 (11.1)	48.4 (10.7)

Definition of abbreviations: 6MWD = 6-minute walk distance; BMI = body mass index; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; EWGSOP2 = European Working Group on Sarcopenia in Older People 2; FNIH = Foundation for the National Institutes of Health; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range; LAS = Lung Allocation Score (measured at time of body composition assessment); Lowest Quartile = distribution-based lowest quartile of sarcopenic study participants; PAH = pulmonary arterial hypertension; SF12-MCS = Short Form 12 Mental Health Composite Score; SF12-PCS = Short Form 12 Physical Health Composite Score; SPPB = Short Physical Performance Battery. Data are presented as *n* (%), mean ± SD, or median [IQR].

*Disease diagnoses used for calculation of LAS.

limited FNIH Sarcopenia Project definition, and 6% had sarcopenia by the expanded version. Thirteen percent of participants had

sarcopenia by the limited EWGSOP2 definition, and 8% of participants had sarcopenia by the expanded version. By

definition, the prevalence of sarcopenia by limited lowest quartile cut-point was 25% (Table 2). Notably, only 12 participants (3%)

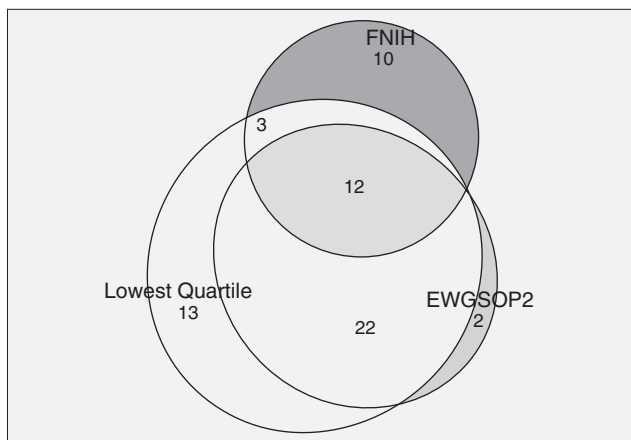


Figure 1. Circles display total number of patients deemed sarcopenic by each expanded definition: EWGSOP2 (35), FNIH (24), Lowest Quartile (52). EWGSOP2 = European Working Group on Sarcopenia in Older People 2; FNIH = Foundation for the National Institutes of Health; Lowest Quartile = distribution-based lowest quartile of sarcopenic study participants.

Table 3. Correlations between muscle mass and conceptually related functional and health-related quality of life variables

Variable	ASM/ht ²	ASM _{BMI}
6MWD	0.16*	0.21*
Frailty (SPPB)	0.15*	0.14*
SF12-PCS	0.11	0.13*
Trails B Test score	-0.05	-0.09
SF12-MCS	-0.02	0.001

Definition of abbreviations: 6MWD = 6-minute walk distance; ASM = appendicular skeletal muscle mass; BMI = body mass index; EWGSOP2 = European Working Group on Sarcopenia in Older People 2; FNIH = Foundation for the National Institutes of Health; SF12-MCS = Short Form 12 Mental Health Composite Score; SF12-PCS = Short Form 12 Physical Health Composite Score; SPPB = Short Physical Performance Battery. ASM/ht² was used in lowest quartile and EWGSOP2 definitions. ASM_{BMI} was used in FNIH definitions.

*Statistically significant at $P < 0.05$. Testing by Pearson correlation coefficient.

met criteria for sarcopenia by all three expanded definitions (Figure 1). Although the proportion of patients deemed to have sarcopenia by the limited FNIH and EWGSOP2 definitions was similar, agreement was minimal (Cohen's $\kappa = 0.32$; $P < 0.0001$). Agreement between the expanded FNIH and EWGSOP2 definitions was also minimal ($\kappa = 0.35$; $P < 0.0001$). Those labeled sarcopenic by an EWGSOP2 definition appeared younger, with a lower BMI and a higher likelihood of being female compared with those labeled sarcopenic by an FNIH definition (Table 2). However, agreement between the limited versions of the EWGSOP2 and lowest quartile definitions was stronger (Cohen's $\kappa = 0.66$; $P < 0.0001$), as was agreement between the expanded versions of these definitions (Cohen's $\kappa = 0.77$; $P < 0.0001$) (Table E3).

Construct Validity

The 6MWD and SPPB correlated with both ASM/ht² and ASM_{BMI}. SF12-PCS correlated with ASM_{BMI} but not with ASM/ht². No measure of muscle mass correlated with Trails B Test score or SF12-MCS (Table 3). Although the magnitudes of correlations were small, muscle mass correlated with a majority of variables believed to be conceptually related to sarcopenia and did not correlate with variables believed to be conceptually unrelated to sarcopenia.

Known-group testing revealed differences in construct validity across definitions. Within the limited definitions, EWGSOP2 exhibited the greatest validity, with 80% of hypotheses maintained, followed equally by the expanded EWGSOP2 definition and both forms of the FNIH and

lowest quartile definitions (60% maintained) (Table 4).

Sarcopenia as a Physical Component of Frailty

After controlling for age, sex, and diagnosis, the relationship between ASM and risk of frailty by both SPPB and FFP appeared to be linear ($P < 0.01$) (Figure 2). Notably, these models did not identify a threshold for muscle mass above which the risk of frailty plateaued.

Predictive Validity

By both EWGSOP2 definitions and the expanded lowest quartile definition, sarcopenia was independently associated with higher pretransplant disability. Sarcopenia by the limited lowest quartile definition showed an association with similar magnitude of effect and CI, although it was not statistically significant. Other definitions were not associated with LT-VLA disability (Table 5). In secondary analyses including Lung Allocation Score as a covariate, the associations between sarcopenia and disability were modestly attenuated (Table E4).

In unadjusted analyses, sarcopenia by the limited EWGSOP2 definition and both the limited and expanded lowest quartile definitions was associated with a higher cumulative probability of delisting/death (Figure 3). In adjusted models, sarcopenia by limited and expanded lowest quartile definitions was associated with a threefold increased risk of delisting or death (hazard ratio [HR], 3.75; 95% confidence interval [CI], 1.42–9.93 for the limited definition and HR, 3.46; 95% CI, 1.09–10.97 for the expanded definition). Similarly, the EWGSOP2 limited and lowest quartile expanded definitions were associated with trends toward similar magnitudes of increased risk. For example, the limited EWGSOP2 definition was associated with a 2.84-fold increased risk of delisting or death, although the CI crossed unity (95% CI, 0.94–8.55) (Table 5). In secondary analyses including Lung Allocation Score as a covariate, the associations between sarcopenia and waitlist delisting/death were moderately, though not entirely, attenuated and were no longer statistically significant (Table E4).

Discussion

In testing six definitions of sarcopenia within a multicenter cohort of adult lung transplant candidates, we found that sarcopenia prevalence varied by definition (6–13%). Not

Table 4. Tests of convergent and discriminant validity of sarcopenia definitions using conceptually related physiologic and functional variables

Convergent Validity									
Limited Definitions									
Variable	EWGSOP2			FNIH			Lowest Quartile		
	Nonsarcopenic	Sarcopenic	P Value	Nonsarcopenic	Sarcopenic	P Value	Nonsarcopenic	Sarcopenic	P Value
6MWD, m	280 [175–366]	203 [109–298]	<0.01*	279 [175–366]	200 [110–298]	<0.01*	278 [179–366]	246 [127–324]	0.01*
SPPB	9.9 ± 2.7	8.3 ± 3.9	<0.01*	9.8 ± 2.9	9.3 ± 3.1	0.27	10.0 ± 2.6	8.9 ± 3.6	<0.01*
SF12-PCS	27.2 ± 9.3	26.0 ± 9.3	0.40	27.1 ± 9.5	26.4 ± 8.4	0.66	27.1 ± 9.3	27.0 ± 9.4	0.94
Expanded Definitions									
Variable	EWGSOP2			FNIH			Lowest quartile		
	Nonsarcopenic	Sarcopenic	P Value	Nonsarcopenic	Sarcopenic	P Value	Nonsarcopenic	Sarcopenic	P Value
6MWD, m	283 [183–367]	185 [100–276]	<0.01*	282 [182–366]	175 [93–226]	<0.01*	282 [183–366]	198 [119–312]	<0.01*
SPPB	10.0 ± 2.7	7.8 ± 3.8	<0.01*	9.9 ± 2.8	8.4 ± 3.4	<0.01*	10.1 ± 2.7	8.1 ± 3.6	<0.01*
SF12-PCS	27.3 ± 9.4	25.8 ± 9.0	0.42	27.2 ± 9.5	26.8 ± 8.2	0.83	27.4 ± 9.5	26.0 ± 8.3	0.41
Discriminant Validity									
Limited Definitions									
Variable	EWGSOP2			FNIH			Lowest Quartile		
	Nonsarcopenic	Sarcopenic	P Value	Nonsarcopenic	Sarcopenic	P Value	Nonsarcopenic	Sarcopenic	P Value
Trails B Test, s	92 [69–119]	104 [76–139]	0.07	92 [69–119]	109 [76–141]	0.053	88 [68–115]	106 [77–142]	<0.01*
SF12-MCS	48.1 ± 10.7	48.8 ± 13.4	0.67	47.9 ± 11.0	50.2 ± 11.5	0.24	48.1 ± 10.7	48.2 ± 12.1	0.96
Expanded Definitions									
Variable	EWGSOP2			FNIH			Lowest Quartile		
	Nonsarcopenic	Sarcopenic	P Value	Nonsarcopenic	Sarcopenic	P Value	Nonsarcopenic	Sarcopenic	P Value
Trails B Test, s	92 [69–119]	105 [85–144]	0.03*	92 [69–118]	117 [95–157]	0.01*	90 [69–117]	110 [81–150]	0.01*
SF12-MCS	48.2 ± 10.8	47.6 ± 12.7	0.75	48.2 ± 11.0	47.8 ± 11.8	0.89	48.2 ± 11.1	48.4 ± 10.7	0.89

Definition of abbreviations: 6MWD = 6-minute walk distance; EWGSOP2 = European Working Group on Sarcopenia in Older People 2; FNIH = Foundation for the National Institutes of Health; Lowest Quartile = distribution-based lowest quartile of sarcopenia study participants; SF12-MCS = Short Form 12 Mental Health Composite Score; SF12-PCS = Short Form 12 Physical Health Composite Score; SPPB = Short Physical Performance Battery. *Statistically significant at $P < 0.05$. “Known-groups” validity testing by Student’s t and Hodge-Lehman tests.

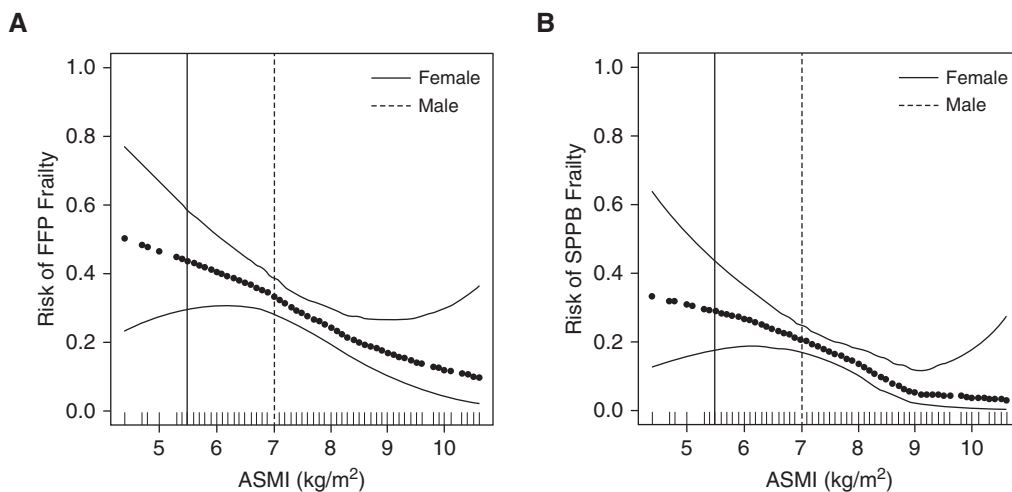


Figure 2. (A and B) Risk of frailty by Fried frailty phenotype (FFP) (A) and short physical performance battery (SPPB) (B) by appendicular skeletal muscle mass index (ASMI). Generalized additive models; horizontal dark dotted black line represents the effect estimates. Surrounding thin lines represent 95% confidence bands. Full-height solid and dashed vertical lines represent sex-specific ASMI cut-points for sarcopenia diagnosis. Each vertical line in the rug plot along the x-axis represents a single study subject. Models are adjusted for age, sex, and diagnosis.

Table 5. Associations between sarcopenia and pretransplant LT-VLA disability and waitlist delisting or death

	Pretransplant Disability	Waitlist Delisting or Death
Definition	Regression Estimate (95% CI)	Hazard Ratio (95% CI)
EWGSOP2		
Limited	0.20* (−0.0001 to 0.41)	2.84 (0.94 to 8.55)
Expanded	0.25† (−0.0004 to 0.51)	1.25 (0.25 to 6.10)
FNIH		
Limited	−0.03 (−0.24 to 0.18)	0.98 (0.26 to 3.70)
Expanded	0.16 (−0.12 to 0.45)	1.00 (0.12 to 8.21)
Lowest Quartile		
Limited	0.07 (−0.09 to 0.23)	3.75‡ (1.42 to 9.93)
Expanded	0.23‡ (0.01 to 0.44)	3.46‡ (1.09 to 10.97)

Definition of abbreviations: CI = confidence interval; EWGSOP2 = European Working Group on Sarcopenia in Older People 2; FNIH = Foundation for the National Institutes of Health; Lowest Quartile = distribution-based lowest quartile of sarcopenic study participants; LT-VLA = Lung Transplant-Specific Valued Life Activities Disability Scale.

Associations between sarcopenia and pretransplant disability evaluated using linear regression. LT-VLA MID = 0.3. Associations between sarcopenia definitions and composite outcome of waitlist delisting or death evaluated using Cox proportional hazards models. One patient who was enrolled after transplant was excluded from Cox analyses. All analyses adjusted for age, sex, race, and diagnosis.

* $P = 0.0501$.

† $P = 0.054$.

‡Statistically significant at $P < 0.05$.

surprisingly, prevalence was lower when definitions of sarcopenia included measures of both muscle mass and quality compared with muscle mass alone. We found that existing sarcopenia definitions demonstrate a range of construct validity when applied to lung transplant candidates. The limited (muscle mass alone) EWGSOP2 definition was found to be most valid in this population. Both EWGSOP2 definitions and the expanded lowest quartile definition were associated with greater pretransplant disability. Sarcopenia by the limited and expanded lowest quartile definitions was associated with increased risk of waitlist delisting or death, and there was a trend toward increased risk by the limited EWGSOP2 definition. These results suggest that assessment of muscle mass alone may be sufficient when measuring sarcopenia in lung transplant candidates and when risk-stratifying patients by sarcopenia status for certain transplant outcomes.

The specific population of individuals labeled sarcopenic varied from one sarcopenia definition to the next. These differences highlight the limitations of adopting and applying definitions without validating them in the population of interest. The variation in these populations means that a patient labeled sarcopenic by one definition may not be sarcopenic by another; in turn, risk stratification for the pretransplant outcomes examined may vary by the definition applied. These findings underscore the importance of further testing the predictive validity of

sarcopenia definitions in larger cohorts and with longer-term outcomes before implementing these candidate definitions in clinical decision-making. The apparent linear relationship between decreased muscle mass and increased risk of frailty supports sarcopenia's role as a physical component of frailty; as an individual becomes more sarcopenic, his or her risk of frailty also increases. This relationship has not previously been demonstrated in advanced lung disease. Notably, the linear relationship between muscle mass and frailty without evidence of a threshold challenges the clinical utility of defining a set cut-point for muscle mass below which a patient is deemed "sarcopenic." Rather, if muscle mass is weighed in clinical decision-making, our findings argue that muscle mass would be better considered on a continuum rather than dichotomizing sarcopenia as present or absent.

The magnitudes of correlations between muscle mass and conceptually related variables of interest were weak. Although speculative, it is possible that the relative contribution of sarcopenia to factors such as 6MWD, frailty, and SF12-PCS may be modest in the setting of end-stage lung disease. Furthermore, our cohort reflects a unique population of patients with end-stage lung disease who are deemed candidates for lung transplantation. It is likely that they represent a less overtly frail and debilitated group than the general population of adults with end-stage lung

disease. These findings highlight limitations and potential risks of applying sarcopenia definitions derived in other populations to candidates for lung transplantation. They also underscore the importance of assessing the validity of potential definitions of sarcopenia before implementing them into clinical or research practice. We caution against extrapolating our findings to adults with end-stage lung disease not being considered for lung transplantation.

Our findings contribute to emerging literature focused on identifying more advanced approaches to evaluating body composition in candidates for solid organ transplantation. Currently, BMI is the most common clinically employed measure of body composition. Many consider obesity ($BMI \geq 30$ or ≥ 35) and underweight status ($BMI \leq 18.5$) to be relative contraindications to transplantation on the basis of associations with mortality after lung transplantation (39). In these instances, BMI is employed as a surrogate for either total body adipose tissue (obesity) or undernourishment, malnourishment, or sarcopenia (underweight). Importantly, BMI fails to directly quantify muscle and fat, resulting in misclassification of both obesity and sarcopenia (40–42). In addition, patients with elevated BMI may have both excess adipose tissue and low muscle mass (a state referred to as "sarcopenic obesity") (42). Our findings raise the possibility that directly quantifying muscle mass and adipose tissue could

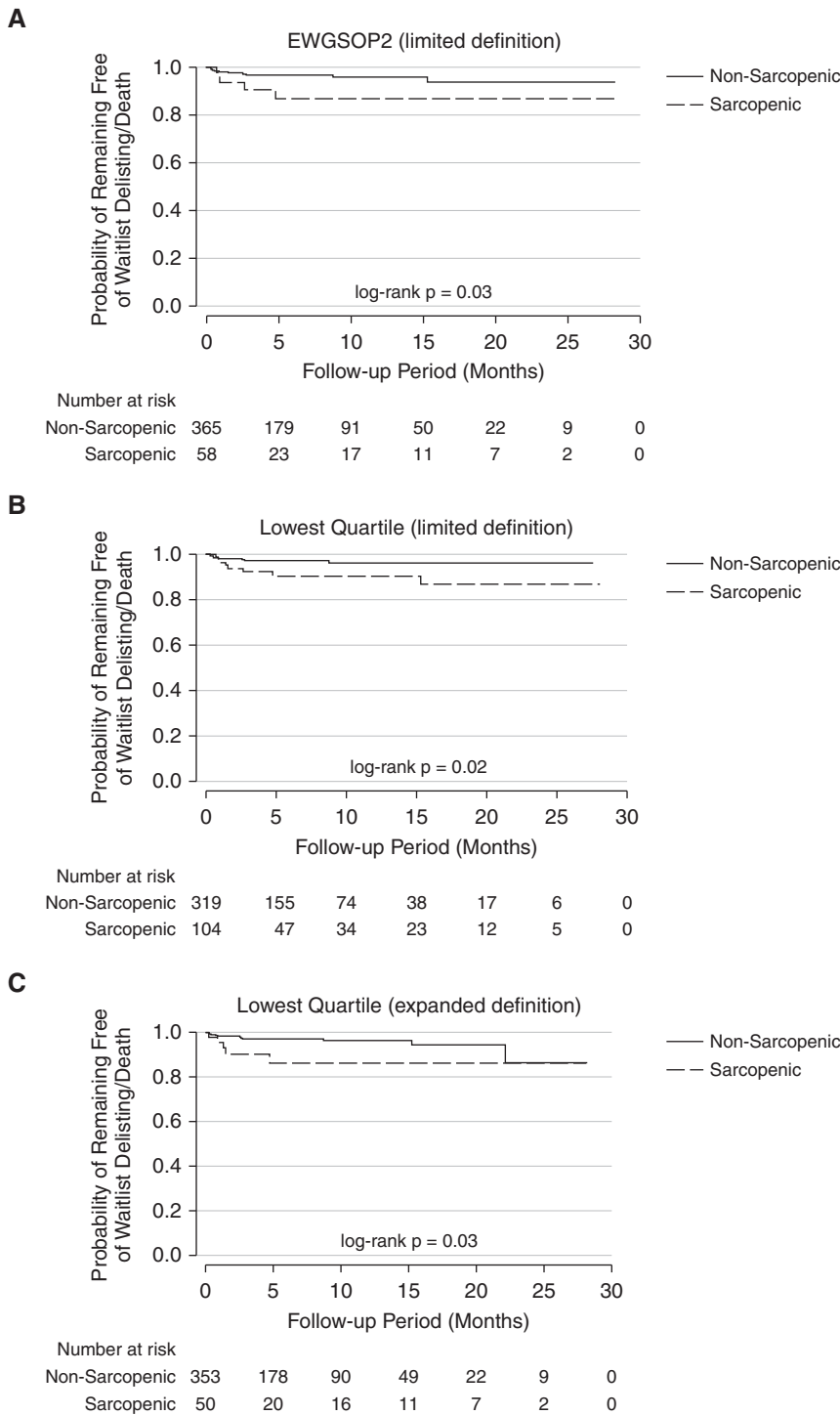


Figure 3. Time to waitlist delisting or death of sarcopenic patients by (A) limited EWGSOP2, (B) limited Lowest Quartile, and (C) expanded Lowest Quartile definitions. EWGSOP2 = European Working Group on Sarcopenia in Older People 2; Lowest Quartile = distribution-based lowest quartile of sarcopenic study participants.

improve the precision and accuracy of candidate risk stratification before transplantation.

This study has limitations. Our study cohort is composed of patients already listed or near listing for lung transplantation; whether our findings can be generalized to other patients with lung disease is unknown. Idiopathic pulmonary fibrosis is the predominant diagnosis within our study population; thus, our study cohort may not be representative of other transplant candidate populations. Unmeasured covariates may explain associations seen between sarcopenia and pretransplant disability or waitlist delisting/death. For example, it is possible that, in a subset of patients, corticosteroid use contributed to our findings. When controlling for Lung Allocation Score (LAS), the association between some definitions of sarcopenia and waitlist delisting/death may be mediated by some factors already included in the LAS. However, the magnitude of the associations, despite controlling for LAS, does suggest that directly measuring body composition may add clinically relevant information not collected as part of the routine clinical evaluation. Finally and importantly, this study did not investigate the impact of sarcopenia on outcomes after lung transplantation. Clarifying this impact and the relevance of sarcopenia across clinically important strata of lung transplant candidates is needed before sarcopenia can be used to inform patient management.

Our study has notable strengths. We examined a large multicenter prospective cohort. Sample size permitted us to control for several covariates when analyzing associations between sarcopenia and pretransplant outcomes. Use of a distribution-based definition of sarcopenia derived from our study population allowed for comparison of construct validity and absolute cut-points for sarcopenia diagnosis between this definition and existing definitions from geriatric literature.

In summary, we found that the prevalence, construct validity, and predictive validity of sarcopenia vary depending on the operational definition used. We also

identified a linear relationship between muscle mass and risk of frailty. Future studies should evaluate associations between sarcopenia and post-transplant morbidity and mortality as well as whether interventions to

improve muscle mass and function improve clinical outcomes. ■

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

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