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Original Investigation

Estimated GFR Trajectories of People Entering CKD Stage 4 and Subsequent Kidney Disease Outcomes and Mortality

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Background: Estimated glomerular filtration rate (eGFR) trajectories of people entering chronic kidney disease (CKD) stage 4 and their associations with subsequent kidney disease outcomes or death are not known.

Study Design: Longitudinal observational cohort study.

Setting & Participants: 26,246 patients in the Veterans Affairs Healthcare System who entered CKD stage 4 in fiscal year 2008 followed up until October 2013.

Factors: 5-year eGFR trajectories, demographic and health characteristics.

Outcomes: Composite kidney disease outcome of kidney failure, dialysis therapy or transplantation, and death.

Results: Latent class group modeling and functional characterization suggest the presence of 3 distinct trajectory classes: class 1 (72%), consistent slow decline with absolute eGFR change of −2.45 (IQR, −3.89 to −1.16) mL/min/1.73 m^2 per year; class 2 (18%), consistent fast decline and eGFR change of −8.60 (IQR, −11.29 to −6.66) mL/min/1.73 m^2 per year; and class 3 (10%), early nondecline and late fast decline with eGFR change of −0.4 mL/min/1.73 m^2 per year in years 1 to 3 and −7.98 and −21.36 mL/min/1.73 m^2 per year in years 4 and 5, respectively. During 4.34 years of follow-up, 9,809 (37%) patients had the composite kidney disease outcome and 14,550 (55%) patients died. Compared to the referent group (trajectory class 1), HRs for 1-year risk for composite kidney disease outcome for trajectory classes 2 and 3 were 1.13 (95% CI, 1.05-1.22) and 0.67 (95% CI, 0.59-0.75), whereas HRs for 1-year risk for death for classes 2 and 3 were 1.17 (95% CI, 1.10-1.28) and 1.29 (95% CI, 1.18-1.42), respectively. The 1-year risk for composite kidney disease outcome was 32% and was 42% more likely than the risk for death in trajectory classes 1 and 2, respectively, whereas the risk for death was 67% more likely than the risk for composite kidney disease outcome in trajectory class 3.

Limitations: Inclusion criteria and mostly male participants limit generalizability of study results.

Conclusions: We characterized 3 different eGFR trajectory classes of people entering CKD stage 4. Our results suggest that the pattern of eGFR trajectory informs the risk for kidney disease outcomes and death.

INDEX WORDS: Chronic kidney disease (CKD); stage 4 CKD; kidney function trajectory; kidney disease outcomes; kidney failure; end-stage renal disease (ESRD); dialysis; transplant; mortality; rate of kidney function decline; comorbid conditions; concordant; discordant; viral infections; estimated glomerular filtration rate (eGFR); eGFR trajectories; renal function trajectory; renal outcomes; disease progression.

Longitudinal assessment of kidney function informs the risk for clinical outcomes.[1-8] Recent observations by Kovesdy et al[6] and Naimark et al[7] suggest that longitudinal estimated glomerular filtration rate (eGFR) changes contribute significantly to the risk for end-stage renal disease (ESRD) and death beyond the current eGFR. In describing the relationship between eGFR change and clinical outcomes, most prior studies used an analytic approach that assumes linearity, including the use of eGFR slopes or absolute change in eGFR (change in eGFR equals final eGFR minus initial eGFR).[1-8] However, longitudinal eGFR change is often nonlinear, especially when the observation window is prolonged.[9] In an analysis of 846 patients from the African American Study of Kidney Disease and Hypertension (AASK), Li et al[9] reported that although linear eGFR decline may occur in some patients, many have nonlinear patterns and extended periods of nonprogression. The authors suggested that future research examine analytical approaches more sophisticated than those based on linear models, especially during long-term follow-up periods.[9]

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In seminal work, O'Hare et al[10] characterized kidney function trajectories of eGFR during the 2-year period before the initiation of long-term dialysis therapy. The investigators used latent class modeling and identified 4 distinct trajectories: persistently low eGFR, progressive loss, accelerated loss, and catastrophic loss of eGFR. The investigators observed that patients with steeper eGFR trajectories were more likely to have been hospitalized and have an inpatient diagnosis of acute kidney injury (AKI), were less likely to have received predialysis care, and had higher risk for death in the first year following dialysis therapy initiation.[10]

Although the trajectories of those entering chronic kidney disease (CKD) stage 5 and requiring initiation of dialysis therapy have been described previously, most people with CKD die before reaching CKD stage 5 and requiring initiation of dialysis therapy or receipt of a kidney transplant.[2,11,12] The national and global disease burden of earlier stages of CKD cannot be overstated.[13] Discussions regarding CKD prognosis and decisions to initiate a transplantation workup, initiation of renal replacement therapies, and access planning are optimal when they are adequately informed and when they precede entry into CKD stage 5.[14,15] However, very little is known about whether eGFR trajectories preceding entry into CKD stage 4 might inform risk stratification and decision making by patients and their providers. In this work, we aimed to characterize the eGFR trajectories of patients entering CKD stage 4, examine the association between type of eGFR trajectory and risk for death or composite kidney outcome, and for each trajectory type, determine whether one outcome (either composite kidney disease outcome or death) is more likely than the other.

METHODS

Patients

Using administrative data from the US Department of Veterans Affairs (VA), we identified users of the VA Healthcare System with at least 2 outpatient eGFR assessments from October 1, 2007, through September 30, 2008, that were 15 to <30 mL/min/1.73 m^2 and separated by at least 90 days (n = 45,951). Patients were included in the cohort only if they had at least 1 outpatient eGFR assessment per year in the 5 years preceding cohort entry (n = 30,915). Patients were excluded if they had undergone kidney transplantation or at least 1 session of dialysis before T_0 (time zero; the time of the last eGFR of 15-<30 mL/min/1.73 m^2 from October 2007 until October 2008), yielding an analytic cohort of 26,246. The timeline for cohort selection is shown in Fig 1. The study (#1163689) was approved by the Institutional Review Board of the VA Saint Louis Health Care System, Saint Louis, MO, which also approved a waiver of informed consent.

Data Sources

We used VA databases including inpatient and outpatient medical SAS data sets (that include utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed patient demographic characteristics and comorbid condition information based on *Current Procedural Terminology* codes and *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic and procedure codes associated with inpatient and outpatient encounters.[16-19] The VA Managerial Cost Accounting Laboratory Results file (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information for outpatient and inpatient serum creatinine measurements.[16,17,20] The VA Vital Status and Beneficiary Identification Records Locator Subsystem (BIRLS) files provided demographic characteristics and death follow-up through September 30, 2013.[16,17] US Renal Data System (USRDS) data provided information about date of first ESRD treatment initiation services.

Primary Outcomes

Primary outcomes were time to death and time to the composite kidney outcome. The composite kidney outcome was defined as the occurrence of kidney failure (defined as the occurrence of an outpatient eGFR < 15 mL/min/1.73 m^2), dialysis therapy, or

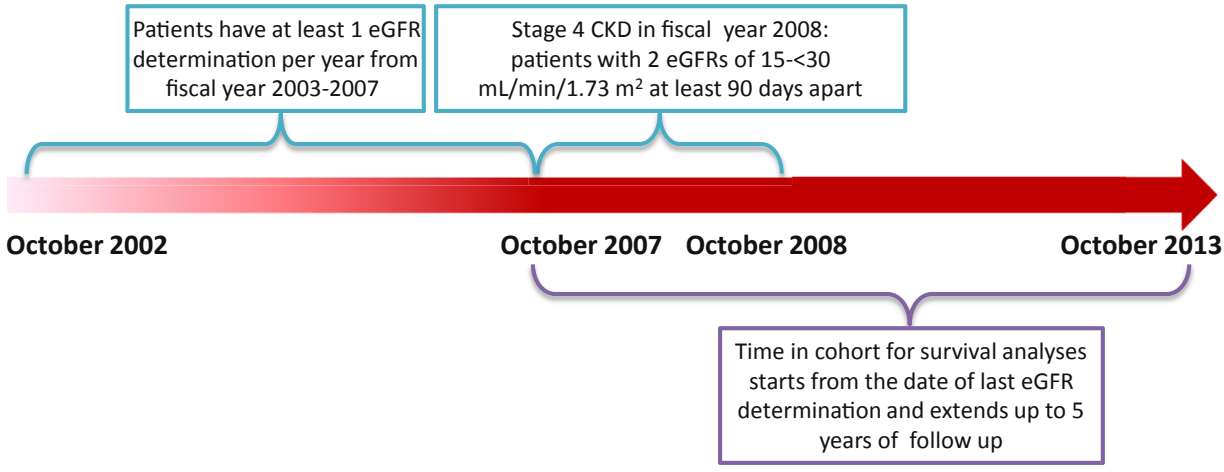

Figure 1. Timeline of cohort assembly. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

kidney transplantation. Outcomes were ascertained from time of cohort entry (T_0) until September 30, 2013.

Covariates

The baseline period was defined as the 5 years preceding cohort entry (T_0). Baseline covariates were captured during the baseline period. Covariates included initial eGFR, number of eGFR assessments, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C virus (HCV), HIV (human immunodeficiency virus), and dementia. Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial/ethnic minority groups). Comorbid conditions were assigned on the basis of relevant *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic and procedures codes and *Current Procedural Terminology* codes in the VA Medical SAS data sets as described previously[8,21,22] (Table S1, available as online supplementary material). eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation based on age, sex, race, and outpatient serum creatinine level.[23] Annual percentage change in eGFR was calculated using the following formula: [(qualifying eGFR − initial eGFR)/initial eGFR)]/[(qualifying date − initial date)/365.25] × 100. Receipt of nephrology care was defined as receipt of outpatient care (other than dialysis) provided by nephrologists. Hospitalization was defined as any inpatient hospital stay that exceeds 23 hours. Three binary comorbid condition variables were created to indicate the presence of the following: concordant comorbid conditions including cerebrovascular disease, cardiovascular disease, diabetes mellitus, hypertension, and peripheral artery disease; discordant comorbid conditions including chronic lung disease, hyperlipidemia, and dementia; and viral infections including HCV and HIV.[24] AKI was defined as a 50% or 0.3-mg/dL increase in serum creatinine level within 30 days.[25] Both inpatient and outpatient serum creatinine levels were used to capture the occurrence of AKI.

Statistical Analysis

In order to construct eGFR trajectories, we used latent class modeling, a nonlinear approach that allows measurement points to be separated by different intervals and allows variability across individuals.[26,27] To characterize eGFR trajectories over a period of 5 years, observation points were set up every 6 months. Patients' eGFR assessments most proximate to the observation points were used in the analyses, resulting in 11 data points per patient. Time of the eGFR measurement was considered as time of this data point in modeling. Latent class models with different numbers of trajectories were built individually to obtain the Bayesian information criterion. The number of trajectories was determined by the model with the lowest Bayesian information criterion compared to the model with 1 more trajectory and the model with 1 less trajectory. Mean group assignment possibilities, which indicate the average possibility of being assigned to the trajectory for all patients in that trajectory, were computed. A higher mean group assignment possibility indicates a better fit. This analysis yielded 6 trajectories (Table S2). We then further grouped trajectories according to pattern of eGFR change over the 5-year prior cohort entry: we computed percentage of eGFR change for each year (years 1-5) in each of the trajectories.[26-28] We applied Ward cluster analysis to determine a final number of trajectories (Item S1).

Analysis of variance test was used to detect differences for parametric continuous variables, Kruskal-Wallis test was used to detect differences for nonparametric continuous variables, and χ^2 test was used to detect proportions of differences between trajectory classes. Multinomial logistic regression was used to evaluate factors correlated with eGFR trajectory class. Hazard ratios (HRs) of the outcome of interest after T_0 were evaluated by Cox survival analysis. Cox models were controlled for all covariates unless otherwise specified. For computing HRs within 1, 2, 3, 4, and 5 years, individuals without an event during the time frame were censored at the end of the time frame. Death and the composite kidney outcome were considered competing risks. Formal evaluation of death as a competing risk was undertaken using Fine and Gray models. In addition, marginal survival models were used to evaluate HRs between outcomes within each trajectory classes.[29] Marginal models combined outcomes, giving them the same baseline hazard function. In addition, an independent variable representing type of outcome event, indicating the risk difference between outcomes while controlling for all other independent variables, was added to the model.[29,30] In survival analyses, a 95% confidence interval (CI) of an HR that does not include unity was considered statistically significant. In all analyses, $P \leq 0.05$ was considered statistically significant. Analyses were performed using Statistical Analysis System (SAS) Enterprise Guide, version 6.1, and SAS, version 9.2 (SAS Institute Inc).

RESULTS

Primary Outcomes

In the overall cohort over a median of 4.34 (interquartile range [IQR], 1.72-5.00) years' follow up, 9,809 (37%) had the composite kidney disease outcome (defined as kidney failure, dialysis therapy, or kidney transplantation) and 14,550 (55%) died. Of those who died, 9,552 (66%) died without having the composite kidney disease outcome and 4,998 (34%) died after having the composite kidney disease outcome.

Trajectory Analysis

We used latent class group modeling to determine the number of distinct kidney function trajectories in patients entering CKD stage 4. The results suggested 6 different trajectories with mean group assignment possibility > 90% (Item S1). We further grouped them into functional trajectory classes according to annual eGFR percentage change (Table S2). Three kidney function trajectory classes were identified (Fig 2): class 1, consistent slow decline; class 2, consistent fast decline; and class 3, early nondecline and late fast decline.

Demographic and clinical characteristics of the overall cohort and according to each trajectory class are presented in Table 1. There were 26,246 patients in the overall cohort. The majority of patients were of white race and were men. The prevalence of comorbid conditions such as hypertension, diabetes mellitus, cardiovascular disease, and chronic lung disease was high.

Absolute eGFR change for each year during the 5 years preceding cohort entry (fifth to first year prior to cohort entry [T_0]) by trajectory class is presented in Table 2. eGFR trajectory class 1 accounted for 72% of patients and is characterized by a median initial eGFR of 36.51 mL/min/1.73 m^2 and stable slow progression over time with absolute eGFR changes

Figure 2. Functional characterization of kidney function trajectories yields 3 trajectory classes: trajectory class 1, consistent slow decline; trajectory class 2, consistent fast decline; and trajectory class 3, early nondecline and late fast decline. Abbreviation: eGFR, estimated glomerular filtration rate.

of −2.45 (IQR, −3.89 to −1.16) mL/min/1.73 m^2 per year. Trajectory class 2 accounted for 18% of patients and is characterized by a median initial eGFR of 67.65 mL/min/1.73 m^2 and rate of eGFR decline consistently faster than −5 (median absolute eGFR change, −8.60 [IQR, −11.29 to −6.66] mL/min/1.73 m^2 per year). Trajectory class 3 accounted for 10% of patients and was characterized by an initial median eGFR of 61.72 mL/min/1.73 m^2 and very minimal progression in first 3 years prior to cohort entry (median absolute eGFR change, −0.4 mL/min/1.73 m^2 per year), followed by fast decline later with corresponding median absolute eGFR changes of −7.98 (IQR, −18.15 to −0.32) and −21.36 (IQR, −33.05 to −12.17) mL/min/1.73 m^2 per year in the second and first years prior to cohort entry, respectively.

Adjusted Associations of Trajectory Classes

We examined adjusted associations of kidney function trajectory classes in a multinomial logistic regression model. Compared to trajectory class 1 (the referent group), those in trajectory classes 2 and 3 were more likely to be younger, men, and black with diabetes mellitus, HCV infection, HIV infection, and chronic lung disease (Table 3). Compared to trajectory class 1, trajectory classes 2 and 3 were associated with increased numbers of hospitalizations and reduced likelihood of having received nephrology care. Those in trajectory class 3 had a higher male preponderance, significant association with dementia, and reduced strength of association with diabetes compared with those in trajectory class 2.

We then categorized comorbid conditions into concordant, discordant, and viral infections. The presence of concordant comorbid conditions was not significantly associated with increased odds of trajectory class 2 or 3. The presence of discordant comorbid conditions and viral infections was associated with increased odds of trajectory classes 2 and 3 (Table 4).

Trajectory Class and Risk for Kidney Disease Outcomes

We then examined the association between trajectory class and risk for the composite kidney disease outcome (kidney failure, dialysis therapy, or kidney transplantation). Compared to trajectory class 1, trajectory class 2 had a slightly increased risk for the composite kidney disease outcome within 1 year (HR, 1.13; 95% CI, 1.05-1.22), whereas trajectory class 3 was associated with decreased risk for the composite kidney disease outcome at 1 to 5 years (HRs at 1 and 5 years of 0.67 [95% CI, 0.59-0.75] and 0.47 [95% CI, 0.43-0.51]; Table 5). Models including AKI as an additional covariate and models built to examine the risk for kidney failure yielded similar results (Tables S3 and S4). We examined the risk for the composite kidney disease outcome and risk for chronic kidney failure in Fine and Gray competing-risk models and results were consistent (tables *a* and *b* of Item S2). We then examined the association between kidney function trajectory classes and risk for treated chronic

Table 1. Demographic and Clinical Characteristics of the Overall Cohort and by Kidney Function Trajectory

		Trajectory Class			
	Overall Cohort	1	2	3	*P*
No. of patients	26,246 (100)	18,887 (72.0)	4,675 (18.0)	2,684 (10.2)	
Age, y[a]	73.17 ± 8.41	74.58 ± 7.67	69.52 ± 9.02	69.58 ± 9.27	<0.001
Sex					0.4
Male	25,429 (97.0)	18,314 (97.0)	4,516 (97.0)	2,599 (97.0)	
Female	817 (3.1)	573 (3.0)	159 (3.4)	85 (3.2)	
Race					<0.001
Black	3,931 (15.0)	2,514 (13.3)	938 (20.1)	479 (18.0)	
White	21,762 (82.9)	15,994 (84.7)	3,628 (77.6)	2,140 (79.7)	
Other	533 (2.1)	379 (2.0)	109 (2.3)	65 (2.4)	
Initial eGFR, mL/min/1.73 m^2[b]	44.63 ± 17.45	36.51 ± 9.30	67.65 ± 14.92	61.72 ± 17.42	<0.001
Qualifying eGFR, mL/min/1.73 m^2[c]	24.41 ± 4.49	24.24 ± 4.28	24.48 ± 4.25	25.47 ± 5.93	<0.001
CBVD	591 (2.3)	414 (2.2)	98 (2.1)	79 (2.9)	0.04
CVD	17,894 (68.2)	12,701 (67.3)	3,244 (69.4)	1,949 (72.6)	<0.001
Dementia	2,417 (9.2)	1,696 (9.0)	393 (8.4)	328 (12.2)	<0.001
Diabetes mellitus	17,150 (65.3)	11,720 (62.1)	3,529 (75.7)	1,891 (70.5)	<0.001
HCV	974 (3.7)	442 (2.3)	320 (6.8)	212 (7.9)	<0.001
HIV	3,321 (12.7)	2,077 (11.0)	739 (15.8)	505 (18.8)	<0.001
Hypertension	25,519 (97.2)	18,365 (97.2)	4,561 (97.6)	2,593 (96.6)	0.06
Hyperlipidemia	22,558 (86.0)	16,226 (85.9)	4,054 (86.7)	2,278 (84.9)	0.09
Chronic lung disease	9,002 (34.3)	5,994 (31.7)	1,779 (38.1)	1,229 (45.8)	<0.001
Peripheral artery disease	3,892 (14.8)	2,762 (14.6)	707 (15.1)	423 (15.8)	0.3
Follow up, y	4.34 [1.72-5.00]	4.41 [1.82-5.00]	4.23 [1.60-5.00]	4.09 [1.22-5.00]	<0.001
Time between initial and qualifying eGFR, y	4.79 [4.60-4.91]	4.80 [4.60-4.91]	4.76 [4.55-4.90]	4.80 [4.61-4.92]	<0.001
No. of eGFRs	23.02 ± 14.19	21.65 ± 13.20	25.35 ± 14.50	28.60 ± 18.00	<0.001
Acute kidney injury	14,482 (55.2)	9,366 (49.6)	3,058 (65.4)	2,058 (76.7)	<0.001
No. of nephrology clinic visits[d]	1 [0-5]	1 [0-6]	1 [0-4]	0 [0-1]	<0.001
No. of hospitalizations[d]	0 [0-2]	0 [0-2]	1 [0-3]	2 [1-5]	<0.001

Note: Values for categorical variables are given as number (percentage [column percentage except for first row]); values for continuous variables, as mean ± standard deviation or median [interquartile range].

Abbreviations and definitions: CBVD, cerebrovascular disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; trajectory class 1, consistent slow decline in eGFR; trajectory class 2, consistent fast decline; trajectory class 3, early nondecline and late fast decline.

[a]Age at time of cohort entry.

[b]Initial eGFR indicates first eGFR recorded in trajectory analysis.

[c]Final qualifying eGFR indicates last eGFR recorded in trajectory analysis.

[d]Number of nephrology clinic visits and hospitalizations were captured within 5 years before patients reached chronic kidney disease stage 4.

kidney failure (defined as receipt of ESRD services in USRDS databases); results were also consistent (table *c* of Item S2).

Trajectory Class and Risk for Death

We examined the association between trajectory class and risk for death. Compared with those in trajectory class 1, both trajectory classes 2 and 3 were associated with increased risk for death at 1, 2, and 3 years (Table 6). HRs for 1-year risk for death for classes 2 and 3 were 1.17 (95% CI, 1.10-1.28) and 1.29 (95% CI, 1.18-1.42), respectively; HRs for 3-year risk for death for classes 2 and 3 were 1.13 (95% CI, 1.07-1.19) and 1.12 (95% CI, 1.05-1.20; Table 6). The association between trajectories and risk for death was attenuated with increased time of follow-up after cohort entry and maintained statistical significance at years 4 and 5 among those in trajectory class 2, whereas there was only a trend in trajectory class 3. Models that included AKI as an additional covariate yielded consistent results (Table S5).

Likelihood of Kidney Disease Outcome Versus Death Within Each Trajectory Class

Using marginal survival models, comparison of risk for the composite kidney disease outcome vis-à-vis risk for death at 1 year suggests that the risk relationship favors the composite kidney disease outcome in trajectory classes 1 and 2 (for which the composite kidney disease outcome was 32% and 42% more likely, respectively) and favors risk for death in trajectory class 3 (outcome of death is 67% more likely; Fig 3A). Comparative evaluation of risk at year 5 suggests that the likelihood of the composite kidney

Table 2. Median Absolute eGFR Change Over 5 Years and by Year in Cohort for Each Trajectory Class

	Absolute Annualized ΔeGFR[a] [IQR]	Absolute ΔeGFR, mL/min/1.73 m^2, by Interval [IQR]				
		T_{-5} to T_{-4}	T_{-4} to T_{-3}	T_{-3} to T_{-2}	T_{-2} to T_{-1}	T_{-1} to T_0
Overall cohort	−3.44 [−6.05 to −1.65]	−1.98 [−9.07 to 3.49]	−2.53 [−8.34 to 2.21]	−2.49 [−7.88 to 2.06]	−3.05 [−8.41 to 1.34]	−4.22 [−9.89 to −0.20]
Trajectory class						
1	−2.45 [−3.89 to −1.16]	−2.03 [−7.57 to 3.16]	−1.98 [−6.30 to 2.28]	−1.89 [−5.90 to 2.15]	−2.19 [−6.16 to 1.59]	−3.05 [−6.93 to −0.15]
2	−8.60 [−11.29 to −6.66]	−6.24 [−16.75 to −0.35]	−9.16 [−18.55 to −0.45]	−8.81 [−17.45 to −0.51]	−7.87 [−15.56 to −0.29]	−6.81 [−13.04 to −1.84]
3	−6.98 [−9.27 to −5.16]	−0.43 [−10.14 to 8.52]	−0.44 [−8.71 to 6.76]	−0.48 [−9.54 to 6.90]	−7.98 [−18.15 to −0.32]	−21.36 [−33.05 to −12.17]

Abbreviations and definitions: ΔeGFR, change in estimated glomerular filtration rate; IQR, interquartile range; T_0, time point of cohort entry; T_{-n}, time point *n* years prior to cohort entry; trajectory class 1, consistent slow decline in eGFR; trajectory class 2, consistent fast decline; trajectory class 3, early nondecline and late fast decline.

[a]Expressed in mL/min/1.73 m^2 per year; calculated over entire 5-year period.

Table 3. Adjusted Correlates of Kidney Function Trajectories

	Trajectory Class 2	Trajectory Class 3
Age	0.93 (0.93-0.94)[a]	0.92 (0.92-0.93)[a]
Sex: male vs female	1.90 (1.56-2.31)[a]	2.46 (1.90-3.18)[a]
Race: black vs white	1.37 (1.25-1.50)[a]	1.31 (1.16-1.49)[a]
Race: other vs white	1.15 (0.92-1.45)	1.34 (1.00-1.78)[a]
Qualifying eGFR	1.02 (1.01-1.03)[a]	1.06 (1.05-1.07)[a]
Cerebrovascular disease	0.82 (0.65-1.04)	0.97 (0.74-1.27)
Cardiovascular disease	1.00 (0.93-1.08)	1.04 (0.94-1.16)
Dementia	0.89 (0.79-1.01)	1.18 (1.02-1.36)[a]
Diabetes mellitus	1.68 (1.56-1.82)[a]	1.29 (1.17-1.42)[a]
HCV	1.61 (1.36-1.90)[a]	1.69 (1.56-1.82)[a]
HIV	1.16 (1.05-1.28)[a]	1.24 (1.10-1.41)[a]
Hypertension	1.04 (0.84-1.29)	0.89 (0.69-1.14)
Hyperlipidemia	1.08 (0.97-1.19)	1.00 (0.88-1.13)
Chronic lung disease	1.19 (1.10-1.28)[a]	1.38 (1.26-1.52)[a]
Peripheral artery disease	0.97 (0.88-1.07)	0.95 (0.84-1.08)
No. of nephrology clinic visits	0.92 (0.91-0.93)[a]	0.81 (0.79-0.82)[a]
No. of hospitalizations	1.12 (1.10-1.13)[a]	1.18 (1.17-1.20)[a]

Note: Values are given as correlate (95% confidence interval). Trajectory class 1 (consistent slow decline in eGFR) is referent group with all correlate values of 1.00. Trajectory class 2, consistent fast decline; trajectory class 3, early nondecline and late fast decline.

Abbreviations: eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a]Statistically significant.

disease outcome remained higher for trajectory classes 1 and 2 (9% and 12%, respectively), and the likelihood of death was significantly higher for trajectory class 3 (88% more likely to have the outcome of death at 5 years than the composite kidney disease outcome; Fig 3B).

DISCUSSION

We characterized kidney function trajectories of people entering CKD stage 4, and our results suggest 3 phenotypically distinct functional trajectories: consistent slow decline (trajectory class 1), consistent fast decline (trajectory class 2), and early nondecline and late fast decline (trajectory class 3). Although trajectory classes 1 and 2 follow a classic pattern of consistent slow or fast decline, trajectory class 3 is particularly interesting in that it shows an inflection point at which a period of nondecline yields to a period of fast deterioration in kidney function. This trajectory class is consistent with prior observations from Li et al[9] and Onuigbo,[31,32] who described a group of patients with early nondecline followed by fast eGFR decline who progress to ESRD. Examination of adjusted demographic and clinical correlates suggests that compared with those with consistent slow decline, others are likely to be younger and of black race and are associated with discordant comorbid conditions and viral infections. Compared with those with consistent slow decline, patients with

Table 4. Association Between Presence of Concordant Comorbid Conditions, Discordant Comorbid Conditions, and Viral Infections With Each Trajectory Class

	Trajectory Class 2	Trajectory Class 3
Concordant comorbid conditions[a]	1.32 (0.82-2.11)	1.05 (0.61-1.80)
Discordant comorbid conditions[b]	1.29 (1.14-1.46)[c]	1.39 (1.17-1.65)[c]
Viral infections[d]	1.30 (1.19-1.43)[c]	1.48 (1.32-1.65)[c]

Note: Values are given as odds ratio (95% confidence interval). Trajectory class 1 (consistent slow decline in eGFR) is referent group with all odds ratios of 1.00. Trajectory class 2, consistent fast decline; trajectory class 3, early nondecline and late fast decline. Models adjusted for receipt of nephrology care, number of hospitalizations, age, sex, race, and qualifying eGFR.

Abbreviation: eGFR, estimated glomerular filtration rate.

[a]Concordant comorbid conditions include cerebrovascular disease, cardiovascular disease, diabetes mellitus, hypertension, and peripheral artery disease.

[b]Discordant comorbid conditions include chronic lung disease, hyperlipidemia, and dementia.

[c]Statistically significant.

[d]Viral infections include hepatitis C virus and human immunodeficiency virus.

consistent fast decline have similar risk for kidney disease outcome but significantly increased risk for death. Those with early nondecline and late fast decline exhibit reduced risk for kidney disease outcomes and significantly increased risk for death. Survival analyses suggest that those with early nondecline and late fast decline are at higher risk for death than for kidney disease outcomes.

To our knowledge, this is the first study to characterize kidney function trajectories of patients entering CKD stage 4 and examine the relationship between different trajectory classes and kidney disease outcomes or death. Most people with CKD die before reaching CKD stage 5 and requiring initiation of dialysis therapies or receipt of a kidney transplant. In this cohort of 26,246 people entering CKD stage 4, the total number of deaths (14,550 [55%]) exceeded the number of those with kidney disease outcomes (9,809 [37%]), the latter number being almost equal to that of cohort participants who died without having the composite kidney disease outcome (9,552). In devising and coordinating a plan of care during the transition from CKD stage 4 to stage 5, trajectory analysis of eGFR—an opportunity largely created by the convergence of multiple factors, including increasing use and availability of electronic health record systems and advances in analytics and data visualization—may help with identification and risk stratification of patients at highest risk for kidney disease outcomes or death, inform resource allocation of finite health care resources, help guide decision support systems, and inform patient preferences regarding their care.[4,33,34]

Table 5. Kidney Function Trajectories and Risk for the Composite Kidney Disease Outcome Within 1, 2, 3, 4, and 5 Years

Composite Kidney Disease Outcome Within:	Trajectory Class 2	Trajectory Class 3
1 y	1.13 (1.05-1.22)[a]	0.67 (0.59-0.75)[a]
2 y	1.05 (0.99-1.12)	0.54 (0.49-0.60)[a]
3 y	1.00 (0.94-1.06)	0.51 (0.46-0.56)[a]
4 y	0.97 (0.91-1.02)	0.48 (0.44-0.53)[a]
5 y	0.96 (0.91-1.01)	0.47 (0.43-0.51)[a]

Note: Values are given as hazard ratio (95% confidence interval). Trajectory class 1 (consistent slow decline) is referent group with all hazard ratios of 1.00. Trajectory class 2, consistent fast decline; trajectory class 3, early nondecline and late fast decline. Models adjusted for receipt of nephrology care, number of hospitalizations, age, sex, race, qualifying estimated glomerular filtration rate, cerebrovascular disease, cardiovascular disease, dementia, diabetes mellitus, hepatitis C virus, human immunodeficiency virus, hypertension, hyperlipidemia, chronic lung disease, and peripheral artery disease.

[a]Statistically significant.

Table 6. Kidney Function Trajectories and Risk for Death Within 1, 2, 3, 4, and 5 Years

Risk for Death Within:	Trajectory Class 2	Trajectory Class 3
1 y	1.17 (1.10-1.28)[a]	1.29 (1.18-1.42)[a]
2 y	1.13 (1.06-1.21)[a]	1.19 (1.11-1.29)[a]
3 y	1.13 (1.07-1.19)[a]	1.12 (1.05-1.20)[a]
4 y	1.12 (1.07-1.18)[a]	1.06 (1.00-1.13)
5 y	1.11 (1.06-1.16)[a]	1.04 (0.98-1.10)

Note: Values are given as hazard ratio (95% confidence interval). Trajectory class 1 (consistent slow decline) is referent group with all hazard ratios of 1.00. Trajectory class 2, consistent fast decline; trajectory class 3, early nondecline and late fast decline. Models adjusted for receipt of nephrology care, number of hospitalizations, age, sex, race, qualifying estimated glomerular filtration rate, cerebrovascular disease, cardiovascular disease, dementia, diabetes mellitus, hepatitis C virus, human immunodeficiency virus, hypertension, hyperlipidemia, chronic lung disease, and peripheral artery disease.

[a]Statistically significant.

Tonelli et al[24] recently introduced the concept of concordant and discordant comorbid conditions as important independent drivers of adverse outcomes associated with CKD. The authors make the case, quite compellingly, that most studies focus on concordant comorbid conditions (conditions that cause CKD or often accompany CKD), but much less attention is directed at discordant comorbid conditions (conditions that are not concordant but clinically relevant).[24] In this report, we found that concordant comorbid conditions were not significantly associated with trajectory class (ie, the presence of a concordant comorbid condition does not allow discrimination between trajectories), whereas discordant comorbid conditions exhibited a significant association with trajectories with consistent fast decline (class 2) and

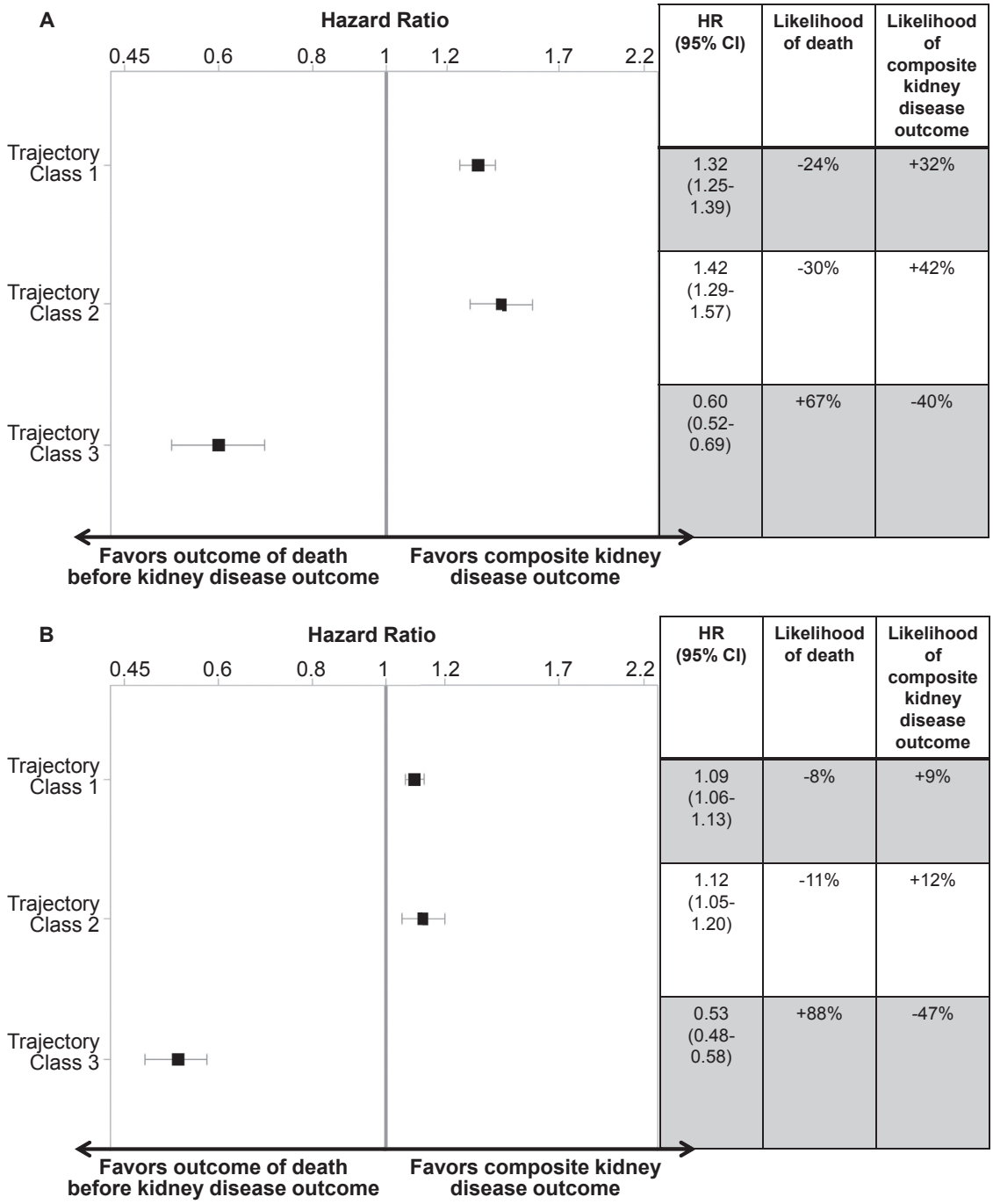

Figure 3. Comparative evaluation of risk for death versus the composite kidney disease outcome in each trajectory class. Comparative risks at (A) 1 year and (B) 5 years. Abbreviations: CI, confidence interval; HR, hazard ratio.

early nondecline and late fast decline (class 3). Similarly, viral infections, including HCV and HIV, exhibited a more significant association with trajectory classes 2 and 3 compared to trajectory class 1. The results suggest that discordant conditions, often disregarded in the context of CKD assessment, may inform the risk for specific trajectory classes.

Numerous approaches have been used to characterize longitudinal eGFR changes, including linear regression models, percent annual decline, absolute change in eGFR, change in eGFR category or stage, and a combination of these.[35-39] Studies by O'Hare et al[10] and others[9] suggest that eGFR trajectories are often not linear and that the probability of linearity is reduced with a prolonged observation window and the approach of ESRD. The fidelity of measures that capture eGFR change over time (or rate of CKD progression) depends on the number of eGFR

assessments and the time in which the rate of eGFR change is assessed.[30] Turin et al[40] note that a rate of eGFR change based on more than 2 serum creatinine measurements over a period of more than 1 year is required to allow better risk prediction. In this study, we assessed kidney function trajectories using latent class models and a median of 10 (IQR, 9-11) eGFR assessments over a median duration of 4.79 (IQR, 4.60-4.91) years. It is important to note that while we reported changes in eGFR per year and for overall duration, the method used to classify trajectory was the latent class model system that groups patients with similar longitudinal eGFR behavior together, and we then clustered them into trajectory classes and used these as primary predictors to estimate risk for kidney disease outcomes and death. Comparative evaluation and validation of different methods to capture eGFR changes over time are needed. The simplified approach to measure annualized change over time using linear regression models or percent change based on initial and last eGFR may not be sufficiently nuanced and does not account for the possibility that kidney function trajectories may not be linear in some patients and that the probability of linearity is significantly reduced with an expanded observation window.[41]

Our study has a number of limitations. The cohort included mostly older white male US veterans who received care at the VA system; thus, results may not be generalizable to less narrowly defined populations. Our data set did not include information for albuminuria and proteinuria. With the inclusion criteria specifying the minimum number of creatinine measurements needed for cohort entry and because the frequency of creatinine measurements is likely a surrogate marker of worse overall health, we might have systematically missed people who seldom seek care within the VA system, and our cohort could be sicker versus a broader population of veterans. Administrative data are not perfect, and this together with the retrospective design of the study might result in sampling bias and inaccurate measurements of predictor variables. We used definitions of comorbid illnesses validated for use in VA administrative data in order to lessen such measurement bias.

In conclusion, we characterized 3 distinct eGFR trajectories of patients entering CKD stage 4: those with consistent slow decline (trajectory class 1), those with consistent fast decline (trajectory class 2), and those with early nondecline and late fast decline (trajectory class 3). The presence of concordant comorbid conditions does not allow discrimination between trajectory classes. However, discordant comorbid conditions associate more strongly with trajectory classes 2 and 3. Trajectory class 3, showing early nondecline and late fast decline, exhibits increased risk for death and comparatively less risk for the kidney disease outcome. Longitudinal eGFR is not linear, especially when the observation window is prolonged. More studies are needed to determine the best methodology of characterizing longitudinal kidney function changes and their relationship with clinical outcomes, and whether the use of analytics and data visualization tools in the clinical environment will help improve patient experience and ultimately outcomes.

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SUPPLEMENTARY MATERIAL

Table S1: *ICD-9-CM* and *CPT* codes used to define covariates.

Table S2: Median percent change in eGFR over 5 y and by year in overall cohort and for each trajectory class before cluster analysis.

Table S3: Kidney function trajectories and risk of ESRD within 1, 2, 3, 4, and 5 y.

Table S4: Kidney function trajectories and risk of composite kidney disease outcomes in fully adjusted models including AKI.

Table S5: Kidney function trajectories and risk of death in fully adjusted models including AKI.

Item S1: Trajectory classification.

Item S2: Competing-risk models of kidney function trajectories and risk of composite kidney outcome and treated vs untreated chronic kidney failure.

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