GFR Decline and Mortality Risk among Patients with Chronic Kidney Disease

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Summary

Background and objectives Estimates of the effect of estimated GFR (eGFR) decline on mortality have focused on populations with normal kidney function, or have included limited information on factors previously shown to influence the risk of death among patients with CKD.

Design, setting, participants, & measurements We retrospectively assessed the effect of rate of eGFR decline on survival of patients with CKD receiving primary care through a large integrated health care system in central Pennsylvania between January 1, 2004, and December 31, 2009.

Results A total of 15,465 patients were followed for a median of 3.4 years. Median rates of eGFR change by those in the lower, middle, and upper tertiles of eGFR slope were −4.8, −0.6, and 3.5 ml/min per 1.73 m^2/yr, respectively. In Cox proportional hazard modeling for time to death, adjusted for baseline proteinuria, changes in nutritional parameters, and episodes of acute kidney injury during follow-up (among other covariates), the hazard ratio for those in the lower (declining) and upper (increasing) eGFR tertiles (relative to the middle, or stable, tertile) was 1.84 and 1.42, respectively. Longitudinal changes in nutritional status as well as episodes of acute kidney injury attenuated the risk only modestly. These findings were consistent across subgroups.

Conclusions eGFR change over time adds prognostic information to traditional mortality risk predictors among patients with CKD. The utility of incorporating eGFR trends into patient-risk assessment should be further investigated.

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Introduction

Non–dialysis-dependent chronic kidney disease (NDD-CKD), affecting up to 15% of the adult US population, increases the risk of death compared with those without CKD, predominantly because of an increased burden of cardiovascular disease (1–3). Traditionally, fixed estimates of GFR (eGFR) at a single point in time have been used to define this risk (4). Several factors—including proteinuria, malnutrition, inflammation, and episodes of acute kidney injury (AKI)—have been proposed as mediators of the cardiovascular morbidity and mortality observed in this population (5–7).

Recently, several retrospective analyses have identified the rate of eGFR decline as an independent risk factor for all-cause and cardiovascular mortality and morbidity (8–11). These studies focused largely on older populations, and/or predominantly included patients with normal, or near normal, kidney function. None of the reported risk models included information about proteinuria or AKI during follow-up, and only one included longitudinal markers of nutritional status—all important mortality predictors in the NDD-CKD population (9).

Using a longitudinal, single health system electronic database with detailed demographic, pharmaceutical, clinical, laboratory, claims, and outcomes information, we investigated the effect of change in eGFR on mortality among a large, primary care population with NDD-CKD in central Pennsylvania between 2004 and 2009. We hypothesized that among those with a higher rate of eGFR decline, when compared with those with more stable longitudinal renal function, mortality risk is increased.

Materials and Methods

This retrospective cohort study was reviewed and approved under "exempt" status by the Geisinger Medical Center IRB in February 2010. The data source was EpicCare, Geisinger Medical Center's electronic health record (12).

Study Population

Patients eligible for the study included the following: those between the ages of 18 and 88 years at the time of first qualifying eGFR value; enrollment for primary care at any Geisinger facility at any time during the period February 1, 2004, through March

31, 2009; baseline NDD-CKD (defined by two outpatient GFR values estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation between 15 and 59 ml/min per 1.73 m^2 on at least 2 dates separated by at least 90 days but no more than 365 days—the CKD-defining window period); and at least one additional eGFR value a minimum of 6 months after the first qualifying value (13). The study index date was the date of the first qualifying eGFR value, once all other eGFR criteria were met. Follow-up for study outcomes occurred through December 31, 2009.

Patients were excluded if they suffered hospital-associated AKI during the CKD-defining window period (defined by an increase of 50% or more in serum creatinine during a hospitalization for any cause, with the baseline serum creatinine defined as the lowest recorded value between 90 days before the index admission and the hospital discharge date) (7). Community-associated AKI (defined as a 50% increase in serum creatinine occurring in the outpatient setting and within 30 days of another outpatient serum creatinine result) during the CKD-defining window period was likewise an excluding event. Additional exclusions included any prior history of solid-organ transplantation (ICD-9-CM diagnostic code V42, V42.0, V42.6, V42.7, V42.8, V42.83, V42.84, V42.89, V42.9, V43, 996.8, 996.80 through 996.87, or 996.89); prior hemo- or peritoneal dialysis (ICD-9-CM diagnostic code 585.5, 585.6, V45.11, V45.12, or V56.31); a diagnosis of metastatic cancer (ICD-9-CM diagnostic code 191.0 or 191.1); or an active prescription for cytotoxic or immunosuppressive therapy (cyclophosphomide, chlorambucil, prednisone, solumedrol, rituximab, tacrolimus, cyclosporine, or mycophenolate mofetil). Patients were censored for ESRD, defined as an eGFR <10 ml/min per 1.73 m^2, renal transplantation, or initiation of maintenance hemo- or peritoneal dialysis (ICD-9-CM diagnostic code 585.5, 585.6, V42.0, 996.81, V45.11, V45.12, or V56.31), or for any 18-month period of time without a serum creatinine result. Thus, qualifying patients were followed from the date of first qualifying eGFR result until ESRD, death, the date of the last recorded serum creatinine value if no additional lab testing was performed during the subsequent 18 months, or end of study (December 31, 2009).

Study Covariates

Demographic and clinical information, along with medication prescription history and laboratory and vital sign data, were extracted from the database. The Charlson Comorbidity Index score was calculated for each patient (14). A diagnosis was coded if present by ICD-9-CM code on the medical history on at least two distinct outpatient encounter dates during the 12 months before the index date. Medication prescriptions active at the time of the index date were coded. The laboratory values and vital sign data closest in time and before (but within 12 months of) the index date were used for all analyses. For proteinuria and hemoglobin A1C, because more than 10% of the cohort did not have a result recorded for these parameters, we created additional dummy variables to indicate whether or not the test was ordered, and included these dummy variables in the univariate and adjusted models, as appropriate (15). We included changes in serum albumin and body mass index (BMI) during study follow-up as covariates in survival modeling (16). In both cases, a linear regression model was fit for each patient to estimate annual change in the nutritional parameter, using a smoothed estimate based on the change from baseline for each additional measurement of the parameter. This estimate was included in the Cox survival model along with the baseline value. Hospital- and community-associated AKI (defined as above) during follow-up were also included as study covariates in a time-dependent fashion. Detailed definitions of study covariates are available as Supplemental Information.

Serum creatinine was measured using the isotope dilution/mass spectroscopy (IDMS)–traceable Roche enzymatic method throughout the entirety of the study period (17). Instrument calibration at Geisinger laboratories is performed according to manufacturer's specifications. Proteinuria was coded as present if any semiquantitative dipstick analysis result was 30 mg/dl or greater, if assessment by urinary protein-to-creatinine ratio was greater than 0.2 mg protein/g creatinine, or if a 24-hour urine collection included at least 300 mg of protein.

Exposure

All eGFR values were obtained using outpatient serum creatinine values and the CKD-EPI estimating formula (13). The slope of the eGFR *versus* time curve was calculated using all available outpatient values. This value was then used to stratify patients by tertile of rate of eGFR change in univariate and Cox proportional hazards models. This stratification scheme resulted in three groups roughly corresponding to declining (lower tertile), stable (middle tertile), and increasing (upper tertile) eGFR trends over time; the terms "declining," "stable," and "increasing" are used throughout the remainder of this report to represent the three tertiles. eGFR change was also analyzed as a continuous variable in a cubic spline model examining the relationship between GFR variability and death.

Outcome

The primary study outcome was death. Information on vital status for Geisinger primary care recipients is updated monthly by query of the Social Security Administration's data set through the National Technical Information Service (18).

Statistical Analyses

Data are presented as mean and SD for continuous variables and as frequency and percentage for categorical variables. Baseline comparisons across the three eGFR groups were made using the Kruskal–Wallis nonparametric and Pearson chi-squared tests, as appropriate. A Poisson regression model was used to estimate the mortality rate across groups and expressed as incident rate ratios.

Time until death was analyzed using the Cox proportional hazard regression model. Variables significant at $P < 0.10$ in the unadjusted analysis, or previously associated with death among patients with NDD-CKD, were included in the model. Estimated changes in BMI and serum albumin by linear regression were used in the Cox

model to account for changes in nutritional status during follow-up. Both hospital- and community-associated AKI were treated as time-dependent variables by sequentially accounting for such events as they occurred before death in survival models. Subgroup analyses were performed to examine the stability of the observed association between eGFR change and death across CKD subpopulations. Interactions also were tested to examine for differential effects of eGFR change across subpopulations in the full Cox proportional hazards regression model.

eGFR change was also analyzed as a continuous variable in unadjusted and fully adjusted models to estimate the relationship between GFR variability and death. A restricted cubic spline was created to parameterize this relationship as it allows for detecting nonlinear effects of exposure-outcome relationship.

Results

A total of 15,465 patients with NDD-CKD were enrolled in the study (Figure 1). The median (interquartile range [IQR]) change in eGFR in the decreasing, stable, and increasing groups was −4.8 (−8.2 to −3.2), −0.6 (−1.4 to 0.0), and 3.5 (1.9 to 6.7) ml/min per 1.73 m^2/yr, respectively. "Cut" points for tertiles were −2.2 and 0.8 ml/min per 1.73 m^2. In this study population, 41.3% had an eGFR that rose over time. The median (IQR) follow-up time was 2.9 (1.8 to 4.7), 4.5 (2.9 to 5.5), and 3.0 (1.9 to 4.5) years in those with decreasing, stable, and increasing eGFR groups over time, respectively. The median (IQR) number of serum creatinine values used to calculate eGFR values was 10 (6 to 17), 11 (7 to 17), and 8 (5 to 14) in the decreasing, stable, and increasing groups, respectively ($P < 0.001$ for the comparison of decreasing and stable eGFR, and increasing and stable eGFR).

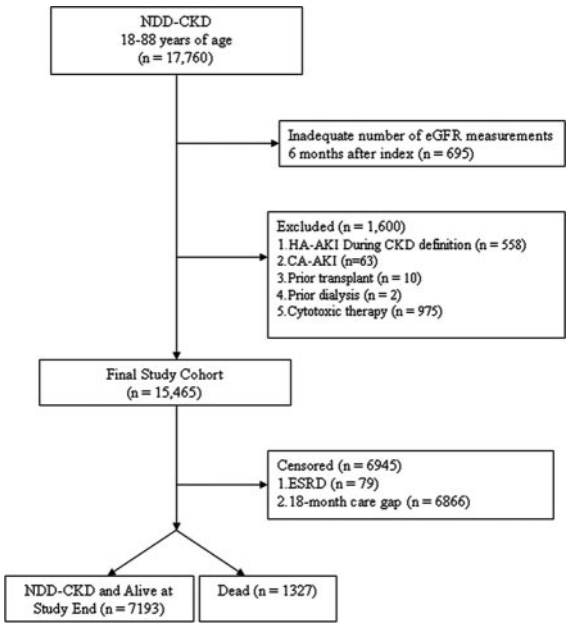

Figure 1. | Cohort development. CA-AKI, community-associated acute kidney injury; eGFR, estimated GFR; HA-AKI, hospital-associated acute kidney injury; NDD-CKD, non–dialysis-dependent chronic kidney disease.

The baseline characteristics of the study population are described in Table 1. Relative to the stable group, those in the decreasing eGFR group were more likely to be men, have a smoking history, and have diabetes mellitus, heart failure, and other comorbid disease conditions (as reflected in higher Charlson Comorbidity Index scores). Interestingly, they were less likely to have hypertension or hyperlipidemia. Proteinuria was more prevalent in decliners than in those with stable kidney function.

During follow-up, AKI was common in all three groups; rates of hospital-associated AKI were 76.2, 34.8, and 60.6 per 1000 patient-years in the declining, stable, and increasing eGFR groups, respectively, whereas rates of community-associated AKI were 38.6, 13.7, and 23.6 per 1000 patient-years, respectively. Nutritional status, as reflected by longitudinal changes in BMI and serum albumin levels, varied over time. Across all three groups, both BMI and serum albumin levels fell during follow-up (Table 2).

There were 560, 379, and 388 deaths (with corresponding mortality rates of 34.7, 17.5, and 24.0 deaths per 1000 patient-years, $P < 0.001$ for all intergroup comparisons) in the declining, stable, and increasing eGFR groups, respectively.

In univariate analyses, baseline covariates associated with death included the following: older age, male gender, and smoking history; a history of heart failure, peripheral vascular disease, dementia, chronic liver disease, or higher Charlson Comorbidity Index score; proteinuria; and a prescription for a beta blocker, loop diuretic, aldosterone antagonist, coumadin, aspirin, calcium acetate, and insulin. Both hospital- and community-associated AKI were likewise associated with a higher likelihood of death. White race, hypertension, hyperlipidemia, increasing BMI over time, and the use of nonsteroidal anti-inflammatory agents at baseline were associated with a lower risk of death. Both declining and increasing eGFR over time were associated with a higher risk of death, relative to those in the stable eGFR group.

In unadjusted and multivariate adjusted Cox proportional hazards models examining time to death, both decreasing and increasing eGFR were independently associated with death, relative to those in the stable group (Table 3). Other factors independently associated with death include older age, male gender, chronic liver disease, a higher Charlson Comorbidity Index score, use of beta blockers, aspirin, or coumadin, and baseline proteinuria. Higher baseline BMI, diastolic BP, eGFR, and HDL cholesterol levels all were associated with a lower risk of death. With the sequential addition of markers of changing nutritional status over time, as well as the inclusion of AKI events (both hospital- and community-associated) in a time-dependent fashion, the association between eGFR change and death was attenuated but qualitatively unchanged. Interactions between beta blockers and heart failure, as well as angiotensin-converting enzyme inhibitors and/or angiotensin receptor blocker use and proteinuria, were not significant. Vital status ascertainment was complete on patients censored for 18-month serum creatinine gaps; the risk of death associated with both decreasing (1.88, 95% confidence interval [CI] 1.68 to 2.10) and increasing (1.64, 95% CI 1.46 to 1.84) eGFR change over time relative to those in the stable eGFR group was not qualitatively different when these censored patients were included and

Table 1. Baseline characteristics of adult patients with NDD-CKD, by tertiles of eGFR change

Variable	Declining eGFR (n = 5103)	Stable eGFR (n = 5255)	Increasing eGFR (n = 5107)	P
Rate of eGFR change, ml/min per 1.73 m^2/yr; median (IQR)	−4.8 (−8.2 to −3.2)	−0.6 (−1.4 to 0.0)	3.5 (1.9 to 6.7)	<0.01
Age, years; mean (SD)	75.5 (10.8)	74.4 (9.8)	72.8 (10.9)	<0.01
Men, *n* (%)	2055 (40.3)	1866 (35.5)	1688 (33.0)	<0.01
White, *n* (%)	4809 (94.4)	5036 (95.8)	4852 (95.0)	0.09
Smoking history, *n* (%)	448 (11.8)	376 (9.2)	418 (10.7)	<0.01
Diabetes mellitus, *n* (%)	1939 (38.0)	1627 (31.0)	1414 (27.7)	<0.01
Atherosclerotic coronary artery disease, *n* (%)	1327 (26.0)	1260 (24.0)	1066 (20.9)	<0.01
Heart failure, *n* (%)	838 (16.4)	542 (10.3)	582 (11.4)	<0.01
Peripheral arterial disease, *n* (%)	727 (14.2)	628 (12.0)	624 (12.2)	0.07
Hypertension, *n* (%)	3674 (72.0)	3940 (75.0)	3563 (69.8)	<0.01
Hyperlipidemia, *n* (%)	2080 (40.8)	2598 (49.4)	2268 (44.4)	<0.01
Dementia, *n* (%)	161 (3.2)	86 (1.6)	129 (2.5)	<0.01
Chronic liver disease, *n* (%)	41 (0.8)	25 (0.5)	37 (0.7)	0.10
Alcohol abuse, *n* (%)	8 (0.2)	7 (0.1)	10 (0.2)	0.73
Charlson Comorbidity Index, *n* (%)				<0.01
0	1899 (37.2)	2331 (44.4)	2325 (45.5)	
1	1482 (29.0)	1583 (30.0)	1348 (26.4)	
2	970 (19.0)	868 (16.5)	903 (17.7)	
3+	752 (14.7)	473 (9.0)	531 (10.4)	
ACEI and/or ARB, *n* (%)	1578 (30.9)	1466 (27.9)	1636 (32.0)	<0.01
Beta blocker, *n* (%)	1677 (32.9)	1627 (31.0)	1739 (34.0)	0.03
Coumadin, *n* (%)	372 (7.3)	242 (4.6)	358 (7.0)	<0.01
Aspirin, *n* (%)	654 (12.8)	547 (10.4)	808 (15.8)	<0.01
HMG co-A reductase inhibitors, *n* (%)	1389 (27.2)	1415 (26.9)	1567 (30.7)	<0.01
Loop diuretics, *n* (%)	1074 (21.0)	763 (14.5)	953 (18.7)	<0.01
Aldosterone antagonists, *n* (%)	132 (2.6)	117 (2.2)	139 (2.7)	0.25
Nonsteroidal anti-inflammatories, *n* (%)	559 (11.0)	675 (12.8)	824 (16.1)	<0.01
Metformin, *n* (%)	425 (8.3)	279 (5.3)	311 (6.1)	<0.01
Insulin, *n* (%)	642 (12.6)	470 (8.9)	504 (9.9)	<0.01
Sulfonylureas, *n* (%)	642 (12.6)	470 (8.9)	504 (9.9)	<0.01
Systolic BP, mmHg; mean (SD)	134.7 (21.0)	133.9 (19.5)	130.4 (19.7)	<0.01
Diastolic BP, mmHg; mean (SD)	71.4 (11.3)	72.2 (10.7)	71.3 (10.9)	<0.01
BMI, kg/m^2; mean (SD)	30.6 (6.9)	30.8 (6.6)	31.0 (7.3)	0.26
Creatinine, mg/dl; mean (SD)	1.3 (0.3)	1.3 (0.4)	1.3 (0.4)	<0.01
GFR, ml/min per 1.73 m^2; mean (SD)	49.0 (9.1)	48.1 (9.4)	47.7 (9.4)	<0.01
Proteinuria,[a] *n* (%)	526 (31.2)	289 (19.6)	342 (19.8)	<0.01
HDL cholesterol, mg/dl; mean (SD)	50.1 (14.1)	51.6 (14.2)	51.3 (14.9)	<0.01
LDL cholesterol, mg/dl; mean (SD)	100.0 (37.4)	103.5 (35.8)	102.0 (36.4)	<0.01
Hemoglobin A1C,[b] % (SD)	7.4 (1.5)	7.1 (1.3)	7.1 (1.3)	<0.01
Albumin, g/dl; mean (SD)	4.0 (0.4)	4.1 (0.4)	4.1 (0.4)	<0.01

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NDD-CKD, non–dialysis-dependent chronic kidney disease.
[a]Data reported as a percentage of those tested for proteinuria: 1686, 1472, and 1726 individuals in the declining, stable, and increasing eGFR groups, respectively, were tested for proteinuria.
[b]Data reported as a percentage of those having a hemoglobin A1C test: 2294, 1969, and 1821 individuals in the declining, stable, and increasing eGFR groups, respectively, underwent such testing.

analyzed in the fully adjusted Cox proportional hazard model.

In fully adjusted subgroup analyses (Figure 2), the point estimate for the risk of death associated with decreasing eGFR over time was relatively consistent across groups. For those with increasing eGFR, the adjusted risk was likewise consistent across subgroups, with the exception of those younger than 60 years of age. Interactions were tested for each subpopulation of interest. Among those with declining (and relative to those with stable) eGFR, the mortality risk for those without diabetes was significantly larger than the risk for those with diabetes (P = 0.02). Among those with increasing (and relative to those with stable) eGFR, the mortality risk for those with proteinuria was significantly larger than the risk for those without proteinuria (P = 0.003). Interactions for all other subgroups with either declining or increasing eGFR were nonsignificant.

Figure 3 details the association between eGFR change as a continuous variable and the risk of death.

Table 2. Change in nutritional parameters (BMI, serum albumin) over time among patients with NDD-CKD, by tertile of eGFR change[a]

Nutritional Parameter	Declining eGFR	Stable eGFR	Increasing eGFR
Mean (SD) BMI change, kg/m^2 per year[b]	−0.3 (1.7)	−0.2 (1.1)	−0.4 (1.9)
Mean (SD) serum albumin change, g/dl per year[c]	−0.1 (5.6)	−0.2 (6.5)	−0.3 (7.0)

"Declining," "stable," and "increasing" eGFR groups refer to the lowest, middle, and upper tertiles of eGFR change, respectively. BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NDD-CKD, non–dialysis-dependent chronic kidney disease.

[a]Median (IQR) number of BMI measurements was 19 (10 to 31), 22 (13 to 33), 16 (9 to 28) in the declining, stable, and increasing eGFR groups, respectively ($P < 0.0001$). Median (IQR) number of serum albumin measurements was 5 (2 to 9), 5 (2 to 9), and 4 (2 to 8) in the declining, stable, and increasing eGFR groups, respectively ($P < 0.0001$).

[b]$P = 0.16$ and <0.0001 for the comparison of BMI change in those with declining *versus* stable and increasing *versus* stable eGFR, respectively.

[c]$P = 0.60$ and <0.0001 for the comparison of serum albumin change in those with declining *versus* stable and increasing *versus* stable eGFR, respectively.

Table 3. Cox proportional hazards for time to death among patients with non–dialysis-dependent CKD and changing kidney function over time

	HR (95% CI)	*P*
Unadjusted model		
declining *versus* stable	2.51 (2.20 to 2.86)	<0.01
increasing *versus* stable	1.79 (1.56 to 2.07)	<0.01
Baseline adjusted model[a]		
declining *versus* stable	2.22 (1.94 to 2.55)	<0.01
increasing *versus* stable	1.73 (1.50 to 2.00)	<0.01
Baseline + HA-AKI during follow-up		
declining *versus* stable	2.13 (1.86 to 2.44)	<0.01
increasing *versus* stable	1.66 (1.44 to 1.92)	<0.01
Baseline + HA-AKI + CA-AKI during follow-up		
declining *versus* stable	2.10 (1.83 to 2.41)	<0.01
increasing *versus* stable	1.66 (1.44 to 1.92)	<0.01
Baseline + HA-AKI + CA-AKI + BMI change during follow-up		
declining *versus* stable	2.05 (1.78 to 2.36)	<0.01
increasing *versus* stable	1.60 (1.38 to 1.86)	<0.01
Baseline + HA-AKI + CA-AKI + BMI change + serum albumin change during follow-up		
declining *versus* stable	1.84 (1.57 to 2.17)	<0.01
increasing *versus* stable	1.42 (1.20 to 1.69)	<0.01

"Declining," "stable," and "increasing" eGFR groups refer to the lowest, middle, and upper tertiles of eGFR change, respectively. BMI, body mass index; CA-AKI, community-associated acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HA-AKI, hospital-associated acute kidney injury; HR, hazard ratio.

[a]Baseline model adjusted for age, gender, race, smoking history, hypertension, dementia, chronic liver disease, heart failure, peripheral vascular disease, and Charlson Comorbidity Index score, present at the time of cohort entry; a prescription for beta blocker, loop diuretic, aldosterone antagonist, calcium acetate, insulin, coumadin, or aspirin at time of cohort entry; systolic and diastolic blood pressure, proteinuria, serum albumin, HDL and LDL cholesterol levels, and eGFR at time of cohort entry.

Discussion

In this study, declining eGFR over time was independently associated with an increased risk of death compared with those with more stable renal function. This risk persisted despite adjusting for factors previously known to be associated with death among patients with CKD, and was consistent across population subgroups.

Rifkin *et al.* evaluated eGFR decline among older community-dwelling adults using a retrospective analysis of 4380 participants with predominantly normal kidney function in the Cardiovascular Health Study (9). Rapid decline was associated with a 50% to 80% increased risk of death, depending on the method used to estimate GFR (19,20). This study included changes in weight over time as a model covariate, but did not include other measures of nutritional status, assessment of proteinuria, or AKI inj in risk modeling.

Unexpectedly, we found that increasing eGFR over time was independently associated with death. Al-Aly *et al.*, reporting on the association between kidney function decline and mortality among a group ($n = 4171$) of military veterans with early stage 3 CKD and rheumatoid arthritis,

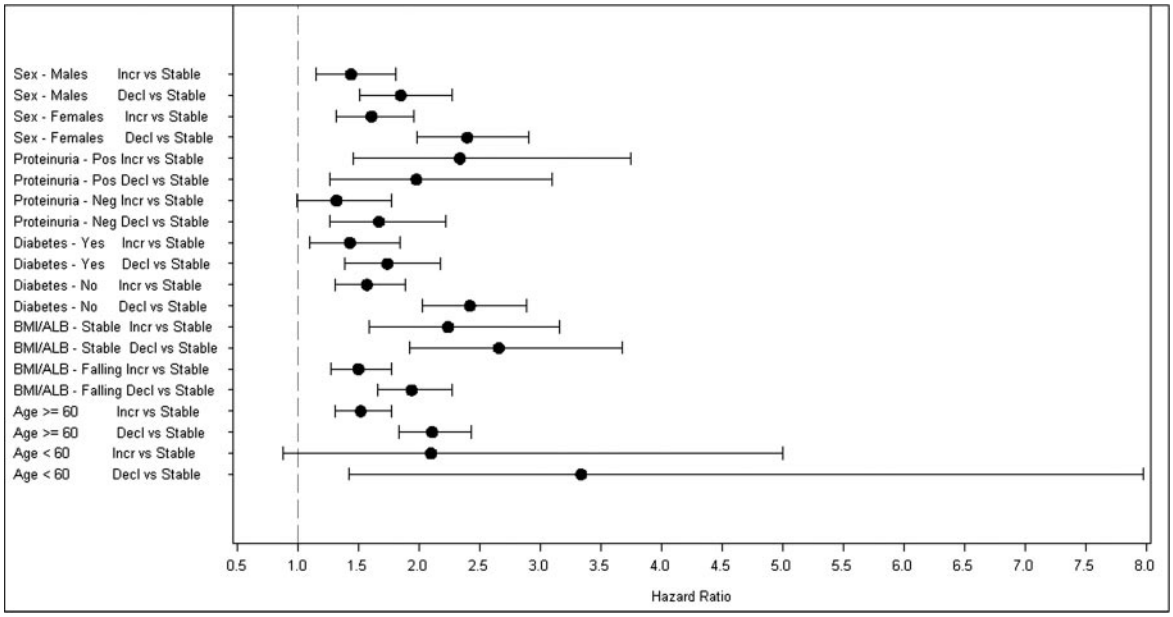

Figure 2. | Risk of death among subgroups of patients with baseline nondialysis dependent CKD, by tertile of eGFR change over time. For the BMI/ALB subgroup analysis, patients with both BMI and serum albumin results (or with either one alone if the other was not assessed in follow-up) at the time of last follow-up equal to or greater than the baseline value were classified as nutritionally stable; those with one or both values less than baseline value were classified as "malnourished." 439 (2.8%) patients had no follow-up BMI or serum albumin; these patients were not included in the analysis of nutritional change. ALB, serum albumin; BMI, body mass index; decl, declining GFR group; incr, increasing GFR group; neg, negative; pos, positive.

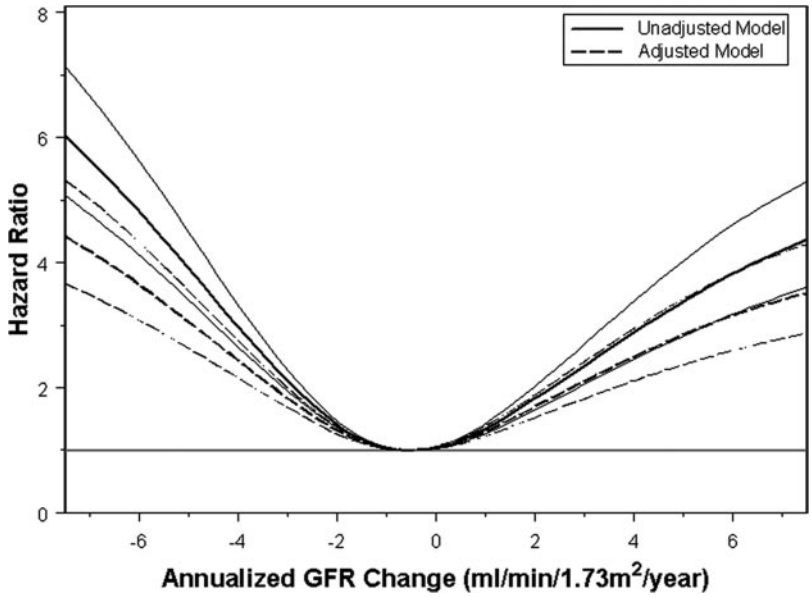

Figure 3. | Functional point estimate (and 95% pointwise confidence band) between estimated GFR change and the hazard ratio for death among patients with non–dialysis-dependent chronic kidney disease, estimated by a restricted cubic spline function. Adjusted model includes age, gender, race, smoking history, hypertension, heart failure, peripheral vascular disease, hypertension, Charlson Comorbidity Index score, and dementia present at the time of cohort entry; a prescription for beta blocker, loop diuretic, aldosterone antagonist, calcium acetate, insulin, coumadin, or aspirin at time of cohort entry; systolic and diastolic BP, proteinuria, HDL and LDL cholesterol levels, estimated GFR at time of cohort entry, hospital- and community-associated acute kidney injury during follow-up, change in body mass index during follow-up, and baseline serum albumin. Bold lines represent point estimates; faint lines represent 95% confidence bands.

found that approximately one third of their cohort had rising eGFR values over time, an observation which is inconsistent with consensus statements about progression of CKD (11,21). In addition to the observation that those with >4 ml/min per year of eGFR decline had approximately a 50% increased risk of death at a median follow-up of nearly 6 years, relative to those with stable kidney function, the investigators found that for those with a rising eGFR over time, there was a nonsignificant trend toward an increased risk of death relative to those with normal, age-related decline in kidney function. The investigators speculate that this observation is explained by malnutrition among those with increasing eGFR over time.

The reasons for our finding that increasing eGFR over time associates with an increased risk of death are not immediately apparent. Loss of lean body mass would be potentially explanatory, as poor nutritional status has been previously identified as a predictor of death among patients with CKD (6). We accounted for nutritional status at baseline (weight, BMI, and serum albumin levels) and during follow-up (changes in BMI and serum albumin); inclusion of these nutritional markers in our risk models only slightly attenuated the mortality risk associated with decline or gain in eGFR. Furthermore, in the subgroup of patients with declining nutritional parameters during follow-up, the adjusted mortality risk associated with an increasing eGFR over time remained robust, at 50% relative to those with stable function. Resolving AKI, while a recognized mortality risk factor in this population, might also account for a rising eGFR over time; however, inclusion of AKI events during follow-up did not qualitatively affect our study findings (and patients with both community- and hospital-associated AKI at entry were excluded). Improving intrinsic renal function is theoretically explanatory, yet is physiologically unlikely to occur in more than 40% of a general geriatric population with a substantial burden of cardiovascular disease and established CKD, and should not exacerbate mortality risk.

Changes in intravascular volume status, due to conditions like heart failure, liver disease, or other hemodynamic insults, might also explain an increase in eGFR over time, due to a dilutional effect on serum creatinine values. Subclinical physiologic changes in intravascular volume status might manifest as a rising eGFR over time, and in turn influence mortality risk among patients with CKD. Fluctuations in serum creatinine (and thus eGFR) due to subtle intravascular volume shifts is particularly common among those with chronic tubulointerstitial disease from small-vessel renal vascular disease. Finally, the statistical phenomenon of mean regression might theoretically explain some degree of eGFR rise over time among those with reduced baseline values. It is important to recognize that this study was not designed to assess the mortality risk associated with improving eGFR over time; thus, the observations reported in this regard remain hypothesis-generating and require further investigation.

Study limitations include the possible persistence of confounders that may have influenced the observed outcomes. These would include, among others, duration of CKD before study entry. The censoring of patients without an eGFR measurement after 18 months may have biased our sample toward a sicker, more resource-intense population with inherently higher risk of death; however, mortality risk did not qualitatively change after inclusion of these censored patients in the sensitivity analysis.

We did not use a gold standard measure of GFR, but measured GFR is not practical for typical clinical use or large epidemiologic studies. Our model assumes a constant rate of eGFR change over time and does not account for the influence of time-dependent rate changes. Given that eGFR slope calculations included data points that qualify as community-associated AKI, the influence of such events relative to the non–AKI associated decline or increase in eGFR over time is difficult to ascertain definitively in this study, despite the inclusion of all types of AKI in survival modeling. Finally, the largely Caucasian population receiving care in this hospital system precludes extrapolation of study findings to non-Caucasian populations.

The results of this study would suggest that identification of eGFR decline over time may enhance risk prognostication for patients with established CKD. Further research testing interventions to address this risk are warranted, as are investigations targeting a better understanding of the relationship between rising eGFR and outcomes among patients with CKD.

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References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
2. Levin A, Djurdjev O, Beaulieu M, Er L: Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis* 52: 661–671, 2008
3. *USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Available at: www.usrds.org [updated September 28, 2010]. Accessed September 30, 2010
4. Weiner DE, Tighouart H, Amin MG, Stark PC, Macleod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: A pooled analysis of community-based studies. *J Am Soc Nephrol* 15: 1307–1315, 2004
5. Chronic kidney disease prognosis consortium: Association of estimated glomerular filtration rate and albuminuria with all-

cause mortality and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet* 375: 2073–2081, 2010
6. Kovesdy CP, George SM, Anderson JE, Kalantar-Zadeh K: Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease. *Am J Clin Nutr* 90: 407–414, 2009
7. Lafrance JP, Miller DR: Acute kidney injury associates with increased long-term mortality. *J Am Soc Nephrol* 21: 345–352, 2010
8. Matsushita K, Selvin E, Bash LD, Franceschini N, Astor BC, Coresh J: Change in estimated GFR associates with coronary heart disease and mortality. *J Am Soc Nephrol* 20: 2617–2624, 2009
9. Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, Newman AB, Sarnak MJ: Rapid kidney function decline and mortality risk in older adults. *Arch Intern Med* 168: 2212–2218, 2008
10. Shlipak MG, Katz R, Kestenbaum B, Siscovick D, Fried L, Newman A, Rifkin D, Sarnak MJ: Rapid decline of kidney function increases cardiovascular risk in the elderly. *J Am Soc Nephrol* 20: 2625–2630, 2009
11. Al-Aly Z, Zeringue A, Fu J, Rauchman MI, McDonald JR, El-Achkar TM, Balasubramanian S, Nurutdinova D, Xian H, Stroupe K, Abbott KC, Eisen S: Rate of kidney function decline associates with mortality. *J Am Soc Nephol* 21: 1961–1969, 2010
12. Wu J, Roy J, Stewart WF: Prediction modeling using EHR data. *Med Care* 48: S106–S113, 2010
13. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chron Dis* 40: 373–383, 1987
15. Cohen J, Cohen P: Missing data. In: *Applied Multivariate Regression: Correlation Analysis for the Behavioral Sciences*, Hillsdale, NJ, Erlbaum, 1983, pp 275–300
16. Kovesdy CP: Rate of kidney function decline associates with increased risk of death. *J Am Soc Nephrol* 21: 1814–1816, 2010
17. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, Hostetter T, Levey AS, Panteghini M, Welch M, Eckfeldt JH; National Kidney Disease Education Program Laboratory Working Group: Recommendations for improving serum creatinine measurement: A report from the laboratory working group of the National Kidney Disease Education Program. *Clin Chem* 52: 5–18, 2006
18. National Technical Information Service. Alexandria, VA, U.S. Department of Commerce. Available at: www.ntis.gov [updated September 30, 2010]. Accessed September 30, 2010.
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann Intern Med* 130: 451–470, 1999
20. Stevens LA, Coresh J, Schmid C, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS: Estimating GFR using serum cystatin C alone and in combination with serum creatinine: A pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 51: 395–406, 2008
21. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 43 [5 Suppl 1]: S1–S290, 2004

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