

Renal Function Predicts Survival in Patients with Acute Ischemic Stroke

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Key Words

Creatinine · Glomerular filtration rate · Renal disease · Cerebrovascular disease · Mortality

Abstract

Background: Among patients with acute ischemic stroke, impaired kidney function has been shown to increase the mortality risk, but the shape of this relationship has not been evaluated in detail. **Methods:** We estimated the glomerular filtration rate (eGFR) at the time of hospitalization in 1,175 consecutive patients hospitalized with acute ischemic stroke at the Beth Israel Deaconess Medical Center and examined the shape of the association between eGFR and all-cause mortality. **Results:** There were 508 deaths during a median follow-up of 40.3 months, resulting in a 'U'-shaped relationship between eGFR and all-cause mortality. The curve was relatively flat between 75 and 110 ml/min/1.73 m² but increased sharply at lower and higher levels of eGFR (test for nonlinearity: $p < 0.0001$). **Conclusions:** Among patients with acute ischemic stroke, a reduced or highly elevated eGFR at hospital admission is associated with a higher mortality rate compared to patients with moderate levels of eGFR.

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Stroke is the third leading cause of death in the USA after heart disease and cancer, and the leading cause of serious, long-term disability, with an estimated direct and indirect cost of USD 65.5 billion for 2008 [1]. According to the Atherosclerosis Risk in Communities study [2], 8–12% of ischemic stroke patients 45–64 years of age die within 30 days, and >30% of the people 40–69 years of age die within 5 years of their first stroke [1]. Recent evidence suggests that reduced kidney function may predict survival after acute ischemic stroke independently of classic risk factors [3–5], but the shape of this relationship has not been explored. While Shlipak et al. [6] found that among the elderly, the association between creatinine and mortality is J-shaped, this connection has not been examined among ischemic stroke patients. Therefore, we studied the shape of the relationship between kidney function and mortality with the Modification of Diet in Renal Disease (MDRD) equation to estimate the glomerular filtration rate (eGFR), an approach that is widely used but, like serum creatinine, may give falsely high estimates of kidney function in the presence of low muscle mass [7].

Using eGFR to identify a high-risk subgroup may improve poststroke survival by targeting renal factors that impact vascular health. Accordingly, we examined the shape and magnitude of the relationship between renal

function and mortality among 1,175 consecutive patients hospitalized for acute ischemic stroke at the Beth Israel Deaconess Medical Center (BIDMC) from the Boston metropolitan region.

Materials and Methods

Study Population

This study was approved by the Committee on Clinical Investigations at the BIDMC. We identified consecutive patients ≥ 21 years of age admitted to the BIDMC between April 1, 1999, and December 31, 2004, with neurologist-confirmed ischemic cerebrovascular disease and residing in the Boston metropolitan region. The patients' medical records were reviewed by trained abstractors to confirm the diagnosis of acute ischemic stroke. Patients with in-hospital strokes or transient ischemic attacks were excluded from further analysis. A coinvestigator (G.S.) arbitrated if the final diagnosis was unclear. For each case, trained abstractors using standardized forms recorded data on patient demographics, presenting symptoms and medical history from patient charts or electronic medical records. Race was categorized as white, African-American or other. History of stroke, coronary artery disease, myocardial infarction, atrial fibrillation, heart failure, valvular heart disease, diabetes and dyslipidemia were recorded as present if noted in the medical records and absent otherwise. For each case, the presumed stroke etiology was evaluated as cardioembolic, small-vessel, large-vessel or other/undetermined according to modified TOAST criteria [8].

Renal Function

Data on serum creatinine drawn at the time of hospital presentation were collected. Serum creatinine was measured by the clinical chemistry laboratory photometrically using the Jaffe reaction, with a coefficient of variation of 6.4% at the level of 0.7 mg/dl and 2.2% at the level of 5.6 mg/dl. We calculated the eGFR using the abbreviated MDRD equation [9] as follows:

$$eGFR = 186 \times Scr^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American}),$$

where *eGFR* is the estimated glomerular filtration rate in milliliters/minute/1.73 square meters, *Scr* is the serum creatinine concentration in milligrams/deciliter and *age* is in years. This formula was originally developed using data on >1,000 patients with various kidney diseases and it was validated on an additional 500 patients [10].

Outcome Assessment

Vital status was obtained from the US Social Security Death Index [11, 12]. Registry records were linked to the death data on the basis of key identifiers including patient name, date of birth, social security number and gender. The Social Security Death Index data were obtained on March 20, 2007.

Statistical Analysis

We report univariate statistics stratified by levels of kidney function as mean \pm standard deviation or as counts with proportions, as appropriate. Cox proportional hazards models were used

to estimate the hazard ratio for all-cause mortality adjusting for age (continuous) and sex and stratifying on calendar year. To examine whether the association between kidney function and mortality changes in a nonlinear fashion across the full range of eGFR, we modeled eGFR as a continuous variable using penalized splines [13] adjusting for age, sex and race. A priori, we selected 3 degrees of freedom based on biologic plausibility. This choice was consistent with that chosen by the software to minimize the Akaike Information Criterion for the fitted model.

For consistency with prior publications, we also created 4 categories of renal function and estimated the association between kidney function and mortality. Those with an eGFR between 75 and 125 ml/min/1.73 m² were compared to people with an eGFR <60 ml/min/1.73 m², those with an eGFR between 60.0 and 74.9 ml/min/1.73 m² and those with an eGFR >125 ml/min/1.73 m². These categories were chosen a priori based on the Valsartan in Acute Myocardial Infarction Trial, which used these eGFR cut-offs in 14,527 patients with cardiovascular disease [14], with an additional category to examine the risk among patients who may have a falsely elevated eGFR due to low muscle mass.

We constructed a multivariate model additionally controlling for race (African-American, white or other), smoking status (never, former, current), and medical history of stroke, coronary artery disease, myocardial infarction, atrial fibrillation, heart failure, valvular disease, diabetes, dyslipidemia and hypertension. We did not adjust for stroke severity, treatment received during the index hospitalization or medications and lifestyle factors following stroke [15–17] in the primary analyses, since these factors may be downstream consequences occurring after the development of reduced or highly elevated eGFR. In sensitivity analyses we additionally controlled for correlates of stroke severity. Although standard measures of stroke severity were not routinely documented in the medical records, we used the number of presenting symptoms (≥ 4 vs. <4), length of hospital stay (≥ 4 vs. <4 days), disposition (home vs. other) and stroke etiology (4 categories) as proxy measures of stroke severity. For tests of quadratic trend, we assigned median eGFR to each category, centered it on mean eGFR and tested for significance using a likelihood ratio test.

We evaluated whether the association between eGFR and mortality differed by sex, age (<75 vs. ≥ 75 years), smoking status or 30-day survival by including interaction terms in the model adjusted for age, sex and race. We verified the proportional hazards assumption using interactions of the predictors and a function of survival time and found no significant violations. We conducted sensitivity analyses excluding Asians (2%) because the MDRD formula does not perform well in Asian populations and patients meeting the criteria for renal replacement therapy (2%), but the results were not materially different. All analyses were carried out using SAS 9.1 (SAS Institute, Inc., Cary, N.C., USA) and R 2.6.2. Two-sided p values <0.05 were considered statistically significant.

Results

We identified 1,180 consecutive patients hospitalized for neurologist-confirmed acute ischemic stroke. Data on serum creatinine at the time of hospital presentation were

Table 1. Baseline characteristics of 1,175 patients with ischemic stroke by eGFR

	<60.0 ml/min/1.73 m ² (n = 391)	60.0–74.9 ml/min/1.73 m ² (n = 296)	75.0–125.0 ml/min/1.73 m ² (n = 434)	>125.0 ml/min/1.73 m ² (n = 54)	p value
Age, years	77.9 ± 10.7	76.9 ± 13.1	67.6 ± 14.4	58.0 ± 15.4	<0.0001
Serum creatinine, mg/dl	1.80 ± 1.39	0.98 ± 0.16	0.81 ± 0.15	0.58 ± 0.09	<0.0001
Creatinine level within reference range	91 (24)	286 (97)	432 (99)	54 (100)	<0.0001
Female	234 (60)	179 (60)	205 (47)	26 (48)	0.0003
African-American	43 (11)	17 (6)	54 (12)	10 (19)	0.0056
Current smokers	36 (9)	38 (13)	70 (16)	24 (44)	<0.0001
Former smokers	101 (26)	71 (24)	110 (25)	13 (24)	0.93
History of					
Stroke	142 (36)	82 (28)	103 (24)	10 (19)	0.0002
Coronary artery disease	144 (37)	73 (25)	89 (21)	6 (11)	<0.0001
Myocardial infarction	63 (16)	35 (12)	47 (11)	5 (9)	0.1012
Atrial fibrillation	119 (30)	66 (22)	88 (20)	6 (11)	0.0005
Heart failure	76 (19)	32 (11)	31 (7)	3 (6)	<0.0001
Valvular heart disease	13 (3)	3 (1)	2 (0.5)	1 (2)	0.0093
Diabetes	152 (39)	73 (25)	111 (26)	19 (35)	<0.0001
Dyslipidemia	165 (42)	106 (36)	155 (36)	13 (24)	0.0321
Hypertension	305 (78)	220 (74)	272 (63)	29 (54)	<0.0001
Length of stay, days	5.3 ± 4.7	5.0 ± 3.7	5.1 ± 4.9	5.5 ± 5.1	0.71
Discharge					0.0008
Home	147 (38)	110 (37)	220 (51)	30 (56)	
Rehabilitation facility	63 (16)	52 (18)	66 (15)	8 (15)	
Skilled nurse facility	74 (19)	59 (20)	57 (13)	5 (9)	
Dead	31 (8)	14 (5)	13 (3)	1 (2)	
Other	76 (19)	61 (21)	78 (18)	10 (19)	
Stroke etiology					0.78
Small-vessel	105 (27)	91 (31)	128 (29)	15 (28)	
Large-vessel	82 (21)	74 (25)	95 (22)	11 (21)	
Cardioembolic	90 (23)	54 (18)	92 (21)	10 (19)	
Other/undetermined	114 (29)	77 (26)	119 (27)	18 (33)	

Figures are means ± standard deviation or numbers of cases with percentages in parentheses. p values for discrete variables derived from χ^2 tests and continuous variables from ANOVA. Serum creatinine reference ranges for the BIDMC laboratory: 0.5–1.2 mg/dl for males and 0.4–1.1 mg/dl for females.

available in 99.6% (n = 1,175) of the patients. The mean eGFR upon presentation was 72 ml/min/1.73 m² (standard deviation 28.2) with 36.9% (n = 434) of the patients presenting with an eGFR between 75 and 125 ml/min/1.73 m² and 33.3% (n = 391) with a value <60 ml/min/1.73 m². Ninety-seven percent (n = 286) of the patients with an eGFR between 60 and 75 ml/min/1.73 m² and 24% (n = 91) of those with an eGFR <60 ml/min/1.73 m² had creatinine values within the normal range for the BIDMC clinical chemistry laboratory (0.5–1.2 mg/dl for males and 0.4–1.1 mg/dl for females). Patients in the lowest category of eGFR were more likely to be female and more likely to have experienced previous cardiovascular diseases than those in the reference category (table 1).

During a median follow-up of 40.3 months, 508 of the 1,175 participants (43%) died.

We used Cox proportional hazard models with penalized splines to evaluate the shape of the relationship between eGFR and all-cause mortality, adjusting for age and sex. There was a ‘U’-shaped association between eGFR and all-cause mortality, with a nadir at approximately 85 ml/min/1.73 m² (fig. 1). The curve was relatively flat between 75 and 110 ml/min/1.73 m² but increased sharply at lower and higher levels of eGFR (test for nonlinearity: p < 0.0001).

For comparison with prior studies, we also modeled the eGFR using 4 categories. Table 2 shows that after adjusting for age and sex there was a graded increase in all-

Fig. 1. Penalized spline fit showing the hazard ratio of all-cause mortality as a function of eGFR among 1,175 patients with ischemic stroke. Data were fitted using a penalized spline Cox proportional hazards model adjusted for age and sex. The solid line represents the hazard ratio and the dashed lines the 95% confidence interval bands. The distribution of eGFR is displayed as vertical lines below the plot.

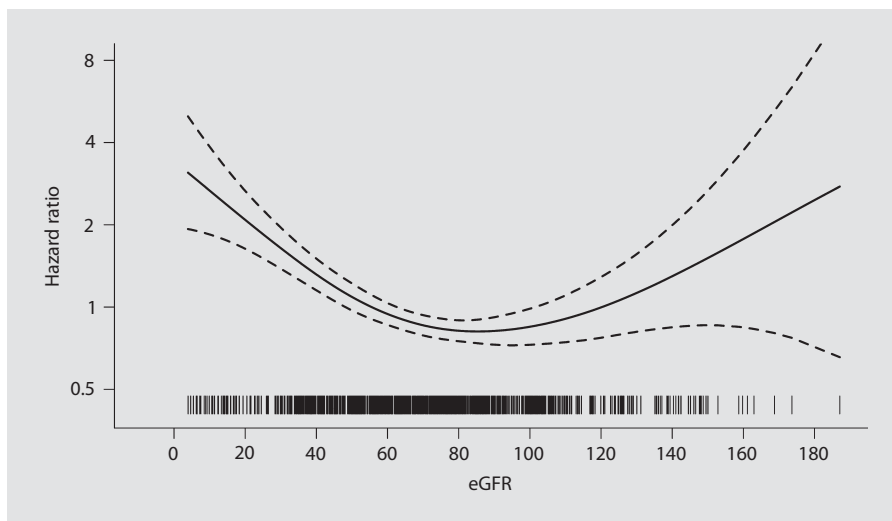


Table 2. Hazard ratio for impaired kidney function and all-cause mortality among 1,175 patients with ischemic stroke

eGFR	Age- and sex-adjusted	Fully adjusted
<60.0 ml/min/1.73 m ²	1.54 (1.23–1.92)	1.48 (1.17–1.86)
60.0–74.9 ml/min/1.73 m ²	1.10 (0.86–1.41)	1.21 (0.94–1.55)
75–125 ml/min/1.73 m ²	1.0 (reference)	1.0 (reference)
>125 ml/min/1.73 m ²	1.63 (0.95–2.80)	1.66 (0.96–2.88)
p quadratic trend	0.002	0.01

Figures in parentheses are 95% CI. Fully adjusted: adjusted for age, sex, race, smoking status (never, former, current), previous stroke, coronary artery disease, myocardial infarction, atrial fibrillation, heart failure, valve disease, diabetes, dyslipidemia and hypertension.

cause mortality with decreasing kidney function (p for quadratic trend = 0.002). In a fully adjusted model that also accounted for race, smoking status, diabetes, dyslipidemia, hypertension, coronary artery disease, myocardial infarction, atrial fibrillation, heart failure, valve disease and previous stroke, we found that compared to patients with an eGFR between 75 and 125 ml/min/1.73 m², the all-cause mortality rate was 21% higher among patients with an eGFR between 60.0 and 74.9 ml/min/1.73 m², 48% higher among those with an eGFR <60 ml/min/1.73 m² and 66% higher among patients with an eGFR >125 ml/min/1.73 m² (p for quadratic trend = 0.01). The results were not materially different upon further adjustment for stroke symptoms, length of stay, disposition

or presumed stroke etiology. The hazard ratios for the association between eGFR and mortality did not vary by sex (p = 0.48), age ≥75 versus age <75 (p = 0.61) or smoking status (p = 0.84). The hazard ratios were also not significantly different in the first 30 days versus during the remainder of the follow-up time (p = 0.30).

Of the 1,175 patients hospitalized, 119 (10.1%) died within 30 days of hospitalization. Adjusting for age, sex and comorbidities, the 30-day case fatality rate was 61% (95% CI: 1.00–2.60) higher among patients with an eGFR <60.0 ml/min/1.73 m² as compared to those with an eGFR between 75 and 125 ml/min/1.73 m². Patients with an eGFR between 60.0 and 74.9 ml/min/1.73 m² were not at increased risk of 30-day mortality [hazard ratio (HR): 1.0; 95% CI: 0.6–1.7]. Only 1 patient with an eGFR >125 ml/min/1.73 m² died within 30 days.

Discussion

In the present study, we sought to determine whether the eGFR in patients hospitalized with acute ischemic stroke provided prognostic information about mortality. Because the eGFR can be falsely elevated in the presence of low muscle mass, we hypothesized that patients with an eGFR >125 ml/min/1.73 m² would also be at elevated risk. We observed a ‘U’-shaped relationship between eGFR and all-cause mortality, with increased risk among those with both low and high levels of eGFR. This was confirmed in an analysis using categories of exposure, which indicated an elevated risk among patients with an

eGFR <75 ml/min/1.73 m² and an apparent elevated risk among patients with an eGFR >125 ml/min/1.73 m² that did not reach statistical significance, independent of age, sex, race and major comorbidities.

Impaired renal function is an established predictor of survival in the general population [18], in patients with myocardial infarction [14, 19–21] or heart failure [22, 23], and those undergoing percutaneous cardiovascular interventions [24] or coronary artery bypass graft surgery [25–27]. However, whether chronic kidney disease predicts survival following acute ischemic stroke, has not been extensively studied. Zuliani et al. [28] found no association between serum creatinine and 30-day mortality among 469 stroke patients ≥65 years of age. In contrast, Macwalter et al. [4] followed 2,042 stroke patients in Scotland and found that creatinine clearance, urea, creatinine concentration, and ratio of urea all predicted survival over 7 years of follow-up. For instance, a creatinine clearance between 51.26 and 66.75 ml/min/1.73 m² was significantly associated with a 30% decrease in mortality compared to those with a creatinine clearance in the lowest quartile, even after adjustment for other risk factors (relative risk: 0.70; 95% CI: 0.53–0.92). Similarly, in a case-control study of 545 white Europeans and 330 age-matched controls, Carter et al. [3] demonstrated a significantly increased risk of mortality among stroke patients across baseline creatinine levels (HR: 1.85; 95% CI: 1.25–2.73; *p* = 0.002). The results of the current study confirm the finding that reduced eGFR is associated with increased mortality among stroke patients and shows that this relationship changes in a nonlinear fashion across the full range of eGFR values.

Participants with chronic diseases may have an elevated eGFR that does not reflect proper kidney function. Similar to our findings, Shlipak et al. [6] showed that the association between quintiles of creatinine and mortality from all causes appeared to be J-shaped among 4,637 participants in the Cardiovascular Health Study, and Inrig et al. [29] found an elevated risk of cardiovascular outcomes among patients with atherosclerotic cardiovascular disease who had an eGFR ≥125 ml/min/1.73 m². This may be due to the fact that eGFR is often falsely elevated among patients with grossly abnormal muscle mass (e.g. amputation, paralysis, muscular disease), low body mass index (<18.5), high or low intake of creatinine or creatine (e.g. dietary supplements, vegetarians), concomitant medication use and rapidly changing kidney function [7, 29, 30].

Interpretations of creatinine levels alone are not sufficient for risk stratification. The eGFR must decline to

approximately half the normal level before the serum creatinine concentration rises above the upper limit of normal. An eGFR <60 ml/min/1.73 m² represents loss of half or more of the adult level of normal kidney function and is associated with an increased prevalence of complications of chronic kidney disease [10], yet one quarter of the patients in this sample with an eGFR <60 ml/min/1.73 m² had creatinine levels in the normal range.

The relationship between kidney function and survival following an acute ischemic stroke may be due to shared risk factors underlying vascular diseases including age, diabetes mellitus, systolic hypertension, left ventricular hypertrophy and low high-density lipoprotein cholesterol [31], or it may represent a unique vascular pathogenesis resulting from reduced renal clearance [32]. Kidney function may be a marker of other predictors of mortality, such as end-organ damage from subclinical hypertension. Alternatively, kidney function may be associated with arterial stiffness and thus pose an increased risk of cardiovascular morbidity and mortality [33]. Based on MRI results from 484 participants from the Rotterdam Scan Study, Ikram et al. [34] found that impaired kidney function is associated with MRI markers of cerebral small-vessel disease and suggested that this relationship may be due to the fact that the blood vessels of both the kidney and the brain have low resistance and are therefore highly susceptible to fluctuations in blood pressure and flow.

Our findings are based on creatinine measurements at the time of hospital admission, but other studies suggest that there is an association between decreased kidney function during the hospital stay and in-hospital mortality [35] and major bleeding [36] after ischemic stroke. Changes during hospitalization also independently predict the 1-year mortality after acute myocardial infarction [19, 37]. Goldberg et al. [19] examined the relation between baseline creatinine clearance and worsening renal function, defined as an increase of ≥0.5 mg/dl in creatinine level at any point during hospital stay, and subsequent in-hospital and 1-year mortality among patients presenting with acute ST elevation myocardial infarction. The authors found that both baseline renal dysfunction (HR: 2.8; 95% CI: 1.6–4.9) and worsening renal function (HR: 7.2; 95% CI: 4.9–10.4) remained independent predictors of 1-year mortality. Thus, in-hospital changes in eGFR may also predict poststroke survival. However, in our cohort there were too few patients with repeat creatinine measurement to evaluate this association.

This study has some limitations that warrant discussion. First, all patients were admitted to a single center

and resided in the same metropolitan area with relatively few African-Americans, possibly limiting the generalizability of these findings. Second, there may have been misclassification of the outcome due to errors in the death records of the Social Security Administration. However, this database has been shown to serve as a valid source of mortality data [11, 12]. Third, the MDRD formula does not perform well in Asian populations [38], but the majority of our cohort were white, with only 2% Asian. In a sensitivity analysis excluding Asian patients, the results were similar. Fourth, standard measures of stroke severity were not available. However, in sensitivity analyses controlling for various correlates of stroke severity, the results were not materially different. Finally, some patients may have had elevated creatinine levels requiring intensive treatment for kidney impairment, which could be associated with prognosis. However, only 2% of the sample had an eGFR between 15 and 29 ml/min/1.73 m², the recommended cutoff for the preparation of renal replacement therapy [10], and only 2% had an eGFR <15 ml/min/1.73 m², the recommended cutoff for the initiation of dialysis. Therefore, any increasing mortality from treatment seems minimal. In a sensitivity analysis excluding patients meeting the criteria for renal replacement therapy, the results were similar to those in the primary analysis. This study has many strengths, including an examination of a nonlinear association, a large sample of unselected patients, detailed clinical data and consistent high-quality follow-up data.

Conclusion

The severity of impaired kidney function in patients hospitalized with acute ischemic stroke is associated with increased all-cause mortality independent of age, sex, race and major comorbidities. These results also indicate that creatinine levels must be used cautiously. Even patients with only mildly reduced kidney function, who often have creatinine levels within the normal reference range for many clinical chemistry laboratories, are at increased risk. Similarly, patients with low muscle mass may have creatinine levels indicative of normal kidney function when indeed they are at increased risk. The eGFR is easy to calculate and may serve as a useful tool for risk stratification of these patients. Therapeutic studies are required to determine whether novel or established secondary prevention measures are particularly efficacious among these high-risk patients.

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