Chronic Kidney Disease and Clinical Outcome in Patients With Acute Stroke

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Background and Purpose—Chronic kidney disease (CKD) is increasingly recognized as an independent risk factor for cardiovascular disease and stroke. Our aim was to examine the association between estimated glomerular filtration rate (GFR) and stroke outcome and to assess whether CKD and its severity affect stroke outcome in a large cohort of unselected patients with acute stroke.

Methods—We examined the association between baseline estimated GFR and CKD and 1-year outcomes in 821 consecutive patients with acute stroke (ischemic or hemorrhagic). GFR was estimated by 2 methods: the Modification of Diet in Renal Disease and the Mayo Clinic quadratic equation. An estimated GFR rate ≥60 mL/min/1.73 m² defined CKD.

Results—Odds ratios (95% CI) for death across levels of estimated GFR based on both equations were estimated. CKD was present in 36% (n=291) of patients based on the Modification of Diet in Renal Disease equation and 18% (n=147) based on the Mayo Clinic equation. The adjusted ORs for mortality after 1-year based on the Modification of Diet in Renal Disease equation were 0.7 (95% CI, 0.4 to 1.2) associated with GFR 45 to 60 and 3.2 (1.7 to 6.4) associated with GFR 15 to 44 as compared with GFR ≥60 mL/min/1.73 m², whereas those based on the Mayo Clinic equation were 2.3 (1.1 to 4.7) and 3.3 (1.6 to 7.1), respectively. The adjusted ORs for Barthel Index ≤75 or death after 1 year were 0.8 (0.5 to 1.5) and 2.1 (0.9 to 4.8) by the Modification of Diet in Renal Disease equation and 1.9 (0.8 to 4.4) and 3.9 (1.5 to 11.0) by the Mayo Clinic equation, respectively.

Conclusions—CKD is a strong independent predictor of mortality and poor outcome in patients with acute stroke. The estimation of the prevalence of CKD and of the GFR cutoffs associated with poor outcome depend on the equation used to estimate GFR. (Stroke. 2009;40:1296-1303.)

Key Words: acute stroke ■ chronic kidney disease ■ prognosis

Chronic kidney disease (CKD) is a worldwide public health problem with an estimated prevalence of 11% of adults in the United States and higher prevalence among patients with cardiovascular disease.1-4 There is growing evidence for an association between CKD and adverse cardiovascular events.2-5 The relationship between renal dysfunction and increased cardiovascular morbidity and mortality extends across the spectrum of renal dysfunction to encompass mild degrees of renal impairment. We have previously shown that CKD is associated with increased risk of incident ischemic stroke among patients with pre-existing atherothrombotic disease.6

In the context of an acute coronary syndrome, CKD has been shown to be a marker of adverse clinical characteristics and was independently associated with adverse outcomes.4,5,7 Data on the association between renal dysfunction and outcome after acute stroke are scarce, and what is known relates to serum creatinine level or other less sensitive indicators of renal function with outcome data limited to survival.8,9 We therefore evaluated the prevalence of CKD using glomerular filtration rate (GFR) estimated by 2 equations in an unselected large cohort of patients with an acute stroke to examine the association between GFR and stroke outcome and to assess whether CKD and its severity affect mortality and functional outcome.

Subjects and Methods

Design
A prospective longitudinal cohort study included 821 consecutive patients hospitalized due to acute stroke throughout a large medical center with a catchment area of approximately 500 000 people. Data were collected on all patients admitted from March 2001 to June 2002 with a diagnosis of acute stroke according to World Health Organization criteria.

Estimation of Glomerular Filtration Rate and Determination of Chronic Kidney Disease
GFR was estimated using 2 equations: (1) the 4-variable Modification of Diet in Renal Disease (MDRD) formula: GFR=186×(SCr)−1.154×(age)−0.203×0.742×1.210 (if female) ×1.035 (if black); (2) the Mayo Clinic quadratic equation: GFR=K (aortic flow) × 1.73 m². A cutoff of ≥60 mL/min/1.73 m² defined CKD.

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1296
(age)$^{-0.203}\times0.742$ (if the subject is female); and (2) the Mayo Clinic quadratic equation:$^{10}$ \[ \frac{\text{GFR}}{\text{exp}(1.911+5.249/S_{\text{cr}})-2.114/S_{\text{cr}}^2-0.00686\times\text{age}-0.205 \text{[if female]}} \] if $S_{\text{cr}} < 0.8 \text{ mg/dL}$, use 0.8 for $S_{\text{cr}}$). Baseline serum creatinine measurements were performed at a central laboratory using the Jaffe assay. CKD was defined following the National Kidney Foundation definition as kidney damage reflected by an estimated GFR of $<60 \text{ mL/min/1.73 m}^2$ of body surface area. We have further categorized CKD into moderate reduction of GFR of 45 to 60 and moderate–severe reduction of 15 to 44 mL/min/1.73 m$^2$. This further categorization is a modification of the National Kidney Foundation classification scheme chosen based on prior studies in patients with cardiovascular disease.

**Data Collection**

Patients were evaluated systematically for risk factors, stroke severity, type, and subtype. Severity of stroke was assessed using the National Institute of Health Stroke Scale.$^{11}$ Intracerebral hemorrhage and ischemic stroke were differentiated by the results of the baseline head CT scan. Ischemic stroke etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment classification.$^{12}$ Throughout hospitalization and at 1-month follow-up, data were collected by clinical evaluations and personal interviews with patients and/or proxies. One year after the stroke, phone follow-up interviews were conducted by professional interviewers from the Israel Center for Disease Control. Functional outcome were assessed using the Barthel Index.$^{13}$ Mortality data were collected from the Israeli Population Registry.

**Statistical Analysis**

GFR at baseline was estimated with the use of the 4-component MDRD and the Mayo Clinic quadratic equations. Estimated GFR (eGFR) derived from each equation was categorized in an exploratory manner with respect to the outcome into distribution derived quintiles and into clinically relevant groups ($<20, 20$ to $29, 30$ to $39, 40$ to $49, 50$ to $59, 60$ to $69, 70$ to $79, 80$ to $89, \geq 90 \text{ mL/min/1.73 m}^2$) with $\geq 90 \text{ mL/min/1.73 m}^2$ serving as the reference group. Higher values in the normal range were not further categorized because the MDRD equation is well known to have substantial errors for GFR estimates in the normal–high range.$^{7,10,14}$ The distribution of the GFR was further divided into 3 groups, based on CKD and its severity (15 to 44, 45 to 60, and $>60 \text{ mL/min/1.73 m}^2$), after excluding patients with $<15 \text{ mL/min/1.73 m}^2$ to focus on mild and moderate CKD rather than kidney failure. Univariate associations between GFR categories and other baseline demographic and clinical variables were evaluated with analysis of variance and $\chi^2$ tests. Unadjusted event rates for the stroke outcome end points were compared across GFR categories with the $\chi^2$ test. Event-free survival rates after a 1-year follow-up of the 3 groups are presented as a Kaplan–Meier curve and compared by means of the log rank test. To examine the relationship between CKD and its severity and outcome, multivariable analyses were conducted. GFR category was entered as 2

![Figure 1. Distribution of estimated GFR among the study cohort: (A) using the MDRD equation; (B) using the Mayo Clinic quadratic equation; and (C) scatterplot of the Mayo Clinic versus the MDRD-estimated GFR.](http://stroke.ahajournals.org/)

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Yahalom et al Chronic Kidney Disease and Outcome After Stroke 1297
dummy variables with GFR ≥60 mL/min/1.73 m$^2$ as the reference group. In the multivariable models, we adjusted for age, gender, stroke type (ischemic or intracerebral hemorrhage), stroke severity, anemia, hypertension, prior disability, diabetes, angina pectoris or past myocardial infarction, other cardiac disease (atrial fibrillation or chronic heart failure or vascular heart disease), past stroke, and malignancy. For the Mayo Clinic equation, the previously mentioned analyses were repeated by including eGFR as a continuous variable, and ORs were computed for a decrease of 1 SD of eGFR. Analyses were performed with SAS statistical software version 8.2 (SAS, Inc, Cary, NC).

Results
The study cohort included 821 patients. The distributions of GFR among the study cohort estimated by the 2 equations and a scatterplot of eGFR by both estimations are presented in Figure 1. The mean±SD eGFR was 64.2±20.0 (range, 5.3 to 140.0) mL/min/1.73 m$^2$ by the MDRD equation and 76.8±24.8 (range, 5.7 to 127.4) mL/min/1.73 m$^2$ by the Mayo Clinic equation. Overall, the proportion of patients having CKD was 36% (n=291) based on the MDRD equation and 18% (n=147) based on the Mayo Clinic equation.

OR (95% CIs) for death at 1 year across the levels of eGFR, categorized into distribution-derived quintiles for each equation, as well as into clinically relevant groups of 10-mL/min/1.73 m$^2$ differences, are shown in Figure 2. Regarding the MDRD equation, one may note that for eGFR ranging from 20 to 50 mL/min/1.73 m$^2$, there is a linear decrease of approximately 1 U in the OR for mortality after 1 year for each 10-mL/min/1.73 m$^2$ increment in the eGFR, whereas from 50 mL/min/1.73 m$^2$ and above, the estimated coefficients are comparable in magnitude with wide overlapping CIs. The corresponding ORs by the Mayo Clinic quadratic equation reveal a decrease across eGFR levels. The unad-
adjusted ORs for 1-year mortality based on a 1-SD (24.8 mL/min/1.73 m²) decrease in the Mayo Clinic eGFR is 2.0 (95% CI, 1.7 to 2.4) and the adjusted OR is 1.6 (95% CI, 1.3 to 2.1).

We have further categorized eGFR into 3 categories based on CKD and its severity after excluding patients with kidney failure. Baseline characteristics of the study cohort across the 3 GFR groups estimated by the MDRD equation are shown in Table 1. Patients with lower GFR were older, were more likely to be women, had more comorbidity, and were less often cigarette smokers. Thus, patients in the lowest category of the GFR had the highest rates of hypertension, prior stroke, prior myocardial infarction or angina, peripheral vascular disease, congestive heart failure, atrial fibrillation, and anemia; had more frequently intracerebral hemorrhage; and less frequently mild stroke severity as compared with those without CKD.

At 1 month after the event, 695 patients (87%) were alive, and 561 (81%) of them had a follow-up evaluation. At 1 year, 642 patients (80%) were alive, and 481 (75%) of them had a phone follow-up interview. Mortality data derived from the Israeli Population Registry were available for all patients. Age of patients assessed after 1 month was 69±13 years and after 1 year 67±12 years. Patients lost to follow-up for the 1-year questionnaire had more often low GFR, more severe strokes, and were more often discharged to a nursing facility.

Decreasing categories of GFR estimated by both equations were associated with increasing rates of poor outcome at both 1 month and 1 year after the index stroke (Table 2). Using the MDRD equation, particularly high mortality and rates of poor functional outcome were observed restricted to those with markedly low GFR of 15 to 44 mL/min/1.73 m². Using the Mayo Clinic equation, there was a more gradual increase in the rates of poor outcome across the 3 categories of GFR. Thus, mortality rates after 1 year increased from 14.8% for patients with no CKD to 35.9% and 47.8% among those with GFR of 45 to 60 and 15 to 44 mL/min/1.73 m², respectively. Kaplan–Meier survival analyses by categories of GFR, estimated by both equations, are depicted in Figure 3.

The adjusted ORs for poor outcomes by categories of GFR are shown in Table 3. Using the group with GFR of at least 60 mL/min/1.73 m² as the reference group yielded adjusted OR for death, institution in a long-term nursing facility, and disability that increased as the degree of renal function deteriorated at both 1 month and 1 year after the stroke. The intermediate category of 45 to 60 mL/min/1.73 m² exhibited

Figure 2. ORs (95% CIs) for death at 1 year according to the level of eGFR: (A) using the MDRD equation; and (B) using the Mayo Clinic quadratic equation. 1, According to quintiles with the highest quintile serving as the reference group; (2) categorization by 10 mL/min/1.73 m² differences in eGFR with ≥90 mL/min/1.73 m² serving as the reference group.
increased adjusted OR when estimated by the Mayo Clinic equation, but not by the MDRD equation. The category with the lowest GFR exhibited approximately 3- to 5-fold increased relative odds for mortality using both the MDRD and the Mayo Clinic equations (adjusted OR at 1 month, 3.7 and 4.5 and at 1 year of 3.2 and 3.3, respectively; \( P \leq 0.0001 \) for all). Further adjustment to baseline serum albumin only mildly attenuated these associations with adjusted OR using the MDRD equation for 1-month mortality of 2.7 (95% CI, 1.2 to 5.9) and 1-year mortality of 2.8 (95% CI, 1.3 to 6.0) for the category with GFR of 15 to 44 mL/min/1.73 m².

Similar dose–response associations between GFR and 1-year mortality were observed in women and men, in patients younger or older than 70 years, in patients with or without diabetes, and in patients with intracerebral hemorrhage as well as ischemic stroke with no evidence of interaction. Rates of 1-year mortality among patients with an ischemic stroke by MDRD-derived eGFR categories of >60, 45 to 60, and 15 to 44 mL/min/1.73 m² were 11%, 15%, and 37%, respectively, among patients with ischemic stroke versus 46%, 36%, and 86% among those with intracerebral hemorrhage (\( P \) for interaction=0.21).

### Discussion

Our main finding is that low eGFR and the presence of CKD constitute strong independent predictors of mortality and poor outcome in patients with acute stroke. The estimation of the prevalence of CKD and of the GFR cutoffs associated with poor outcome depend, however, on the equation used to estimate GFR.

Data on the association between renal dysfunction and outcome after acute stroke are scarce.\(^8\) Friedman et al have found an association between serum creatinine levels and mortality in a group of patients with stroke.\(^8\) MacWalter et al have found that higher serum creatinine and reduced admission calculated creatinine estimated by the Cockcroft-Gault formula is associated with higher mortality rates.\(^8\) Inference of renal dysfunction from the serum creatinine level alone is complicated by the differing rates of creatinine production among persons, mainly because of variations in muscle mass. Women and the elderly often have deceptively low serum creatinine levels despite substantial reductions in GFR. Estimation of the GFR by the MDRD and the Mayo Clinic equations were found to be more accurate than the Cockcroft-Gault formula.\(^15,16\)

The MDRD equation, used in the current study, has now been validated extensively in multiple samples with and without CKD and is recommended for estimation of GFR by
authoritative guidelines. There are, however, substantial errors for GFR estimates in the normal–high range, and creatinine-based estimations are not reliable in those with particularly low creatinine generation. We have estimated the GFR using also the more recently developed Mayo Clinic equation, which was previously suggested to be more accurate than the MDRD. The population studied for developing this equation had a younger mean age, but this equation was found to best identify subjects at increased risk for mortality among community-dwelling elderly subjects. Although both equations consistently show the poor outcome associated with renal dysfunction, the GFR values and the cutoffs associated with poor outcome in our study cohort depend on the equation used with overall higher OR estimates obtained using the Mayo Clinic equation.

Patients with end-stage renal disease experience markedly advanced atherosclerotic disease of the cerebral vasculature and an extraordinary high risk of stroke as patients compared with individuals without end-stage-renal disease. Furthermore, hemodialysis treatment is an independent indicator for poor functional outcome and mortality after stroke. In our cohort, eGFR <20 mL/min/1.73 m² was associated with an approximately 7-fold increased odds for mortality after 1 year by the MDRD equation and approximately 13-fold by the Mayo Clinic equation.

There is a growing body of evidence regarding the relationship between renal dysfunction and cardiovascular morbidity and mortality. CKD is also associated with increased risk of incident ischemic stroke. Recently, Khatri et al found that CKD was associated with a greater burden of white matter hyperintensities as seen in brain MRI, and Ikram et al showed that persons with lower GFR had less deep white matter volume and more white matter lesions, adding to a growing body of evidence that kidney disease is an important, independent risk factor for cerebrovascular diseases.

Mechanisms by which renal dysfunction increases cardiovascular risk are under investigation. The progressive increase in cardiovascular risk with worsening GFR is partly
explained by factors associated with renal decline, including anemia, oxidative stress, increase in plasma asymmetrical dimethylarginine, a powerful inhibitor of nitric oxide synthesis, inflammation, and conditions promoting coagulation,22–25 all of which are associated with accelerated atherosclerosis and endothelial dysfunction. Other markers that progressively increase with renal decline include albuminuria, proteinuria, fibrinogen, homocysteinemia, and elevated uric acid levels.26–30

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<th>Strength and Limitations</th>
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| Data are based on a large cohort of consecutive unselected patients presenting with acute stroke. GFR was not directly measured in the current study and creatinine measurements, although performed at a central laboratory, were not calibrated to creatinine reference standards. Direct measurement is, however, cumbersome and expensive and is not performed in routine clinical practice. The difference between the estimated and true GFR may have led to misclassification of some subjects, although misclassification would likely lead to underestimation of the strength of the associations. We have focused our analyses, however, on eGFR in the borderline or prevalent kidney disease range for which the estimation equations are calibrated to creatinine reference standards. Direct measurement of acute cerebral infarction: a clinical examination scale. A 7-year follow-up study. Stroke. 2002;33:1630–1635.


Disclosures

None.

References


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<th>Table 3. Logistic Regression Models for Prediction of Outcomes by GFR Estimated by the MDRD and Mayo Clinic Equations</th>
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<td><strong>MDRD-Estimated GFR (mL/min/1.73 m²)</strong></td>
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*Adjusted for age, gender, stroke type (ischemic or intracerebral hemorrhage), stroke severity, anemia, hypertension, prior disability, diabetes, angina pectoris or past myocardial infarction, other cardiac disease (atrial fibrillation or chronic heart failure or vascular heart disease), past stroke, and malignancy.


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