# The impact of frailty on outcomes in dialysis

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Advances in the assessment of frailty among dialysis patients have improved our understanding of the association between frailty and poor outcomes. We review recent studies that assess the association between frailty and mortality, falls and fractures, hospitalizations, cognitive impairment, and other less traditional outcomes. A greater understanding of these associations may provide more accurate prognostic information, allow tailored interventions, and improve discussions between patients and providers about the risks and benefits of the dialysis procedure.

**Keywords**
dialysis, dialysis outcomes, frailty

## DEFINING FRAILTY: AN AGREEMENT TO DISAGREE?

Frailty is a clinical state marked by a loss of resilience and diminished capacity to respond to health stressors [1]. It has been recognized that frail patients are at high risk for morbidity and mortality, with chronic kidney disease (CKD) further amplifying this risk. Since the 1990s, researchers have sought to operationally define this clinical state and determine its risk factors and sequelae. In 2007 and again in 2012, consensus conferences failed to agree on a single operational definition of frailty that would satisfy all experts [2], likely because of the multifaceted nature of frailty. However, experts agree that frailty is not encompassed fully by existing definitions of disability, sarcopenia, or multimorbidity despite significant overlap between these concepts and frailty [2,3].

## FRAILTY: A PREDICTOR OF POOR OUTCOMES

Among community-dwelling, nondialysis-dependent older populations, frail individuals have higher mortality, more frequent hospitalizations, higher incidence of fractures, and loss of independence in activities of daily living (ADLs) compared with their nonfrail counterparts [4]. In a review published in 2010, Brown and Johansson [5] suggested that frailty may be a more meaningful predictor of important outcomes than age due to the stronger correlation with 1-year mortality and hospitalizations, consistent with the idea that frailty encompasses a more comprehensive portrait of an individual than age or comorbidity alone [6]. These associations with poor outcomes have also been observed among dialysis patients [6–8].

In fact, these adverse outcomes have led some to question whether clinicians are adequately preparing frail elderly patients for key medical transitions such as end-stage renal disease [9–11]. In one study, fewer than 10% of patients followed by a nephrologist for CKD care (stages 4 or 5 CKD, on dialysis, or having received a kidney transplant) reported having a discussion about end-of-life care issues, and 62% of dialysis patients later regretted their decision to start dialysis [12]. Furthermore, there has been a trend toward higher rates of withdrawal from dialysis in the last several years [13]. It is possible that a deeper understanding of the association between frailty and outcomes could lead to better prognostic information, which could improve the quality of discussions regarding end-of-life care issues [14].

## ASSESSING AND OPERATIONALIZING FRAILTY

Despite three decades of investigation into how to quantify frailty, there remains little consensus as to its best measure. Initial studies in the early 1990s that attempted to assess prognosis in the elderly dialysis population (going beyond age alone) relied on simple measures such as ADLs, the Karnofsky Activity Score, and the Charlson comorbidity index

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## KEY POINTS

- Despite no clear gold standard for assessing frailty, researchers have recently favored a physical definition of frailty, defined as having at least three of five criteria: shrinking or weight loss, weakness, poor endurance and energy, slowness, and low physical activity level.
- Frailty is associated with poor outcomes such as higher mortality, falls, hospitalizations, cognitive impairment, vascular access failure, and poorer quality of life among dialysis patients, regardless of how it is measured or defined.
- Understanding the association between frailty and poor outcomes may improve discussions between providers and patients on the risks and benefits of the dialysis procedure.

[15,16]. Researchers suggested that timely identification and prevention of frailty could improve quality of life and reduce costs associated with loss of employment, but a translatable and easily replicated measure that encompassed the complexity of frailty was needed [17]. In the interim 20 years, researchers have published and adapted various operational definitions of frailty. These are largely divided into three constructs: a physical construct of frailty (i.e. the frailty phenotype), a subjective construct of frailty (i.e. the frailty score), and a deficit construct of frailty (i.e. the frailty index).

The physical construct of frailty was developed and validated by Fried *et al.* [1] in a cohort of community-dwelling elderly in 2001. Individuals were considered frail if three of five major physical components of frailty were identified: shrinking or weight loss, weakness, poor endurance and energy, slowness, and low physical activity level [1]. Fried's original frailty construct has been validated in other elderly populations [2] as well as the dialysis population [18]. In an extended physical construct used in the Netherlands, the Groningen Frailty Indicator (GFI), a 15-item questionnaire assessing four different domains (physical functioning, cognitive functioning, social functioning, and psychological functioning), has also been used in both nondialysis and dialysis populations [19]. The cognitive and psychosocial domains included in the GFI had not been assessed previously in frailty measures [20], but are also thought to be important contributors to frailty.

The subjective frailty construct, developed by Rockwood *et al.* [21], is the 7-point Canadian Study of Health and Aging Clinical Frailty Score based on clinical judgment and validated in an elderly Canadian population with individuals having a score of 5 or higher considered frail. Between 2001 and 2008, Mitnitski and Rockwood also developed and validated a deficit construct that consisted of 40 'deficits' (i.e. symptoms, signs, functional impairments, and laboratory abnormalities), with individuals being in the lowest quintile considered as frail [22,23].

These methods of assessing frailty in patients with kidney disease, including their strengths and limitations, have recently been reviewed in this journal [24]. Although the best measure of frailty has not yet been identified, researchers evaluating outcomes related to frailty have recently favored the physical construct of frailty (see Table 1) [25▪], perhaps due to its use of objective measures that appear to facilitate comparisons across studies.

Studies have noted a wide variation in the prevalence of frailty in the dialysis population. For example, using variations of a physical frailty construct, prevalence ranged from 30 to 73% [26–28]. The large variability is likely explained by using substitutions for Fried's original criteria with more readily obtainable self-reported or alternative measures (e.g. substituting a sit-to-stand time for grip strength [28]). The impact of substituting self-reported physical functioning for physical performance measures has been investigated in two studies [20,29], and prevalence was higher using self-report measures (78 and 53%) than using performance measures (24 and 29%, respectively) in both. Researchers in Taiwan

**Table 1.** Utilization of various frailty constructs in studies assessing outcomes in dialysis patients

| | Study | Outcomes |
|---|---|---|
| Physical construct of frailty (i.e. frailty phenotype) | Chao *et al.* [45▪▪] | Vascular access failure |
| | Yadla *et al.* [32] | Death, falls, hospitalization |
| | Lee *et al.* [33▪] | Death, hospitalization |
| | Johansen *et al.* [34] | Death |
| | Ng *et al.* [35] | Death, hospitalization |
| | McAdams-DeMarco *et al.* [42▪] | Cognitive function |
| | Delgado *et al.* [44] | Falls, fractures |
| | Meulendijks *et al.* [19] | Death, hospitalization |
| | McAdams-DeMarco *et al.* [36] | Death, hospitalization |
| | McAdams-DeMarco *et al.* [43] | Falls |
| | Bao *et al.* [26] | Death |
| | Johansen *et al.* [18] | Death |
| Subjective construct of frailty (i.e. frailty score) | Iyasere *et al.* [46▪▪] | Quality of life |
| | Alfaadhel *et al.* [37] | Death |

used six different frailty constructs within the same cohort and found that the prevalence of frailty ranged from 19.6 to 82.6% [30]. Thus, comparisons among populations and studies utilizing different frailty measures will remain challenging, and consensus is still needed on an easy-to-administer, consistent, and reliable operational definition of frailty [29].

In a more recent study, Salter *et al.* [31▪▪] compared perceived frailty with the measured physical frailty phenotype to ascertain differences in providers' and patients' perceptions in comparison to an actual measured construct. Perceptions were determined by asking providers if they felt that their patient was frail and asking patients if they themselves felt that they were frail [31▪▪]. They found that agreement between measured and perceived frailty was only 64% for nephrologists, 67% for nurse practitioners, and 55% for patients themselves (κ: 0.24, 0.27, and 0.07, respectively) [31▪▪]. It is worth mentioning that older, non-African American, and female patients were more likely to be incorrectly perceived as frail [31▪▪]. These interesting findings indicate that clinical gestalt may not be sufficiently accurate to identify frail dialysis patients, and a formal measured gold standard is warranted.

## FRAILTY OUTCOMES IN THE DIALYSIS POPULATION

### Frailty and mortality

Several recent studies have confirmed the association between frailty and mortality in dialysis patients (Table 1) [18,19,26,32,33▪,34–36]. Here, we highlight more recent work and some interesting findings related to mortality.

In 2012, a study by Bao *et al.* [26] not only looked at the association between frailty and mortality, but also noted that higher eGFR at dialysis initiation was associated with mortality (hazard ratio: 1.12 per 5 ml/min/1.73 $m^2$, 95% CI 1.02–1.23), an association that was no longer statistically significant once frailty was accounted for (hazard ratio: 1.08 per 5 ml/min/1.73 $m^2$, 95% CI 0.98–1.19). This suggested that frail patients may have overlapping signs and symptoms with uremia, perhaps prompting earlier dialysis initiation [26].

Looking at various stages of frailty, McAdams-DeMarco *et al.* [36] performed an analysis of 146 prevalent dialysis patients showing that even those classified as intermediate frail (meeting only two of five physical frailty criteria) had a 2.6-fold (95% CI 1.02–7.07) higher risk of death, independent of age, sex, comorbidity, and disability.

Lee *et al.* [33▪] recently studied a large prospective cohort of 1658 prevalent dialysis patients in Korea and noted that the physical frailty phenotype was associated with mortality (hazard ratio: 3.05, 95% CI 1.55–6.00), which remained significant even after adjustment for other important risk factors (hazard ratio: 2.37, 95% CI 1.11–5.02). Interestingly, an investigation in India looking at outcomes among 205 impoverished prevalent dialysis patients (mean age 45 years, 82% considered frail by the physical construct of frailty) found no significant association between frailty and death (hazard ratio: 0.75, 95% CI 0.30–1.88) [32]. In this study, only 38 patients were not frail and only 26 patients died during follow-up [32]. Unsurprisingly, frail patients were at statistically significantly higher risk of falls and hospitalization in the same cohort [32], suggesting that low study power may have accounted for the mortality differences compared with other studies.

With respect to use of a subjective frailty construct, a study by Alfaadhel *et al.* [37] in 2015 showed higher mortality in 390 incident dialysis patients with higher frailty scores (hazard ratio:1.22 per 1-point higher frailty score, 95% CI 1.02–1.43). Thus, frailty appears to be associated with mortality regardless of the general frailty construct used.

### Frailty and cognitive outcomes

Like frailty, cognitive impairment is a mechanistically complex phenomenon with multiple proposed links including hormonal and nutritional deficiencies, cardiovascular risks, chronic inflammation, and poor mental health [38]. Indeed, frailty and cognitive impairment share many of the same risk factors such as age and cardiovascular disease [38], leading some researchers to propose incorporating cognitive domains into the frailty construct instead of considering them as possible sequelae [19,24,39]. However, as there is some evidence that frailty is independently associated with cognitive impairment in nondialysis populations [40,41], it may be reasonable to consider cognitive impairment as a mediator between frailty and poor outcomes. Given our current understanding of the complex pathophysiology between frailty and cognitive impairment, considering cognitive impairment as a predictor or as an outcome of frailty are likely reasonable, so long as the analytical method is sound.

In a longitudinal study, McAdams-DeMarco *et al.* [42▪] assessed the association between frailty and cognitive impairment at dialysis initiation and 1-year follow up in 324 incident dialysis patients. They observed that Fried's physical frailty construct was associated with lower cognitive function at cohort entry relative to nonfrail individuals, that

there was a dose-dependent association of higher frailty with worse cognitive function at dialysis initiation, and that patients who were frail at dialysis initiation had lower mini-mental status test scores after 1 year of dialysis compared with those who were not frail at the time of dialysis initiation [42▪]. However, there were no differences in measures of cognitive processing speed and executive function (Trail Making Tests A and B) among frail and nonfrail patients after 1 year [42▪]. The authors concluded that the discordant results may be due to lack of statistical power, as only about half of the patients completed cognitive testing at 1 year [42▪].

### Frailty and falls/fractures

Several recent studies have addressed the association between frailty and risk of falls and fractures. In 2013, McAdams-DeMarco *et al.* [43] utilized Fried's physical frailty construct in a prospective cohort and noted that frailty predicted a 3.89-fold greater number of falls over a median of 6.7 months of follow-up in an adjusted model (95% CI 1.78–8.49) compared with nonfrail dialysis patients. In 2015, Delgado *et al.* [44] also used a physical frailty construct and confirmed that frailty was associated with a higher risk of fall or fracture (hazard ratio: 1.60, 95% CI 1.16–1.20). These studies raise the possibility that if we could improve physical aspects of frailty, we might lower the risk of falls and potentially reduce patient morbidity and healthcare costs.

### Frailty, vascular access failure, and quality of life

Researchers have also recently looked into less traditional outcomes. For example, Chao *et al.* [45▪▪] investigated a potential link between a physical frailty construct and vascular access failure in a cohort of 51 prevalent dialysis patients in rural Taiwan with a mean age of 68 years. They found that frailty was associated with higher risk of vascular access failure (hazard ratio: 2.63, 95% CI 1.03–6.71) and hypothesized that endothelial dysfunction in end-stage renal disease (ESRD) accompanied by oxidative stress and low-grade inflammation may lead to frailty and also predispose patients to have complications related to their vascular access [45▪▪].

In 2016, Iyasere *et al.* [46▪▪] used a subjective frailty scale and noted that frailty was associated with worse quality of life based upon several measures including the Short Form-12 questionnaire, hospital anxiety and depression scale (HADS), and the illness intrusiveness rating scale. They also noted a graded association between frailty and depression (as assessed using the HADS), such that the odds of depression were 53% higher for each point higher in frailty score (OR 1.53, 95% CI 1.12–2.07) [46▪▪].

## TIMING OF FRAILTY ASSESSMENT

Although frailty is associated with poor outcomes, there has not been widespread adoption of assessing frailty in the dialysis setting. This is likely due to the time-intensive task of gathering data, even for self-reported measures. More readily obtainable measurements in the dialysis unit have been suggested, such as the 'Sit-to-Scale' score, a measure of gait speed that can be instituted on dialysis rounds or even on a daily basis [47].

As more elderly patients are being started on dialysis, it will be important to assess frailty. An assessment at dialysis initiation and 1–2 years after initiation can provide rich prognostic information that will inform dialysis practitioners and patients of potential risks and benefits of dialysis continuation [48▪]. Better prognostication would undoubtedly help to improve the decision-making process whenever considering dialysis in the elderly frail.

Early identification of frailty may also assist with improving overall outcomes, but timing of initial assessment has been a crucial question. Identification of frailty may need to begin at earlier stages of CKD. Two recent studies looking at frailty in the predialysis population have confirmed that frailty is still a predictor of mortality in CKD patients, and assessment of frailty may lead to patients selecting a more conservative treatment approach or having more realistic expectations if they choose dialysis [19,49].

Trials have also suggested that exercise may improve physical functioning among dialysis patients, but more studies are needed to assess whether increased muscle mass translates to decreased mortality risk in these patients [50–52]. There is speculation that the uremic milieu present in dialysis patients may contribute to poor muscle function [53], suggesting that we may be able to further improve physical performance by coupling better dialysis performance with an aggressive exercise regimen. Unfortunately, published studies of vigorous exercise interventions have been limited by waning patient enthusiasm and high dropout rates [52]. Perhaps gradual rehabilitation with the assistance of physical therapists may be beneficial to those unable or unwilling to perform more vigorous or more independent interventions.

## CONCLUSION

Despite significant advances in the assessment of frailty among dialysis patients and our understanding that frailty makes patients vulnerable to poor

outcomes, we still lack consensus on a single, easily adapted operational definition of frailty that would allow improved quantification and adequate comparison between studies. Perhaps widespread adoption of frailty assessment may not occur until a simpler construct is achieved. Alternatively, expansion of electronic health records and development of advanced data mining strategies might facilitate collection of frailty markers from various sources, including within or outside the dialysis unit. Identification of these high-risk patients may allow tailored interventions, provide more accurate prognostic information, and improve provider-to-patient discussions on the risks and benefits of the dialysis procedure.

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*There are no conflicts of interest.*

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