Association of Performance-Based and Self–Reported Function–Based Definitions of Frailty with Mortality among Patients Receiving Hemodialysis

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Abstract

Background and objectives Frailty is common among patients on dialysis and increases vulnerability to dependency and death.

Design, setting, participants, & measurements We examined the predictive ability of frailty on the basis of physical performance and self-reported function in participants of a US Renal Data System special study that enrolled a convenience sample of 771 prevalent patients on hemodialysis from 14 facilities in the Atlanta and northern California areas from 2009 to 2011. Performance-based frailty was assessed using direct measures of grip strength (weakness) and gait speed along with weight loss, exhaustion, and low physical activity; poor self–reported function was substituted for weakness and slow gait speed in the self–reported function–based definition. For both definitions, patients meeting three or more criteria were considered frail.

Results The mean age of 762 patients included in analyses was 57.1±14.2 years old; 240 patients (31%) met the physical performance–based definition of frailty, and 396 (52%) met the self–reported function–based definition. There were 106 deaths during 1.7 (interquartile range, 1.4–2.4) years of follow-up. After adjusting for demographic and clinical characteristics, the hazard ratio (HR) for mortality for the performance-based definition (2.16; 95% confidence interval [95% CI], 1.41 to 3.29) was slightly higher than that of the self–reported function–based definition (HR, 1.93; 95% CI, 1.24 to 3.00). Patients who met the self-report–based definition but not the physical performance definition of frailty (n=192) were not at statistically significantly higher risk of mortality than those who were not frail by either definition (n=330; HR, 1.41; 95% CI, 0.81 to 2.45), but those who met both definitions of frailty (n=204) were at significantly higher risk (HR, 2.46; 95% CI, 1.51 to 4.01).

Conclusions Frailty, defined using either direct tests of physical performance or self–reported physical function, was associated with higher mortality among patients receiving hemodialysis. Future studies are needed to determine the utility of assessing frailty in clinical practice.

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Introduction

Frailty is a medical syndrome with multiple causes and contributors characterized by diminished strength and endurance and reduced function across multiple physiologic systems that increase an individual's vulnerability to dependency and death (1). A recent expert panel concluded that the designation of frailty can be useful in primary care settings and that it is essential for health workers to detect frailty to prevent clinical deterioration and functional dependence (2).

Fried *et al.* (3) developed a definition of frailty on the basis of meeting at least three of five criteria: weight loss, weakness, slow gait speed, exhaustion, and low physical activity. The Fried frailty definition has become a standard of physical frailty that has been applied to not only older community–dwelling adults, in whom it was first described, but also, older patients undergoing elective surgery, patients with CKD (4), and patients with ESRD undergoing hemodialysis (HD) (5,6). We and other investigators have invoked frailty definitions that substitute alternative criteria for some or all of the original five (7–11). Not surprisingly, such substitution has led to variations in the reported prevalence of frailty across studies (4–6,8–13). Specifically, frailty is more prevalent when patients' self–reported physical function are used in the definition than when physical performances are measured (11,12). Although all definitions of frailty have been associated with adverse outcomes, variations in patient populations and frailty definitions have made it impossible to identify a best definition. In fact, alternative definitions may be superior or inferior depending on the purpose (*e.g.*, screening in medical practice and inclusion criterion or end point in clinical trial).

In a cross-sectional analysis of patients on HD, we determined that substituting patients' self–reported physical functioning for the performance-based criteria (gait speed and grip strength) identified a larger proportion of patients as frail (12). Interestingly, patients who reported limitations in physical function but did not meet the thresholds of low performance appeared to have nutritional status, body composition, and markers of inflammation that were intermediate between individuals who were frail on the basis of performance and those who were not frail.

Given that the self–reported function–based definition of frailty uses data potentially available from the Kidney Disease Quality of Life (KDQOL) instrument for three of its components, it would require considerably less incremental time and effort to incorporate into dialysis practice than the performance-based definition if it were to prove useful in identifying patients at high risk for mortality. In addition, we considered the possibility that patients who are frail by self-reported function but not by physical performance might constitute an intermediate category, similar to those designated as prefrail in the performance-based definition. We sought to examine the association of the most common performance–based and self–reported function–based definitions of frailty with mortality and determine whether meeting the self–reported function–based definition alone signals a prefrail condition or intermediate state of risk.

Materials and Methods

Participants

A Cohort to Investigate the Value of Exercise/Analyses Designed to Investigate the Paradox of Obesity in ESRD (ACTIVE/ADIPOSE) was a cohort study of prevalent patients receiving dialysis from the Atlanta metropolitan and San Francisco Bay areas conducted jointly by the US Renal Data System (USRDS) Nutrition and Rehabilitation and Quality of Life Special Studies Centers (14). Patients were enrolled between June of 2009 and August of 2011 from 14 dialysis facilities. Inclusion criteria were age ≥18 years old, English or Spanish speaking, on HD for ≥3 months, and capable of giving informed consent. Exclusion criteria included active malignancy, pregnancy, and incarceration. The protocol was approved by the Committee on Human Research at the University of California, San Francisco; the Research and Development Committee at the San Francisco Veterans Affairs Medical Center; and the Emory University Institutional Review Board. All participants provided written informed consent.

At baseline, physical performance was assessed before a midweek HD session as described below. In addition, patients provided demographic information and reported on their physical activity and function during the same visit (14). Medical history was obtained through chart review and linkage with the ESRD Medical Evidence Report (Form Centers for Medicare and Medicaid Services [CMS] -2728). Study coordinators measured height using a stadiometer and recorded the most recent postdialysis weight for calculation of body mass index (BMI). Blood was drawn immediately before a dialysis session. Serum albumin and C–reactive protein (CRP) concentrations were measured in duplicate using a Beckman Array 360 Nephelometer (Beckman Coulter, Inc., Brea CA). Data on death were ascertained through linkage with the USRDS through December 31, 2011.

Frailty

We determined whether patients were frail using two definitions: the Fried Frailty Index, which includes measures of walking speed and grip strength and is one of the most widely applied measures of frailty (3), and a definition that substitutes patient-reported measures available on the Medical Outcomes Study 36-Item Short Form (SF-36) for the physical performance and exhaustion criteria (7). Specifically, the performance-based definition included weight loss, exhaustion, low physical activity, weak grip, and slow walking. Each domain was given a score of zero or one on the basis of the following criteria, and patients meeting three or more criteria were considered frail.

(*1*) Unintentional weight loss of ≥10 lb in the last year.
(*2*) Exhaustion measured by responses to questions about endurance and energy from the Center for Epidemiologic Studies depression scale (15).
(*3*) Low physical activity ascertained from the short version of the Minnesota Leisure Time Physical Activity Questionnaire, which asks about the frequency and duration of activities over a 2-week period (16).
(*4*) Weakness on the basis of handgrip strength measured using a handheld dynamometer (Jamar; Lafayette Instrument, Lafayette, IN) immediately before a dialysis session. Patients performed three tests with each hand. The mean measurement of the strongest hand was used in scoring.
(*5*) Slow walking speed on the basis of a 15-ft timed walk. Patients were asked to walk the course twice at their usual pace immediately before a dialysis session. The faster of the two trials was recorded and scored.

For physical activity, grip strength, and gait speed, we used the thresholds established by Fried *et al.* (3), which were on the basis of the lowest sex–specific quintiles among community-dwelling elderly and have now been used as standard thresholds in other populations, including ESRD (Supplemental Table 1) (5,6,17).

For the self–reported function–based definition, the weight loss and physical activity criteria were identical to the performance-based definition, but participants' scores on the SF-36 Physical Functioning scale were used in place of the walking test and grip strength measurements. Patients with a score <75 were considered to meet the slow walking and weak grip criteria and given 2 points toward the overall frailty score as previously developed in a cohort of elderly women and applied among patients with ESRD (7,8). The vitality scale of the SF-36 (score <55) was used for the exhaustion criterion (7). A patient with three or more of the criteria was considered frail, such as for the performance-based definition.

Statistical Analyses

Patient characteristics on the basis of frailty status were compared using chi-squared, ANOVA, or Kruskal–Wallis tests as appropriate. Associations between frailty and death were assessed using multivariable proportional

hazards regression models. Potential covariates included known predictors of adverse outcomes in the dialysis population and included age, sex, race (white, black, or other), BMI according to the World Health Organization classification (underweight, <20 kg/m^2; normal weight, 20 to <25 kg/m^2; overweight, 25 to <30 kg/m^2; and obese, ≥30 kg/m^2), serum albumin and CRP concentrations, use of a catheter for dialysis access, diabetes mellitus, atherosclerotic heart disease, and heart failure.

The performance-based and the self–reported function–based definitions of frailty were each the primary predictor in separate models. In addition, the performance-based and the self–reported function–based definitions were also considered in combination within a single model using a model that reflects a strategy of screening with the self–reported function–based designation of frailty and applying the performance-based definition only among those who meet the self–reported function definition. We fit primary models that did not include serum albumin and CRP concentrations or dialysis *via* a catheter, because we hypothesize that inflammation is a potential cause of frailty and that catheters could induce inflammation or be used more frequently when patients are frail. Thus, we reasoned that inclusion of these variables might constitute overadjustment. Nevertheless, we also fitted models that included these variables to determine whether constructs of frailty provide information independent of laboratory and clinical data that might be instantly available to clinicians.

All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). Two–sided *P* values <0.05 were considered statistically significant.

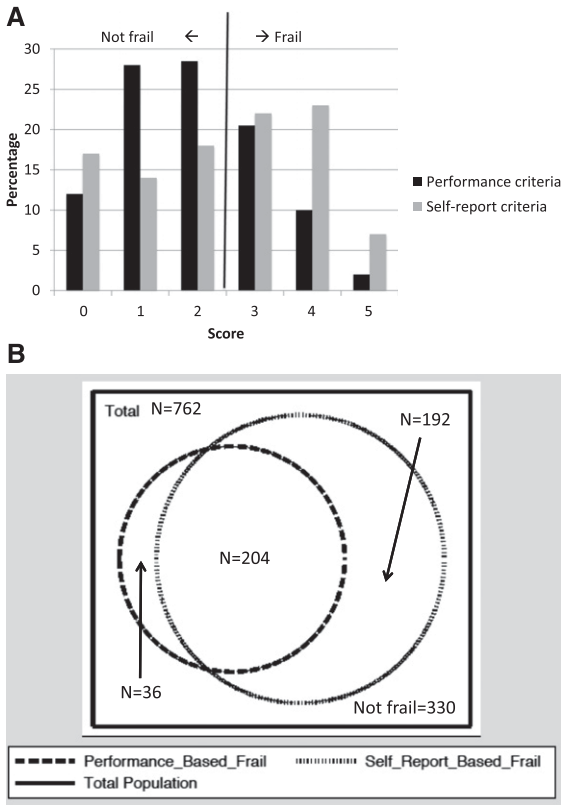

Figure 1. | Number of individual frailty components and overall frailty prevalence according to the performance-based and self-report-based definitions. (A) Histogram of raw frailty scores. (B) Venn diagram of frailty prevalence. The dashed circle represents frailty defined by physical performance (Fried Frailty Index) and the dotted circle represents a frailty designation using patients' self-reports of physical function.

Results

In total, 771 patients were enrolled in ACTIVE/ADIPOSE, of whom 762 (99%) had complete data available to ascertain frailty status using both frailty scores; 240 patients (31%) met the performance-based definition of frailty, and 396 (52%) met the self–reported function–based definition (Figure 1). Patient characteristics associated with frailty by both definitions included older age, women, diabetes, peripheral arterial disease, history of stroke or transient ischemic attack, dialysis using a central venous catheter, and low serum albumin and high CRP concentrations, similar to other studies of frailty. Table 1 shows patient characteristics across the four groups defined by both definitions.

Median follow-up was 1.7 (interquartile range, 1.4–2.4) years. There were 106 deaths, and the overall mortality rate was 74.9/1000 person-years. Frailty was associated with higher mortality according to both definitions (Table 2). Fifty-five patients (22.9%) meeting the physical performance definition of frailty died during follow-up (mortality rate of 137.8/1000 person-years versus 50.2/1000 person-years among those not frail by the performance-based definition) (Table 2). Seventy-three (18.4%) of those meeting the self-report definition died during follow-up, with a death rate of 104.2/1000 person-years compared with 46.2/1000 person-years among those not frail by the self-report–based definition.

After adjusting for age, sex, race, BMI, and comorbidity, the hazard ratio (HR) for the performance-based definition (2.20; 95% confidence interval [95% CI], 1.41 to 3.30) was nominally higher than that of the self-report–based definition (HR, 1.93; 95% CI, 1.24 to 3.00), but the 95% CIs overlapped substantially. We added performance-based frailty to the fully adjusted model containing frailty by self-report, and it did not significantly improve the model (*P*=0.08). Frailty remained associated with higher mortality after additional adjustment for serum albumin and use of a central venous catheter for dialysis (HR, 1.79; 95% CI, 1.16 to 2.80 for the performance-based definition and HR, 1.67; 95% CI, 1.07 to 2.60 for the self-report–based definition).

Considering both definitions together, we created a proportional hazards model to reflect a potential clinical strategy that would use the self–reported function–based definition as a screening tool and then follow with performance testing only in those who are designated as frail by self-report. In this construct, we classified participants as nonfrail by self-reported function (*n*=366), frail by self-reported function only (*n*=192), or frail by self-reported function and performance (*n*=204). Patients who met the self-report–based definition but not the physical performance definition of frailty did not have a statistically significantly higher risk of mortality than those who were not frail by the self-report–based definition (HR, 1.40; 95% CI, 0.82 to 2.38). Those who met both definitions of frailty were at statistically significantly higher

Table 1. Patient characteristics on the basis of performance and self–reported function definitions of frailty

Variable	All, *n*=762	Not Frail, *n*=330	Frail by Self-Report Only, *n*=192	Frail by Performance Only, *n*=36	Frail by Performance and Self-Report, *n*=204	*P* Value
Age, yr	57.1 (14.2)	54.1 (14.4)	56.4 (12.8)	53.1 (14.9)	63.5 (13.1)	<0.001
Sex, % women	40.7	34.5	44.8	38.9	47.1	0.02
Race, % black	61.5	61.8	67.2	72.2	53.9	0.13
Diabetes mellitus	50.9	42.4	50.5	58.3	63.7	<0.001
Heart failure	29.0	21.5	29.2	27.8	41.2	<0.001
CAD	31.4	21.8	32.8	33.3	45.1	<0.001
PAD	9.7	5.8	7.3	2.8	19.6	<0.001
CVA or TIA	10.2	7.6	9.9	5.6	15.7	0.02
Dialysis vintage, yr	2.7 (1.2, 5.4)	2.9 (1.3, 5.8)	2.9 (1.4, 5.3)	2.0 (0.7, 4.8)	2.4 (1.0, 4.8)	0.14
Hemoglobin, g/dl	11.5 (1.3)	11.6 (1.3)	11.6 (1.3)	11.4 (1.2)	11.4 (1.3)	0.13
Serum albumin, g/dl	4.0 (0.4)	4.1 (0.3)	4.0 (0.3)	4.0 (0.5)	3.9 (0.4)	<0.001
CRP, mg/L	3.9 (1.5, 9.8)	3.1 (1.2, 7.3)	3.9 (1.7, 9.8)	4.5 (1.8, 16.1)	5.1 (1.6, 12.4)	0.004
BMI, kg/m^2	28.2 (6.9)	27.4 (6.2)	28.7 (7.4)	27.6 (7.7)	29.1 (7.4)	0.05
SBP, mmHg	151 (23)	152 (22)	153 (24)	152 (19)	149 (23)	0.28
DBP, mmHg	81 (15)	83 (15)	82 (15)	80 (14)	76 (15)	<0.001
Dialyzing *via* catheter, %	20.7	16.4	26.6	5.6	25.0	0.002

Values are means±SDs, medians (interquartile ranges), or percentages. CAD, coronary artery disease; PAD, peripheral arterial disease; CVA, cerebrovascular accident; TIA, transient ischemic attack; CRP, C-reactive protein; BMI, body mass index; SBP systolic BP; DBP, diastolic BP.

risk than those who met the self–reported function–based definition alone, and the association remained significant in the partially and fully adjusted models (Table 2). Because this strategy includes the few patients who met only the performance-based definition of frailty in the nonfrail group, we also modeled frailty according to all four combinations using the two definitions, and results were similar (Supplemental Table 2).

Discussion

We and others have previously shown that a substantial percentage of patients receiving dialysis is frail (5,8,12) and that the prevalence depends on how frailty is defined (12). This study begins to explore the potential utility of two definitions of frailty as predictors of mortality in this already high–risk population. We found that both the physical performance–based definition of frailty (Fried Index) and an alternative definition using self-reported function were associated with higher mortality among patients on dialysis in univariate and multivariable models. Relatively few patients were not frail by self-reported function but deemed frail by performance.

Our results are of potential clinical and policy relevance, because the CMS is currently developing measures of functional status for inclusion in the dialysis Quality Improvement Program (18). Our results indicate that the performance-based definition of frailty identified a subset of patients at slightly but not statistically significantly higher risk of mortality than the self–reported function–based definition, suggesting that measurement of gait speed and grip strength might be reasonable choices. However, three of the components of the self–reported function–based definition can be determined or derived using data from the KDQOL, which is routinely administered in dialysis facilities, although additional validation of the self-report definition using the short version of the KDQOL (and hence, SF-12) may be needed (9). In addition, the weight loss criterion of both frailty definitions can be readily obtained from the dialysis clinical record.

The association between both definitions of frailty and mortality remained statistically significant after adjustment for demographic characteristics and even serum albumin concentration and catheter use, suggesting that frailty, on the basis of self-report or direct measurement of physical performance, might also provide a meaningful contribution to a risk score that incorporated such clinical data (19). Additional studies will be needed to determine whether assessments of frailty can be improved. It would also be worthwhile to evaluate whether inclusion of frailty by one or more definitions can help clinicians identify patients for whom targeted interventions aimed to enhance physical function might be most successful and whether frailty can improve risk assessment tools, providing better case mix adjustment to allow regulators to evaluate quality of care and outcomes.

Our data could support a strategy of screening all patients using the questionnaire–based frailty definition, with performance testing only in those who test positive. In such a scenario, fewer patients (52%) would require performance testing. In this cohort, such a strategy missed the 5% who met the performance-based definition of

Table 2. Multivariable Cox proportional hazards models of the association of frailty with mortality

Frailty Definition	Deaths per 1000 person-yr, 106 Total Events	Univariate, *n*=762		Model 1,[a] *n*=732		Model 2,[b] *n*=728		Harrell c Statistic[c]
		Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	
Single definitions in individual models								
Performance based								
No	50.2	1.0 (reference)		1.0 (reference)		1.0 (reference)		
Yes	137.8	2.74 (1.87 to 4.02)	<0.001	2.16 (1.41 to 3.29)	<0.001	1.78 (1.15 to 2.80)	<0.01	0.73
Self–reported function based								
No	46.2	1.0 (reference)		1.0 (reference)		1.0 (reference)		
Yes	104.2	2.25 (1.49 to 3.40)	<0.001	1.93 (1.24 to 3.00)	0.004	1.66 (1.06 to 2.60)	0.02	0.72
Performance and self–reported physical function in a single model								
Not frail by self-reported function	46.2	1.0 (reference)		1.00 (reference)		1.00 (reference)		
Frail by self-reported function only	64.5	1.40 (0.82 to 2.38)	0.22	1.41 (0.81 to 2.45)	0.23	1.33 (0.76 to 2.32)	0.31	0.73
Frail by both definitions	145.3	3.15 (2.03 to 4.89)	<0.001	2.46 (1.51 to 4.01)	<0.001	1.95 (1.19 to 3.20)	<0.01	

95% CI, 95% confidence interval.
[a]Primary analysis adjusted for age, sex, race, body mass index, diabetes, heart failure, and coronary artery disease.
[b]Model 2 also adjusted for serum albumin and C–reactive protein concentrations and dialysis *via* central venous catheter.
[c]For the fully adjusted models.

frailty without meeting the self–reported function–based definition. In addition, one quarter reported low functioning without having poor performance, and this group may need additional study to determine whether they are destined to develop poor physical performance (*e.g.*, are prefrail) and increase their risk of mortality over time in the absence of intervention.

However, some object to the substitution of self-reported functioning for objectively measured performance in frailty assessment on the basis that it is not the same construct (11) or that the subjective nature of self-report could lend itself to manipulation by patients or providers if decisions regarding transplantation or payment might be affected. Both gait speed and grip strength could be measured in dialysis facilities with relatively inexpensive equipment (stopwatch and handheld dynamometer) and limited staff training.

Ultimately, the choice of which frailty instrument to use in the dialysis population or indeed, whether to assess frailty at all will depend on a balance between the burden of data collection and the utility of the information, which will need to be determined in larger prospective studies. The Technical Expert Panel convened to provide input on the development of functional status quality measures has recommended a two-step approach, with initial self-report followed by performance testing in a subset (18). Additional testing and discussions are planned before final measures and implementation strategy are adopted, and more information is needed about the evolution of frailty, including its natural history and the extent to which targeted interventions can reverse functional limitations to inform the conversation.

Both definitions of frailty would require collection of physical activity data, which is not currently a part of routine dialysis care. Given that physical activity is extremely low in the dialysis population (20) and may be the component of frailty that is most modifiable, the effort of collecting these data may be worthwhile. Furthermore, clinical practice guidelines currently recommend that physical activity should be routinely assessed among patients on dialysis (21).

In this prospective study, we assessed frailty by two methods that have been previously developed and validated among community-dwelling elders (3,7) rather than improvising a frailty construct from available data. Thus, we can compare the prevalence of frailty in this population with that observed in previous studies. We found a similar prevalence among patients on HD using the performance-based definition as McAdams-DeMarco *et al.* (5) found in a cohort of patients from the Baltimore area. However, the prevalence was more than threefold higher than that in community-dwelling elders in the Cardiovascular Health Study (3) and the Women's Health Initiative (7), although our population was not restricted to individuals age >65 years old.

Nevertheless, our study had several limitations. We did not have enough outcome events to allow development and validation of a mortality prediction rule to determine whether inclusion of frailty in such a model would improve its performance. We estimated associations of frailty with outcomes on the basis of a single baseline evaluation rather than longitudinal data updating frailty, which may have attenuated the associations if frailty status changed over time. Our study population is drawn from the Atlanta and San Francisco Bay areas and does not mirror the racial distribution of the United States prevalent HD population, having a larger proportion of black patients. However, we did not find a significant association between race and frailty, which other investigators also have not found when examining frailty among patients on ESRD (5). We excluded patients who could not provide informed consent because of cognitive dysfunction, and it may not be possible to apply these frailty constructs in such patients. In addition, there may have been selection bias toward a healthier cohort on the basis of healthier patients agreeing to participate. For all of these reasons, our results should be considered preliminary, and additional study will be needed to assess the generalizability of these findings to the broader United States dialysis population. Finally, although we found that being frail indicates that patients are more vulnerable to death, this study did not investigate the possible reasons for this association or associations of frailty with other outcomes that might affect patients' quality of life.

In conclusion, frailty, defined using either direct tests of physical performance or patients' self–reported physical function, was associated with higher mortality among patients receiving HD. In dialysis practice, a two-step strategy of using a questionnaire-based assessment of (self-reported) frailty followed by a performance-based assessment would likely be more efficient at identifying patients at higher risk of death than either diagnostic strategy alone and may allow for identification of patients most likely to benefit from efforts aimed at enhancing physical function and performance in this vulnerable population.

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The interpretation and reporting of the data presented here are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US Government.

Disclosures

None of the authors have any financial conflict of interest with the information presented in this manuscript. G.M.C. serves on the Board of Directors of Satellite Healthcare, Inc. (San Jose, CA)

and the Scientific Advisory Board of DaVita Clinical Research (Minneapolis, MN).

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