The Association between Glomerular Filtration Rate Estimated on Admission and Acute Stroke Outcome: The Shiga Stroke Registry

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Aim: Although renal dysfunction has been identified as a novel risk factor affecting stroke prognosis, few have analyzed the association within large-scale population-based setting, using wide-range estimated glomerular filtration rate (eGFR) category. We aimed to determine the association of admission eGFR with acute stroke outcomes using data from a registry established in Shiga Prefecture, Japan.

Methods: Following exclusion of patients younger than 18 years, with missing serum creatinine data, and with onset more than 7 days prior to admission, 2,813 acute stroke patients registered in the Shiga Stroke Registry year 2011 were included in the final analysis. The Japanese Society of Nephrology equation was used to estimate GFR. Multivariable logistic regression was performed to analyze the association of eGFR with all-cause in-hospital death (modified Rankin Scale [mRS] 6), and at-discharge death/disability (mRS 2–6). Separate analyses were conducted within stroke subtypes.

Results: Compared to eGFR 60–89 mL/min/1.73 m², adjusted odds ratios (ORs) and 95% confidence interval [95% CI] for in-hospital death (in the order of eGFR < 45, 45–59, and ≥90 mL/min/1.73 m²) were 1.54 [1.04–2.27], 1.07 [0.72–1.58], and 1.04 [0.67–1.59]. Likewise, adjusted ORs [95% CI] for at-discharge death/disability were 1.54 [1.02–2.32], 0.97 [0.73–1.31], and 1.48 [1.06–2.05]. Similar pattern was further evident in the eGFR < 45 mL/min/1.73 m² group for both outcomes within acute ischemic stroke patients.

Conclusions: Our study has ascertained that in acute stroke, particularly ischemic stroke, low eGFR was significantly associated with in-hospital death and at-discharge death/disability. Additionally, high eGFR was found to be associated with at-discharge death/disability.

Key words: Stroke, Glomerular filtration rate, Mortality, Morbidity

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Institutional Review Board of Shiga University of Medical Science. Civil registration number 19 to 31 December 2011. Following exclusion of patients younger than 18 years (age < 19). Stroke was further categorized as ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, with the latter two grouped into hemorrhagic stroke. All cases were confirmed both clinically and radiologically, and the final diagnosis was made by two independent investigators.

Variables and Outcome
Data gathered included age, gender, comorbidities (hypertension, diabetes, myocardial infarction, atrial fibrillation, dyslipidemia), previous stroke, smoking status, admission details (systolic and diastolic blood pressure, modified Rankin Scale (mRS), Japan Coma Scale (JCS)), intervention/surgical therapy performed, tissue plasminogen activator administered, days from onset until death/hospital discharge, and discharge mRS score. Interventional therapy consisted of endovascular recanalization and coil embolization, whereas surgical therapy involved decompression, hematoma evacuation, cerebrospinal fluid diversion, thrombectomy, and aneurysm clipping by means of endoscopic and/or conventional cranioectomy. The outcomes of this study were all-cause in-hospital death (mRS of 6) and at-discharge death/disability (mRS 2–6).

Renal Function Evaluation
Admission serum creatinine was measured using enzymatic method in local laboratories and used to estimate GFR based on the Japanese Society of Nephrology equation: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine [mg/dL])^{-1.094} × (age [year])^{-0.287} × 0.739 (for female). The estimated GFR was then categorized as < 45, 45–59, 60–89, and ≥ 90 mL/min/1.73 m^2, with eGFR 60–89 mL/min/1.73 m^2 being the reference group. Patients with eGFR < 45 mL/min/1.73 m^2 were pooled together due to small number, whereas patients on renal replacement therapy (RRT) were gathered into a separate group due to their particular feature.

Statistical Analysis
Continuous variables were presented as mean (standard deviation) or median (interquartile range) as appropriate, and categorical variables as proportions. Differences in means or medians between two groups were analyzed using Student’s t-test or Mann–Whitney U test, respectively, while χ^2 or Fisher exact test was conducted to find differences in proportions as appropriate. Probability trends were determined by treating eGFR in its continuous nature and fitting it into linear/logistic regression models with variables of interest. Next, multivariable logistic regression analyses, adjusting for covariates regarded and/or identified from literatures to be significantly associated with stroke outcomes, were performed to determine the association of eGFR with both outcomes. Separate analyses were done within stroke subtypes. Finally, sensitivity analyses were conducted for the outcome of at-discharge death/depenency (mRS 3–6) on all stroke subtypes. All analyses
Results

Characteristics of Patients by RRT Status

Table 1 shows basic characteristics of adult acute...
stroke patients by RRT status. Compared with non-RRT group, several significant differences were identified in RRT group: patients’ age was younger; hypertension, diabetes, previous stroke, and pre-admission significant disability were more prevalent; admission JC5 score was worse; admission eGFR was extremely lower; and in-hospital death was higher.

**Characteristics of Study Subjects by eGFR Category**

Table 2 presents basic characteristics of study subjects by eGFR category. Of 2,743 non-RRT patients, 15.7% presented with eGFR of ≤45 mL/min/1.73 m², 20.8% with eGFR 45–59 mL/min/1.73 m², 47.6% with eGFR 60–89 mL/min/1.73 m², and 15.9% with eGFR ≥90 mL/min/1.73 m². Compared to other groups, in the eGFR ≤45 mL/min/1.73 m² group, patients were significantly older; prevalence of hypertension, diabetes, myocardial infarction, atrial fibrillation, recurrent stroke, and never smokers were higher; admission systolic and diastolic blood pressure were lower, admission
Table 3. Prevalence and odds ratio (95% confidence interval) of each eGFR category for outcomes in all stroke

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>N (%)</th>
<th>45-59 (n=571)</th>
<th>60-89 (n=1306)</th>
<th>≥90 (n=435)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death (mRS 6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>20 (28.6)</td>
<td>113 (26.2)</td>
<td>81 (14.2)</td>
<td>152 (11.6)</td>
</tr>
<tr>
<td>Model 1</td>
<td>3.04 (1.76-5.24)</td>
<td>2.70 (2.05-3.55)</td>
<td>1.26 (0.94-1.68)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>3.33 (1.91-5.81)</td>
<td>2.09 (1.57-2.77)</td>
<td>1.06 (0.79-1.43)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.03 (0.90-4.58)</td>
<td>1.54 (1.05-2.27)</td>
<td>1.07 (0.72-1.58)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Death/disability (mRS 2-6)</strong></td>
<td>55 (78.6)</td>
<td>376 (87.2)</td>
<td>437 (76.5)</td>
<td>913 (69.9)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.58 (0.88-2.83)</td>
<td>2.94 (2.17-4.00)</td>
<td>1.40 (1.12-1.76)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.87 (1.01-3.46)</td>
<td>1.95 (1.42-2.69)</td>
<td>1.04 (0.82-1.33)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.89 (0.39-2.03)</td>
<td>1.54 (1.02-2.32)</td>
<td>0.97 (0.73-1.31)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Prevalence of Outcomes by eGFR Category and the Association of eGFR with Outcomes in Ischemic and Hemorrhagic Strokes

Tables 4 and 5 show prevalence of outcomes by eGFR category and the association of eGFR with outcomes in ischemic and hemorrhagic strokes. In-hospital death and at-discharge death/disability had similar reverse relationship with eGFR in both stroke subtypes as in all stroke. In the same manner, eGFR <45 mL/min/1.73 m² group in ischemic stroke displayed maintained significant association with in-hospital death (from unadjusted OR [95% CI] of 3.46 [2.37-5.05] to multivariable-adjusted OR [95% CI] of 1.60 [1.00-2.57]) and with at-discharge disability (from unadjusted OR [95% CI] of 3.53 [2.50-4.99] to multivariable-adjusted OR [95% CI] of 1.74 [1.10-2.76]). Still within the same stroke subtype, eGFR >90 mL/min/1.73 m² group also showed maintained significant association with at-discharge disability (multivariable-adjusted OR [95% CI] of 1.52 [1.01-2.31]). As for hemorrhagic stroke, with the exception of RRT group that preserved its significant association with in-hospital death (from unadjusted OR [95% CI] of 3.64 [1.61-8.25] to multivariable-adjusted OR [95% CI] of 5.27 [1.43-19.50]), no other significant associations were identified.

Sensitivity Analyses: The Association of eGFR With At-Discharge Death/Dependency in All Strokes and Its Subtypes

Table 6 presents the association of eGFR with at-discharge death/dependency in all strokes and its...
1.73 m²) was shown to be significantly and positively associated with all stroke outcome: its ORs for in-hospital death and at-discharge death/disability were 1.54 times higher than the reference group. Additionally, high eGFR (≥90 mL/min/1.73 m²) was significantly associated with at-discharge death/disability, its OR was 1.48 higher than the reference group. Further analyses within each stroke subtypes, as well as sensitivity analyses, discovered the same pattern to be strongly evident in the ischemic stroke. In regard to RRT patients,

### Discussion

In the current study, low eGFR (<45 mL/min/1.73 m²) was shown to be significantly and positively associated with all stroke outcome: its ORs for in-hospital death and at-discharge death/disability were 1.54 times higher than the reference group. Additionally, high eGFR (≥90 mL/min/1.73 m²) was significantly associated with at-discharge death/disability, its OR was 1.48 higher than the reference group. Further analyses within each stroke subtypes, as well as sensitivity analyses, discovered the same pattern to be strongly evident in the ischemic stroke. In regard to RRT patients,

### Table 4. Prevalence and odds ratio (95% confidence interval) of each eGFR category for outcomes in ischemic stroke

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>RRT (n=45)</th>
<th>&lt;45 (n=322)</th>
<th>45-59 (n=418)</th>
<th>60-89 (n=850)</th>
<th>≥90 (n=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death (mRS 6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>8 (17.8)</td>
<td>66 (20.5)</td>
<td>46 (11)</td>
<td>59 (6.9)</td>
<td>18 (8.5)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.90 (1.29-6.51)</td>
<td>3.46 (2.37-5.05)</td>
<td>1.66 (1.11-2.49)</td>
<td>1.00</td>
<td>1.24 (0.71-2.15)</td>
</tr>
<tr>
<td>Model 1a</td>
<td>2.97 (1.29-6.85)</td>
<td>2.17 (1.46-3.23)</td>
<td>1.26 (0.83-1.91)</td>
<td>1.00</td>
<td>1.66 (0.94-2.92)</td>
</tr>
<tr>
<td>Model 2b</td>
<td>0.91 (0.27-3.07)</td>
<td>1.60 (1.00-2.57)</td>
<td>1.20 (0.74-1.94)</td>
<td>1.00</td>
<td>0.92 (0.45-1.86)</td>
</tr>
<tr>
<td><strong>Death/disability (mRS 2-6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>35 (77.8)</td>
<td>277 (86)</td>
<td>305 (73)</td>
<td>540 (63.5)</td>
<td>133 (62.4)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.01 (0.98-4.11)</td>
<td>3.53 (2.50-4.99)</td>
<td>1.55 (1.20-2.00)</td>
<td>1.00</td>
<td>0.95 (0.70-1.30)</td>
</tr>
<tr>
<td>Model 1a</td>
<td>1.89 (0.89-4.02)</td>
<td>2.08 (1.44-3.01)</td>
<td>1.02 (0.78-1.35)</td>
<td>1.00</td>
<td>1.41 (0.99-2.00)</td>
</tr>
<tr>
<td>Model 2b</td>
<td>0.96 (0.36-2.57)</td>
<td>1.74 (1.10-2.76)</td>
<td>0.91 (0.65-1.28)</td>
<td>1.00</td>
<td>1.54 (1.02-2.33)</td>
</tr>
</tbody>
</table>

### Table 5. Prevalence and odds ratio (95% confidence interval) of each eGFR category for outcomes in hemorrhagic stroke

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>RRT (n=25)</th>
<th>&lt;45 (n=108)</th>
<th>45-59 (n=153)</th>
<th>60-89 (n=455)</th>
<th>≥90 (n=219)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death (mRS 6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>12 (48)</td>
<td>46 (42.6)</td>
<td>35 (22.9)</td>
<td>92 (20.2)</td>
<td>42 (19.2)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>3.64 (1.61-8.25)</td>
<td>2.93 (1.88-4.57)</td>
<td>1.17 (0.75-1.82)</td>
<td>1.00</td>
<td>0.94 (0.62-1.41)</td>
</tr>
<tr>
<td>Model 1a</td>
<td>4.53 (1.92-10.66)</td>
<td>2.46 (1.56-3.88)</td>
<td>1.67 (0.76-1.64)</td>
<td>1.00</td>
<td>0.97 (0.72-1.66)</td>
</tr>
<tr>
<td>Model 2b</td>
<td>5.27 (1.43-19.50)</td>
<td>1.66 (0.80-3.42)</td>
<td>0.85 (0.42-1.72)</td>
<td>1.00</td>
<td>0.54 (1.83)</td>
</tr>
<tr>
<td><strong>Death/disability (mRS 2-6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>20 (80)</td>
<td>98 (90.7)</td>
<td>132 (86.3)</td>
<td>372 (81.8)</td>
<td>170 (77.6)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.89 (0.33-2.45)</td>
<td>2.19 (1.09-4.37)</td>
<td>1.40 (0.84-2.36)</td>
<td>1.00</td>
<td>0.77 (0.52-1.15)</td>
</tr>
<tr>
<td>Model 1a</td>
<td>1.30 (0.45-3.77)</td>
<td>1.61 (0.79-3.28)</td>
<td>1.20 (0.70-2.05)</td>
<td>1.00</td>
<td>0.95 (0.68-1.58)</td>
</tr>
<tr>
<td>Model 2b</td>
<td>0.51 (0.11-2.25)</td>
<td>0.71 (0.28-1.81)</td>
<td>1.08 (0.55-2.12)</td>
<td>1.00</td>
<td>1.18 (0.68-2.06)</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; mRS, modified Rankin Scale

*Adjusted for age and sex
*Adjusted for age, sex, hypertension, diabetes, myocardial infarction, atrial fibrillation, previous stroke, smoking status, diastolic blood pressure, admission Japan Coma Scale and modified Rankin Scale, intervention/surgery, and recombinant tissue plasminogen activator administration

All regression analyses result are in odds ratio (95% confidence interval)
this group displayed a notable association with death only within hemorrhagic stroke.

Despite growing interest in similar subject, divulging the association either in overall stroke7-9, ischemic10-14 or hemorrhagic subtypes15-17 in-between study findings have been contradictory, for example, while Yahalom et al33 and Tsagalis et al7 showed significant and positive result between low eGFR and mortality and poor outcome after stroke, the opposite was reported by Yang et al8. Result interpretations were complicated by small sample size7-9,12-15,17, non-population-based setting7,8,11,12,14, narrow-range eGFR category7,11,13-15, or lack of control for stroke severity12,19. The present study deals with these issues by employing data from a large-scale population-based setting registry, implementing wide-range eGFR category, and separating analyses between non-RRT and RRT patients. The latter, particularly, is paramount as aging and atherosclerosis, may explain our finding related to the detrimental effect of low eGFR, especially in patients with ischemic stroke. Although atherosclerosis of large cerebral arteries was reported to be related to the development of atherothrombotic brain infarction, the role of serum high-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol may be different in both stroke subtypes28,29. On the contrary, the adverse outcome in relation to high eGFR found in this study is probably related to kidney hyper filtration, which has been associated with unfavorable cardiovascular outcomes10-30. High eGFR, however, may not represent true renal function in patients with atypically reduced muscle mass, such as the elderly, amputees, and others suffering from chronic muscle diseases31,32. Vis-à-vis the association of RRT with in-hospital death within hemorrhagic stroke, similar result was identified in a study by Lin et al33, in which prior stroke and diabetes, both were prevalent among RRT group in our study, strongly predict mortality in this particular group. A more extensive investigation in the future on this particular issue will be of importance. In addition, we realize that our finding is inconsistent with other studies describing the “U”- or “J”-shaped association12,14. This may be due to inevitable differences in study population, eGFR equations, or study design. Recently, non-traditional vascular risk factors, such as oxidative stress, decreased platelet function, and anemia caused by reduced erythropoietin production34,35, have been suggested to adding up
clot formation and infarct growth by decreasing perfusion distal to obstruction. They might also contribute to secondary cerebral injury due to metabolic stress and tissue hypoxia\textsuperscript{36}, promoting hematoma growth and perihematomal edema, eventually worsening hemorrhagic stroke outcome\textsuperscript{17,37}.

As a consequence of undesirable effects associated with renal dysfunction, a more vigilant management of acute stroke patients with this condition is warranted. Increased risk of intracerebral hemorrhage with thrombolysis administration\textsuperscript{38}, decreased responsiveness of antiplatelet\textsuperscript{39}, and limited use of anticoagulants\textsuperscript{40} are few of the limitations critical to be recognized in providing medical therapy to these high-risk patients. Should any indication for interventional/surgical therapy arise, cautioned peri-, intra-, and postoperative management is imperative, covering aspects such as fluid and electrolytes therapy, anesthetic agent selection, and contrast agent use\textsuperscript{41,42}. Promotion and preventive measures to manage cardiovascular disease risk factors in community level, specifically in renal dysfunction patients, is of no less importance. A recent study investigating lipid management targets in Japan showed inadequate attainment rates in the population, raising alarm for its improvement\textsuperscript{43}.

Besides the aforementioned strength of this study, eGFR 60–89 mL/min/1.73 m\textsuperscript{2} was selected as the reference group, considering the specific range of which to better represent the aging nature of stroke patients by taking into account study subjects’ mean eGFR and age. However, because only Japanese patients were studied, results may not be applicable to other populations. Serum creatinine was only measured on admission and in individual centers, thereby influencing its accuracy. Furthermore, admission NIHSS, a strong predictor of stroke outcome\textsuperscript{43}, was not incorporated due to its high rate of missing data. However, we perceive this issue to be overcome by using JCS, a Japanese-based consciousness level score developed in the same year as the Glasgow Coma Scale, which has been proven to have good predictability of stroke outcome\textsuperscript{22}.

In conclusion, our study has ascertained that in acute stroke, particularly in ischemic stroke, low eGFR was associated with in-hospital death and at-discharge death/disability. Additionally, high eGFR was also found to be associated with at-discharge death/disability. These findings reemphasize the importance of having great awareness among clinicians managing these stroke patients with renal dysfunction.

Acknowledgement and Notice

None.

Conflict of Interest

None.

References


12) Mostofsky E, Wellenius GA, Noheria A, Levitan EB, Bur-


