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Association of Slopes of Estimated Glomerular Filtration Rate With Post–End-Stage Renal Disease Mortality in Patients With Advanced Chronic Kidney Disease Transitioning to Dialysis

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Abstract

Objective: To investigate the association of estimated glomerular filtration rate (eGFR) slopes before dialysis initiation with cause-specific mortality after dialysis initiation.

Patients and Methods: In this retrospective cohort study of 18,874 US veterans who had transitioned to dialysis from October 1, 2007, through September 30, 2011, we examined the association of pre–end-stage renal disease (ESRD) eGFR slopes with all-cause, cardiovascular, and infection-related mortality during the post-ESRD period over a median follow-up of 2.0 years (interquartile range, 1.1-3.2 years). Associations were examined using Cox models with adjustment for potential confounders.

Results: Before the 18,874 patients transitioned to dialysis, 4485 (23.8%), 5633 (29.8%), and 7942 (42.1%) experienced fast, moderate, and slow eGFR decline, respectively, and 814 (4.3%) had increasing eGFR (defined as eGFR slopes of less than −10, −10 to less than −5, −5 to <0, and ≥0 mL/min per 1.73 m^2 per year). During the study period, a total of 9744 all-cause, 2702 cardiovascular, and 604 infection-related deaths were observed. Compared with patients with slow eGFR decline, those with moderate and fast eGFR decline had a higher risk of all-cause mortality (adjusted hazard ratio [HR], 1.06; 95% CI, 1.00-1.11; and HR, 1.11; 95% CI, 1.04-1.18, respectively) and cardiovascular mortality (HR, 1.11; 95% CI, 1.01-1.23 and HR, 1.13; 95% CI, 1.00-1.27, respectively). In contrast, increasing eGFR was only associated with higher infection-related mortality (HR, 1.49; 95% CI, 1.03-2.17).

Conclusion: Rapid eGFR decline is associated with higher all-cause and cardiovascular mortality, and increasing eGFR is associated with higher infection-related mortality among incident dialysis cases.

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Despite numerous advances in our understanding of chronic kidney disease (CKD) progression, the incidence of end-stage renal disease (ESRD) remains exceedingly high. Each year, as many as 115,000 patients transition from advanced non–dialysis dependent CKD (NDD-CKD) to maintenance dialysis in the United States.[1] Furthermore, patients who newly initiate dialysis treatment experience the highest mortality within the first few months after the transition to dialysis.[1-3] In order to improve outcomes in this vulnerable population, intense study and dedicated efforts are needed to identify modifiable risk factors and interventions that may ameliorate the exceptionally high mortality risk of this transition period.[4] At this time, the optimal approach to transitioning patients from NDD-CKD to maintenance dialysis remains unclear.

In recent years, there has been growing interest in the association between change in kidney function and risk of adverse outcomes. Several studies have found strong associations between change in estimated glomerular filtration rate (eGFR) over 1 year and risk of ESRD,[5,6] cardiovascular disease,[7,8] and mortality[5,7-10] among patients with NDD-CKD.

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However, these studies have focused primarily on patients with relatively preserved kidney function, and only a few studies have examined the association between increasing eGFR trajectory and risk of adverse outcomes.[6,11-14] Other than one study in patients with advanced CKD,[15] no previous studies have examined the association of change in eGFR including increasing eGFR in late-stage NDD-CKD with cause-specific mortality after dialysis initiation.

In this study, we investigated the association of eGFR slopes before dialysis initiation with all-cause, cardiovascular, and infection-related mortality after dialysis initiation in a national cohort of US veterans with advanced CKD transitioning to dialysis.

PATIENTS AND METHODS

Study Population

We analyzed data from the Transition of Care in Chronic Kidney Disease study, a retrospective cohort study examining US veterans transitioning to dialysis from October 1, 2007, through September 30, 2011. A total of 52,172 US veterans were identified from the US Renal Data System (USRDS)[1] as an initial cohort. In this study, we used only outpatient serum creatinine measurements available from Veterans Affairs (VA) medical centers because of the potential fluctuation of serum creatinine levels among sick inpatients. Therefore, patients whose serum creatinine levels were measured outside the VA medical centers (which were not available for our analyses) or those with only inpatient serum creatinine measurements were excluded (n=24,769). Patients were also excluded if they had less than 2 outpatient serum creatinine measurements before dialysis initiation or if they did not have any serum creatinine measurement at a VA medical center within 6 months of dialysis initiation (n=7823). We also excluded patients who had no serum creatinine measurements for periods of at least 90 days (n=650) and those with insufficient follow-up data (n=56). The final cohort consisted of 18,874 patients (Figure 1).

Covariates

Data from the USRDS patient and medical evidence files were used to determine patients' demographic data including age, sex, race/ethnicity, and marital status at the time of dialysis initiation. We used the national VA Corporate Data Warehouse LabChem data files to extract data about serum creatinine.[16] Laboratory variables except serum creatinine were collected using the Decision Support System National Data Extracts Laboratory Results file,[17] and baseline values were defined as the last quarterly average of each variable before dialysis initiation or the second to last quarterly average if the last one was not available. Data related to medication exposure were obtained from both Centers for Medicare and Medicaid Services (CMS) data and VA pharmacy dispensation records.[18] Patients who received at least one dispensation of medications within 6 months of dialysis initiation were recorded as having been treated with these medications. Information about comorbidities (including the Charlson comorbidity index score) at the time of dialysis initiation was extracted from the VA Inpatient and Outpatient Medical SAS Datasets,[19] using the *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic and procedure codes and Current Procedural Terminology codes, as well as from VA/CMS data. Cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, myocardial infarction, or cerebrovascular disease. We calculated the Charlson comorbidity index score using the Deyo modification for administrative data sets, without including kidney disease.[20]

Exposure Variable

Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[21] Although 2 indices of decline in eGFR, percentage change and slope (annual change in eGFR), have been used to define CKD progression, we used eGFR slope as the main predictor for the survival models because it has been suggested to be a better predictor for mortality risk than percentage change.[6] The eGFR slope was calculated from an ordinary least squares regression model using all available outpatient eGFR measurements starting not more than 7 years before dialysis initiation. Considering the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline that defined rapid CKD progression as a decline in eGFR of more than 5 mL/min per 1.73 m^2 per year,[22]

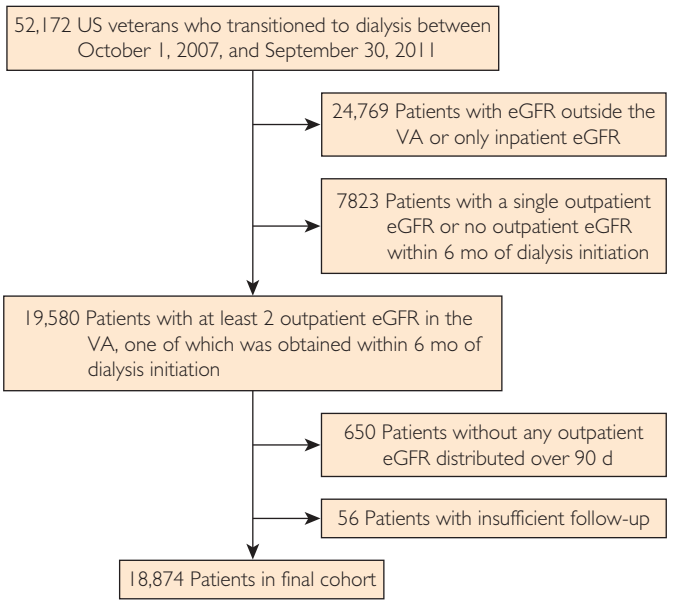

FIGURE 1. Flowchart of the study population. eGFR = estimated glomerular filtration rate; VA = Veterans Affairs medical centers.

we stratified pre-ESRD eGFR slopes into 4 a priori categories as follows: fast eGFR decline (eGFR slope less than −10 mL/min per 1.73 m^2 per year), moderate eGFR decline (eGFR slope −10 to less than −5 mL/min per 1.73 m^2 per year), slow eGFR decline (eGFR slope −5 to <0 mL/min per 1.73 m^2 per year), and increasing eGFR (eGFR slope ≥0 mL/min per 1.73 m^2 per year). We used the slow eGFR decline category (eGFR slope −5 to <0 mL/min per 1.73 m^2 per year) as reference in all analyses under the assumption that mortality risk is lowest in that category. The eGFR slope was also treated as a continuous variable to examine a nonlinear association using a restricted cubic spline analysis.

Outcome Assessment

The coprimary outcomes of this study were all-cause, cardiovascular, and infection-related mortality after dialysis initiation. Death data were obtained from VA and USRDS sources.[1] Cause-specific mortality data were obtained from the USRDS.

Statistical Analyses

Data are presented as the number (percentage) for categorical variables and mean ± SD for continuous variables with a normal distribution or median (interquartile range [IQR]) for those with a skewed distribution. Categorical variables were analyzed with the χ^2 test. Continuous variables were compared using *t* tests (or Mann-Whitney *U* tests) or analysis of variance, as appropriate. Survival analyses were performed using Cox proportional hazards regression to determine the association of eGFR slopes before dialysis initiation with all-cause, cardiovascular, and infection-related mortality after dialysis initiation. Patients were followed up until death or other censoring events including renal transplant, loss of follow-up, or until December 27, 2012, whichever occurred first. For cause-specific mortality, the patients were followed up until death or other censoring events including renal transplant, loss of follow-up, or until October 6, 2011, whichever happened first. The effect of potential confounders was analyzed by constructing models with incremental adjustments based on a priori considerations: model 1— unadjusted; model 2—age, sex, race/ethnicity (whites, African Americans, Hispanics, and others), and marital status (married, divorced, single, and widowed); model 3—model 2 plus body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), comorbid conditions (diabetes mellitus, hypertension, and Charlson comorbidity index score), and last eGFR before dialysis initiation; and model 4—model 3 plus medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; β-blockers; calcium channel blockers; vasodilators; loop, thiazide, and potassium-sparing diuretics; statins; active vitamin D analogues; phosphate binders [calcium acetate, sevelamer, or lanthanum]; nonsteroidal anti-inflammatory drugs; sodium bicarbonate; and erythropoiesis-stimulating agents [ESAs]). Restricted cubic spline models were used to investigate nonlinearity in fully adjusted associations between eGFR slopes and mortality. The associations of eGFR slopes with all-cause, cardiovascular, and infection-related mortality were examined in subgroups of patients categorized by age, race, BMI, the presence of diabetes mellitus, and last eGFR level before dialysis initiation. Interactions were formally tested by the inclusion of interaction terms.

Of the variables included in multivariate models, data points were missing for race in

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421 of the 18,874 patients (2.2%), BMI in 818 of the 18,874 patients (4.3%), and Charlson comorbidity index score in 2 of the 18,874 patients (0.01%). Information about cause of death was also missing in 4602 of the 9744 deaths (47.2%) in this cohort. Compared with patients in whom cause of death was missing, those in whom cause of death was available were less likely to be African American (967 of 5142 [18.8%] vs 1083 of 4602 [23.5%]) and had a slightly higher prevalence of cardiovascular disease (2966 of 5142 [57.7%] vs 2458 of 4602 [53.4%]) and congestive heart failure (3476 of 5142 [67.6%] vs 2890 of 4602 [62.8%]) (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Of the 18,874 patients, 17,660 (93.6%) had complete data available for multivariate adjusted analyses. Missing values were not imputed in primary analyses but were substituted after adding the laboratory data (serum albumin [2000 of 18,874 (10.6%) missing], serum bicarbonate [1229 of 18,874 (6.5%) missing], and whole blood hemoglobin [2042 of 18,874 (10.8%) missing]) to the adjustment with the use of multiple imputation procedures using the Stata statistical software (StataCorp) "mi" set of command in sensitivity analyses. Because deaths from cardiovascular or infection-related causes are competing events, we also performed sensitivity analyses to examine the association of eGFR slopes with cardiovascular and infection-related mortality using Fine and Gray competing risks proportional hazards regressions.[23]

The reported *P* values are 2-sided, and $P<.05$ was considered significant for all analyses. All of the analyses were conducted using Stata/MP version 12. The study was approved by the institutional review boards of the Memphis, Tennessee, and Long Beach, California, VA medical centers, with exemption from informed consent.

RESULTS

The patients' baseline characteristics according to category of eGFR slope are presented in Table 1. Among the 18,874 patients, the mean age was 69.1±11.3 years, 98.2% were male, 28.6% were African American, and 72.2% were diabetic. During the prelude pre-ESRD period to dialysis initiation, there were a median (IQR) of 18 (10-29) serum creatinine measurements per patient, and the median (IQR) eGFR slope was −5.4 (−9.7 to −2.9) mL/min per 1.73 m^2 per year over a median (IQR) period of 4.0 years (3.0-5.2 years). Among these patients, 4485 (23.8%), 5633 (29.8%), and 7942 (42.1%) experienced fast, moderate, and slow eGFR decline, respectively, whereas 814 patients (4.3%) had increasing eGFR. The median (IQR) eGFR slopes in the fast, moderate, and slow decline and the increasing slope categories were −14.6 (−19.4 to −11.9), −6.9 (−8.3 to −5.9), −2.9 (−3.9 to −1.9), and 1.4 (0.5-3.2) mL/min per 1.73 m^2 per year, respectively. Patients with fast eGFR decline were younger; were more likely to be African American; had a higher prevalence of diabetes mellitus and a lower prevalence of cardiovascular disease, congestive heart failure, and malignant disease; had higher serum cholesterol and phosphorus levels; and had lower serum albumin, bicarbonate, calcium, and whole blood hemoglobin levels. Conversely, patients with increasing eGFR were more likely to be white, had a lower prevalence of diabetes mellitus, and were less likely to use vitamin D analogues, phosphate binders, bicarbonate, and ESAs.

During a median follow-up of 2.0 years (IQR, 1.1-3.2 years; total time at risk, 41,027 patient-years [PYs]) after dialysis initiation, a total of 9744 all-cause deaths occurred (mortality rate, 237.5 per 1000 PYs; 95% CI, 232.8-242.3 per 1000 PYs), including 2702 deaths from cardiovascular causes (mortality rate, 65.9 per 1000 PYs; 95% CI, 63.4-68.4 per 1000 PYs) and 604 deaths from infection-related causes (mortality rate, 14.7 per 1000 PYs; 95% CI, 13.6-15.9 per 1000 PYs). Table 2 shows the hazard ratios (HRs) and corresponding 95% CIs for all-cause mortality according to categories of eGFR slopes using Cox proportional hazards models. In univariate analyses, compared with patients with slow eGFR decline, those with moderate or fast eGFR decline were at lower risk of all-cause mortality (HR, 0.81; 95% CI, 0.77-0.84; and HR, 0.66; 95% CI, 0.63-0.70, respectively), whereas those with increasing eGFR exhibited a higher risk of all-cause mortality (HR, 1.30; 95% CI, 1.19-1.42). After multivariate adjustment for baseline covariates, decrement in eGFR slope categories was associated with a stepwise increase in risk of all-cause

TABLE 1. Patient Characteristics at the Initiation of Dialysis, Stratified by eGFR Slope Categories[a,b,c]

Variable	Total cohort (N=18,874)	eGFR slope (mL/min/1.73 m^2/y)				P value
		Fast decline (less than −10) (n=4485)	Moderate decline (−10 to less than −5) (n=5633)	Slow decline (−5 to <0) (n=7942)	Increasing (≥0) (n=814)	
Age (y)	69.1±11.3	61.6±10.0	68.3±10.5	73.6±10.3	71.8±10.8	<.001
Sex (male)	18,533 (98.2)	4376 (97.6)	5532 (98.2)	7821 (98.5)	804 (98.8)	.002
Race						<.001
White	13,072 (69.3)	2443 (54.5)	3725 (66.1)	6242 (78.6)	662 (81.3)	
African American	5390 (28.6)	1922 (42.9)	1757 (31.2)	1565 (19.7)	146 (17.9)	
Asian	246 (1.3)	66 (1.5)	91 (1.6)	88 (1.1)	1 (0.1)	
Other	153 (0.8)	49 (1.1)	56 (1.0)	44 (0.6)	4 (0.5)	
Marital status						<.001
Married	10,365 (54.9)	2012 (44.9)	3029 (53.8)	4843 (61.0)	481 (59.1)	
Divorced	4551 (24.1)	1505 (33.6)	1424 (25.3)	1465 (18.4)	157 (19.3)	
Single	1521 (8.1)	573 (12.8)	456 (8.1)	438 (5.5)	54 (6.6)	
Widow	1958 (10.4)	283 (6.3)	566 (10.1)	1010 (12.7)	99 (12.2)	
Unknown	479 (2.5)	112 (2.5)	158 (2.8)	186 (2.3)	23 (2.8)	
Body mass index (kg/m^2)	30.0±6.7	30.1±7.1	30.4±6.8	29.7±6.4	30.4±7.2	<.001
Diabetes mellitus	13,632 (72.2)	3536 (78.8)	4145 (73.6)	5434 (68.4)	517 (63.5)	<.001
Hypertension	18,421 (97.6)	4350 (97.0)	5535 (98.3)	7780 (98.0)	756 (92.9)	<.001
Cardiovascular disease	8972 (47.5)	1638 (36.5)	2636 (46.8)	4291 (54.0)	407 (50.0)	<.001
Congestive heart failure	10,594 (56.1)	2213 (49.3)	3128 (55.5)	4788 (60.3)	465 (57.1)	<.001
Liver disease	2494 (13.2)	873 (19.5)	721 (12.8)	773 (9.7)	127 (15.6)	<.001
Malignant disease	4848 (25.7)	837 (18.7)	1408 (25.0)	2355 (29.6)	248 (30.5)	<.001
Charlson comorbidity index score	5 (3-7)	5 (3-6)	5 (3-7)	5 (3-7)	5 (3-7)	<.001
Medications						
ACEI/ARB	9552 (50.6)	2463 (54.9)	2880 (51.1)	3799 (47.8)	410 (50.4)	<.001
Diuretic	14,603 (77.4)	3599 (80.2)	4443 (78.9)	6030 (75.9)	531 (65.2)	<.001
Statin	12,375 (65.6)	2723 (60.7)	3792 (67.3)	5348 (67.3)	512 (62.9)	<.001
Vitamin D analogue	6136 (32.5)	1193 (26.6)	1975 (35.1)	2870 (36.1)	98 (12.0)	<.001
Phosphate binder[d]	6145 (32.6)	1851 (41.3)	1967 (34.9)	2215 (27.9)	112 (13.8)	<.001
Bicarbonate	4078 (21.6)	1152 (25.7)	1278 (22.7)	1554 (19.6)	94 (11.6)	<.001
ESA	6257 (33.2)	1816 (40.5)	2017 (35.8)	2312 (29.1)	112 (13.8)	<.001
Laboratory parameters						
Serum albumin (g/dL)	3.4±0.6	3.1±0.7	3.4±0.6	3.5±0.6	3.5±0.7	<.001
Serum cholesterol (mg/dL)	153.2±50.5	167.8±60.3	152.5±49.2	145.4±43.4	150.9±45.8	<.001
Serum bicarbonate (mEq/L)	22.9±4.2	22.0±3.9	22.6±4.1	23.4±4.3	25.3±4.3	<.001
Serum potassium (mEq/L)	4.5±0.6	4.5±0.6	4.5±0.6	4.5±0.6	4.3±0.5	<.001
Serum calcium (mg/dL)	8.7±0.8	8.4±0.8	8.7±0.8	8.9±0.8	8.9±0.7	<.001
Serum phosphorus (mg/dL)	5.2±1.4	5.5±1.4	5.3±1.4	5.0±1.3	4.6±1.5	<.001
Serum ALP (U/L)	97.8±62.9	103.9±75.3	95.6±58.2	95.3±57.8	102.9±60.5	<.001
Serum intact PTH (pg/mL)	219 (125-366)	230 (136-378)	237 (134-377)	202 (115-342)	154 (87-256)	<.001
Hemoglobin (g/dL)	10.6±1.6	10.2±1.5	10.5±1.5	10.9±1.6	11.6±2.0	<.001
Whole blood WBC (1000/mm^3)	7.9±3.2	8.0±3.0	7.8±3.1	7.8±3.4	8.1±3.5	.005
Serum urea nitrogen (mg/dL)	64.8±24.9	65.2±23.2	67.0±23.6	65.2±25.6	43.2±25.2	<.001
Serum creatinine (mg/dL)	5.0±2.5	5.7±2.8	5.3±2.5	4.5±2.3	2.7±1.9	<.001
eGFR (mL/min/1.73 m^2)	13.0 (9.5-18.6)	11.9 (8.8-16.3)	12.1 (9.0-16.5)	13.7 (10.0-19.7)	31.7 (18.9-57.6)	<.001
Last outpatient eGFR (mL/min/1.73 m^2)	12.9 (9.2-19.5)	11.6 (8.3-16.6)	11.9 (8.6-16.9)	13.9 (9.9-21.0)	40.9 (22.7-66.7)	<.001
Last eGFR (mL/min/1.73 m^2)	12.0 (8.5-17.6)	10.8 (7.7-15.3)	11.3 (8.0-15.8)	12.9 (9.1-19.0)	28.5 (14.5-56.4)	<.001
Time between last outpatient eGFR and dialysis initiation (d)	32 (10-78)	22 (7-60)	27 (8-65)	40 (13-89)	75 (32-123)	<.001
Time between first and last eGFR (y)	4.0 (3.0-5.2)	3.5 (2.5-4.7)	4.1 (3.1-5.2)	4.3 (3.3-5.4)	3.4 (2.2-4.6)	<.001

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TABLE 1. Continued

Variable	Total cohort (N=18,874)	eGFR slope (mL/min/1.73 m^2/y) Fast decline (less than −10) (n=4485)	Moderate decline (−10 to less than −5) (n=5633)	Slow decline (−5 to <0) (n=7942)	Increasing (≥0) (n=814)	*P* value
eGFR slope (mL/min/1.73 m^2/y)	−5.4 (−9.7 to −2.9)	−14.6 (−19.4 to −11.9)	−6.9 (−8.3 to −5,9)	−2.9 (−3.9 to −1.9)	1.4 (0.5-3.2)	<.001
Number of serum creatinine measurements	18 (10-29)	17 (10-27)	19 (11-31)	18 (10-30)	10 (5-17)	<.001

[a]ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ALP = alkaline phosphatase; eGFR = estimated glomerular filtration rate; ESA = erythropoiesis-stimulating agent; PTH = parathyroid hormone; WBC = white blood cell count.

[b]Data are presented as No. (percentage), mean ± SD, or median (interquartile range). Percentages may not total 100 because of rounding.

[c]SI conversion factors: To convert albumin values to g/L, multiply by 10; to convert cholesterol values to mmol/L, multiply by 0.0259; to convert bicarbonate values to mmol/L, multiply by 1.0; to convert potassium values to mmol/L, multiply by 1.0; to convert calcium values to mmol/L, multiply by 0.25; to convert phosphorus values to mmol/L, multiply by 0.323; to convert ALP values to μkat/L, multiply by 0.0167; to convert PTH values to ng/L, multiply by 0.1053; to convert hemoglobin values to g/L, multiply by 10.0; to convert WBC values to $\times 10^9$/L, multiply by 0.001; to convert urea nitrogen values to mmol/L, multiply by 0.357; to convert creatinine values to μmol/L, multiply by 88.4.

[d]Phosphate binders include calcium acetate, sevelamer, or lanthanum.

mortality among patients who experienced decline in eGFR (HR, 1.06; 95% CI, 1.00-1.11; and HR, 1.11; 95% CI, 1.04-1.18 for moderate and fast eGFR decline, respectively). The association between increasing eGFR and all-cause mortality was attenuated and no longer significant (HR, 0.97; 95% CI, 0.87-1.07) after multivariate adjustment (Table 2). A similar trend was observed between eGFR slopes and risk of cardiovascular mortality (Table 3). In contrast, no significant associations were found between eGFR decline and infection-related mortality; however, increasing eGFR was associated with higher infection-related mortality (HR, 1.49; 95% CI, 1.03-2.17) (Table 3).

Figure 2 shows the fully adjusted association of eGFR slope as a continuous variable with the risk of all-cause, cardiovascular, and infection-related mortality. There was a linear association of eGFR slope with all-cause and cardiovascular mortality, with higher mortality seen in those with faster eGFR decline (Figure 2, A and B), whereas a U-shaped association was observed between eGFR slope and infection-related mortality (Figure 2, C). The association of faster eGFR decline with higher all-cause mortality was present in most of the examined subgroups, and similar trends, albeit without reaching statistical significance, were present for cardiovascular mortality (Figure 3, A and B). The association of increasing eGFR with infection-related mortality was stronger among patients age 65 years or older, those with a BMI of less than 30 kg/m^2, and those with diabetes mellitus, although a statistically significant interaction was not detected (Figure 3, C).

TABLE 2. Association of eGFR Slopes With All-Cause Mortality After Dialysis Initiation[a,b]

eGFR slopes (mL/min/1.73 m^2/y)	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value	Model 4 HR (95% CI)	*P* value
Increasing (≥0)	1.30 (1.19-1.42)	<.001	1.35 (1.23-1.47)	<.001	0.96 (0.87-1.06)	.44	0.97 (0.87-1.07)	.55
Slow decline (−5 to <0)	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA	1.00 (reference)	NA
Moderate decline (−10 to less than −5)	0.81 (0.77-0.84)	<.001	1.03 (0.98-1.08)	.30	1.06 (1.00-1.11)	.04	1.06 (1.00-1.11)	.03
Fast decline (less than −10)	0.66 (0.63-0.70)	<.001	1.11 (1.05-1.18)	<.001	1.12 (1.05-1.19)	<.001	1.11 (1.04-1.18)	.001

[a]eGFR = estimated glomerular filtration rate; HR = hazard ratio; NA = not applicable.

[b]Data are adjusted for the following covariates: model 1—unadjusted; model 2—age, sex, race/ethnicity, and marital status; model 3—model 2 plus body mass index, diabetes mellitus, hypertension, Charlson comorbidity index score, and last eGFR; model 4—model 3 plus medications.

TABLE 3. Association of eGFR Slopes With Cardiovascular and Infection-Related Mortality After Dialysis Initiation[a,b]

eGFR slopes (mL/min/1.73 m^2/y)	Cardiovascular mortality HR (95% CI)	*P* value	Infection-related mortality HR (95% CI)	*P* value
Increasing (≥0)	1.13 (0.93-1.37)	.21	1.49 (1.03-2.17)	.04
Slow decline (−5 to <0)	1.00 (reference)	NA	1.00 (reference)	NA
Moderate decline (−10 to less than −5)	1.11 (1.01-1.23)	.03	1.08 (0.88-1.33)	.48
Fast decline (less than −10)	1.13 (1.00-1.27)	.04	1.18 (0.92-1.51)	.18

[a]eGFR = estimated glomerular filtration rate; HR = hazard ratio; NA = not applicable.
[b]Data are adjusted for age, sex, race/ethnicity, marital status, body mass index, diabetes mellitus, hypertension, Charlson comorbidity index score, last eGFR, and medications.

Results of analyses in which imputed values for missing variables were used yielded similar results (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). Competing risks analyses also showed similar trends of association between eGFR slope and cardiovascular and infection-related mortality (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

In this retrospective cohort study of 18,874 patients transitioning to dialysis, we examined the association of eGFR slopes in late-stage NDD-CKD with all-cause, cardiovascular, and infection-related mortality after dialysis initiation. Compared with slow eGFR decline, both moderate and fast eGFR decline were associated with higher all-cause and cardiovascular mortality. Interestingly, a small proportion of patients (4.3%) experienced increasing eGFR before transitioning to dialysis, and these patients experienced significantly higher infection-related mortality (*P*=.04).

Previous studies have identified several factors prognosticating survival of patients with ESRD; however, the impact of pre-ESRD conditions on post-ESRD outcomes in patients transitioning to dialysis remains unclear, largely because of the limitation of registry data that lacks most core data before dialysis initiation. With regard to the change in eGFR, studies have consistently found that 1-year change in eGFR is strongly related to the risks of ESRD,[5,6] cardiovascular disease,[7,8] and mortality[5,7-10] among patients with NDD-CKD. Recently, not only declining eGFR but also increasing eGFR has been reported to be independently associated with higher mortality.[6,11-14] Perkins et al[12] examined the effect of rate of eGFR decline on survival in 15,465 patients with NDD-CKD receiving primary care at a single institution and reported 84% and 42% increases in mortality for those with declining eGFR (−4.8 mL/min per 1.73 m^2 per year) and increasing eGFR (3.5 mL/min per 1.73 m^2 per year), respectively, compared with those with stable eGFR. Similarly, in a community-based cohort of 529,312 adults in Canada, Turin et al[14] reported that compared with stable eGFR, both decline in eGFR (−5 mL/min per 1.73 m^2 per year or less) and increase in eGFR (≥5 mL/min per 1.73 m^2 per year) were independently associated with higher mortality (HR, 1.52 and 2.20, respectively). These studies have focused largely on the association of change in eGFR with risk of adverse outcomes among patients with relatively preserved kidney function. To our knowledge, there are only a few studies that have described the association of change in eGFR with mortality after dialysis initiation. O'Hare et al[15] identified 4 distinct trajectories of eGFR during the 2-year period before dialysis initiation in patients with CKD transitioning to dialysis and found that those with more rapid loss of eGFR were at higher risk for death during the first year after initiation. Onuigbo[24] investigated an incident hemodialysis cohort at Mayo Clinic in Rochester, Minnesota, between 2001 and 2013 and reported the newly described syndrome of rapid-onset ESRD after acute kidney injury (AKI), which was related to subsequent cardiovascular mortality with high rates of dialysis catheter use.[25] In these studies, however, no information has been provided on patients with increasing eGFR and on the association of change in eGFR with different causes of death.

Our study is the first to examine eGFR slopes including both declining and increasing slopes among patients with advanced CKD transitioning to dialysis and the first to provide evidence of the association of eGFR slopes with post-ESRD cause-specific mortality. Several causal mechanisms underlying the association between eGFR decline and increased mortality have been implicated in previous studies. The worsening of kidney function could be a marker of subclinical atherosclerosis, endothelial

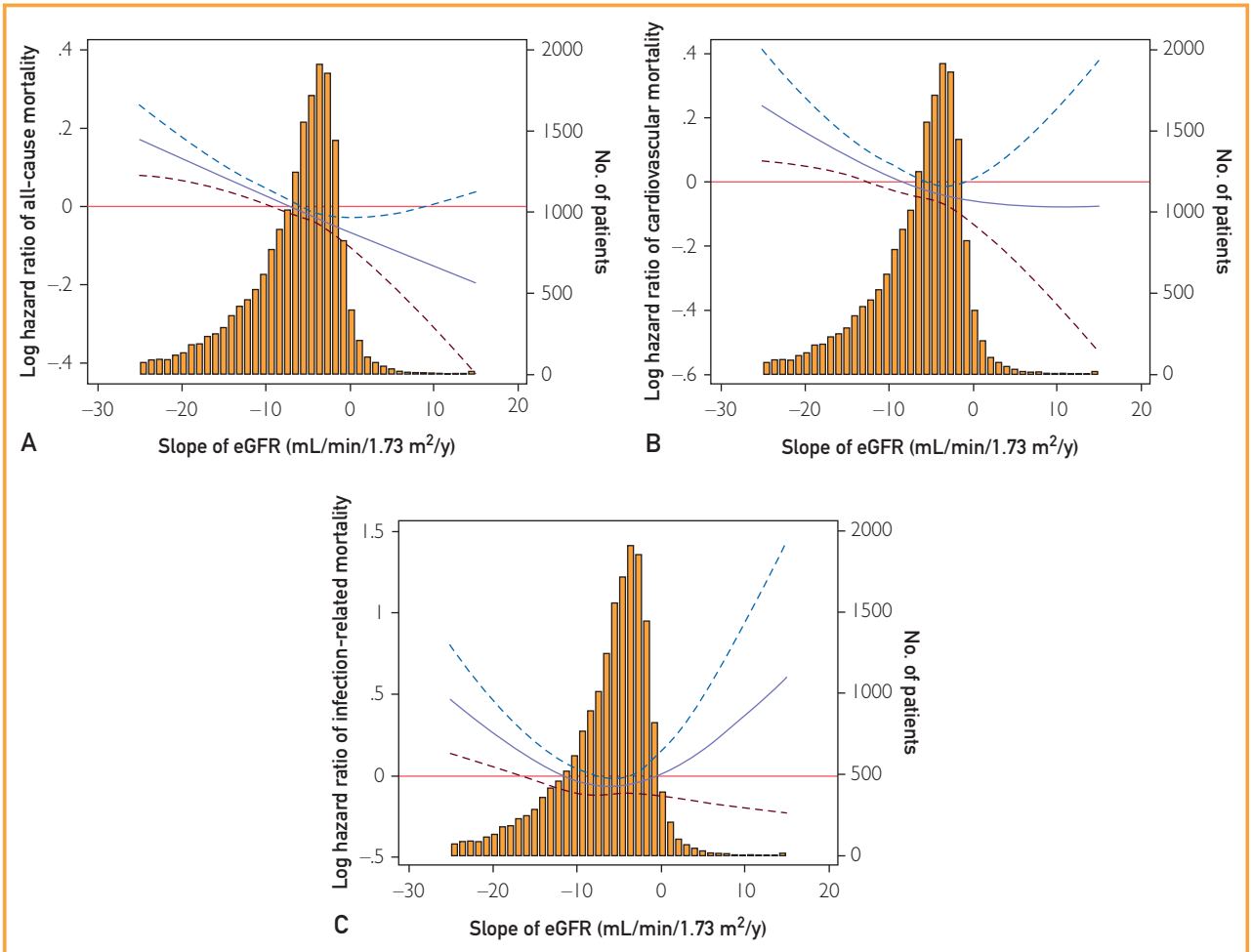

FIGURE 2. Multivariate adjusted hazard ratios of post–end-stage renal disease (ESRD) all-cause (A), cardiovascular (B), and infection-related (C) mortality associated with pre-ESRD estimated glomerular filtration rate (eGFR) slopes in Cox model using restricted cubic splines, adjusted for age, sex, race/ethnicity, marital status, body mass index, diabetes mellitus, hypertension, Charlson comorbidity index score, last eGFR, and medications. The bars represent the number of patients with eGFR slope levels grouped in increments of 1 mL/min per 1.73 m^2 per year.

dysfunction, or oxidative stress,[26] which contribute to increased risk of cardiovascular disease. Other potential pathways that could mediate this association include the activation of the renin-angiotensin system, blood pressure dysregulation, disordered bone and mineral metabolism, and chronic inflammation.[8,27,28] In addition, worsening kidney function in patients with advanced CKD may lead to decreased appetite, decreased physical function, and overall frailty,[9,29,30] which may indirectly contribute to increased risk of mortality among these patients. Notably, patients who experience more rapid decline in eGFR are likely to die before reaching ESRD,[9] and hence, some of the observed differences in baseline characteristics across eGFR slope categories could be explained by immortal time bias in this study. For instance, compared with patients with slow eGFR decline, patients who experienced fast eGFR decline but survived to the point of initiating dialysis were younger and had lower prevalence of cardiovascular disease and congestive heart failure; nevertheless, those patients were still at a higher risk of all-cause and cardiovascular mortality.

As previously reported,[6,11-14] increasing eGFR is also associated with excess mortality in patients with NDD-CKD. We observed a similar association and also provided additional information on increasing eGFR, that

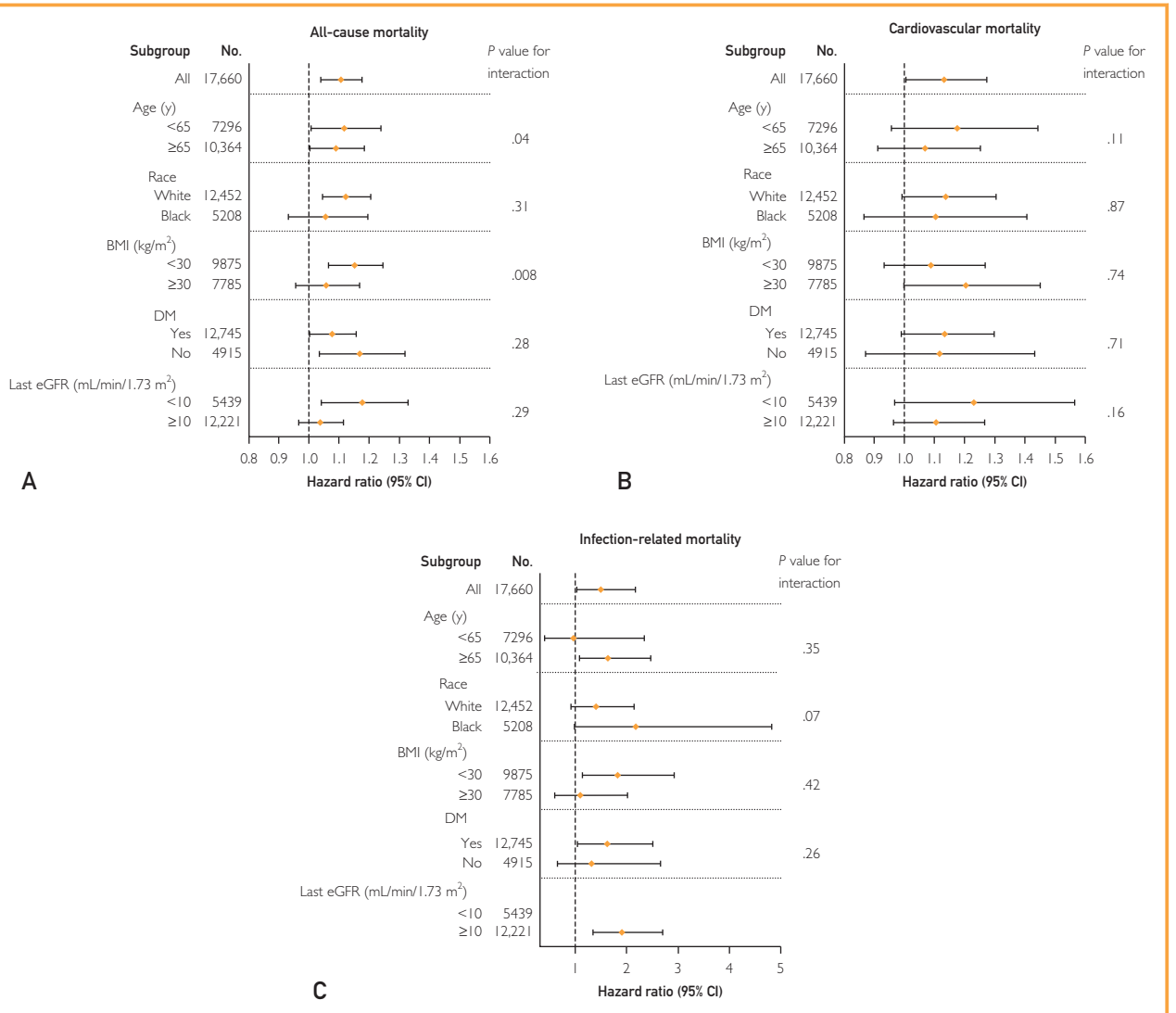

FIGURE 3. Hazard ratios (95% CIs) for 17,660 patients who had complete data available for multivariate adjusted analyses of all-cause (A) and cardiovascular (B) mortality associated with fast estimated glomerular filtration rate (eGFR) decline and infection-related (C) mortality associated with increasing eGFR, compared respectively to slow eGFR decline, overall and in selected subgroups. Models were adjusted for age, sex, race/ethnicity, marital status, body mass index (BMI), diabetes mellitus (DM), hypertension, Charlson comorbidity index score, last eGFR, and medications. The result in the last eGFR <10 subgroup was omitted due to low number of events.

is, increasing eGFR associates with higher infection-related mortality. The mechanisms underlying the higher infection-related mortality seen in patients with increasing eGFR remain speculative. The finding of increasing eGFR may be attributable to a decline in serum creatinine generation as a consequence of loss of muscle mass associated with chronic debilitating conditions.[11,31] Although we did not measure nutritional status and muscle mass in a time-dependent fashion, the almost identical levels of mean BMI across eGFR categories and the lower level of mean serum creatinine in increasing eGFR categories at baseline might reflect loss of lean body mass accompanied by fluid gain in patients with increasing eGFR. Muscle wasting may lead to the emergence of circulating actin that can consume plasma gelsolin, which has salutary and protective actions[32] through inactivation of bioactive lipid mediators including lysophosphatidic acid,[33] lipopolysaccharide endotoxin,[34] and platelet-activating factor.[35] Recent evidence indicates that a low level of

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plasma gelsolin is associated with higher mortality in patients undergoing dialysis,[36] potentially because of impaired antimicrobial defenses induced by low levels of gelsolin.[37] These underlying pathophysiologic mechanisms could explain the association between increasing eGFR and higher infection-related mortality. Interestingly, we found a significantly lower percentage of use for certain medications such as vitamin D analogues, phosphate binders, bicarbonate, and ESAs that are typically associated with more advanced CKD among patients with increasing eGFR (all $P<.001$), which suggests that these patients may indeed have had less advanced CKD and perhaps started dialysis because of AKI events during a hospitalization immediately preceding dialysis initiation. These AKI events preceding dialysis initiation and underlying chronic illness could also serve as a potential explanation for the observed association. Furthermore, their strong associations observed in the subgroups of patients aged 65 years or older, those with BMI of less than 30 kg/m^2, and patients with diabetes mellitus, all of which could increase infectious risk in patients with CKD, may also support the explanation for this association.

This study must be interpreted in light of several limitations. Our study was observational, and hence, the results do not allow us to infer causality but merely associations. About half of the patients in the initial cohort were excluded because their outpatient serum creatinine levels were not measured in VA medical centers. Most of our patients were male US veterans; therefore, the results may not be generalizable to women or the general US population. Kidney function was not measured using a criterion standard method but was estimated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation,[21] which can be affected by several non-GFR factors. Nevertheless, its widespread use affords clinical applicability to our results. Given that inpatient eGFR measurements were excluded to avoid the effects of potential hospital-acquired AKI, the influence of fluctuation in eGFR over time related to community-acquired AKI on eGFR slopes was not completely eliminated in this study. We adjusted our analyses for a variety of important covariates as potential confounders, but we cannot eliminate the possibility of unmeasured confounders such as proteinuria, muscle mass, and changes in volume status that might affect eGFR slopes over time.

CONCLUSION

Compared with slow eGFR decline, more rapid eGFR decline and increasing eGFR were associated with higher all-cause and cardiovascular mortality and infection-related mortality, respectively, after dialysis initiation independent of comorbid conditions and other known risk factors at baseline. These findings highlight the importance of the change in eGFR in the risk for post-ESRD mortality and suggest that the eGFR slope is an additional predictor of mortality among incident dialysis cases.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AKI** = acute kidney injury; **BMI** = body mass index; **CKD** = chronic kidney disease; **CMS** = Centers for Medicare and Medicaid Services; **eGFR** = estimated glomerular filtration rate; **ESA** = erythropoiesis-stimulating agent; **ESRD** = end-stage renal disease; **HR** = hazard ratio; **IQR** = interquartile range; **NDD** = non–dialysis dependent; **PY** = patient-year; **USRDS** = United States Renal Data System; **VA** = Veterans Affairs

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