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Frailty in CKD–Is Only Seeing Worth Believing?

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Frailty is a distinct clinical syndrome of physiologic vulnerability to stress. Originally developed in gerontology research to identify older adults who are most vulnerable to external stressors, the frailty phenotype has been shown to capture cumulative declines over multiple physiologic systems and associates with future disability, hospitalization, and mortality.[1-4] In the older adult population, the classic phenotype of frailty has been associated with greater clinical and subclinical comorbid disease burden.[5,6] The prevalence of frailty increases with age among community-dwelling older adults and is common among middle-aged persons with chronic kidney disease (CKD), lending credence to the concept that kidney disease is a surrogate physiologic state of accelerated aging.

Studies of patients with kidney failure treated with long-term dialysis and those with earlier stages of CKD have reported a frailty prevalence of 21%-30%, depending on the specific definition of frailty and the underlying population.[7,8] In both community-dwelling older adults and middle-aged referred patients who have CKD, lower estimated glomerular filtration rate is associated with a greater risk of frailty.[7,9] Not only is the frailty phenotype highly prevalent among patients with CKD, but it also is associated robustly with the burden of disability (particularly that related to mobility) and premature death or dialysis therapy initiation.[7,10,11] The final common pathway of the frailty phenotype is skeletal muscle dysfunction (sarcopenia). Because the frailty definition captures a decline in skeletal muscle function that is shared by both CKD and aging, applying the frailty phenotype to the CKD population represents a novel approach for identifying disease burden and assessing risks of adverse health outcomes.

To reconcile heterogeneous definitions of frailty, Fried et al[12] published a landmark report defining a standardized frailty phenotype using data from a community-based cohort of older adults. This classic frailty phenotype was defined as possessing 3 of 5 characteristics: physical inactivity, exhaustion, weight loss, slow gait speed, and weak strength.[12] Three of these characteristics (inactivity, exhaustion, and weight loss) were classified by self-report, and 2 (slow gait and weakness) were measured by objective testing. Difficulties applying this definition to patients with CKD include varying cutoff points for each frailty component across populations and lack of readily available objective functional data from large populations of patients with CKD. Moreover, the classic frailty definition may not optimally capture the frailty phenotype in CKD; most patients with CKD are overweight or obese and

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thus have a unique phenotype that generally is characterized by physical inactivity, diminished lower-extremity physical performance, and exhaustion.[7,13]

In this issue of *AJKD*, Johansen et al[14] take an important step toward tailoring the frailty definition to patients treated with long-term dialysis. In their previous study of frailty from the Dialysis Morbidity and Mortality Wave 2 Study,[10] this group demonstrated a strong association of self-report-based frailty with greater risks of death and hospitalization, after adjustment for comorbid conditions. Of the self-reported frailty components, poor self-reported physical function was associated most strongly with adverse outcomes. However, the cutoff point for poor physical function that was used in that study derived from the lowest quartile 36-Item Short Form Health Survey (SF-36) Physical Function scores from a healthy reference population (Women's Health Initiative)[15]. In their current study, Johansen et al[14] attempt to create a new tool for measuring frailty that is tailored to patients treated with long-term dialysis. This tool uses internal cutoff points of self-reported function data from a multicenter, racially diverse, prospective cohort study of patients treated with long-term dialysis (ACTIVE/ADIPOSE [A Cohort to Investigate the Value of Exercise/ Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD]). To substitute for measured grip strength and walking speed used in the classic frailty definition, the authors developed a modified 2–cutoff point measure of self-reported function using the same questions from the SF-36 Physical Function. They evaluated the performance of this new measure in a randomly generated validation subset of their study population. The major finding of the study is that the new frailty instrument, based on self-reported function, has reasonably good validity compared to the gold-standard method that combines self-report and measured performance. The self-reported function assessment also categorizes a greater number of dialysis patients as “frail.”

The fundamental analytical question posed by this study is whether results of grip strength and gait speed testing can be predicted using the self-reported SF-36 Physical Function scale. To this end, it would be helpful to see the specific validity data relating these characteristics in addition to the general validity data for the full frailty definition. The relatively poor to fair correlations of self-reported physical function with grip strength (r = 0.38) and gait speed (r = 0.53) reported in the study[14] suggest that measured performance and self-reported physical function may capture 2 distinct stages of declining function. This finding may emphasize differences between functional limitations measured objectively and self-reported accommodations to a patient's environment in response to functional limitations. However, the authors suggest that compared to the gold-standard frailty definition that combines self-report and measured performance, the modified 2–cutoff point self-report definition misclassifies only a small proportion of the study sample as nonfrail. This finding prompts the question: what is the role of physical performance testing in evaluating frailty in CKD?

Two recent studies of patients with earlier stages of CKD demonstrate that a single assessment of physical performance[13] or self-reported physical function[16] is associated with all-cause mortality in a continuous fashion. However, after controlling for comorbid conditions and kidney function, lower-extremity physical performance—but not self-reported physical function— remains associated independently with mortality. This

discrepancy may indicate that for patients with CKD, these 2 methods of assessing physical capacity capture different steps in the disablement process. One potential benefit of performance testing is its ability to identify functional limitations before they are recognized and self-reported by the patient. Standardized performance testing complements self-reported function assessment by circumventing environmental differences that could influence the way an individual perceives his or her functioning. For instance, a patient may not report difficulty bathing if they have a walk-in shower, whereas a patient with a less accommodating bathtub might.

What are the potential clinical implications of the current study by Johansen et al?[14] There are potential practical and theoretical advantages of a self-report–based frailty definition that is tailored to the dialysis population. The first is the potential use of the refined self-report–based frailty criteria as part of a screening program that can be implemented easily in the current dialysis center and outpatient clinical workflow. Expedient screening for frailty based on entirely self-reported items may come at the expense of a small degree of misclassification. The second potential benefit as cited by the authors is in identifying a pre- or intermediate frail phenotype that later could progress to frailty, but is more likely to respond to early intervention. In particular, the findings that dialysis patients who had frailty by self-report also had nutritional, catabolic, body composition, physical performance, and activity of daily living disability characteristics intermediate between those who were classified as nonfrail and frail using the classic performance-based definition is important and worthy of further investigation.

So what are the next steps? The diagnosis of frailty requires accurate and clinically meaningful criteria in the general dialysis population. Although internally valid, the measures of screening performance for the novel modified self-report–based definition of frailty needs further validation in other dialysis populations to strengthen its generalizability. Furthermore, investigation of longitudinal associations of this novel definition with adverse health outcomes is needed to demonstrate the clinical utility justifying its use as a surveillance tool. There already is evidence and understanding that exercise can benefit physical performance and quality of life in the dialysis population.[17] The final step is for the nephrology community to cross the chasm between understanding and implementing these effective screening tools and cost-effective interventions for high-risk prefrail and frail patients with CKD.

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