# Rate of Kidney Function Decline and Risk of Hospitalizations in Stage 3A CKD

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## Abstract

**Background and objectives** Risk of hospitalizations is increased in patients with CKD. We sought to examine the association between rate of kidney function decline and risk of hospitalization in a cohort of patients with early CKD.

**Design, settings, participants, & measurements** We built a cohort of 247,888 United States veterans who had at least one eGFR measurement between October 1999 and September 2003 and an additional eGFR between October 2003 and September 2004. We selected patients whose initial eGFR was between 45 and 59 ml/min per 1.73 $m^2$. Rate of eGFR change (in milliliters per minute per 1.73 $m^2$ per year) was categorized as no decline (>0), mild (0 to −1, and served as the referent group), moderate (−1 to −5), or severe (>−5) eGFR decline. We built survival models to examine the association between the rate of kidney function decline and the risk of hospitalization and readmission and linear regression to estimate length of hospital stay.

**Results** Over a median observation of 9 years (interquartile range, 5.28–9.00), patients with moderate and severe eGFR decline exhibited a higher risk of hospitalizations (hazard ratio [HR], 1.22; 95% confidence interval [95% CI], 1.19 to 1.26; and HR, 1.33; 95% CI, 1.28 to 1.39, respectively). Among patients with moderate and severe eGFR decline, the association between the rate of decline and the risk of hospitalizations was more pronounced with an increased number of hospitalizations ($P<0.01$). Patients with moderate and severe eGFR decline had a higher risk of readmission (HR, 1.19; 95% CI, 1.13 to 1.26; and HR, 1.53; 95% CI, 1.43 to 1.63, respectively). Among patients with severe eGFR decline, the association between the rate of kidney function decline and the risk of readmission was stronger with an increased number of readmissions ($P<0.01$). Patients with moderate and severe eGFR decline experienced an additional length of stay of 1.40 (95% CI, 0.88 to 1.92) and 5.00 days per year (95% CI, 4.34 to 5.66), respectively.

**Conclusions** The rate of kidney function decline is associated with a higher risk of hospitalizations, readmissions, and prolonged length of hospital stay.


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## Introduction

CKD is associated with a higher risk of hospitalizations (1,2). CKD is a dynamic disease that progresses in some but not all patients (3). The association between the rate of kidney function decline and the risk of death has been examined previously and illustrates that beyond the risk characterization provided by cross-sectional data, incorporating the rate of change over time adds valuable prognostic information (4,5).

Hospitalizations are costly and potentially preventable events (6). Numerous observations from cross-sectional analyses have demonstrated a strong relationship between CKD and risk of hospitalizations (1,7–9). James *et al.* reported a strong relationship between reduced eGFR and risk of hospitalization with pneumonia (7). Fischer *et al.* reported that among patients who were hospitalized with acute coronary syndrome and discharged on the antiplatelet agent clopidogrel, those with reduced eGFR had a higher risk of hospitalization for acute myocardial infarction (10). Findings from studies by Wiebe *et al.* suggest that the risk of hospitalization in patients with CKD is highest among remote dwellers and those with comorbid conditions including heart failure and liver disease (11). Nitsch *et al.* studied the relationship between CKD and hospital admission in a cohort of community-dwelling older adults and reported a trend of higher risk among those with an eGFR between 45 and 59 ml/min per 1.73 $m^2$ (12). Mix *et al.* evaluated the incidence of prior hospitalization in patients who reached ESRD and found that hospitalization rates gradually increased as ESRD approached, peaking in the 3 months immediately after the initiation of dialysis therapy (13).

All prior studies evaluated the association between cross-sectional measures of kidney function and risk of hospitalization. The relationship between rate of kidney function decline and risk of hospitalization has not been previously examined. Further understanding of the relationship between longitudinal kidney

  

function behavior and risk of hospitalization fills a knowledge gap, might help identify patients with kidney disease who are at the highest risk for hospitalization, and may inform strategies aimed at reducing risk of hospitalizations in these patients. We hypothesized that patients with a rapid decline in kidney function experience a longer hospital stay and are at a higher risk of future hospitalization as well as readmission within 30 days. We therefore examined the association between the rate of kidney function decline and hospitalizations, readmissions within 30 days, and length of hospital stay in a cohort of 247,888 US veterans with early CKD stage 3.

## Materials and Methods

### Patients

Using administrative data from the US Department of Veterans Affairs (VA), we identified users of the VA Healthcare System who had at least one outpatient serum creatinine measurement between October 1, 1999 and September 30, 2003, and at least one outpatient serum creatinine between October 1, 2003 and September 30, 2004 ($n$=2,180,280). We selected patients whose first eGFR was between 45 and <60 ml/min per 1.73 $m^2$, and whose first and last creatinine measurements are at least 90 days apart. Patients were excluded if they had received a kidney transplant or had undergone at least one session of dialysis before time zero (the time of the last eGFR measurement), yielding an analytic cohort of 247,888 individuals. Timeline for cohort selection is depicted in Figure 1. This study was approved by the Institutional Review Board of the VA Saint Louis Health Care System (Saint Louis, MO).

### Data Sources

We used VA databases including inpatient and outpatient medical SAS data sets (which include utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed patient demographic characteristics and comorbidity information based on Current Procedural Terminology (CPT) codes, as well as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes associated with inpatient and outpatient encounters (14–17). The VA Decision Support System Laboratory Results file (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information on outpatient and inpatient serum creatinine measurements during the 5-year period preceding cohort entry (14,15,18). The VA Vital Status and Beneficiary Identification Records Locator Subsystem files provided demographic characteristics and death follow-up through September 30, 2013 (14,15).

### Primary Predictor Variable

The primary predictor variable for all analyses was the rate of change in eGFR over time. For each patient, we calculated the eGFR slope by fitting an ordinary least-squares regression line to all outpatient eGFR measures from October 1, 1999 through September 30, 2004. The slope of the regression line ($\beta$) describes the rate of change in kidney function (eGFR) over time. For the primary analysis, eGFR was calculated using the abbreviated four-variable Chronic Kidney Disease Epidemiology Collaboration equation based on age, sex, race, and serum creatinine level (19). We identified four patient categories on the basis of the rate of change in eGFR: (*1*) those who did not experience any decline (rate of change of eGFR >0 ml/min per 1.73 $m^2$ per year) and those who experienced (*2*) mild decline in kidney function over time (rate of eGFR loss of 0 to −1 ml/min per 1.73 $m^2$ per year), (*3*) moderate decline (rate of eGFR loss of −1 to −5 ml/min per 1.73 $m^2$ per year), and (*4*) severe decline (rate of eGFR loss <−5 ml/min per 1.73 $m^2$ per year) (3,20). The cutoff points in these groups are based on studies showing that an eGFR decline of 0 to −1 ml/min per year is associated with least risk of untoward clinical outcomes, whereas a decline that exceeds 5 ml/min per year represents rapid progression (3,21–26). In sensitivity analyses, the annual percentage change in eGFR was calculated using the following formula: [(final eGFR − initial eGFR)/initial eGFR)]/[(final date − initial date)/365.25] × 100. Participants

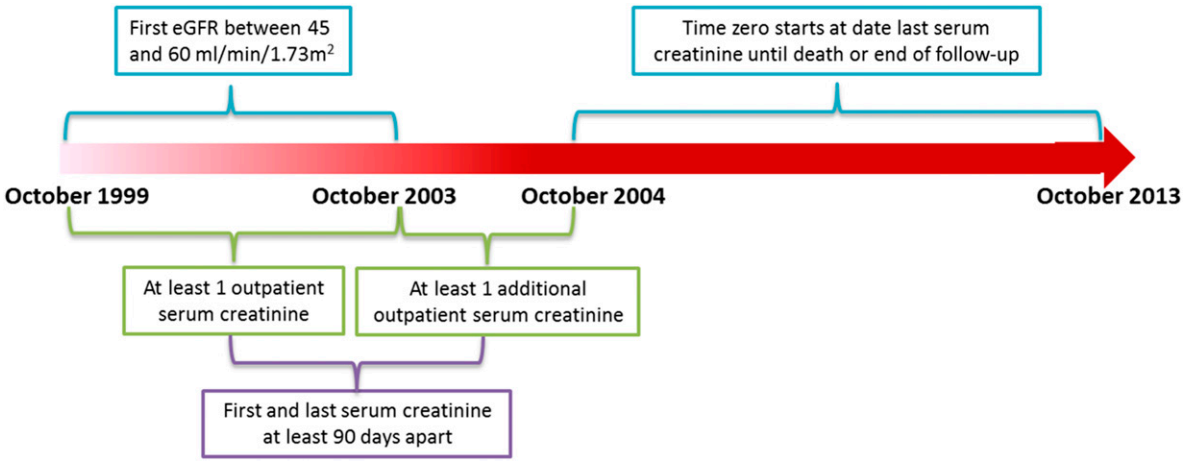


**Figure 1.** | **Timeline of cohort selection.**

**Table 1. Baseline characteristics according to rate of kidney function decline category**

| Characteristic | Overall Cohort | CKD Progression by eGFR Change Values | | | |
|---|---|---|---|---|---|
| | | No Decline in Kidney Function ( >0) | Mild (Between 0 and −1) | Moderate (Between −1 and −5) | Severe (<−5) |
| Number of patients | 247,888 | 111,318 (44.9) | 36,132 (14.6) | 74,117 (29.9) | 26,321 (10.6) |
| **Patient study outcome** | | | | | |
| Without hospitalizations | 170,668 (68.9) | 77,535 (69.7) | 25,613 (70.9) | 49,336 (66.6) | 18,184 (69.1) |
| With hospitalizations | 77,220 (31.2) | 33,783 (30.4) | 10,519 (29.1) | 24,781 (33.4) | 8137 (30.9) |
| With hospitalizations without readmission | 53,465 (69.2) | 24,198 (71.6) | 7466 (71.0) | 16,630 (67.1) | 5171 (63.6) |
| With readmissions | 23,755 (30.8) | 9585 (28.4) | 3053 (29.0) | 8151 (32.9) | 2966 (36.5) |
| Age, average (SD) | 70.3 (8.3) | 69.0 (8.9) | 71.1 (7.8) | 71.7 (7.3) | 71.1 (7.7) |
| **Race** | | | | | |
| White | 216,775 (87.5) | 96,785 (86.9) | 31,880 (88.2) | 65,045 (87.8) | 23,065 (87.9) |
| Black | 26,714 (10.8) | 12,583 (11.3) | 3640 (10.1) | 7662 (10.3) | 2829 (10.8) |
| Other | 4399 (1.8) | 1950 (1.8) | 612 (1.7) | 1410 (1.9) | 427 (1.6) |
| Male sex | 237,128 (95.7) | 105,816 (95.1) | 34,427 (95.3) | 71,371 (96.3) | 25,514 (96.9) |
| Diabetes mellitus | 87,807 (35.4) | 33,797 (30.4) | 11,120 (30.8) | 30,218 (40.8) | 12,672 (48.1) |
| Hypertension | 207,621 (83.8) | 88,960 (79.9) | 29,607 (81.9) | 65,517 (88.4) | 23,537 (89.4) |
| Cardiovascular disease | 116,593 (47.0) | 47,009 (42.2) | 16,342 (45.2) | 38,551 (52.0) | 14,691 (55.8) |
| Hyperlipidemia | 176,627 (71.3) | 76,557 (68.8) | 25,845 (71.5) | 55,421 (74.8) | 18,804 (71.4) |
| Peripheral artery disease | 12,396 (5.0) | 4344 (3.9) | 1553 (4.3) | 4698 (6.3) | 1801 (6.8) |
| Cerebrovascular disease | 2331 (0.9) | 817 (0.7) | 324 (0.9) | 876 (1.2) | 314 (1.2) |
| Chronic lung disease | 58,418 (26.6) | 25,491 (22.9) | 7953 (22.0) | 18,681 (25.2) | 6293 (23.9) |
| Hepatitis C | 3964 (1.6) | 1955 (1.8) | 438 (1.2) | 1023 (1.4) | 548 (2.1) |
| HIV | 14,376 (5.8) | 6245 (5.6) | 2006 (5.6) | 4770 (6.4) | 1355 (5.2) |
| Dementia | 10,995 (4.4) | 4663 (4.2) | 1484 (4.1) | 3612 (4.9) | 1236 (4.7) |
| Death | 108,478 (43.8) | 42,239 (37.9) | 14,301 (39.6) | 36,197 (48.8) | 15,741 (59.8) |
| **eGFR, average (SD)** | | | | | |
| Initial | 54.0 (4.2) | 53.9 (4.2) | 54.1 (4.2) | 53.9 (4.2) | 54.3 (4.2) |
| Final | 54.5 (13.5) | 63.7 (11.3) | 53.4 (6.9) | 46.8 (8.4) | 39.1 (11.0) |
| Rate of eGFR change (ml/min/1.73m$^2$/year)[a] | 0.2 (6.2) | 4.4 (6.1) | −0.5 (0.3) | −2.6 (1.1) | −8.5 (4.8) |
| Median follow-up, yr[b] | 9.0 (5.3–9.0) | 9.0 (6.2–9.0) | 9.0 (6.2–9.0) | 9.0 (4.7–9.0) | 7.4 (3.2–9.0) |
| Median no. of eGFR measures | 7 (4–11) | 6 (4–9) | 7 (3–11) | 8 (5–13) | 6 (3–12) |
| Median duration between first and last eGFR, yr | 3.2 (2.0–4.2) | 3.0 (1.9–4.0) | 3.4 (2.0–4.3) | 3.7 (2.6–4.4) | 2.3 (1.3–3.6) |
| Patients with hospitalizations during the baseline period[c] | 51,566 (20.8) | 21,445 (19.3) | 6223 (17.2) | 17,197 (23.2) | 6701 (25.5) |
| **No. of hospitalizations, average (SD)** | | | | | |
| During baseline period[c] | 0.5 (1.4) | 0.4 (1.3) | 0.4 (1.1) | 0.5 (1.4) | 0.7 (1.7) |
| After time zero | 1.0 (2.3) | 0.9 (2.2) | 0.9 (2.2) | 1.1 (2.5) | 1.1 (2.6) |

**Table 1. (Continued)**

| Characteristic | Overall Cohort | CKD Progression by eGFR Change Values | | | |
|---|---|---|---|---|---|
| | | No Decline in Kidney Function (>0) | Mild (Between 0 and −1) | Moderate (Between −1 and −5) | Severe (<−5) |
| **Length of hospital stay, d/yr** | | | | | |
| Median | 2.0 (0.8–5.7) | 1.7 (0.7–4.8) | 1.8 (0.7–4.8) | 2.3 (0.8–6.3) | 3.2 (1.0–9.1) |
| Average (SD) | 7.3 (22.6) | 6.3 (20.3) | 5.9 (18.5) | 7.9 (23.3) | 11.8 (31.4) |
| No. of patients without baseline hospitalizations | 196,322 (79.2) | 89,873 (45.8) | 29,909 (15.2) | 56,920 (29.0) | 19,620 (10.0) |
| No. of patients with baseline hospitalizations | 51,566 (20.8) | 21,445 (41.6) | 6223 (12.1) | 17,197 (33.3) | 6701 (13.0) |

Data are presented as *n* (%) or median (interquartile range) unless otherwise indicated. eGFR change values are given in ml/min per 1.73 $m^2$ per year. Percentages represent the column percentage.

[a]Values reflect the rate of change of eGFR per year calculated using an ordinary least-squares regression method fitted to all outpatient eGFR readings for each patient. The slope of the regression line describes the rate of change in kidney function (eGFR) over time.

[b]Follow-up time is the time between time zero and censorship.

[c]The baseline period ranges from October 1999 to the last eGFR (time zero).

were categorized into four groups corresponding to those in primary analyses: using an average eGFR of 53.99, −1 ml/min per 1.73 $m^2$ per year corresponds to a −2% change per year, and −5 ml/min per 1.73 $m^2$ per year corresponds to a −9% change per year (26–29).

### Outcomes

The primary outcome was the time from cohort entry to hospitalization. Hospitalization was defined as any inpatient hospital stay that exceeds 23 hours. Readmission was defined as any hospitalization <30 days from a prior hospital stay. Length of hospital stay was defined as number of days in the hospital per year.

### Covariates

Baseline covariates were ascertained at the time of cohort entry and for the preceding 5-year period (October 1, 1999 to September 30, 2004). Covariates included age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, and dementia. We built separate models controlling additionally for initial and last eGFR measurements. A number of additional covariates were used in sensitivity analyses, including the number of eGFR measurements, the number of hospitalizations during the baseline period (the period in which the rate of eGFR change is captured), and eGFR variability (calculated as previously reported) (26). Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial/ethnic minority group). Comorbidities were assigned on the basis of relevant ICD-9-CM diagnostic and procedures codes and CPT codes in the VA Medical SAS data sets.

### Statistical Analyses

The time period for the assessment of eGFR change ranged from October 1, 1999 to September 30, 2004. For the survival analyses, time in the cohort (time zero) started at the time of the last eGFR measurement; patients were followed until censorship or the end of follow-up on September 30, 2013. Because of the competing risk of death in patients with CKD, we used competing risk models to evaluate the association between the rate of kidney function decline and readmission as well as the risk of hospitalizations. For recurrent events including recurrent hospitalizations and recurrent readmissions, we used marginal survival models, in which each event was considered as a separate process (30). The time for each event started at the beginning of the follow-up period for each participant. A robust sandwich estimator of the covariance matrix was used to correct the estimated variances and to account for the intrapersonal correlation between different numbers of events. To evaluate the hazard of having at least 1, 2, 3, 4, and 5 events (hospitalizations or readmissions) in different CKD progression groups, marginal survival models included an independent variable representing five different strata. Every patient was considered at risk for all strata. An interaction between CKD progression group and event stratum was included to determine whether the stratum modified the relationship between the CKD progression group and the

event. A difference in hazard ratios (HRs) of the CKD progression group between a stratum and its preceding stratum, within the same CKD progression group, was detected by the *P* value of interaction between that CKD progression group and the proceeding stratum. To determine whether there was an increasing trend in the HR based on stratum, an interaction between CKD progression group and a continuous stratum variable was used. A significant *P* value for a positive $\beta$ estimate indicates the hazard difference between the mild CKD progression group (the referent group) and progression of the group of interest increases as the stratum increases. We built multivariate regression models to examine the effect of the rate of kidney function decline on length of hospital stay. In survival analyses, a 95% confidence interval (95% CI) of a HR that does not include unity was considered statistically significant. In all analyses, a *P* value of $\leq$0.05 was considered statistically significant. All analyses were performed using SAS Enterprise Guide software (version 6.1; SAS Institute, Cary, NC).

## Results

Among 247,888 patients in the overall cohort, 170,668 (68.8%) were never hospitalized and 77,220 (31.1%) were hospitalized at least once. Among those hospitalized at least once, 53,465 (69.2%) had no readmissions and 23,755 (30.8%) had at least one readmission (Table 1). In the overall cohort, 111,318 (44.9%) did not experience any kidney function decline, whereas 36,132 (14.5%), 74,117 (29.9%), and 26,324 (10.6%) experienced mild, moderate, and severe eGFR decline, respectively (Table 1). Tables 1 and 2 present the rate of eGFR change according to pattern of hospitalization after time zero and according to hospitalization status during the baseline period, respectively. The majority of patients were white and were men. The prevalence of comorbid conditions such as hypertension, diabetes mellitus, cardiovascular disease, and chronic lung disease was high. Baseline characteristics according to pattern of hospitalization are presented in Supplemental Table 1.

### Rate of Kidney Function Decline and the Risk of Hospitalizations

In the overall cohort, and over a median follow-up of 9.00 years (interquartile range [IQR], 5.28 to 9.00), 77,220 (31.2%) patients were hospitalized at least once. There were 33,783 (30.4%), 10,519 (29.1%), 24,781 (33.4%), and 8,137 (30.9%) patients who were hospitalized at least once in the groups of patients with no decline, mild, moderate, and severe eGFR decline, respectively (Table 1). In a fully adjusted Cox survival analysis for initial eGFR and other covariates, we found that compared with patients who experienced mild eGFR decline, patients who experienced moderate and severe eGFR decline exhibited higher risk of hospitalizations (HR, 1.22; 95% CI, 1.19 to 1.26; and HR, 1.33; 95% CI, 1.28 to 1.39, respectively) (Table 3). Models adjusted for covariates but not adjusted for initial or final eGFR showed consistent results (Table 3). Models adjusted for last eGFR showed that risk of hospitalization remains significant (HR, 1.17; 95% CI, 1.13 to 1.20; and HR, 1.18; 95% CI, 1.13 to 1.23 for moderate and severe CKD progression, respectively) (Table 3).

In fully adjusted models for last eGFR and other covariates, we examined the association between rate of kidney function decline and risk of having at least 1, 2, 3, 4, or $\geq$5 hospitalizations. We found that among those with moderate and severe decline in kidney function, the association between the rate of decline and the risk of hospitalization was modified by the number of hospitalizations and became increasingly more pronounced with an increased number of hospitalizations (*P* for interaction $<$0.01) (Table 4). Models that adjusted for initial eGFR showed similar results (Supplemental Table 2).

### Rate of Kidney Function Decline and the Risk of Readmission within 30 Days

In the overall cohort, and over a median follow-up of 9.00 years (IQR, 5.28–9.00), and among those hospitalized at least once (*n*=77,220), 23,755 (30.8%) experienced at least one readmission; 9585 (28.4%), 3053 (29.0%), 8151 (32.9%), and 2966 (36.4%) patients experienced at least one readmission in the groups of patients with no decline or mild, moderate, and severe eGFR decline, respectively.

In fully adjusted models for initial eGFR and other covariates, there was a significant and graded association between the rate of kidney function decline and future readmission risk (two hospital admissions $<$30 days apart). Compared with patients with a mild decline in kidney function, patients with moderate and severe kidney function decline had a higher risk of future readmission (HR, 1.19; 95% CI, 1.13 to 1.26; and HR, 1.53; 95% CI, 1.43 to 1.63, respectively). Models adjusted for last eGFR show that the association between CKD progression and risk of hospital readmission remained significant (HR, 1.12; 95% CI, 1.06 to 1.18; and HR, 1.29; 95% CI, 1.20 to 1.39 for moderate and severe CKD progression, respectively) (Table 3).

**Table 2. Rate of eGFR change according to baseline hospitalizations**

| Rate of eGFR Change per Year | Patients with Baseline Hospitalizations (*n*=51,566) | Patients without Baseline Hospitalizations (*n*=196,322) |
|---|---|---|
| Average (SD) | −0.44 (6.21) | 0.35 (6.14) |
| Median (IQR) | −0.70 (−3.05, 1.67) | −0.34 (−2.40, 2.32) |

eGFR change values are given in ml/min per 1.73 $m^2$ per year. Baseline hospitalizations are hospitalizations during the period in which eGFR change was assessed (October 1999 to September 2004). IQR, interquartile range.

**Table 3. Hazard ratio for the association between rate of kidney function decline and risk of hospitalization and readmission**

| Risk Model | CKD Progression by eGFR Change Values | | | |
|---|---|---|---|---|
| | No Decline in Kidney Function ( >0) | Mild (Between 0 and −1) | Moderate (Between −1 and −5) | Severe (<−5) |
| **Risk of hospitalization** | 111,318 (44.9) | 36,132 (14.6) | 74,117 (29.9) | 26,321 (10.6) |
| Model 1 | 0.99 (0.96 to 1.02) | 1.00 | 1.22 (1.19 to 1.26) | 1.32 (1.27 to 1.38) |
| Model 2 | 0.99 (0.96 to 1.02) | 1.00 | 1.22 (1.19 to 1.26) | 1.33 (1.28 to 1.39) |
| Model 3 | 1.06 (1.03 to 1.10) | 1.00 | 1.17 (1.13 to 1.20) | 1.18 (1.13 to 1.23) |
| **Risk of readmission** | 33,783 (43.8) | 10,519 (13.6) | 24,781 (32.1) | 8137 (10.5) |
| Model 1 | 0.97 (0.92 to 1.03) | 1.00 | 1.19 (1.13 to 1.26) | 1.51 (1.42 to 1.62) |
| Model 2 | 0.97 (0.92 to 1.02) | 1.00 | 1.19 (1.13 to 1.26) | 1.53 (1.43 to 1.63) |
| Model 3 | 1.07 (1.01 to 1.13) | 1.00 | 1.12 (1.06 to 1.18) | 1.29 (1.20 to 1.39) |

Data are presented as *n* (%) or hazard ratios (95% confidence intervals). eGFR change values are given in ml/min per 1.73 $m^2$ per year. Model 1 was adjusted for age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, and dementia. Model 2 includes covariates in model 1 and initial eGFR. Model 3 includes covariates in model 1 and last eGFR.

In fully adjusted models for last eGFR and other covariates, we examined the association between the rate of kidney function decline and the risk of recurrent readmissions in marginal survival models for recurrent events. We found that compared with the reference group, patients with severe CKD decline had a higher risk of having at least 1,2, 3, 4, or ≥5 readmissions (Table 4). This relationship was modified by number of readmissions and became increasingly more robust with the increased number of readmissions (*P* for interaction <0.01). Models that adjusted for initial eGFR showed similar results (Supplemental Table 3).

**Table 4. Hazard ratio of the association between rate of kidney function decline and risk of at least 1, 2, 3, 4, 5 or more hospitalizations or readmissions controlling for last eGFR**

| Risk of at Least | CKD Progression by eGFR Change Values | | | |
|---|---|---|---|---|
| | No Decline in Kidney Function ( >0) | Mild (Between 0 and −1) | Moderate (Between −1 and −5) | Severe (<−5) |
| **Hospitalizations** | | | | |
| 1 | 1.07 (1.04 to 1.10) | 1.00 | 1.11 (1.09 to 1.14) | 1.07 (1.03 to 1.11) |
| 2 | 1.06 (1.03 to 1.09) | 1.00 | 1.16 (1.13 to 1.20)[a] | 1.15 (1.11 to 1.20)[a] |
| 3 | 1.04 (1.00 to 1.08) | 1.00 | 1.20 (1.16 to 1.25)[b] | 1.22 (1.17 to 1.28)[a] |
| 4 | 1.05 (1.00 to 1.09) | 1.00 | 1.25 (1.19 to 1.30)[b] | 1.31 (1.24 to 1.38)[a] |
| 5 | 1.04 (0.99 to 1.09) | 1.00 | 1.29 (1.22 to 1.36)[b] | 1.39 (1.31 to 1.48)[a] |
| *P* value for trend | 0.16 | N/A | <0.001 | <0.001 |
| **Readmissions** | | | | |
| 1 | 1.08 (1.03 to 1.13) | 1.00 | 1.10 (1.05 to 1.15) | 1.23 (1.16 to 1.30) |
| 2 | 1.06 (1.00 to 1.13) | 1.00 | 1.14 (1.07 to 1.21) | 1.37 (1.27 to 1.48)[a] |
| 3 | 1.06 (0.97 to 1.16) | 1.00 | 1.16 (1.06 to 1.27) | 1.50 (1.35 to 1.67)[b] |
| 4 | 1.04 (0.92 to 1.17) | 1.00 | 1.23 (1.09 to 1.38) | 1.69 (1.48 to 1.94)[b] |
| 5 | 1.02 (0.87 to 1.19) | 1.00 | 1.20 (1.03 to 1.40) | 1.66 (1.39 to 1.97) |
| *P* value for trend | 0.47 | N/A | 0.09 | <0.001 |

Data are presented as *n* (%) or hazard ratios (95% confidence intervals). eGFR change values are given in ml/min per 1.73 $m^2$ per year. Models were adjusted for last eGFR value, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, and dementia. *P* value for interaction denotes a significant interaction between CKD progression group and stratum (number of hospitalizations) and indicates that the stratum's hazard ratio is significantly different from the previous stratum in the same CKD progression group. *P* value for trend was obtained from an interaction between CKD progression group and number of hospitalizations while treating number of hospitalizations as a continuous variable. A significant *P* value for trend indicates that compared with the referent category (patients with mild CKD progression), the hazard ratio of the category of interest significantly increases as the number of hospitalizations increases. N/A, not applicable.

[a]*P* value for interaction <0.001.

[b]*P* value for interaction <0.05.

### Length of Hospital Stay

Among those hospitalized at least once ($n$=77,220), median length of hospital stay was 2.00 days per patient per year (IQR, 0.75–5.67); median length of stay was higher among those with at least one readmission (median 5.86 days per patient per year; IQR, 2.85–12.14) (Supplemental Table 1) and among those with moderate and severe kidney function decline (Table 1). In multivariate regression models (adjusted for first eGFR and other covariates), compared with patients in the reference group, patients with moderate and severe decline in kidney function experienced an additional length of stay of 1.55 (95% CI, 1.02 to 2.07) and 5.29 (95% CI, 4.62 to 5.95) days per year, respectively (Figure 2). In a model that additionally controls for the number of hospitalizations, compared with patients with a mild decline in kidney function, patients with moderate and rapid kidney function decline experienced an additional hospital stay of 1.40 (95% CI, to 0.88 to 1.92) and 5.00 (95% CI, 4.34 to 5.66) days per year, respectively.

### Sensitivity Analyses

To evaluate the consistency of our study findings, we (*1*) included baseline hospitalizations as a covariate, (*2*) restricted cohort entry to those without prior hospitalizations, (*3*) included the number of eGFR measurements as a covariate, (*4*) restricted cohort entry to patients with at least five eGFR measurements, and (*5*) included eGFR variability as a covariate in the models and obtained the same results (Table 5). We used a different threshold to define severe kidney function decline (eGFR loss $<-4$ ml/min per 1.73 $m^2$ per year) and obtained similar results (data not shown). We calculated eGFR change using the annual percentage change, and we found that those who experience an annual percent decline >2% had a higher risk of hospitalizations and readmissions (Supplemental Table 4). In addition, we used the Modification of Diet in Renal Disease study equation to estimate GFR (31). We censored patients at the time of renal transplantation, ESRD, or dialysis, and we restricted the analyses to those who remained alive until the end of the study follow-up. We evaluated the associations in competing risk models for death and consistently found the same results, in that the direction and magnitude of risk remained essentially unchanged (Supplemental Table 5).

## Discussion

Previous studies have reported that a faster rate of kidney function decline is associated with a higher risk of all-cause mortality, ESRD, and cardiovascular events. A number of studies reported an association between cross-sectional measures of kidney function and risk of hospitalizations (1,6–13,32). This study further expands on these findings and demonstrates that after controlling for initial or final eGFR, the rate of decline remains a significant predictor of future risk of hospitalization, readmission, and

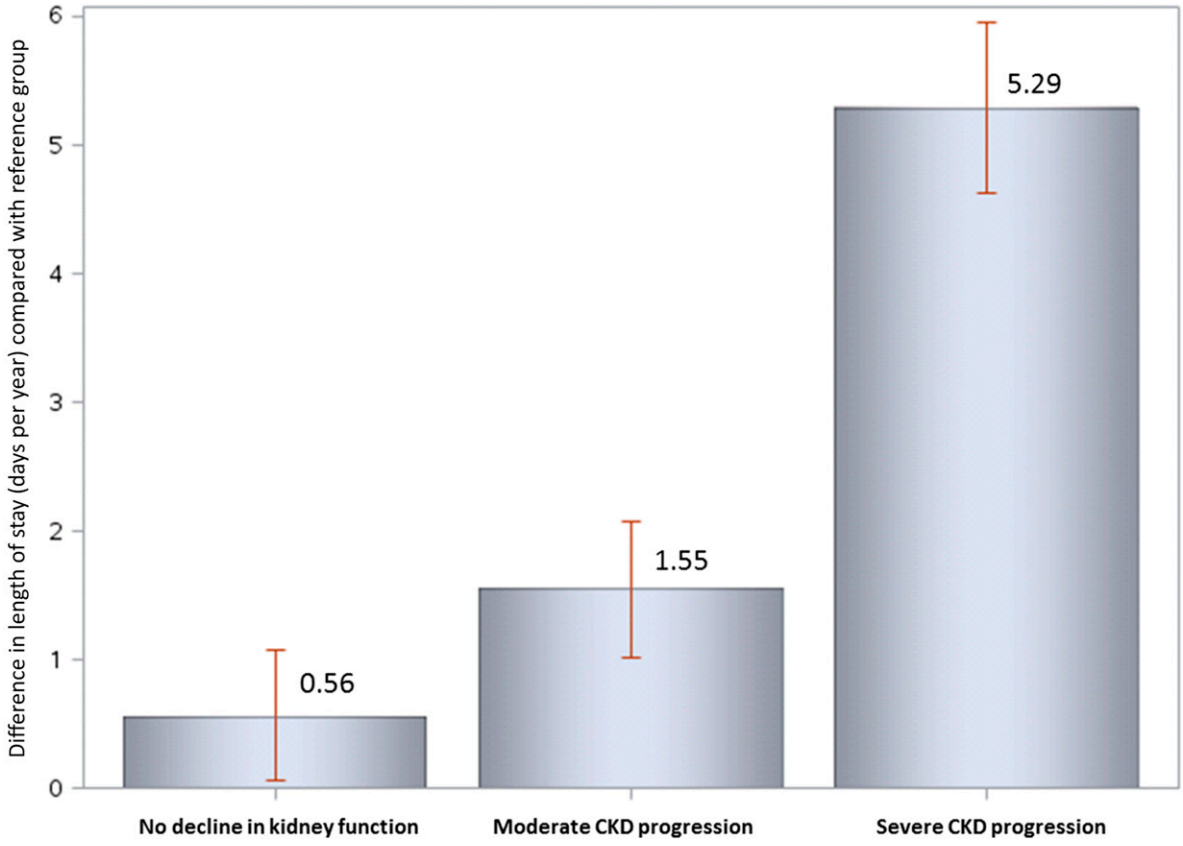


**Figure 2. | Additional length of hospital stay in days per year by CKD progression group relative to the reference group (patients with mild CKD progression; eGFR decline of 0 to −1 ml/min per 1.73 $m^2$ per year).** Error bars represent 95% confidence intervals.

**Table 5. Results of sensitivity analyses**

| Analysis | CKD Progression by eGFR Change Values | | | |
|---|---|---|---|---|
| | No Decline in Kidney Function ( >0) | Mild (Between 0 and −1) | Moderate (Between −1 and −5) | Severe (<−5) |
| **No hospitalizations before cohort entry (*n*=196,322)** | | | | |
| Risk of hospitalizations | 89,873 (45.8) | 29,909 (15.2) | 56,920 (29.0) | 19,620 (10.0) |
| | 0.97 (0.94 to 1.01) | 1.00 | 1.19 (1.14 to 1.24) | 1.15 (1.09 to 1.22) |
| Risk of readmissions | 20,419 (46.0) | 6474 (14.6) | 13,625 (30.7) | 3904 (8.8) |
| | 0.96 (0.90 to 1.04) | 1.00 | 1.19 (1.10 to 1.28) | 1.43 (1.30 to 1.58) |
| **Including no. of hospitalizations before cohort entry as a covariate in the models (*n*=247,888)** | | | | |
| Risk of hospitalizations | 111,318 (44.9) | 36,132 (14.6) | 74,117(29.9) | 26,321 (10.6) |
| | 0.98 (0.95 to 1.01) | 1.00 | 1.18 (1.14 to 1.22) | 1.24 (1.19 to 1.30) |
| Risk of readmissions | 33,783 (43.7) | 10,519 (13.6) | 24,781(32.1) | 8137 (10.5) |
| | 0.96 (0.91 to 1.02) | 1.00 | 1.16 (1.10 to 1.23) | 1.47 (1.37 to 1.58) |
| **Including no. of eGFR measurements as a covariate in the models (*n*=247,888)** | | | | |
| Risk of hospitalizations | 111,318 (44.9) | 36,132 (14.6) | 74,117(29.9) | 26,321 (10.6) |
| | 1.03 (1.00 to 1.06) | 1.00 | 1.16(1.12 to 1.20) | 1.29 (1.24 to 1.35) |
| Risk of readmissions | 33,783 (43.7) | 10,519 (13.6) | 24,781 (32.1) | 8,137 (10.5) |
| | 1.01 (0.95 to 1.07) | 1.00 | 1.16 (1.10 to 1.23) | 1.53 (1.43 to 1.64) |
| **Restricted the cohort to patients with at least five eGFR measurements (*n*=172,770)** | | | | |
| Risk of hospitalizations | 72,502 (42.0) | 24,045 (13.9) | 59,719 (34.6) | 16,504 (9.5) |
| | 0.97 (0.94 to 1.01) | 1.00 | 1.13 (1.09 to 1.17) | 1.46 (1.40 to 4.52) |
| Risk of readmissions | 27,235 (41.5) | 9013 (13.7) | 22,623 (34.5) | 6743 (10.3) |
| | 0.99 (0.93 to 1.05) | 1.00 | 1.20 (1.13 to 1.28) | 1.67 (1.55 to 1.80) |
| **Including eGFR variability as a covariate in the models (*n*=226,636)** | | | | |
| Risk of hospitalizations | 100,737 (44.4) | 31,108 (13.7) | 71,951 (31.7) | 22,840 (10.1) |
| | 0.92 (0.90 to 0.95) | 1.00 | 1.10 (1.07 to 1.14) | 1.15 (1.10 to 1.20) |
| Risk of readmissions | 32,363 (43.4) | 9968 (13.4) | 24,509 (32.9) | 7748 (10.4) |
| | 0.95 (0.90 to 1.01) | 1.00 | 1.15 (1.09 to 1.22) | 1.42 (1.32 to 1.52) |

Data are presented as *n* (%) or hazard ratios (95% confidence intervals). eGFR change values are given in ml/min per 1.73 $m^2$ per year. Models are adjusted for first eGFR value, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, and dementia.

length of hospital stay. These findings help advance our understanding of the complex relationship between the rate of eGFR change over time and clinical outcomes. Identification of patients at highest risk of hospitalizations, readmissions, and lengthened hospital stay may inform resource allocation of finite healthcare resources and help focus attention on high-risk groups. However, important knowledge gaps remain to be addressed, including the cause of hospitalizations in these patients, whether some are indeed preventable or avoidable, and whether interventions to slow eGFR decline or more intensive outpatient management models (multidisciplinary, transdisciplinary, patient-centered, or nephrologist-focused care models) of high-risk patients with faster eGFR decline will prove to be effective in ameliorating clinical outcomes in these individuals (33).

In a series of seminal studies, Turin *et al.* examined the association between rate of change in eGFR over time and a number of clinical outcomes, and they found that controlling for last eGFR did not change the association between eGFR changes and mortality, but it did diminish the association with ESRD and cardiovascular events (29,34–36). Studies by Coresh *et al.* showed a strong relationship between declines in eGFR and subsequent risk for ESRD and mortality when controlling for initial (or first) eGFR. Whether rate of eGFR change over time contributes to risk assessment models above and beyond the last eGFR measurement may depend on the method used to compute the rate of eGFR change, the number of eGFR measures, the length of the time window in which eGFR change is captured, and the outcome considered (*i.e.,* mortality, ESRD, cardiovascular events, hospitalizations) (5,20,22,29,35,37–42). Our data inform this discussion and suggest that the rate of eGFR change—computed in this study using linear models, with a median number of seven eGFR measurements (IQR, 4–11) over a median duration of 3.22 years (IQR, 2.0–4.1) —adds information about hospitalization risk beyond that provided by the last known eGFR.

We also note the significant interaction between the rate of kidney function decline and the number of hospitalizations and readmissions. This is particularly important because some patients may be hospitalized once for an acute insignificant illness that does not portend long-term adverse consequences. However, recurrent hospitalizations are likely the result of a serious health condition or poor overall health. We posited that the association between the rate of kidney function decline and the risk of hospitalization (or readmission) is stronger with a higher number of hospitalizations (or readmissions) (*i.e.,* the relationship between the rate of kidney function decline and the risk of hospitalization is stronger when the outcome is ≥2 hospitalizations versus ≥1 hospitalizations). Our results suggest that this is indeed the case, lending further strength to the notion that the rate of kidney function decline is more intimately associated with poorer outcomes and may be valuable in estimating the risk of serious health events.

We did not examine cause-specific hospitalizations and readmissions in this report. It is likely that the increased burden of health care utilization is attributable in part to deteriorating kidney function and its attendant metabolic and cardiovascular complications. It is also plausible that the associations reflect the possibility that the rate of kidney function decline may be a surrogate marker of poor overall health.

The cohort included mostly white men; thus, these results may not be generalizable to less narrowly defined populations. The imperfect nature of administrative data and the retrospective design of the study may also lead to sampling bias and inaccurate measurements of the predictor variables. To minimize such measurement bias, we used published definitions of comorbid illnesses that are validated for use in administrative data. Because of inclusion criteria specifying the minimum number of creatinine measurements required to fulfill criteria for cohort entry, and because the frequency of creatinine measurements is probably a surrogate marker of poorer overall health, we may have systematically missed those who rarely seek care within the VA system and our cohort may be sicker than a broader population of veterans. Furthermore, our data set did not include hospitalizations outside the VA system, which also likely introduced bias and may have resulted in underestimation of risk.

In conclusion, in a large national cohort of United States veterans, the rate of kidney function decline was associated with a higher risk of hospitalizations, a higher risk of readmissions within 30 days, and an increased length of hospital stay. A steeper decline in kidney function was also associated with a higher risk of recurrent hospitalizations and recurrent readmissions.

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