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Original Investigation

A Prospective Study of Frailty in Nephrology-Referred Patients With CKD

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Background: Frailty is a construct developed to characterize a state of reduced functional capacity in older adults. However, there are limited data describing the prevalence or consequences of frailty in middle-aged patients with chronic kidney disease (CKD).

Study Design: Observational study.

Setting & Participants: 336 non–dialysis-dependent patients with stages 1-4 CKD with estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 (by the CKD-EPI [CKD Epidemiology Collaboration] serum creatinine–based equation) or evidence of microalbuminuria enrolled in the Seattle Kidney Study, a clinic-based cohort study. Findings were compared with community-dwelling older adults in the Cardiovascular Health Study.

Outcome: Prevalence and determinants of frailty in addition to its association with the combined outcome of all-cause mortality or renal replacement therapy.

Measurements: We defined frailty according to established criteria as 3 or more of the following characteristics: slow gait, weakness, unintentional weight loss, exhaustion, and low physical activity. We estimated kidney function using serum cystatin C concentrations ($eGFR_{cys}$) to minimize confounding due to relationships of serum creatinine levels with muscle mass and frailty.

Results: The mean age of the study population was 59 years and mean $eGFR_{cys}$ was 51 mL/min/1.73 m^2. The prevalence of frailty (14.0%) was twice that of the much older non-CKD reference population ($P < 0.01$). The most common frailty components were physical inactivity and exhaustion. After adjustment including diabetes, $eGFR_{cys}$ categories of <30 and 30-44 mL/min/1.73 m^2 were associated with a 2.8- (95% CI, 1.3-6.3) and 2.1 (95% CI, 1.0-4.7)-fold greater prevalence of frailty compared with GFR_{cys} ≥60 mL/min/1.73 m^2. There were 63 events during a median 987 days of follow-up. After adjustment, the frailty phenotype was associated with an estimated 2.5 (95% CI, 1.4-4.4)-fold greater risk of death or dialysis therapy.

Limitations: Cross-sectional study design obscures inference regarding temporal relationships between CKD and frailty.

Conclusions: Frailty is relatively common in middle-aged patients with CKD and is associated with lower $eGFR_{cys}$ and increased risk of death or dialysis therapy.

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INDEX WORDS: Frailty; chronic kidney disease; mortality; functional limitation.

Frailty is a construct that originally was designed by gerontologists to describe cumulative declines across multiple physiologic systems that occur with aging. The frailty phenotype incorporates disturbances across interrelated domains to identify individuals who have diminished functional reserve, which places them at risk of adverse health outcomes.[1,2] Across diverse populations, the frailty phenotype consistently is associated with future risks of disability, institutionalization, hospitalization, and premature death.[3-5] The prevalence of frailty is associated strongly with advancing age; nonetheless, even for very old adults, strategies such as exercise conditioning have been shown to counteract physical frailty.[6]

Chronic kidney disease (CKD) is a state of accelerated metabolic aging, evidenced by accumulation of advanced glycation end products, oxidative stress,

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chronic inflammation, insulin resistance, vascular calcification, and osteoporosis.[7-10] Given that many of these physiologic mechanisms and conditions are associated with frailty in older people, it is conceivable that frailty might be highly prevalent in middle-aged and younger patients with CKD and may serve as a useful construct to summarize the cumulative burden of physiologic impairments that occur in this setting. Individuals who have CKD often present with signs and symptoms that may be consistent with the frailty syndrome.[11-13]

Previous studies of frailty in CKD have been conducted in either community-based studies,[14] in which the prevalence and severity of CKD are low, or long-term dialysis patients,[15] for whom metabolic disturbances are most severe. Moreover, previous studies have focused exclusively on older individuals with CKD and used nonstandardized methods to describe the frailty phenotype.[16] The prevalence, determinants, and long-term consequences of frailty in middle-aged patients with CKD not treated with dialysis are unknown.

In this study, we determine the prevalence of frailty in a cohort of patients with CKD not treated with dialysis using established methodology. We then delineate associations of frailty with kidney function and disability and estimate associations of individual frailty components and the frailty phenotype with risk of death or initiation of long-term dialysis therapy.

METHODS

Study Population

The Seattle Kidney Study (SKS) is a clinic-based prospective cohort study of non–dialysis-dependent patients with CKD based in Seattle, WA. The SKS was designed to evaluate long-term complications of CKD with an emphasis on physical functioning measurements. The SKS began recruiting in 2004 from outpatient nephrology clinics at Harborview Medical Center and the Veterans Affairs Puget Sound Medical Center. General SKS eligibility criteria are age older than 18 years and CKD stages 1-4 not currently requiring dialysis. The presence of CKD was defined as estimated glomerular filtration rate by the serum creatinine–based CKD-EPI (CKD Epidemiology Collaboration) equation ($eGFR_{cr}$) <90 mL/min/1.73 m^2 or the presence of albuminuria (urine albumin-creatinine ratio >30 mg/g from a 12-hour urine collection). Exclusion criteria are an expectation that the patient will start renal replacement therapy or leave the area within 3 months, kidney transplant, dementia, institutionalization, participation in a clinical trial, non–English speaking, or inability to undergo the informed consent process. Institutional review boards at the University of Washington and Veterans Affairs Puget Sound Health Care System approved the SKS and all participants provided written informed consent.

For the purpose of this study, we analyzed SKS participants who were alive and not on dialysis therapy at the time the study initiated frailty assessments in August 2006 (Fig 1). From 462 potential SKS participants, we excluded 100 who did not complete the frailty assessment and 26 who were ineligible, leaving 336 participants for analysis (Fig 1). Compared with participants who did not complete the frailty assessment, those included in the study were on average younger (aged 59 vs 66 years), had a higher eGFR by the nonstandardized cystatin C CKD-EPI equation (51 vs 41 mL/min/1.73 m^2), and had a lower proportion of diabetes (51% vs 72%) and activity of daily living (ADL) disability (6% vs 28%; Table S1, available as online supplementary material).

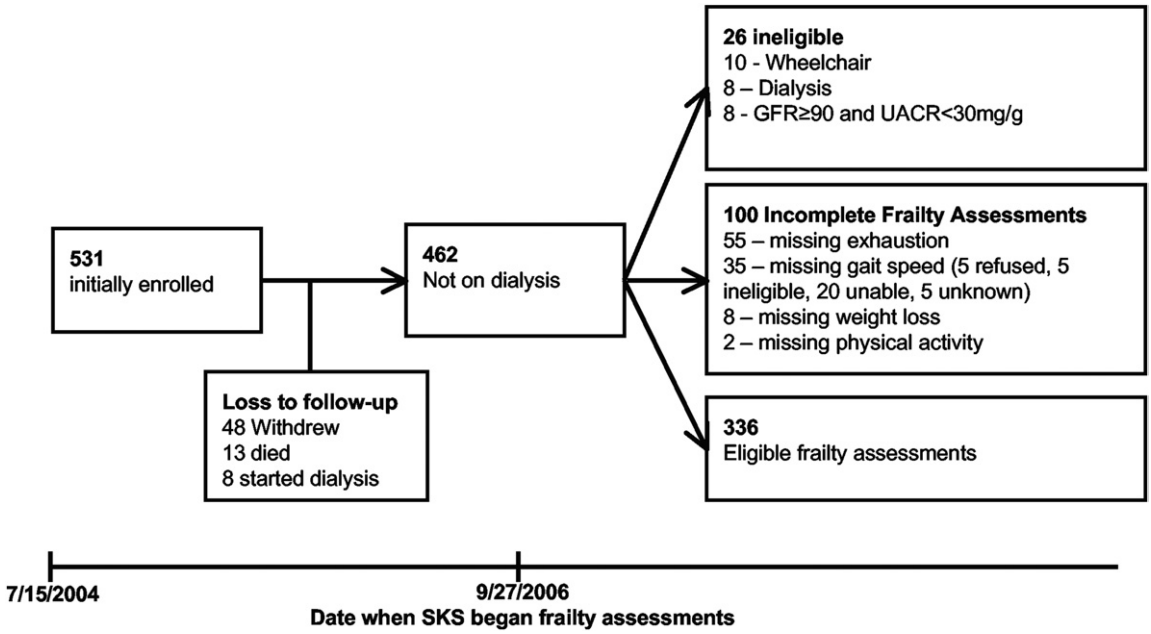

Figure 1. Flow diagram of Seattle Kidney Study (SKS) participants included in this study. Abbreviations: GFR, glomerular filtration rate (estimated by the serum creatinine-based CKD-EPI equation and given in mL/min/1.73 m^2); UACR, urine albumin-creatinine ratio.

Table 1. Operational Definitions and Prevalence of Frailty

	CHS (mean age 76 y)		SKS (mean age 59 y)	
	Definition	Prevalence	Definition	Prevalence
Weight loss	Self-reported ≥10-lb unintentional weight loss in past y	6%	Self-reported ≥10-lb unintentional weight loss in past 6 mo	10%
Weakness	Lowest sex- and BMI-specific 20th percentile grip strength	20%	Same absolute cutoffs as CHS[1,17]	16%
Low activity	Lowest sex-specific 20th percentile kcal/wk[a]	20%	Self-reported exercise <1×/wk	35%
Exhaustion	Positive response to either exhaustion item on CES-D[b]>	17%	Lowest 20th percentile exhaustion score on SF-36[c]	32%
Slowness	Lowest sex- and height-specific 20th percentile walking pace assessed over 15-ft course	20%	Same absolute cutoffs as CHS; walking pace assessed over 4-m (13.1-ft) course	26%
Frailty	—	7%	—	14%
Intermediate frailty	—	47%	—	52%

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CHS, Cardiovascular Health Study; SF-36, 36-Item Short Form Health Survey (from RAND Corp); SKS, Seattle Kidney Study.

[a]Physical activity kilocalories per week measured using Minnesota Leisure Time Activity questionnaire.

[b]Exhaustion items on the CES-D are "I felt that everything I did was an effort," and "I could not get going."

[c]Percentile score on the SF-36 derived from adults 65 years and older used to create the standard normal (score <37.5).

Assessment of Frailty

We defined frailty using slight modifications of criteria originally established by Fried et al[1] for exhaustion, physical activity, and self-reported weight loss (Table 1; Item S1), which were based on data from the Cardiovascular Health Study (CHS), a community-based study of adults 65 years and older. We defined frailty as the presence of at least 3 of the following 5 conditions: unintentional weight loss, weakness, exhaustion, slow gait, and inactivity. We defined an intermediate frailty phenotype as having 1 or 2 of these conditions. We defined weight loss as an unintentional 10-lb weight loss during the previous 6 months based on responses to the SKS questionnaire compared with during 12 months in the CHS. We measured grip strength in each participant's dominant hand using an analogue dynamometer (Takei Scientific Instruments Co, Ltd, www.takei-si.co.jp/en/index.html) and analyzed the maximal reading from 3 consecutive efforts. We defined weakness by grip strength less than the lowest sex- and body mass index (BMI)-specific 20th percentile score in the CHS.[1,17] We performed usual gait speed assessments twice per participant walking at his or her normal pace over a 4-m course and analyzed the faster of the 2 in meters per second. We defined a slow walk as gait speed less than the lowest sex- and height-specific 20th percentile in the CHS.[1,17] We scored the 4-item energy/fatigue domain of the 36-Item Short-Form Health Survey (SF-36) and defined exhaustion as a score less than the lowest 20th percentile for adults older than 65 years from the SF-36 normogram sample compared with a positive response to either the exhaustion item on the Center for Epidemiologic Studies Depression Scale in the CHS. We assessed physical activity from self-reported exercise habits similar to a prior study of frailty in participants with end-stage renal disease.[15] Participants who reported never exercising or exercising less than once weekly were considered to be physically inactive compared to the CHS, which defined physical activity as the lowest sex-specific quintile kilocalories per week.

Measurement of Covariates

Prevalent diseases were defined based on participant responses to the SKS questionnaire, medication use, laboratory findings, and hospitalizations that occurred after initial SKS enrollment, but prior to frailty assessment (see Item S1 for prevalent disease definitions). Medication use was assessed by the inventory method at the Harborview Medical Center study site and using the electronic pharmacy database at the Veterans Affairs Puget Sound Medical Center study site; missing medication data were completed by chart review. At each study visit, SKS study coordinators measured blood pressure and collected serum, plasma, and 12-hour timed urine samples on the same day as the frailty assessment. Three seated blood pressure measurements were recorded 5 minutes apart using an automated sphygmomanometer and the average of the last 2 readings was used for analysis. Samples were centrifuged for 20 minutes at 3,300 RPM, transferred to cryovials, and stored at −80°C. General chemistries were measured from frozen serum using a Beckman-Coulter DXC autoanalyzer (www.beckmancoulter.com). We measured serum cystatin C and C-reactive protein (CRP) concentrations using a Siemens Nephelometer (www.medical.siemens.com) that used a particle-enhanced immunonephelometric assay (N Latex Cystatin C).[18] Calibration of cystatin C was performed using manufacturer's standards along with daily quality controls to ensure a coefficient of variation <15%. All samples were analyzed using assays from the same lot.

Intra- and interassay coefficients of variation for cystatin C measured from 20 serum samples run in triplicate were 2.59% and 1.08%, respectively. We measured urinary albumin concentration by immunoturbimetry and urinary creatinine concentration by the modified Jaffé method.

A priori, we decided to use cystatin C–based estimates of GFR for this study due to the relationship between serum creatinine level and muscle mass and frailty. We used the CKD-EPI equation that incorporates nonstandardized cystatin C (CysC) level, age, sex, and race to calculate eGFR: $eGFR_{cys} = 127.7 \times CysC^{-1.17} \times age^{-0.13} \times (0.91 \text{ if female}) \times (1.06 \text{ if black})$.[19] Cystatin C– and serum creatinine–based equations provide similar precision and accuracy compared with gold-standard radioisotope dilution methods.[19,20] We also evaluated eGFR using the original serum creatinine–based CKD-EPI equation[21] (which uses isotope-dilution mass spectrometry–traceable serum creatinine level) as a secondary exposure (denoted $eGFR_{cr}$).

Assessment of Disability

Physical function was assessed by asking about difficulties with 15 tasks of daily life, including ADLs, instrumental ADLs (IADLs), and mobility tasks.[22] Mobility tasks include the ability to walk from room to room, walk up one flight of stairs, and walk half a mile. In keeping with previous studies, we categorized ADLs, IADLs, and mobility disabilities as the presence of one or more disability versus none.[1]

Follow-up and Outcomes

Study coordinators contacted participants by telephone every 6 months and in person every year through annual study examination to assess renal outcomes of long-term renal replacement therapy or kidney transplant. Coordinators assessed vital status using medical record review, contact with family members, and the Social Security Death Index.

Statistical Analyses

We calculated the unadjusted prevalence of frailty as the number of frail individuals divided by the total number of individuals in the study population. We indirectly compared the unadjusted prevalence of frailty in the SKS to that of the CHS reference population using a z test for proportions, and we estimated 95% confidence intervals (CIs) by referencing the binomial distribution. We categorized $eGFR_{cys}$ and $eGFR_{cr}$ using a priori–accepted categories of ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2. We used Poisson regression with robust variance estimation to estimate cross-sectional associations of kidney function with the prevalence of frailty (yes vs no) after adjustment for potential confounding variables. We prefer Poisson regression to logistic regression when the outcome of interest is not rare in order to best model the relative risk. We used a Cox proportional hazards model with robust standard variance estimation to estimate associations of frailty components with time to death or dialysis therapy after adjustment for potential confounding variables. Sensitivity analysis was performed excluding those from the analysis who started dialysis therapy less than 90 days after the study enrollment.

We investigated groups of potential confounding factors using nested multivariate models: model 1 adjusted for age, sex, and race (white vs nonwhite); model 2 added diabetes, BMI, prevalent cardiovascular disease, and log(CRP). We performed sensitivity analysis using a third model, which added education, systolic blood pressure, albumin level, and hemoglobin level. Given 12% missing data for education, we performed multiple imputation for this variable using chained equations.[23] We tested for a multiplicative interaction among $eGFR_{cys}$, albuminuria, and frailty by including a product term in the model ($eGFR_{cys}$ × log[albuminuria]) and testing its significance with the Wald test. Parallel analyses were performed using $eGFR_{cr}$. All analyses were conducted using Stata, version 11.2 (Stata Corp, www.stata.com).

RESULTS

Characteristics of the Cohort

For the entering cohort, mean age was 59±13 (25th-75th percentile, 51-67) years, 81% of participants were men, 26% were African American, and 51% had prevalent diabetes (Table 2). Median $eGFR_{cys}$ for the cohort was 46 (25th-75th percentile, 32-63) mL/min/1.73 m^2.

Prevalence of Frailty

There were 47 SKS participants who met criteria for frailty, resulting in an unadjusted prevalence of 14.0% (95% CI, 10.5%-18.2%; Table 1). The unadjusted prevalence of intermediate frailty was 51.8%. In contrast, the unadjusted prevalence of frailty was 7.0% for the reference CHS population (mean age, 74 years) that was used to create the frailty definition ($P < 0.001$). For male and female SKS participants, the prevalence of frailty was 13% and 17%, respectively. For diabetic patients, the prevalence of frailty was 18% compared with 10% for nondiabetic patients. The most common frailty components in the SKS cohort were inactivity (35.1%), exhaustion (31.8%), and slowness (25.9%).

Characteristics of Frail Individuals

Frail participants in the SKS were more likely to be African American; more likely to have prevalent diabetes, heart failure, and angina; and more likely to be obese (Table 2). Weight was a major distinction between frail (mean BMI, 34.7±9.8 [SD] kg/m^2) versus nonfrail (mean BMI, 30.8±6.8 kg/m^2) study participants. Frail individuals also had lower $eGFR_{cys}$ and higher urine albumin-creatinine ratios compared with those who were not frail. Consistent with decreased kidney function, frail individuals had lower hemoglobin and albumin concentrations and higher serum CRP and phosphorus concentrations. In contrast, the mean age of frail versus nonfrail participants in the SKS was similar (58.0 vs 58.9 years).

Association of Kidney Function With Frailty

The prevalence of frailty for $eGFR_{cys}$ categories ≥45 mL/min/1.73 m^2 was 8.1% (Fig 2A). Prevalence estimates increased sharply to 21.6% and 18.7% for $eGFR_{cys}$ categories of 30-44 and <30 mL/min/1.73 m^2, respectively. After adjustment for age, sex, and race, relative prevalences of frailty for $eGFR_{cys}$ categories of 30-45 and <30 mL/min/1.73 m^2 were 3.3 (95% CI, 1.5-7.4) and 2.6 (95% CI, 1.1-5.9), respectively, compared to $eGFR_{cys}$ ≥60 mL/min/1.73 m^2 (Table 3). After further adjustment for diabetes, prevalent cardiovascular disease, and CRP level, prevalence estimates were decreased, but the trend across $eGFR_{cys}$ categories remained statistically significant (P for trend = 0.01). When participants were stratified according to both kidney function and albuminuria status, a higher prevalence of frailty was observed for both measures of reduced kidney function in combination (P for interaction = 0.06; Fig 2B). A parallel sensitivity analysis using $eGFR_{cr}$ did not show an association of $eGFR_{cr}$ with frailty (Table S2).

Sensitivity analysis adding hemoglobin level, albumin level, systolic blood pressure, education, and antidepressant use to the model modestly attenuated the strength of association between $eGFR_{cys}$ and frailty.

Table 2. Characteristics of Seattle Kidney Study Participants Who Completed the Frailty Assessment

			Frail	
	% Complete	All (N = 336)	No (n = 289)	Yes (n = 47)
Demographic data	100			
VA Medical Center		158 (47)	139 (48)	19 (40)
Harborview Medical Center		178 (53)	150 (52)	28 (60)
Age (y)		58.7 ± 13.0	58.9 ± 13.1	58.0 ± 12.6
Male sex		272 (81)	236 (82)	36 (77)
Race	100			
White		225 (67)	195 (67)	25 (53)
Black		86 (26)	69 (24)	17 (36)
Hispanic		10 (3)	9 (3)	1 (2)
Other		15 (4)	16 (6)	4 (9)
Education	88			
Some high school or less		43 (15)	39 (15)	4 (10)
Completed high school		162 (55)	137 (53)	25 (64)
Completed college or more		91 (30)	81 (32)	10 (26)
Current smoking	99	63 (19)	53 (19)	10 (22)
Current alcohol use	99	117 (35)	103 (36)	14 (30)
Physical examination data				
SBP (mm Hg)	100	132.5 ± 19.9	132.1 ± 19.3	135.1 ± 23.6
Body mass index (kg/m^2)	100	31.4 ± 7.4	30.8 ± 6.8	34.7 ± 9.8
Obese	100	174 (52)	144 (50)	30 (64)
Waist circumference (in)	98	42.2 ± 6.8	41.8 ± 6.5	45.1 ± 8.2
Laboratory data				
$eGFR_{cys}$ (mL/min/1.73 m^2)	100	50.9 ± 27.1	52.5 ± 27.6	41.1 ± 21.3
$eGFR_{cr}$ (mL/min/1.73 m^2)	100	46.4 ± 25.5	47.2 ± 25.4	41.6 ± 25.9
Creatinine (mg/dL)	100	2.1 ± 1.3	2.0 ± 1.2	2.5 ± 1.7
Urine albumin (mg/g Cr)	97	111.5 [13.9-688.7]	102 [10.0-592.9]	311.2 [52.6-1,395.7]
Hemoglobin (g/dL)	90	13.0 ± 2.0	13.2 ± 2.0	12.2 ± 1.9
Bicarbonate (mEq/L)	100	24.5 ± 3.6	24.4 ± 3.5	24.9 ± 4.3
CRP (mg/dL)	99	2.4 [0.9-5.3]	2.1 [0.9-5]	3.8 [1.0-8.0]
LDL-C (mg/dL)	95	104.0 ± 44.0	103.3 ± 43.4	114.9 ± 46.7
HDL-C (mg/dL)	100	39.6 ± 15.6	39.5 ± 15.4	39.8 ± 16.8
Serum albumin (g/L)	100	3.8 ± 0.6	3.9 ± 0.6	3.6 ± 0.7
Phosphate (mg/dL)	100	3.8 ± 0.8	3.7 ± 0.8	4.1 ± 1.0
Prevalent diseases				
Diabetes	99	170 (51)	140 (49)	30 (64)
Heart failure	100	49 (15)	35 (12)	14 (30)
COPD	98	85 (26)	76 (27)	9 (20)
Myocardial infarction	100	56 (17)	46 (16)	10 (21)
Angina	100	79 (24)	63 (22)	16 (34)
PVD	100	78 (23)	66 (23)	12 (26)
Stroke	100	44 (13)	38 (13)	6 (13)
Any CVD	100	145 (43)	123 (43)	22 (47)
Cancer	79	35 (13)	28 (12)	7 (18)
Current dialysis access	100	16 (5)	12 (4)	4 (9)
Medications	99			
Statin		189 (57)	162 (57)	27 (57)
ACEi or ARB		252 (76)	217 (76)	35 (74)
Any antihypertensive		309 (93)	263 (92)	46 (98)
Antianginal		28 (8)	22 (8)	6 (13)
Erythropoietin		13 (4)	12 (4)	1 (2)
Antidepressant		110 (33)	89 (31)	21 (45)

Note: Values for categorical variables given as number (percentage); values for continuous variables given as mean ± standard deviation or median [25th-75th percentile].

Abbreviations and definitions: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; $eGFR_{cr}$, estimated glomerular filtration rate calculated by the serum creatinine–based CKD-EPI equation; $eGFR_{cys}$, estimated glomerular filtration rate calculated by the CKD-EPI equation incorporating nonstandardized cystatin C level, age, sex, and race; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PVD, peripheral vascular disease; SBP, systolic blood pressure; VA, Veterans Administration;.

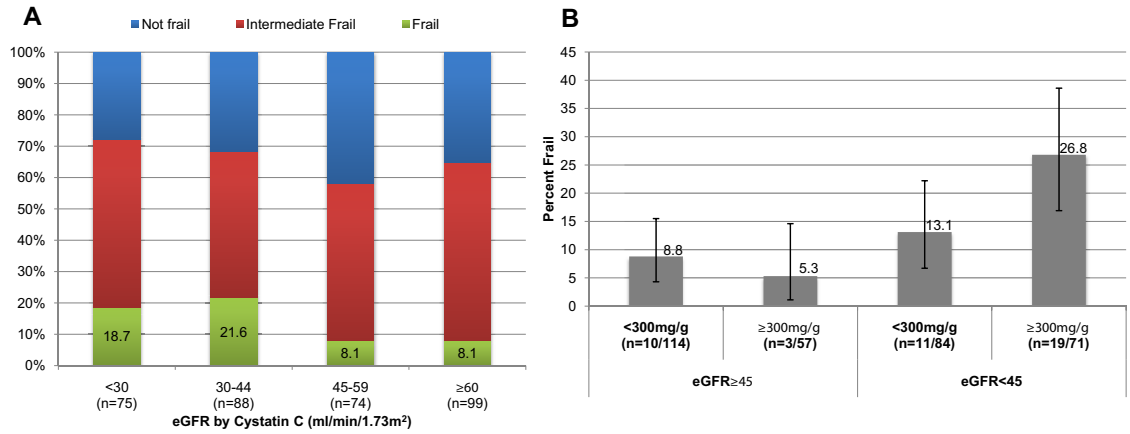

Figure 2. (A) Prevalence of frailty and intermediate frailty by estimated glomerular filtration rate (eGFR) calculated from serum cystatin C concentration. (B) Prevalence of frailty by eGFR and urine albumin excretion (*P* for interaction = 0.06). Error bars represent 95% confidence interval. Numbers under each bar graph represent number of frail participants over total in each category of cystatin C–based eGFR and albuminuria (<300 vs ≥300 mg/g).

In this analysis, relative prevalences for $eGFR_{cys}$ categories of 30-45 and <30 mL/min/1.73 m^2 were 2.38 (95% CI, 0.98-5.79) and 2.14 (95% CI, 0.83-5.51), respectively, compared with $eGFR_{cys}$ ≥60 mL/min/1.73 m^2 (*P* for trend = 0.06).

Association of Frailty With Disability

Disabilities in ADLs, IADLs, and mobility were each more common for frail versus nonfrail study participants (Fig 3). The proportions of frail individuals who had at least one ADL, IADL, and mobility disability were 15%, 60%, and 40%, respectively. In comparison, the proportions of nonfrail individuals with at least one ADL, IADL, and mobility disability were 5% ($P = 0.009$), 28% ($P < 0.001$), and 18% ($P = 0.001$), respectively.

Association of Frailty Components With Death or Dialysis

Median follow-up was 967 days; range, 1 day to 4.8 years. Thirty-five participants initiated dialysis therapy, whereas 30 participants died before dialysis therapy, for a total of 65 participants (19%). Median time to death was 794 days (range, 27 days to 4 years). Median time to initiation of dialysis therapy was 514 days (range, 1 day to 3.9 years). The unadjusted rate of the combined end point was 63 events/1,000 person-years in those who had no frailty components compared with 181 events/1,000 person-years in those

Table 3. Association of Kidney Function With Frailty Prevalence in the Seattle Kidney Study

	Frail Cases (no./no. at risk)	Model 1 (n = 336)	Model 2 (n = 336)
$eGFR_{cys}$			
≥60 mL/min/1.73 m^2	8/99	1.0 (reference)	1.0 (reference)
45-59 mL/min/1.73 m^2	6/74	1.3 (0.5-3.6)	1.2 (0.4-3.3)
30-44 mL/min/1.73 m^2	19/88	3.3 (1.5-7.4)	2.8 (1.3-6.3)
<30 ml/min/1.73m^2	14/75	2.6 (1.1-5.9)	2.1 (1.0-4.7)
$eGFR_{cys}$ *P* for trend		0.01	0.01
Age (per 10-y older)		0.9 (0.7-1.1)	0.9 (0.8-1.2)
Nonwhite race		1.8 (1.1-3.1)	1.9 (1.1-3.3)
Female		0.9 (0.5-1.6)	1.2 (0.6-2.2)
BMI (per 5-kg/m^2 difference)		—	1.2 (1.0-1.4)
Diabetes		—	1.4 (0.8-2.4)
Any cardiovascular disease		—	1.0 (0.6-1.7)
Log(CRP)		—	1.2 (0.9-1.5)

Note: Except where indicated, values shown are prevalence ratio (95% confidence interval). Model 1: eGFR, sex, age, race (white vs other). Model 2: model 1 + BMI + diabetes + any cardiovascular disease + log(CRP).

Abbreviations: BMI, body mass index; CRP, C-reactive protein; $eGFR_{cys}$, estimated glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration equation incorporating nonstandardized cystatin C level, age, sex, and race.

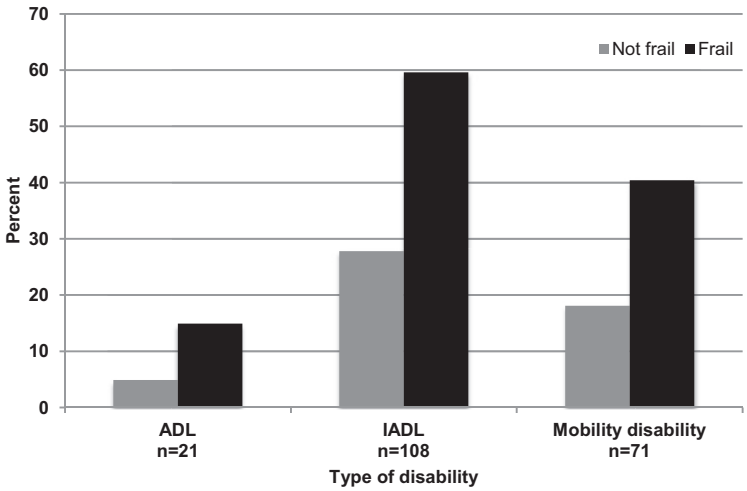

Figure 3. Disability according to frailty status. Numbers under each bar represent number of each disability. Abbreviations: ADL, activities of daily living, IADL, instrumental activities of daily living.

who had 3 or more frailty components. After adjustment for age, sex, BMI, $eGFR_{cys}$, diabetes, and cardiovascular disease, the frailty phenotype was associated with a 2.5 (95% CI, 1.4-4.4)-fold greater risk of death or dialysis therapy. Of the individual frailty components, weight loss, physical inactivity, and slow gait speed were associated most strongly with the combined end point (Fig 4; Table S3). Risk of death or dialysis therapy appeared to be 1.5-fold greater in those with diabetes (95% CI, 0.9-2.87; $P = 0.2$) and 1.6-fold greater in those with cardiovascular disease (95% CI, 0.9-2.7; $P = 0.1$), but these associations did not reach statistical significance (Table S3).

DISCUSSION

In a cohort of patients with CKD not requiring dialysis, the prevalence of the frailty phenotype was 14%. This prevalence estimate is 2-fold greater than that of the reference population used to establish the frailty phenotype, which was on average 15 years older. The most common frailty components in individuals with CKD were low physical activity, exhaustion, and slow gait speed. After adjustment for diabetes and other comorbid conditions, frailty was associated strongly with obesity and reduced kidney function, but not with age. In particular, the prevalence of frailty was substantially greater for those with $eGFR_{cys}$ <45 mL/min/1.73 m^2. The frailty phenotype in CKD was associated with disability across multiple domains. Furthermore, the frailty phenotype was associated with greater risk of death or dialysis after adjustment for diabetes and other comorbid conditions. These findings suggest that the frailty construct is useful as a measure for global comorbid disease burden in persons with CKD.

The original frailty construct characterized a wasting disorder of older age with weight loss as a diagnostic criterion.[1] When the classic definition of frailty

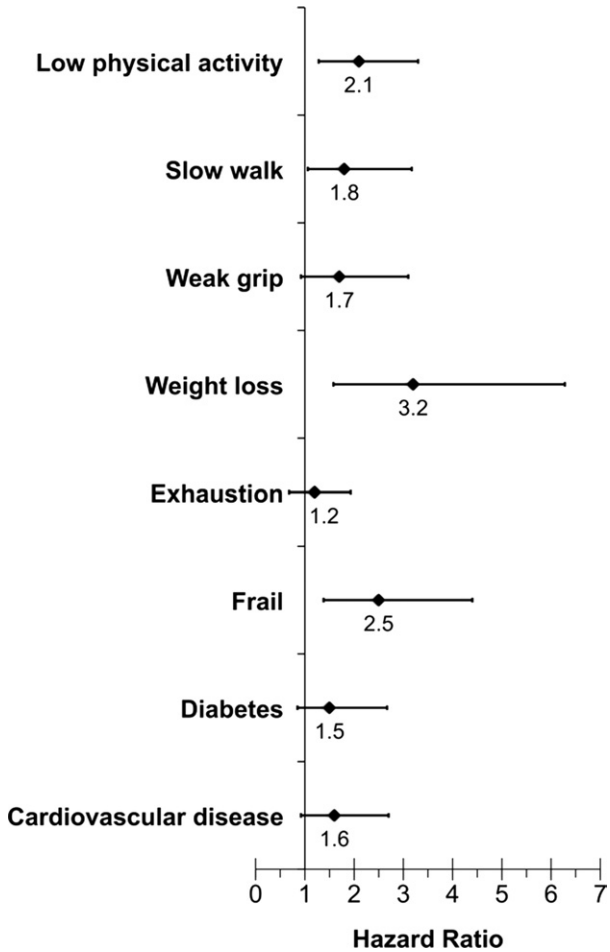

Figure 4. Forest plot of adjusted hazard ratios for death or dialysis therapy comparing individual frailty components to the frailty phenotype and comorbid conditions. Error bars represent 95% confidence interval. Estimated hazard ratios are adjusted for age, sex, body mass index, diabetes, cardiovascular disease, and $eGFR_{cys}$ (cystatin C–based estimated glomerular filtration rate). Abbreviations: DM, diabetes mellitus; CVD, cardiovascular disease.

was applied to a middle-aged CKD population, frail individuals were found to be generally obese and physically inactive with frequently reported symptoms of exhaustion. In parallel with obesity, we found evidence for skeletal muscle dysfunction in individuals with CKD, demonstrated by the relatively high prevalence of low grip strength and slow walking speed that were similar to those of much older adults in the general population. These findings suggest a phenotype of altered body composition in CKD in which fat mass is increased and effective skeletal muscle mass and function are reduced.

There are many physiologic consequences of CKD and obesity that may increase the risk of frailty. Kidney disease is known to adversely affect muscle structure and metabolic function through mechanisms of chronic inflammation, protein-energy wasting, and insulin resistance,[24-27] all of which overlap with physiologic impairments associated with frailty.[28,29] Pathophysiologic processes and complications of obesity are intertwined with those of kidney disease.[30,31] Obesity and metabolic syndromes have been shown to contribute to an elevated risk of progressing to end-stage renal disease.[32] Purported mechanisms of renal and muscle dysfunction in obesity include oxidative stress and endothelial dysfunction mediated in part by insulin resistance and inflammatory adipokines and cytokines.[33,34] Despite the elevated BMI in obese individuals, percent muscle mass has been demonstrated to be lower and associated with poor muscle quality.[35]

Previous associations of obesity with frailty suggest a biological link through heightened inflammation, insulin resistance, and decreased muscle quality.[35,36] CKD and obesity culminate in a final common pathway toward frailty; sarcopenia, which links the metabolic effects of CKD to functional consequences. Furthermore, the distinguishing characteristics of frailty in our study, exhaustion, inactivity, and weakness, suggest an adverse impact of nondialysis CKD on sarcopenic obesity, a process previously described in both the general and dialysis populations.[37,38] Our findings strengthen and extend previously reported associations of CKD with frailty, suggesting that the malnutrition-inflammation complex of CKD may predispose to frailty in a younger cohort without stereotypic features of hypercatabolic wasting prior to the onset of dialysis therapy.

Our study has several limitations. First, the cross-sectional study design obscures inference regarding temporal relationships between CKD and frailty. However, longitudinal follow-up confirms that the frailty construct is associated with higher risk of mortality or progression to dialysis therapy. Second, generalizability of our findings may be limited due to study of only 2 clinic sites characterized by a high proportion of male patients with CKD. Further studies are needed to confirm these findings in women with CKD. Nonetheless, the fact that physical frailty is more common in community-dwelling older adult women than men[1,39] may suggest that our estimates are conservative. Third, estimates of frailty in those with $eGFR_{cys}$ <30 mL/min/1.73 m^2 were similar to $eGFR_{cys}$ of 30-44 mL/min/1.73 m^2. This likely is the result of random sampling error and the lower number of participants in the lowest $eGFR_{cys}$ category. In addition, there are multiple non-GFR factors associated with cystatin C in addition to BMI and CRP, such as proteinuria and white blood cell count, that may contribute to residual confounding.[40,41] Nonetheless, frailty was associated more closely with $eGFR_{cys}$ than for creatinine-based estimates, which showed no association. This may be a consequence of confounding by muscle mass on the association between creatinine-based estimates of GFR and frailty consistent with findings from the Health, Aging, and Body Composition Study demonstrating a U-shaped association between creatinine-based eGFR and physical performance.[42] Fourth, our findings cannot reliably separate whether frailty in individuals with CKD is attributable to the complex burden of comorbid illnesses found in even moderately reduced kidney function or results from direct complications of kidney failure. Given the known overlap of cardiovascular disease with frailty and biologic effects of uremia on skeletal muscle impairment, it is likely that both processes contribute. Finally, there was a large number of individuals missing completed frailty assessments. However, the observation that individuals with missing frailty assessments had worse kidney function and a greater comorbid burden suggests that the estimate of frailty prevalence may be conservative. Nonetheless, these findings point out the high degree of multidomain functional impairment in the CKD setting as a means to inform clinicians and researchers about the nature of the problem and encourage further investigations in this area.

In summary, we document a high prevalence of frailty in a middle-aged cohort of individuals with CKD and show an increased risk of mortality or long-term renal replacement therapy associated with the frailty phenotype. Further studies are needed to probe potential pathophysiologic mechanisms and elucidate potential health consequences of the frailty phenotype in individuals with CKD. Such research could lead to successful treatment strategies in frail persons with CKD. One particular strategy may be resistance exercise conditioning, which has been shown to counteract muscle weakness and physical frailty in older adults.[6] Similarly, a small randomized controlled trial of resistance training and low-protein

diet in persons with CKD demonstrated improvements in muscle mass, strength, nutritional status, and decreased interleukin 6 levels compared with a low-protein diet alone.[43,44] Resistance exercise–induced increase in muscle mitochondrial content was associated with decreased inflammation in CKD and insulin sensitivity in diabetic patients.[45,46] A more recent study suggests that exercise-induced autophagy is one potential mechanism leading to improved glucose tolerance.[47] However, the potential benefit of early exercise intervention on counteracting the consequences of the adverse metabolic environment of kidney failure in frail persons with CKD on outcomes of disability or progression to dialysis therapy or death remains to be investigated.

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SUPPLEMENTARY MATERIAL

Table S1: Comparison of missing and study participants.

Table S2: Association of kidney function and other clinical characteristics with the prevalence of frailty.

Table S3: Risk of death or maintenance dialysis among individual frailty components, the frailty construct, and individual comorbidities.

Item S1: Supplementary methods.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2012.05.017) is available at www.ajkd.org

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