Association between estimated glomerular filtration rate and clinical outcomes in patients with acute ischaemic stroke: results from China National Stroke Registry†

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Abstract

Background: The impact of estimated glomerular filtration rate (eGFR) on stroke clinical outcomes remains controversial. We examined the association between eGFR and all-cause mortality, recurrent stroke, and stroke disability in patients with acute ischaemic stroke.

Methods: We analysed 8865 patients with acute ischaemic stroke in the China National Stroke Registry (CNSR) between September 2007 and August 2008. Multivariate logistic regression analysis was used to evaluate the association between eGFR and 1-year all-cause mortality, recurrent stroke, and stroke disability. Low eGFR was defined as <45 ml/min/1.73 m2.

Results: Of 8865 acute ischaemic stroke patients included in the analysis, eGFR of <45 ml/min/1.73 m2 occurred in 394 (4.4%), eGFR of 45–59 ml/min/1.73 m2 in 675 (7.6%), eGFR of 60–89 ml/min/1.73 m2 in 3533 (39.9%), and eGFR of ≥90 ml/min/1.73 m2 in 4263 (48.1%) at baseline. Patients with reduced renal function were more likely to die, experience recurrent stroke or have stroke disability than patients with preserved renal function. After adjusting for both demographic and clinical risk factors, an eGFR of <45 ml/min/1.73 m2 was independently associated with 1-year all-cause mortality (OR: 2.65; 95% CI: 1.95–3.59) and recurrent stroke (OR: 1.97; 95% CI: 1.51–2.56) but not for stroke disability defined as modified Rankin Score of 2–6 (OR: 1.26; 95% CI: 0.95–1.67). These results were consistent in stratified analyses by age, diabetes or hypertension.

Conclusions: A low eGFR was associated with increased risks of all-cause mortality and recurrent stroke independent of the traditional vascular risk factors in Chinese stroke patients.

Keywords: acute ischaemic stroke, estimated glomerular filtration rate, outcome, epidemiology, older people

Introduction

Stroke is the leading cause of death and adult disability in China [2, 3]. There are currently >7 million Chinese suffering from stroke and ~2 million new and recurrent strokes diagnosed each year [4, 5]. Improving stroke care quality and clinical outcome has become a national priority in China [6]. Managing stroke risk factors might play a pivotal role in primary and secondary stroke prevention. Chronic kidney
disease (CKD) is a worldwide public health problem with an estimated prevalence of 10.8% in Chinese adults [7–9]. Low-estimated glomerular filtration rate (eGFR) as an important metric of kidney function has been identified as an independent risk factor for all-cause mortality and other adverse cardiovascular outcomes [10–12]; additionally, a moderate-to-severe decrease in eGFR was also associated with all-cause mortality and first-ever stroke in an ethnic Chinese population-based cohort [13]. However, it remains unclear whether reduced eGFR is associated with worse outcomes once patients experienced a stroke event [14–16]. Thus, our goal was to evaluate the impact of eGFR on all-cause mortality, recurrent stroke and stroke disability in acute ischaemic stroke in China.

Methods

The China National Stroke Registry (CNSR), sponsored by the Ministry of Science and Technology of China, is a national hospital-based, prospective cohort study designed to evaluate the quality of care for hospitalised stroke patients in China. The design of CNSR has been described previously [17]. In brief, 12,415 consecutive stroke patients 18 years or older, presenting within 14 days of symptom onset of stroke, were enrolled from 132 hospitals in China between September 2007 to August 2008. The eligibility of each stroke case was confirmed by brain imaging (computed tomography or magnetic resonance imaging). The study was approved by the central institutional review board at Beijing Tiantan Hospital.

Trained research coordinators at each institute collected baseline information including patient demographics, vascular risk factors, stroke severity, medication use, imaging study, diagnosis and complications. Vascular risk factors analysed included a history of stroke, hypertension, diabetes, dyslipidaemia, atrial fibrillation, coronary heart disease, current or previous smoking and moderate or heavy alcohol consumption (≥2 standardised alcohol drinks per day). Hypertension was defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, any use of antihypertensive drug or self-reported history of hypertension. Diabetes was defined as fasting glucose concentration ≥7.0 mmol/L, non-fasting glucose concentration ≥11.1 mmol/L with classic symptoms of hyperglycaemia or hyperglycaemic crisis, any use of glucose-lowering drugs, or any self-reported history of diabetes. Dyslipidaemia was defined as serum triglyceride ≥150 mg/dl, low-density lipoprotein cholesterol ≥130 mg/dl, high-density lipoprotein cholesterol ≤40 mg/dl, any use of lipid-lowering drugs, or any self-reported history of dyslipidaemia. Atrial fibrillation was defined as a history of atrial fibrillation confirmed by at least one electrocardiogram or the presence of the arrhythmia during hospitalisation. Written informed consent was signed by patient or legally authorised representatives during the index hospitalisation. Patients were interviewed at 12 months after stroke onset via call centre by trained study personnel. Standardised, structured questionnaire were used to obtain information on all-cause death, vascular events and modified Rankin score. Study personnel were blinded to patient’s baseline characteristics during the interview.

Renal function and outcome measures

We collected serum creatinine on admission and calculated eGFR using the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation which could more appropriately categorise individuals on their clinical risks than Modification of Diet in Renal Disease (MDRD) study equation and may suite better in general populations [18]. Given each participating centre is likely to use its own protocol rather than standardised isotope-dilution mass spectrometry for serum creatinine measure, value of the serum creatinine was reduced by 5% for the eGFR calculation [19]. The following was the CKD-EPI equation with adjusted coefficient of 1.1 for the Asian population [20, 21]: eGFR = 141 × min (SCr/κ, 1)α × max (SCr/κ, 1)−1.209 × 0.993SCr/0.8 × 1.018 [if female], where SCr was serum creatinine, κ was 0.7 for females and 0.9 for males, α was −0.329 for females and −0.411 for males, min was the minimum of SCr/κ or 1 and max indicated the maximum of SCr/κ or 1. The eGFR values were categorised into four categories: <45, 45 to 59, 60 to 89 and ≥90 ml/min/1.73 m² according to the classification by National Kidney Foundation [22].

The primary outcome measures were 1-year all-cause mortality, recurrent cerebrovascular event (ischaemic stroke, intracranial haemorrhage and subarachnoid haemorrhage) and stroke disability. Stroke disability was defined as modified Rankin Scale of 2–6. We also evaluated the combined endpoint of death or recurrent stroke as the secondary outcome.

Statistical analysis

Continuous variables are expressed as means with standard deviation (SD) or median with inter-quartile range (IQR), as appropriate. Categorical data are presented as proportions. The t-test was used to test the difference between eGFR categories for continuous variables and the χ² or Fisher exact test for categorical variables.

We perform logistic multivariate regression to evaluate the independent effect of the eGFR on outcomes. Following candidate variables known to be associated with adverse stroke outcomes were included in the final model: age, sex, history of stroke, hypertension, diabetes, dyslipidaemia, atrial fibrillation, coronary heart disease, current or previous smoking, moderate or heavy alcohol, body mass index (BMI) at admission, baseline National Institutes of Health Stroke Scale (NIHSS), antplatelet agent usage, drugs at discharge for the control of diabetes or hypertension and pneumonia or urethral infection. The model also contained random effect for intra-hospital correlation. Additionally, since the effect of eGFR on clinical outcomes might be confounded by other risk factors such as age, hypertension and diabetes [23], we also performed a series of stratified analyses by age (≤65 versus >65 years), presence of hypertension and diabetes. To examine effect modification by age, hypertension
or diabetes, we used a post-estimation Wald test in multivariable-adjusted logistic model to get an omnibus P-value for interaction between eGFR categories and variables of interest. Lastly, we further explored the pattern and magnitude of associations between eGFR and risks of adverse stroke outcomes using a logistic regression model with restricted cubic splines for eGFR adjusting for covariates. eGFR of 95 ml/min/1.73 m² were treated as the reference and the knots for spline were placed at 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125 and 130 ml/min/1.73 m². All statistical analyses were performed with the SAS Version 9.2 software (SAS Institute, Inc., USA).

Results

Of 12 415 acute ischaemic stroke patients enrolled in CNSR, 3550 were excluded due to lack of serum creatinine value on admission (n = 2695) and/or missing follow-up information at the 1-year visit (n = 855). After these exclusions, 8865 patients were included in the final analysis. Except for NIHSS (median, 4 versus 5; P < 0.001), patients included or excluded were similar in terms of baseline demographic and clinical characteristics. (Supplementary data are available in Age and Ageing online, Table S1).

Demographic and clinical characteristics of patients are shown in Table 1. Of 8865 patients with acute ischaemic stroke, eGFR of <45 ml/min/1.73 m² occurred in 394 (4.4%), eGFR of 45–59 ml/min/1.73 m² in 675 (7.6%), eGFR of 60–89 ml/min/1.73 m² in 3533 (39.9%) and eGFR of ≥90 ml/min/1.73 m² in 4263 (48.1%) at baseline. Patients with low eGFR were older, more likely to be female, had a higher NIHSS score and higher proportion of a history of stroke, hypertension, diabetes, atrial fibrillation, coronary heart disease and infection than those with the eGFR of ≥90 ml/min/1.73 m². In addition, they were more likely to have higher systolic blood pressure and lower diastolic blood pressure. There was no statistically significant difference in dyslipidaemia and BMI among eGFR categories.

In unadjusted analyses, patients with lower eGFR were more likely to die within 1 year (43.4, 25.9, 14.3 and 8.8% for eGFR <45, 45–59, 60–89, ≥90 ml/min/1.73 m², respectively, P < 0.001), experience recurrent stroke events (41.9, 27.4, 20.0 and 14.3% P < 0.001) or have stroke disability (68.5, 59.7, 47.8 and 37.7% P < 0.001). After adjusting for age, sex, history of stroke, diabetes, hypertension, dyslipidaemia, atrial fibrillation, coronary heart disease, current or previous smoking, moderate or heavy alcohol use, BMI at admission, baseline NIHSS, antplatelet agent usage, drugs at discharge for the control of diabetes or hypertension, and infection, eGFR of <45 ml/min/1.73 m² was associated with higher odds of all-cause mortality (OR: 2.65; 95% CI: 1.95–3.59) compared with patients with eGFR ≥90 ml/min/1.73 m². The odds of recurrent stroke also increases by 97% with eGFR of <45 ml/min/1.73 m² (OR: 1.97; 95% CI: 1.51–2.56); In addition, eGFR of <45 ml/min/1.73 m² was associated with composite of death or recurrent stroke (OR: 2.00; 95% CI: 1.55–2.59), but not associated with stroke disability (OR: 1.26; 95% CI: 0.95–1.67) (Table 2).

Table 3 shows the adjusted odds ratios (OR) and 95% confidence interval (CI) for outcomes in relationship to eGFR levels for subjects stratified by risk factors of interest. In general, eGFR of <45 ml/min/1.73 m² was positively associated with higher odds of all-cause death or recurrent stroke but not for stroke disability, when compared with the reference group (eGFR of ≥90 ml/min/1.73 m²) in stratified analyses by age, hypertension or diabetes. And the
exploring analysis for associations between clinical outcomes and eGFR showed the result similar to those presented by Table 3 (Supplementary data are available in Age and Ageing online, Figures S1–4). Additionally, there were no statistically significant statistical interactions between categories of eGFR and age, diabetes or hypertension (Supplementary data are available in Age and Ageing online, Tables S2 and 3).


**Discussion**

From the largest stroke registry to date in China, we found that a reduced eGFR (<45 ml/min/1.73 m$^2$) was associated with the increased odds of all-cause mortality and recurrent stroke independent of traditional vascular risk factors in Chinese patients. The odds of 1-year mortality and 1-year recurrent stroke in patients with eGFR of <45 ml/min/1.73 m$^2$ were ∼2.5 times and 2 time greater than those in patient with eGFR of ≥90 ml/min/1.73 m$^2$. These findings were consistent in stratified analysis by age, hypertension or diabetes. Furthermore, there were no statistically significant interactions between categories of eGFR and interesting variables used for subject stratification.

The relationship between low eGFR and adverse stroke outcomes in patients with stroke remained controversial [14–16]; the inconsistency of study results might be attributed to the difference in time frames of outcome assessment: the positive association may exist in studies with the long-term follow-up period (one year or more than) [14,15] while the negative relationship would do in those with the short-term period (at discharge) [16]. More recently, Lee et al. [24] showed that, among stroke patients mainly from the area of North America, low eGFR is associated with a higher risk of two-year major vascular events and recurrent stroke. Our study further demonstrated that reduced eGFR (<45 ml/min/1.73 m$^2$) independently predicted 1-year all-cause mortality and recurrent stroke among Chinese patients with acute ischaemic stroke. One of the principal kidney-specific mechanisms involved in the association has been proposed to be endothelial dysfunction. The presence of renal dysfunction as well as other risk factors such as hypertension and diabetes leads to the increased concentration of asymmetric dimethylarginine inhibiting generation of nitric oxide, the low-grade inflammation raising oxidative stress, dyslipidaemia and the elevated activity of the renin–angiotensin system stimulating production of superoxide and cytokines [25–27]. The aforementioned pathophysiological mechanisms might play an important role in the association of CKD and adverse stroke outcomes. Thus, our study demonstrated that there is a strong association between low eGFR and death or recurrent stroke, which may help in identifying patients at a higher risk of adverse clinical outcomes after acute ischaemic stroke among different racial or ethnic population.

Our study found that low eGFR was associated with a higher risk of 1-year stroke disability in unadjusted analysis (Table 2). However, the association between low eGFR and stroke disability became less significant after adjusting confounding factors including baseline stroke severity in primary or stratified analysis. Little impact of low eGFR on stroke disability was also found in ischaemic stroke patients with atrial fibrillation [28]. The reason is unclear and the possible explanation is that recurrent stroke might make little change on subsequent stroke severity in disabling-stroke patients who had serious neurological deficit on admission.

In our study, analysis stratified by age, hypertension or diabetes showed similar result across strata, that is, there was a higher risk of death or recurrent stroke in patients with low eGFR (<45 ml/min/1.73 m$^2$), but no significant interaction with the interesting variables at any eGFR categories (Table 3). The eGFR association with adverse stroke outcomes did not differ significantly by hypertension or diabetes although these risk factors were independently associated not only with stroke but also with CKD [15,29]. In addition, the more recent study has shown that diabetes does not modify nor increase the risk relation between all-cause mortality and renal impairment [30]. A meta-analysis also demonstrated that the overall interaction was not significant between the eGFR and age or diabetes on all-cause mortality in general or high-risk population [31]. Possible explanation included that shared risk factors lead to symptomatic vascular injuries both in the brain and kidney, and impaired renal dysfunction in turn independently increases the risk of adverse stroke outcomes possibly through the aforementioned mechanism [25–27]. Consequently, there might be less significant interaction between eGFR and the traditional risk factors for all-cause death or recurrent stroke. This finding needs to be verified in the future studies with large population.

The current analysis found that low eGFR (<45 ml/min/1.73 m$^2$) was associated with adverse stroke outcomes in diabetes; and the association also existed in non-diabetics; that is, regardless of diabetes status, patients with low eGFR might have poor stroke outcomes. Additionally, our previous analysis demonstrated the detrimental effect of high eGFR (≥120 ml/min/1.73 m$^2$) on adverse outcomes of stroke in diabetes possibly due to kidney hyperperfusion [1]. In this study we did not explore the association between high eGFR and stroke outcomes in non-diabetics. But it would be interesting in the future study to compare the characteristics of the association between high eGFR and stroke outcomes in diabetic versus non-diabetic patients.

Our study is the largest to date to investigate the relationship between eGFR and recurrent stroke, all-cause mortality and stroke disability in Chinese acute ischaemic stroke patients. In addition, MDRD equation might underestimate eGFR at higher values because its derivative is based on patients with CKD defined as eGFR <60 ml/min/1.73 m$^2$ [19,20]. Accordingly, we employed the new Chinese-modified CKD-EPI equation to calculate eGFR. The new equation offered more accurate assessment of the entire range of the eGFR with respect to the testing of the impact of the reduced eGFR on stroke outcomes, when compared with the MDRD equation [32].

Our study has limitations. Firstly, albuminuria has been proved to be an important independent risk factor for many adverse clinical outcomes, it was not available in CNSR, so we could not evaluate eGFR and albuminuria simultaneously along with other factors that are important for stroke outcomes. Secondly, we were unable to control for post-discharge medication use which might have impact on long-term outcomes. Thirdly, approximately one-quarter of stroke patients enrolled in CNSR were excluded due to missing data on serum creatinine and loss to follow-up, which might cause selection bias. Fourthly, data on concurrent acute
kidney injury were not available in the study; thus, the extent
to which it would directly affect outcomes was unknown.
Lastly, the aetiology of the CKD has not been defined as
only the degree of GFR has been correlated with the out-
comes; additionally, the cause of death was not also defined
but rather the all-cause mortality.
In conclusion, our study showed that a low eGFR of <45
ml/min/1.73 m² was associated with increased risks of all-
cause mortality and recurrent stroke independent of the traditional vascular risk factors in Chinese stroke patients. When the outcome of stroke patients is predicted, the presence of CKD might be a poor prognostic indicator.

Key points
- This study examined the association between eGFR and all-
cause mortality, recurrent stroke and stroke disability in patients with acute ischaemic stroke.
- A low eGFR was associated with increased risks of all-
cause mortality and recurrent stroke independent of the
traditional vascular risk factors in Chinese stroke patients.
- CKD might be a prognostic indicator to predict the
outcomes of stroke patients.

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Supplementary data

Supplementary data mentioned in the text is available to sub-
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References

More attention to pain management in community-dwelling older persons with chronic musculoskeletal pain

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Abstract

Background: persistent pain is a major problem in older people, but little is known about older persons’ opinion about the treatment of persistent pain.

Objective: the objective of this study was to investigate the factors associated with older participants having chronic musculoskeletal pain and hoping persistently that physician would pay more attention to the pain management.

Methods: this 3-year follow-up study was a part of large population-based Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study. The population sample (n = 1000) of the GeMS study was randomly selected from older inhabitants (≥75 years) of Kuopio city, Finland, and participants were interviewed annually in the municipal health centre or in the participant’s current residence by three study nurses. The current substudy included participants with chronic musculoskeletal pain (n = 270). Participants were asked specifically whether they hoped that more attention would be paid to pain management by the physician.

Results: at baseline, 41% of the community-dwelling older participants with chronic musculoskeletal pain hoped the physician would pay more attention to pain management. Of those participants, 49% were still continuing to hope after 1 year and 31% after 2 years.

More attention to pain management in community-dwelling older persons

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