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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

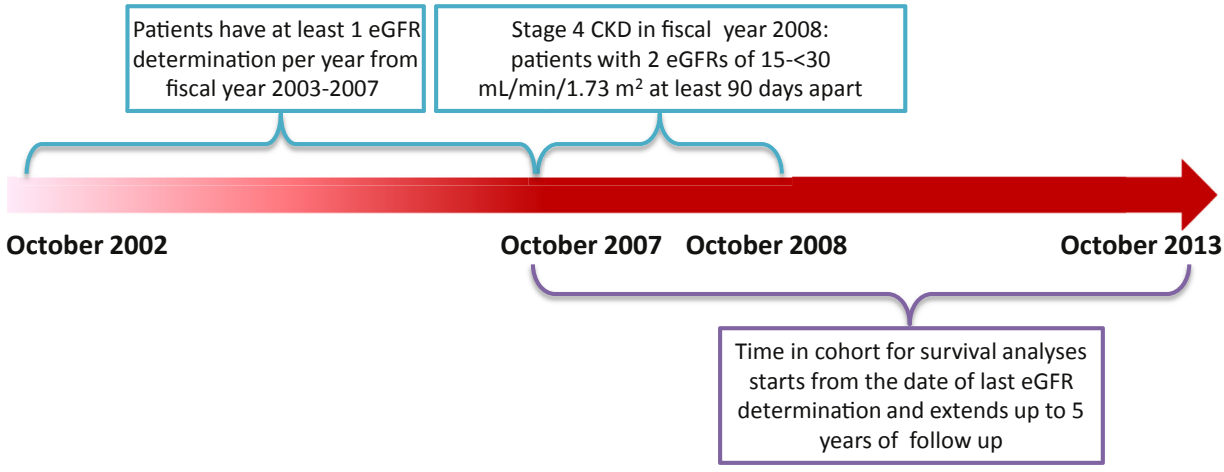

Figure 1. Timeline of cohort assembly. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.