ISHLT CONSENSUS STATEMENT

Assessing and Addressing Frailty in Candidates for Lung Transplantation: An ISHLT Consensus Statement

Michaela Restivo Anderson, MD, MS,[a] Selim M. Arcasoy, MD, MPH,[b] Christian Benden, MD, MBA, FCCP, FERS,[c] Marie Budev, DO,[d] Marlene Cano, MD, PhD,[e] Kam Man Larissa Chandra, MHLM, BAppSc (Occupational Therapy),[f] Malachy J. Clancy, PhD, OTR/L,[g] Joshua Diamond, MD, MSCE,[h] Ioannis Dimarakis, MD, PhD,[i] Alexander Dragnich, MD,[j] Louise Fuller, PhD, BAppSci(Physio),[k] Vasiliki Gerovasili, MD,[l] Laurent Godinas, MD,[m] Zubair A. Hashmi, MD,[n] Are M. Holm, MD, PhD,[o] Brittany Koons, PhD, RN,[p] Zsofia Kovacs, MD,[q,1] Jin Gu Lee, MD,[r] Erin M. Lowery, MD, MS,[s] Julia Maheshwari, MD,[t] Federica Meloni, MD,[u] Elyn Montgomery, PhD, RN,[v,1] Catherine Myers, MD,[w] Justin Rosenheck, DO,[x,1] Aman Sidhu, MD,[y] Lianne G. Singer, MD, FRCPC,[y,1] Laurie D. Snyder, MD, MHS,[z,1] Syed Tousheed, MD,[aa] Rhea Varughese, MD, MS,[ab] James R. Walsh, BPhty, PhD,[ac,1] Barbara Wilkey, MD,[ad] Monique Malouf, MBBS, FRACP,[f] and Jonathan P. Singer, MD, MS[t]

[a]University of Pennsylvania, Philadelphia, PA; [b]Columbia University Medical Center, New York, NY; [c]Boston Children's Hospital and Harvard Medical School, Boston, MA; [d]Cleveland Clinic, Cleveland, OH; [e]Washington University St Louis Medical Center, St Louis, MO; [f]St Vincent's Hospital Sydney, Darlinghurst, Australia; [g]Thomas Jefferson University, Philadelphia, PA; [h]GlaxoSmithKline, London, UK; [i]University of Washington, Seattle, WA; [j]Vanderbilt University Medical Center, Nashville, TN; [k]The Alfred, Melbourne, Australia; [l]Harefield Hospital, Harefield, UK; [m]UZ Leuven, Leuven, Belgium; [n]Virginia Commonwealth University, Richmond, VA; [o]Oslo University Hospital, Oslo, Norway and Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [p]Villanova University, Villanova, PA; [q]Medical University of Vienna, Vienna, Austria; [r]Yonsei University College of Medicine, Seoul, Korea; [s]University of Wisconsin, Madison, WI; [t]University of California San Francisco, San Francisco, CA; [u]University of Pavia Policlinico San Matteo, Pavia, Italy; [v]University of Technology Sydney, Sydney, Australia; [w]Northwestern Feinberg School of Medicine, Chicago, IL; [x]Ohio State University Wexner Medical Center, Columbus, OH; [y]University Health Network, Toronto, Canada; [z]Duke University, Durham, NC; [aa]The Royal Papworth Hospital Trust, Cambridge, UK; [ab]University of Alberta, Edmonton, CA; [ac]The Prince Charles Hospital, Brisbane, Australia; [ad]The University of Colorado, Aurora, CO.

The ISHLT Consensus document for the selection of lung transplant candidates recommends frailty assessment as part of a comprehensive candidacy evaluation. Missing from this and other recent consensus documents were practical recommendations on which frailty measures to consider and what to do with the information once obtained. In this consensus document, we address practical and logistical issues regarding the assessment and management of frailty in lung transplant candidates.
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KEYWORDS:
Frailty; Lung transplantation

Abbreviations: BIA, bioelectrical impedance assay; BTT, bridge to transplantation; CF, Cystic Fibrosis; CENTRAL, Cochrane Central Register of Controlled Trials; CLAD, chronic lung allograft dysfunction; DASI, Duke activity status index DASI; ECMO, extracorporeal membrane oxygenation; EMBASE, Excerpta Medica Database; FI, Frailty Index; FFP, Fried Frailty Phenotype; ICU, Intensive Care Unit; ISHLT, International Society of Heart and Lung Transplantation; LOS, length of stay; LT-FS, Lung Transplant Frailty Score; SPPB, Short Physical Performance Battery

[1] Denotes section lead.

Corresponding author: Michaela R Anderson, MD, MS, 3400 Spruce Street Gates 9W 09041 S, Philadelphia, PA, 19104.
E-mail address: michaela.anderson@pennmedicine.upenn.edu.

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1. BACKGROUND

Interest in frailty in lung transplantation has grown over the last decade, driven by evolving candidate characteristics, including older age, greater disease severity, and multiple co-morbidities.[1–3] Frailty is now established as a risk factor for disability, death, and delisting prior to lung transplantation,[4] as well as prolonged hospitalization,[5] discharge to an acute rehabilitation facility,[6] and mortality[7] after lung transplantation. The most recent International Society of Heart and Lung Transplantation (ISHLT) international consensus on lung transplant candidate selection recommends incorporating frailty assessment into candidate evaluation.[8] How to practically implement frailty assessment into candidate evaluation and management, however, has not been previously addressed.

An informative and useful frailty measure in lung transplant candidates must be reproducible and fair. Subjective assessments of frailty (i.e., the "eyeball test") may vary by gender, underweight, obesity, and age.[9,10] In addition to risks of bias, subjective assessments can be inconsistent across providers and fail to identify milder forms of frailty associated with poor transplant outcomes.[11,12] Objective measures are required to ensure equitable evaluation of all candidates.

For clinical implementation, programs should select a frailty measure with an established evidence base supporting its use in lung transplant populations. Most frailty measures were originally developed in community-dwelling older adults, who differ significantly from lung transplant candidates. Frailty measures used in lung transplant clinical decision-making must therefore have demonstrated associations with clinically important lung transplant outcomes.[13,14] Although many lung transplant centers have incorporated frailty assessment into their evaluation process,[15] the specific measures used vary widely. In renal transplant, a national survey found that 40% of programs never assessed frailty, while 38% performed frailty testing in all candidates. Among programs that did frailty assessments, 18 different measurement tools were used across programs.[16] The optimal tool(s), timing, and frequency of frailty assessments in lung transplant candidates and, once identified, what to do about frailty, have not been addressed in prior guidelines or consensus statements.

Valid, informative, standardized frailty assessments can help set patient and caregiver expectations, facilitate listing decisions, identify candidates who would benefit from targeted intervention, assess program performance, and inform institutional resource planning. In this consensus document, we address practical and logistical issues regarding the assessment and management of frailty in lung transplant candidates. To do so, we performed a systematic literature review and developed expert consensus focused on the practical considerations required to integrate frailty into lung transplant candidate evaluations, including (i) how to choose a frailty measure, (ii) when to repeat measurements, and (iii) what to do once frailty is identified.

2. METHODOLOGY

The ISHLT follows a formal process to request proposals for the development of standards and guidelines documents and solicit member participation. This consensus document was proposed in 2024. After the proposal was approved, the ISHLT Standards and Guidelines (S&G) Committee invited MRA, MM, and JPS to lead the development of this consensus statement. A public announcement of the intent to write a consensus statement was posted on the open ISHLT forum inviting interested ISHLT members to participate in formulating this statement.

2.1. Panel Composition

The statement leads worked with the ISHLT S&G Committee to identify writing committee members and leads for the 3 main sections of this document. Members were selected from those who expressed interest in participation as well as other experts in the community. To establish a statement that reflects the diverse practices of the worldwide lung transplant community, the team sought to include diversity by geography, gender, level of seniority, and sub-specialty. Section leads and writing group members were approved by the ISHLT S&G Committee, and the project began in August of 2024.

2.2. Literature Search

A subset of members of the writing committee volunteered to lead the literature search. The search aimed to identify publications broadly relevant to frailty and lung transplantation or lung disease. Methods and final search criteria are available in the Supplemental Methods.

The literature search was performed by a librarian at Oslo University Hospital in the following databases: Ovid Medline, Excerpta Medica Database (EMBASE), and the Cochrane Central Register of Controlled Trials (CENTRAL). Studies published from January 1, 2000, to August 27, 2024 were considered. The literature review team identified 2069 potential publications for inclusion. Using the Covidence online review program (Covidence, Melbourne, and Australia), each title and abstract of all potential publications were reviewed by 2 members of the literature search team to identify those relevant to the statement. If there was disagreement between the 2 members about relevance, a third member of the team reviewed and adjudicated the publication for inclusion. The final list included 401 potential publications for inclusion.

Each writing section was given access to these 401 publications. Each writing section then developed specific approaches to reviewing full-text documents for consideration of inclusion in their section and could add additional references as deemed appropriate. Writing sections then synthesized the available publications and crafted a narrative summary. The project leads then organized the sections and provided a draft of the full document to all writing group members for final review and editing.

2.3. Recommendations

Consensus recommendations were drafted by each writing section and reviewed and revised by project leaders to ensure clear, non-overlapping language. All writing team members reviewed and edited consensus recommendations over multiple iterations. Final consensus recommendations were then circulated to the full writing committee for voting on the level of agreement. Participants were asked to report their level of agreement with the statement using a 5-point Likert scale (Strongly Disagree, Disagree, Neither Agree nor Disagree, Agree, and Strongly Agree). Final consensus is reported by combining responses of Strongly Agree and Agree. Further breakdown by strength of agreement is available in the Supplementary Appendix.

3. DEFINING FRAILTY: MOVING FROM CONCEPT TO OPERATIONAL MEASURES

3.1. Frailty as a Concept Relevant to Lung Transplant Candidates and Recipients

Frailty is defined as a multidimensional syndrome resulting in decreased physiological reserve and resistance to stressors.[17] Frailty exists on a spectrum from robust health through a pre-frail state to severe frailty with overt disability. Pre-frail and frail individuals are more likely to experience severe and disproportionate manifestations from an acute insult or stress, including hospitalization, intensive care unit (ICU) admission, prolonged recovery, disability, or even death. Lung transplant surgery itself is a major acute stressor, highlighting the potential impact of the interaction between pre-operative frailty and transplant surgery on outcomes.

Multiple pathways have been implicated in the pathogenesis of frailty, including senescence and stem cell exhaustion, hormone dysregulation, changes in metabolism and body composition, and inflammation.[18] Chronic lung diseases share some of these pathophysiological features.[4] This is consistent with emerging evidence identifying an interdependent relationship between frailty and chronic lung disease, wherein one may potentiate the other.[19] Other factors associated with lung disease, such as fatigue, depression, and reduced physical activity, can also contribute to nutritional decline and sarcopenia, potentially accelerating frailty.[20]

Multiple frailty instruments have been developed to capture different aspects of this complex clinical syndrome. These instruments generally fall into 3 measurement categories: physical frailty, cumulative deficits, and broader geriatric assessments that also assess cognitive and social frailty. Yet, lung transplant candidates represent a population with different characteristics than the community-dwelling older adults in whom these frailty measures were originally developed. Due to the nature of the transplant process, lung transplant candidates tend to be younger and less likely to experience social isolation or cognitive impairment than the general community-dwelling older population in which frailty measures were first developed, though lung transplant candidate characteristics are changing with increasing numbers of older adults undergoing transplantation.[1–3] Frailty assessments of the lung transplant candidate, therefore, have largely focused on measures of physical frailty and cumulative physiologic deficits. Given the available evidence base, this statement focuses on measures of physical and cumulative deficit frailty, recognizing that other domains (e.g., cognitive impairments, social isolation) are also relevant in the field.

3.2. Frailty and Waitlist Outcomes

Frailty is prevalent in lung transplant candidates. Depending on the measure used, 10% to 45% of adult lung transplant candidates are frail at the time of listing.[21] Across a variety of measures, pre-transplant frailty has repeatedly been associated with worse outcomes. Pre-transplant physical frailty is associated with greater disability, reduced exercise capacity, and increased risk of waitlist death or delisting, independent of disease severity.[22–25] Pre-transplant cumulative deficit frailty is similarly associated with an increased risk of waitlist death or delisting.[5,26,27] Consistent associations between frailty and pre-transplant morbidity and mortality highlight the potential for frailty measures to inform assessments of risk of death without transplantation and waitlist timing.

3.3. Frailty and Post-transplant Outcomes

Pre-transplant frailty is also associated with worse post-transplant outcomes. Greater pre-transplant physical frailty is associated with post-operative delirium, decreased hospital-free days, and decreased survival after transplantation.[7,28–30] Greater cumulative deficit frailty is similarly associated with post-operative delirium, decreased hospital free days, increased risk of readmissions within 1-year of transplant, and decreased survival after transplantation.[5,28,31,32] Long-standing clinical experience and these findings informed the latest ISHLT consensus statement on the selection of lung transplant candidates that lists “limited functional status (e.g., non-ambulatory) with poor potential for post-transplant rehabilitation” as an absolute contraindication to transplant.[8] Thus, some programs may consider severe frailty with poor potential for post-transplant rehabilitation as an absolute contraindication.

Given the consistent associations between frailty and poorer outcomes across measures, pre-transplant frailty assessments can serve multiple purposes. They can inform patient and caregiver expectations of the post-operative course, inform institutional resource planning (e.g., physical and occupational therapy needs, ICU length of stay, etc.) and identify candidates who would benefit from targeted intervention before and after transplantation.

Despite these strong and consistent associations, however, pre-transplant frailty can resolve after transplantation. In some patients, pre-transplant frailty may be primarily driven by advanced lung disease itself (i.e., lung disease-attributable frailty). Disease-attributable frailty would be expected to resolve with transplant. Consistent with this theory, pre-transplant physical frailty does resolve after transplant in up to 84% of surviving frail recipients, with the greatest improvement occurring in the first 6 months post-transplant.[33] Additionally, patients with pre-transplant physical frailty may experience greater quality-of-life and functional benefit from transplant compared to those who are not frail.[34,35] Yet, recipients in whom post-transplant frailty persists or newly develops have increased risk of unplanned readmissions, decreased health-related quality of life, and increased risk of death.[34,36] At present, existing tools cannot differentiate lung disease-attributable from “systemic” or ”age-related” frailty, which is a key gap in the literature. Future research is needed to establish whether repeated measures of muscle strength such as quadriceps force or grip strength, functioning such as gait speed or chair stands, or early improvements in repeat frailty testing in response to prehabilitation inform assessments of reversibility.[37] In the absence of empirical evidence, programs could consider improving frailty scores in response to prehabilitation as one method of assessing reversibility. Given this imperfect ability to predict which patient with pre-operative frailty will experience major post-operative complications and/or death, programs should consider pre-transplant frailty with potential for improvement after surgery as part of a holistic evaluation of transplant candidacy.

RECOMMENDATION:

1. Pre-transplant physical frailty attributable to advanced lung disease may reverse after lung transplantation.
   Strength of Agreement: 100%

2. Programs should consider potential reversibility of frailty and program capacity to support recovery when selecting candidates with frailty for lung transplantation. *Strength of Agreement: 97%*

3.4. Physical Frailty Measures

Physical frailty measures quantify characteristics and limitations focused on the physiologic and biologic syndrome of frailty. Physical frailty measurements must be performed prospectively by trained staff. In general, staff can be trained in 30 to 40 minutes to perform assessments consistently. The physical frailty measures evaluated in lung transplant candidates are briefly detailed below. Comparisons between measures can be found in Table 1 with additional details in Supplemental Table 1. Links to case report forms for obtaining these measures can be found in Supplemental Table 2.

The Fried Frailty Phenotype (FFP) measures 5 physiological domains: weight loss, exhaustion, physical activity, muscle strength, and mobility.[13] The FFP includes physical tests for gait and grip strength and self-reported assessments of unintentional weight loss, low activity, and exhaustion. The FFP scoring ranges from 0 to 5. It can be operationalized as a continuous (higher scores indicating worsening frailty), categorical (≥3 frail, 1-2 pre-frail, and 0 not frail), or dichotomous variable (≥3 frail, 0-2 not frail).[25] The FFP takes 10–30 min to complete depending on the methods used to assess each domain.

The Short Physical Performance Battery (SPPB) evaluates lower extremity mobility, strength and energy, and physical activity.[38] It is based on 3 timed tasks: balance, walking speed, and timed stands from the seated position. The results of each subtest are combined (SPPB score range 0-12). The score can be interpreted as a continuous (higher scores indicating less limitation), categorical (frail, prefrail, not frail), or dichotomous variable; varying cut-offs have been published (≤7 or ≤9 or 10).[4,33,39] The SPPB takes 5 to 10 minutes to complete.

The lung transplant frailty score (LT-FS) is a disease-CF-FI with construct and predictive validity for mortality superior to existing tools.[29] The LT-FS offers 3 models (LTFS-base, -body composition, and -biomarker) based on routinely collected clinical variables and biomarker data, allowing flexible application. Like the FFP, the LT-FS requires a dynamometer for assessment of grip strength. The body composition model requires bioelectrical impedance measure of muscle mass. The LT-FS is scored as a dichotomous variable (frail vs non-frail) and takes 10 to 15 minutes to complete.

The *Clinical Frailty Scale* is a semi-quantitative tool utilized to evaluate an individual's degree of frailty on a scale of 1 (active, robust) to 9 (terminally ill).[40] The measurements are based on observations of the individual by a health-care professional and a review of medical records. The time to complete the measure varies.

3.5. Cumulative Deficit Measures

Cumulative deficit measures conceptualize frailty as a complex, multidimensional condition characterized by the accumulation of deficits across multiple health domains. The construct underlying these measures posits that the accumulation of health deficits serves as a quantitative proxy for aging, physiologic reserve, and fitness.[41] Cumulative deficit measures can be obtained retrospectively using routinely collected clinical data. In lung transplantation, these indices can be calculated using data from the candidate evaluation. Yet, without integration into the electronic health record to automate abstraction and calculation, these can be time-intensive to obtain. The cumulative deficit measurement tools evaluated in lung transplant candidates are briefly detailed below.

The *Frailty Index* (FI) assesses 20 to 40 comorbidities, laboratory values, and functional status indicators. Each item is scored as absent or present (0/1). The score is operationalized as the number of deficits present divided by the number of deficits available for evaluation, with the score ranging from 0 to 1 (higher score indicating more deficits). It can be operationalized as a continuous or dichotomous variable or with frailty defined as a score ≥0.25.[5,26]

The Cystic Fibrosis (CF) Specific Frailty Index (CF-FI) combines assessments of CF-specific complications, laboratory values, and medications with additional comorbidities and laboratory values. Each item is scored as absent or present (0/1). Similarly to the FI, the score is operationalized as the number of deficits present divided by the number of deficits available for evaluation with the score ranging from 0 to 1 (higher score indicating more deficits). It can be operationalized as a continuous or dichotomous variable with various cut-points used to define frailty.[27]

Table 1 Comparison of Frailty Measures

	Components	Transplant populations studied	Outcomes measured	Testing characteristics	Practicality
Physical Frailty Measures					
SPPB 21 citations	3 physical measures of lower extremity function -Chair Stand -Balance -Gait Speed	Lung transplant candidates and recipients Outpatients Some inpatients, including MV and ECLS	-Response to prehab and rehab -Response to LTx -Disability and HRQoL -Death/delisting on waitlist -Post-Tx: MV duration, ICU/Hosp LOS and complications (e.g., delirium, fractures), readmission, survival	Sensitivity: +++ Specificity: ++	Ease: ++ Reproducibility: +++ Cost: + Time: 5-10 min Reversibility: ++ Performed by: Allied Health Providers or research coordinators Performed remotely: Yes
FFP Modified FFP FFP-DASI 14 citations	Subjective and objective measures: -Weight loss -Gait Speed -Grip strength -Exhaustion -Activity level by MLTA or DASI	Lung transplant candidates Outpatients Some inpatients, including MV and ECLS	-Response to prehab and rehab -Response to LTx Disability and poorer HRQoL -Death/delisting on waitlist -Post-Tx survival	Sensitivity: ++ Specificity: ++	Ease: ++ Reproducibility: +++ Cost: + Time: 10-30 min Reversibility: ++ Performed by: Allied Health Providers or research coordinators Performed remotely: No
LT-FS 1 citation	*Base:* SPPB balance and gait measures, FFP Grip strength, CRP *Body composition*: Base + appendicular skeletal muscle index by BIA	Lung transplant candidates Outpatients Some inpatients, including MV and ECLS	-Death/delisting on waitlist -Disability and poorer HRQoL -Hospital LOS -Post-Tx 1-year survival	Sensitivity: +++ Specificity: +++	Base/ Body Composition Ease: ++/++ Reproducibility: +++/+++ Cost: +/+ Time: 5-10/10-15 min Reversibility: Unknown Performed by: Allied Health Providers or research coordinators Performed remotely: No/No
Clinical Frailty Scale 2 citations	Clinician judgment	Lung transplant candidates Outpatient Inpatient including MV and ECMO	-Post-Tx survival	Unclear	Ease: +++ Reproducibility: ++ Cost: + Time: 3-5 min Reversibility: +++ Performed by: Clinicians Performed remotely: Yes

Continued

Table 1 Comparison of Frailty Measures

	Components	Transplant populations studied	Outcomes measured	Testing characteristics	Practicality
Cumulative Deficit Measures					
Frailty Index 3 citations	Multiple components, generally obtainable from EMR/standard transplant work-up 20-40 variables in models assessed	Transplant candidates (retrospective review post LTx) Outpatients	-Hospital free days -Delisting or death on waitlist -1- and 3-year Post-Tx Survival	Sensitivity: ++ Specificity: ++	Ease: + Reproducibility: +++ Cost: + Time: 10-30 min depending on data availability Reversibility: + Performed by: Anyone with EHR access and trained to identify clinical conditions Performed remotely: Yes
CF Specific FI 1 citation	Lung Disease Severity Index consists of: Frailty Index (FI) - 66 components	Waitilsted CF patients (retrospective review post LTx)	-Worsening on Waitlist -Survival post-Tx -Graft failure (Death or retransplant) -ICU LOS -Hospital LOS	NPV for early mortality: +++	Ease: + Reproducibility: +++ Cost: + Time: 10-30 min depending on data availability Reversibility: + Performed by: Anyone with EHR access Performed remotely: Yes
Multidimensional Measures					
Edmonton Frail Scale 1 citation	Patient self-report and objective testing/data	Waitlisted transplant outpatients	-6MWD -Grip strength -Anxiety and depression	Unclear	Ease: +++ Reproducibility: ++ Cost: + Time: 5-10 min Reversibility: Unknown Performed by: Clinicians Performed remotely: No
FRS 1 citation	12 biopsychosocial factors + 4 biomarkers	Outpatients, unclear if also inpatients	-Hospital LOS -# of readmissions -Death	Unclear	Ease: + Reproducibility: ++ Cost: ++ Time: 10-30 min Reversibility: Unknown Performed by: Clinicians, Researchers Performed remotely: Yes

CF, cystic fibrosis; CLAD, chronic lung allograft dysfunction; DASI, Duke Activity Status Index; ECLS, extracorporeal life support; ECMO BTT, extracorporeal membrane oxygenation as a bridge to transplantation; EHR, electronic health record; FFP, Fried Frailty Phenotype; FI, frailty index; HRQoL, health-related quality of life; ICU, intensive care unit; LOS, length of stay; LT-FS, lung transplantation frailty scale; LTx, lung transplantation; MLTA, Minnesota Leisure Time Physical Activity questionnaire; MV, mechanical ventilation; SPPB, short physical performance batter.

3.6. Multidimensional Frailty Measures

While multiple tools are available to measure sociodemographic and cognitive frailty, there is limited data on their use in lung transplantation.

The *Edmonton Frail Scale* includes 7 questions regarding self-reported health status, a clock test for cognition, and an assessment of gait speed. The total score ranges from 0-17 with a higher score indicating greater frailty. The Edmonton Frail Scale takes 5 to 10 minutes to complete.[42]

The *Frailty Risk Score (FRS)* is a chart-review-based measure of 16 factors derived by analyzing medical charts.[43] A modified FRS form was validated on lung transplant recipients in which the FRS was operationalized as a dichotomous variable where a score of ≥3 indicating frailty was associated with increased risk of readmission. The modified FRS has 2 items that query cognitive impairments and social support, distinguishing it from other cumulative deficit measures.[32]

Additional work is required to understand the role of these tools alongside physical or cumulative deficit frailty assessments.

3.7. Sarcopenia- A Frailty-related Measure

Sarcopenia, the combination of low skeletal muscle mass with diminished muscle function, has been an area of particular interest in lung transplant candidates. The absence of an agreed-upon standard definition or measure for sarcopenia within lung transplantation likely contributes to the inconsistent association between sarcopenia and lung transplant outcomes.[4,31,44–50] This document therefore does not offer guidance on which specific methods should be used to assess sarcopenia.

4. CHOOSING A MEASURE(S) TO ASSESS FRAILTY IN LUNG TRANSPLANT CANDIDATES: BEST PRACTICES

Consensus has been lacking on the ideal instrument, or combination of instruments, to identify frailty, assess its reversibility, and determine its impact on outcomes. Frailty assessments can be performed in multiple ways - prospectively or retrospectively, in outpatients or inpatients, once or repeatedly. Each transplant program has unique resources, models of peri-transplant care, and approaches for transplant candidate selection. Rather than recommending a single frailty instrument for all programs, we instead provide a framework for instrument selection based on program-specific goals. Recommendations are based on current knowledge and expert opinion with the likelihood of revision as more data emerge in the coming years.

RECOMMENDATION:

3. We recommend that objective frailty measures be incorporated into the multidisciplinary candidate evaluation and selection process. *Strength of Agreement:* 100%.
4. We recommend that programs select a measure that has been rigorously studied in a lung transplant population and supports the reliable capture and use of data to inform clinical decision-making. *Strength of Agreement:* 100%.

4.1. Program Goals

Transplant programs must consider the goals of their program when determining how to use frailty assessments and how frailty assessments will affect listing decisions, inform clinical care, and impact patient counseling. Knowledge of the presence or absence of frailty may help programs: (i) set patient and caregiver expectations regarding pre- and post-transplant outcomes, (ii) decide whether to list frail patients and if so, when (iii) identify patients for targeted pre- and post-transplant interventions, (iv) quantify program performance for quality improvement, and (v) ensure teams are adequately staffed, including physical and occupational therapists, nutrition, speech-language pathology, and social work services, and have adequate resources to manage complications in order to help frail patients recover.

Details on the potential application of each frailty instrument in service of programmatic goals is provided in Table 2.

Table 2 Guide to Selecting a Frailty Measure Based on Program Goals

Program goal	Clinical considerations	Recommended Measure*	Who to screen	Timing of screening
Listing Decisions	Determine transplant candidacy Timing of waitlisting Candidate for ECMO BTT	Physical Frailty: SPPB, FFP, LT-FS Cumulative Deficit: Frailty Index, CF-SI	Universal	At evaluation
Intervention	Pre-Transplant interventions Post-Transplant Management: intensified rehabilitation, duration of post-transplant rehabilitation, nutritional management, swallow assessments, delirium prevention	Physical Frailty: SPPB, FFP Cumulative Deficit: None	Universal	At evaluation and post intervention
Setting expectations for post-operative course	ICU and hospital LOS Discharge to home vs rehabilitation Risks of delirium, early readmission, quality of life, mortality	Physical Frailty: SPPB, FFP, LT-FS Cumulative Deficit: Frailty Index, CF-SI, FRS	Universal	After listing
Program performance assessment	Prevalence of pre- and post-Tx frailty Adequacy of rehabilitation	Physical Frailty: SPPB, FFP Cumulative Deficit: Frailty Index, CF-SI, FRS	Universal	At evaluation and closer to time of LTx
Resource planning	Estimate ICU and hospital LOS for staffing decisions Estimate rehabilitation needs for staffing decisions	Physical Frailty: All Cumulative Deficit: All	Universal or Selective	Closer to time of LTx

*Decision regarding whether to recommend a specific frailty measure was based on whether there is any data evaluating the association between the listed measure and the relevant outcome(s) in lung transplant candidates.

ECMO BTT, extracorporeal membrane oxygenation as a bridge to transplantation; ICU, intensive care unit; LOS, length of stay; LTx, lung transplantation.

RECOMMENDATION:

5. We recommend that programs identify programmatic goals prior to selecting and implementing a frailty assessment instrument. *Strength of Agreement:* 86%
6. We recommend that transplant programs incorporate results from standardized frailty assessments into discussions with individual patients and their caregivers to help set care-related expectations. *Strength of Agreement:* 97%
7. We recommend that programs track relevant findings and outcomes to evaluate whether assessments are achieving the stated programmatic goals. *Strength of Agreement:* 97%

4.2. Selecting a Measure(s)

When selecting instruments to assess frailty, programs must weigh supporting data with programmatic resources and goals. As described above, 2 primary types of instruments exist—those assessing physical frailty and those measuring cumulative deficit frailty.

The most frequently studied physical frailty instruments in the lung transplant population are the SPPB and FFP. SPPB is a sensitive tool, objectively measuring lower extremity performance. FFP contains both objective and subjective elements and more wholly captures the syndrome of frailty. Modifications to the FFP such as the Duke activity status index are intended to better capture the physical activity of adults with advanced lung disease.[25] Both the SPPB and FFP are prospectively collected, easily performed, and readily reproducible. Minimal training is required to complete these measures (Table 1).

The LT-FS was designed specifically for a lung transplant population and includes 3 models of increasing complexity.[29] All 3 models generally have better predictive performance than the SPPB and FFP for waitlist death/delisting and 1-year post-transplant survival. The LT-FS base model requires demographics, physical testing, and clinical lab work. Like the FFP, it requires a dynamometer for assessment of grip strength. The LT-FS body composition model requires measurement of muscle mass by bioelectrical impedance assay (BIA). While feasible to obtain in clinical practice, BIA may not be readily available in all centers. The LT-FS biomarker model boasts the highest predictive validity for waitlist death or delisting but requires measurement of multiple peptides that can only be obtained at research laboratories, making this model impractical for routine clinical use.

Cumulative deficits indices are calculated using detailed clinical variables, which can be obtained via prospective assessment or retrospective chart review. Given the resource intensity of data collection, they may be less feasible for repeated measurement or tracking of frailty trajectory, unless data extraction can be automated. A benefit of these indices is their ability to identify treatable factors contributing to frailty, such as medical comorbidities.[51] The CF-FI may have limited relevance with fewer transplants performed for CF.

4.3. Feasibility

Physical frailty assessments such as the SPPB, FFP, and LT-FS can be completed quickly with good repeatability. Many programs use physical or occupational therapists to complete these tests, though they can be performed by any team member with adequate training. Cumulative frailty indices may be obtained through comprehensive review of the medical record, or more specifically, the transplant evaluation.

Patient selection for frailty assessment should be standardized at each center to ensure reproducibility, feasibility, and sustainability. These decisions should be guided by programmatic goals and available resources (Table 2). Universal frailty screening ensures equity across all candidates and therefore should be performed by programs using frailty to set patient and caregiver expectations, to inform listing decisions, or to refer for frailty interventions. Universal screening would also be preferred for programs seeking to use frailty as a program performance metric. Selective frailty screening (e.g., screening only those above certain age cutoffs or if there is clinical suspicion for frailty) could be considered for programs using frailty assessments exclusively for resource planning, as it would not be expected to lead to inequities in this setting. There was less consensus on the use of selective frailty screening for this specific programmatic goal, highlighting concerns about this approach.

RECOMMENDATION:

8. We recommend that all transplant programs perform frailty screening on all transplant candidates. *Strength of Agreement:* 93%
9. Selective frailty screening may be considered if the frailty assessments are used exclusively for institutional resource planning. *Strength of Agreement:* 69%

4.4. Best Practices for Assessing Frailty in the Outpatient Setting

Individual program characteristics and goals will dictate when frailty measures are best completed (Table 2). Programs choosing to tailor risk/benefit discussions or implement pretransplant frailty-based interventions would benefit from having a frailty assessment earlier in the transplant evaluation. Programs can then choose to prescribe a prehabilitation regimen to improve pretransplant frailty (Section 5). Frailty assessments are not identical for isolated lung transplant candidates and those being considered for combined heart and lung transplant. This document focuses on isolated lung transplant candidates.

By comparison, those using data from a frailty assessment for post-operative risk assessments, resource planning, and for designing post-operative interventions may assign higher value to an assessment performed immediately prior to listing or to repeating measures over time. Given the known association between frailty and unplanned readmissions, assessments performed after listing and/or closer to the time of transplantation may better inform post-operative resource planning and inform additional discussions of expectations regarding potential longer, more complex recovery and readmissions.[32,36]

4.5. Best Practices for Assessing Frailty in the Inpatient Setting

Frailty assessments can inform the decision to transplant acutely ill and severely hypoxemic hospitalized patients. In patients who remain functional and ambulatory without critical hypoxemia can be assessed using the same instrument as that in the outpatient setting. This approach ensures consistency in frailty evaluation across care settings.

A substantial and growing proportion of lung transplant candidates require intensive care unit (ICU) admission prior to transplantation with increasing use of extracorporeal membrane oxygenation (ECMO) as a bridge to transplant (BTT).[52] While studies have attempted to include these critically ill candidates, findings are limited by small sample sizes, the requirement for patients to be alert and able to provide informed consent, and between-center variability in protocols for intubation and ambulation. Given the limitations that exist in BTT patients, only specific components of physical frailty assessments may be practical to perform (e.g., grip strength, balance, self-reported weight loss). Cumulative deficit measures may be more feasibly performed. Inadequate data exists to recommend the use of a specific frailty measure in critical illness. Validated measures of physical frailty that are feasible and can be reproducibly performed in this critically ill population, including body composition measurement and biomarkers, are urgently needed.

If available, frailty assessments performed prior to decompensation could inform decisions on whether to provide invasive support as a BTT strategy as discussed in the ISHLT statement on candidate selection for the use of ECMO BTT.[53] Those with pre-existing frailty may not benefit from an ECMO BTT strategy, whereas patients who were not frail may improve or maintain their mobility with additional mechanical support and potentially become better candidates. These recommendations reflect expert opinion; further research is required to understand the role of ECMO BTT in frail candidates.

RECOMMENDATION:

10. We recommend that hospitalized lung transplant candidates have a frailty assessment upon their initial admission or initial lung transplant consultation to guide intervention strategies, including discussions of ECMO BTT. *Strength of Agreement:* 86%
11. We recommend development of a frailty measure specific for use in critically ill lung transplant candidates. *Strength of Agreement:* 100%

5. WHAT TO DO WHEN FRAILTY IS IDENTIFIED

There is growing evidence that frailty can be prevented or reversed through targeted intervention. Treating frailty before lung transplantation could improve outcomes by allowing patients to undergo surgery in an optimized state. The primary intervention to prevent and reverse frailty before lung transplant involves exercise and is also known as "prehabilitation." Prehabilitation is recommended for candidates being evaluated for and while awaiting solid organ transplantation.[54] For the purposes of this document, prehabilitation refers to rehabilitation specific to lung transplant candidates in the run-up to surgery. When the phrase "pulmonary rehabilitation" is used, it is in reference to literature that did not specify lung transplant candidates and includes a structured, supervised exercise intervention. The phrase "exercise interventions" may reflect interventions in pulmonary rehabilitation programs or unstructured/unsupervised programs.

5.1. Exercise Interventions

Exercise interventions are recommended for people with chronic lung disease, including those considered frail, to reverse and/or prevent worsening of frailty.[55] Exercise interventions within a pulmonary rehabilitation program improve exercise capacity and peripheral muscle strength, as well as pre- and early post-transplant physical functioning and HRQL.[39,55–62] The benefits of pulmonary rehabilitation are consistent across age groups, highlighting its therapeutic role even in younger candidates.[63] Exercise interventions are effective for treating frailty in both outpatient and inpatient settings.[39,56,57] Therefore, all lung transplant candidates, including those on mechanical support, should participate in prehabilitation.

Exercise intervention performed at least 3 times per week preserves exercise capacity and training volumes.[56] Greater exercise, up to 5 times per week, further improves exercise capacity and HRQL.[58] This response is consistent with work demonstrating that quadriceps strength is modifiable and can be decoupled from disease progression in lung transplant candidates.[62]

Various types of exercise modalities have been explored, including aerobic exercises, resistance training, and functional exercises.[39,56–58,60] Combining these different exercise modalities is effective in improving frailty and should be selected based on individual and institutional resources. These exercises can be performed in the hospital setting, outpatient clinic, or in home-based programs.

Prehabilitation regimens have traditionally focused on center-based programs. Participants in center-based programs experience benefits, including more social support, a peer network spanning the pre- to post-transplant journey, and greater perceived safety and comfort, due to the presence of an instructor.[64] However, patients with advanced lung disease face significant barriers to regular participation in center-based programs. Additionally, many transplant centers serve large geographical areas, leading to patient challenges accessing reliable transportation and associated caregiver burden.[65,66] Limited mobility, greater fatigue, and the need to transport supplemental oxygen are additional barriers to center-based prehabilitation.[64,67,68] Amplifying the challenges of center-based prehabilitation, the presence of frailty doubles the risk of not completing an outpatient pulmonary rehabilitation program for those who are able to initiate it.[69] A consensus report from the *American Thoracic Society* notes that unpredictable pulmonary exacerbations, psychological barriers with negative self-perceptions, and lack of trust in pulmonary rehabilitation centers are additional barriers to participation for patients with frailty and lung disease.[70]

Home-based and virtual rehabilitation programs are an appealing alternative. There is growing evidence that home-based rehabilitation can be effective, though this is largely based on small single-center studies. Home-based rehabilitation has been associated with increased or maintained 6-minute walk distance,[59] improved physical frailty, and increased exercise capacity.[60,68] Home-based rehabilitation may also allow for greater personalization; routines can be built around what the patient has at home and may include more interaction with the therapist than center-based programs.[64]

Yet there are challenges to home-based rehabilitation programs for lung transplant candidates, including dispersion of the multidisciplinary team, lack of access to equipment, trouble getting or staying motivated, less in-person support, and safety-related concerns, particularly with high supplemental oxygen requirements and/or pulmonary hypertension.[64] Home-based programs often require access to technological resources and skills and may be more challenging for those with impairments in vision, hearing, communication, or cognition.[66] Success of these home-based programs also relies on the ability of the exercise team to optimize online methods and personalize treatment.

Despite the limitations of center-based and virtual prehabilitation programs, consistent exercise is the most effective intervention to prevent and treat frailty. Therefore, we recommend exercise interventions in all lung transplant candidates; both in-person and virtual prehabilitation can be effective.[59,60,68,71]

RECOMMENDATION

12. All lung transplant candidates, including those on mechanical support, should be considered for exercise interventions, in parallel with the evaluation process. *Strength of Agreement:* 100%
13. The recommended frequency for exercise interventions is at least 3 sessions per week, but daily exercise is recommended for all lung transplant candidates. *Strength of Agreement:* 86%
14. The recommended exercise interventions for prehabilitation should include lower limb resistance/strength training and endurance (mobilization and or stationary cycling) as tolerated. *Strength of Agreement:* 83%
15. Home-based and virtual exercise interventions are acceptable alternatives to center-based programs, depending on the candidate's situation and resources of the transplant center. *Strength of Agreement:* 90%

5.2. Nutritional Interventions

Both malnutrition and sarcopenia are components of frailty[44,72] as inadequate energy and protein intake contribute to muscle wasting. Data on how to optimize nutritional status and sarcopenia comes from older adults or those with chronic respiratory failure and has been extrapolated to lung transplant candidates. Multi-nutrient and protein supplementation each improve handgrip strength and chair rise time in sarcopenic older adults.[73] In COPD, nutritional intervention leads to weight gain in stable malnourished patients and prevents the onset of sarcopenia in patients with acute exacerbation.[74,75] Administration of probiotic or fatty acid therapy also improves handgrip strength and gait speed in COPD.[76,77] A qualified dietician should evaluate specific deficits in energy, protein, and micronutrient intake and determine appropriate individualized targeted interventions while minimizing the risk of liver or kidney dysfunction that could imperil transplant candidacy.[78,79] Combination therapy, such as the addition of nutritional intervention to exercise training, helps to maintain and increase muscle mass, leading to greater walking distance, exercise capacity, and muscle strength.[80]

RECOMMENDATION

16. We recommend that individualized nutritional supplementation be used alongside exercise interventions to reverse sarcopenia and prevent or improve frailty in lung transplant candidates. *Strength of Agreement:* 94%
17. We recommend that all candidates be screened for malnutrition and have nutritional status monitored throughout the continuum of care. *Strength of Agreement:* 97%

5.3. Other Factors Associated With Frailty and Potential Interventions

The physical limitations of frailty often lead to increase in care needs and hospitalizations, which can impact patients' mental health and cognitive function, further exacerbate frailty, and impose greater burden on caregivers.[20,81–83] This cycle highlights the critical importance of caregiver support for this population and consideration of interventions that support patient mental health and cognitive function and caregiver burnout in parallel with frailty management.

Dyspnea can affect cognitive capacity, including the ability to concentrate and coordinate complex movements and exercise.[82,84] Access to appropriate supplemental oxygen for exercise may mitigate frailty and dyspnea.[85,86] Although a detailed review of interventions focused on dyspnea is beyond the scope of this document, integration of strategies to mitigate hypoxemia and dyspnea, such as energy conservation techniques, is important for the success of frailty interventions in lung disease.

5.4. Integrating Response to Exercise Interventions into Clinical Decision-making

It is critical to assess the response to any exercise intervention and to modify the treatment plan if needed. Response to exercise interventions can be measured using frailty assessments or frailty-related markers such as the 6 to minute walk distance and peripheral muscle strength. The pulmonary rehabilitation literature generally assesses response after 6 to 8 weeks.[70] If response to an exercise intervention is being used to inform decisions of waitlist timing, programs are encouraged to set specific criteria and standards to ensure equity and consistency.

Like other testing performed in lung transplant candidates, we recommend repeating frailty assessments when the results would inform clinical decision-making or with a significant change in clinical status (e.g., hospitalization). As discussed above (Section 4), the decision to perform repeat testing and the timing of that testing should be informed by programmatic goals.

RECOMMENDATION

18. Frailty assessments should be repeated at intervals when their results are likely to inform or influence clinical team decision-making. *Strength of Agreement:* 100%

5.5. Considerations for Post-transplant Frailty

Treatment for frailty should be continued after transplantation. In the early post-transplant period, comprehensive multidisciplinary rehabilitation programs improve exercise capacity, skeletal muscle strength, quality of life, and body composition.[87–90] The optimal format, duration, and structure of these early post-transplant programs, including the role of home-based rehabilitation, requires additional research.

The effect of frailty on later post-transplant outcomes is nascent. Recent work identified post-transplant frailty is a risk factor for worse HRQL, death, and CLAD.[91,92] Further work is required to elucidate mechanisms linking frailty to CLAD and to evaluate the effects of frailty on other late post-transplant outcomes, including quality of life. Optimal treatments for frailty in the later post-transplant period are poorly studied. Rehabilitation may assist with dyspnea control and improve quality of life, as it does in lung transplant candidates.[93]

RECOMMENDATION

19. Assessment of frailty after lung transplantation should be performed using similar measures and managed using similar interventions to the pretransplant approach. *Strength of Agreement:* 90%

Table 3 Knowledge Gaps on Identification and Management of Frailty in Lung Transplant Candidates

Knowledge Gap	Specific Research Opportunities
Sub-phenotypes	• Identification of frail recipients with disease-attributable vs systemic/age-related frailty • Identification of frail candidates for whom prehabilitation does not improve frailty • Identification of candidates at-risk of frailty for whom MV/ECMO BTT can prevent frailty
Mechanisms of Frailty	• Identification of targetable mechanisms to prevent, treat, or reverse frailty • Standardization of measures for assessing sarcopenia
Critical illness	• Valid and reproducible measures in critically ill, mechanically ventilated, and ECMO bridge to transplant candidates • Standardized programs for frailty treatment in critically ill candidates
Frailty in pediatrics	• Identification of optimal tools for assessing frailty • Responsiveness of frailty to prehabilitation
Biomarkers	• Identification of clinically-available biomarkers associated with frailty, outcomes, and response to treatment • Biomarkers distinguishing pathological frailty from chronological aging
Interventions	• Optimal duration, format, supervision for prehabilitation • Evaluation of optimal timing and frequency for re-assessing frailty • Evaluation of adjunctive therapies or novel treatments for frailty • Evaluation of specific nutritional interventions for prevention and treatment of frailty • Define the role of telerehabilitation
Post-Transplant	• Optimal rehabilitation and maintenance program • Risk factors for post-transplant frailty • Association between frailty and chronic lung allograft dysfunction • Define the role of telerehabilitation
Multidimensional measures	• Validate tools for assessment of sociodemographic and cognitive frailty

20. Changes in clinical status after lung transplantation, such as the development of CLAD, may warrant repeat frailty assessments and interventions to improve symptoms and quality of life. *Strength of Agreement:* 100%

5.6. Gaps in Knowledge and Opportunities for Future Research

Despite extensive work establishing the validity of frailty in lung transplantation, additional work is required. Knowledge gaps are outlined in Table 3. We specifically highlight the urgent need for work evaluating frailty measures in[1] critical illness,[2] pediatric populations, and[3] to identify those with lung-attributable vs age/systemic frailty. Data on frailty in pediatric lung transplant candidates is scarce given the small number of children undergoing lung transplantation as a therapy option.

6. CONCLUSION

This consensus statement addresses the growing importance of assessing and managing frailty in lung transplant candidates. While frailty is recognized as a key risk factor for worse pre- and post-transplant outcomes, prior guidelines lacked practical recommendations for implementation of frailty assessments into clinical practice. This document fills that gap by offering expert guidance on selecting validated frailty measures, determining appropriate timing and frequency of assessments, and integrating results into clinical and programmatic decision-making. There is not a single recommended tool for lung transplant; instead, we recommend that programs select a validated tool that fits their goals and resources. We emphasize that frailty should not be viewed as an absolute contraindication to lung transplantation, as it may be reversible post-transplant, and frail recipients may experience the greatest gains in quality of life from transplantation. We advocate for universal, objective screening—tailored to institutional resources and goals—to minimize bias and optimize outcomes. The consensus further emphasizes the importance of prehabilitation, nutritional support, and reassessment in response to clinical changes, aiming to improve outcomes, enhance care planning, and ensure adequate resource allocation.

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CONFLICT OF INTEREST

A complete list of author disclosures are available in Supplemental Table 4.

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APPENDIX A. SUPPORTING INFORMATION

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