Risk Factors for Frailty in a Large Prevalent Cohort of Hemodialysis Patients

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Abstract: *Background:* Although individuals with kidney disease, including those dependent on dialysis, often present clinically with signs and symptoms consistent with frailty, there is limited information about sociodemographic and clinical risk factors that may be associated. *Methods:* Seven hundred forty-five patients undergoing hemodialysis-between 2009 and 2011 in 7 Atlanta dialysis clinics and 7 San Francisco bay area dialysis clinics were assessed using the validated Fried frailty index (recent unintentional weight loss, reported exhaustion, low grip strength, slow walk speed, low physical activity) that defines frailty as the presence of 3 or more criteria. Study coordinators interviewed participants; measured grip strength, walk speed, and body composition; and reviewed records for clinical and laboratory parameters. Logistic regression models were used to estimate the association of patient characteristics with frailty. *Results:* In adjusted analyses, peripheral vascular disease and cardiac diseases, including dysrhythmia, atrial fibrillation, tachycardia, pericarditis, and cardiac arrest, were associated with higher odds for frailty, whereas black race and higher serum albumin concentration were associated with lower odds for frailty. *Conclusions:* In multivariable analyses, the risk for frailty in patients undergoing hemodialysis, as assessed by the presence of 3 or more criteria that comprise the Fried frailty index, was increased in association with peripheral vascular disease and cardiac conditions, such as dysrhythmia and atrial fibrillation, and was decreased for those with higher serum albumin concentration and for blacks compared with whites. Among patients who met the Fried definition of frailty, 78% scored as frail on walk speed and 56% scored as frail on grip strength, the 2 physical performance measures.

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Frailty is a construct that connotes a state of low physiologic reserve and vulnerability to stressors, conveying increased likelihood of adverse health outcomes. Thus, individuals identified as frail are more likely to incur the need for assistance with activities of daily living, to fall, to require institutionalization, and to die.[1,2] Although older adults have been the primary focus of research on frailty, there is increasing evidence that frailty is also associated with adverse health outcomes in chronic disease populations who are not exclusively geriatric.[3–8] This evidence includes a small number of studies of patients with chronic kidney disease[3,4] and dialysis-dependent end-stage renal disease (ESRD).[6–8]

The frailty index developed and validated by Fried et al is widely used to identify frailty.[9] Fried et al[1] characterized frailty as a syndrome marked by recent unintentional weight loss, poor endurance and energy (exhaustion), muscle weakness, slowed gait speed, and low physical activity, with the presence of 3 or more of these elements, providing an operational definition of frailty. Gyamiani et al[10] observed that individuals with kidney disease are especially likely to present with signs and symptoms consistent with components of the frailty syndrome, but empirical investigation remains limited. Studies that have explored frailty in ESRD patients undergoing dialysis lacked physical performance assessments or had limited power to detect subgroup differences because of small sample size.[6–8] In this study, we applied the Fried measurement protocol to assess frailty in a large cohort of ESRD patients undergoing conventional hemodialysis (HD) in outpatient dialysis clinics, which is the ESRD therapy used by approximately 400,000 treated ESRD patients in the United States.[11]

PATIENTS AND METHODS

Study Population

ACTIVE/ADIPOSE (A Cohort Study to Investigate the Value of Exercise in ESRD/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD) is a multicenter study of prevalent patients on HD coordinated by the United States Renal Data System (USRDS).[12] The data collection sites are 7 outpatient dialysis clinics in the Atlanta, GA metropolitan area, and 7 outpatient dialysis clinics in the San Francisco bay area, CA, at which 771 patients were enrolled and participated in baseline assessments during 2009 through 2011. Study participants included adults (≥18 years), who are English or Spanish speaking, who are on HD for at least 3 months, and who are capable of providing informed consent. Exclusion criteria included current treatment by peritoneal dialysis or home HD, evidence of active malignancy, and imminent geographic relocation; vulnerable populations (pregnant women, prisoners, persons with significant mental illness) were also excluded. Amputees and patients with previous or pending transplantation were eligible. Among eligible patients undergoing HD at the study clinics during the 2-year enrollment period, 85% provided informed consent and were enrolled. Reasons most frequently given by those who declined to participate were that they were "not interested," "too busy," or "enrolled in another study."

Institutional Review Boards at the Emory University and the University of California San Francisco approved the study, and all participants provided written informed consent. This report focuses on 745 participants who can be evaluated for

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frailty, that is, had information for 3 or more nonmissing components of the Fried index, as specified in the methodology described by Fried et al.[1] Only 26 study participants (3.4%) lacked sufficient information for determining frailty status based on the measures of Fried et al, and their sociodemographic characteristics did not differ significantly from the other 745 patients.

Measures and Data Collection

Indicators specified by Fried et al[1] were used to assess the 5 criteria that comprise the frailty index: (1) weight loss in the past 12 months; (2) poor endurance and energy; (3) weakness, defined by grip strength; (4) slowness, defined by timed walk speed; and (5) low physical activity level (Table 1). Data sources included a brief interview with participants, performance measures of grip strength and walk speed, measured height and waist circumference, and current clinical and laboratory data abstracted from medical records. The maximal grip strength in kilograms was identified from 3 trials in both hands. Walk speed was the fastest time in seconds from 2 trials to walk 15 feet at the participant's usual pace. Consistent with previous studies, participants unable to walk were classified in the slowest quintile for that indicator.[9] Physical performance was assessed before HD on the midweek treatment day, and consistency of measurement procedures among study coordinators was monitored by the investigators. Study coordinators rescheduled the physical performance assessments as needed to accommodate participants who were tired, ill, or otherwise declined to complete the physical assessments on an originally scheduled day.

Demographic variables, including age, sex, race, Medicaid coverage (socioeconomic indicator), primary ESRD diagnosis, and length of time since ESRD treatment start (ie, "vintage"), were ascertained from patient report and USRDS Standard Analysis Files. Race was reported by patients; for the small number of participants who declined to specify their race, race information was taken from the USRDS Medical Evidence Standard Analysis File. Age was categorized as $\geq$65 versus $<$65. ESRD therapy duration was categorized as 1 year or less versus more than 1 year because of the high morbidity and mortality known to be associated with patients' first year of therapy. Patients reported the highest education level that they had attained and their smoking history. Comorbidities and laboratory data were abstracted from clinic medical records. Body mass index was calculated in kilograms/square meter, using measured height and pre-HD weight recorded on the day that physical performance assessments were made.

Statistical Analyses

Sociodemographic and clinical characteristics of the study cohort were described using summary statistics (% and mean [standard deviation]). The association of sociodemographic and clinical characteristics with "frail" status was estimated in univariable and multivariable logistic regression models that included all variables for which the summary statistics indicated significant differences between frail and nonfrail participants, as well as gender, educational status, chronic obstructive pulmonary disease, body mass index, serum phosphate, and ESRD vintage $\leq$1 year. The interactions of age and vintage with all other variables were examined. In a sensitivity analysis, the race reference group was defined as white non-Hispanic, and white Hispanics, blacks, and others were then compared with this reference group.

Statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). Multivariable models included participants with data for all covariates; no missing data were imputed.

RESULTS

Patient Characteristics

The ACTIVE/ADIPOSE cohort was similar to the U.S. prevalent center HD population in sex distribution (59.5% male versus 55.7% male in the overall center HD population) and in the proportion of patients with diabetes and hypertension as primary causes of ESRD (71.1% versus 74.0% in the overall center HD population).[11] Higher proportions of black patients and patients of other races were represented, as would be expected from the selected study sites, and the overall age of the study population was younger (28.2% aged 65+ years versus 44.7% of the overall center HD population aged 65+ years). Most of the cohort (82%) had been receiving ESRD therapy for more than 1 year. The mean time since ESRD treatment start was 5.0 $\pm$ 5.1 years, with median vintage of 3.3 years. Participants' sociodemographic and clinical characteristics are shown in Table 2, for the cohort as a whole and separately for patients classified as frail and patients not classified as frail.

Association of Patient Characteristics With Frailty

In unadjusted associations of sociodemographic and clinical variables with frailty, participants classified as frail were less likely to be black. Participants classified as frail were more likely to be 65 years or older and to have diabetes and cardiovascular conditions, including congestive heart failure, coronary artery disease or myocardial infarction, cerebrovascular accident or transient ischemia attack, peripheral vascular

TABLE 1. Fried frailty index: criteria and indicators[1]

Frailty criteria	Indicators
Weight loss	Loss of $>$10 pounds in the past 12 months, unintentional
Exhaustion	Response of "a moderate amount of the time (3–4 d)" or "most of the time" to either of 2 CES-D scale items: "I felt that everything I did was an effort"; "I could not get going" during the past week
Weakness	Maximal grip strength in kilograms using Jamar handheld dynamometer. Lowest 20%, stratified by gender and BMI quartiles
Slowness	Time in seconds to walk 15 feet at usual pace. Slowest 20%, stratified by gender and standing height
Low physical activity level	Weighted score of kilocalories expended per week in physical activities "you have done in the past 2 wk" reported on short version of Minnesota Leisure Time Activity questionnaire. Lowest 20% for each gender
Frailty	Presence of 3 or more of the above criteria

BMI, body mass index; CES-D, Center for Epidemiologic Studies-Depression.