

Frailty and the Potential Kidney Transplant Recipient: Time for a More Holistic Assessment?

Henry H.L. Wu,^{1,2} Alexander Woywodt,^{1,2} and Andrew C. Nixon^{1,3}

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Introduction

Frailty is an age-related clinical syndrome characterized by a decline in physiologic reserve and an associated decreased ability to respond to stressor events (1). Importantly, frailty is associated with an increased risk of adverse outcomes, including falls, hospitalization, poorer health-related quality of life (HRQOL), and ultimately earlier than expected death (1). Frailty is a significant health burden for patients with advanced CKD (2). The decline from fitness to frailty is influenced by an array of factors, such as sarcopenia, infection and inflammation, cognitive impairment, reduced physical exercise threshold, vitamin D deficiency, metabolic acidosis, and cellular senescence (2–7). Pathophysiologic processes inherent to CKD exacerbate this decline (2). Although the concept of frailty has received more attention in recent years within nephrology, there remain uncertainties as to how it should be best used to inform shared decision making around RRT, including transplantation.

Research has been performed on frailty in solid organ (other than kidney) and stem cell transplantation. A recent consensus conference sponsored by the American Society of Transplantation concluded that the optimal methods by which frailty should be measured in each organ group are yet to be determined, and that interventions to reverse frailty vary among organ groups and appear promising if unproven (8). Frailty is generally well accepted as a predictor of short-term mortality with surgery (9) and after admission to critical care environments (10). One may wonder about the relevance of frailty in lung transplantation in what is perhaps the most vulnerable group of patients pre- and post-transplant. An earlier study suggested increased risk of death and delisting in lung transplant candidates living with frailty (11). We also know that frailty is common at discharge after lung transplantation (12). Somewhat surprisingly, frailty does not seem to correlate with length of hospital stay nor with 1-year mortality (13). In comparison, in patients listed for heart transplantation, frailty was an independent predictor of mortality (14). Hematologists have developed an interest in frailty with some proposing the Comprehensive Geriatric Assessment (CGA) as part of routine assessment for hematologic stem cell transplantation (15).

In this article, we will highlight recent debates on the perceptions of frailty and how the presence of intercurrent illness may affect the assessment of frailty. We will discuss factors associated with frailty in patients living with advanced CKD and provide an update on recent evidence relating to kidney transplantation outcomes for this patient group. Several tools to assess frailty are in use concurrently and the field has been hampered by the lack of a unified approach. Evidence is also lacking as to which level of frailty should be seen as a contraindication to transplantation. Taking account of these uncertainties, we propose possible approaches to frailty screening and assessment in potential kidney transplant recipients. Finally, we will explore the potential benefits that a CGA may offer, including the identification of geriatric impairments, and how integration of CGA values into the assessment and wait-listing periods may inform shared decision making at different points of the transplant workup process and optimization of frailty status.

Perception and Differential Diagnoses of Frailty in Patients Living with CKD

How we perceive frailty has attracted intriguing debate since the early days of this concept >20 years ago (16). It is clear that frailty must not become a variant of ageism but that it could be used as an objective predictor of adverse outcomes as well as a tool to inform treatment decisions (16–18). The benefits of frailty assessment and resulting interventions are not yet fully understood (16). The coronavirus disease 2019 (COVID-19) pandemic has highlighted these issues further, because frailty assessments have been used to guide escalation of care decisions (19). It is also evident that frailty assessment can be compounded by intercurrent illness or injury (20). These confounding factors suggest we should consider other differential diagnoses before labeling patients as frail. Questions regarding the suitability to perform frailty assessments for any patients under age 65 with stable long-term disabilities such as cerebral palsy or those with learning disability have been raised during this pandemic, leading to guideline amendments (21,22). Future research efforts should study the perceptions of

¹Department of Renal Medicine, Lancashire Teaching Hospitals National Health Service Foundation Trust, Royal Preston Hospital, Preston, United Kingdom

²Faculty of Medical and Human Sciences, University of Manchester, Manchester, United Kingdom

³Division of Cardiovascular Sciences, University of Manchester, Manchester, United Kingdom

Correspondence: Dr. Andrew C. Nixon, Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Sharoe Green Lane, Preston PR2 9HT, United Kingdom. Email: andrew.nixon3@nhs.net

frailty among a wider population of health professionals, patients, relatives, and the general public to address this controversial topic.

Should Patients Living with Frailty Be Listed for Kidney Transplantation?

Factors associated with frailty in patients with advanced CKD have been extensively studied (2). Sarcopenia and malnutrition is consistently observed in patients with CKD, with reduced energy intake relating to uremia, superimposed infections, inflammation, and side effects of medication (2–4). Inflammation can lead to sarcopenia and frailty through imbalanced muscle protein homeostasis and increased energy expenditure at rest (3,4). Up to one third of patients with ESKD present with anorexia (3). Dietary requirements to prevent sarcopenia involve adequate intake of protein and carbohydrates (23). This is particularly challenging for patients with ESKD, who also have to restrict phosphate intake to reduce risks of secondary hyperparathyroidism and CKD-mineral bone disease (23). Dialysis itself leads to further loss of amino acids in patients with ESKD (24). In addition, cognitive impairment is commonly observed in advanced CKD and leads to reduced dietary intake, which can contribute to progression of sarcopenia (25).

Physical inactivity develops naturally with aging, but marked decline in activity levels are more frequently observed in patients with CKD (4,5). Reduced lean body mass, gait speed, and leg strength due to physical inactivity influences the development of frailty and sarcopenia (4,5). Reduction of active 1,25-dihydroxyvitamin D levels from CKD affects muscle metabolism and consistent muscle contraction, which may increase progression toward sarcopenia and frailty if not addressed (6). Inability of the kidney to remove acid load contributes to metabolic acidosis in CKD (26). Pathophysiologic pathways related to metabolic acidosis increases protein catabolism, which could lead to sarcopenia (3,4,26). Processes such as cellular senescence, alongside mitochondrial dysfunction, increased production of free radicals, and reduced ability for DNA repair are synonymous with aging (7). Pathophysiologic processes at a cellular level are expected to occur more prematurely with uremia (27). Holistic decline in bodily function due to this contributes to advancement of the frailty syndrome (27).

Outcomes for patients with advanced CKD who are living with frailty are poor whether they undergo transplantation, dialysis, or conservative management when compared with individuals who are nonfrail. McAdams-DeMarco *et al.* (28) assessed outcomes for 537 transplant recipients over a 5-year period prospectively and concluded that physical frailty was independently associated with a 2.17-fold (95% confidence interval [95% CI], 1.01 to 3.65) higher risk of death. Similarly, poor mortality outcomes have been described after initiation of dialysis in patients with frailty. Among participants in the Comprehensive Dialysis Study, frailty was independently associated with both mortality (hazard ratio [HR], 1.57; 95% CI, 1.25 to 1.97) and time to first hospitalization (HR, 1.26; 95% CI, 1.09 to 1.45) (29). Frailty is also associated with poor HRQOL outcomes in advanced CKD. In an extension of the Frail and Elderly Patients on Dialysis Study comparing HRQOL outcomes

between patients with CKD living with frailty receiving dialysis and those receiving conservative care, it was concluded that frailty was associated with worse HRQOL outcomes irrespective of treatment received (30). However, there may be some individuals living with frailty for whom transplantation is associated with improved outcomes compared with alternative management strategies. Reese *et al.* (31) retrospectively evaluated self-reported physical function, often a feature of physical frailty, of 19,242 kidney transplant candidates receiving dialysis. They demonstrated that, regardless of functional status, transplantation was associated with a gradual improvement in survival over time compared to dialysis (31). There is also evidence suggesting improvements of HRQOL after renal transplantation (32). Among 443 renal transplant recipients monitored over 3 years, there was a greater improvement in physical and kidney disease-specific HRQOL for participants categorized as frail compared with those who were nonfrail (32).

The frailty syndrome is considered a vicious cycle associated with progressively worsening functional status. However, it may be possible to reverse this process in some patients living with frailty and advanced CKD. Admittedly, Kurella Tamura *et al.* (33) demonstrated that initiation of dialysis in elderly nursing home residents with advanced CKD was associated with a substantial decline in functional status. However, Johansen *et al.* (34) revealed a varied trend in frailty status in prevalent hemodialysis participants, with approximately equal numbers improving as worsening. The latter study demonstrated that markers of inflammation and hospitalization were independently associated worse frailty status (34). McAdams-DeMarco *et al.* (35) demonstrated that frailty status can in fact improve post-transplantation, with only 26% of participants that were frail at the time of transplantation remaining frail 3 months post-transplantation. Thus, transplantation, particularly live donor transplantation, may be associated with better outcomes for certain patients living with frailty, possibly those with lower overall inflammatory burden, compared with other treatment modalities (34,36,37). The challenge for geriatric nephrology going forward will be to establish a robust method of differentiating this group of patients from those with greater risks of perioperative morbidity and mortality.

How Should Frailty Be Identified in the Potential Kidney Transplant Recipient?

The relative merits of individual frailty measures continue to spark debate, although transplant nephrologists are increasingly acknowledging the importance of frailty in clinical practice (38). Within the United Kingdom, the Clinical Frailty Scale (CFS) is widely used in clinical practice, both in geriatric and specialty medicine. Recently, it has been incorporated within the National Institute for Health and Care Excellence COVID-19 critical care guideline, which suggests that the CFS is performed in adults admitted to hospital aged 65 years and over (19). The revised CFS describes a nine-point frailty scale (Figure 1), expanded from the original seven-point scale presented by Rockwood *et al.* (39) in 2005, and relies on a health professional's judgment of an individual's frailty status. A score of one describes an individual who is very fit, active, and robust relative to their age; whereas a score of eight reflects an individual who is

Clinical Frailty Scale*



1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.



2 Well – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.



3 Managing Well – People whose **medical problems are well controlled**, but are **not regularly active** beyond routine walking.



4 Vulnerable – While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being “showed up”, and/or being tired during the day.



5 Mildly Frail – These people often have **more evident slowing**, and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.



6 Moderately Frail – People need help with **all outside activities** and with **keeping house** inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.



7 Severely Frail – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).



8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.



9 Terminally Ill – Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise evidently frail**.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005, 173:489-495.

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Figure 1. | The Clinical Frailty Scale. The 9-point Clinical Frailty Scale was adapted from the 7-point scale used in the Canadian Study of Health and Aging and has been reprinted with permission from Geriatric Medicine Research, Dalhousie University, Halifax, Nova Scotia, Canada.

severely frail, completely dependent, approaching end of life, and susceptible to difficult recovery even from minor acute illness. A score of nine reflects individuals who are terminally ill with a life expectancy <6 months, but who are otherwise not evidently frail.

The CFS is considered a practical frailty measure, taking only a few minutes to complete. Importantly, the CFS has good diagnostic accuracy for identifying physical frailty (40). Nixon *et al.* (40) identified the CFS as the most accurate nonphysical assessment frailty screening tool to diagnose frailty compared with other screening tests such as the PRISMA-7, CKD Frailty Index (FI), and CKD FI-LAB. Furthermore, the CFS has been shown to be predictive of outcomes in patients with advanced CKD (41). Alfaadhel *et al.* (41) investigated a prospective cohort of 390 patients on dialysis who had a CFS assessment at initiation of dialysis treatment. Over 4 years, a higher severity of frailty, categorized by the CFS, was associated with higher mortality, with each increase in CFS point reflecting a HR of 1.22 (95% CI, 1.04 to 1.43; $P=0.02$) (41). Therefore, the CFS has potential as a screening tool in the transplant workup clinic to identify patients at risk of physical frailty. Further study is needed to evaluate the ability of CFS to prognosticate post-transplant outcomes.

After initial screening, we suggest patients identified at risk of frailty using the CFS should undergo further

extensive assessment. Physical frailty, identified by the frailty phenotype (FP), is predictive of outcomes post-transplantation (42,43). It includes assessments of unintentional weight loss, handgrip strength, self-perceived exhaustion, walking speed, and physical activity (42). It is not particularly practical to perform this assessment on all potential kidney transplant recipients due to the time required. Nonetheless, there is a compelling case for performing an FP assessment in those screened as at risk of frailty, given the numerous studies that have demonstrated an association between frailty, as identified by the FP, and post-transplant outcomes (28,35). Simpler measures, such as walking speed or the Timed Up and Go Test, do not seem to be as good of a predictor of outcomes (44,45). Schaanman *et al.* (46) performed a pilot study evaluating the feasibility and utility of a simple chart review-based Frailty Risk Score (FRS) to predict post-transplant outcomes. Their pilot study demonstrated that the FRS is a feasible approach and the preliminary results suggested that the FRS may be able to predict hospital length of stay and rehospitalization risk after operation (46). The FRS requires further evaluation before it can be recommended for use in clinical practice. For the time being, performing a more comprehensive assessment of physical frailty appears to be the most robust measure to educate and inform discussions with patients about the risks and benefits of proceeding with transplantation.

Thereafter, monitoring of frailty status during the transplant wait-listing period should be considered. Within a prospective cohort, Chu *et al.* (47) observed that frailty status between assessment and renal transplantation was unchanged for only 54% of patients. Frailty transitions during wait-listing were associated with peritransplant and post-transplant outcomes, particularly length of hospitalization and mortality (47). Further work is needed to assess more practical approaches to capture change in frailty status from assessment to transplantation.

Should the Potential Kidney Transplant Recipient Be Offered CGA?

The CGA is defined as “a multidimensional, multidisciplinary process which identifies medical, social and functional needs, and the development of an integrated/coordinated care plan to meet those needs” and is now the accepted standard of care of the older patient living with frailty (48). Studies have demonstrated that the CGA (or a modified version) is feasible within renal services and can be used to identify geriatric impairments in CKD populations (49). Goto *et al.* (50) showed that geriatric impairments, such as impaired functional status and cognition, are highly prevalent in older patients with advanced CKD. Without a structured investigational approach and subsequent management plan, geriatric impairments may go unnoticed and unaddressed, which has implications for patient outcomes. For example, the CGA can identify impaired physical functioning in patients living with frailty and CKD, which is a potentially modifiable risk factor of adverse post-transplant outcomes. Optimization of physical function is particularly important given that frailty is a dynamic process and patients may therefore have a decline in their frailty status during the wait-list period (47). Studies have suggested that prehabilitation may be associated with improved outcomes after surgery (51). Research evaluating the benefits of prehabilitation in the context of renal transplantation

is limited, although a recent pilot study demonstrated that prehabilitation before kidney transplantation is feasible (52). Research is needed to determine if prehabilitation leads to improved outcomes after kidney transplantation.

The investigational approach throughout transplant workup should involve continuous clinical assessment and investigations as needed. Prompt identification of risk factors and involvement of the multidisciplinary team, such as therapists and dieticians, to address concerns could bring significant improvements to prognosis after transplantation. Considering existing evidence, Figure 2 illustrates our proposed approach to the assessment, monitoring, and optimization of frailty and associated geriatric impairments in potential kidney transplant recipients, with awareness that further work to validate this approach is required.

Conclusion

Frailty is an emerging concept with relevance for transplant assessment. Age as an isolated criterion for or against transplant listing has been criticized before and rightly so. Most transplant centers no longer operate a cutoff age beyond which patients are denied access to transplant. Although there remain controversies regarding our perceptions of frailty, frailty status is a predictor of outcomes post-transplantation and therefore should be considered as part of pretransplant assessment. Frailty must not become (or be seen as) a new form of ageism that prevents access to intervention and it will be important to study and take into account perceptions of patients, relatives, and carers around this topic. A holistic assessment, such as a CGA, could be used to identify, monitor, and manage geriatric impairments in patients with advanced CKD who are living with frailty. The identification of frailty and associated geriatric impairments could in turn inform shared decision making between clinician and patient. Research is needed to evaluate the ability of pragmatic frailty screening tools to predict wait-list and post-transplant outcomes (Table 1). The wider

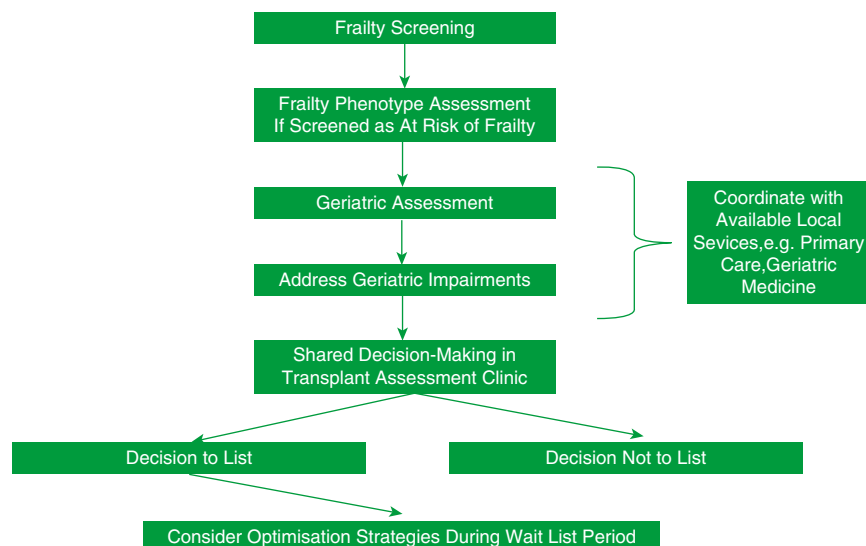


Figure 2. | Suggested approach to assessment, monitoring, and optimization of frailty and associated geriatric impairments in the potential kidney transplant recipient.

Table 1. Future research considerations for frailty and transplantation

Future Research Considerations
Evaluation of frailty screening measures' ability to predict waiting list and post-transplant outcomes
Exploration of biomarkers able to refine risk stratification of post-transplant outcomes in patients living with frailty
Develop a practical approach to capture changes in frailty status from assessment to transplantation
Determine the most effective approach to implement geriatric assessment in the transplant assessment clinic
Identify geriatric impairments in patients living with frailty amenable to intervention before transplantation
Demonstrate that interventions aimed at improving frailty pretransplant improve outcomes
Study perceptions of patients, relatives, and carers around frailty as a criterion for transplant assessment

field should endeavor to come up with some form of consensus regarding tools for the assessment of frailty. We also need proof that strategies aiming to optimize patients living with frailty before transplantation actually improve outcomes. Given the existing evidence from gerontology and other specialties, we encourage transplant nephrologists to consider a quality improvement approach to evaluate the local impact of frailty assessment and intervention in the transplant workup clinic.

Author Contributions

A. Nixon and H. Wu wrote the original draft; A. Nixon and A. Woywodt conceptualized the study; and A. Nixon, A. Woywodt, and H. Wu reviewed and edited the manuscript, had final approval before submission, and agree to be accountable for all aspects of the work.

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