Narrative Review: Clinical Implications and Assessment of Frailty in Patients With Advanced CKD

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Frailty is a multidimensional clinical syndrome characterized by low physical activity, reduced strength, accumulation of multiorgan deficits, decreased physiological reserve, and vulnerability to stressors. Frailty has key social, psychological, and cognitive implications. Frailty is accelerated by uremia, leading to a high prevalence of frailty in patients with advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD) as well as contributing to adverse outcomes in this patient population. Frailty assessment is not routine in patients with CKD; however, a number of validated clinical assessment tools can assist in prognostication. Frailty assessment in nephrology populations supports shared decision-making and advanced communication and should inform key medical transitions. Frailty screening and interventions in CKD or ESKD are a developing research priority with a rapidly expanding literature base.

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Frailty is a clinical syndrome characterized by immobility and inactivity, reduced strength and muscle loss, accumulation of multiple end-organ impairments, and decreased physiological reserve.[1,2] Frailty is a state of accelerated and pathological aging which is prevalent and clinically relevant in nephrology populations. Pathophysiology reflects an accumulation of vascular, inflammatory, nutritional and age-related insults, all of which are compounded by the presence of comorbidity and uremia.[3] People living with frailty experience increased functional dependency and key social and cognitive sequelae that interact with physical manifestations.[4,5] Frailty threatens independence and quality of life, and predicts nonroutine recovery and increased healthcare utilization patterns.[6] In nephrology settings, frailty is associated with accelerated disease progression, dialysis and transplant complications, as well as increased mortality risk.[7,8] National and international data registries indicate that among patients with ESKD, those aged >65 years represent the largest and most rapidly growing patient population, accounting for up to 45% of people accepted for renal replacement therapy.[9-11] Although poorly captured by registry data, frailty likely contributes substantially to the increased case complexity noted among patient populations referred for nephrology care.[12] This emphasizes the importance of recognizing frailty in kidney disease populations.

Other reviews of frailty in kidney disease have been presented. This current paper offers new insights including an emphasis on the nonphysical aspects of frailty, including social frailty, cognitive frailty, and emotional/psychological frailty which emerge as primary concerns to people living with frailty. We compare the CKD experience of frailty with other chronic end-organ disease populations and explore the complex interaction of sarcopenia and estimated glomerular filtration rate calculations which obscure assessment of both kidney disease and frailty in CKD settings. We also explore the lived experience of frailty and significance of self-identified frailty and implications for medical decision-making. This current review incorporates the updated literature, particularly new clinical practice guidelines and interventions for frailty management. We describe how frailty has implications for caregiver burden and healthcare utilization patterns, including dialysis withdrawal. The review explores validated tools for frailty assessment to

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complement nephrology practice and highlights key risk factors and clinical markers that should alert clinicians to the presence of frailty. Lastly, we outline how recognition of frailty in nephrology settings may improve communication and access to palliative and supportive care.

Prevalence of Frailty in Nephrology Populations: an Epidemic of Public Health Significance

Frailty is highly prevalent among nephrology populations, occurring at more than twice the rate compared to community-dwelling older adults and increasing with CKD progression.[13-16] Compared to chronic disease populations with heart and lung pathology, patients with kidney disease demonstrate greater functional disability.[17] Systematic reviews examining frailty in kidney disease report that frailty prevalence varies with population demographics, research settings, and diagnostic definitions. We refer to our recently published scoping review which provides an overview of frailty prevalence by nephrology population and choice of frailty assessment tool.[18] A number of studies report variation in frailty prevalence using different screening tools within the same study population, allowing a comparison of frailty metrics.[19-22] Among patients with advanced CKD, frailty ranges from 42.6% to 74.1% in patients with stage 4 CKD and 53.8 to 4.7% in predialysis populations.[18,23,24] Frailty appears to develop alongside kidney disease progression with incidence rate of 44.5% described in one heterogenous CKD cohort.[25] Rates as high as 82% have been described in hemodialysis (HD) populations[26] and up to 75% in patients incident to peritoneal dialysis.[27] Duration of HD appears to predict severity of frailty.[28] Functional assessments are frequently utilized as a proxy measure of frailty in the nephrology literature.[29] Studies that have examined functional status longitudinally report increased dependency in activities of daily living within 3 months[30] and 12 months[31] of dialysis initiation. Longitudinal assessments of Fried frailty within HD cohorts demonstrate that progression of frailty occurs as often as frailty remission, although the individual frailty domains of physical inactivity and grip strength decline significantly with time.[32-34] Conservatively managed populations have notably been underexamined for frailty; a single study reports prevalence of 62%.[21] A growing body of evidence examining frailty in kidney transplantation informs waitlisting and transplantation practices.[35,36] Frailty within kidney transplant centers has been described in a number of studies with many indicating prevalence of about 20% among waitlisted candidates and following successful transplantation.[36-42]

In addition to kidney disease, risk factors for frailty include older age, female sex, diabetes, and peripheral artery disease.[32,43,44] Polypharmacy is also associated with frailty, demonstrating a dose-response relationship, and in particular predicting greater risk of exhaustion and physical inactivity.[45] Presence of these risk factors should alert clinicians to the increased probability of frailty and also offering insights into pathophysiologic processes. Few studies have explored how frailty behaves in kidney disease models with high inflammatory and immunosuppressive burden such as glomerulonephritis; these conditions provide opportunity for further study and enhanced understanding of frailty in CKD.[46] Recognition of frailty and its risk factors may improve clinical prognostication and strengthen shared decision-making.

Pathophysiology of Frailty

Frailty pathogenesis may be characterized by the accumulation of senescent cells in multiple tissues and proinflammatory signaling, leading to a concept of "inflammageing"[47]. The pathophysiological mechanisms and relationship between organ systems remains poorly defined and largely speculative. Cell senescence is believed to be triggered by multiple stimuli, including telomere shortening, accumulation of DNA damage, oncogene activation, epigenetic alterations, mitochondrial dysfunction, and environmental factors. Senescent cells may acquire a secretory phenotype and produce inflammatory signals that act in a paracrine fashion to mediate cellular death in neighboring cells. The aging immune system exhibits a reduction in T-lymphocyte production, blunted B-cell-mediated antibody response, and reduced phagocytic activity among neutrophils and macrophages that fails to adequately respond to acute inflammatory or infective threat.[48] Inflammation appears to play a central role in frailty pathogenesis through an aberrant, low-grade inflammatory response that persists beyond the removal of the inciting inflammatory stimulus. Several inflammatory mediators, including interleukin-6, C-reactive protein, tumor-necrosis factor α, and advanced glycation end-products have been implicated in aging, chronic disease, and mortality.[47,49] Changes in gut microbiota and permeability are thought to contribute to a chronic proinflammatory state.[50] Inflammation mediates T-cell senescence, bone loss, and physical and cognitive decline.[47] Oxidative stress and inflammation promote imbalances in protein metabolism, infiltration of intermuscular fat (myosteatosis), and decreased type II myofibers contributing to sarcopenia and insulin resistance.[51,52] Hyperactivity of the hypothalamic-pituitary-axis contributes to neuronal deterioration associated with aging, manifest as chronic raised diurnal cortisol concentrations, increased stress responsiveness, and vulnerability to stressors.[53] Persistently high levels of cortisol contribute to catabolism, loss of muscle mass, anorexia, weight loss, and reduced energy expenditure.[54-56] Changes in synaptic function, protein transport, and mitochondrial function particularly in the prefrontal cortex and the hippocampus coincide with functional changes to microglial cells—the central nervous system equivalent of macrophages—producing hyper-responsive inflammatory changes to neuronal death that are implicated in cognitive decline, impaired learning and are postulated to have an important role in the pathophysiology of delirium.[53,57-59]

CKD is an intensely inflammatory state characterized by metabolic dysregulation and protein catabolism due to uremia and metabolic acidosis, insulin resistance, accumulation of advanced glycation end-products, oxidative stress, anemia and impaired oxygen delivery, extensive vascular calcification, bone demineralization, and frequent comorbid infection.[60] Dysregulation of renin-angiotensin activity is implicated in the induction of reactive oxygen species, cellular hypertrophy and apoptosis, fibroblast proliferation and collagen synthesis with end-organ effects, which manifest in cardiac and vascular tissues. The central role of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers in the prevention or regression of age-associated and CKD-related disease such as ischemic heart disease, left ventricular hypertrophy, atrial fibrillation, stroke, and diabetes offers indirect evidence for the role of renin-angiotensin in systemic disease and frailty.[61] Abnormalities within renin-angiotensin are implicated in sarcopenia through impaired muscle regeneration and accelerated proteolysis.[62] Uremia, insulin resistance, hypogonadism, and vitamin D deficiency are also contributary to sarcopenia.[63,64] Myostatin is elevated in uremic states and impairs muscle regeneration and promotes muscle degradation.[65] Sarcopenia increases progressively with loss of renal function in patients with CKD, reflecting type II fiber atrophy, mitochondrial depletion, and altered protein turnover.[64] Metabolic acidosis, inflammation, anorexia, and malnutrition further aggravate this cycle of deconditioning.[60,66,67] Derangements of the hypothalamic-pituitary axis are prominent in kidney disease states and may be implicated in the development and progression of frailty.[68] Serum cyanate, which exists in equilibrium with urea, promotes protein carbamylation, contributing to erythropoietin resistance, renal fibrosis, disordered immune response, insulin resistance, and vascular damage.[69]

Protein-energy wasting is frequently identified in patients with CKD and ESKD, where metabolic derangements coincide with nutritional deficiencies, characterized by loss of systemic body protein and energy stores. Clinical criteria for identifying catabolism include low serum albumin, weight loss and low body mass index, reductions in fat and muscle mass, and identification of deficient dietary intake.[70] Dietary restrictions, dysgeusia, and uremic nausea or vomiting may contribute to anorexic states, socioeconomic factors, and depression (Figure 1).

Recognizing the role of inflammation in CKD or frailty has important clinical implications. Clinicians should consider the possibility of frailty where inflammatory markers are elevated alongside sarcopenia and malnutrition in patients with CKD. In particular, hypoalbuminemia, decreased transferrin levels, increased

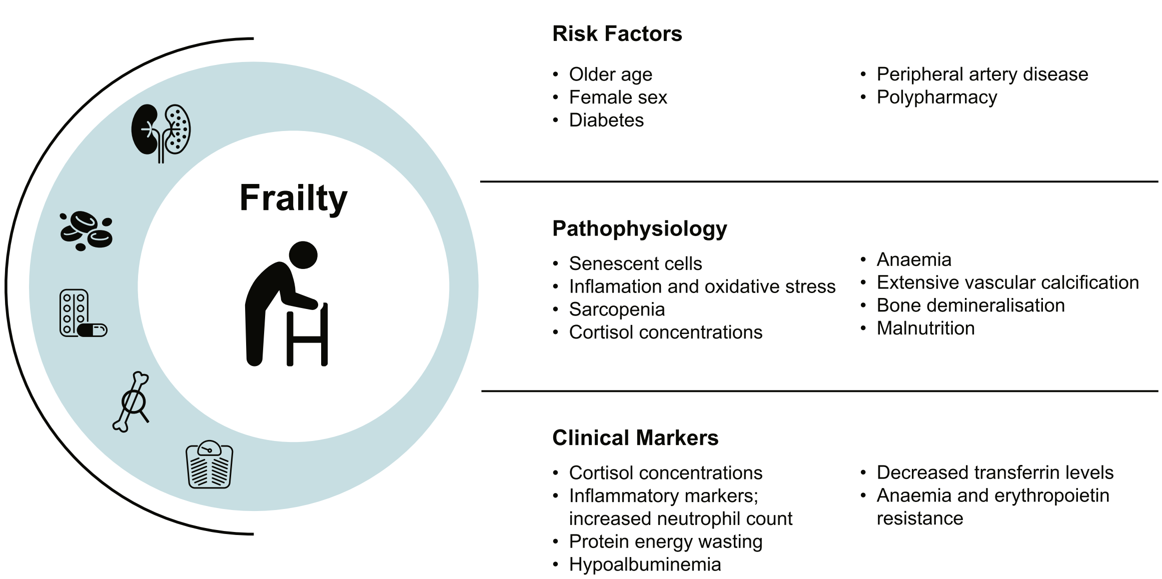

Figure 1. Risk factors, pathophysiological mechanisms, and clinical markers of frailty in the kidney disease context.

neutrophil count, elevated c-reactive protein, and the presence of erythropoietin resistance frequently accompany frailty.[71] Visceral adiposity predicts not only increased risk of frailty but also progressive renal function decline, offering opportunity for early metabolic intervention. Moreover, in the setting of CKD and ESKD, reductions in serum creatinine may reflect sarcopenia and hypercatabolism rather than improvements in renal function or dialysis adequacy. In frail and sarcopenic populations, alternative measures of renal function which are independent of muscle mass, emerge as the optimal research tool. Observational studies using cystatin-C report an independent association with frailty and glomerular filtration rate.[14,72,73]

Clinical Implications of Frailty in Kidney Disease

The presence of frailty in patients with nondialysis CKD predicts a number of adverse patient outcomes (see Table 1). Frailty predicts an approximately 2- to 6-fold increase in risk of death, hospitalization, and progression to dialysis.[14,74] Both objective measures of frailty and subjective assessments are associated with not-for-dialysis conservatively managed choice.[75,76-79] Whether assessed objectively or subjectively, frailty appears to increase the probability of initiation of in-center rather than home-based dialysis modality.[75,80] Frailty in home dialysis populations predicts technique failure and death.[81] A single study has examined survival outcomes specifically in frail patients undertaking dialysis compared to conservative care and reported no differences in survival outcomes when adjusted for sex, comorbidity, or age.[75]

Predialysis frailty predicts earlier dialysis commencement, possibly reflecting misidentification of the manifestations of frailty as uremic symptoms.[85,86] Presence of frailty while undergoing maintenance dialysis treatment is associated with excess infections and cardiovascular events as well as dialysis complications including prolonged postdialysis recovery time, increased interdialytic weight gain, hypoalbuminemia, and reduced medication adherence.[105-108] Studies report that frailty is associated with higher probability of initial and recurrent vascular access failure.[109,110] A limited number of cross-sectional studies have compared the risk of frailty progression based on maintenance dialysis modality; most of these studies conclude no difference between HD and PD, but patient selection bias confounds the interpretation of this data.[7,85,91,93,111-116] Frailty in PD populations remains a neglected area of research activity.[18,29] Studies of dialysis populations consistently report 1.4- to 3-fold increased risk of hospitalization and emergency department presentations and 2- to 5-fold hazard ratio for mortality, when adjusted for age and comorbidity.[7,8,33,44,74] Hospitalization contributes to frailty progression and deterioration in frailty scores.[32] Decreased physical performance and frailty are associated with reduced likelihood of transplant referral and waitlisting, and increased removal from waitlist and death on waitlist.[38,40,117-120] Studies enrolling patients with frailty incident to dialysis report transplantation rates of just 4%.[93] International data registries confirm that frailty and its surrogate measures increase the odds of dialysis withdrawal as primary cause of death.[121-123] Falls and particularly hip fracture-related mortality are also common frailty sequelae, with one study describing a 25% and 58% 30-day and 1-year mortality rate, respectively, for patients undergoing HD.[87]

Risk stratification using frailty assessment demonstrates increasing uptake and much research interest.[18,124,125] Transplant centers that assess frailty as part of clinical practice demonstrate better patient-level outcomes, including waitlist mortality and death-censored graft loss.[126] Such improvements in patient outcomes appear to come at the cost of reduced access to transplantation among frail candidates, although a number of centers did describe provision of additional social and home support, along with prehabilitation.[124] Importantly, such benefits were only realized where validated frailty assessment tools were utilized, illustrating the risk of discrimination associated with subjective measures of frailty.[126] Presence of frailty at transplantation is predicted by dialysis duration before transplantation.[28] Frailty at the time of transplantation is associated with postoperative complications, including delayed graft function, extended hospital length-of-stay, readmission, immunosuppression intolerance, graft loss, and death with graft function.[41,99,100,102,127,128] Frailty may be improved by kidney transplantation, following a period of early postoperative exacerbation.[129]

Frailty is associated with increased symptom burden and impaired quality of life. Qualitative studies of community-dwelling elderly populations report themes of progressive deterioration and vulnerability, loss of meaning, agency, and social identity.[130,131] Social isolation and geographic contraction are common with community mobility and participation in life-spaces threatened by the experience of CKD and further disrupted by the introduction of dialysis.[132,133] Frailty independently predicts worse health-related quality of life, symptom burden, and depression.[24,31,134,135] The lived experience of frailty in CKD for both patients and their caregivers deserve further examination. Pilot work suggests patients experience prominent fatigue and lack of social support and prioritize the ability to live independently.[136]

Table 1. Adverse outcomes associated with frailty among kidney disease populations

Study population	Outcomes of interest	HR/OR, risk difference (95% CI)	References
CKD	Choice of RRT over nondialysis conservative care	OR 0.62 (0.51–0.75)	Pyart *et al.*[75]
	Dialysis initiation	HR 5.42 (1.06– 27.64)	Vezza *et al.*[82]
	In-center dialysis over home therapy	OR 3.41 (1.56– 7.44)	Brar *et al.*[80]
	Hospitalization	HR 18.80 (2.36– 150.00)	Vezza *et al.*[82]
	All-cause mortality	HR 4.28 (1.22– 14.9)	Ali *et al.*[83]
		HR 1.96 (1.47– 2.61)	Brar *et al.*[80]
		HR 1.51 (1.10– 2.10)	Delgado *et al.*[84]
		HR 2.32 (0.23– 23.12)	Vezza *et al.*[82]
		HR 3.0 (2.2– 4.1)	Wilhelm-Leen *et al.*[16]
	Death or dialysis	HR 2.5 (1.4– 4.4)	Roshanravan *et al.*[14]
HD	Earlier dialysis commencement	OR 1.44 (1.23– 1.68)	Bao *et al.*[85]
		OR 1.16 per frailty symptom (1.06– 1.28)	Tamura *et al.*[86]
	Falls	HR 3.09 (1.38– 6.90)	McAdams-DeMarco *et al.*[87]
		HR 2.1 (1.21– 3.92)	Yadla *et al.*[26]
	Emergency department visits	HR 2.20 (1.58– 3.08)	Garcia-Canton *et al.*[88]
		IRR 2.78 (1.70– 4.60)	Li- *et al.*[89]
		HR 2.28 (1.30– 3.98)	Vinson *et al.*[90]
	Time to first hospitalization	HR 1.26 (1.09– 1.45)	Bao *et al.*[85]
	Hospitalization	HR 2.09 (1.38– 3.18)	Garcia-Canton *et al.*[88]
		HR 1.80 (1.38– 2.36)	Lee *et al.*[91]
		HR 1.43 (1.00– 2.03)	McAdams-DeMarco *et al.*[8]
		HR 1.35 (1.20– 1.53)	Nixon *et al.*[92]
		HR 2.31 (1.24– 4.32)	Van Loon *et al.*[93]
		HR 2.06 (1.18– 3.58)	Yadla *et al.*[26]
	Hospitalization (LOS >2 weeks post kidney transplantation)	HR 2.02 (1.20– 3.40)	Chu *et al.*[34]
	12-month mortality	HR 7.22 (2.47– 21.13)	Van Loon *et al.*[93]
	All-cause mortality	HR 1.57 (1.25– 1.97)	Bao *et al.*[85]
		HR 3.77 (1.10– 12.92)	Fitzpatrick *et al.*[94]
		HR 2.34 (1.39– 3.95)	Garcia-Canton *et al.*[88]
		HR 2.16 (1.41– 3.29)	Johansen *et al.*[95]
		HR 5.22 (2.28– 11.97)	Johansen *et al.*[33]
		HR 2.37 (1.11– 5.02)	Lee *et al.*[91]
		HR 4.10 (1.09– 15.43)	Li *et al.*[89]
		HR 2.60 (1.04– 6.49)	McAdams-DeMarco *et al.*[8]
		HR 2.15 (1.63– 2.85)	Nixon *et al.*[92]
	Postkidney transplant mortality	HR 2.27 (1.11– 4.65)	Chu *et al.*[34]
		HR 2.30 (1.12– 4.74)	Nastasi *et al.*[96]
	No survival advantage to dialysis where frailty is present	HR 1.2 (0.69–2.06)	Pyart *et al.*[75]
Home therapy (Home HD or PD)	Composite technique failure and death	HR 2.10 (1.09– 3.99)	Brar *et al.*[81]
Peritoneal dialysis	All-cause mortality	HR 1.79 (1.09– 2.94)	Chan *et al.*[97]
		HR 12.2 (2.27– 65.5)	Kamijo *et al.*[98]
Kidney transplant recipient	Postoperative complications	HR 14.54 (7.90– 21.18)	Schopmeyer *et al.*[99]
		RR 2.14 (1.01– 4.54)	Dos Santos Mantovani *et al.*[41]
	Delayed graft function	RR 1.94 (1.13– 3.36)	Garonzik-Wang *et al.*[100]
	Early hospital readmission	RR 1.61 (1.18– 2.19)	McAdams-DeMarco *et al.*[101]
	Immunosuppression intolerance	HR 1.29 (1.01– 1.66)	McAdams-Demarco *et al.*[102]
	All-cause mortality	HR 2.17 (1.01– 4.65)	McAdams-DeMarco *et al.*[103]
		HR 2.61 (1.14– 5.97)	McAdams-DeMarco *et al.*[104]

CKD, chronic kidney disease; HD, hemodialysis; HR, hazard ratio; LOS, length of stay; OR, odds ratio; PD, peritoneal dialysis.

Frailty in CKD is independently associated with poorer cognitive function, increasing in prevalence across CKD stages and highly prevalent in dialysis populations.[137,138] Impairment is more frequently vascular rather than amyloid-related in nature, with implications for executive function, attention, behavior control, and working memory.[139-141] Coincident depression worsens cognitive performance further.[142] These frailty manifestations have implications for therapeutic engagement, ability to self-care, adherence to therapy, and management of complex medication regimens. Nephrologists increasingly face questions of decision-making capacity. Skilled practitioners will recognize frailty as an opportunity for advanced communication, offer supported decision-making, and timely advance care planning.

Table 2. Comparison of frailty assessment tools validated for use in kidney disease populations

Frailty metric	Strengths as a diagnostic tool	Limitations as a diagnostic tool
Fried frailty phenotype[1]	Objective Robust data across different CKD states and settings	Fatigue and weight/fluid status components may vary with dialysis timing Potentially cumbersome
Clinical frailty scale[145]	Easy to use Quantitative Potential for retrospective assessment Smart-phone app	Relies on subjective clinical impression. Heavily focused on disability. Over-categorizes frailty in dialysis (Minimum frailty scale 3) Insensitive tool in kidney disease populations
Frailty Index[146]	Quantitative Electronic form available	Focused on disability and comorbidity
Comprehensive Geriatric Review[2]	Gold standard for frailty diagnosis and management Only tool to incorporate cognitive, social and caregiver components.	Resource intensive and arduous for patients
Short Physical Performance Battery[147]	Objective Lower limb function highly predictive of outcomes in kidney disease populations	Potentially cumbersome Unable to be utilized in some patients with lower limb amputation or bedbound status
Hand-grip strength[148]	Can be performed in patients with lower limb amputation or bedbound status	Lower limb disability more predictive of outcome in kidney disease populations
Voorend's CKD geriatric assessment tool[149]	Holistic assessment of objective physical function, functional dependence, polypharmacy, cognition, nutrition, social and caregiver appraisal	Resource intensive and potentially arduous for patients/ caregivers Frailty assessments are relevant in nongeriatric (younger) patient age groups

CKD, chronic kidney disease.

Frailty is an important clinical phenomenon whose presence outperforms biochemical assessment in predicting patient-level outcomes. Recognizing frailty and individualizing management decisions to prevent its progression is a crucial skill for improving patient well-being and optimizing healthcare utilization. Improvement in dialysis outcomes has stalled in recent years; recognition of frailty before dialysis initiation offers opportunity to substantially improve morbidity and mortality events. Rapid progression of frailty precipitated by dialysis commencement reinforces prompt access to transplant work-up as a valid key performance indicator for ensuring equitable care. Accelerated aging in CKD populations has implications for healthcare policy, justifying earlier access to Aged Care Assessment, support, and funding. Healthcare systems that fail to proactively address frailty within our aging chronic disease population risk overwhelming healthcare expenditure and compromised quality of care.

Diagnostic Approaches to Frailty

A large number of frailty metrics which have been validated in nephrology populations exist for use but vary by frailty conceptualization and resource demands (Table 2). Frailty should be objectively assessed, noting that subjective frailty judgements risk misclassification and discrimination and do not afford the same improved patient level outcomes following their use.[126,143] The emerging body of literature in nephrology research settings appears to favor use of Fried frailty phenotype, which defines frailty based on presence of 3 or more features of weight loss or sarcopenia, exhaustion, weakness, slowness, and low physical activity.[1] It allows definition of a prefrail state to facilitate earlier intervention. Fried frailty can be feasibly incorporated into routine nephrology outpatient and dialysis assessments, noting that weight is regularly assessed and that fatigue and low activity or poor mobility can be triangulated from many symptom assessment tools.[24] Slowness may be assessed over 10 meters or by 6-minute walk distance, while grip strength can be rapidly assessed with inexpensive equipment. Several nephrology care models have embedded these assessments with success, acknowledging that in these well-resourced settings, Fried frailty assessments have been largely performed by auxiliary allied health professionals attached to the nephrology outpatient clinic.[24,144]

The 9-point Clinical Frailty Scale comprises a standard set of clinical descriptors to capture frailty based on reported mobility and activities of daily living.[145] It is available as a smartphone App and endorsed by clinicians working with frail CKD populations for its usability.[125] It has excellent construct validity and interrater reliability and performs with prognostic accuracy in dialysis populations.[116] It may, however, be insufficiently sensitive to identify relevant changes in frailty dynamics in CKD populations.[19,46]

The Frailty Index allows disability and comorbidity to be quantitatively captured with good construct validity and feasibility in outpatient settings, as well as opportunity for electronic data capture.[146] In nephrology settings, it has been most frequently operationalized in nondialysis CKD populations where competing comorbidities were of equal or equivalent relevance.[18,29]

Comprehensive geriatric review is the gold standard frailty assessment and cornerstone of geriatric medicine, capturing functional dependence, polypharmacy, sensory deficits, and falls history alongside social, cognitive, and psychological domains.[2] An objective physical measure of frailty is assessed in a short physical performance battery of tests. This structured appraisal of geriatric syndromes affords development of an integrated multidisciplinary treatment plan and evaluation of progression and subsequent adjustment of care needs. Comprehensive geriatric assessment (CGA) improves awareness of holistic and palliative care needs while facilitating appropriate multidisciplinary referral and advance care planning.[92,150] In geriatric settings, CGA adoption and subsequent management in acute hospital settings is associated with superior patient outcomes, including performance status, avoidance of residential aged care admission, cognition, and mortality.[151] This process of structured multidisciplinary appraisal of health needs has been used successfully outside of geriatric medicine settings;[152,153] however, its use in routine nephrology practice is limited by its resource-heavy demands and assessment burden to consumers. Studies in CKD and HD populations to date demonstrate its feasibility for implementation in nephrology settings with its ability to identify overburdened caregivers.[27,92,154] Pilot studies indicate that use of CGA may substantially improve functional independence and avoidance of nursing home admission within median 48.5 days of assessment.[155]

The short physical performance battery has also been used as a stand-alone assessment of frailty in several studies, particularly favored in studies examining participants with advanced CKD and transplant candidates.[18] Briefly, short physical performance battery examines lower extremity function through standing balance assessment, repeated chair stand maneuver, and gait speed (usually over 4 m or 15 ft). In ambulatory geriatric settings, it demonstrates association with mortality, quality of life, and functional decline as well as responsiveness to intervention.[147] Performing differently from Fried frailty assessment, short physical performance battery impairment predicts dialysis modality choice, home dialysis technique failure, all-cause mortality, and posttransplant mortality; and is a potentially modifiable objective measure for renal replacement therapy risk prediction.[22,80,81,96] Handgrip strength might also offer prognostic utility, demonstrating correlation with gait speed and kidney transplant assessment outcomes, as well as sensitivity to change over acute admission.[125,156,157] However, impairment of lower limb function, rather than upper limb function, is most predictive of outcomes in CKD studies.[22,158]

To date, there remains no consensus on the most appropriate tool for frailty assessment in nephrology populations. Voorend and colleagues propose a definitive CKD geriatric assessment tool comprising functional assessment of activities of daily living, objective physical assessment based on handgrip strength, symptom assessment by patient-reported outcome measures, cognitive appraisal using Montreal Cognitive Assessment, frailty assessment by Clinical Frailty Scale, nutritional assessment, polypharmacy review, and measurement of caregiver burden.[149] This tool can be completed within an hour utilizing both patient questionnaire and nurse-administered components.

It is likely that different instruments offer distinctive advantages that lend themselves to specific clinical settings. Frailty is critically dynamic, with some studies reporting clinically meaningful changes (improvement or decline) in performance at 3-month or longer intervals.[32,159,160] Fluctuations in frailty status over the course of hospitalization events, dialysis treatments, and transplantation justify frequent and repeated assessments at critical transitions in care.[30,156] The challenge for nephrology workforces is to familiarize themselves with different aspects of frailty assessment and embed this is in clinical practice.

Intervention for CKD/Frailty: Renal Rehabilitation

Guidelines recommend screening for frailty in elderly patients with advanced CKD to direct in-depth geriatric assessment and rehabilitation.[161] Currently, there is limited evidence to guide maintenance or improvement in frailty in nephrology contexts. This contrasts with cardiology settings where an "essential frailty toolkit" and international consensus statements endorse frailty and cognitive assessment followed by multidisciplinary evidence-based primary, secondary, and tertiary prevention strategies.[162-164] The Kidney Disease Improving Global Outcomes initiative recommends physical activity and exercise in a graduated, supervised, and individualized program.[165] Exercise guidelines specific to PD populations have recently been published by the International Society of Peritoneal Dialysis in collaboration with the Global Renal Exercise Network.[166] Exercise-based interventions for patients undergoing HD may be either intradialytic or home-based interdialytic programs, with equal benefits observed in performance parameters in both modalities.[167] Long-term outcomes such as hospitalization and mortality have not been examined to date. A number of trials and systematic reviews in nondialysis CKD settings have demonstrated that exercise intervention improves inflammatory markers, physical fitness, muscular functioning, and cardiovascular dimensions; also slows or resolves progression of kidney disease and proteinuria as well as improving renal hemodynamics.[168-175] Psychological parameters, sleep quality, and quality of life also improved.[168] Few studies have examined the impact of exercise intervention on frail nephrology populations; recent scoping review identified just 3 randomized controlled trials, in their infancy.[18] The current Ex-FRAIL trial and CYCLE-HD will examine the impact of home-based exercise and interdialytic cycling on frailty in CKD, noting some difficulties with retention and recruitment.[176-178] Yamaguchi and colleagues report considerable durability of the impact on performance status and self-efficacy when frail patients were offered flexible (both home-based and interdialytic) exercise program.[179] Acute inpatient geriatric rehabilitation for CKD and HD populations demonstrates equivalent outcomes to non-CKD elderly adults but remains underutilized.[180-182]

Successful frailty interventions are likely to be broader in scope than exercise alone, addressing the psycho-emotional-cognitive aspects of frailty alongside physical manifestations. The Japanese Society of Renal Rehabilitation proposes "a long-term comprehensive program consisting of exercise therapy, diet therapy and water management, drug therapy, education, psychological and mental support to alleviate the physical and mental effects of kidney disease and dialysis therapy, prolong life, and improve psychological and occupational circumstances".[183] Its guidelines emphasize the psycho-emotional-social needs of this vulnerable patient population, endorsing multidisciplinary and multimodal interventions that "exhaust all support options to help kidney disease patients smoothly achieve social rehabilitation instead of simply implementing exercise therapy". Within the geriatric literature, there is evidence to support the use of multicomponent interventions incorporating social, nutritional, and cognitive elements in addition to exercise program for improving frailty, cognitive, social, and emotional outcomes in frail and prefrail community-dwelling elderly.[184-186] These programs demonstrate high recruitment and retention rates, suggesting acceptability among consumers. An ambitious randomized controlled trial of exercise intervention alongside psychological and nutritional care in predialysis patients with CKD to examine the impact on frailty, hospitalization, and mortality has been proposed.[187] The published protocol does not specify details of the dietary intervention. There is evidence to support the use of megestrol acetate and dietary supplements in this patient population.[188,189] Dietary recommendations suggest that 1.2g/kg/day protein intake is appropriate in end-stage renal disease, where efficient dialysis or quality of life can be prioritized over CKD progression.[70]

Outcomes pertaining to frailty assessment are likely to be poorly captured, reflecting poor attention to patient priorities within research agendas. Consumer-focused research such as the Standardised Outcomes in Nephrology initiative and James Lind Alliance prioritize patient perspectives in research and clinical outcomes, noting that neither have specifically explored frailty perspectives in nephrology populations.[190,191] The lived experience of frailty and CKD remains unexamined. The implementation of CGA and multidisciplinary follow-up appears to enhance education, training, and awareness of palliative care needs among clinicians serving this patient population while facilitating delivery of holistic care plans, which incorporate discussions of treatment options through appropriate referral and advance care planning.[92,150,192] Although not formally measured, studies evaluating CGA in nephrology populations frequently report improvement and individualization in treatment options and reinforced social supports.[150,192,193] Interventions addressing the socioeconomic determinants of health and wellbeing offer opportunity to address key inequities characterizing the experience of frailty.[136] Patient care priorities include provision of emotional and practical support, maintenance of mobility, and supported decision-making.[29] Caregiver needs remain undiscovered with recent systematic reviews highlighting the high level of burden involved in caring for people with advanced CKD.[194,195] Health economics studies should be used to capture efficiency or intervention, with cost of frailty intervention compared against healthcare utilization patterns. Early data suggest that exercise intervention in HD populations is cost-effective, affording avoidance of hospitalization and additional care costs, noting that participants with frailty were not specifically identified or evaluated in this analysis.[196]

Conclusions

Frailty in the kidney disease context is an important clinical syndrome characterized by uremic symptom burden and a subjective psycho-emotional-social experience, with specific implications for healthcare utilization and caregiver burden. Although underdiagnosed, frailty is highly prevalent and directs important clinical outcomes. Recognition of frailty emerges as a core nephrology skill that is crucial to the assessment of patients with CKD, for those approaching dialysis, and planning for renal transplantation. Successful frailty intervention is likely longitudinal and multidisciplinary, addressing the multisystemic components of frailty while supporting shared decision-making and advance care planning. Future nephrology research should incorporate evaluations of frailty status to add meaning to key patient-level outcomes. This includes database registries which require frailty data capture to furnish understanding of big data. Frailty in the CKD context and its implications for healthcare delivery should be a clinical and research priority for nephrology workforces, public health systems, and policy writers.

DISCLOSURE

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