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## Frailty and Aging-Associated Syndromes in Lung Transplant Candidates and Recipients

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### Abstract

Many lung transplant candidates and recipients are older and frailer compared to previous eras. Older patients are at increased risk for pre- and post-transplant mortality, but this risk is not explained by numerical age alone. This manuscript represents the product of the American Society of Transplantation (AST) conference on frailty. Experts in the field reviewed the latest published research on assessment of elderly and frail lung transplant candidates.

Physical frailty, often defined as slowness, weakness, low physical activity, shrinking, and exhaustion, and frailty evaluation is an important tool for evaluation of age-associated dysfunction. Another approach is assessment by cumulative deficits, and both types of frailty are common in lung transplant candidates. Frailty is associated with death or delisting before transplant, and may be associated with post-transplant mortality. Sarcopenia, cognitive dysfunction, depression, and nutrition are other important components for patient evaluation. Aging-associated inflammation, telomere dysfunction, and adaptive immune system senescence may also contribute to frailty.

Developing tools for frailty assessment and interventions holds promise for improving patient outcomes before and after lung transplantation.

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## Introduction

With the rise in the number of older lung transplant candidates and recipients, there is increasing interest in the study of frailty in transplantation. To this end, the American Society of Transplantation (AST) sponsored a consensus conference on frailty in kidney, liver, heart and lung transplantation in 2018 [1]. This conference brought together experts from the transplant community and provided an opportunity for exchange of ideas and discussion of best practices for frailty assessment. Given the special challenges regarding frailty in lung transplantation, a separate committee was convened to describe the approach to frailty in the evaluation of lung transplant candidates and recipients in greater detail.

Frailty is a concept initially associated with aging that has been defined in the field of geriatrics, and is commonly defined as an aging-associated physiological vulnerability to stressors leading to adverse health outcomes [2]. Although common in older patients, aging associated syndromes, including sarcopenia, impaired cognition, depression, and poor nutrition, have been shown to occur in all chronologic age groups. These aging-associated syndromes could be better described as associated with biological, as opposed to chronologic age (Figure 1). As a result, it has been observed that even younger patients with end stage organ disease can develop aging-associated syndromes, including frailty. Although the larger concept of frailty can be applied to wide range of aging-associated syndromes, for the purposes of this manuscript, we will use the term “frailty” for physical frailty or cumulative deficits and the term “aging associated syndromes” for the other components that are associated with frailty (i.e. cognition, depression, nutrition, sarcopenia).

The numbers of older patients undergoing transplantation each year is rising, with 35% who are 65 years of age or older, according to the 2018 the Organ Procurement and Transplant Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) Report [3]. Older patients undergoing lung transplantation clearly demonstrate a significant decrease in 1- and 5-year survival compared with patients under 60 years old. This increased burden of mortality in patients ≥ 60 years old is seen in the most recent International Society of Heart and Lung Transplantation (ISHLT) report [4]. With increased knowledge regarding frailty and aging associated syndromes combined with the increased number of older patients (≥ 60 years old) considered for lung transplantation, it is therefore crucial that the lung transplant community develop a comprehensive approach for patients undergoing lung transplantation. Prior to application of frailty testing, evaluation of frailty and other age-associated syndromes should be assessed in the context of end stage pulmonary disease, as patient characteristics and performance of frailty assessment would be predicted to differ between patients with lung disease compared with those with other types of end stage organ disease. This lung-focused approach should allow for development of tools to distinguish between frailty and other aging-associated syndromes in the context of the physical limitations related to advanced lung disease, which would be expected to improve after lung transplantation.

In reporting the results of this consensus panel discussion, we summarize the latest data, provide expert opinion on the assessment of frailty in lung transplantation, and develop a path forward to new areas in need of further investigation.

## Methods

Approach to the design and execution of the AST conference on frailty has been described previously [1]. The in-person meeting took place in February 2018; this meeting was preceded by a series of conference calls among members of the lung transplant group to discuss topics related to frailty and aging associated syndromes in the evaluation of the lung transplant candidate and recipient. After publication of the Report from the AST on frailty in solid organ transplantation, the lung transplant group focused on frailty and aging associated syndromes that were specific to lung transplant candidates and recipients. Given the breadth of this topic, the team members felt that a secondary report that provided further data with a lung centered focus was necessary to fully inform the lung transplant community. To ensure the most up to date analysis would be presented, an updated literature review was performed through December 2019 to ensure inclusion of any peer-reviewed literature published after the date of the in-person meeting. This report represents a synthesis of these findings.

## Results

### “Frailty” assessment in lung transplantation

Frailty is not a uniform construct; various definitions and conceptual frameworks exist, and different approaches may be warranted depending upon the intended use of frailty assessments. Frailty instruments differ significantly in the assessed domains, inclusion of objective tests, and data sources, with each instrument having strengths and limitations [5]. The physical frailty model, also known as phenotypic or syndromic frailty, and the cumulative deficit frailty model, also known as stochastic frailty, are the predominant models of frailty [5]. Physical frailty is considered to be distinct from disability and comorbidity.

**Tools for frailty assessment and their use in lung disease**—Physical frailty is most commonly evaluated as an aggregate score of five features, often termed the Fried Physical Frailty Phenotype (FFP): low physical activity, slowness, weakness, shrinking, and exhaustion [5]. A modified version of the FFP was developed for advanced lung disease and transplant that better quantifies the low activity construct in the setting of lung disease by replacing the Minnesota Leisure Time Physical Activity (MLTA) questionnaire with the Duke Activity Status Index (DASI). This better quantification using DASI improved multiple tests of validity including improved prediction of transplant candidate waitlist delisting or death [6]. The Short Physical Performance Battery (SPPB) is a 3-component battery that includes gait speed, chair stands, and balance that measures lower extremity performance and has been utilized in several studies as a measurement of frailty [5]. Lower SPPB scores reflect increased impairment. Given its focus on objective functional measurements, the SPPB is also grounded in the physical frailty framework.

The cumulative deficits model conceptualizes frailty as an individual’s accumulation of age-associated deficits over time, which may include symptoms, signs, diseases, disabilities, or laboratory measurements [2]. Each deficit is identified and quantified where higher scores reflect increased frailty [5]. In this model, frailty may be defined as different sets of deficits and still exhibit consistent relationships with adverse outcomes such as mortality [2]. These

indices, however, may be limited by the fact the list of deficits measured may vary in different applications of this tool. However, although possibly less responsive to rehabilitation or interventions targeting mechanisms of frailty, cumulative deficits measure may be more prognostic of outcomes.

Most frailty instruments have been used in cohort studies of community-dwelling older adults and were not developed specifically for patients with pulmonary disease [5], although a few studies have looked at other chronic pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) with other types of chronic pulmonary disease [7]. In patients with pulmonary disease, physical disability may be secondary to physiologic limitations created by chronic lung disease. Frailty has been associated with shortness of breath and airflow limitation in patients with COPD, suggesting a potential interaction with the disease itself [7].

Individual factors in frailty assessments may drive the association between frailty and poor outcomes. For example, gait speed may be the best indicator of frailty in the FFP. It has been shown to predict risk of readmission in patients hospitalized for COPD exacerbation [8] and mortality in patients with idiopathic pulmonary fibrosis [9]. Other refinements of current frailty assessments may be necessary to better discriminate differences in patients with lung disease.

**Performance of frailty testing in the context of lung transplantation**—Emerging work has shown that both physical and cumulative deficit frailty are prevalent in lung transplant candidates. Depending on the measure used, 10–45% of lung transplant candidates are frail at the time of assessment [10–12]. Before transplant, both types of frailty are independently associated with worse exercise capacity by cardiopulmonary exercise testing, shorter distance walked in six minutes, and worse disability and health-related quality of life (HRQL) [10–13]. Pre-operative frailty is also associated with increased risk of death or delisting from the waitlist [10]. Pre-operative frailty has been associated with mortality after transplant; however, this association has not been observed uniformly in the literature [10–12,14,15]. In one single-center study, which included routine pre- and post-operative pulmonary rehabilitation, pre-transplant physical frailty was associated with greater improvements in HRQL and six-minute walk distance (6-MWD) with transplantation within the first 3–6 months post-transplant, without an increase in post-transplant mortality [12]

Data are more limited on the prevalence and predictive ability of frailty after lung transplantation. In the immediate post-transplant period, the incidence of frailty may rise, perhaps related to peri-operative complications, disuse atrophy, and malnutrition. Physical frailty at the time of hospital discharge from surgery was observed in approximately 50% of lung transplant recipients. Frailty at discharge was associated with increased risk of subsequent unplanned readmission [16].

Physical frailty appears dynamic in lung transplant patients. Pre-transplant physical frailty improves in most—but not all—lung transplant candidates within the first 6 months after transplant surgery [17]. This suggests that existing measures of physical frailty should not be

used in isolation to exclude potential candidates being evaluated for lung transplantation. Frailty may also be modifiable. In a small pilot intervention trial targeting physical frailty in lung transplant candidates, use of a mobile health-technology enabled home-based intervention improved frailty, measured with the SPPB, in over half of the participants [18]. For transplant recipients who were frail at the time of discharge, an outpatient physical therapy program was associated with frailty resolution in the majority within the first two post-operative months [16].

Efforts to explore the pathobiology of frailty in lung transplant candidates are just underway. Compared with those who were not frail, frail lung transplant candidates had higher blood biomarker levels of interleukin-6 and tumor necrosis factor receptor-1 (systemic inflammation) and lower levels of leptin (wasting/sarcopenia) and insulin-like growth factor-1 (neurohormonal function) [10]. Recent work has established a strong association between adiposity—a proinflammatory phenotype associated with impaired muscle function—and frailty [19].

### Other age-associated syndromes

While frailty assessment has been the primary approach for evaluation for older patients, other types of evaluation have also been applied for measurement of age-associated syndromes as described below.

**Sarcopenia**—Sarcopenia is the loss of skeletal muscle mass and function associated with aging [20]. To date, there is no established universal definition of sarcopenia measurement in lung transplant candidates [20]. Irrespective of the definition, there is significant overlap between sarcopenia and frailty with similar mechanisms including chronic inflammation, physical inactivity, malnutrition, and aging [7]. Thus, sarcopenia may be an important risk factor for development of frailty and interventions targeting skeletal muscle function may help prevent or mitigate frailty.

Several sarcopenia measurements have been utilized in lung transplant candidates as a predictor of outcomes. Skeletal muscle mass measurement has been the most common marker measured retrospectively using thoracic [21] and abdominal computed tomography scans [22,23]. Associations with transplant outcomes have been variable across studies with lower pre-transplant skeletal muscle mass associated with increased post-transplant mortality [22,24], whereas other investigations demonstrate only associations with intensive care unit days, ventilator days, or hospital length of stay [21,23,25]. To date, only one study evaluated the association of sarcopenia on early post-transplant outcomes combining all three elements of the definition (muscle mass, strength and physical function) [21]. Rozenberg et al. observed that increased number of skeletal muscle impairments and lower quadriceps strength were correlated with longer hospital length of stay post-transplant, but no association was seen with pre- or early post-transplant mortality. Thus, there is increasing evidence that individual measures of sarcopenia are associated with adverse pre- and post-transplant outcomes, but additional research is required to establish the optimal method of sarcopenia measurement and the clinical implications of sarcopenia in the presence of frailty.

**Cognitive dysfunction**—Mild cognitive impairment in a patient with physical frailty is sometimes termed cognitive frailty. As seen in the general population, the effects of cognition and physical frailty may have multiplicative effects on disability and mortality after lung transplantation [26]. Smith et al. showed that 45% of patients had neurocognitive impairment prior to lung transplantation [27]. Associations with lower neurocognitive function included non-CF pretransplant disease, age, lower education status, and perioperative delirium [27]. Cognitive impairment in lung transplant recipients may be multifactorial including lack of oxygen, comorbid depression, comorbid malnutrition, and immunosuppression medications.

Cognitive function may be reversible with appropriate interventions; therefore, early identification is important. For example, in a study of 24 lung transplant recipients with a past medical history of COPD, subjects who underwent a 3-week inpatient pulmonary rehab program had significant improvement in their memory, learning skills, and psychomotor speed [28].

There are multiple measurements of the various components of cognitive dysfunction. These include different aspects of cognitive dysfunction: 1) global cognition: Severe Impairment Battery and Mini Mental State Examination; 2) executive function: Verbal Fluency Test Category/Letters, Clock Drawing Test, and Trail Making Test-B; and 3) attention: Digit Span Forward, Digit Span Backward, and Trail Making Test-A [29]. In the lung transplant population, many of the measures have been employed [26,27,30,31]; however, no systematic review has demonstrated which instrument is the best to use in this specialized population.

**Depression**—In the general population above 60 years old, depression and frailty commonly co-exist. In a meta-analysis of 8023 people, those who met criteria for frailty were 2.6 (95% confidence interval (CI): 1.6–4.4) times more likely to have depression compared to those who were not frail after adjusting for confounders [32]. Additionally, patients with depression were at an increased risk of frailty (OR: 4.1 (95% CI: 1.9–8.6) [32]. There is significant overlap in the diagnostic criteria of depression and frailty, namely in decreased stamina and unintentional weight loss. Co-existing depression and frailty are associated with worse cognitive impairment and disability, and both entities are independently associated with increased morbidity and mortality [27]. Depression is a common psychiatric condition in lung transplant candidates and recipients [33]. Several studies suggest that pre-transplant depression is associated with increased mortality after lung transplantation [34–36]. Depression is speculated to increase mortality by lowering medical adherence, worsening coping strategies, and reducing engagement in pulmonary rehabilitation after transplantation [35]. These effects may result in increased hospitalizations, graft failure, infection, and mortality.

Given the implications of depression on outcomes after lung transplantation, it is important to identify those at risk. The 2019 ISHLT Consensus Statement on Psychosocial Evaluation outlines recommendations for a mental health history [37]. These include an assessment of 1) past and current mood, anxiety, or personality disorders; 2) severity and chronicity of symptoms; 3) receipt, adherence, and response to psychiatric treatment; willingness to seek



treatment 4) current or past suicidal ideation; and 5) mental health history of immediate family members [37].

**Nutrition**—Frailty and malnutrition may be associated conditions in patients with chronic lung disease [38]. As lung disease becomes more severe, metabolic demands increase, which can result in a worsened catabolic and malnourished state. Severe malnourishment has significant post-operative implications after lung transplantation including an impaired immune response, delayed wound healing, sepsis, decreased diaphragm muscle strength, and increased risk of mortality [39].

Body mass index (BMI) is frequently used as a measure of nutritional status given its availability, accuracy, reproducibility, and low cost. A low pre-transplant BMI has been shown to be associated with a lower survival in lung transplant recipients in several studies [40,41]. In addition to BMI, a nutritional assessment tool called the Prognostic Nutritional Index (PNI) has been studied in lung transplant candidates [42]. The PNI is derived from a number of variables including the leukocyte count, albumin, transferrin and skin folds. Kim et al performed a receiver operator characteristics analysis to determine the optimal cut-point of the PNI of 41.14 in lung transplant candidates. In addition, it was shown that patients with a PNI of < 41.15 had a significantly lower survival compared to those with a PNI > 41.15 ( $p < 0.001$ ) [42]. Further research in a different cohort can help establish the external validity of the PNI.

**Interventions to address frailty**—Studies to date have been limited by the small numbers studied, but have suggested that frailty may improve after intervention in lung transplant candidates or recipients. Preliminary data suggests that exercise interventions may be helpful to treat or prevent elements of physical frailty prior to lung transplantation. For example, patients who underwent supervised aerobic and strength training for the entire pre-transplant period had preserved 6-MWD and experienced an increase in muscle training volumes and treadmill speed [43]. Patients with idiopathic pulmonary fibrosis awaiting lung transplant who completed all 36 sessions of supervised aerobic and strength training had a lower risk of death following lung transplant [44]. Additionally, a 23-session exercise and educational program significantly improved the 6-MWD for patients awaiting lung transplantation with the largest improvements seen in those with the lowest starting 6-MWD [45].

Data are similarly encouraging post-transplantation. Frailty is associated with an increased risk of mortality both on the waiting list and after lung transplantation. However, of 37 subjects who were frail prior to transplant and survived the first six months following transplant, 31 demonstrated frailty improvement (83.7%) [17]. Two studies showed an improvement in the trajectory of frailty in adults undergoing lung transplantation [16,17].

## The immune system and the (biologically) older patient

Immune dysfunction associated with aging is another important issue of associated with adverse clinical outcomes including infections and impaired vaccine response, involving changes in the innate and adaptive arms of the immune system [46]. Cellular senescence is

an important aspect of vulnerability to infection and impaired wound healing, and is also strongly associated with inflammation [47]. The most striking aspects of the impaired adaptive immune response, with decreased frequency of naïve T cells and increased frequency of senescent CD28- T cells, which are associated with impaired vaccine response but increased levels of inflammation [46]. B cells, and innate immune cells including neutrophils, macrophages, and NK cells are also affected by aging [46]. Despite the extensive amount of data regarding impaired immune response and aging, little is known in the context of chronic lung disease and lung transplantation.

Inflammation is a component of cellular senescence, sometimes termed “inflammaging”, and has been directly linked to physical frailty and vulnerability to age-associated morbidity and mortality [47,48]. Hallmarks of inflammation associated with frailty, sarcopenia, and cognitive dysfunction include cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF- $\alpha$ ) [48]. These frailty- and inflammation-associated biomarkers are associated with outcomes in lung transplant candidates and recipients including death on the waiting list, primary graft dysfunction, and ICU length of stay [10].

Another important aspect of immune dysfunction is telomere shortening, an age-associated change related to senescence and fibrosis associated with prolonged cellular replication [49]. Shortened telomere length in either lung transplant donors or recipients can be associated with CLAD and shorter survival. Donor telomere dysfunction can drive airway remodeling and fibrosis directly, while recipient telomere dysfunction has been linked to impaired control of infection [49,50]. Telomere dysfunction may also impact alloimmune responses and tolerance of immunosuppression. The interaction between these aspects of immune dysfunction and physical frailty is an important area for future study.

## Conclusion

Given the growing numbers of older lung transplant patients, many reports have appeared suggesting benefits of evaluation of transplant candidates. The presence of end stage lung disease can impair the performance of traditional approaches to patient assessment, making re-evaluation of previously studied methods for the assessment of frailty and other aging associated syndromes in the setting of lung transplantation critical for guidance in application of these tools. Our review of the literature reveals the importance of assessment from an interdisciplinary team to identify variables most predictive of clinical outcomes, including physical frailty, frailty by cumulative deficits, sarcopenia, cognitive assessment, psychological assessment, nutritional status, and immunologic alterations. An approach based on measurement of biologic age and immunologic competence through cellular function, inflammation, and telomere length may be beneficial to apply in the pre-transplant assessment. This approach could additionally be applied to post-transplant evaluation for monitoring and personalizing immune suppression.

The data presented here on frailty and sarcopenia evaluation as well as assessment of cognitive, nutritional, and immunologic status of lung transplant candidates suggests that these approaches could be utilized for patient risk stratification. Future work needs to focus on risk prediction, which would be able to assign individual patients an absolute risk for an



event such as death, as compared to currently published work which has defined group level relative risk. The methodology needed for clinical prediction are different from approaches used in the frailty literature to date and would require derivation and validation cohorts, ideally from different centers. That would then enable centers to make patient-specific risk decisions and, importantly, would provide the patient important information so they can make informed decision making. There is currently active NIH-funded research to reassess the ideal platform for assessing frailty in this patient population. In addition to validating domains from existing frailty measures, multicenter center studies are currently ongoing to combine frailty domain assessment with imaging and blood-based biomarkers to develop a comprehensive prediction tool.

Developing a tool for assessing and diagnosing frailty specific to the lung transplant population with high level of discriminant validity would go a long way towards improving our ability to study and potentially intervene to reverse frailty and other aspects of aging-associated dysfunction to further improve clinical outcomes.

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### Abbreviations

<b>AST</b>	American Society of Transplantation
<b>OPTN/SRTR</b>	Organ Procurement and Transplant Network/Scientific Registry of Transplant Recipients
<b>ISHLT</b>	International Society of Heart and Lung Transplantation
<b>FFP</b>	Fried Frailty Phenotype
<b>MLTA</b>	Minnesota Leisure Time Physical Activity
<b>DASI</b>	questionnaire with the Duke Activity Status Index
<b>SPPB</b>	Short Physical Performance Battery
<b>COPD</b>	chronic obstructive pulmonary disease
<b>HRQL</b>	Health-Related Quality of Life
<b>CI</b>	confidence interval
<b>OR</b>	odds ratio

<b>CI</b>	confidence interval
<b>BMT</b>	body mass index
<b>PNI</b>	Prognostic Nutritional Index
<b>CLAD</b>	chronic lung allograft dysfunction
<b>CMV</b>	cytomegalovirus

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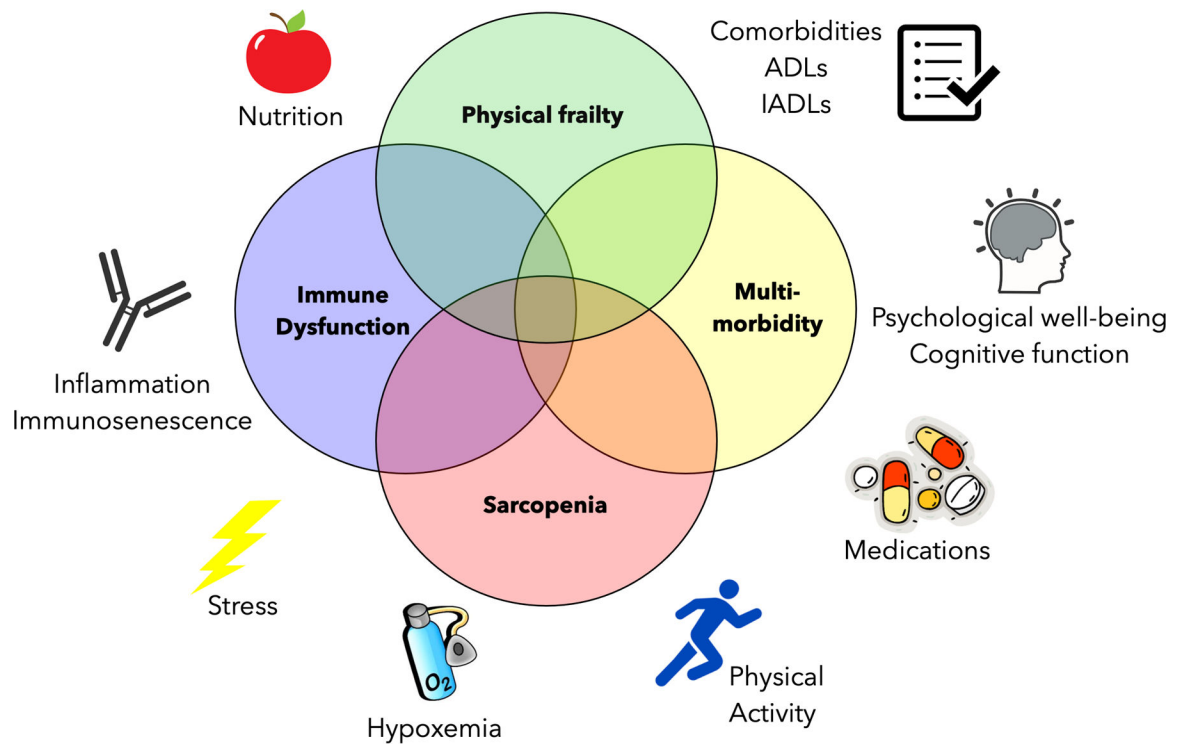
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**Figure 1:** Conceptual Framework of Frailty and Aging-associated Dysfunction in Lung Transplant Candidates. Venn diagram demonstrates the age-related biologic constructs that may overlap with frailty, including multi-morbidity, sarcopenia, and immune system dysfunction, along with health-related issues that may contribute to these manifestations of aging.