# Mortality Risk Stratification in Chronic Kidney Disease: One Size for All Ages?

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**Current National Kidney Foundation Kidney Disease Outcomes Quality Initiative staging criteria for chronic kidney disease (CKD) are intended to apply to all age groups. However, it is unclear whether different levels of estimated GFR (eGFR) have the same prognostic significance in older and younger patients. The study cohort was composed of Department of Veterans Affairs (VA) patients who were aged 18 to 100 yr and had at least one outpatient serum creatinine measurement between October 1, 2001, and September 30, 2002 ($n$ = 2583,911). Patients with ESRD were excluded. GFR was estimated using the Modification of Diet in Renal Disease equation using each patient's first outpatient creatinine measurement during the study period. The association of eGFR with survival was measured by age group. Twenty percent of cohort patients had an eGFR <60 ml/min per 1.73 m$^2$, ranging from 3% among 18- to 44-yr-olds to as high as 49% among 85- to 100-yr-olds. Fifty-two percent ($n$ = 266,421) of cohort patients with an eGFR <60 ml/min per 1.73 m$^2$ had "very" moderate reductions in eGFR into the 50- to 59-ml/min per 1.73 m$^2$ range. The association of eGFR with mortality was weaker in the elderly than in younger age groups: Whereas severe reductions in eGFR were associated with an increased risk for death in all age groups, "very" moderate reductions in eGFR (50 to 59 ml/min per 1.73 m$^2$) were associated with an increased adjusted risk for death only among patients who were younger than 65 yr. Age-related attenuation of the association of eGFR with mortality was also present among women and black patients. In the clinical setting, mortality risk stratification in elderly patients should not be based on the same eGFR cut points as for younger age groups and would benefit from finer categorization of the 30- to 59-ml/min per 1.73 m$^2$ eGFR group.**

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Chronic kidney disease (CKD) is a common condition that affects >8 million Americans (1). Whereas traditional concerns have focused on the risk for progression to ESRD among patients with CKD, it has recently become clear that the competing risks for death and cardiovascular events are substantial in this population (2–8). To improve detection and management of CKD, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) has developed CKD practice guidelines (http://www.kidney.org/professionals/kdoqi/guidelines_bone/index.htm). These guidelines advocate a stepped approach to slowing progression of CKD and reducing CKD-related morbidity and mortality on the basis of each patient's disease stage (9).

Current guidelines recommend that the same criteria be used to diagnose CKD in older as in younger patients. Thus, all patients, regardless of their age, are considered to have at least moderate CKD when their estimated GFR (eGFR) is <60 ml/min per 1.73 m$^2$. However, limited data suggest that GFR decreases as part of normal aging (10) and that decrements in eGFR are exceedingly common in some elderly populations (11). Furthermore, the Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) equations may not be accurate in elderly patients; neither was developed in an elderly patient cohort (12,13), and serum creatinine, on which both equations are based, is a poor marker of renal function in older patients. Finally, little is known about the prognostic significance of decreased eGFR in elderly individuals (http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p9_approach.htm).

We examined the prevalence and prognostic significance by age group of different levels of MDRD eGFR on the basis of outpatient serum creatinine measurements in the Department of Veterans Affairs (VA) health care system, the largest integrated health care provider in the United States. A better understanding of the prognostic importance of decrements in eGFR measurements obtained in the clinical setting could serve as a foundation both for real-world clinical decision making in the elderly and for a better appreciation of the policy implica-

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tions of applying KDOQI guidelines to a growing elderly population.

## Materials and Methods

### *Patients*

A total of 4,436,334 veterans who were aged 18 to 100 yr had at least one outpatient visit to a VA medical center between October 1, 2001, and September 30, 2002. During this time frame, at least one outpatient serum creatinine measurement was available for 2,598,548 of these patients who were cared for at 128 different VA medical centers across the United States. Patients entered this study at the time of their first creatinine measurement during the period under study. For patients with more than one creatinine measurement during the study period, we based our analyses on the first measurement. To focus the study on patients with non–dialysis-dependent CKD, we excluded 14,637 who had reached ESRD or who had undergone at least one episode of dialysis before cohort entry. This left an analytic cohort of 2,583,911 patients.

### *Data Sources*

We used data from the VA, Medicare, and United States Renal Data System data for this study:

1. The VA Decision Support System Laboratory Results file was used to ascertain serum creatinine and glucose measurements associated with outpatient visits among cohort patients (http://www.virec.research.med.va.gov/References/VirecInsights/Insights-v01n2.pdf).
2. VA administrative databases (the National Patient Care Database and VA Fee Basis files) were used to ascertain demographic and comorbidity information for cohort patients from 1997 onward (http://www.virec.research.med.va.gov/References/VirecInsights/Insights-v01n3.pdf) (14).
3. The VA Beneficiary Identification and Records Locator Subsystem was used to ascertain date of death (15–17).
4. The Medicare denominator file was used as the primary source of race data for veterans with Medicare coverage based on its superior reliability to VA data sources (18,19).
5. We used inpatient and outpatient Medicare claims from 1999 to the time of cohort entry as an additional source of information on comorbid conditions for veterans with Medicare coverage.
6. We used data from United States Renal Data System, a national ESRD registry, to exclude from the cohort patients who had ESRD.

### *Primary Predictor*

The primary predictor variable for all analyses was eGFR calculated using the abbreviated MDRD formula based on age, gender, race, and serum creatinine level (9). When race data were missing, we made no adjustment for black race. The National Kidney Foundation defines an eGFR of ≥60 ml/min per 1.73 $m^2$ as being "normal" or "mildly reduced." Moderate CKD is defined as an eGFR of 30 to 59 ml/min per 1.73 $m^2$, severe CKD as an eGFR of 15 to 29 ml/min per 1.73 $m^2$, and renal failure as an eGFR of <15 ml/min per 1.73 $m^2$ or dialysis dependence. In this analysis, we excluded patients with ESRD and used a finer classification of eGFR to distinguish between different levels of moderate CKD (≥60, 50 to 59, 40 to 49, 30 to 39, 15 to 29, and <15 ml/min per 1.73 $m^2$).

### *Covariates*

All analyses were stratified by age group (18 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, and 85+). Multivariate analysis was adjusted for age; race (black *versus* nonblack); gender; and presence of diabetes, coronary artery disease (defined as a previous diagnosis of coronary artery disease, angina, or myocardial infarction or previous coronary artery bypass graft or angioplasty), congestive heart failure, peripheral arterial disease (defined as a previous diagnosis of peripheral arterial disease or previous lower extremity amputation or revascularization procedure), chronic obstructive lung disease, and cerebrovascular disease (defined as previous stroke or transient ischemic attack). Comorbidities were assigned on the basis of relevant *International Classification of Diseases, Ninth Revision* diagnostic and procedure codes and CPT procedure codes in the VA National Patient Care Database and Fee Basis files from October 1, 1997, to the time of cohort entry and in the inpatient and outpatient Medicare claims from January 1, 1999, through the time of cohort entry. We classified patients with a random serum glucose measurement of ≥200 mg/dl during the 3-mo period before cohort entry as having diabetes.

### *Outcome*

The outcome for this analysis was time from study entry to death. Death data were ascertained through June 17, 2005.

### *Statistical Analyses*

We compared patient characteristics by age group using tests for trend. We calculated annual mortality by age and eGFR category using Poisson regression. We used Cox proportional hazard analysis to measure the association of eGFR with time from study entry to death after stratification for age group. Patients were censored at the end of follow-up. All analyses were adjusted for a fixed effect for center to accommodate between-center differences in creatinine measurement.

To determine the prognostic significance of "stable" eGFR measurements, we repeated the primary analysis among the subgroup of patients who underwent repeat creatinine measurement between 3 and 6 mo after cohort entry and whose eGFR fell in the same range at both time points. We also repeated the primary analyses among women and among black patients. Finally, we used creatinine cut points instead of eGFR measurements to define patients with moderate and severe renal insufficiency. For this analysis, we used cut points of 1.3 and 1.8 mg/dl for women and 1.5 and 2.0 mg/dl for men. We were unable to use the Cockroft-Gault equation because patient weight was not available. This study was approved by the Institutional Review Board at the University of California, San Francisco, and the Research Committee at the VA San Francisco.

## Results

The mean age of the study population was 63.6 ± 14 yr; 5% of cohort patients were women ($n$ = 140,021), 12% were black, 75% were white or other race, and 13% were missing race data. The percentage of female and black patients decreased and the percentage of patients with diagnosed comorbid conditions increased across age groups (Table 1).

Twenty percent of cohort patients had an eGFR of <60 ml/min per 1.73 $m^2$ ($n$ = 514,850). Fifty-two percent of these patients had very moderate reductions in eGFR to 50 to 59 ml/min per 1.73 $m^2$ (Figure 1). From the youngest to the oldest age groups, the prevalence of an eGFR of <60 ml/min per 1.73 $m^2$ ranged from 3 to 49%. Differences in the prevalence of moderately (rather than severely) reduced eGFR accounted for most of this variability.

A mean of 3.17 ± 0.62 yr per person and a total of 8,218,817 yr of follow-up were available for study. A total of 218,246 deaths occurred during this period. Death rates increased both

*Table 1.* Cohort patient characteristics by age group

| | Age Group (Yr) | | | | | | *P* for Trend |
|---|---|---|---|---|---|---|---|
| | 18 to 44 ($n$ = 239,906) | 45 to 54 ($n$ = 501,258) | 55 to 64 ($n$ = 537,230) | 65 to 74 ($n$ = 686,702) | 75 to 84 ($n$ = 566,286) | 85 to 100 ($n$ = 53,339) | |
| Black race (%) | 31 | 24 | 15 | 10 | 8 | 10 | <0.001 |
| Female gender (%) | 21 | 8 | 4 | 1 | 3 | 3 | <0.001 |
| Diagnosed comorbid conditions (%) | | | | | | | |
| diabetes | 10 | 22 | 29 | 36 | 35 | 30 | <0.001 |
| coronary artery disease | 6 | 18 | 28 | 46 | 56 | 58 | <0.001 |
| congestive heart failure | 1 | 5 | 9 | 18 | 27 | 36 | <0.001 |
| cerebrovascular disease | 2 | 5 | 9 | 19 | 28 | 33 | <0.001 |
| peripheral vascular disease | 1 | 5 | 9 | 19 | 27 | 32 | <0.001 |
| chronic obstructive lung disease | 14 | 21 | 24 | 33 | 37 | 40 | <0.001 |

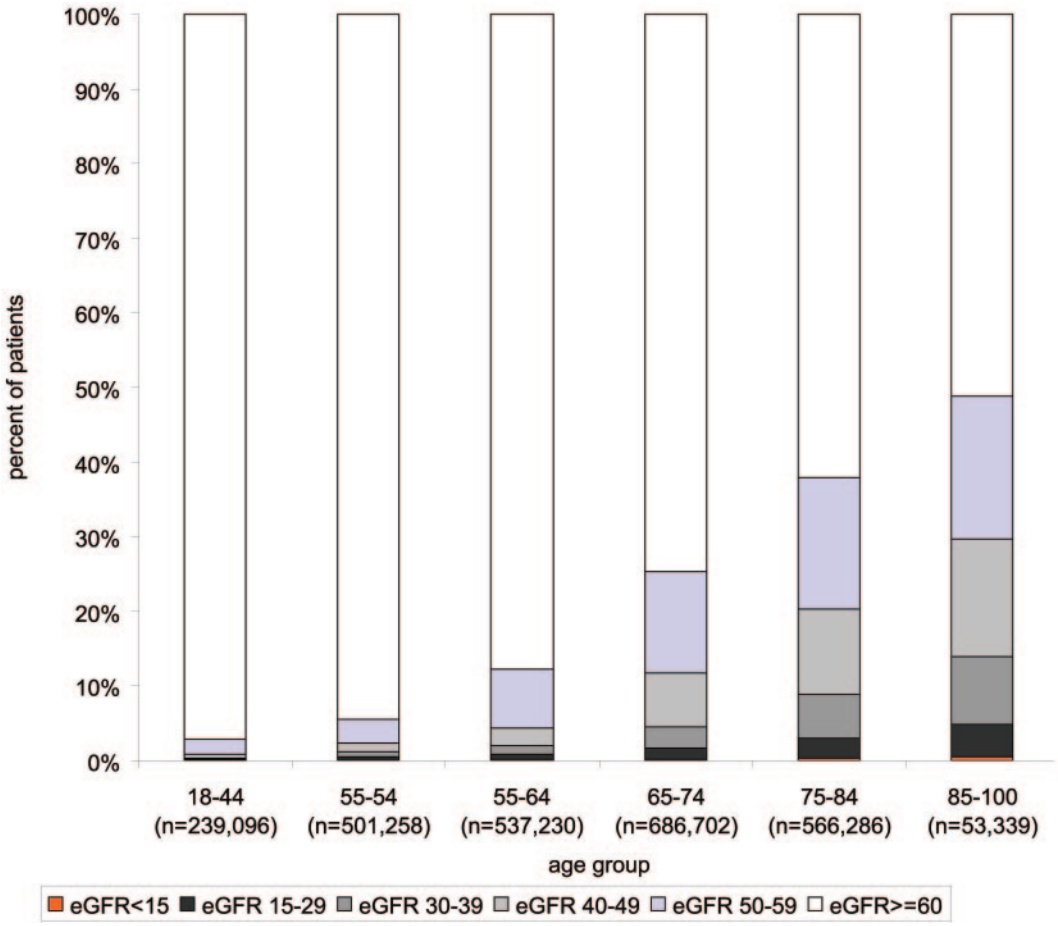
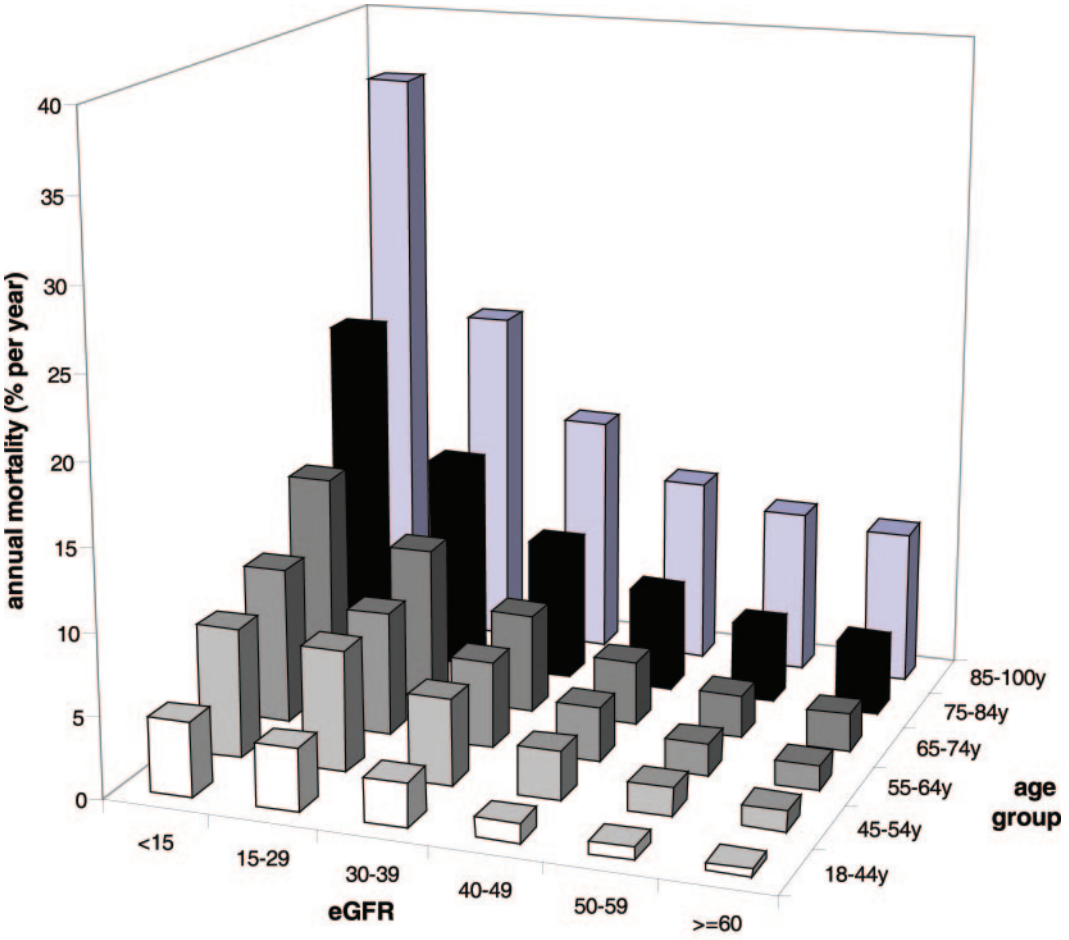



*Figure 1.* Prevalence of low estimated GFR (eGFR) by age group.

with increasing age and with falling eGFR (Figure 2). Baseline mortality rates among elderly patients with eGFR levels of ≥60 ml/min per 1.73 $m^2$ were much higher than for younger patients. Among elderly patients with eGFR levels in the 40- to 59-ml/min per 1.73 $m^2$ range, mortality rates were only slightly higher than for the group with an eGFR ≥60 ml/min per 1.73 $m^2$. However, for all age groups, mortality rates increased dramatically at eGFR levels <40 ml/min per 1.73 $m^2$, with the highest rates occurring in the oldest age groups.

In unadjusted analysis, risk for death was increased at all levels of eGFR <60 ml/min per 1.73 $m^2$ regardless of age (Table 2). However, the association of eGFR with mortality was weaker among older than among younger patients. For example, reductions in eGFR to 50 to 59 ml/min per 1.73 $m^2$ were




| | 18-44 | 45-54 | 55-64 | 65-74 | 75-84 | 85-100 |
|---|---|---|---|---|---|---|
| ≥60 | 0.42 | 1.25 | 1.48 | 2.31 | 4.40 | 9.47 |
| 50-59 | 0.76 | 1.73 | 1.95 | 2.62 | 4.78 | 10.07 |
| 40-49 | 1.20 | 2.99 | 3.33 | 3.92 | 6.19 | 11.40 |
| 30-39 | 2.68 | 5.30 | 5.33 | 6.08 | 8.60 | 14.74 |
| 15-29 | 3.81 | 7.42 | 7.54 | 9.50 | 13.16 | 20.95 |
| <15 | 4.55 | 7.96 | 9.54 | 13.32 | 21.24 | 35.99 |

*Figure 2.* Annual mortality by age group and eGFR.

associated with an 80% increase in unadjusted risk for death among the youngest age group but with only a 6% increase among those aged 85 to 100. After adjustment for demographic characteristics, comorbid conditions, and VA medical center, patients who were aged 65 and older and had an eGFR of 50 to 59 ml/min per 1.73 $m^2$ did not have an increased risk for death compared with those with an eGFR above this level. However, an eGFR of 50 to 59 ml/min per 1.73 $m^2$ was still associated with an increased risk for death among all age groups under 65 yr.

*Subgroup Analyses*

Results of subgroup analysis among women and among black patients yielded similar results. In sensitivity analysis using serum creatinine cut points, 11% of patients had an elevated creatinine (≥1.3 mg/dl for women and ≥1.5 mg/dl for men). This ranged from 2 to 30% from the youngest to the oldest age groups. The risk for death associated with elevated creatinine was also attenuated with advancing age. For women with creatinine values in the 1.3- to 1.7-mg/dl range and men with values in the 1.5- to 1.9-mg/dl range, the adjusted risk for death was 1.64 (95% confidence interval [CI] 1.37 to 1.96) in the youngest and 1.14 (95% CI 1.10 to 1.19) in the oldest age groups. For women with creatinine values ≥1.8 mg/dl and men with values ≥2.0 mg/dl, the adjusted risk for death ranged from 4.27 (95% CI 3.53 to 5.17) in the youngest to 1.67 (95% CI 1.59 to 1.75) in the oldest age groups.

Thirty percent ($n$ = 777,092) of cohort patients underwent at least one repeat creatinine measurement between 3 and 6 mo after cohort entry. The percentage of patients who underwent repeat creatinine measurements varied by age group (19% of 18- to 44-yr-olds, 29% of 45- to 54-yr-olds, 32% of 55- to 64-yr-olds, 32% of 65- to 74-yr-olds, 32% 75- to 84-yr-olds, and 30% of

*Table 2.* Risk for death by eGFR after stratification by age group[a]

| Age Group (Yr) | eGFR 50 to 59 ($n$ = 266,421) | eGFR 40 to 49 ($n$ = 142,257) | eGFR 30 to 39 ($n$ = 67,659) | eGFR 15 to 29 ($n$ = 33,213) | GFR < 15 ($n$ = 5,300) |
|---|---|---|---|---|---|
| Unadjusted HR (95% CI) | | | | | |
| 18 to 44 ($n$ = 239,096) | 1.80 (1.50 to 2.16) | 2.85 (2.03 to 4.00) | 6.34 (4.52 to 8.88) | 9.01 (6.72 to 12.10) | 10.73 (7.18 to 16.03) |
| 45 to 54 ($n$ = 501,258) | 1.39 (1.30 to 1.48) | 2.40 (2.21 to 2.60) | 4.24 (3.87 to 4.66) | 5.94 (5.41 to 6.52) | 6.37 (5.47 to 7.42) |
| 55 to 64 ($n$ = 537,230) | 1.32 (1.27 to 1.38) | 2.26 (2.13 to 2.38) | 3.60 (3.38 to 3.84) | 5.09 (4.75 to 5.45) | 6.43 (5.71 to 7.24) |
| 65 to 74 ($n$ = 686,702) | 1.14 (1.11 to 1.16) | 1.70 (1.65 to 1.74) | 2.63 (2.54 to 2.72) | 4.11 (3.95 to 4.27) | 5.75 (5.28 to 6.26) |
| 75 to 84 ($n$ = 566,286) | 1.09 (1.07 to 1.11) | 1.41 (1.38 to 1.43) | 1.95 (1.91 to 2.00) | 2.99 (2.90 to 3.07) | 4.81 (4.50 to 5.16) |
| 85+ ($n$ = 53,339) | 1.06 (1.02 to 1.11) | 1.20 (1.15 to 1.26) | 1.55 (1.15 to 1.26) | 2.20 (2.07 to 2.34) | 3.76 (3.18 to 4.45) |
| Adjusted[b] HR (95% CI) | | | | | |
| 18 to 44 ($n$ = 239,096) | 1.56 (1.30 to 1.88) | 1.90 (1.35 to 2.67) | 3.58 (2.54 to 5.05) | 4.92 (3.65 to 6.63) | 5.86 (3.91 to 8.80) |
| 45 to 54 ($n$ = 501,258) | 1.27 (1.19 to 1.36) | 1.89 (1.74 to 2.06) | 2.89 (2.63 to 3.18) | 3.95 (3.59 to 4.35) | 4.47 (3.84 to 5.21) |
| 55 to 64 ($n$ = 537,230) | 1.18 (1.13 to 1.23) | 1.75 (1.65 to 1.85) | 2.43 (2.27 to 2.59) | 3.19 (2.97 to 3.42) | 4.29 (3.81 to 4.84) |
| 65 to 74 ($n$ = 686,702) | 1.02 (0.99 to 1.05) | 1.35 (1.32 to 1.39) | 1.81 (1.75 to 1.87) | 2.61 (2.51 to 2.72) | 3.82 (3.50 to 4.16) |
| 75 to 84 ($n$ = 566,286) | 1.02 (0.99 to 1.04) | 1.21 (1.18 to 1.23) | 1.55 (1.51 to 1.58) | 2.21 (2.14 to 2.27) | 3.68 (3.44 to 3.95) |
| 85+ ($n$ = 53,339) | 1.02 (0.97 to 1.06) | 1.10 (1.05 to 1.15) | 1.36 (1.29 to 1.44) | 1.86 (1.74 to 1.98) | 3.60 (3.05 to 4.26) |

[a]CI, confidence interval; HR, hazard ratio; eGFR, estimated GFR (ml/min per 1.73 $m^2$) based on the Modification of Diet in Renal Disease formula. Referent category is GFR ≥60 ml/min per 1.73 $m^2$.
[b]Adjusted for age, race, gender, diabetes, congestive heart failure, coronary artery disease, peripheral arterial disease, stroke, chronic obstructive lung disease, and VA medical center.

85- to 100-yr-olds). At the time of follow-up creatinine measurement, 627,056 (81%) patients were in the same eGFR category as they were at baseline, 64,102 (8%) had moved to a higher eGFR category, and 85,936 (11%) had moved to a lower eGFR category. Among the 627,054 patients who were in the same eGFR category at the time of their second creatinine measurement, an eGFR measurement in the 50- to 59-ml/min per 1.73 $m^2$ range was not associated with a statistically significantly increased adjusted mortality risk in any age group (Table 3). Indeed, patients who were aged 65 to 84 yr and had an eGFR in this range had a lower adjusted mortality risk than those in their age group with an eGFR ≥60 ml/min per 1.73 $m^2$. Among patients with a stable eGFR of 40 to 49 ml/min per 1.73 $m^2$, those who were 75 yr or older did not have a higher risk for death than the referent group. With the exception of the small group with an eGFR <15 ml/min per 1.73 $m^2$, relative risk for death generally decreased with advancing age.

## Discussion

Guidelines for the care of patients with CKD advocate a stepped approach toward slowing progression of CKD and reducing CKD-related morbidity and mortality on the basis of each patient's stage of CKD (9). Estimated level of GFR (calculated using either the Cockroft-Gault or MDRD equation) is a key determinant of CKD stage. Although little is known about the accuracy of these equations or the health effects of a low GFR in elderly individuals, current staging criteria for CKD do not differ by age group (http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p9_approach.htm). The findings reported here of a high prevalence of decreased eGFR in elderly patients and substantial variation across age groups in the prognostic significance of low eGFR suggest that mortality risk stratification should not be based on the same eGFR cut points in the elderly as in younger age groups.

*Table 3.* Adjusted risk for death by age and eGFR among cohort members with stable repeat creatinine measurements[a]

| Age Group (Yr) | Adjusted[b] HR (95% CI) | | | | |
|---|---|---|---|---|---|
| | eGFR 50 to 59 ($n$ = 38,274) | eGFR 40 to 49 ($n$ = 25,146) | eGFR 30 to 39 ($n$ = 13,983) | eGFR 15 to 29 ($n$ = 10,054) | GFR < 15 ($n$ = 1,917) |
| 18 to 44 ($n$ = 42,477) | 1.24 (0.72 to 2.15) | —[c] | 2.77 (1.30 to 5.87) | 2.25 (1.16 to 4.37) | 4.21 (2.40 to 7.37) |
| 45 to 54 ($n$ = 132,344) | 0.86 (0.70 to 1.05) | 2.49 (1.21 to 1.84) | 1.90 (1.50 to 2.40) | 2.92 (2.46 to 3.47) | 3.26 (2.56 to 4.16) |
| 55 to 64 ($n$ = 148,669) | 0.96 (0.87 to 1.06) | 1.28 (1.12 to 1.48) | 1.77 (1.51 to 2.06) | 2.43 (2.15 to 2.76) | 3.27 (2.69 to 3.97) |
| 65 to 74 ($n$ = 167,874) | 0.90 (0.85 to 0.96) | 1.16 (1.09 to 1.24) | 1.55 (1.44 to 1.67) | 2.46 (2.29 to 2.64) | 2.73 (2.34 to 3.19) |
| 75 to 84 ($n$ = 125,313) | 0.94 (0.90 to 0.99) | 1.05 (1.00 to 1.10) | 1.43 (1.36 to 1.51) | 2.12 (2.00 to 2.23) | 3.06 (2.67 to 3.50) |
| 85+ ($n$ = 10,377) | 0.93 (0.83 to 1.04) | 1.04 (0.93 to 1.16) | 1.32 (1.17 to 1.49) | 1.83 (1.61 to 2.07) | 4.02 (2.94 to 5.51) |

[a]Referent category is GFR ≥60 ml/min per 1.73 $m^2$ ($n$ = 537,680).
[b]Adjusted for age, race, gender, diabetes, congestive heart failure, coronary artery disease, peripheral arterial disease, stroke, chronic obstructive lung disease, and VA medical center.
[c]It was not possible to estimate the risk for mortality in this small group ($n$ = 98) because there were no deaths during the follow-up period.

When we used the MDRD equation to estimate GFR in a large national cohort with outpatient serum creatinine measurements, we found that the percentage of patients with moderate reductions in eGFR increased dramatically with advancing age. At the same time, the associations between eGFR and absolute and relative mortality risk varied considerably between age groups: At all levels of renal function, most deaths occurred in elderly patients, but the relative risk for death associated with each level of renal function decreased markedly with age. In fact, very moderate reductions in eGFR (50 to 59 ml/min per 1.73 $m^2$) were not associated with an increased relative or absolute risk for death in patients who were older than 65 yr. At lower levels of eGFR, the presence of a decrement in eGFR explained a smaller percentage but larger absolute number of deaths in older compared with younger age groups. Among the one third of cohort patients with stable repeat creatinine measurements within 3 to 6 mo of cohort entry, an eGFR of 50 to 59 ml/min per 1.73 $m^2$ was not associated with increased adjusted mortality risk in any age group, and an eGFR of 40 to 49 ml/min per 1.73 $m^2$ was not associated with increased relative or absolute adjusted mortality risk among patients who were 75 yr or older. These findings suggest the potential value both of dividing the moderately decreased eGFR group into finer categories and of repeating creatinine measurements 3 to 6 mo later to distinguish the large number of patients with moderate reductions in eGFR with no increase in mortality risk from those with some increase in risk.

Patients with "very" moderate decrements in eGFR (in whom mortality risk was not increased compared with the referent) account for a large proportion of the elderly population with CKD. Thirty-nine percent of cohort members with moderate CKD and 49% of elderly (≥65 yr) cohort members with moderate CKD had an eGFR of 50 to 59 ml/min per 1.73 $m^2$. The absence of an association of "very" moderate reductions in eGFR with mortality at older ages could occur as a result of inaccuracy of the MDRD equation in elderly patients. This equation was not developed in an elderly cohort (13), and creatinine may be a poor indicator of renal function in elderly individuals. Alternatively, age-related differences in the relative risk for death at each level of eGFR may represent true variation across age groups in the impact of low eGFR on mortality.

Most previous studies that examined the association of CKD with mortality adjusted for age but did not examine how risk for death attributable to CKD varies as a function of age (2–8). However, the results of population-based studies of advanced CKD in the United Kingdom indicate that the relative risk for mortality associated with CKD may be lower in older patients (20,21). Consistent with this, age has been shown to have an impact on associations between several other common conditions and mortality. For example, higher BP is associated with better rather than worse survival in patients who are 80 yr and older, whereas the reverse is true for younger patients (22–27). A similar phenomenon seems to exist for subclinical hypothyroidism, for which patients who are 80 yr or older and have mildly elevated levels of thyrotropin seem to have a lower risk for death than those with levels in the normal range (28). The lower relative risk for death attributable to CKD at older ages most likely reflects the higher background mortality risk and higher prevalence of other comorbidities at older ages, lessening the potential for a single comorbidity such as CKD to have an impact on mortality. The presence of a survival advantage among elderly patients with prevalent CKD (over those without CKD) may also be a consideration.

The prevalence of CKD in this cohort was much higher than expected on the basis of population estimates for older individuals in the general population (1,29). This is probably accounted for in large part by the characteristics of our study population (veteran health care users *versus* a representative sample of the civilian population). The higher-than-expected prevalence of CKD in our cohort may also have occurred as a result of differences in creatinine calibration between the MDRD reference laboratory and the various laboratories at which creatinine measurements were obtained for cohort patients (30,31). Although it is recommended that individual clinical laboratories calibrate creatinine measurements to the MDRD laboratory (9), this is not practiced routinely in the clinical setting. Our findings argue for caution in applying the MDRD equation to clinical populations of elderly patients, particularly when (as is most commonly the case) creatinine measurements are not calibrated to the MDRD laboratory.

Our analysis has the following limitations. (*1*) We address only mortality risk. Further studies are needed to evaluate other important disease-related outcomes such as progression of renal disease, cardiovascular or other morbid events, and patient quality of life. (*2*) Although our results probably reflect (at least in part) the inaccuracy of the MDRD equation among elderly patients and in the setting of uncalibrated creatinine measurements, we cannot confirm these possibilities because creatinine measurements that are calibrated to the MDRD laboratory and directly measured GFR are not routinely obtained in the clinical setting. (*3*) The results of subgroup analysis among patients with repeat creatinine measurements must be interpreted with caution because only one third of the original cohort underwent repeat creatinine measurements within the prespecified time frame, and this sample included relatively few younger patients with CKD. As a result of these limitations, comparison of the prognostic value of a single creatinine measurement *versus* two creatinine measurements drawn 3 to 6 mo apart must be interpreted with some caution. (*4*) Our study is limited by the use of administrative data to define comorbid conditions, which provided us with limited ability to adjust for the severity of comorbid conditions in our analysis. However, inadequate adjustment for severity of comorbid conditions is unlikely to have biased our results toward the null hypothesis. (*5*) Although the large size and older age structure of this cohort afforded us a unique opportunity to examine in detail the complex association of CKD with mortality across age groups, use of a veteran population that is predominantly male and white may raise concern that our results are not generalizable to other populations. However, our findings were reproduced in subgroup analysis among women and black patients. Therefore, there is no reason to expect that our major finding of

an age-related attenuation in the association of eGFR with mortality would be different in other populations.

## Conclusion

In a real-world clinical setting, the MDRD equation identified large numbers of patients who met KDOQI criteria for moderate CKD. Most of these patients were elderly, and many had "very" moderate reductions in eGFR that were not associated with an increased relative or absolute risk for death. These findings suggest that in the clinical setting, mortality risk stratification in elderly patients should not be based on the same eGFR cut points as for younger age groups and would benefit both from finer categorization of the 30- to 59-ml/min per 1.73 $m^2$ eGFR group and from use of serial creatinine measurements.

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