Significance of Frailty among Dialysis Patients

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ABSTRACT

The construct of frailty has been associated with adverse outcomes among elderly individuals, but the prevalence and significance of frailty among patients with end-stage renal disease have not been established. The aim of the current study was to determine the prevalence and predictors of frailty among a cohort of incident dialysis patients and to determine the degree to which frailty was associated with death and hospitalization. We studied a cohort of 2275 adults who participated in the Dialysis Morbidity and Mortality Wave 2 study, of whom two-thirds met our definition of frailty: a composite construct that incorporated poor self-reported physical functioning, exhaustion/fatigue, low physical activity, and undernutrition. Multivariable logistic regression analysis suggested that older age, female sex, and hemodialysis (rather than peritoneal dialysis) were independently associated with frailty. Cox proportional hazards modeling indicated that frailty was independently associated with higher risk of death (adjusted hazard ratio [HR] 2.24, 95% confidence interval [CI] 1.60–3.15) and with the combined outcome of death or hospitalization (adjusted HR 1.63, 95% CI 1.41–1.87). Frailty is extremely common and is associated with adverse outcomes among incident dialysis patients. Given its prevalence and consequences, increased research efforts should focus on interventions aimed to prevent or attenuate frailty in the dialysis population.

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Chronic kidney disease (CKD) and ESRD are associated with many of the same clinical manifestations as advanced age in the absence of kidney disease, such as inactivity, loss of muscle mass, comorbid conditions, and decline in physical and cognitive functioning. In the geriatric literature, these clinical manifestations have been identified as important contributors to a "frailty phenotype."[1–4] The degree to which adverse outcomes that are associated with CKD and ESRD are mediated by frailty is unknown.

Frailty is a multidimensional construct reflecting the decline in health and functioning observed in the elderly, ultimately resulting in increased risk for disability, hospitalization, institutionalization, and death.[1,5] Fried *et al.*[6] developed and validated a screening tool for frailty. The screening criteria consist of weight loss, muscle weakness, fatigue or exhaustion, low physical activity, and slow gait. The presence of three or more of these criteria defines the frailty phenotype. This tool was validated by its ability to predict disability, hospitalization, and mortality among participants of the Cardiovascular Health Study (CHS), a cohort study of 5888 community-dwelling individuals who were ≥65 yr of age at study inception. Because some of the criteria, such as grip strength, may not be readily available to investigators in clinical settings, Woods *et al.*[7] developed a set of measures that could be ascertained

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by patient report using standard instruments such as the Medical Outcomes Study Short-Form 36-Item Questionnaire (SF-36).[8,9] These investigators applied their modified definition of frailty to participants in the Women's Health Initiative Observational Study and found that frailty was associated with poor outcomes, including death, hip fracture, reduced capacity to complete activities of daily living, and hospitalization, even after adjustment for demographic characteristics, health behaviors, other disability, and comorbid conditions.[7]

Two studies[10,11] reported a high prevalence of frailty among elderly individuals with mild to moderate CKD; however, the frailty construct has not previously been applied to the ESRD population. Incorporation of the geriatric construct of frailty into the dialysis care setting has the potential to improve the identification of patients who are at risk for adverse, frailty-associated outcomes and might benefit from interventions designed to improve functioning or prevent decline; therefore, we undertook analyses using data from the US Renal Data System (USRDS) to establish the prevalence and predictors of frailty among incident dialysis patients and to determine the degree to which frailty was associated with death and hospitalization.

RESULTS

Of the 3931 patients enrolled in the Dialysis Morbidity and Mortality Study (DMMS) Wave 2, 2393 completed the Patient Questionnaire, making it possible to determine whether they were frail. Of these, 75 had missing survival data and 43 were younger than 18 yr; 2275 patients were included in the analytic cohort. Table 1 shows the baseline characteristics for those with and without data related to frailty. Those with available data were slightly younger; had a slightly higher serum albumin concentration; were more likely to be white, to be married, to have completed high school, and to be employed; and were less likely to have a history of stroke or to have Medicaid coverage.

Prevalence and Predictors of Frailty

Overall, two thirds of the study population met the study definition of frailty (Table 2). Although older age was clearly related to frailty, a significant proportion of patients in the younger age groups were also frail, including 44% of patients who were younger than 40 yr and more than half of patients who were aged 40 to 50 yr. Women were more likely than men to be frail in all age categories. Table 3 shows the results of multivariable analysis of the predictors of frailty. Frailty was more common among patients with comorbid conditions, although the associations reached statistical significance only for diabetes, stroke, and lower serum albumin concentrations. Patients who were on hemodialysis were more likely to be frail than those who were on peritoneal dialysis. Early nephrology referral and predialysis erythropoietin use were not associated with frailty (data not shown), but, among hemodialysis patients, those with a permanent vascular access (fistula or graft) were less likely to be frail (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.51 to 0.98). These results suggest that frailty is associated with lack of permanent vascular access independent of time of nephrology referral.

Table 1. Baseline characteristics by availability of frailty criteria

Variable	Complete Data (n = 2275)	Incomplete Data (n = 1538)	P
Age (yr; mean ± SD)	58.2 ± 15.5	59.8 ± 15.9	0.002
Gender (% male)	53.4	52.2	0.29
Race (%)			0.0005
white	65.4	60.2	
black	26.5	30.8	
Asian	2.3	3.2	
other	5.8	5.7	
Serum albumin (mg/dl; mean ± SD)[b]	3.5 ± 0.6	3.4 ± 0.6	<0.0001
BMI (kg/m^2; mean ± SD)	25.8 ± 5.8	25.2 ± 5.5	0.0007
Peritoneal dialysis (%)	48.1	49.7	0.32
Comorbidity (%)			
diabetes	47.6	50.2	0.11
CAD	31.4	31.7	0.86
cerebrovascular disease	8.7	11.6	0.003
peripheral vascular disease	15.3	17.4	0.08
cancer	8.4	8.3	0.94
Current smoker (%)	13.9	12.6	0.23
Married (%)	56.4	51.8	0.005
Employed (%)	13.8	1.9	<0.0001
High school graduate (%)	69.8	62.6	<0.0001
Medicaid (%)	26.8	32.9	0.0002

[a]BMI, body mass index; CAD, coronary artery disease.
[b]To convert mg/dl to g/L, multiply by 10.

Table 2. Proportion of patients overall and by age meeting individual and collective criteria for frailty

Patients	*n*	Frail	PF <75	Vitality <55	Inactive	Undernourished
Overall	2275	67.7	78.3	68.7	35.9	11.8
Age (yr)						
<40	306	44.4	55.9	58.5	26.1	10.1
40 to 50	352	61.1	71.3	64.2	31.2	8.2
50 to 60	440	66.4	79.6	62.0	35.4	8.9
60 to 70	570	74.2	84.6	73.3	40.2	11.9
70 to 80	475	78.1	85.9	77.0	39.0	17.7
>80	132	78.8	90.9	76.5	42.4	13.6

Table 3. Predictors of frailty[a]

Variable	OR	95% CI
Age	1.02	1.01 to 1.03
Female gender	1.55	1.27 to 1.88
Race		
white	1.0 (referent)	
black	0.90	0.72 to 1.13
Asian	0.56	0.30 to 1.05
other	1.01	0.26 to 3.92
BMI (kg/m^2)		
<19	1.41	0.93 to 2.13
19 to <25	1.0 (referent)	
25 to <30	0.98	0.78 to 1.22
≥30	1.00	0.77 to 1.30
Serum albumin concentration (g/dl)		
<3.2	1.89	1.43 to 2.49
3.2 to <3.5	1.32	1.00 to 1.76
3.5 to <3.9	1.06	0.84 to 1.35
≥3.9	1.0 (referent)	
Dialysis modality (PD)	0.80	0.65 to 0.97
Comorbidity		
diabetes	1.35	1.10 to 1.65
CAD	1.17	0.92 to 1.48
PAOD	1.19	0.88 to 1.60
CVA	1.55	1.05 to 2.29
cancer	1.39	0.95 to 2.04

[a]CVA, cerebrovascular accident; PAOD, peripheral arterial occlusive disease; PD, peritoneal dialysis.

Frailty, Mortality, and Hospitalization

On univariate analysis, frail patients were more than three times as likely to die within 1 yr (HR 3.42; 95% CI 2.45 to 4.76; Figure 1). After adjustment for age, gender, race or ethnicity, body size, dialysis modality, comorbidities, serum albumin, and other factors, frailty remained strongly associated with mortality (adjusted HR 2.24; 95% CI 1.60 to 3.15; Table 4). Frail patients were also more likely to be hospitalized for any reason or die (HR 1.90; 95% CI 1.67 to 2.17; Figure 2), a finding that persisted after adjustment for multiple potential risk factors for hospitalization (adjusted HR 1.56; 95% CI 1.36 to 1.79). When the analysis was repeated including only non–vascular access–related hospitalizations, the results were similar (adjusted HR 1.98; 95% CI 1.41 to 1.87). These results were not materially different when limited to patients who were older than 65 yr ($n = 915$; data not shown). It is interesting that frailty was similarly hazardous regardless of age, gender, or race (interaction terms $P > 0.20$ for all variables and all analyses).

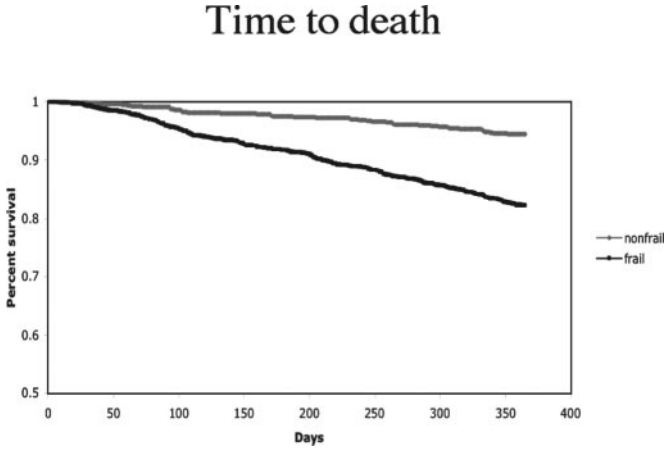

Figure 1. Time to death. Kaplan-Meier plot of the association between frailty and survival. Gray line, nonfrail patients; black line, frail patients.

When the components of frailty were examined individually, each was found to be associated with mortality after adjustment for other predictors (Table 5). When the components all were included in the same model, Physical Functioning (PF) score <75, inactivity, and categorization as undernourished remained independently associated with mortality, whereas vitality score <55 did not reach statistical significance (Table 5). On the basis of these results, a modified frailty score was created with one point assigned to each of PF <75, inactivity, and undernourished status. This score was associated with mortality and provided better discriminative power than the simpler frailty definition derived from data of Woods *et al.*[7] (HR 1.87; 95% CI 1.59 to 2.20 per one-point increase; Figure 3). Similar analyses for non–vascular access–related hospitalization are presented in Table 5 and show that each of the components of the frailty phenotype is independently associated with hospitalization to a similar degree.

DISCUSSION

This study showed that an extremely high proportion of incident patients with ESRD met a definition of frailty similar to definitions established in community-dwelling elderly popu-

Table 4. Multivariable analysis of the association of frailty with 1-yr mortality

Variable	HR (95% CI)
Frailty	2.24 (1.60 to 3.15)
Age	1.03 (1.02 to 1.04)
Female gender	1.09 (0.86 to 1.38)
Race	
white	1.0 (referent)
black	1.01 (0.75 to 1.36)
Asian	0.91 (0.40 to 2.06)
other	0.84 (0.12 to 6.02)
Hispanic	1.20 (0.82 to 1.78)
BMI (kg/m^2)	
<19	1.11 (0.78 to 1.58)
19 to <25	1.0 (referent)
25 to <30	0.62 (0.46 to 0.82)
≥30	0.57 (0.40 to 0.81)
Serum albumin concentration (g/dl)[a]	
<3.2	1.83 (1.30 to 2.59)
3.2 to <3.5	1.09 (0.74 to 1.59)
3.5 to <3.9	1.04 (0.73 to 1.49)
≥	1.0 (referent)
Dialysis modality (PD)	1.03 (0.81 to 1. 31)
Comorbidity	
diabetes	1.10 (0.86 to 1.41)
CAD	1.36 (1.07 to 1.73)
peripheral vascular disease	1.55 (1.19 to 2.00)
CVA	1.13 (0.81 to 1.56)
cancer	1.26 (0.90 to 1.76)
Employment status	0.47 (0.25 to 0.87)
Marital status	0.86 (0.68 to 1.09)
Smoking	1.25 (0.88 to 1.77)

[a]To convert mg/dl to g/L, multiply by 10.

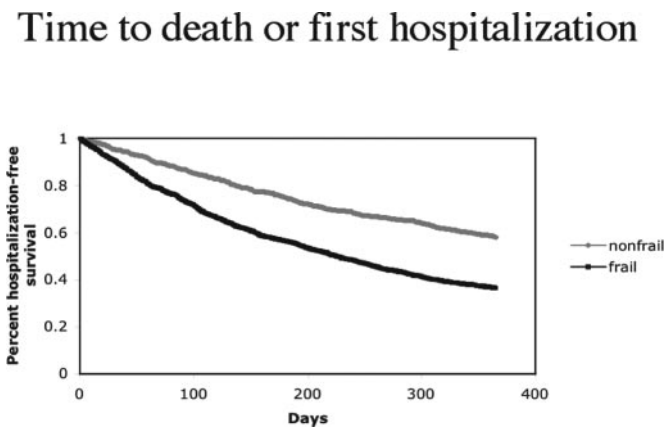

Figure 2. Time to hospitalization or death. Kaplan-Meier plot of the association between frailty and hospitalization-free survival. Gray line, nonfrail patients; black line, frail patients.

lations.[6,7,12] To put these data into perspective, the original CHS cohort, from which the Fried definition of frailty was developed, consisted of >5000 men and women who were ≥65 yr of age, 6.9% of whom were frail at baseline. More than 40,000 women between the ages of 65 and 79 were included in the Women's Health Initiative (WHI) cohort, which was used to establish the questionnaire-based frailty definition that was approximated in this study.[7] In that cohort, 16.3% of participants were classified as frail at baseline. Although the DMMS cohort had a mean age <60 yr, there was a higher prevalence of frailty than previously described among community-dwelling elderly individuals. Furthermore, our results are likely to be an underestimation of the prevalence of frailty in an unselected incident dialysis population because the Wave 2 cohort oversampled peritoneal dialysis patients and the subset of Wave 2 patients with complete data to allow assessment of frailty was somewhat healthier than the overall Wave 2 cohort (Table 1).

As in elderly community-based cohorts, frailty was found to be predictive of poor outcomes among patients with ESRD. These results are unique in that the population under study was an incident dialysis cohort that was not exclusively elderly. Furthermore, the lack of an interaction between age and frailty suggests that frailty or its components are relevant among younger and older dialysis patients.

Because this was the first study to examine the frailty construct among patients with ESRD, we were faced with the challenge of translating and validating criteria developed in otherwise healthy elderly populations to a population whose health is adversely affected by organ failure across a broader spectrum of age. We believe that the high proportion of frailty among young and middle-aged individuals with ESRD is especially noteworthy. Indeed, proposed mediators of accelerated decline in functioning, such as inflammation, oxidative stress, and endocrinopathies (*e.g.*, growth hormone and testosterone deficiency), are common and often severe in ESRD,[13–15] prompting some to propose ESRD as a model for accelerated aging.

Our results are consistent with the current understanding of the biologic underpinnings of frailty as a complex and cumulative expression of altered homeostatic responses to multiple stresses.[5] Such stresses could include chronic disease, aging, and an altered metabolic balance, manifested by cytokine overexpression and/or hormonal decline. The high proportion of frail patients in this cohort compared with those without kidney disease suggests that ESRD as a chronic disease may be a major contributor to the development of frailty such that it can occur in patients who are younger than those who typically are expected to be frail; however, aging also seems to be an independent contributor because the prevalence of frailty was associated with older age within the DMMS Wave 2 cohort.

The application of a frailty phenotype in this population allowed us to compare the prevalence and significance of frailty with that of several elderly cohorts in the literature. in this cohort, however, the individual components of frailty were independently associated with outcomes; therefore, a count of the number of these factors seems to provide a more nuanced assessment of risk for mortality and hospitalization than a single indicator of frailty. The information needed to determine patients' degree of frailty can be gathered relatively easily, making frailty assessment potentially useful in clinical practice.

This study has several strengths. Wave 2 of the DMMS was a nationally representative incident cohort, except for over-

Table 5. Multivariable analyses of the association of the components of frailty with outcomes individually (model 1) and in a combined model (model 2)[a]

Predictor	Death				Hospitalization or Death			
	Model 1		Model 2		Model 1		Model 2	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Frailty	2.24	1.60 to 3.15			1.56	1.36 to 1.79		
PF <75	2.30	1.48 to 3.57	2.07	1.33 to 3.24	1.53	1.30 to 1.80	1.41	1.19 to 1.66
Vitality <55	1.55	1.16 to 2.08	1.30	0.97 to 1.76	1.40	1.22 to 1.59	1.26	1.10 to 1.45
Inactive	1.82	1.45 to 2.28	1.79	1.42 to 2.25	1.25	1.12 to 1.40	1.20	1.07 to 1.35
Undernourished	1.75	1.32 to 2.32	1.79	1.35 to 2.37	1.24	1.05 to 1.47	1.24	1.05 to 1.47

[a]Each model is adjusted for the following variables: Age, gender, race, BMI, serum albumin, dialysis modality, comorbidities, employment status, marital status, and smoking. For each outcome, model 1 includes only individual components of frailty, and model 2 includes all of the components of frailty in the same adjusted model.

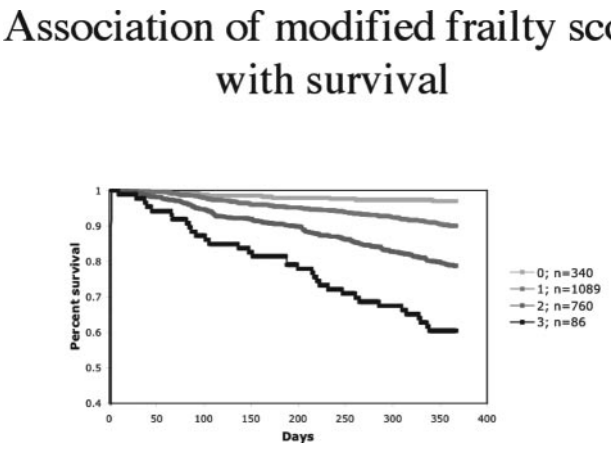

Figure 3. Association of modified frailty score with survival. Kaplan-Meier plot of the association between the modified frailty score and survival.

sampling of peritoneal dialysis patients to allow for comparisons between modalities. Comorbid conditions and laboratory data were assessed by qualified personnel after review of medical charts. The associations among frailty, mortality, and hospitalization were determined using multivariable methods to adjust for confounding.

The study also has several important limitations. First, it would have been interesting to evaluate frailty longitudinally in dialysis patients so that the cumulative effects of dialysis therapy on frailty could be explored. Second, blood samples were not taken in the DMMS Wave 2 study. It would have been informative to explore associations among frailty, inflammation, oxidative stress, and endocrinopathy. Third, the analysis was limited by data available in the DMMS Wave 2 questionnaires. In particular, the physical activity question and the assessment of undernourishment were crude measures. It is possible that more precise measures of these or measurement of actual physical performance would permit the development of a definition of frailty with better discriminative power than that developed with the current tools. Finally, the DMMS Wave 2 cohort seemed to be slightly younger and healthier than the general ESRD population (owing in part to the intended oversampling of home peritoneal dialysis patients), and patients who completed the Kidney Disease Quality of Life (KDQOL) seemed to be slightly healthier than the overall DMMS Wave 2 cohort; therefore, the prevalence of frailty in ESRD was probably underestimated, and the consequences may be even more severe than we have suggested here.

Using the USRDS DMMS Wave 2 cohort, we describe an exceptionally high prevalence of frailty in the ESRD population. Frailty and its components were strongly associated with mortality and hospitalization, even after adjustment for well-established risk factors across multiple domains. To date, the care of patients with ESRD has focused on the dosage of dialysis (defined by Kt/V_{urea}), management of anemia with erythropoietic stimulating proteins and intravenous iron, and management of CKD mineral bone disorder with phosphate binders and vitamin D derivatives. Interventions aimed at delaying functional decline and/or preventing disability have not been at the forefront of dialysis care. Identification of frailty early in the course of ESRD could lead to earlier or more intensive interventions to slow functional decline, which might reduce the need for hospitalization and reduce the risk for death among dialysis patients. Although we should not ignore dialysis dosage or the other laboratory parameters in ESRD, until we are able to delay or prevent pervasive functional decline, we cannot consider that we have delivered "adequate" dialysis.

CONCISE METHODS

Study Design

We used the USRDS DMMS Wave 2 to evaluate the cross-sectional prevalence of frailty and association of patient characteristics with frailty as well as to determine the association of frailty with mortality and hospitalization. The DMMS Wave 2 was a prospective study of 3931 incident dialysis patients who started dialysis therapy in 1996 or early 1997.[16] Wave 2 included approximately equal numbers of peritoneal dialysis and hemodialysis patients. Questionnaires about patients' baseline demographic characteristics, comorbid conditions, and laboratory data were completed by dialysis unit personnel, and responses were based on information from the patient's medical chart. A determination of nutritional status (undernourished or not) was made by the medical chart abstractor. Patients completed a ques-

tionnaire pertaining to quality of life, pre-ESRD care, modality choice, and rehabilitation at approximately 60 d after dialysis start.

The Wave 2 patient questionnaire incorporated items from the KDQOL instrument,[17] including 36 items known as the RAND-36 that are identical to items in the SF-36. In addition to KDQOL items, participation in physical activity was assessed by a single question that asked participants to report how often they exercised (did physical activity in their leisure time).[18] Wave 2 data were linked to the Patient Profile and Hospitalization files to ascertain time to death or first hospitalization within 1 yr of study start.

Definition of Frailty

A phenotype of frailty was established using criteria similar or identical to the modification by Woods *et al.* of Fried's criteria for frailty (Table 6)[7] Specifically, a score of <75 on the PF scale of the SF-36 was used as a marker of weakness and slowness, whereas a score of <55 on the vitality scale of the SF-36 was used to define poor endurance or exhaustion. Similar to Woods *et al.*, available physical activity data were substituted for the exact instrument originally used in the Fried criteria. In the DMMS Wave 2, patients who reported that they "almost never or never" exercised were

Table 6. Definitions of frailty in the CHS,[6] the WHI,[7] and the USRDS DMMS Wave 2

Components of Frailty	CHS	WHI	USRDS DMMS Wave 2
Slowness/ weakness	Slowness: Slowest quintile on a 15-ft walk test, stratified by gender and height Weakness: Weakest quintile in grip strength measured by handheld dynamometer, stratified by gender and BMI quartiles	Rand-36 PF <75. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf Lifting or carrying groceries Climbing several flights of stairs Climbing one flight of stairs Bending, kneeling, or stooping Walking more than a mile Walking several blocks Walking one block Bathing or dressing yourself	Rand-36 PF <75
Poor endurance/ exhaustion	Based on two questions from the CES-D Depression Scale: a. I felt that everything I did was an effort. b. I could not get going. How often in the last week did you feel this way? 0 = rarely or none of the time (<1 d) 1 = some or a little of the time (1 to 2 d) 2 = a moderate amount of the time (3 to 4 d) 3 = most of the time. Individuals answering 2 or 3 to either of these questions were categorized as meeting the exhaustion criterion.	Rand-36 Vitality <55 How much of the time during the last 30 d. . . Did you feel worn out? Did you feel tired? Did you have a lot of energy? Did you feel full of pep?	Rand-36 Vitality <55
Physical inactivity	Based on the short version of the Minnesota Leisure Time Activity questionnaire. The lowest quintile of activity stratified by gender was considered inactive.	Detailed physical activity questionnaire assessing frequency and duration of walking and mild, moderate, and strenuous activities. Kcal of weekly energy expenditure was calculated, and those in the lowest quartile were scored positive for inactivity.	How often do you *exercise* (do physical activity during your leisure time)? Daily or almost daily 4 to 5 times a week 2 to 3 times a week About once a week Less than once a week Almost never or never Individuals answering "almost never or never" were classified as inactive.
Unintentional weight loss	"In the last year, have you lost more than 10 pounds unintentionally (*i.e.*, not due to dieting or exercise)?" Individuals who responded "yes" met the weight loss criterion.	No measure was available at baseline. At follow-up, measured weight loss or subject-reported weight loss was used.	Undernourished or cachectic (malnourished), as assessed by data abstractor

classified as inactive. A classification of the patient as "undernourished" by dialysis staff (ascertained using information available in the medical chart within 30 d before study entry) was used in place of the criterion of unintentional weight loss used by Fried and Woods *et al.* A total of 5 points was possible, with 2 points for a low PF score and 1 point for each of the other criteria. Consistent with the modified definition of frailty developed by Woods *et al.*, patients scoring ≥3 were defined as frail.

Predictor Variables

To determine which variables were associated with frailty, we identified a set of factors *a priori* that we suspected might be associated with frailty and for which data were available in the DMMS Wave 2. These included such demographic factors as age, gender, and race; such comorbidity data as cigarette smoking (ever *versus* never smoked), diabetes, peripheral vascular disease, cardiac disease, cerebrovascular disease, and cancer; serum albumin concentration; body mass index; dialysis modality (peritoneal dialysis *versus* hemodialysis); level of education; and whether the patient had Medicaid coverage at dialysis start (as a surrogate for socioeconomic status). In addition, we evaluated the association between patients' preparedness to start dialysis and frailty, using early referral to a nephrologist, use of erythropoietin before dialysis, and use of a permanent vascular access among hemodialysis patients as indicators of better preparation.

Body mass index was calculated as weight in kilograms divided by height in meters squared and was divided into the following categories: <19, 19 to <25, 25 to <30, and ≥30 kg/m^2. These categories were chosen to conform to World Health Organization classifications of underweight, normal weight, overweight, and obese.[19] Albumin was entered into the models as a categorical variable using quartiles of serum albumin (<3.2, 3.2 to <3.5, 3.5 to <3.9, and ≥3.9 g/dl). Missing values (n = 196 [8%]) were imputed using multivariable linear regression.

Outcome Variables

Date of death was obtained from the Patients Standard Analysis File of the USRDS. Date of first hospitalization and first non–vascular access–related hospitalization after study entry were obtained from the DMMS Hospitalization Standard Analysis File. For determination of the date of first non–vascular access–related hospitalization, hospitalizations in which the primary diagnosis contained the following *International Classification of Diseases, Ninth Revision* codes were excluded: 996.1, 996.62, 996.74, 996.5, 996.7, or 996.73. The primary outcome variables were (*1*) time to death and (*2*) time to first all-cause hospitalization or death or time to first non–vascular access–related hospitalization or death up to 1 yr after study enrollment.

Statistical Analyses

Baseline characteristics for patients in the Wave 2 study with and without frailty data were compared by unpaired t test (continuous variables) and χ^2 analysis (categorical variables). Multivariable logistic regression analysis was used to determine which patient characteristics were associated with frailty at baseline. Survival analysis was conducted using a Cox proportional hazards regression model. Models were adjusted for the same set of predictor variables as already described. For determination of whether the effects of frailty varied according to patient age, gender, or race, interaction terms were added to each model. As a sensitivity analysis, hospitalization-related analyses restricted to patients who were ≥65 yr of age were also performed because of the possibility that some hospitalizations among younger patients might not have been captured by Medicare claims. For assessment of the relative contributions of the components of the frailty phenotype and whether the components were independently associated with outcomes, multivariable models of the association of the individual components of frailty with mortality and hospitalization or death were also constructed, along with models containing all of the components together. Two-tailed $P < 0.05$ was considered statistically significant. All analyses were completed using SAS 9.1 (SAS Institute, Cary, NC).

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DISCLOSURES

None.

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