The Prevalence, Association, and Clinical Outcomes of Frailty in Maintenance Dialysis Patients

So-Young Lee, MD, PhD,* Dong Ho Yang, MD, PhD,* Eunah Hwang, MD, PhD,† Seock Hui Kang, MD, PhD,‡ Sun-Hee Park, MD, PhD,§ Tae Woo Kim, MD, PhD,¶ Duk Hyun Lee, MD, PhD,** Kisoo Park, MD, PhD,†† and Jun Chul Kim, MD, PhD‡‡

Objective: To investigate the clinical implications of frailty in chronic kidney disease patients undergoing maintenance hemodialysis and chronic peritoneal dialysis.

Design: In this prospective study, all of the participants completed the Short Form of the Kidney Disease Quality of Life questionnaire, Korean version, to determine their frailty phenotype. We also obtained blood chemistry and demographic data at enrollment. Data regarding the history of hospitalization and death were collected during the follow-up period.

Subjects: We recruited 1,658 patients (1,255 maintenance hemodialysis and 403 chronic peritoneal dialysis) from multidialysis units (n = 27). We excluded patients who had been hospitalized in the previous 3 months.

Main Outcome Measures: Hospitalization and survival rate during study period.

Results: The participants' mean age was 55.2 ± 11.9 years old, and 55.2% were male. Among the participants, 34.8% were rated as frail and 45.7% as prefrail. Multivariate analysis demonstrated significant associations of frailty with age, comorbidity, disability, unemployment, higher body mass index, and a lower educational level. During the follow-up period (median 17.1 months), 608 patients (79 not frail, 250 prefrail, and 279 frail) were hospitalized, and 87 patients (10 not frail, 24 prefrail, and 53 frail) died ($P < .001$). Frailty was associated with hospitalization (adjusted hazard ratio, 1.80; 95% confidence interval: 1.38-2.36) and mortality (hazard ratio, 2.37, 95% confidence interval: 1.11-5.02).

Conclusion: The frailty phenotype was common even in, prevalent end-stage renal disease patients on dialysis, and was significantly associated with higher rates of hospitalization and mortality.

Introduction

FRAILTY IS A biological syndrome characterized by decreased reserves and resistance to stressors resulting from cumulative decreases across multiple physiologic systems.[1-6] Frail individuals are therefore vulnerable to adverse outcomes, which can include disability, dependency, falls, institutionalization, hospitalization, and death.[1-7] The concept of frailty was primarily developed and has evolved to define geriatric syndromes, and chronological aging has been positively correlated with the increasing prevalence of the frail phenotype.[1,8]

According to annual reports from the United States Renal Data System, 44.5% of end-stage renal disease (ESRD) patients undergoing dialysis are aged 65 years and older,[9] and the prevalence per million continues to increase more rapidly among older age groups.[10] The Korean nationwide ESRD patient registry reported that the mean age of these patients has sharply increased from 55.2 years in 2005 to 60.3 years in 2014, and the proportion of people with ESRD aged 65 years and older increased from 28% to 40.7% during the same period.[11] The incidence and prevalence of ESRD have also been rising rapidly, especially in

*Department of Internal Medicine, Division of Nephrology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea.
†Department of Internal Medicine, Division of Nephrology, Keimyung University School of Medicine, Daegu, South Korea.
‡Department of Internal Medicine, Division of Nephrology, Yeungnam University Hospital, Daegu, South Korea.
§Department of Internal Medicine, Division of Nephrology, Kyungpook National University Hospital, Daegu, South Korea.
¶Department of Internal Medicine, Division of Nephrology, Soonchunhyang University Gumi Hospital, Gumi, South Korea.
**Department of Internal Medicine, Division of Nephrology, Daegu Fatima Hospital, Daegu, South Korea.
††Department of Preventive Medicine, School of Medicine Gyeongsang National University, Jinju, South Korea.
‡‡Department of Internal Medicine, Division of Nephrology, CHA Gumi Medical Center, CHA University, Gumi, South Korea.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Support: This research was supported by a grant of the Research Driven Hospital R&D project, funded by the CHA Bundang Medical Center (grant number: BDCHA R&D 2015-35).

Address correspondence to Jun Chul Kim, MD, PhD, 12, Sinsi-ro 10-gil, Gumi-si, Gyeongsangbuk-do 39295, South Korea. E-mail: truedoc1@hanmail.net

1051-2276/$36.00
http://dx.doi.org/10.1053/j.jrn.2016.11.003

people older than 65 years.[9,11] In addition, chronic kidney disease (CKD) per se accelerates the aging process at the cell, tissue, and organ level via protein energy wasting, various uremic toxins, inflammation, and oxidative stresses.[12–14] These combined effects of chronological and pathological aging could explain why the frailty phenotype is much more common in the CKD population regardless of dialysis therapy use and age, compared with the general population with no impairment of kidney function.[15–17]

Individuals with ESRD requiring dialysis still have high hospitalization and mortality rates despite continuous and vigorous efforts to reduce known related risk factors such as anemia, hypertension, inflammation, hyperparathyroidism, etc.[18–20] For this reason, it is important to identify other potential factors that may lead to the many adverse clinical outcomes in this population.

Several studies have examined the frailty phenotype and its clinical implications for ESRD patients on dialysis.[15,16,21–23] However, most of those studies focused on patients who were starting maintenance dialysis therapy, and data on peritoneal dialysis patients are limited. The aim of our study was to investigate the prevalence of the frailty phenotype and its relation to clinical outcomes such as hospitalization and mortality in maintenance hemodialysis (MHD) and chronic peritoneal dialysis (CPD) patients.

Methods

Subjects and Design

The inclusion criteria for MHD and CPD patients were as follows: (1) age $\geq$ 20 years, (2) dialysis duration $\geq$ 6 months, (3) no hospitalizations during the previous 3 months, except for vascular access repair, (4) able to ambulate with or without assistive devices, (5) sufficient cognitive function to communicate with the interviewer to complete the questionnaires without help from others, and (6) willingness to give informed consent. The exclusion criteria included the following: (1) any acute infectious or other inflammatory illnesses, (2) active cancer except basal cell carcinoma, and (3) current severe heart or lung failure with unstable vital signs.

The study participants were recruited from 27 dialysis centers in the Daegu/Kyungsangbuk-do area of South Korea. Eligible patients who met the inclusion criteria were recruited from July 2012 to December 2012. We followed them until December 31, 2014, to evaluate the associations of frailty status with hospitalization and mortality.

To minimize the likelihood of the study subjects misunderstanding the interview questions, well-trained interviewers directly administered the questionnaire, which consisted of the Kidney Disease Quality of Life questionnaire, Korean version,[24] and the physical activity pattern survey at enrollment and helped the participants complete it correctly. Demographic data and hospitalization and death records for the study period were obtained via medical record review. Cardiac diseases were defined when the patient had any medical history of angina pectoris, acute myocardial infarction, congestive heart failure, positive cardiac exercise test results, or interventions such as percutaneous transluminal coronary angioplasty or coronary artery bypass surgery. Cerebrovascular diseases were defined when the participant had any history of transient ischemic attack, cerebrovascular infarction, or hemorrhage. The blood test results are the averages of the monthly measurements obtained for the 3 months immediately prior to obtaining other study measurements to capture a reliable and consistent picture of each participant's condition. The blood chemistry data included hemoglobin, serum albumin, blood urea nitrogen (BUN), creatinine, potassium, total cholesterol, calcium, phosphate, intact parathyroid hormone (iPTH), total iron binding capacity (TIBC), and high-sensitive C-reactive protein.

This study was approved by the IRB of six medical school-affiliated hospitals (Keimyung University School of Medicine, Yeungnam University Hospital, Kyungpook national University Hospital, Soonchunhyang University Gumi hospital, Daegu Fatima Hospital, and CHA Gumi Medical Center at CHA University). All of the study subjects gave informed written consent.

Definition of Frailty

Our study adopted a definition of frailty with components that were identical or similar to those used in the Dialysis Morbidity and Mortality Study (DMMS) Wave 2,[15] which were modified from the frailty definitions of the Cardiovascular Health Study by Fried et al.[1] and the Women's Health Initiative Observational Study by Woods et al.[7] A trained interviewer asked the study participants questions pertaining to the frailty components of slowness, weakness, exhaustion, shrinking, and physical inactivity using the RAND 36-item Short Form (SF 36). We used a Korean version of the Kidney Disease Quality of Life SF 36™, which was linguistically validated.[25] The presence or absence of slowness and weakness was determined using of the Physical Function (PF) Scale of the SF 36, which consists of 10 items pertaining to physical activities usually performed during a typical day. The limitations of each physical activity were classified into 3 categories: "limited a lot," "limited a little," and "not limited at all," and each response yielded a score of 0, 50 or 100, respectively. The final score was determined by summing the scores for the 10 physical activity items and dividing the total by 10. A score lower than 75 on the PF scale of the SF 36 was considered to indicate slowness and weakness, thus counting for 2 points. Exhaustion was measured with vitality scale, consisting of four questions about how the respondent feels and how things have been during the previous 4 weeks as follows: "Did you feel full of pep?", "Did you have a lot of energy?", "Did you feel worn out?", and "Did you feel tired?" The average score for these 4 questions was calculated; exhaustion was indicated if the score was lower

than 55, and the patient then received 1 point. Shrinking was defined as the unintentional loss of more than 4.5 kg (10 pounds) or 5% of the baseline body weight (BW) for the past year; in such cases 1 point was added to the patient's score. Low regular physical activity of less than once per week during leisure time for the previous 3 months was considered physical inactivity and was scored as 1 point.

The points for each frailty component were totalled, and the possible scores ranged from 0 to 5 point(s). Participants with 3 or more points were considered "frail" and those with 1 or 2 points were considered "prefrail." Patients with 0 points were described as "not frail."

Definition of Disability

Upon enrollment, we asked the participants four questions regarding activities of daily living (ADLs), including whether they currently needed help from another person to have a meal, dress/undress, get out of bed/lie in bed and take a bath/shower. The respondents indicated the degree of their need for help to complete these physical activities with one of three responses: no need for help, some need for help and help is needed for the entire process. Disability was defined as the inability to perform at least one of the 4 domains of ADLs with no help.[7]

Statistical Analysis

The baseline characteristics of the patients in this study were compared with the frailty status data using the unpaired *t* test or ANOVA (continuous variables) and χ^2 analysis (categorical variables). Multivariable logistic regression analysis was used to determine the patient characteristics that were associated with frailty at baseline. A survival analysis was conducted using a Cox proportional hazards regression model. The models were adjusted for the same set of predictor variables, including age, sex, comorbidities, disability, dialysis modality, unemployment, body mass index (BMI), educational levels, serum albumin, iPTH, and hemoglobin. Two-tailed P values $< .05$ were considered statistically significant. All of the analyses were completed using SPSS software, for Windows (version 22; SPSS, Chicago, Ill., USA).

Results

Eligible patients (n = 1,658: 1,255 MHD and 403 CPD patients) were recruited from all prevalent maintenance dialysis patients (n = 2,737: 1,994 MHD and 743 CPD patients) at 27 dialysis centers to participate in this study (Fig. 1). The median follow-up period was 17.1 months. The baseline demographic and blood chemistry characteristics are described in Table 1. The mean age was 55.9 ± 12.9 years, 25.6% were aged 65 year old and older, 55.7% were male, and 39.4% had diabetes. The mean time on dialysis was 5.2 ± 4.5 years. Disability was observed in 19.1% of the patients.

Of the total study subjects, 577 (34.8%) and 757 (45.7%) patients met the study definitions of frail and prefrail

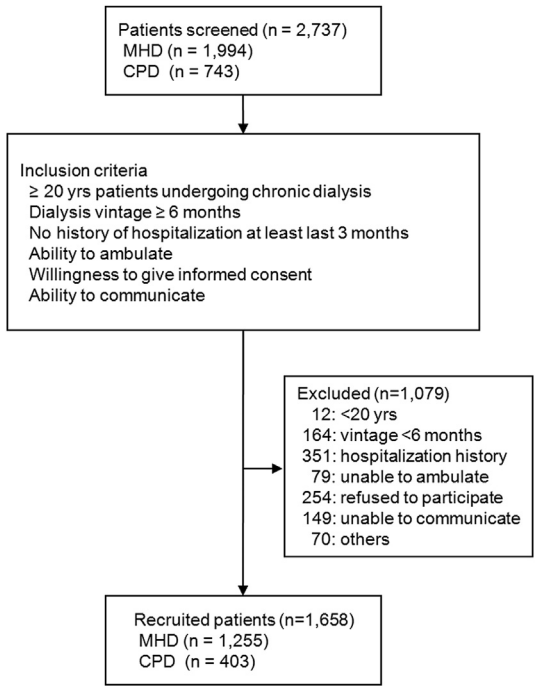

Figure 1. Study flow diagram. CPD, chronic peritoneal dialysis; MHD, maintenance hemodialysis.

groups, respectively (Table 1, Fig. 2). Figure 2 shows the increasing tendency of the prevalence of frailty as the patients became older and the decreasing tendency of the prevalence of prefrailty with age. In all age groups, a poor Vitality (VT) score (scored <55) was the most common factor among the frailty components, followed in order by inactivity, PF score <75 and shrinking (Fig. 2).

Maintenance dialysis patients who were female, older, had a higher BMI, were not employed, had a lower educational level, were disabled and with comorbid conditions, such as diabetes mellitus and cardiac and cerebrovascular disease, were significantly more likely to be frail, but dialysis modality and duration were not related to frailty (Table 1). Some nutritional markers in blood testing, such as BUN, serum creatinine, and TIBC, showed significantly negative relationships with frailty status; however, others, such as serum albumin, total cholesterol, and high-sensitive C-reactive protein, failed to show any significant relation to frailty. Lower serum levels of potassium and phosphorus were significantly associated with frailty (Table 1).

After adjustment for all related covariates (age, sex, unemployment, disability, BMI, education level, dialysis modality, comorbidity, hemoglobin, phosphorous, serum albumin, potassium, TIBC, iPTH, BUN, and creatinine), the variables that showed significant associations with frailty were age, comorbid conditions, disability, unemployment, higher BMI, and lower education level (Table 2).

Of the total group of patients, 608 (37%) were hospitalized at least once, 87 died, and 66 underwent kidney transplantation during the 30-month follow-up period. The

Table 1. Baseline Characteristics of Study Population According to Frailty Status

Characteristics	Overall (n = 1,658)	Not Frail (n = 324)	Prefrail (n = 757)	Frail (n = 577)	*P* Value
Male, n (%)	923 (55.7)	205 (63.3)	446 (58.9)	272 (47.1)	<.001
Age, y	55.9 ± 12.9	53.8 ± 11.6	53.1 ± 12.1	60.8 ± 13.2*	<.001
MHD, n (%)	1,255 (75.7)	251 (77.5)	581 (76.8)	423 (73.3)	.247
Vintage, y	5.2 ± 4.5	5.4 ± 4.6	5.2 ± 4.4	5.1 ± 4.5	.744
BMI, kg/m^2	22.4 ± 3.2	22.1 ± 2.9	22.2 ± 3.1	22.7 ± 3.6*†	.017
Employed, n (%)	440 (26.5)	103 (31.8)	263 (31.8)	74 (12.8)	<.001
Educational level, n (%)					<.001
6th grade	362 (21.9)	42 (13.0)	126 (16.7)	194 (33.6)	
7th-12th grade	947 (57.2)	187 (57.9)	456 (60.3)	304 (52.7)	
>12th grade	347 (21.0)	94 (29.1)	174 (23.0)	79 (13.7)	
Diabetes, n (%)	654 (39.4)	105 (32.4)	255 (33.7)	294 (51.0)	<.001
Cardiac, n (%)	255 (15.4)	37 (11.4)	92 (12.2)	126 (21.8)	<.001
Cerebrovascular, n (%)	145 (8.7)	24 (7.4)	44 (5.8)	77 (13.3)	<.001
Disability, n (%)	317 (19.1)	23 (7.1)	70 (9.2)	224 (38.8)	<.001
Hemoglobin, g/dL	10.4 ± 1.0	10.4 ± 0.9	10.4 ± 1.0	10.3 ± 1.1	.297
Albumin, mg/dL	3.7 ± 0.7	3.6 ± 0.8	3.8 ± 0.7*	3.7 ± 0.7†	.005
BUN, mg/dL	58.6 ± 16.3	59.6 ± 17.2	59.9 ± 15.5	56.3 ± 16.5*†	<.001
Creatinine, mg/dL	10.2 ± 3.1	10.5 ± 3.2	10.7 ± 3.2	9.4 ± 2.9*†	<.001
Potassium, mEq/L	5.0 ± 0.8	5.0 ± 0.8	5.1 ± 0.8	4.9 ± 0.8*†	<.001
T. cholesterol, ug/dL	154.3 ± 37.3	152.0 ± 36.9	154.8 ± 37.3	154.9 ± 37.2	.476
Calcium, mg/dL	8.6 ± 1.0	8.6 ± 1.0	8.7 ± 1.0	8.6 ± 1.0†	.070
Phosphate, mg/dL	5.2 ± 1.4	5.2 ± 1.4	5.4 ± 1.4*	5.0 ± 1.0*†	<.001
iPTH, pg/dL	278.9 ± 344.5	252.2 ± 248.0	297.4 ± 345.1	269.3 ± 386.6	.107
TIBC, ug/dL	228.9 ± 48.8	228.6 ± 49.9	234.5 ± 49.9	221.6 ± 45.9*†	<.001
hsCRP, mg/dL	0.7 ± 1.7	0.6 ± 1.7	0.6 ± 1.6	0.8 ± 1.7	.133

BMI, body mass Index; BUN, blood urea nitrogen; hsCRP, high-sensitive C-reactive protein; iPTH, intact parathyroid hormone; MHD, maintenance hemodialysis; T. cholesterol, total cholesterol; TIBC, transferrin iron binding capacity.

Post hoc analysis was done by LSD test.

*$P < .05$ versus not frail patients.

†$P < .05$ versus prefrail patients.

hospitalization rate was 24.4% for the nonfrail, 33.0% for the prefrail, and 48.4% for frail patients ($P < .001$). The causes of hospitalization included infectious diseases (29.3%), cardiovascular diseases (12.0%), gastrointestinal bleedings (11.4%), cerebrovascular disease (4.0%), and others (Table S1). The univariate analysis showed that the prefrail and frail patients were 1.4 (95% confidence interval [CI]: 1.07-1.78) and 2.4 (95% CI: 1.87-3.08) times more likely, respectively, to be hospitalized over the 30-month study period (Table S2). Moreover, the proportion of patients with two or more hospitalizations was significantly higher (25.3%) among the frail patients than among the

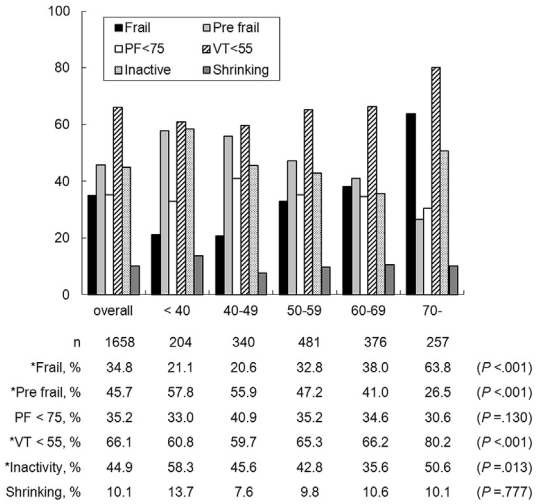

Figure 2. The prevalence of frailty and its components by age. *$P < .05$. PF, physical performance; VT, vitality.

Table 2. Predictors of Frailty Analyzed by Multiple Logistic Regression

Characteristics	OR (95% CI)	*P*
Age (per y)	1.03 (1.01-1.04)	<.001
Female gender	1.23 (0.92-1.63)	.157
Diabetes	1.44 (1.11-1.87)	<.001
Cardiac	1.43 (1.01-1.98)	.029
Cerebrovascular	1.56 (1.04-2.35)	.031
Disability	5.60 (4.12-7.62)	<.001
Dialysis modality (PD)	1.11 (0.77-1.61)	.571
Unemployed	1.89 (1.36-2.62)	<.001
BMI (kg/m^2)	1.06 (1.02-1.10)	.002
Education level		
≤6th grade	1.00 (referent)	
7th-12th grade	0.67 (0.49-0.91)	.012
>12th grade	0.53 (0.35-0.82)	.010
Albumin (g/dL)	1.23 (0.98-1.55)	.069

BMI, body mass index; CI, confidence interval; OR, odds ratio; PD, peritoneal dialysis.

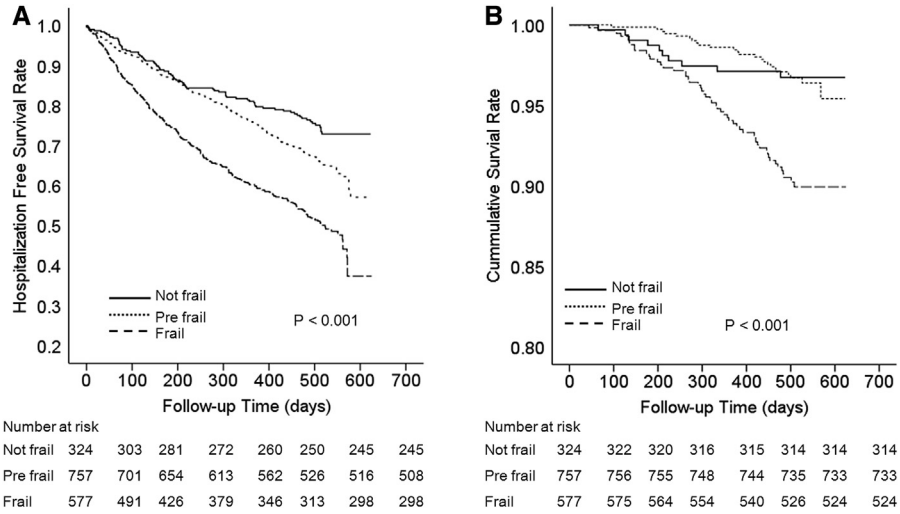

Figure 3. (A) Kaplan–Meier estimates of hospitalization-free survival probability of chronic dialysis patients in relation to frailty status and (B) Kaplan–Meier estimates of cumulative survival probability of chronic dialysis patients in relation to frailty status.

nonfrail (9.6%) and prefrail (12.5%) patients ($P < .001$, Table S3). Figure 3 shows the lower hospitalization-free survival and cumulative survival rates in the frail group compared with the prefrail or nonfrail groups ($P < .001$). After adjustment for age, sex, comorbidities, dialysis modality, disability, serum albumin and creatinine, and the other factors shown in Table 3, frailty remained significantly associated with hospitalization (adjusted hazard ratio [HR], 1.80; 95% CI: 1.38-2.36; Table 3). However, prefrail status was not related to hospitalization after those adjustments (Table 3).

The mortality rates were 3.1% for nonfrail, 3.2% for prefrail, and 9.2% for frail patients ($P < .001$) during the study period. The three most common causes of death were infection-related (24.1%), cardiovascular (23%), and cerebrovascular diseases (12.6%), in that order (Table S1). The univariate analysis indicated that the frail patients were three times more likely to die during the follow-up period than the patients in the other groups (HR, 3.05; 95% CI: 1.55-6.00; Table S2). This significant relationship persisted even after adjustments for multiple other potential risk factors of mortality (HR, 2.37; 95% CI: 1.11-5.02; Table 3). Prefrailty did not show any significant associations with mortality in either the univariate or multivariate analysis (Table 3).

Discussion

This study indicates that the overall prevalence of the frailty phenotype in patients undergoing maintenance dialysis therapy was substantially high (34.8%) compared with

Table 3. Multivariable Analysis of the Association of Frailty With Mortality and Hospitalization

	Mortality		Hospitalization	
Characteristics	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Status of frailty				
Prefrail	1.01 (0.48-2.12)	.980	1.29 (1.00-1.67)	.050
Frail	2.08 (1.04-4.16)	.039	1.83 (1.41-2.37)	<.001
Age (y)	1.03 (1.01-1.05)	.002	1.01 (1.00-1.02)	.012
Female gender	0.56 (0.36-0.88)	.012	0.77 (0.64-0.93)	.006
Diabetes	2.07 (1.30-3.29)	.002	1.52 (1.59-2.31)	<.001
Cardiac	2.22 (0.42-1.13)	.137	1.43 (1.17-1.75)	.001
Dialysis modality (PD)	1.97 (1.18-3.28)	.010	1.92 (1.59-2.31)	<.001
Unemployed	1.83 (0.97-3.69)	.091	1.41 (1.13-1.77)	.003
BMI (kg/m^2)	0.91 (0.85-0.97)	.006	0.99 (0.97-1.02)	.563
iPTH (pg/dL)	1.00 (1.00-1.01)	.012	1.00 (1.00-1.01)	.002
Hemoglobin (g/dL)	0.76 (0.62-0.92)	.006	0.89 (0.83-0.97)	.006
Education level				
≤6th grade	—	—	1.00 (referent)	
7th-12th grade	—	—	0.92 (0.75-1.15)	.469
>12th grade	—	—	0.60 (0.43-0.81)	.001

BMI, body mass Index; CI, confidence interval; iPTH, intact parathyroid hormone; PD, peritoneal dialysis.

that of community-dwelling older adults (6.9% in the Cardiovascular Health Study and 16.3% in the women's Health Initiative Observational Study),[1,7] although our study population was relatively young (74.4% were younger than 65 years old) and in stable physical condition according to the inclusion criteria described above.

Even in predialysis stage, CKD patients are more likely to be frail than people with normal kidney function. Shilpak et al.[17] reported a higher prevalence of frailty in CKD patients than in those without renal dysfunction (15% vs. 6%; $P < .001$) and an increasing trend as kidney function decreased. Consistent findings have been observed in populations with CKD stages 1-4[26,27] and in the Third National Health and Nutrition Evaluation Survey.[28]

Much higher prevalence of frailty has been reported in CKD patients on dialysis than in the predialysis CKD population. Johansen et al.[15] reported that the frailty prevalence of incident hemodialysis and peritoneal dialysis patients was 67.7% in the DMMS Wave 2, and it was 73.3% for the Comprehensive Dialysis Study participants.[21] Our study reported a frailty prevalence among CKD patients on dialysis (34.8%) that was higher than that of the predialysis CKD patients and much lower than that of the in incident dialysis patients from the DMMS Wave 2 and Comprehensive Dialysis Study. Other studies including subjects on prevalent MHD showed frailty prevalence from 13.8% to 41.8%.[16,29,30]

The reasons CKD patients are more likely to be frail are thought to be: (1) a trend toward a rapidly increase in the number of elderly CKD patients,[9,11,14] (2) a "premature" or "accelerating" aging process caused by CKD itself,[12-14,31] and (3) the combination of aging and CKD.[14] The differences in the frailty prevalence among CKD patients could be caused by the different definitions of frailty that each study adopted.[32-34] We adopted the modified Fried frailty criteria based on self-report, which can be easily implemented in routine clinical practice and has been validated in frailty studies of CKD patients.[32-34] This modified Fried criteria has proven to be predictive of adverse outcomes such as hip fracture, disability, hospitalization, and mortality in large population–based studies.[7] However, several reports have shown that this tool tended to overestimate the frailty prevalence compared with the use of objective criteria.[32]

The factors shown to be significantly related to the frailty phenotype in this study (older age, comorbidities, disability, unemployment, higher BMI and lower education level; Table 2) were found also in other frailty studies of the general population[1] and CKD patients receiving dialysis,[15,21,29] but differences also exist. Johansen et al.[15] showed that female gender and dialysis modality (MHD) were significant predictors of frailty, but we did not. Some studies reported that a low serum albumin level had a positive relationship with frailty,[15,30] whereas others did not.[21] This inconsistency seems to result from differences in the characteristics of study populations, the complexity of pathophysiology depending on the CKD stage, the collected/analyzed data, the definition of frailty, and other factors.

The adverse effects of frailty on clinical outcomes have been widely examined in people without or with CKD across all stages. Large-scale prospective frailty studies have revealed high HRs of disability (HR, 1.79-3.15), hip fracture (HR, 1.57), hospitalization (HR, 1.27-1.95), and mortality (HR, 1.63-2.24) in elderly community-dwelling people.[1,7] Frailty was also significantly associated with high risks of death and dialysis initiation (HR, 2.0-2.5) in predialysis CKD patients.[26,28] More falls or fractures (HR, 1.60),[22] earlier or more frequent hospitalization (HR, 1.26-1.56), and higher mortality (HR, 1.22-2.60) were also significantly associated with the frailty phenotype in incident and prevalent dialysis patients.[15,16,21,23] In our study, the frailty phenotype was also associated with higher risks of hospitalization (HR, 1.80; 95% CI: 1.38-2.36; Table 3) and mortality (HR, 2.37; 95% CI: 1.11-5.02; Table 3) in the multivariate analysis. These associations of adverse clinical outcomes with frailty described in our study are consistent with and comparable to the results of other studies.

Our study had several strengths. First, it included large number of participants (n = 1,658) recruited from 27 dialysis centers for the specific subgroup of prevalent dialysis patients, that is, ambulatory ESRD patients with no recent admission history. Second, a relatively large proportion of CPD patients (n = 403) was also included. Third, well-trained study assistants interviewed all of the study participants directly to minimize misunderstandings when completing the questionnaire.

There are also several limitations. First, we did not use a physical performance–based definition of frailty; rather, we adopted self-reported (perceived) constructs to define frailty. It has been reported that perceived frailty reports tend to overestimate the frailty prevalence, compared with measured frailty.[32-34] However, considering the prevalence rate and significant associations with adverse health outcomes shown in this study, the modified criteria for the frailty construct that we used seemed to be quite reliable and more easily applicable than the classic criteria, especially for this type of large-scale study. Second, no significant clinical implications of prefrailty were found here, whereas other studies have reported a significant relationship between prefrailty or intermediate frailty and an increased mortality risk in people with CKD on dialysis.[15,16,23] We suggest that the follow-up period of future studies be sufficiently long to prove the clinical significance of prefrailty in the CKD population.

Practical Application

The findings show a high prevalence of frailty in ambulatory chronic dialysis patients without a recent admission

history. The frail phenotype is significantly associated with hospitalization and mortality. Therefore, we should pay more attention to the frailty status of patients, even those who appear to be in a good condition, to improve their morbidity and mortality.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1053/j.jrn.2016.11.003.

References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-M156.
2. Lipsitz LA, Goldberger AL. Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. *JAMA*. 1992;267:1806-1809.
3. Buchner DM, Wagner EH. Preventing frail health. *Clin Geriatr Med*. 1992;8:1-17.
4. Bortz WM 2nd. The physics of frailty. *J Am Geriatr Soc*. 1993;41:1004-1008.
5. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. *Age Ageing*. 1997;26:315-318.
6. Hamerman D. Toward an understanding of frailty. *Ann Intern Med*. 1999;130:945-950.
7. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc*. 2005;53:1321-1330.
8. Lam M, Jassal SV. The concept of frailty in geriatric chronic kidney disease (CKD) patients. *Blood Purif*. 2015;39:50-54.
9. Collins AJ, Foley RN, Chavers B, et al. US renal data system 2013 annual data report. *Am J Kidney Dis*. 2014;63:A7.
10. Saran R, Li Y, Robinson B, et al. US renal data system 2014 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2015;66:S1-S305. Svii.
11. Jin DC. Major changes and improvements of dialysis therapy in Korea: review of end-stage renal disease registry. *Korean J Intern Med*. 2015;30:17-22.
12. Stenvinkel P, Larsson TE. Chronic kidney disease: a clinical model of premature aging. *Am J Kidney Dis*. 2013;62:339-351.
13. Kooman JP, Broers NJ, Usvyat L, et al. Out of control: accelerated aging in uremia. *Nephrol Dial Transplant*. 2013;28:48-54.
14. Kim JC, Kalantar-Zadeh K, Kopple JD. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J Am Soc Nephrol*. 2013;24:337-351.
15. Johansen KL, Chertow GM, Jin C, et al. Significance of frailty among dialysis patients. *J Am Soc Nephrol*. 2007;18:2960-2967.
16. McAdams-DeMarco MA, Law A, Salter ML, et al. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *J Am Geriatr Soc*. 2013;61:896-901.
17. Shlipak MG, Stehman-Breen C, Fried LF, et al. The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis*. 2004;43:861-867.
18. Kalantar-Zadeh K, Block G, Humphreys MH, et al. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int*. 2003;63:793-808.
19. Longenecker JC, Coresh J, Powe NR, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol*. 2002;13:1918-1927.
20. Beto JA, Bansal VK, Gohlke NP, et al. Using the hemodialysis prognostic nutrition index and urea reduction ratio to predict morbidity and mortality: a pilot study of the 1995 council on renal nutrition national research question. *J Ren Nutr*. 1998;8:21-24.
21. Bao Y, Dalrymple L, Chertow GM, et al. Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med*. 2012;172:1071-1077.
22. Delgado C, Shieh S, Grimes B, et al. Association of self-reported frailty with falls and fractures among patients new to dialysis. *Am J Nephrol*. 2015;42:134-140.
23. Alfaadhel TA, Soroka SD, Kiberd BA, et al. Frailty and mortality in dialysis: evaluation of a clinical frailty scale. *Clin J Am Soc Nephrol*. 2015;10:832-840.
24. Park HJ, Kim S, Yong JS, et al. Reliability and validity of the Korean version of Kidney Disease Quality of Life instrument (KDQOL-SF). *Tohoku J Exp Med*. 2007;211:321-329.
25. Park KS, Cho MH, Ha IS, et al. Validity and reliability of the Korean version of the pediatric quality of life ESRD module. *Health Qual Life Outcomes*. 2012;10:59.
26. Roshanravan B, Khatri M, Robinson-Cohen C, et al. A prospective study of frailty in nephrology-referred patients with CKD. *Am J Kidney Dis*. 2012;60:912-921.
27. Dalrymple LS, Katz R, Rifkin DE, et al. Kidney function and prevalent and incident frailty. *Clin J Am Soc Nephrol*. 2013;8:2091-2099.
28. Wilhelm-Leen ER, Hall YN, K Tamura M, et al. Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. *Am J Med*. 2009;122:664-671.
29. Johansen KL, Dalrymple LS, Delgado C, et al. Association between body composition and frailty among prevalent hemodialysis patients: a US renal data system special study. *J Am Soc Nephrol*. 2014;25:381-389.
30. Kutner NG, Zhang R, Huang Y, et al. Risk factors for frailty in a large prevalent cohort of hemodialysis patients. *Am J Med Sci*. 2014;348:277-282.
31. Walker SR, Wagner M, Tangri N. Chronic kidney disease, frailty, and unsuccessful aging: a review. *J Ren Nutr*. 2014;24:364-370.
32. Painter P, Kuskowski M. A closer look at frailty in ESRD: getting the measure right. *Hemodial Int*. 2013;17:41-49.
33. Johansen KL, Dalrymple LS, Delgado C, et al. Comparison of self-report-based and physical performance-based frailty definitions among patients receiving maintenance hemodialysis. *Am J Kidney Dis*. 2014;64:600-607.
34. Salter ML, Gupta N, Massie AB, et al. Perceived frailty and measured frailty among adults undergoing hemodialysis: a cross-sectional analysis. *BMC Geriatr*. 2015;15:52.