

Risks for All-Cause Mortality: Stratified by Age, Estimated Glomerular Filtration Rate and Albuminuria

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Keywords

Serum creatinine · Incidence rate ratios · Relative risk · Absolute risk

Abstract

The relative reduction of risk for all-cause mortality among the elderly has been described as attenuated compared to younger subjects, but the risk for all-cause mortality increases with age when absolute risk is considered. The objectives of the present inquiry were to calculate the relative and absolute risks of all-cause mortality based on incidence rate ratios, and summarize these risks for age, gender, and race strata. We conclude that strata-specific risk summaries are more informative than a single all-encompassing risk summary, and that gender- and race-specific strata need to be considered as well as age-specific strata.

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Introduction

Chronic kidney disease (CKD) staging, based on estimated glomerular filtration rate (eGFR) categories, was recently revised to include risk strata for urinary albumin-to-creatinine ratio (ACR) [1]. The associations between eGFR and ACR categories by age for all-cause

mortality risk and end-stage renal disease (ESRD) have been studied in a meta-analysis [2].

Our objective was to compare relative risks and absolute risks for all-cause mortality among adults stratified by eGFR, ACR, and demographic categories. Previous publications have emphasized an attenuation of relative risk for all-cause mortality for older individuals compared to younger individuals [3–5], and have suggested adoption of an age-calibrated definition of CKD. We now report similar apparent attenuation of relative risk for all-cause mortality for female gender and black subjects in the study cohort. Rather than adopting strata-specific definitions of CKD, we believe the same ultimate goal can be achieved by adopting strata-specific risk summaries (“heat maps”) to describe the risk for all-cause mortality.

Materials and Methods

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study cohort included 30,239 black and white individuals who were ≥45 years, between January 2003 and October 2007 [6, 7]. Additional methodological details and description of the cohort are provided elsewhere [6–8]. The present analysis excluded

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Table 1. Baseline characteristics and outcomes for age-strata: 26,887 participants with 3,980 deaths (15%), excluding participants with missing values

Characteristics	Total ^a	Age: ≤60 ^a	Age: 60–70 ^a	Age: ≥70 ^a
Patients, <i>n</i> (%)	26,887 (100)	9,384 (35)	9,215 (34)	8,288 (31)
Age, years, median (IQR)	64 (58–71)	56 (52–58)	65 (63–67)	75 (72–79)^b
Males, %	12,251 (46)	3,836 (41)	4,322 (47)	4,093 (49)^b
Blacks, % ^c	10,670 (40)	4,084 (44)	3,689 (40)	2,897 (35)^b
eGFR _{creat} , mL/min/1.73 m ² , mean (SD)	86 (19)	96 (17)	86 (17)	74 (18)^b
eGFR _{creat} <60 mL/min/1.73 m ² , %	2,760 (10.3)	260 (2.8)	726 (7.9)	1,774 (21)^b
ACR >30 mg/g, %	3,796 (14)	986 (11)	1,207 (13)	1,603 (19)^b
SBP, mm Hg, mean (SD)	127 (17)	124 (16)	128 (16)	131 (17)^b
Total cholesterol, mean (SD)	192 (40)	197 (40)	193 (40)	187 (40)^b
BMI, kg/m ² , median (IQR)	28 (25–32)	29 (25–34)	29 (25–33)	27 (24–31)^b
CVD, %	5,692 (21)	1,192 (13)	1,944 (21)	2,556 (31)^b
Diabetes, %	5,413 (20)	1,627 (17)	2,026 (22)	1,760 (21)
Current smoking, %	3,820 (14)	1,860 (20)	1,315 (14)	645 (7.8)^b
Outcomes, %				
Deaths, %	3,980 (15)	505 (5.4)	1,032 (11)	2,443 (30)^b
Incidence rate, per 1,000-person years	21.3 (20.7–22.0)	7.7 (7.1–8.5)	15.5 (14.6–16.5)	45 (43–46)^b
Incidence rate ratio		1.00 (reference)	2.00 (1.80–2.22)	5.74 (5.22–6.32)^b

Values are given as number (percentage), means (SD); medians (IQR); incidence rates and incidence rate ratios (95% CI).

ACR, urinary albumin-to-creatinine ratio; BMI, body mass index; CVD, prevalent cardiovascular disease; eGFR_{creat}, creatinine-based estimated glomerular filtration rate, CKD Epidemiology Collaboration; IQR, interquartile range, 25th–75th quartile; SBP, systolic blood pressure.

p < 0.001, bold text used to indicate significance for comparisons of characteristics to the reference group by ANOVA for means, signed rank test for medians, and chi-square test for proportions.

^a Row percentages; all others are column percentages.

^b *p* < 0.05 for comparison between 3rd and 2nd categories (Dunnett test for multiple comparisons) or chi-square test or proportions.

^c Race or ethnic group was self-reported, and further classified as black or non-black.

participants with missing values for covariates. The effect variable was the standardized creatinine-based CKD-Epidemiology Collaboration eGFR [9]. All-cause mortality was ascertained as previously described [6–8]. The UAB Institutional Review Board approved the protocol and all participants gave written informed consent.

Mortality Rates, Incidence Rates and Absolute Rates for All-Cause Mortality

Mortality rates (percentage), incidence rates (per 1,000-person years; Stata command *stptime*), and incidence rate ratios with ±95% CIs were calculated with multi-variable adjusted Poisson regression models for eGFR strata (>100, 80–100, 60–80, 45–60, and <45 mL/min/1.73 m²), ACR strata (<30 and ≥30 mg/g), and age strata (<60, 60–70, and >70 years). Absolute incidence rates were obtained from the incidence rate ratios by multiplying each by the rate for eGFR for 80–100 mL/min/1.73 m², ACR <30 mg/g, and age <60 years [10].

Dunnett method was used for making comparisons with a reference category for pairwise comparisons of means. Incidence rate ratios were calculated with Poisson regression for eGFR deciles between 25 and 125 mL/min/1.73 m². Mean values (±95% CI) are used as the relative risk for each interval with covariates fixed at their mean values (Stata command *argins*, *atmeans*). Stata (version 14.1, College Park Station, TX, USA) was used for statistical analysis.

Results

Baseline Characteristics

Baseline characteristics and deaths are shown for the age strata in Table 1 for 26,887 with 3,989 deaths (15%). Of the entire cohort, 40% were African-American and 25% were <58 years of age at enrollment. Male preponderance, systolic blood pressure, prevalent cardiovascular disease, albuminuria >30 mg/dL, and eGFR <60 mL/min/1.73 m² increased across the age strata. The number of blacks, total cholesterol, and current smoking status decreased across the age strata. As expected, all-cause mortality rates increased with age.

Risk Summaries for All-Cause Mortality: “Heat Maps”

Table 2a shows all-cause mortality across age, eGFR, and ACR strata, with the number of deaths expressed as a percentage. Higher mortality rates were associated with lower eGFR categories, and especially for subjects with

Table 2

a. Counts and all-cause mortality rates: age, eGFR, and ACR strata^a

eGFR_creat, mL/min/1.73 m ²	Age: <60		Age: 60–70		Age: >70	
	ACR <30 mg/g	ACR ≥30 mg/g	ACR <30 mg/g	ACR ≥30 mg/g	ACR <30 mg/g	ACR ≥30 mg/g
>100	3,370 151 (4.5)	439 50 (11)	1,430 146 (10)	241 46 (19)	370 67 (18)	80 28 (35)
80–100	3,825 141 (3.7)	309 31 (10)	3,897 315 (8.1)	418 86 (21)	2,667 597 (22)	480 178 (37)
60–80	1,037 64 (6.2)	144 19 (13)	2,189 200 (9.1)	314 65 (21)	2,437 606 (25)	480 206 (43)
45–60	145 15 (10)	51 11 (22)	396 49 (12)	137 44 (32)	893 288 (32)	319 163 (51)
<45	21 3 (14)	43 20 (47)	96 20 (21)	97 61 (63)	318 139 (44)	244 171 (70)

Values are *n* or *n* (%).

^a The mortality rates were calculated as the percentage of deaths in each cell.

b. Relative risk (±95% CI) for all-cause mortality: age, eGFR, and ACR strata^b

eGFR, mL/min/1.73 m ²	Age: <60		Age: 60–70		Age: >70	
	ACR <30 mg/g	ACR ≥30 mg/g	ACR <30 mg/g	ACR ≥30 mg/g	ACR <30 mg/g	ACR ≥30 mg/g
>100	1.20 (0.95–1.52)	2.49 (1.77–3.49)	1.12 (0.97–1.38)	1.78 (1.29–2.45)	0.87 (0.67–1.12)	1.57 (1.07–2.31)
80–100	1.00 (reference) ^a	2.02 (1.36–3.01)	1.00 (reference) ^a	2.28 (1.79–2.91)	1.00 (reference) ^a	1.69 (1.42–2.00)
60–80	1.58 (1.17–2.12)	2.28 (1.40–3.73)	1.12 (0.94–1.34)	1.92 (1.46–2.53)	1.13 (1.01–1.26)	1.88 (1.60–2.12)
45–60	2.11 (1.23–3.61)	4.00 (2.13–7.51)	1.47 (1.08–1.99)	3.21 (2.32–4.43)	1.48 (1.28–1.70)	2.38 (2.00–2.84)
<45	2.96 (0.94–9.30)	6.80 (4.08–11.3)	2.59 (1.64–4.08)	7.13 (5.36–9.50)	2.22 (1.84–2.67)	3.71 (3.12–4.42)

^a Incidence rate ratio; relative to reference group for each age strata.

Color coding for relative risk of all-cause mortality: green, <1.5; yellow, >1.5 and <2.5; orange, >2.5 and <4.0; red, >4.0. Color version available online.

c. Absolute incidence rate (±95% CI) for all-cause mortality: age, eGFR, and ACR strata^b

eGFR, mL/min/1.73 m ²	Age: <60		Age: 60–70		Age: >70	
	ACR <30 mg/g	ACR ≥30 mg/g	ACR <30 mg/g	ACR ≥30 mg/g	ACR <30 mg/g	ACR ≥30 mg/g
>100	1.23 (0.05–2.42)	5.37 (3.71–7.04)	4.25 (3.05–5.45)	6.99 (5.27–8.71)	7.29 (5.78–8.80)	10.1 (8.02–12.2)
80–100	5.13 (4.35–6.05)*	4.25 (2.26–6.26)	3.32 (2.30–4.34)	7.95 (6.57–9.34)	8.40 (7.45–9.35)	10.9 (9.71–12.0)
60–80	2.53 (1.02–4.05)	5.30 (2.82–7.77)	3.94 (2.83–5.05)	7.32 (5.80–8.84)	8.99 (8.04–9.94)	11.3 (10.2–12.4)
45–60	4.89 (2.15–7.62)	8.21 (5.05–11.4)	5.46 (3.79–7.13)	9.93 (8.14–11.7)	10.3 (9.34–11.3)	12.5 (11.3–13.7)
<45	6.32 (0.46–12.2)	11.5 (8.96–14.0)	8.47 (6.06–10.9)	14.1 (12.6–15.7)	12.4 (11.1–13.6)	14.8 (13.6–16.0)

^a Incidence rate; deaths per 1,000 patient year.

The incidence rate ratios in Table 2c were calculated for each gender and age >70 years; the reference group had eGFR >80 and <100 mL/min/1.73 m² and ACR <30 mg/g creatinine.

Color coding for absolute risk of all-cause mortality: green, <6.0; yellow, >6.0 and <8.0; orange, >8.0 and <12.0; red, >12.0. Color version available online.

The absolute mortality rates (Table 2b) for each cell were obtained by multiply the incidence rate ratios by the mortality rate for the eGFR 80–100, ACR <30 mg/g group in column 1 (indicated by*).

ACR, urinary albumin-to-creatinine ratio; eGFR, creatinine-based estimated glomerular filtration rate.

Table 3**a. Relative risk ($\pm 95\%$ CI) for all-cause mortality: race, age >70, eGFR, and ACR strata^a**

eGFR, mL/min/1.73 m ²	Age: >70		Age: >70; white		Age: >70; black	
	ACR <30 mg/g	ACR \geq 30 mg/g	ACR <30 mg/g	ACR \geq 30 mg/g	ACR <30 mg/g	ACR \geq 30 mg/g
>100	0.87 (0.67–1.12)	1.57 (1.07–2.31)	1.67 (0.86–3.24)	9.09 (2.91–28.4)	0.80 (0.60–1.08)	1.44 (0.94–2.19)
80–100	1.00 (reference) ^a	1.69 (1.42–2.00)	1.00 (reference) ^a	1.83 (1.49–2.24)	1.00 (reference) ^a	1.45 (1.08–1.96)
60–80	1.13 (1.01–1.26)	1.88 (1.60–2.12)	1.10 (0.96–1.26)	1.87 (1.53–2.28)	1.17 (0.95–1.44)	1.90 (1.44–2.50)
45–60	1.48 (1.28–1.70)	2.38 (2.00–2.84)	1.54 (1.30–1.81)	2.34 (1.88–2.82)	1.34 (1.03–1.75)	2.42 (1.80–3.26)
<45	2.22 (1.84–2.67)	3.71 (3.12–4.42)	2.14 (1.71–2.69)	3.21 (2.54–4.06)	2.30 (1.65–3.21)	4.58 (3.50–6.00)

Color version available online

b. Relative risk for all-cause mortality: gender, age >70, eGFR, and ACR strata^a

eGFR, mL/min/1.73 m ²	Age: >70		Age: >70; males		Age: >70; females	
	ACR <30 mg/g	ACR \geq 30 mg/g	ACR <30 mg/g	ACR \geq 30 mg/g	ACR <30 mg/g	ACR \geq 30 mg/g
>100	0.87 (0.67–1.12)	1.57 (1.07–2.31)	1.27 (0.91–1.77)	1.25 (0.70–2.25)	0.57 (0.38–0.87)	1.95 (1.17–3.27)
80–100	1.00 (reference) ^a	1.69 (1.42–2.00)	1.00 (reference) ^a	1.72 (1.38–2.14)	1.00 (reference) ^a	1.68 (1.29–2.20)
60–80	1.13 (1.01–1.26)	1.88 (1.60–2.12)	1.21 (1.05–1.40)	1.91 (1.55–2.34)	1.00 (0.83–1.20)	1.90 (1.46–2.46)
45–60	1.48 (1.28–1.70)	2.38 (2.00–2.84)	1.62 (1.34–1.95)	2.54 (2.04–3.17)	1.30 (1.05–1.62)	2.15 (1.61–2.88)
<45	2.22 (1.84–2.67)	3.71 (3.12–4.42)	2.57 (1.98–3.35)	3.47 (2.75–4.38)	1.87 (1.43–2.43)	4.12 (3.18–5.35)

^a Incidence rate ratio; relative to the reference group for each age strata.

Color coding for absolute risk of all-cause mortality: light green, <1.0; green, >1 and <1.5; yellow, >1.5 and <2.5; orange, >2.5 and <4.0; red, >4.0. Color version available online.

ACR, urinary albumin-to-creatinine ratio; eGFR, creatinine-based estimated glomerular filtration rate [9].

ACR >30 mg/g. As expected, higher mortality rates were observed with increasing age categories for all strata.

Relative risks for mortality across the age strata, relative to a common reference at eGFR between 80 and 100 mL/min/1.73 m² and ACR <30 mg/g are shown in Table 2b. Arbitrary color coding corresponds to increasing relative risk (see legend). The relative risk for all-cause mortality was attenuated for older subjects, and the relative risk is similar for eGFR strata >45 mL/min/1.73 m² and ACR <30 mg/g.

Table 2c shows the absolute risk for mortality across the age strata. Incidence rate ratios were calculated relative to a common reference at eGFR between 80 and 100 mL/min/1.73 m², ACR <30 mg/g, and age <60 years. Arbitrary color coding corresponds to increasing absolute risk (see legend). The absolute risk for all-cause mortality was increased for older REGARDS participants (age >70 years), and the absolute risk was similar for eGFR strata >45 mL/min/1.73 m², and ACR <30 mg/g was similar for subjects <70 years. The absolute risk for mortality increased with age and ACR >30 mg/g.

Table 3 shows the relative risk for mortality for race and gender strata, among subjects >70 years of age. Arbitrary color coding corresponds to increasing absolute risk (see legend). The relative risk for all-cause mortality was attenuated for black subjects compared to white subjects >70 years of age (Table 3a), and for female subjects compared to male subjects >70 years of age and ACR <30 mg/g (Table 3b).

Discussion

We describe mortality risk for REGARDS participants based on demographic strata, eGFR, and ACR categories using incidence rates and incidence rate ratios for all-cause mortality. Risk summaries (“heat maps”) show notable differences across demographic strata.

The relative risks for all-cause mortality were attenuated for the older age strata (Table 2b), while the absolute risk for mortality increased with age (Table 2c). For example, the relative risks for mortality among participants with eGFR >60 and <80 mL/min/1.73 m², and

ACR <30 mg/g was 1.58 (95% CI 1.17–2.12) for age <60 years; 1.12 (95% CI 0.94–1.34) for age >60 and <70 years; and 1.13 (95% CI 1.01–1.26) for age >70 years (Table 2b). In contrast, the absolute risk for mortality among the same participants was increased across the age strata: 2.53 (95% CI 1.02–4.05) for age <60 years; 3.94 (95% CI 2.83–5.05) for age >60 and <70 years; and 8.99 (95% CI 8.04–9.94) for age >70 years (Table 2c). Similar patterns were seen across the same eGFR and age strata for ACR >30 mg/g.

Previous commentaries have emphasized the attenuation of the relative risk for all-cause mortality among older subjects [4]. The present analysis confirms this finding, but also extends the analysis to show the expected increase in absolute risk for all-cause mortality with increasing age. Similar observations about the increase in mortality rates with age and ACR levels are described by Hallan et al. [2].

Furthermore, the gender and race differences in relative risk for all-cause mortality shown in Table 3a and b suggest that these strata as well as age should also be considered when assessing the relative risk for all-cause mortality among a specified cohort of patients. This conclusion is consistent with longitudinal descriptions of the risk for all-cause mortality described for elderly Swedish women [11].

The KDIGO Controversies Conference Report [10] included “heat maps” for separate outcome events, including all-cause mortality, cardiovascular mortality, ESRD, acute kidney injury, and progressive CKD. The relative risk summary table for all-cause mortality [10] is similar to the absolute risk summary. It used similar reference groups (ACR <10 and <30 mg/g, eGFR 90–105 and 80–100 mL/min/1.73 m²), with mortality incidence rates of 7.0 and 5.13 deaths per 1,000-person years, respectively. Absolute risk in Table 2c was generated by multiplying incidence rate ratios by the absolute risk for the reference group, as previously described [10]. As expected, the risk for all-cause mortality increased with aging.

With the goal of confirming a single all-encompassing risk summary scheme [1], Hallan et al. [2] examined risk summaries for age strata, eGFR, and ACR categories with a meta-analysis of 33 general population cohorts, including over 2 million participants with 112,325 deaths, including 27,306 REGARDS participants. Risk for all-cause mortality differ across age strata, both for relative risk and absolute risk [2], supporting the use of different risk summaries for different outcome events, demographic strata, and eGFR and ACR strata.

We conclude that the differences between relative and absolute risks for all-cause mortality have not received sufficient emphasis. Furthermore, there may be differences in the absolute and relative risks across age-strata that require further analyses for gender and race strata. The REGARDS cohort is not large enough to fully define these strata, and was recruited with the goal of including subjects >45 years of age, and an equal number of men, women, and white and black participants. Additional meta-analysis of combined general population cohorts seems worthwhile.

It has been proposed that the cutpoints for CKD stages be adjusted for age strata, described as an age-calibrated definition of CKD [3–5], to account for the attenuation of relative risk for all-cause mortality observed with older subjects. This approach has not been widely accepted [12], and represents a post-hoc modification of risk assessment that does not address the underlying weaknesses inherent when such analyses include eGFR as an effect variable [8]. The current proposal to use separate heat maps for age, race, and gender strata rather than a single all-encompassing risk summary may accomplish the basic goal of providing risk assessments in CKD that reflect the demographic and kidney-specific factors for an individual patient.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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