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Report from the American Society of Transplantation on Frailty in Solid Organ Transplantation

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Supporting Information

Additional supplemental material may be found online in the Supporting Information section of this article.

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Abstract

A consensus conference on frailty in kidney, liver, heart and lung transplantation, sponsored by the American Society of Transplantation (AST) and endorsed by the American Society of Nephrology (ASN), the American Society of Transplant Surgeons (ASTS) and the Canadian Society of Transplantation (CST), took place on February 11, 2018 in Phoenix, Arizona. Input from the transplant community through scheduled conference calls enabled wide discussion of current concepts in frailty, exploration of best practices for frailty risk assessment of transplant candidates and for management after transplant, and development of ideas for future research. A current understanding of frailty was compiled by each of the solid organ groups and is presented in this paper. Frailty is a common entity in patients with end-stage organ disease who are awaiting organ transplantation, and affects mortality on the wait-list and in the post-transplant period. The optimal methods by which frailty should be measured in each organ group are yet to be determined, but studies are underway. Interventions to reverse frailty vary among organ groups and appear promising. This conference achieved its intent to highlight the importance of frailty in organ transplantation and to plant the seeds for further discussion and research in this field.

Introduction

A consensus conference on frailty in solid organ transplantation sponsored by the American Society of Transplantation (AST) and endorsed by the American Society of Nephrology (ASN), the American Society of Transplant Surgeons (ASTS) and the Canadian Society of Transplantation (CST) took place on February 11, 2018 in Phoenix, Arizona. The conference served to update the solid organ transplant community on current concepts in frailty, generate ideas for optimal metrics of frailty assessment of transplant candidates, and pose pertinent questions for future research related to the implications and management of frailty in transplantation. Prior to the meeting, a series of conference calls were organized within each of the four solid organ groups (kidney, liver, heart and lung). During each conference call, different topics in frailty were discussed with up to 30 members from the respective AST Community of Practice participating in each call. Altogether, more than 120 AST members representing 56 transplant centers participated in these conference call discussions (Appendix A). At the conference, 32 AST members representing all four solid

organs met to discuss the information that was generated by each organ group. This paper represents the current understanding of frailty in solid organ transplantation.

Frailty is a pathobiological process characterized by loss of physiologic reserve and increased vulnerability to stressors. It is an independent domain of risk, overlapping with but distinct from comorbidity (such as physiologic aging) and disability; and portends worse outcomes for patients with end-stage organ disease and patients undergoing solid-organ transplantation (1). Identifying potential reversible components contributing to frailty associated with organ failure could allow for education of transplant candidates and referring providers, identify opportunities for intervention, optimize timing for transplantation and improve outcomes.

Before the conference, attendees were invited to participate in an online survey. A total of 257 responses were submitted by physicians, surgeons and allied health professionals from across the solid organ specialties. An overwhelming 98.6% of respondents viewed frailty as a useful concept for evaluating transplant candidates. Further, 93% of respondents believed that a frailty assessment should be incorporated into the selection process for transplant candidates. Common survey question results pertinent to all organ groups are presented in Table 1.

Pathophysiology of Frailty

Frailty is considered a complex and multifactorial process that is characterized by dysregulation of multiple physiological systems that cause an altered immune response, neuroendocrine changes, and cognitive impairment. Pathophysiological mechanisms of frailty and aging somewhat overlap. An important difference between chronological aging and frailty is that frailty has the inability to maintain homeostasis. Genetic susceptibility, co-morbidities, physiological aging and environmental factors, also play a role in the pathophysiology of frailty (1).

Frailty symptoms have been linked to disease severity such as the MELDNa score in liver transplantation (2). Biomarkers for frailty have been suggested, based on the concept that aging represents a low-grade chronic inflammatory process, sometimes termed, “inflammaging”. IL-6, TNF-α, CXCL-10, neopterin, lower CD4:CD8 ratios, higher numbers of memory T-cells, and cell-free mitochondrial DNA are reported specific biomarkers of frailty (3–5).

Sarcopenia (loss of skeletal muscle mass) may be a precursor to the development of frailty and its adverse health outcomes (6). In many studies it has been described as measurement of the psoas muscle (7–11). Sarcopenia and frailty share similar underlying mechanisms, such as physical inactivity, chronic inflammation, and endocrine dysregulation (7,8,12). As with frailty, studies of sarcopenia are limited by the lack of universally accepted definitions and methods of measurement (13). Sarcopenia, like frailty, may be a risk factor for worse outcomes in lung transplant candidates; however, data are conflicting, with some studies showing lower pre-transplant skeletal muscle mass measured radiographically being a risk factor for worse outcomes (9,14), and others showing risk for longer hospital stays but not mortality (15,16). Identification and early diagnosis of sarcopenia and interventions

targeting the skeletal muscle may help to prevent or manage frailty (10). More information is needed to determine the definition and criteria for determination of sarcopenia, the optimal method of measurement, and the prognosis of frailty with and without the coexistence of sarcopenia (17,18).

Frailty Measures

There are numerous instruments to assess frailty. Most screening tools for frailty are based on two concepts: “physical” or “phenotypic” frailty, versus “deficit accumulation” or “index” frailty (19).

The most extensively validated tool is the Fried Frailty Phenotype (FFP) (20) consisting of five components, including unintentional weight loss, low physical activity, exhaustion, slow gait speed and weak handgrip strength. The testing takes under ten minutes to administer, is easily implemented, and can be interpreted by non-geriatricians. According to Fried, a score of 3–5 is defined as frail, 1–2 as pre-frail and 0 is non-frail. A higher score on the FFP has been used to predict morbidity and mortality in inpatient and community dwelling populations. Handgrip strength and gait speed, the quantitative criteria of the FFP, may more objectively assess frailty than the other components. Limitations of the FFP criteria are the need for hand dynamometer equipment, ability to ambulate and the omission of assessment tools such as cognition, mood and nutrition.

Another widely used approach conceptualizes frailty as an index of cumulative deficits. The Frailty Index (Rockwood Accumulation of Deficits Index) is based on 30–70 deficits measured by clinical symptoms, functional impairments, laboratory findings, disabilities, and comorbidities. The ratio of the number of deficits present to the total number of items assessed gives the index score. The Frailty Index result gives a more quantitative measure of the severity of frailty than the FFP score and may include a wider range of deficits (such as comorbidities and disabilities) not captured by the FFP. Although the index may be more time consuming to administer, and therefore less practical, it may be more useful for evaluating response to treatment (21). The Short Physical Performance Battery (SPPB), a tool to measure lower extremity function that is associated with physiologic reserve, has also been commonly used to assess frailty and has been validated in various organ groups (22–26). Low muscle mass and function (known as sarcopenia) has also been used as an objective indicator of frailty and can be reliably measured by dual-energy X-ray absorptiometry (DEXA), or estimated by computed tomography (CT), magnetic resonance imaging, or bioimpedance (27). Finally, a questionnaire commonly used to assess patient inactivity is the modified Minnesota Leisure Time Activity scale, which contains activities that are likely less relevant to the advanced organ failure population who rarely participate in activities such as jogging or bowling (28).

Current Understanding of Frailty in Each of the Organ Transplant Groups

As a result of the pre-meeting conference calls and breakout session at the convening frailty conference, a current understanding of frailty was compiled from each of the solid organ groups. What follows is a summary of these discussions.

Frailty Considerations in Kidney Transplantation—In a systematic review of studies on the association of frailty and chronic kidney disease (CKD) that included over 36,000 patients, Chowdhury et al found that the FFP (20) was the most commonly used frailty assessment tool, accounting for 72% of studies, although there was substantial heterogeneity in its interpretation.

CKD is associated with frailty and the incidence of frailty in CKD increases with progressive decline in kidney function (29). Fitzpatrick and colleagues demonstrated that 52% of dialysis patients were frail using the FFP (30). A large, multi-center study of frailty among kidney transplant candidates (n=3,938; enrolled at the time of evaluation) and kidney transplant recipients (n=1,291; enrolled at admission) is currently ongoing. In this cohort, McAdams-DeMarco and colleagues found that 18% of patients on the wait-list for kidney transplant (31) and 20% of kidney transplant recipients, were frail by the FFP (32).

Additionally, in this large cohort, McAdams-DeMarco and colleagues found that frailty at the time of kidney transplant evaluation was associated with a 2.8-fold higher odds of fair or poor health-related quality of life (HRQOL) and a 2.9-fold higher risk of declining HRQOL while waiting for kidney transplantation (33) and 2.2 fold increased risk of wait-list mortality (31). Furthermore, frail kidney transplant recipients are at 2.1 fold increased risk of delirium following kidney transplantation (34) and a 1.6-fold higher risk of longer length of stay (35), 1.9-fold higher risk of delayed graft function (26), 1.6-fold higher risk of early hospital readmission (36), 1.3-fold higher risk of immunosuppression intolerance (37), and 2.2-fold higher risk of mortality (38).

Low physical function assessments and inability to perform Activities of Daily Living (ADLs) have both been associated with higher risk of mortality in patients with end-stage renal disease (ESRD) (39,40). Using the Medical Outcomes Study Short Form-36 (SF-36) Physical Component Scale (PCS) questionnaire to evaluate physical function, analysis of the United Network for Organ Sharing (UNOS) registry data of 10,875 kidney transplant recipients identified low physical function as an independent predictor of mortality (HR = 1.7) (41). Lower extremity impairment using SPPB, another objective measure related to frailty, is also associated with poor outcomes after kidney transplant and an increased length of stay for the kidney transplant hospitalization (16). In a recent study, the prevalence of lower extremity impairment was higher in the group of kidney transplant recipients classified as being frail (70%) compared to the entire cohort of frail and non-frail (47%) kidney transplant recipients (42). Importantly, impairment was associated with a 2.3-fold higher risk of mortality independent of the frailty phenotype.

Systematic review has demonstrated that most investigations of frailty have focused on developing risk assessment tools (31%), studying the etiology of frailty (22%), and developing methods (14%) and biomarkers (12%) for frailty assessment (43). Indeed, markers of inflammation and serum albumin levels are associated with frailty among ESRD patients, but significant variation is observed in the patient frailty scores from year to year (44). Strikingly the data suggest that nephrologists cannot correctly identify which dialysis patients are frail (45). One reason could be that some of the FFP component measurement

such as unintentional weight loss can be challenging in a ESRD patient with fluctuating fluid weight as suggested by the Delphi study conducted of 42 ESRD providers (46).

Small, randomized trials of patients with CKD and ESRD have demonstrated the potential benefits of rehabilitation programs to prevent or reverse sarcopenia and improve physical function in dialysis patients (47–50). Integrated inpatient rehabilitation may help dependent hemodialysis patients regain functional status (51).

Key points in kidney transplantation:

1. Frailty is common in patients with CKD (pre- and post-transplantation) and ESRD with numerous negative implications for health status.
2. The ideal components of the frailty metric for kidney transplant candidates and recipients are unknown; studies to compare metrics, harmonize measurements, and identify an ESRD-specific measure of frailty would be of value.
3. Patients identified to be frail may benefit from physical therapy and rehabilitation, and additional studies are needed to understand how such interventions affect outcomes in kidney transplant candidates and recipients.

Frailty Considerations in Liver Transplantation—Applications of frailty in liver transplantation have largely focused on the physical dimension of the frailty construct (e.g., FFP), and more recently, they have expanded to tools that capture functional capacity and disability. Physical frailty is prevalent in patients with cirrhosis: among outpatients, the prevalence of frailty ranged from 17–35% by the FFP (22,52) and was estimated to be 38% by the SPPB (22); among inpatients, 68% were functionally impaired as defined by the Karnofsky Performance Scale ≤ 70% (53). Frailty has consistently been shown to be a critical determinant of liver transplant outcomes, including hospitalizations, and mortality both before (52,54–58) and after liver transplantation (53,59–62).

A range of tools to measure frailty and physical function have been studied in this population, and recent efforts to standardize frailty measurement in liver transplantation have yielded the Liver Frailty Index (54). Consisting of handgrip strength, chair stands, and balance testing, the Liver Frailty Index was derived specifically to capture the construct of physical frailty in liver transplant candidates and is strongly predictive of wait-list mortality. In fact, it more accurately classifies wait-list mortality than the Model for End-stage Liver Disease (MELDNa) score alone. This metric is easy to administer and scored on a continuous scale, making it well-suited for the liver transplant setting. We advocate for the use of the Liver Frailty Index in the baseline and longitudinal assessments of liver transplant patients to standardize incorporation of frailty into center-level transplant decision-making.

True to the multi-dimensional construct of frailty, the pathogenesis of frailty in patients with cirrhosis is multi-factorial and includes under-nutrition from inadequate oral intake, low physical activity, systemic inflammation, and hypogonadism. Unique to cirrhosis are the contributions of hepatic synthetic dysfunction on accelerating muscle protein breakdown, as well as the deleterious effects of impaired detoxification of ammonia on muscle health (11). Each of these factors accelerates the development of sarcopenia, which plays a central role

in frailty pathogenesis. The prevalence of sarcopenia among liver transplant candidates ranges from 22–70% (63).

Understanding the pathogenesis of cirrhosis-specific frailty has provided multiple targets for intervention, which is rapidly emerging as the next frontier of frailty research in liver transplantation. In patients with cirrhosis, several small trials of exercise interventions, some of which have also included dietary counseling, have demonstrated improvements in muscle mass, muscle strength, exercise capacity, HRQOL, and reductions in portal hypertension (64). A single randomized clinical trial of intramuscular testosterone in hypogonadal men with cirrhosis demonstrated improvements in muscle mass, with a trend to increases in strength (65).

While data on the topic of rehabilitation prior to liver transplantation are currently limited, early studies are promising, leading to the conclusion that physical frailty—or at least some of its components—is modifiable in liver transplant candidates. More research should focus on developing rehabilitation programs that target frailty components with the goal of improving outcomes—including both survival and HRQOL—before and after liver transplantation.

Key points in liver transplantation:

1. Frailty is prevalent and a critical determinant of poor outcomes.
2. Frailty measurements should be standardized and performed routinely in patients undergoing evaluation for liver transplantation.
3. Although subjective screening tools may be useful for quickly identifying patients vulnerable to poor outcomes, performance-based tools better assess response to interventions and inform candidate selection.
4. Poor caloric intake, low physical activity, and muscle depletion are integral components of frailty and represent potential targets for intervention through rehabilitation programs.

Frailty Considerations in Lung Transplantation—There are emerging data suggesting that frailty may be associated with greater morbidity and mortality pre- and post-lung transplantation. Three studies to date have evaluated the prognostic utility of frailty in lung transplantation. Singer et al demonstrated that phenotypic frailty, utilizing either the FFP or the SPPB, was prevalent in lung transplant candidates and was associated with disability and delisting or death prior to transplant as well as 1- and 4-year mortality after transplant (23,24). Similarly, Wilson and colleagues showed that increased cumulative deficits using the frailty deficit index demonstrated a high prevalence of frailty (45% in 102 patients) and was independently associated with lower post-transplant survival (66).

Measuring frailty before transplant offers the potential for improving risk stratification and refining candidate selection. It is important to note that the appropriate frailty measure should accurately quantify risk for the outcome of interest. For example, the FFP incorporates elements that are likely to be improved by lung transplantation (e.g. slowness,

weight loss), whereas the cumulative frailty deficits index may change less or even worsen with the development of new extrapulmonary comorbidities (e.g. diabetes, renal dysfunction) even after a successful transplant.

Sarcopenia is thought to be a key precursor to the development of frailty. In lung transplantation, studies of sarcopenia are limited by the lack of a universally accepted definition. Nonetheless, lung transplant candidates and recipients have been shown to have decreased muscle mass, strength and function, which are key components of sarcopenia. Data regarding sarcopenia in lung transplantation are somewhat conflicting, with some studies showing lower pre-transplantation skeletal muscle mass being a risk factor for worse outcomes (9,14) and others not showing a higher risk of mortality among patients with low muscle mass (15,16). A systematic review of sarcopenia in lung transplantation included 18 studies that have shown that fat-free mass and quadriceps strength were lower than in controls, declined further in the early post-transplant period, and then recovered during long-term follow-up (67). Therefore, body composition assessed by DEXA or by single-slice CT or MRI may be useful.

A number of questions remain with respect to the optimal frailty measure, applicability of frailty tools for candidate selection, and which frailty criteria are most amenable to rehabilitation pre- and post-lung transplantation. In a cohort of non-transplanted chronic obstructive pulmonary disease patients, phenotypic frailty was reversible in those patients who completed pulmonary rehabilitation, suggesting that frail lung transplant candidates could derive significant benefit from rehabilitation (68). A small pilot study of a home-based rehabilitation program in lung transplant candidates demonstrated that frailty, measured by SPPB and FFP, improved in over half of participants (25). Several smaller studies and one randomized, controlled trial evaluating patients receiving pre- and post- lung transplant rehabilitation, suggest that there may be some improvement in muscle function (six-minute walk test and physical activity time) and strength (measured by quadriceps torque) by six months post-transplant (69,70).

Several interventions were discussed to improve frailty in candidates for lung transplantation, with the recognition that additional studies are needed to assess the benefit of these interventions. These interventions included:

1) Consultation with nutrition specialist and consideration of nutritional supplementation; 2) Enrollment in a physical therapy program and/or integrated pulmonary rehabilitation program 3) Geriatric consultation to identify and improve factors which may be contributing to frailty eg polypharmacy, cognitive impairment. Social work assessment to optimize social support.

Key points in lung transplantation:

1. Phenotypic frailty is prevalent in lung transplant candidates.
2. Increased cumulative deficits are independently associated with lower post-transplant survival.

3. Candidate selection is fundamentally dependent on establishing the validity of frailty measures and demonstrating their strong and independent association with outcomes after lung transplantation.

4. Potential interventions to reverse frailty that require further study include pulmonary rehabilitation and nutritional supplementation.

Frailty Considerations in Heart Transplantation—Within advanced heart failure the prevalence of frailty ranges from 25–78% depending on the instrument and individual criteria used to define frailty. Heart failure and frailty share a common set of symptoms that can be attributed to either state (e.g. fatigue, exhaustion, weight loss) (71).

Only a few frailty measures have been prospectively assessed in patients with heart failure and most have used a modification of the FFP (20). Jha and colleagues demonstrated that a third of their heart failure population was identified as being frail and was independent of age, sex, or ejection fraction (72). The one-year actuarial survival for frail patients was 54% compared to 79% in non-frail patients. Further, non-frail patients who went on to receive a heart transplant had a one-year post-transplant survival of 100%, compared to 52% in frail patients. Another tool to measure frailty is sarcopenia of the pectoralis muscle on chest CT which has been shown to be highly discriminatory in its ability to predict risk of death after mechanical circulatory support device (MCSD) therapy (73).

There has been an interest in rehabilitation of frail patients prior to cardiac transplantation. The placement of a MCSD (to aid rehabilitation) in advanced heart failure patients suggests that approximately 50% of patients have an improvement in their frailty level, but importantly, the majority of patients would still be considered pre-frail (74,75). Notably, the heart group did not feel that rehabilitation alone was a viable therapeutic option for patients as improvement in frailty would be minimal and would expose patients to a heightened risk of death. These patients should be considered for MCSD therapy, if appropriate, which would enable rehabilitation to proceed. An MCSD would allow for normalization of cardiac output, restore end-organ homeostasis, reverse the catabolic state of heart failure, improve muscle mass and eliminate inactivity.

The heart group recognized the critical need for additional evidence to define the ideal frailty measures in heart failure and to determine the potential prognostic power of these measures compared to already accepted tools. Nevertheless, given the substantial amount of data surrounding the FFP, it was strongly felt that a modification of the FFP was the best measure, at this time, to assess frailty in our clinical practice and that it should be included in future research investigations. Modifications to the standard FFP include the exclusion of weight loss (due to expected volume shifts) and the use of the Duke Activity Status Index (DASI) to measure activity. Since many patients with end-stage organ failure are hospitalized or critically-ill during the transplant evaluation process, a complete FFP is not realistic and in these patients, a handgrip strength alone should be considered to assess frailty. Although depression and cognition are important to consider, the added predictive value of these domains needs to be validated further before recommending their incorporation into the standard physical frailty assessments.

Key points in heart transplantation:

1. When evaluating patients for heart transplantation or MCSD, a modified FFP should be used and is currently the most well-validated tool.
2. Frailty is at least partially reversible with durable MCSD through improved circulation, nutrition and structured rehabilitation programs.
3. A multi-center Frailty in Advanced Heart Disease Consortium should be developed to assess the relationship between the proposed frailty measures and outcomes. Patient reported outcomes such as quality of life after an intervention (e.g. MCSD implantation or heart transplantation) are important and should be collected serially.

Summary

Accurately gauging the prevalence of frailty in end-stage organ failure populations is challenging. There is significant overlap between the features of organ failure and the signs of frailty (e.g., patients with cirrhosis and refractory ascites; patients with recurrent heart failure exacerbation). Tools for assessing physical activity in the general population, such as the Minnesota Leisure Time Activity scale, are unable to make this distinction. Therefore, a multidimensional tool that incorporates objective and dynamic measures of frailty and allows for assessment of potential interventions is needed for individuals with organ failure.

A single frailty tool for all solid organ transplant patients would be ideal but might be unrealistic. Although there was agreement that frailty is a multi-dimensional construct, certain aspects were considered more important in some solid-organ populations compared to others. For example, whereas cognitive function may be important in patients with advanced heart disease, altered cognition may simply reflect transient hepatic encephalopathy in patients with cirrhosis. Unexplained weight loss is another example. A patient with advanced CKD may experience significant weight loss after starting hemodialysis whereas a heart failure patient might experience weight gain from fluid retention. Neither of these states is related to frailty. Table 2 summarizes potential assessment tools for frailty components as discussed in each organ group. It is clear that there is no consensus as yet on how to define frailty across organ systems and the assessment tools listed would require validation in a prospective cohort. Interventions to reverse frailty also varied among organ groups, albeit with some overlap. Table 3 summarizes proposed interventions for each organ group.

Despite these challenges, there are metrics that are common to all patients with end-stage organ disease. Core components might include handgrip strength and chair stands, both of which were identified as important components of frailty in the pre-conference survey. Sarcopenia also appears to have clinical implications with the degree of frailty and might be included as an additional metric. These components would enable comparisons among cohorts, identification of common associations with transplant-related outcomes, and development of transplant-wide rehabilitation programs.

Research is underway to develop organ-specific frailty scores such as the Liver Frailty Index (54) for patients with cirrhosis awaiting liver transplantation or the Essential Frailty Toolset for older adults with advanced aortic valve disease undergoing valve replacement (76) (which has not yet been applied to the heart transplant setting). A list of proposed future research is noted in Table 4.

Conclusion:

Frailty is a common entity in patients with end-stage organ disease. There is universal consensus that frailty is a useful concept in evaluating candidates for solid organ transplantation. Frailty is known to impact both mortality on the wait-list as well as in the post-transplant period. The optimal methods to measure frailty are yet to be determined but studies are underway. Interventions to reverse frailty vary among organ groups and some strategies appear promising. This conference achieved its intent to highlight the importance of frailty in organ transplantation and to plant the seeds for further discussion and research in this field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADL	Activities of Daily Living
ASN	American Society of Nephrology
AST	American Society of Transplantation
ASTS	American Society of Transplant Surgeons
CKD	Chronic Kidney Disease
CST	Canadian Society of Transplantation
CT	Computed Tomography
DASI	Duke Activity Status Index
DEXA	Dual Energy X-Ray Absorptiometry
ESRD	End-Stage Renal Disease
FFP	Fried Frailty Phenotype

HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
MELDNa	Model for End-Stage Liver Disease and Sodium
MCSD	Mechanical Circulatory Support Device
MRI	Magnetic Resonance Imaging
SPPB	Short Physical Performance Battery

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Table 1.

Results of the Pre-Conference Survey. The Survey Includes Generic Frailty Questions Pertinent to All Organ Groups.

Question	Answers	Survey Results			
		Kidney Group (N=98)	***Liver Group (N=41)***	***Lung Group (N=59)***	***Heart Group (N=58)***
In your view, is frailty a useful concept in evaluating candidacy for solid organ transplantation?	Yes	98.9%	95.6%	100.0%	100.0%
	No	1.1%	4.4%	0.0%	0.0%
Do you currently perform a standardized frailty assessment as part of evaluation for transplant candidacy in your practice?	Yes-Always	23.9%	23.3%	27.1%	30.0%
	Yes-Sometimes	44.3%	32.6%	27.1%	31.7%
	No-Never	31.8%	40.0%	42.4%	36.7%
	Not Sure	0.0%	4.7%	3.4%	1.7%
If you currently perform a frailty assessment as part of evaluation for transplant at your center, who performs the assessment?	We do not perform	10.3%	24.4%	34.5%	29.8%
	Physician	31.0%	9.8%	10.3%	7.0%
	Physical Therapist	10.4%	9.8%	20.7%	12.3%
	Occupational Therapist	0.0%	0.0%	0.0%	3.5%
	Nutritionist	12.1%	24.4%	5.2%	15.8%
	Nurse	19.0%	9.8%	6.9%	12.3%
	Other	10.3%	17.1%	19.0%	14.0%
	Not Sure	6.9%	4.9%	3.5%	5.3%
What tool for the assessment of frailty do you currently use routinely?	Fried Frailty Phenotype	3.6%	16.7%	43.8%	34.7%
	Deficit Index	1.2%	2.4%	4.2%	6.1%
	Short Physical Performance Battery	3.0%	38.1%	35.4%	28.6%
	Rockwood Scale	0.0%	2.4%	2.1%	4.1%
	Montreal Cognitive Assessment	7.1%	2.4%	6.3%	34.7%
	Other	85.1%	52.4%	41.7%	34.7%
In your area of practice, do you think frailty in transplant candidates is a risk factor for adverse outcomes before transplantation (e.g. waiting list mortality)?	Yes	98.9%	97.8%	98.3%	96.7%
	No	1.1%	2.2%	1.7%	3.3%

Question	Answers	Survey Results			
		Kidney Group (N=98)	*Liver Group (N=41)*	*Lung Group (N=59)*	*Heart Group (N=58)*
Do you think the results of a frailty assessment should be used to influence decisions regarding the timing of transplantation (i.e. determination of medical urgency)?	Yes	68.9%	91.1%	84.5%	66.7%
	No	31.1%	8.9%	15.5%	33.3%
In your area of practice, do you think frailty in transplant candidates is a risk factor for adverse outcomes after transplantation (e.g. affecting length of stay or post-transplant mortality)?	Yes	98.9%	100.0%	100.0%	100.0%
	No	1.1%	0.0%	0.0%	0.0%
In your view, should biological age be considered in assessing frailty?	Yes	67.1%	60.0%	67.9%	75.0%
	No	32.9%	40.0%	32.1%	25.0%
In your view, is there a need for the development of a frailty score in the setting of transplantation?	Yes	93.3%	95.5%	98.3%	94.9%
	No	6.7%	4.5%	1.7%	5.1%
In defining frailty, which of the following features are important to consider? (Please rank most important to least important, with “1” being most important.)	Functional limitations (e.g. walking speed, grip strength, sarcopenia)	64.0%	83.7%	78.7%	87.2%
	Co-Morbidity (e.g. diabetes mellitus)	10.7%	11.4%	6.6%	10.2%
	Psychosocial status (e.g. depression or anxiety)	2.2%	2.3%	8.2%	0.0%
	Cognitive ability (e.g. memory or attention)	19.6%	4.6%	6.6%	18.6%
In your view, what components are essential in assessing frailty? (Please rank relative importance for each - “Important”/”Less Important”)	Grip strength (ranked “important”)	64.8%	72.7%	70.7%	76.7%
	Gait speed	82.2%	59.1%	74.1%	68.3%
	Sit to stand	88.8%	81.8%	81.4%	80.0%
	Exhaustion	73.0%	56.8%	55.9%	31.0%
	Unintentional weight Loss	86.8%	63.6%	86.2%	75.9%

Question	Answers	Survey Results			
		Kidney Group (N=98)	***Liver Group (N=41)***	***Lung Group (N=59)***	***Heart Group (N=58)***
	Low physical activity	85.0%	75.6%	85.0%	56.9%
	Cognitive function	73.6%	56.8%	78.0%	84.5%
	Mood	30.7%	18.2%	43.9%	29.3%
	Skeletal muscle mass	80.2%	88.6%	83.1%	83.3%
	Laboratory markers	38.6%	35.6%	17.5%	51.7%
	Need for activities of daily living assistance	97.9%	81.8%	86.75	86.4%
What interventions before transplantation do you think are useful to improve frailty?	*Free-form responses*	• Optimization of dialysis/ fluid status • Nutrition stimulation or supplements • Physical therapy • Psychotherapy	• Nutrition stimulation or supplementation • Physical therapy • Psychotherapy	• Mechanical device support • Nutrition stimulation or supplementation • Physical therapy • Psychotherapy	• Mechanical device support • Nutrition stimulation or supplementation • Physical therapy • Psychotherapy

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Table 2.

Suggested Tools by Organ-Group Consensus for Assessing Areas of Frailty

	Physical Reserve Measures	Strength	Nutritional Status	Social Engagement	Cognition
Kidney	Modified Fried Phenotype	SPPB	BMI, albumin, Vitamin D levels	Kidney Disease Quality of Life	MOCA
Liver	Liver Frailty Index	Liver Frailty Index Handgrip	Muscle mass (skeletal or psoas muscle index) Handgrip BMI, body composition, and albumin are less applicable due to edema and underlying hepatic synthetic dysfunction	CLDQ	Less applicable due to hepatic encephalopathy
Lung	MLTA, DASI, 6-minute walk test	Handgrip MIP/MEP	BMI, body composition, albumin, Vitamin D levels	TBA	MOCA
Heart	Modified Fried Phenotype, 6-minute walk test, DASI, MLTA	Handgrip	Less applicable due to edema	TBA	MOCA

Abbreviations BMI: Body Mass Index; CDI: Cognitive Depression Index; CLDQ: Chronic Liver Disease Questionnaire; DASI: Duke Activity Status Index; MEP: Maximum Expiratory Pressure; MIP: Maximum Inspiratory Pressure; MLTA: Minnesota Leisure Time Activities; MOCA: Montreal Cognitive Assessment; SPPB: Short Performance Physical Battery; TBA: to be agreed

Table 3.

Possible Interventions for Optimizing Frail Transplant Candidates

	Interventions
Kidney	• Exercise • Physical therapy • Intergrated inpatient rehabilitation
Liver	• Center-based rehabilitation programs • BMI-stratified caloric intake targets (20 to 40 kcal/kg/day • Targeted protein intake (1.2–1.5 g/kg/day • Exercise
Lung	• Nutrition supplementation • Physical therapy • Pulmonary rehabilitation • Intervention by social workers/psychologists
Heart	• Nutrition supplementation • Exercise • Physical rehabilitation • Mechanical circulatory support device

Table 4.

Areas for Future Research

• Comparing frailty metrics for patient outcomes on the waiting list.
• Determining whether interventions that improve pre-transplant frailty also improve wait-list outcomes as well as outcomes after transplant.
• Understanding the role of cognition in the frail phenotype in transplant candidates.
• Measuring frailty and its prognostic value in the peri-transplant period.
• Identifying novel measures of frailty such as biomarkers, imaging and body composition analysis.
• Coordinating trials of nutritional supplementation via oral/enteral feeding or total parenteral nutrition.
• Serially collecting patient reported outcomes such as quality of life.
• Further assessing measures of cognition and sarcopenia.