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Implications of Frailty for Peritransplant Outcomes in Kidney Transplant Recipients

Xingxing S. Cheng, MD¹, Krista L. Lentine, MD, PhD², Farrukh M. Korashy, MD, PhD², Jonathan Myers, PhD³, and Jane C. Tan, MD, PhD¹

¹Department of Medicine, Division of Nephrology, Stanford University, Stanford CA

²Department of Medicine, Division of Nephrology, Saint Louis University, St. Louis MO

³Department of Medicine, Division of Cardiology, Palo Alto VA Hospital and Stanford University, Palo Alto CA

Abstract

Purpose of Review—Research over the past few decades points to the importance of frailty, or the lack of physiologic reserve, in the natural history of chronic diseases and in modifying the impact of potential interventions. End-stage kidney disease (ESKD) and the intervention of kidney transplantation are no exception. We review the recent epidemiologic and cohort-based evidence on the association between frailty and kidney transplant outcomes and provide a framework of questions with which to approach future research endeavors and clinical practice.

Recent Findings—Frailty in kidney transplant candidates can be measured in numerous ways, including descriptive phenotype, description scores, functional testing, and surrogate measures. Regardless of the metric, the presence of frailty is strongly associated with inferior pre- and posttransplant outcomes compared to the absence of frailty. However, some frail patients with ESKD can benefit from transplant over chronic dialysis. Evidence-based approaches for identifying frail ESKD patients who can benefit from transplant over dialysis, with acceptable posttransplant outcomes, are lacking. Interventional trials to improve frailty and physical function before transplant (prehabilitation) and after transplant (rehabilitation) are also lacking.

Conclusion—Frailty is increasingly recognized as highly relevant to peritransplant outcomes, but more work is needed to: 1) tailor management to the unique needs of frail patients, both pre- and posttransplant; 2) define phenotypes of frail patients who are expected to benefit from transplant over dialysis; and 3) develop interventions to reverse frailty, both pre- and post-transplant.

Corresponding Author: Krista L. Lentine MD, PhD, Address: Saint Louis University Center for Abdominal Transplantation, 1402 S. Grand Blvd., St. Louis, MO, 63104. Phone: (314) 577-8765; krista.lentine@health.slu.edu.

Compliance with Ethical Standards

Conflict of Interest

Xingxing S. Cheng, Krista L. Lentine, Farrukh M. Korashy, Jonathan Myers, and Jane C. Tan report no conflicts of interest or funding for this work. XSC, KLL and JCT are members of the Frailty Consensus workgroup formed by the American Society of Transplantation (AST) Kidney-Pancreas Community of Practice; KLL is the American Society of Nephrology (ASN) Quality Committee representative to the workgroup.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Assessment; Frailty; Kidney transplant; Outcomes; Prehabilitation; Survival

Introduction

Frailty is a state of decreased physiologic reserve and diminished ability to recover from physiologic stressors¹. Functional status may decline and fail to recover after a medical illness or intervention, placing the individual at higher risk for complications. Literature on frailty and kidney transplant outcomes use a wide range of definitions and myriad of metrics including:

- descriptive phenotype (Fried criteria²);
- descriptive scores (Frailty Index³, health-related quality of life [HRQOL] scores⁴);
- physical function testing (SPPB⁵, measures of lower extremity strength and grip strength⁶);
- cardiopulmonary exercise testing (peak VO₂)⁷, other functional tests (6-minute walk test, sit-to-stand, or timed walking tests⁸);
- other surrogate measures (days of hospitalization⁹, falls¹⁰).

Frailty exists on a spectrum, ranging from mild decrements in reserve (sometimes termed “prefrailty”) to severe functional impairment¹. Frailty has been associated with poor health outcomes in almost all conditions, from community-dwelling older adults¹ to solid organ transplant recipients¹¹.

Frailty is common in kidney transplant candidates. Studies in dialysis-dependent patients suggest a frailty prevalence of up to 70%^{12–14}. Even among kidney transplant candidates, generally the healthiest of dialysis-dependent patients, approximately 20% meet criteria for frailty¹¹. Advanced chronic kidney disease (CKD)/uremia and commonly-associated comorbid conditions, including anemia, diabetes mellitus and heart disease, all contribute to the frailty phenotype¹⁵. Understanding frailty and its effect on transplant outcomes therefore has significant implications for patient education and clinical management, including the pursuit of and acceptance for kidney transplantation as a treatment option.

To better assess and utilize frailty in the peri-transplant clinical setting, the following questions need answers:

1. Is there a frailty threshold at which the risk of transplantation exceeds that of continuing maintenance dialysis?
2. Should the type of transplant considered be tailored based on frailty status? For example, should some frail candidates only consider living donor kidney transplantation to minimize the risks associated with delayed graft function and further deterioration in the post-transplant course?

3. To what extent is frailty reversible after transplant, and how long does this process take?
4. What interventions may be effective to mitigate frailty, both pre- and post-transplant?

This review seeks to illuminate some of the above issues. Herein we will review the associations between frailty and transplant outcomes, an active research area over the last 5–10 years. We then seek to apply that knowledge to the questions of pre- and posttransplant management of frail patients and highlight knowledge deficits to be addressed by future research efforts.

Frailty and Outcomes Before - Transplant

Emerging literature on the association between frailty and outcomes in kidney transplant candidates and recipients are predominantly observational. These studies demonstrate a higher risk of mortality and morbidity among patients who are frail compared to non-frail patients, both before and after transplantation. It is important to note, however, that under the current candidate selection practices, survival benefit with transplantation may be seen even among some candidates who are frail.

Multiple studies have established an association between patient-reported or surrogate measures of frailty and adverse outcomes in transplant candidates on the waiting list. In a large multicenter cohort study of 1,975 patients, the Fried frailty phenotype is associated with higher waitlist mortality (HR $_{1.26}2.19_{3.79}$)¹⁶. In a large retrospective study using registry data, Reese *et al.*¹⁷ noted that kidney transplant candidates in the lowest baseline physical function score quartile (based on the Medical Outcomes Study 36-Item Short Form Health Survey - SF-36) were less likely to undergo transplantation, more likely to be inactivated and have a lower survival at 3 years compared to the highest quartile (84% vs 92%). Survival benefit conferred by transplantation persisted in every physical function quartile. Limitations of the study include selection bias of patients both for waitlisting and for transplantation, and the use of indirect measures of physical functioning, albeit ones that have been validated in the dialysis-dependent population. In another registry data-based study, Lynch *et al.*⁹ studied whether hospital days in the first year of waitlist can be used as a measure of fitness for transplant. Based on registry data for 51,111 patients, those with higher hospitalization burden were noted to have higher waitlist mortality (1–7 hospital days: HR $_{1.20}1.24_{1.28}$; 8–14 days: HR $_{1.42}1.49_{1.56}$; 15 days: HR $_{1.99}2.07_{2.15}$; versus 0 days). Those with a high hospitalization burden had lower post-transplant survival, but survival was significantly better than remaining on the waitlist. Furthermore, in a single-center study of 96 transplant candidates, Locke *et al.*¹⁸ observed that lean muscle mass (measured via morphometric assessments of psoas muscle attenuation and paraspinous lean volume) was associated with a small but significant decreased risk of death (HR $_{0.91}0.93_{0.96}$ for higher psoas muscle attenuation and HR $_{0.96}0.98_{0.99}$ for increase in lean paraspinous volume) over a 5–6 year follow-up period. Together, these studies demonstrate that the association between frailty and pre-transplant mortality is robust across different frailty measures. Frailty assessments may be particularly important where the patient comorbidity burden is lower, in identifying high-risk patients who may not be noticed otherwise¹⁹. These

data also show that some frail ESKD patients can benefit from transplant over chronic dialysis, although how to identify those who will benefit and have acceptance posttransplant outcomes is not yet known.

One study applied an objective measure of cardiovascular reserve and arrived at a similar conclusion. Ting *et al.*²⁰ studied 240 waitlisted patients followed for 5 years. They quantified cardiovascular reserve using cardiopulmonary exercise testing and found that patients with an impaired peak VO₂ (based on percentage of age-predicted peak VO₂) had a significantly lower survival compared to those with a better reserve. However, among patients with low cardiovascular reserve, transplanted patients had significantly greater survival compared to non-transplanted patients (HR=0.090.220.56).

Frailty and Outcomes After Transplant

Studies of post-transplant outcomes in transplant recipients have utilized both the Fried frailty phenotype and other measures of frailty. Outcomes examined include short-term (delayed graft function and hospitalization) and long-term (death) measures (Table 1). Frailty, as assessed by varying metrics in these studies, is associated with worse short-term outcomes after transplant. Frailty defined by Fried index, a combination of self-reported and objective measures, was associated with an almost 2-fold increase in risk of delayed graft function, 1.2-fold increase in risk of protracted initial hospital stay, and 1.6-fold increase in risk of hospital readmission within 1 month²². The effect of frailty on length of stay is especially pronounced in patients with depressive symptoms (1.9 fold increase in risk).²³ Pre-transplant hospitalization, a surrogate measure of frailty, is also associated with increase post-transplant hospitalization (0 hospital days: 73%; 1–7 days: 70%; 8–14 days: 75%; 15 days: 80% hospitalization by 12 months of transplant)²⁴.

Frailty is also associated with long-term transplant outcomes, including mortality and graft survival. The association is strong, whether frailty is measured by Fried index¹¹ or other metrics. Among the 5 components of the Fried index, the combination of poor grip strength, low physical activity and slow walking speed were especially strongly associated with increased mortality (HR 1.42.6 1.5 97)²⁵. Other studies employed alternative measures of frailty, including 6-minute walk test²⁶, Short Physical Performance Battery²⁷, morphometric age²⁸, and hospitalization in the first-year of waitlist²⁴. All these studies confirmed the strong association with frailty measures and posttransplant mortality (compared to the absence of frailty). Importantly, the studies available to date are observational, and how frailty should inform transplant candidacy is currently controversial.

Frailty and Transplant Candidacy

The kidney implantation procedure and peri-transplant immunosuppression represent significant physiologic stressors, from which the frail recipient may, by definition, have a protracted recovery (Figure 1). During the recovery period, complications may arise which further reduce physical performance. McAdams-DeMarco *et al.* outlined mechanisms by which frail transplant recipients may be prone to transplant complications, including increased hospitalization²¹, immunosuppression intolerance²⁹, and delirium³⁰. A threshold,

or thresholds, for frailty may exist for which certain frail candidates are better off remaining on dialysis and others should only accept living donor kidneys to minimize the extent of peritransplant physiologic stress. Indeed, approximately 5% of transplant candidates were removed from the waitlist in 2016 because they were too sick for transplant³¹; many of them may have had an unacceptably high level of irreversible frailty. The only existing surrogate measure for frailty/physical function that is mandated reporting nationally is the Karnofsky scale, which is a rough surrogate³². Lack of a systematic approach and standardized instruments to assess frailty in transplant candidates makes it difficult to determine and evaluate frailty thresholds for informing transplant candidacy.

Preliminary data suggest that, under current practices at certain centers, measures of frailty may improve posttransplant. In a cohort of 349 transplant recipients at Johns Hopkins Hospital³³, 20% had the frailty phenotype (meeting at least 3 of the Fried criteria), and a higher percentage became frail within 1–2 months of transplant. At 3-months post-transplant, 74% of the initially frail recipients became less frail. The choice of the Fried phenotype, a non-quantitative instrument, to quantify frailty improvement is a limitation of this study, as is the high likelihood of selection bias in the study protocol. Longitudinal fluctuations in measuring the frailty phenotype may also account for part of the observed improvement. In a follow-up study of 443 transplant recipients from Johns Hopkins and University of Michigan Hospital³⁴, the physical and kidney-disease specific health-related quality of life (HRQOL) scores posttransplant improved in both initially frail and non-frail recipients. The improvement was more marked in frail recipients, especially in the domains of general health, effects of kidney disease, cognitive function, and social interaction. At these study centers, most frail transplant candidates appear to recover post-transplant and experience improvements in functional status and quality of life. Relatedly, in a large registry study, even patients with low physical function scores experience a survival advantage conferred by transplant over dialysis¹⁷, but this finding may be affected by unmeasured selection factors. Replication of these studies using quantitative frailty instruments, pre-specified assessment intervals, and longer follow-up at different transplant centers (with different thresholds for recipient and organ acceptance and different transplant protocols) will confirm (or disprove) these initial observations and lend empirical credence to our proposed paradigm in Figure 1.

If most frail transplant recipients improve posttransplant, then the higher mortality and adverse outcome rates in frail recipients may be attributed to either stochastic post-transplant events or the presence of patient subsets whose post-transplant trajectories diverge from non-frail patients. Predicting these “high-risk” frail candidates may enable us to refine transplant candidacy criteria and avoid the unfortunate outcome of making a patient worse with a failed transplant. All existing studies on this topic confront the inescapable limitations that: 1) stochastic post-transplant events cannot be predicted; 2) a strong selection bias exists, as perceived frailty is already contributing to decisions of transplantation; and 3) a model to be used in shared decision making regarding whether to proceed with a transplant or remain on maintenance dialysis will need an extremely high degree of accuracy (*i.e.* ability to provide the correct estimates for the probability of an adverse outcome). Existing models include the Estimated Post-Transplant Survival (EPTS) score³⁵ which accounts for only age and limited comorbidities (diabetes, length of time on dialysis, and prior transplant), and various models

including measures of frailty^{9,11,32}. In the most discriminating of these models⁹ (based on days of hospitalizations in the first year of waitlist), recipients in the highest category of risk have 3-year death or graft loss rates of 30%: whether such a failure rate warrants proceeding with kidney transplant is a decision to be made at the individual level by shared decision making.

Timing of Frailty Assessments

The timing of pre-transplant frailty assessment warrants brief discussion. Literature to date has reported frailty measures at one pretransplant time point, mostly immediately prior to transplant¹¹ or at study enrollment²⁰. Such timing is practical and useful for research studies but requires modification for useful clinical practice. Measuring frailty at the time of transplant evaluation can help inform transplant candidacy and type of transplant offered but may miss deceased donor transplant candidates who become frail while awaiting transplant³⁶. Measuring frailty immediately prior to transplant can help guide post-transplant management but will have little bearing on decisions and counseling regarding transplant candidacy. Ideally, frailty will be assessed longitudinally while awaiting a transplant and more frequently as candidates move toward the top of the wait-list (Figure 2). Such reassessment should be framed in the context of other patient factors, such as chronologic age, social support and other comorbidity. However, for the vast majority of transplant candidates whose primary or nephrology care is not delivered by transplant center affiliates, repeat frailty testing will necessitate either repeat visits to transplant centers or close coordination between transplant centers and local nephrology practices and dialysis units. Implementation of full, longitudinal pre-transplant frailty monitoring will require a more integrated care coordination model than what is currently available.

Frailty and Pretransplant Management

In addition to better assessment of frail patients with ESKD who are expected to benefit from transplant, effective interventions to modify frailty may allow more frail patients to become suitable transplant candidates. However, the optimal strategy to address frailty before transplantation is not known. Physical activity interventions, with or without nutritional interventions, have demonstrated reduction of frailty measures in community-dwelling elderly adults³⁷. Whether this can be consistently achieved in the advanced CKD population is debatable. Physical or exercise therapy delivery in the advanced CKD population is challenging. Implementation of intradialytic or supervised interdialytic exercise is limited by staffing challenges, competing priorities, and reimbursement^{38,39}. Home-based exercise therapy may result in a modest improvement in 6-minute walk test performance and lower extremity strength⁴⁰. How the positive effects persist beyond the study period is unknown. The myriad of barriers to exercise reported by patients, including fatigue, comorbidities, and limitations related to dialysis access⁴¹, may explain the high attrition rate (20–50%) reported in most exercise intervention studies in the CKD population (*cf* Table 1 in review by Cheng *et al.*⁴²). Prehabilitation, or physical rehabilitation completed prior a major procedural intervention, has shown some success in intra-abdominal surgeries (*cf* Table 2 in review by Cheng *et al.*⁴²). In the kidney transplant setting, prehabilitation may theoretically leverage the higher motivation of patients at the top of the waitlist, but this

conjecture has yet to be empirically evaluated. Response to prehabilitation, or lack thereof, may also provide an additional data point for assessing a frail patient's ongoing kidney candidacy (Figure 3). For all these reasons, prehabilitation in kidney transplantation warrants more study.

Frailty and Posttransplant Management

There are limited data to inform modification of posttransplant care based on frailty status. Potential modifications include:

- Aggressive and planned physical rehabilitation after transplantation in high-risk candidates
- Immunosuppression modification
- Accommodation of patients with cognitive deficits

Compared to prehabilitation, posttransplant rehabilitation is potentially easier to arrange logistically. Two randomized controlled exercise trials exist. In a US trial⁴³ (N=54 in exercise arm), an individualized home exercise regimen, tele-monitored via phone, improved objective and self-reported physical functioning over usual care. The average age of transplant patients was quite low (40 ± 13 in the exercise arm), and no frailty screening was done at recruitment. A small UK pilot trial⁴⁴ (N=13 in exercise arm) recruited older patients within 1 year of transplant and tested the effects of 12 weeks of supervised structured exercise classes twice per week. They reported a statistically non-significant trend toward an improvement in peak VO_2 attributable to aerobic training that persisted for 6 months beyond the intervention end date. Replication of these studies with higher numbers stratified by pretransplant frailty will help to delineate the benefits of rehabilitation and are necessary for obtaining insurer approval for covering the service.

The optimal approach to immunosuppression may differ between elderly frail and non-frail, non-elderly kidney transplant recipients⁴⁵. The altered pharmacokinetics of medications in elderly individuals may alter their exposure to immunosuppressants. Rejection and death-censored graft failure rates decrease with increasing recipient age^{46,47}, implying age-related immune senescence or heightened immunosuppression exposure in elderly patients under current protocols. Side-effects and immunosuppressant intolerance are also more common in frail individuals²⁹. Overall, the balance between suppressing alloimmunity and minimizing side effects may call for lower immunosuppression in frail transplant recipients, but this hypothesis warrants focused studies.

Transplant centers under-recognize cognitive deficits, such as delirium, to which frail transplant recipients are particularly prone³⁰. Targeted efforts to address cognitive deficits in frail transplant recipients include better delirium prevention and treatment along with targeted measures for medication safety and adherence. These are therefore reasonable steps to mitigate the downstream effects of frailty, although the optimal approach remains unknown.

Conclusions

As has been recognized in other populations, frailty is an important determinant of outcomes in kidney transplant candidates and recipients and exerts a significant impact on a patient's course, both pre- and posttransplant. In the past 5–10 years, a proliferation of studies has demonstrated a robust link between frailty, measured by varying metrics, and transplant outcomes. These studies also provide insight into the mechanistic basis for the link and suggest possible intervention venues, including prehabilitation, rehabilitation, immunosuppression modification and closer attention to cognitive impairment. The observation that frailty may not preclude benefit from transplant over dialysis argues for liberal referral to transplant centers, allowing programs to make candidacy determinations, rather than denying referral based on perception that a patient may be too unfit. At this time, minimization of pretransplant dialysis exposure through early referral, effective education on the potential benefits of living donor transplantation, and consideration of non-standard deceased donor organs to increase transplant options are particularly important to elderly and frail patients. Defining characteristics of frail patients who can benefit from transplant over dialysis with acceptable posttransplant outcomes, is a vital research priority. Prospective study of interventions and management strategies to improve frailty and mitigate adverse outcomes are also needed. All stakeholders—including patients, referring physicians, transplant programs, policy makers, insurers, and researchers—should recognize the importance of frailty as a determinant of kidney transplant success and convene on interventions to improve transplant outcomes (Figure 4).

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ABBREVIATIONS and ACRONYMS

CKD	chronic kidney disease
EPTS	Estimated Post-Transplant Survival
ESKD	end-stage kidney disease
HRQOL	health-related quality of life

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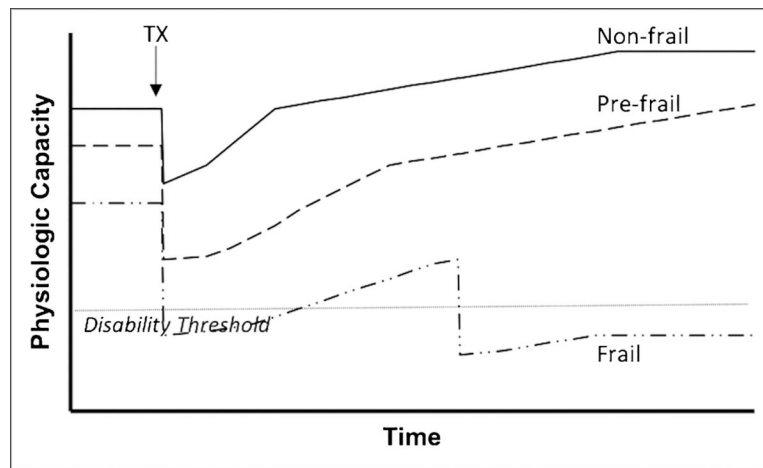


Figure 1.

A schematic of frailty as the loss of functional reserve. A non-frail patient (solid line) receives a kidney transplant (arrow): physiologic capacity decreases post-operatively and recovers to a better baseline than pretransplant. A prefrail patient (hashed line) experiences a greater decline and slower recovery of physiologic capacity, but ultimately achieves better physiologic capacity than pretransplant. A frail patient (dotted and hashed line) experiences a great decline in physiologic capacity to the point of losing dependence (horizontal dotted line), at which point recovery is prolonged and also plagued by further setbacks, which eventually results in a permanent loss of functional independence and poor outcome.

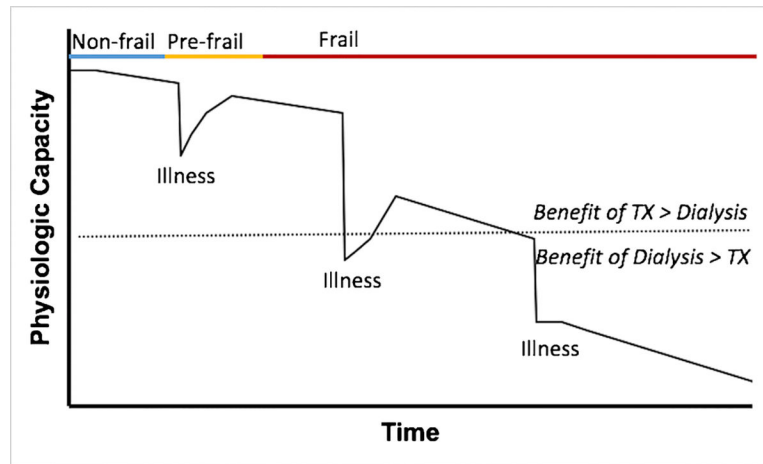


Figure 2.

A schematic of the functional trajectory of a patient on the kidney transplant waitlist. Re-assessments, especially after major illnesses, are crucial in properly phenotyping patients on the frailty spectrum and making the appropriate transplant-related decisions. TX: transplant. Benefit: Projected benefit of transplant or dialysis.

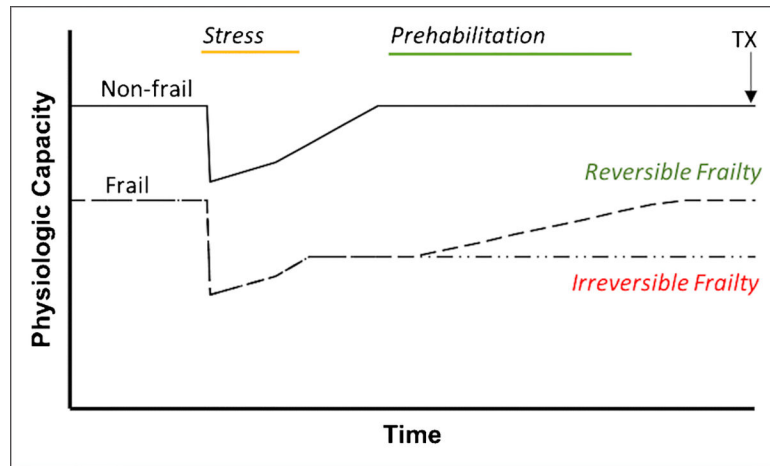


Figure 3.

A schematic of the functional trajectories of non-frail, reversibly frail, and irreversibly frail patients on the kidney transplant waitlist. A trial of prehabilitation may be useful in distinguishing the reversibly frail from irreversibly frail patient before transplant occurs.

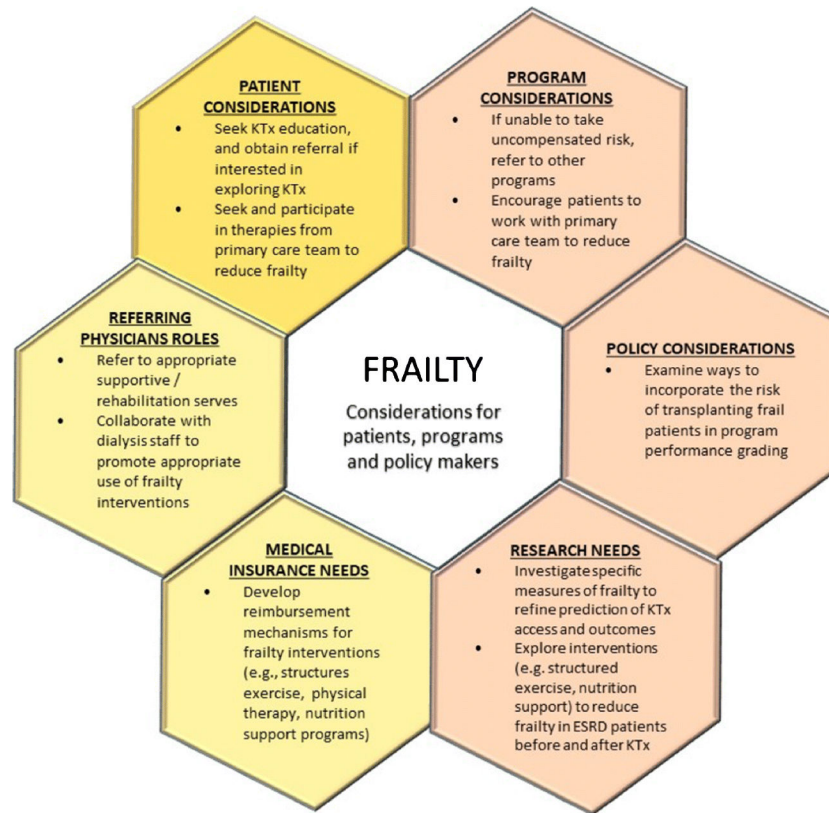


Figure 4. Frailty considerations for key stakeholders.

Table 1:

Summary of recent studies of frailty and outcomes after kidney transplantation, adopted from ⁴².

Reference, year	Study design and Participants	Frailty measure, timing and prevalence	Outcome/s associated with frailty	Other key findings	Study limitations
Garonzik-Wang, Arch Surg 2012 ⁴⁸	Prospective cohort Single center 12/2008–4/2010 N=183 (35% LDKTx)	Fried Frailty Score 3–5 at the time of admission for transplant Frailty at KTx: 25.1%	DGF: 30% vs 15% in frail vs non-frail, aHR 1.13 ^{1.96,3.36}	Deceased donor serum creatinine level and cold ischemia time was also associated with DGF.	Single center Observational Small sample size
McAdams-Demarco, AJT 2013 ¹¹	Retrospective cohort Single center 12/2008–12/2012 N=383 (39% LDKTx)	Fried Frailty Score 3–5 at the time of admission for transplant Frailty at KTx: 18.8%	Early (within 30 days) hospital readmission (aHR): 46% vs 28% in frail vs non-frail, aRR 1.18 ^{1.61 2.19} .	Frailty improved EHR risk prediction by improving the area under the ROC curve and the net reclassification index.	Single center Observational Frail sample included more men (71% vs 58%, P=0.046)
McAdams-Demarco, JAGS 2015 ³³	Prospective cohort Single center 12/2008–3/2014 N=349 (37% LDKTx) <i>Cohort overlaps with other McAdams studies</i>	Fried Frailty Score 3–5 at the time of admission for transplant Frailty at KTx: 19.8%	Change in frailty score after KTx: The only risk factor associated with improvement in frailty score was pre-KT frailty (aHR 1.17 ^{2.55,3.82}).	Pre-KT frailty status, diabetes mellitus, and DGF were independently associated with long-term changes in frailty score.	Single center Observational Short follow up
McAdams-Demarco Transplantation 2017 ²⁵	Prospective cohort Single center N=663 12/2008–8/2015 <i>Cohort overlaps with other McAdams studies</i>	Fried Frailty Score 3–5 at the time of admission for transplant Frailty at KTx: 19.5%	3 yr death: Associated with combinations of exhaustion and slowed walking speed (HR 1.17 ^{2.43,03}) and poor grip strength, exhaustion, and slowed walking speed (HR 1.14 ^{2.61,5.97}).	Frailty associated with older age (adjusted prevalence ratio aPR 1.21 ^{2.22,4.07}) IADL disability (1.73 ^{3.22,6.06}), depression (3.02 ^{1.31,31.82}), less than high school education (1.30 ^{3.10,7.36}), and low HRQOL (1.48 ^{3.71,9.31}).	Single center Observational
McAdams-Demarco, Transplantation 2018 ³⁴	Prospective cohort 2 US centers N=443 (34.8% LDKTx) 5/2014–5/2017 <i>Updated cohort from prior McAdams studies.</i>	Fried Frailty Score 3–5 at the time of admission for transplant	HRQOL: physical and kidney-disease specific elements are worse in frail recipients, but mental elements are similar. HRQOL change at 3 months post-KTx: • change in physical element 1.35 vs 0.34 points per month in frail vs non-frail • kidney disease-specific: 3.75 vs 2.41 points per month in frail vs non-frail	Observational Single instrument Short follow-up Unclear testing protocol	Observational Single instrument Short follow-up Unclear testing protocol
Nastasi, Transplantation 2018 ²⁷	Prospective cohort 2 US centers N=719 <i>Cohort overlaps with prior McAdams study</i>	Fried Frailty Score 3–5 at the time of admission for transplant Lower extremity functional impairment	Death: associated with lower extremity functional impairment (aHR 1.12 ^{2.30,4.74}), after adjustment		Observational

Reference, year	Study design and Participants	Frailty measure, timing and prevalence	Outcome/s associated with frailty	Other key findings	Study limitations
Alhamad ATC abstract 2016 ²⁶	Retrospective cohort Single center N=383 2000–2014	6 minute walk test (6MWT) <1000ft	of other risk factors including Fried Frailty Score.		Single center Observational
Lynch, Ann Surgery 2016 ²²	Registry based: linkage of USRDS & Medicare claims. N=37,623 (Medicare-insured) 1/2000 – 12/2010	Hospitalization days within 1 year before KTx: 0-: 51% 1-7: 25% 8-14: 11% 5+: 13%	Graft failure & death: 6MWT <1000ft not associated with graft failure or patient death at 1, 3, and 5 years. At 10 years, short 6MWT <1000ft associated with graft failure (aHR 1.8,4,2,9,6) but not death. Admission in 1 yr after KTx: grade association with pre-KTx hospitalization (aHR 1.17,1.28,1.70). 3yr death: grade association with pre-KTx hospitalization (aHR 1.20,1.42,1.70). 3yr graft loss: grade association with pre-KTx hospitalization (aHR 1.15,1.30,1.44).	Hospitalization associated with female, prior KTx recipients, diabetic, CHF, atherosclerotic vascular disease, and COPD Pre-KTx hospitalization associated with greater length of stay during transplant admission and greater service needs at discharge.	Observational Registry data Medicare only
Lynch, AIT 2017 ⁹	Registry based: linkage of USRDS & Medicare. N=51,111 (wait-listed KTx candidates) 1/2000–12/2010	Hospitalization days in the 1st year of wait-list: 0-: 47% 1-7: 23% 8-14: 12% 15+: 19%	Death on waitlist: grade association with pre-KTx hospitalization (aHR 1.24,1.49,2.07). Survival benefit of KTx vs staying on waitlist: Significant across all grades of pre-KTx hospitalization. Predictive model using admissions while on waitlist alone had higher accuracy for post-listing mortality than EPTS.	Hospitalization associated w same risk factors as the prior Lynch study.	Observational Registry data Medicare only
Terjimanian, Clin Transplant 2017 ²⁶	Retrospective cohort Single center 2005 – 2014 N=158	Morphometric age: calculated through analytic morphometrics on CT scan within 1 yr pre-KTx	Death: associated with morphometric age (HR 1.03,1.06,1.08 per year) but not chronologic age.	In chronologically oldest patients, those with younger morphometric age had greater survival rates.	Observational Single center Small sample size single center Surrogate measure not established in ESRD

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EPTS, expected post-transplant survival; KTx, kidney transplant; LDKTx, living donor kidney transplant; SR, self-report; PF, physical function; USRDS, United States Renal Data System; aRR, adjusted risk ratio; aHR, adjusted hazard ratio