

Review Article Nephrology

## Frailty in end-stage kidney disease: A multidimensional approach to risk stratification and personalized care

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### ABSTRACT

**Background:** Frailty is increasingly recognized as a critical determinant of outcomes in end-stage kidney disease (ESKD), affecting up to 70% of dialysis patients and 20% of kidney transplant candidates.

**Objective:** This review synthesizes current evidence on frailty in ESKD, focusing on definition, assessment, outcomes, modality differences, interventions, and implementation strategies.

**Key Findings:** Frailty in ESKD results from complex interactions between uremia-related factors, comorbidities, and aging processes. While the Fried Frailty Phenotype remains the most widely used assessment tool, the clinical frailty scale (CFS) offers practical advantages in clinical settings. Frailty independently predicts mortality (2.6-fold increased risk), hospitalization, falls, and post-transplant complications. Comparative studies suggest that while frailty prevalence is similar between hemodialysis and peritoneal dialysis patients (approximately 40–43%), some frail patients still derive survival benefit from kidney transplantation despite increased perioperative risks. Multimodal interventions combining nutritional support, exercise training, and cognitive rehabilitation show promise in attenuating frailty progression.

**Conclusion:** Incorporating frailty assessment into routine nephrology care enables risk stratification and personalized management strategies. The CFS represents a practical tool for resource-limited settings.

**Keywords:** Dialysis, End-stage kidney disease, Frailty, Kidney transplantation, Risk stratification

### INTRODUCTION

Frailty, a multidimensional syndrome characterized by decreased physiologic reserve and increased vulnerability to stressors, has emerged as a critical concept in nephrology practice.<sup>[1,2]</sup> While initially studied in geriatric populations, frailty has particular relevance in end-stage kidney disease (ESKD), where its prevalence far exceeds age-matched controls.<sup>[3]</sup> The uremic milieu, combined with metabolic and inflammatory burden, creates a physiologic environment that accelerates frailty development even in younger patients.<sup>[4]</sup>

The clinical significance of frailty in ESKD is critically important. Across dialysis modalities and kidney transplantation, frailty independently predicts mortality, hospitalization, falls, and quality of life impairment.<sup>[5,6]</sup> Despite this prognostic importance, frailty assessment remains underutilized in routine nephrology care, particularly in low and middle-income countries.<sup>[7]</sup>

Recent research has illuminated the differential impact of frailty across renal replacement modalities, with implications for modality selection and timing of transitions.<sup>[8,9]</sup> Simultaneously,

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emerging evidence suggests that frailty in ESKD may be partially reversible through targeted interventions.<sup>[10]</sup>

This review provides a comprehensive examination of frailty in ESKD, synthesizing current evidence on its definition, pathophysiology, assessment, impact on outcomes, and management strategies, with particular emphasis on practical approaches to implementation in diverse clinical settings. Specifically, we aim to (1) critically evaluate current definitions and assessment approaches for frailty in ESKD, (2) examine the complex pathophysiologic mechanisms underlying frailty in the uremic environment, (3) analyze the impact of frailty on clinical outcomes across different renal replacement modalities, (4) assess the effectiveness of interventions targeting frailty, and (5) propose practical implementation strategies for diverse clinical settings.

## METHODS

### Literature search strategy

For this narrative review, we conducted a comprehensive literature search using PubMed, Embase, and Web of Science databases from January 2015 to May 2025. Search terms included combinations of “frailty,” “end-stage kidney disease,” “chronic kidney disease,” “dialysis,” “hemodialysis (HD),” “peritoneal dialysis,” “kidney transplantation,” “assessment,” “outcomes,” and “interventions.” We prioritized peer-reviewed articles published in English, including systematic reviews, meta-analyses, randomized controlled trials (RCTs), observational studies, and relevant clinical practice guidelines. Additional articles were identified through reference lists of selected publications and recent nephrology conference proceedings.

### Selection criteria

Articles were selected based on relevance to the following key domains: (1) Definition and pathophysiology of frailty in ESKD, (2) frailty assessment tools validated in kidney disease populations, (3) impact of frailty on clinical outcomes, (4) comparative studies of frailty across renal replacement modalities, (5) interventions targeting frailty in ESKD, and (6) implementation strategies for resource-limited settings. We prioritized studies with larger sample sizes, longer follow-up periods, and methodological rigor. Case reports and small case series were excluded unless they provided unique insights not available from larger studies.

### Data extraction and synthesis

From each selected article, we extracted information on study design, population characteristics, frailty definition and assessment methods, key findings, and limitations. Data were synthesized narratively by thematic domain,

with particular attention to consistency of findings across studies and applicability to clinical practice. Where available, we highlighted evidence specific to different ESKD subpopulations, including elderly patients, those with diabetes, and patients in low-resource settings.

## DEFINITION AND PATHOPHYSIOLOGY

### Defining frailty in ESKD: controversies and consensus

The most widely used operational definition of frailty in nephrology research is the Fried Frailty phenotype (FFP), which identifies frailty based on the presence of three or more of five physical components: Slowness (measured by gait speed), weakness (measured by grip strength), unintentional weight loss, self-reported exhaustion, and low physical activity.<sup>[1]</sup> Alternative conceptualizations include the deficit accumulation model (Frailty Index [FI]) and the clinical frailty scale (CFS).<sup>[11,12]</sup>

A significant controversy in the field centers on whether generic frailty tools developed in geriatric populations are appropriate for ESKD patients, or whether kidney disease-specific adaptations are necessary. The Fried criteria, while extensively validated, may not fully capture the unique aspects of frailty in ESKD, such as dialysis-related fatigue, vascular access issues, and fluid shifts.<sup>[13]</sup> Some researchers advocate for ESKD-specific tools that incorporate disease-specific elements, while others argue that maintaining standardized definitions enables cross-population comparisons.<sup>[14]</sup>

Another area of debate concerns the dimensional structure of frailty in ESKD—whether it represents primarily a physical phenotype or a broader multidimensional construct encompassing cognitive, psychological, and social domains. The physical frailty phenotype dominates research in nephrology, but growing evidence suggests that cognitive impairment and psychological factors significantly contribute to adverse outcomes in this population.<sup>[15]</sup>

It is important to distinguish frailty from related but distinct concepts such as comorbidity, disability, and sarcopenia. While these conditions frequently coexist with frailty in ESKD patients, frailty represents a unique physiologic state not fully explained by specific diseases, functional limitations, or muscle wasting alone.<sup>[16]</sup>

### Prevalence and risk factors

The prevalence of frailty in ESKD far exceeds that of the general population. While community-dwelling older adults exhibit frailty prevalence rates of approximately 2.8–10%, studies in ESKD populations report rates ranging from 20.9% in advanced chronic kidney disease (CKD) to 41–70% in dialysis-dependent patients.<sup>[17,18]</sup> Nair *et al.*, found that 41% of CKD stage 5 patients met criteria for frailty, with similar

prevalence between those on HD (43%) and those receiving pre-dialysis care (40%).<sup>[19]</sup>

Certain subgroups demonstrate particularly high frailty burden. Among ESKD patients over 55 years of age, frailty prevalence reaches 82%, while diabetic ESKD patients show rates of approximately 75%.<sup>[19]</sup> Other factors associated with increased frailty risk include female sex, lower socioeconomic status, and higher comorbidity burden.<sup>[20,21]</sup>

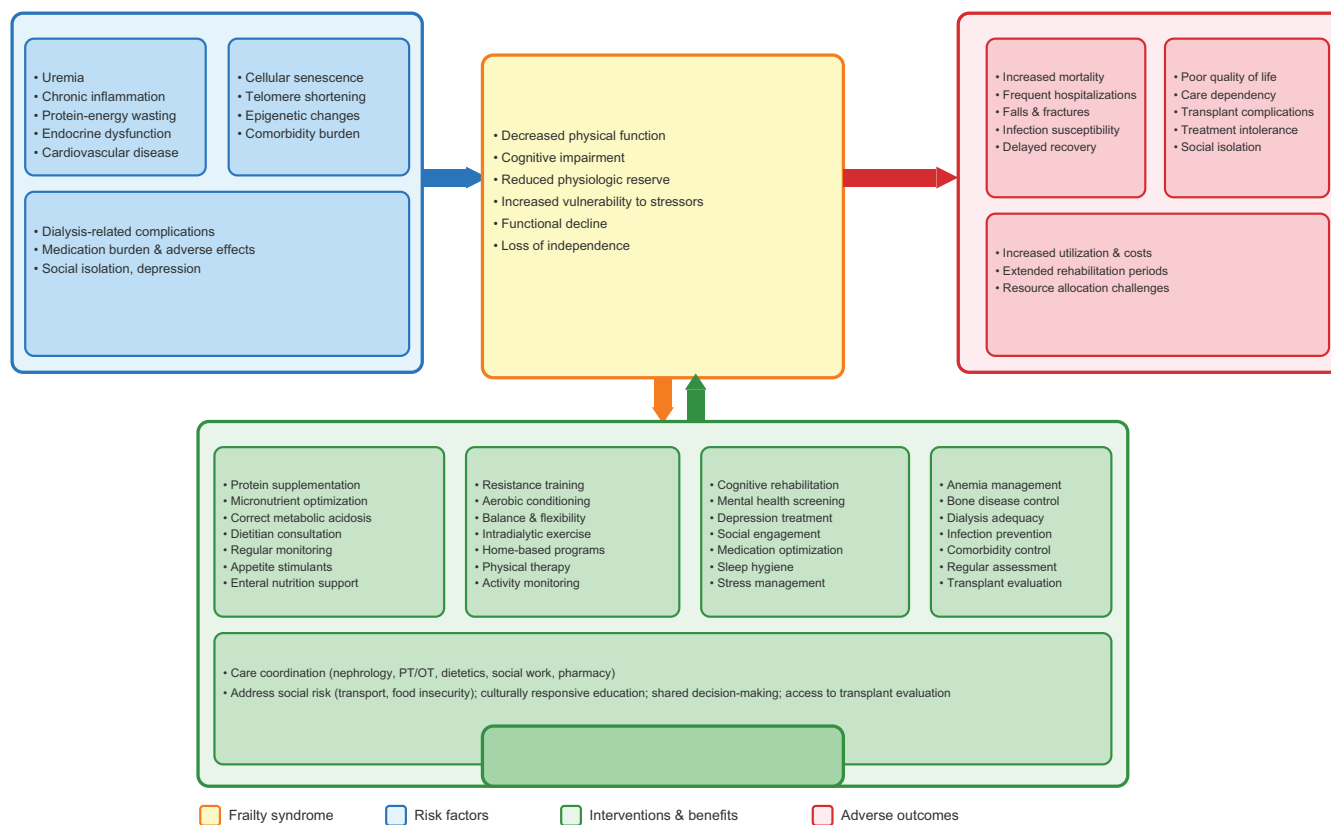
### Pathophysiologic mechanisms: An integrated model

The pathophysiology of frailty in ESKD involves complex interactions between kidney disease-specific factors and aging-related processes [Figure 1]. We propose an integrated conceptual model where uremia serves as the central driver, initiating and amplifying multiple pathophysiologic pathways that converge to produce the frailty phenotype:

1. Protein-energy wasting: Affecting 20–50% of dialysis patients through inadequate nutrient intake, dialysis-related protein losses, metabolic acidosis, and inflammation-induced hypercatabolism.<sup>[22]</sup> This pathway directly contributes to muscle wasting, weakness, and fatigue-core components of the frailty phenotype.
2. Chronic inflammation: ESKD creates a persistent pro-inflammatory state characterized by elevated

levels of interleukin (IL-6), tumor necrosis factor- $\alpha$ , and C-reactive protein.<sup>[23]</sup> This inflammatory milieu promotes muscle catabolism, anorexia, and endothelial dysfunction. Importantly, inflammation serves as a central mediator connecting multiple pathophysiologic pathways, amplifying the effects of protein-energy wasting, cardiovascular dysfunction, and cellular senescence.

3. Endocrine dysregulation: Kidney disease disrupts multiple endocrine pathways relevant to frailty pathogenesis, including resistance to anabolic hormones (insulin, insulin-like growth factor-1), vitamin D deficiency, secondary hyperparathyroidism, and dysregulated adipokine production.<sup>[24]</sup> These endocrine abnormalities promote sarcopenia, bone fragility, and metabolic dysfunction.
4. Cardiovascular dysfunction: The high prevalence of cardiovascular disease in ESKD contributes to frailty through reduced cardiac output, impaired peripheral oxygen delivery, and exercise intolerance.<sup>[25]</sup> Volume shifts during HD may further compromise hemodynamic stability, with intradialytic hypotension showing a significant association with frailty ( $P = 0.002$ ).<sup>[19]</sup>
5. Accelerated aging processes: ESKD is characterized by accelerated cellular senescence, telomere shortening,



**Figure 1:** Pathophysiology of frailty in end-stage kidney disease. PT: Physical therapy, OT: Occupational therapy.

and epigenetic changes that mirror physiologic aging.<sup>[4]</sup> These processes affect multiple organ systems and contribute to the global decrease in physiologic reserve that defines frailty.

Our integrated model proposes that these pathways do not operate in isolation but rather form a complex network of bidirectional interactions. For example, inflammation promotes protein-energy wasting, which further exacerbates inflammation; cardiovascular dysfunction limits physical activity, contributing to muscle deconditioning; and cellular senescence amplifies inflammatory processes. This network of interactions creates multiple self-reinforcing cycles that accelerate frailty progression in ESKD patients.

The model also highlights potential intervention targets at multiple levels: Nutritional support to address protein-energy wasting, anti-inflammatory strategies, hormone replacement, cardiovascular optimization, and senolytic approaches targeting cellular aging processes. The complexity of these interactions underscores the need for multimodal interventions addressing multiple pathways simultaneously.

## ASSESSMENT TOOLS

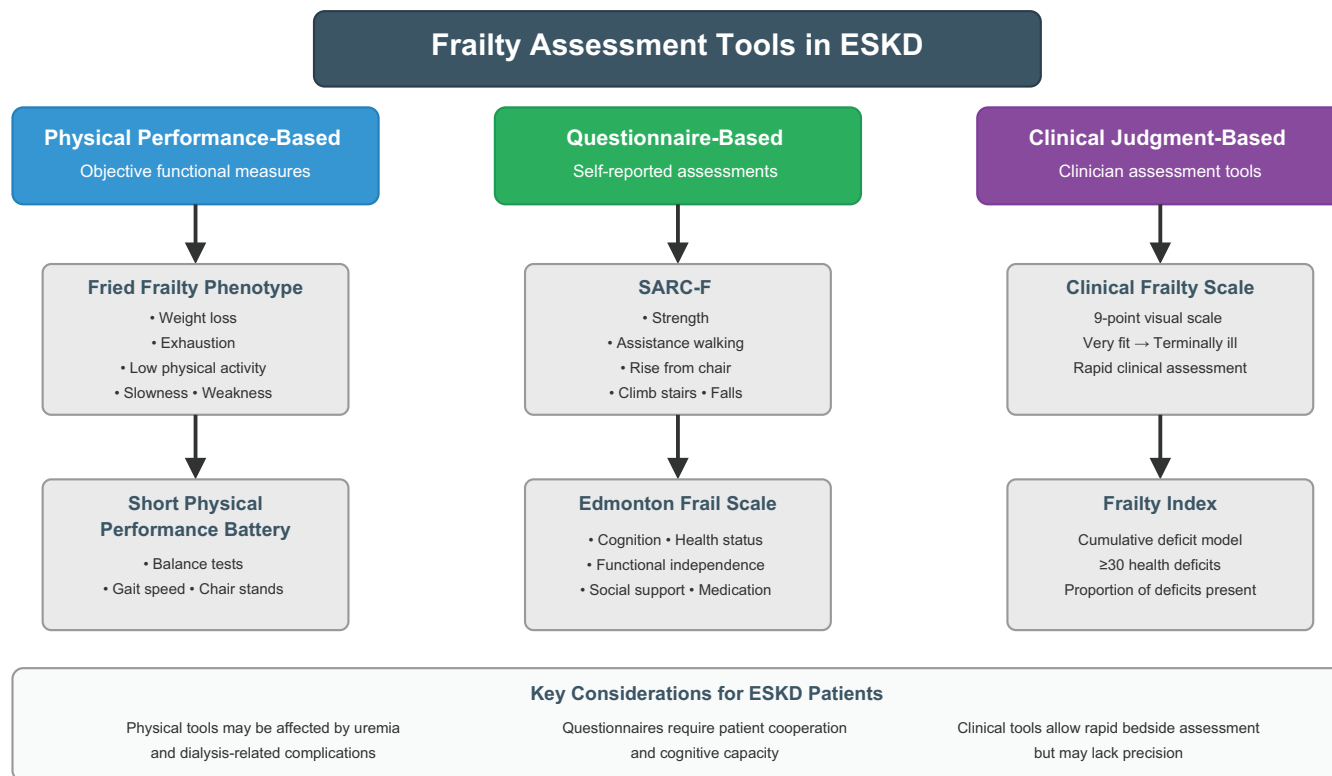
### Summary of assessment tools

Multiple validated instruments are available for frailty assessment in ESKD populations, each with distinct advantages

and limitations. Performance-based tools like the Fried frailty phenotype (FFP) and short physical performance battery (SPPB) offer objective measurements but require equipment and time. Clinical judgment scales such as the clinical frailty scale (CFS) provide rapid assessment with minimal resources. Comprehensive instruments like the frailty index (FI) and Edmonton frail scale capture multidimensional aspects of frailty but demand more extensive evaluation. Self-report questionnaires like the Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls (SARC-F) enable screening with minimal staff involvement. The choice of assessment tool should be guided by the clinical context, available resources, and intended purpose—either for research, comprehensive clinical evaluation, or rapid screening. Figure 2 provides a visual comparison of these major assessment tools, highlighting their key components, administration time, and resource requirements to facilitate selection of the most appropriate instrument for specific clinical settings.

### FFP

The FFP remains the most widely used assessment tool in nephrology research, employed in approximately 54.9% of frailty studies in kidney disease populations.<sup>[18]</sup> This physical performance-based measure defines frailty based on five criteria: Slowness (measured by gait speed), weakness (measured by grip strength), unintentional weight loss, self-reported exhaustion, and low physical activity. Patients meeting



**Figure 2:** Assessment tools for frailty in end-stage kidney disease. ESKD: End stage kidney disease, SARC-F: Strength, assistance with walking, rising from a chair, climbing stairs, and falls.

three or more criteria are classified as frail, those with one or two criteria as pre-frail, and those with no criteria as robust.

The FFP has demonstrated strong predictive validity for mortality, hospitalization, falls, and other adverse outcomes in dialysis and transplant populations.<sup>[8,26]</sup> Its objective measurement components enhance reliability, but implementation challenges include the need for specialized equipment and time requirements.<sup>[27]</sup>

### **CFS**

The CFS has gained increasing traction due to its simplicity and clinical utility. This 9-point pictorial scale ranges from 1 (very fit) to 9 (terminally ill), with scores  $\geq 5$  indicating frailty.<sup>[11]</sup> Recent validation studies in ESKD populations demonstrate a strong correlation between CFS scores and outcomes, with each one-point increase associated with a 1.22-fold (95% confidence interval [CI] 1.04–1.43) higher mortality risk.<sup>[28]</sup> The primary advantages include rapid administration (<1 min), no equipment requirements, and minimal training needs.

### **FI**

The FI applies the deficit accumulation model to quantify frailty as the proportion of potential health deficits present in an individual.<sup>[12]</sup> These deficits encompass symptoms, signs, diseases, disabilities, and laboratory abnormalities, typically including 30–70 variables. A FI score  $>0.25$  generally indicates frailty, with higher scores reflecting greater severity.

The FI provides a comprehensive assessment of health status and demonstrates excellent predictive validity across healthcare settings.<sup>[29]</sup> In ESKD populations, FI scores correlate strongly with mortality (Hazard ratio [HR] 1.93, 95% CI 1.29–2.78), hospitalization, and functional decline.<sup>[30]</sup> The primary limitation is the time required for a comprehensive assessment and the need for detailed health information.

### **Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F)**

The SARC-F questionnaire is a simple 5-item screening tool originally developed for sarcopenia but increasingly used for frailty assessment.<sup>[31]</sup> In dialysis populations, SARC-F scores  $\geq 4$  demonstrate good correlation with physical frailty (sensitivity 0.71, specificity 0.85) and predict adverse outcomes, including mortality (HR 1.63, 95% CI 1.21–2.19) and hospitalization.<sup>[32]</sup>

### **Edmonton frail scale**

The Edmonton frail scale provides a comprehensive 10-domain assessment covering cognition, general

health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance.<sup>[33]</sup> It demonstrates good validity in ESKD populations but requires more time than simpler screening tools.

### **Short physical performance battery (SPPB)**

The SPPB assesses lower extremity function through gait speed, chair stand, and balance tests.<sup>[34]</sup> SPPB scores correlate with frailty status and predict adverse outcomes in ESKD, with scores  $<7$  associated with significantly higher mortality risk (HR 2.46, 95% CI 1.72–3.52).<sup>[35]</sup>

Table 1 summarizes the comparative performance of major frailty assessment tools in ESKD populations.

## **IMPLEMENTATION CONSIDERATIONS**

Despite strong evidence supporting the prognostic value of frailty assessment, implementation in routine nephrology practice remains suboptimal.<sup>[7]</sup> Key barriers include time constraints, competing clinical priorities, lack of standardized protocols, and limited awareness of available tools. Successful implementation strategies include:

1. Integration with existing workflows: Incorporating brief frailty screening during routine clinic visits or dialysis sessions minimizes additional burden on patients and providers.
2. Tiered assessment approach: Initial screening with simple tools (e.g., CFS) followed by more comprehensive assessment for those identified as high risk optimizes resource utilization.
3. Multidisciplinary involvement: Training nursing staff, physical therapists, and other team members to perform frailty assessments distributes workload and leverages diverse expertise.
4. Electronic health record integration: Standardized documentation templates and automated risk calculation facilitate consistent assessment and longitudinal monitoring.
5. Defined assessment timepoints: Systematic assessment at key transition points (dialysis initiation, transplant evaluation, hospitalization) ensures timely identification of high-risk patients.

The selection of specific assessment tools should consider the intended application, available resources, and patient population characteristics. For research purposes and detailed phenotyping, the FFP provides a comprehensive evaluation with established validity. For routine clinical screening and resource-limited settings, the CFS offers an excellent balance of predictive validity and implementation feasibility.

**Table 1:** Comparison of frailty assessment tools in ESKD

Tool	Components	Administration time	Equipment needed	Sensitivity	Specificity	Predictive validity	Implementation considerations
Fried frailty phenotype	Slowness (gait speed) Weakness (grip strength) Weight loss Exhaustion Low physical activity	10-15 minutes	Dynamometer Stopwatch Measured walkway	0.81	0.85	HR for mortality: 2.60 (95% CI 1.72-3.92)	Gold standard in research Requires specialized equipment Time-intensive May be difficult for severely ill patients
Clinical frailty scale	Pictorial scale with clinical descriptions Ranges from 1 (very fit) to 9 (terminally ill)	<1 minute	None	0.76	0.80	HR for mortality: 1.22 (95% CI 1.04-1.43) per point increase	Rapid administration No equipment needed Minimal training required Subjective assessment
Frailty index	30-70 health deficits across multiple domains Calculated as proportion of deficits present	15-30 minutes	None	0.84	0.82	HR for mortality: 1.93 (95% CI 1.29-2.78)	Comprehensive assessment Requires detailed health information Time-intensive Flexible in included variables
SARC-F	5 items: Strength, assistance with walking, rise from chair, climb stairs, falls	2-3 minutes	None	0.71	0.85	HR for mortality: 1.63 (95% CI 1.21-2.19)	Very brief administration Self-reported Originally developed for sarcopenia May miss pre-frailty
Edmonton frail scale	10 domains including cognition, health status, functional independence, social support, medication use, nutrition, mood, continence, functional performance	5-10 minutes	Clock-drawing test materials	0.75	0.77	OR for adverse outcomes: 2.15 (95% CI 1.51-3.06)	Multidimensional assessment Moderate time requirement Includes cognitive assessment Validated in multiple settings
Short physical performance battery	Gait speed Chair stand Balance tests	10 minutes	Stopwatch Standard chair Measured walkway	0.79	0.81	HR for mortality: 2.46 (95% CI 1.72-3.52) for scores <7	Objective performance measures Standardized protocol Focuses on lower extremity function Requires physical performance

ESKD: End stage kidney disease, HR: Hazard ratio, OR: Odds ratio, CI: Confidence interval.

## IMPACT ON OUTCOMES

### Mortality

Frailty consistently demonstrates strong and independent associations with mortality in ESKD patients. Frail dialysis patients exhibit 2.6 times higher mortality risk compared to non-frail counterparts, even after adjustment for age, gender, comorbidity, and disability.<sup>[5]</sup> This mortality differential persists across age groups, challenging the notion that frailty is merely a proxy for advanced age or comorbidity burden.

In the transplant population, frailty at the time of transplantation independently predicts post-transplant mortality. Frail kidney transplant recipients demonstrate higher 1-, 3-, and 5-year mortality compared to non-frail recipients.<sup>[36]</sup> Particularly concerning is the finding that worsening frailty status while awaiting transplantation carries an especially poor prognosis.<sup>[37]</sup>

### Hospitalization

Frailty is strongly associated with increased hospitalization risk, extended hospital stays, and readmission rates in ESKD patients.<sup>[38]</sup> Frail dialysis patients have 1.4 times higher risk of hospitalization, independent of age, gender, and comorbidity.<sup>[14]</sup> Hospital utilization patterns differ between frail and non-frail ESKD patients, with frail individuals demonstrating not only more frequent admissions but also longer length of stay (mean difference 2.6 days,  $P < 0.001$ ) and higher likelihood of discharge to skilled nursing facilities (odds ratio [OR] 2.65, 95% CI 1.89–3.71).<sup>[27]</sup>

### Transplant-specific outcomes

Frailty exerts significant influence on multiple transplant-related outcomes. On the waitlist, frail candidates demonstrate a lower likelihood of receiving transplantation, higher rates of waitlist inactivation, and a greater risk of removal due to deteriorating health.<sup>[39]</sup> Post-transplant complications occur with greater frequency and severity in frail recipients, including delayed graft function (OR 1.94, 95% CI 1.13–3.36), post-operative complications, and longer hospital stays.<sup>[40]</sup>

Despite these increased risks, frail ESKD patients may still derive a survival benefit from transplantation compared to remaining on dialysis.<sup>[41]</sup> This finding underscores the need for individualized risk-benefit assessment rather than categorical exclusion of frail candidates from transplant consideration.

### Other clinical outcomes

Frailty is strongly associated with increased fall risk in ESKD patients, with an adjusted relative risk of 3.09.<sup>[42]</sup> This elevated fall risk translates to increased fracture incidence, with frail patients experiencing more frequent and severe fractures.<sup>[43]</sup> Emerging evidence suggests associations between frailty and vascular access complications, cognitive impairment, and reduced quality of life.<sup>[15,44,45]</sup>

Table 2 summarizes the impact of frailty on outcomes across renal replacement modalities.

Outcome	Hemodialysis	Peritoneal dialysis	Kidney transplantation
Mortality	HR 2.60 (95% CI 1.72-3.92) Independent of age, gender, comorbidity	HR 2.47 (95% CI 1.49-4.10) Similar effect size to HD	HR 1.94 (95% CI 1.13-3.36) Higher 1-, 3-, and 5-year mortality
Hospitalization	RR 1.40 (95% CI 1.22-1.62) Mean LOS difference: 2.6 days ( $P < 0.001$ )	RR 1.35 (95% CI 1.17-1.57) Higher peritonitis-related admissions	RR 1.61 (95% CI 1.18-2.19) 30-day readmission OR 1.61 (95% CI 1.18-2.19)
Falls/Fractures	Fall RR 3.09 (95% CI 1.38-6.90) Hip fracture HR 1.81 (95% CI 1.13-2.89)	Limited data, similar trends to HD	Limited data Higher fracture risk post-transplant
Quality of life	SF-36 PCS mean difference: -8.9 points ( $P < 0.001$ )	SF-36 PCS mean difference: -7.6 points ( $P < 0.001$ )	Improvement in 33% of frail recipients at 1 year
Modality-specific outcomes	Higher intradialytic hypotension (OR 2.37, $P = 0.002$ ) Higher vascular access complications	Higher technique failure (HR 1.80, $P = 0.01$ ) Higher peritonitis risk	Delayed graft function (OR 1.94, 95% CI 1.13-3.36) Longer LOS (mean difference 2.2 days, $P < 0.001$ )
Modality considerations	Transportation burden Hemodynamic stress Facility-based care	Manual dexterity requirements Cognitive demands Home-based care	Surgical risk Immunosuppression management Potential for frailty improvement

HR: Hazard ratio, RR: Relative risk, OR: Odds ratio, CI: Confidence interval, LOS: Length of stay, SF-36 PCS: Short form-36 physical component summary.

## FRAILITY ACROSS DIFFERENT RENAL REPLACEMENT MODALITIES

### HD

HD patients demonstrate among the highest prevalence of frailty in the ESKD population, with 43% meeting frailty criteria in recent studies.<sup>[19]</sup> Several HD-specific factors demonstrate significant association with frailty, including intradialytic hypotension ( $P = 0.002$ ) and edema ( $P < 0.001$ ).<sup>[19]</sup> Interestingly, the duration of dialysis therapy does not show a significant association with frailty prevalence ( $P = 0.838$ ), suggesting that frailty development may be more closely related to patient-specific factors and comorbidities than to dialysis vintage.<sup>[19]</sup>

### Peritoneal dialysis (PD)

The prevalence of frailty in PD populations appears comparable to HD cohorts in most studies.<sup>[46]</sup> PD presents unique considerations regarding frailty, including the home-based nature of therapy, eliminating transportation burden, but requiring sufficient manual dexterity, visual acuity, and cognitive function.<sup>[45]</sup> Nutritional considerations are particularly relevant in frail patients, with peritoneal protein losses potentially exacerbating protein-energy wasting.<sup>[47]</sup>

### Kidney transplantation

Approximately 20% of kidney transplant candidates meet criteria for frailty, lower than the dialysis population but substantially higher than age-matched individuals without kidney disease.<sup>[38]</sup> Frailty at the time of transplantation independently predicts post-transplant complications and mortality, including delayed graft function, longer hospital stays, and higher long-term mortality.<sup>[40]</sup>

Interestingly, frailty status may improve following successful transplantation in some patients. McAdams-DeMarco *et al.* reported that 33% of frail recipients no longer met frailty criteria 1-year post-transplant, suggesting partial reversibility of the frailty phenotype with improved kidney function.<sup>[48]</sup>

### Modality selection considerations

Modality selection for frail ESKD patients should consider multiple factors beyond frailty status alone, including social support, cognitive function, physical limitations, comorbidity profile, and patient preferences. The potential for prehabilitation to improve candidacy for preferred modalities represents an emerging area of interest.<sup>[49]</sup>

## INTERVENTIONS: CRITICAL APPRAISAL AND IMPLEMENTATION BARRIERS

### Nutritional interventions

Nutritional deficiencies contribute significantly to frailty pathogenesis in ESKD through multiple mechanisms.<sup>[22]</sup> While evidence from RCTs specifically targeting frail dialysis patients remains limited, several promising approaches have emerged:

1. **Protein supplementation:** Studies examining protein supplementation (20–30 g following dialysis sessions) have shown modest improvements in lean body mass (mean increase 1.1 kg,  $P = 0.03$ ) and physical function measures.<sup>[50]</sup> Whey protein appears particularly beneficial due to its high essential amino acid content and rapid absorption profile, with one trial demonstrating a 9% improvement in handgrip strength after 12 weeks of intradialytic supplementation (20 g thrice weekly).<sup>[51]</sup>
2. **Oral nutritional supplements:** Energy-dense, protein-rich oral supplements (providing 400–600 kcal and 25–30 g protein daily) have demonstrated efficacy in improving nutritional parameters (serum albumin increase of 0.2–0.4 g/dL) and physical function in malnourished dialysis patients.<sup>[52]</sup> However, long-term adherence remains problematic, with dropout rates of 30–45% in trials extending beyond 3 months.
3. **Vitamin D supplementation:** Observational studies show associations between vitamin D status and frailty severity in ESKD, though interventional data remain limited.<sup>[53]</sup> One small RCT ( $n = 42$ ) demonstrated that cholecalciferol supplementation (50,000 IU weekly for 8 weeks) improved physical performance measures in dialysis patients, but effects on overall frailty status were not assessed.<sup>[54]</sup>
4. **Individualized dietary counseling:** Personalized nutritional intervention by renal dietitians has shown promise, with one trial demonstrating a 38% reduction in frailty progression when combined with exercise compared to standard care.<sup>[55]</sup> However, resource limitations often restrict the availability of specialized dietetic services.

Critical limitations of the current evidence base include small sample sizes (most trials  $n < 100$ ), short follow-up periods (typically 3–6 months), heterogeneous intervention protocols, and focus on surrogate endpoints rather than frailty status itself. In addition, most studies exclude severely frail patients, limiting generalizability to the highest-risk population.

### PHYSICAL ACTIVITY INTERVENTIONS

Physical activity interventions demonstrate a strong evidence base among frailty-targeted approaches in ESKD. Multiple

RCTs support the efficacy of structured exercise programs in improving physical function, quality of life, and potentially survival.<sup>[56]</sup> Key approaches include:

1. **Resistance training:** Progressive resistance exercise targeting major muscle groups has consistently improved strength measures in dialysis patients, with meta-analyses showing mean improvements of 25–30% in muscle strength and 7–10% in physical performance measures.<sup>[57]</sup> The magnitude of benefit appears dose-dependent, with supervised, high-intensity programs (60–80% of 1-repetition maximum) showing greater effects than low-intensity or home-based approaches.
2. **Aerobic exercise:** Structured aerobic training improves cardiorespiratory fitness (mean increase in VO<sub>2</sub> peak [peak oxygen uptake/consumption] of 10–15%), blood pressure control, and inflammatory markers in ESKD.<sup>[58]</sup> Intradialytic cycling programs of moderate intensity (rating of perceived exertion 12–14) for 30–45 min thrice weekly have demonstrated the most consistent benefits, with one trial showing a 35% reduction in frailty prevalence after 6 months.<sup>[59]</sup>
3. **Multicomponent programs:** Combined interventions addressing strength, endurance, balance, and flexibility demonstrate superior outcomes compared to single-component approaches, with meta-analyses showing effect sizes 1.5–2 times larger for physical performance measures.<sup>[60]</sup> The exercise in chronic kidney disease trial (EXCITE) trial, the largest exercise intervention in dialysis patients to date ( $n = 296$ ), demonstrated a 35% improvement in the SPPB score and significant reductions in mortality (HR 0.73, 95% CI 0.56–0.96) with a combined aerobic and resistance program.<sup>[59]</sup>

Despite this compelling evidence, implementation in routine ESKD care remains suboptimal. Key barriers include:

1. **Patient-level barriers:** Fatigue, comorbidities, transportation difficulties, and low motivation significantly limit participation, with recruitment rates in exercise trials typically below 50% of eligible patients and dropout rates of 20–30%.<sup>[61]</sup>
2. **Provider-level barriers:** Knowledge gaps regarding exercise safety and benefits, competing clinical priorities, and lack of training in exercise prescription limit provider engagement.<sup>[62]</sup>
3. **System-level barriers:** Resource constraints, lack of reimbursement for exercise programs, space limitations in dialysis units, and fragmented care delivery impede systematic implementation.<sup>[63]</sup>
4. **Research-practice gap:** Most successful interventions have been implemented in research settings with dedicated personnel and resources not typically available in routine clinical care.<sup>[64]</sup>

Successful implementation strategies include intradialytic exercise to overcome transportation barriers, gradual progression based on individual tolerance, and motivational strategies to enhance adherence. However, sustainable models for widespread implementation remain elusive.

### Multimodal approaches

The multifactorial nature of frailty in ESKD suggests that multimodal interventions addressing multiple contributing factors simultaneously may yield superior outcomes compared to single-domain approaches.<sup>[65]</sup> The frailty intervention through nutrition education and exercise studies demonstrates that combined nutritional education and exercise training more effectively prevent frailty progression than either intervention alone, with a 38% reduction in frailty incidence over 12 months compared to 15–20% with single-component interventions.<sup>[55]</sup>

Comprehensive geriatric assessment followed by targeted intervention addressing identified deficits shows promise, with one trial in pre-dialysis CKD patients demonstrating a 33% reduction in frailty prevalence compared to standard care.<sup>[66]</sup> However, such approaches require substantial resources and multidisciplinary expertise rarely available in routine nephrology practice.

The fundamental barriers to successful implementation of frailty interventions in ESKD include:

1. **Complexity of the frailty syndrome:** The multidimensional nature of frailty necessitates complex, multicomponent interventions that are challenging to implement and sustain in clinical practice.
2. **Resource constraints:** Effective interventions typically require specialized personnel, equipment, and time commitments beyond what is available in many clinical settings.
3. **Reimbursement structures:** Current payment models rarely support preventive interventions targeting frailty, creating financial disincentives for implementation.
4. **Care fragmentation:** Frailty management requires coordination across multiple specialties and settings, which is challenging in siloed healthcare systems.
5. **Evidence limitations:** Most intervention studies have methodological limitations, including small sample sizes, short follow-up periods, and selected populations, creating uncertainty about real-world effectiveness.

Table 3 summarizes evidence-based interventions for frailty in ESKD, including the magnitude of effects and implementation considerations.

**Table 3:** Evidence-based interventions for frailty in ESKD

Intervention type	Specific approaches	Magnitude of effect	Evidence quality	Implementation considerations
Nutritional interventions	Protein supplementation (20-30g post-dialysis)	Lean body mass: +1.1 kg ( $p=0.03$ ) Handgrip strength: +9% with whey protein	Moderate small RCTs ( $n=20-60$ ) Short follow-up (3-6 months)	Relatively low cost Easy to implement during HD Adherence challenges Taste fatigue
	Oral nutritional supplements (400-600 kcal, 25-30g protein daily)	Serum albumin: +0.2-0.4 g/dL Physical function improvements in 60-70%	Moderate Heterogeneous protocols High dropout rates (30-45%)	Higher cost Reimbursement challenges Long-term adherence issues
	Vitamin D supplementation (50,000 IU weekly)	Physical performance measures improved Effects on frailty status not assessed	Low Limited RCT data in ESKD Small sample sizes	Low cost Simple administration Safety monitoring needed
	Individualized dietary counseling	38% reduction in frailty progression when combined with exercise	Moderate Limited data specific to frailty	Resource-intensive Requires specialized dietitians Reimbursement challenges
Physical activity interventions	Resistance training (2-3 sessions/week, 60-80% 1RM)	Muscle strength: +25-30% Physical performance: +7-10%	High Multiple RCTs Consistent effects	Equipment needs Supervision requirements Safety concerns Transportation barriers
	Aerobic exercise (Intradialytic cycling, 30-45 min, 3x/week)	VO <sub>2</sub> peak: +10-15% Frailty prevalence: -35% after 6 months	High Large RCTs (EXCITE trial, $n=296$ )	Equipment costs Space constraints in dialysis units Staff training needs
	Multicomponent programs (Combined strength, aerobic, balance)	Effect sizes 1.5-2x larger than single-component SPPB score: +35% Mortality: HR 0.73 (95% CI 0.56-0.96)	High Multiple RCTs Meta-analyses	Most resource-intensive Highest expertise requirements Greatest potential benefit
Multimodal approaches	Combined nutritional and exercise interventions	Frailty incidence: -38% vs. -15-20% with single components	Moderate Limited data specific to ESKD	Coordination challenges Resource-intensive Reimbursement barriers
	Comprehensive geriatric assessment and intervention	Frailty prevalence: -33% vs. standard care	Moderate Limited data in ESKD	Requires multidisciplinary team Time-intensive Limited availability
	Cognitive training	Limited data in ESKD Promising results in general geriatric population	Low Few studies in ESKD	Low resource requirements Can be group-based Adherence challenges

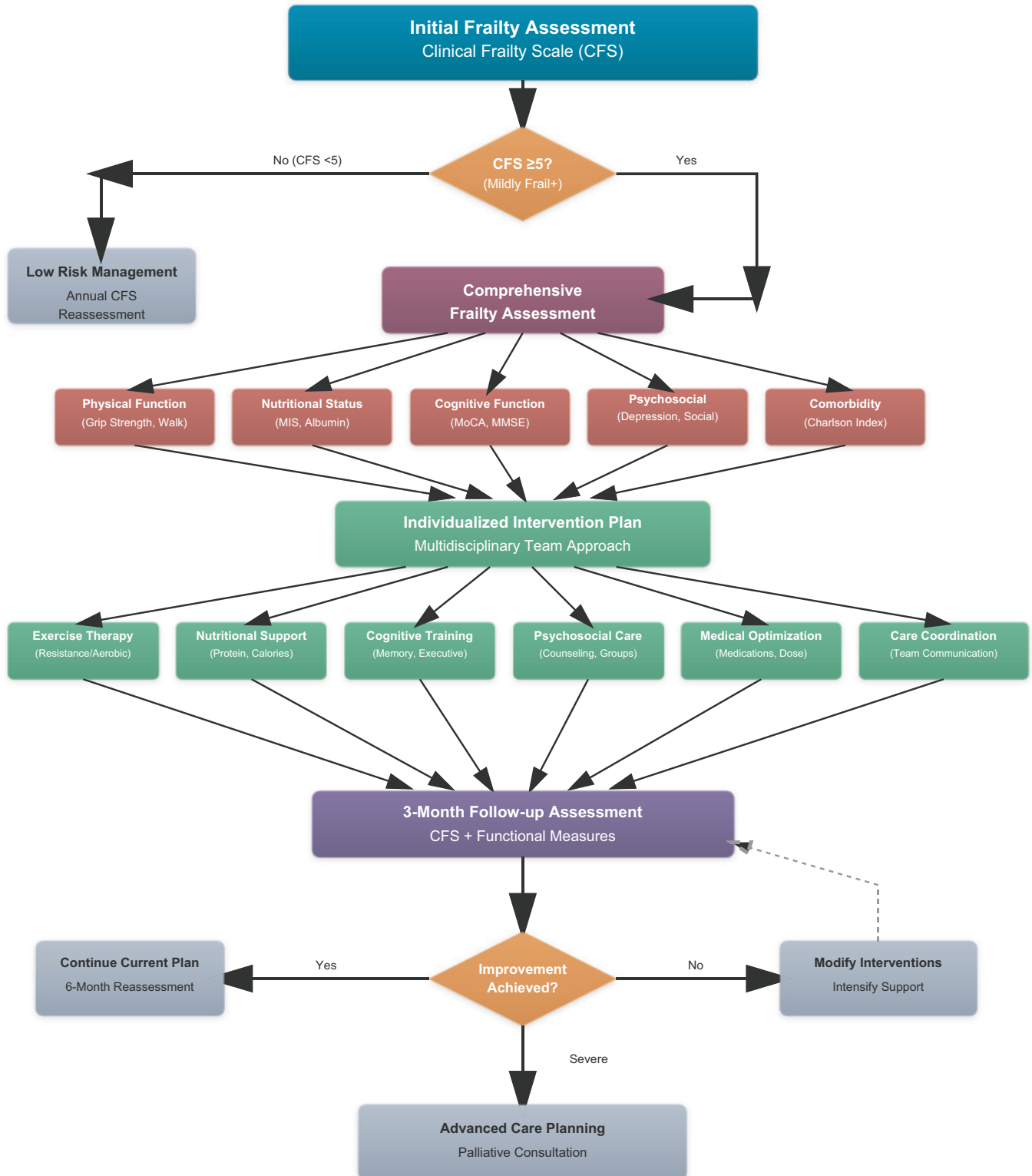
RCT: Randomized controlled trial, 1RM: One-repetition maximum, SPPB: Short physical performance battery, HR: Hazard ratio, CI: Confidence interval, ESKD: End stage kidney disease.

## IMPLEMENTATION IN LOW-RESOURCE SETTINGS

### Challenges in low-resource settings

Low-resource settings face substantial constraints that may impede frailty assessment and management, including equipment limitations, workforce shortages, financial

barriers, and infrastructure challenges.<sup>[7]</sup> Equipment limitations include a lack of specialized tools, such as dynamometers for grip strength measurement and standardized walkways for gait speed assessment. Workforce shortages refer to insufficient numbers of healthcare professionals with appropriate training in geriatric assessment and frailty management, particularly in settings



**Figure 3:** Implementation flowchart for frailty assessment and management in end-stage kidney disease. MIS: Malnutrition Inflammation Score, MoCA: Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination, CFS: Clinical Frailty Scale.

where nephrologist-to-patient ratios may exceed 1:200.<sup>[67]</sup> Beyond resource limitations, healthcare system factors such as fragmented care, acute care focus, knowledge gaps, and absence of context-specific guidelines further complicate implementation.<sup>[68]</sup>

### Simplified assessment tools

Despite these challenges, several frailty assessment approaches demonstrate feasibility and utility in resource-limited settings. The CFS has emerged as a particularly valuable tool, requiring no specialized equipment, minimal training, and typically less than one minute to administer.<sup>[28]</sup> Self-administered questionnaires such as SARC-F and the frail scale offer another approach to frailty screening with minimal staff involvement.<sup>[31]</sup>

### Implementation strategies

Successful implementation of frailty assessment and management in low-resource settings requires pragmatic strategies addressing local constraints. These include integration with existing workflows (dialysis initiation, routine clinic visits), task-shifting approaches (nursing staff training, community health worker involvement), and prioritization strategies focusing on high-risk populations.<sup>[7]</sup>

Figure 3 presents an implementation flowchart for clinical practice.

## DISCUSSION AND IMPLICATIONS

### Clinical implications

Frailty assessment provides valuable prognostic information that can inform multiple aspects of ESKD management. For dialysis patients, frailty status may guide decisions regarding vascular access type, dialysis prescription, and advanced care planning.<sup>[5]</sup> In the transplant setting, frailty evaluation contributes to comprehensive candidate assessment without serving as an absolute contraindication.<sup>[36]</sup>

The heterogeneity of frailty presentation in ESKD necessitates individualized intervention strategies. Comprehensive assessment identifying specific deficits across physical, cognitive, nutritional, and psychosocial domains enables targeted approaches addressing modifiable contributors to frailty.<sup>[66]</sup> Emerging evidence suggests that earlier intervention, ideally before severe frailty is established, yields greater benefit than attempting to reverse advanced frailty.<sup>[65]</sup> This finding underscores the importance of frailty staging, with the CFS providing gradations from mild (CFS 5) to moderate (CFS 6) to severe frailty (CFS 7–8), each stage requiring progressively more intensive intervention approaches.<sup>[69]</sup>

### Research implications

Despite significant advances in understanding frailty in ESKD, several knowledge gaps require attention in future research, including standardized assessment approaches, intervention effectiveness in rigorous trials, biological mechanisms, implementation science, and economic evaluation.

### Policy implications

The substantial burden of frailty in ESKD and its strong association with adverse outcomes have important implications for healthcare policy, including incorporation of frailty assessment into quality metrics, reimbursement policies supporting comprehensive geriatric assessment, workforce development combining nephrology and geriatrics expertise, and resource allocation decisions in limited-resource settings.

## CONCLUSION

Frailty represents a critical yet underrecognized determinant of outcomes in ESKD. This multidimensional syndrome affects 40–70% of dialysis patients and approximately 20% of kidney transplant candidates, with robust associations to mortality, hospitalization, falls, and quality of life impairment across all renal replacement modalities.

Frailty assessment provides valuable information beyond traditional risk factors, enabling more accurate prognostication and personalized management approaches. The potentially modifiable nature of frailty offers opportunities for targeted intervention, with multimodal approaches combining nutritional support, exercise training, and cognitive rehabilitation showing the greatest promise.

Incorporating frailty assessment into routine nephrology care represents a paradigm shift from disease-focused to patient-centered approaches. By recognizing frailty as a modifiable risk factor rather than an inevitable consequence of kidney failure and aging, we can develop more effective strategies to improve outcomes in this vulnerable population.

For clinical practice, we recommend (1) implementing routine frailty screening using the CFS at key transition points, including dialysis initiation, transplant evaluation, and hospitalization, and (2) developing structured, multimodal intervention programs combining nutritional support and supervised exercise, particularly for patients with mild-to-moderate frailty who may derive the greatest benefit.

For future research, priorities include (1) developing and validating ESKD-specific frailty assessment tools that capture the unique aspects of frailty in this population and (2) conducting larger, longer-duration randomized trials of multimodal interventions with patient-centered outcomes.

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