ORIGINAL RESEARCH

Renal Dysfunction and In-Hospital Outcomes in Patients With Acute Ischemic Stroke After Intravenous Thrombolytic Therapy

Zhen-Zhen Rao, PhD, MPH; Hong-Qiu Gu, PhD; Xian-Wei Wang, MD; Xue-Wei Xie, MD, PhD; Xin Yang, MD, PhD; Chun-Juan Wang, MD, PhD; Xingquan Zhao, MD, PhD; Ying Xian, MD, PhD; Yi-Long Wang, MD, PhD; Zi-Xiao Li, MD, PhD; Rui-Ping Xiao, MD, PhD; Yong-Jun Wang, MD, PhD; on behalf of the Chinese Stroke Center Alliance investigators*

***Background*—**The impact of estimated glomerular filtration rate (eGFR) on clinical short-term outcomes after stroke thrombolysis with tissue plasminogen activator remains controversial.

***Methods and Results*—**We analyzed 18 320 ischemic stroke patients who received intravenous tissue plasminogen activator at participating hospitals in the Chinese Stroke Center Alliance between June 2015 and November 2017. Multivariate logistic regression models were used to evaluate associations between eGFR (<45, 45–59, 60–89, and ≥90 mL/min per 1.73 m^2) and in-hospital mortality and symptomatic intracerebral hemorrhage, adjusting for patient and hospital characteristics and the hospital clustering effect. Of the 18 320 patients receiving tissue plasminogen activator, 601 (3.3%) had an eGFR <45, 625 (3.4%) had an eGFR 45 to 59, 3679 (20.1%) had an eGFR 60 to 89, and 13 415 (73.2%) had an eGFR ≥90. As compared with eGFR ≥90, eGFR values <45 (6.7% versus 0.9%, adjusted odds ratio, 3.59; 95% CI, 2.18–5.91), 45 to 59 (4.0% versus 0.9%, adjusted odds ratio, 2.00; 95% CI, 1.18–3.38), and 60 to 89 (2.5% versus 0.9%, adjusted odds ratio, 1.67; 95% CI, 1.20–2.34) were independently associated with increased odds of in-hospital mortality. However, there was no statistically significant association between eGFR and symptomatic intracerebral hemorrhage.

***Conclusions*—**eGFR was associated with an increased risk of in-hospital mortality in acute ischemic stroke patients after treatment with tissue plasminogen activator. eGFR is an important predictor of poststroke short-term death but not of symptomatic intracerebral hemorrhage. **(*J Am Heart Assoc*. 2019;8:e012052. DOI: 10.1161/JAHA.119.012052.)**

Key Words: glomerular filtration rate • ischemic stroke • outcome • renal function • tissue-type plasminogen activator

Stroke remains a major health issue worldwide and a leading cause of death and adult disability in China.[1,2] Chronic kidney disease (CKD) is also a worldwide health problem with an estimated prevalence of 10.8% in Chinese adults and a higher prevalence among patients with cardiovascular diseases and stroke.[3,4] Low estimated glomerular filtration (eGFR), one of the key indicators of CKD, has been associated with an increased risk of stroke.[5,6] Although tissue plasminogen activator (tPA) is a generally acknowledged criterion standard and effective treatment for acute ischemic stroke (AIS), there are concerns regarding whether tPA increases the risk of intracranial hemorrhage in patients with AIS and CKD.[7,8] Other published studies have assessed outcomes among AIS patients with CKD after treatment with tPA and reported conflicting results.[9–15] However, none of these studies examined the associations of different categories of CKD with short-term mortality and symptomatic intracerebral

From the Institute of Molecular Medicine, Yingjie Center, Peking University, Beijing, China (Z.-Z.R., R.-P.X.); China National Clinical Research Center for Neurological Diseases, Beijing, China (H.-Q.G., X.-W.W., X.-W.X., X.Y., C.-J.W., X.Z., Y.-L.W., Z.-X.L., Y.-J.W.); National Center for Healthcare Quality Management in Neurological Diseases, Beijing, China (H.-Q.G., X.Y., C.-J.W., X.Z., Z.-X.L., Y.-J.W.); Vascular Neurology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China (C.-J.W., X.Z., Y.-L.W., Z.-X.L., Y.-J.W.); Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, China (C.-J.W., X.Z., Y.-L.W., Y.-J.W.); Center for Stroke, Beijing Institute for Brain Disorders, Beijing, China (C.-J.W., Y.-L.W., Z.-X.L., Y.-J.W.); Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (Y.X.).

Accompanying Appendix S1, Table S1, and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012052

*A complete list of the Chinese Stroke Center Alliance investigators can be found in the Supplemental Material.

Correspondence to: Zi-Xiao Li, MD, PhD, and Yong-Jun Wang, MD, PhD, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No. 119 South 4th Ring West Rd, Fengtai District, Beijing 100070, China. E-mails: lizixiao2008@hotmail.com; yongjunwang@ncrcnd.org.cn

Received January 17, 2019; accepted August 29, 2019.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Clinical Perspective

What Is New?

- In this nationwide population-based multisite study of 18 320 ischemic stroke patients receiving tissue plasminogen activator treatment, the associations of different categories of chronic kidney disease with short-term mortality and symptomatic intracerebral hemorrhage were examined in Chinese acute ischemic stroke patients.
- The new Chronic Kidney Disease Epidemiology Collaboration equation was used to provide more accurate measurement than the Modification of Diet in Renal Disease equation to calculate estimated glomerular filtration rate in our study.

What Are the Clinical Implications?

- This study provided evidence that in acute ischemic stroke patients receiving tissue plasminogen activator, in-hospital mortality increased across all categories of estimated glomerular filtration rate, which indicated that estimated glomerular filtration rate is an important predictor of poststroke short-term death.
- However, in acute ischemic stroke patients treated with tissue plasminogen activator, estimated glomerular filtration rate was not robustly associated with increased in-hospital symptomatic intracerebral hemorrhage.

hemorrhage (sICH) among AIS patients after treatment with tPA in a multicenter study. It remains uncertain whether low eGFR is associated with poor in-hospital outcomes when AIS patients are treated with tPA.

Therefore, we aimed to assess the association between eGFR and in-hospital mortality and sICH among AIS patients who were treated with tPA in the CSCA (Chinese Stroke Center Alliance), a nationwide stroke registry.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Patient Population

We used data obtained from 511 306 stroke patients aged 18 years old or older who were admitted with ischemic stroke between June 2015 and November 2017 at 1624 hospitals participating in the CSCA. The details of the CSCA program have been previously published.[16] CSCA is a voluntary, national, quality-improvement initiative improvement program that collects data on stroke/transient ischemic attack patients' characteristics, diagnosis, treatment, and adherence to quality measures and outcomes. The China National Clinical Research Center for Neurological Diseases serves as the data analysis center. Trained hospital personnel use a web-based patient management tool (GaiDe, Inc., Beijing, China) to collect patient clinical data. Participating hospitals received either clinical quality assessment and research approval to collect data in CSCA without requiring individual patient informed consent under the common rule or a waiver of authorization and exemption from their Institutional Review Board.

A total of 418 282 ischemic stroke patients of 511 036 CSCA patients were abstracted for initial assessment. Of the 418 282 ischemic patients, 399 604 (95.5%) were excluded because they did not receive tPA treatment or tPA treatment status was missing, leaving 18 678 patients for the study sample. Of the 18 678 AIS patients with tPA treatment, 358 were further excluded because of a lack of data for admission serum creatinine or missing information regarding death or age. The remaining 18 320 patients with acute ischemic stroke who were treated with tPA at 1092 participating hospitals were included in the analysis. Figure S1 shows a detailed study flow chart.

Renal Dysfunction Definition and Outcome Measures

We used the Chronic Kidney Disease Epidemiology Collaboration equation to estimate eGFR with an adjusted coefficient of 1.1.[17,18] Thus, $eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female], where SCr was the admission serum creatinine level, 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 higher of SCr/κ or 1.[19] The Chronic Kidney Disease Epidemiology Collaboration equation can more accurately calculate and categorize individuals' risks than the Modification of Diet in Renal Disease study. In the Modification of Diet in Renal Disease equation, creatinine was not standardized to isotope dilution mass spectrometry values in VALIANT (Valsartan in Acute Myocardial Infarction Trial). To apply VALIANT serum creatinine values, value of the serum creatinine was reduced by 5% for the eGFR calculation in the Chronic Kidney Disease Epidemiology Collaboration.[20] eGFR was stratified into 4 categories, including <45, 45 to 59, 60 to 89, and ≥90 mL/min per 1.73 m^2, with reference to the classifications of the National Kidney Foundation.[21] In-hospital mortality included all-cause death before discharge and post tPA sICH. According to the 1995 NINDS (National Institute of Neurological Disorders and Stroke) trial, post tPA sICH was defined as neurological worsening within 36 hours of tPA administration verified by computed tomography or magnetic resonance imaging, as documented by the physician.[22]

Covariates

The covariates for the adjusted analysis of the association of eGFR with in-hospital mortality and sICH included the following variables: (1) demographics: age, sex, and body mass index; (2) medical history: hypertension, diabetes mellitus, previous stroke or transient ischemic attack, coronary artery disease/previous myocardial infarction, dyslipidemia, current or previous smoking, and pneumonia during index hospitalization; (3) other patient characteristics: National Institutes of Health Stroke Scale (NIHSS) score, antihypertensive drug use, glucose-lowering drug use, antiplatelet therapy, tPA dose, onset-to-treatment time (OTT); and (4) hospital characteristics, such as hospital level. The variables that were included in the interaction analysis with eGFR were selected based on literature reviews and clinical interests. Four variables, including age, tPA dose, OTT, and severity NIHSS, were selected for the interaction.

Statistical Analysis

We compared patient and hospital characteristics stratified by eGFR groups using medians with interquartile ranges for continuous variables and proportions for categorical variables. Differences in baseline were compared using Pearson's χ^2 tests or Kruskal–Wallis tests, as appropriate.[23] To explore the association between eGFR and in-hospital outcomes, multivariable logistic regression with generalized estimating equations was applied. Generalized estimating equations were used to account for hospital clustering to generate both unadjusted and adjusted models.[24] The results are reported as odds ratios (ORs) with 95% CIs. The eGFR ≥90 group was used as a reference.

Furthermore, we performed stratified analysis by clinically relevant subgroups of age, NIHSS, dose, and OTT. Doses of tPA were calculated as the total tPA amount (mg) divided by the patient's weight (kg). After calculation, the median of dose of tPA was 0.89 mg/kg. Therefore, tPA dose was categorized as 2 groups: ≥0.89 and <0.89 mg/kg. Unadjusted and adjusted logistic regression with generalized estimating equations models were applied for each risk factor of interest.

In addition to eGFR categories, we evaluated the pattern and linear relationship between eGFR and outcomes, using a multivariable logistic regression model with restricted cubic splines for eGFR after adjusting for all potential covariates in patients. The range for each eGFR variable shown in the graphs indicates approximately the first to 99th percentile of its distribution. The median eGFR was 103 mL/min per 1.73 m^2 and was used as the reference, and the spline knots were placed at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, and 165 mL/min per 1.73 m^2. In addition, OR, 95% CI, and observed event rates were calculated for in-hospital outcomes for eGFR values in 15 mL/min per 1.73 m^2 increments, over the full range of values. All analyses were conducted with SAS Version 9.4 software (SAS Institute). Two-tailed $P<0.05$ were considered statistically significant.

Results

Of 18 320 patients, 601 (3.3%) had an eGFR <45, 625 (3.4%) had an eGFR 45 to 59, 3679 (20.1%) had an eGFR 60 to 89, and 13 415 (73.2%) had an eGFR ≥90 mL/min per 1.73 m^2. Table 1 shows the baseline patient and hospital characteristics. Patients with eGFR <45, eGFR 45 to 59, and eGFR 60 to 89 were older, with median ages of 72, 75, and 73 years, respectively. Approximately 34% of the cohort was female. Overall, the patients with lower eGFR were more likely to be female and nonsmokers and to have lower body mass index and higher NIHSS scores. A history of hypertension, diabetes mellitus, stroke/transient ischemic attack, myocardial infarction, and pneumonia was more common in patients with lower eGFR than in those with eGFR ≥90. Patients with eGFR <45, eGFR 45 to 59, and eGFR 60 to 89 were more likely to take antihypertensive medications, antiglucose medications, and lipid-lowering medications compared with those with eGFR ≥90. The plot showing the kernel density distribution of eGFR is presented in Figure 1.

In-Hospital Mortality

In the unadjusted analysis, AIS patients with lower eGFR were more likely to die in the hospital (6.7, 4.0, 2.5, and 0.9% for eGFR <45, 45–59, 60–89, ≥90 mL/min per 1.73 m^2, respectively, $P<0.05$). After adjusting for related covariates, when compared with GFR ≥90, all other eGFR levels were independently associated with higher odds of in-hospital mortality, including the risk among those with eGFR <45 (6.7% versus 0.9%, adjusted odds ratio, 3.59; 95% CI, 2.18–5.91), eGFR 45 to 59 (4.0% versus 0.9%, adjusted odds ratio, 2.00; 95% CI, 1.18–3.38), and eGFR 60 to 89 (2.5% versus 0.9%, adjusted odds ratio, 1.67; 95% CI, 1.20–2.34).

In-Hospital sICH

In our total cohort, sICH was most common among those with an eGFR 45 to 59 (n=59; 9.4%) and least common in those with an eGFR ≥90 (n=623; 4.6%). sICH occurred in 8.0% (n=48) of patients with an eGFR <45 and 6.8% (n=249) with an eGFR 60 to 89. After adjusting for related covariates, sICH was not statistically significant for eGFR <45 (OR, 0.86; 95% CI, 0.59–1.24), eGFR 45 to 59 (OR, 1.08; 95% CI, 0.79–1.48), or eGFR 60 to 89 (OR, 0.90; 95% CI, 0.76–1.07) relative to eGFR ≥90 (Figure 2).

Table 1. Baseline Patient Characteristics of Acute Stroke Patients With eGFR Status

Characteristics	eGFR Status				
	Total (N=18 320)	eGFR <45 (N=601)	eGFR 45 to 59 (N=625)	eGFR 60 to 89 (N=3679)	eGFR ≥90 (N=13 415)
Age, median (IQR), y	65.0 (56.0–74.0)	72.0 (63.0–80.0)	75.0 (67.0–81.0)	73.0 (65.0–79.0)	63.0 (54.0–70.0)
Female, n (%)	6251 (34.1)	264 (43.9)	288 (46.1)	1480 (40.2)	4219 (31.4)
Medical history, n (%)					
Hypertension	11 022 (60.2)	426 (70.9)	483 (77.3)	2481 (67.4)	7632 (56.9)
Diabetes mellitus	3241 (17.7)	151 (25.1)	143 (22.9)	656 (17.8)	2291 (17.1)
Previous stroke or TIA	4633 (25.3)	218 (36.3)	188 (30.1)	1053 (28.6)	3174 (23.7)
Myocardial infarction	2669 (14.6)	126 (21.0)	152 (24.3)	751 (20.4)	1640 (12.2)
Current or previous smoking	7544 (41.2)	218 (36.3)	198 (31.7)	1260 (34.2)	5868 (43.7)
Pneumonia	2777 (15.2)	146 (24.3)	179 (28.6)	791 (21.5)	1661 (12.4)
NIHSS score, median (IQR)	7.0 (4.0–12.0)	10.0 (5.0–17.0)	9.0 (5.0–15.0)	8.0 (4.0–14.0)	6.0 (3.0–11.0)
BMI, median (IQR), kg/m^2	23.4 (21.3–25.5)	23.0 (20.8–25.3)	23.0 (20.6–25.4)	23.1 (20.8–25.2)	23.5 (21.5–25.6)
Hospital level					
Secondary	4587 (25.0)	129 (21.5)	136 (21.8)	889 (24.2)	3433 (25.6)
Tertiary	13 733 (75.0)	472 (78.5)	489 (78.2)	2790 (75.8)	9982 (74.4)
Antihypertensive drug, n (%)	7657 (41.8)	323 (53.7)	381 (61.0)	1836 (49.9)	5117 (38.1)
Glucose-lowering drug, n (%)	2411 (13.2)	110 (18.3)	116 (18.6)	507 (13.8)	1678 (12.5)
Lipid-lowering drug, n (%)	1763 (9.6)	112 (18.6)	96 (15.4)	438 (11.9)	1117 (8.3)
Time from symptom onset to tPA, h					
0–3	10 125 (55.3)	340 (56.6)	382 (61.1)	2068 (56.2)	7335 (54.7)
≥3	8189 (44.7)	261 (43.4)	243 (38.9)	1611 (43.8)	6074 (45.3)
Dose of IV alteplase, mg/kg					
<0.89	8374 (45.7)	288 (47.9)	286 (45.8)	1643 (44.7)	6157 (45.9)
≥0.89	9946 (54.3)	313 (52.1)	339 (54.2)	2036 (55.3)	7258 (54.1)

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; tPA, tissue plasminogen activator.
All the *P* values were <0.0001.

eGFR and Outcome Measures

Applying a logistic regression model with restricted cubic spline, a J-shaped/U-shaped curve between eGFR and outcomes was not observed. The *P* value that tests for linearity was <0.0001, which confirmed that there was a linear relationship between eGFR and in-hospital mortality. The restricted cubic spline curve showed a larger magnitude of associations between eGFR and in-hospital mortality, and the unadjusted and adjusted odds increased with eGFR. Similarly, the restricted cubic spline curve indicated that there was a linear relationship between eGFR and sICH. However, this relationship was not obvious relative to the mortality curve, and it became less significant after adjusting for covariates (Figure 3).

Stratified Analysis

Table 2 shows the adjusted ORs and 95% CI of eGFR levels in relation to in-hospital mortality and sICH for subjects stratified by risk factors of interest. Overall, eGFR <45 mL/min per 1.73 m^2 was positively associated with higher odds of in-hospital death but not sICH than that found for the reference group (eGFR of ≥90 mL/min per 1.73 m^2) in analyses stratified by age, tPA dose, OTT, and severity quantified by NIHSS. Furthermore, there was no statistically significant interaction between different eGFR levels and age, tPA dose, OTT, and NIHSS. No significant statistical interactions were found between in-hospital death and eGFR categories and points (*P*=0.90, 0.99, 0.89, and 0.55 for age, dose, OTT, and NIHSS, respectively). Additionally, no

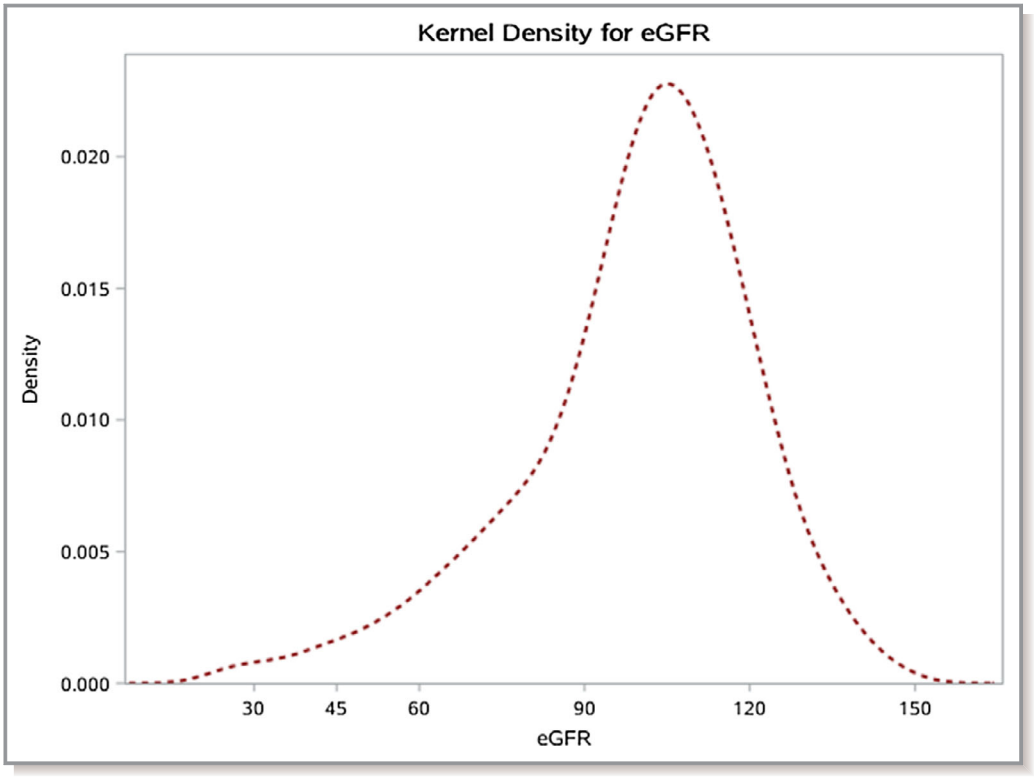


Figure 1. Distribution of estimated glomerular filtration rates (eGFRs) calculated by Chronic Kidney Disease Epidemiology Collaboration equation based on kernel density estimation.

significant statistical interactions were found between sICH and eGFR categories and points (P=0.65, 0.14, 0.57, and 0.09 for age, dose, OTT, and NIHSS, respectively).

Table S1 shows the unadjusted and adjusted ORs for in-hospital mortality and sICH in the general AIS patient population by different eGFR categories. The results were similar to previous in-hospital outcomes in AIS patients treated with tPA, which are presented in Figure 2.

Discussion

In this large study of AIS with tPA treatment, decreased eGFR was associated with an increased risk of in-hospital mortality. After adjusting for relevant covariates, in-hospital mortality was highest among patients with an eGFR <45, with ≈3.6 times higher odds than in those with an eGFR ≥90. Furthermore, the crude odds in our analysis showed an increased association between all eGFR levels and sICH. However, after adjusting for confounding variables, our study did not find an increased risk for sICH after tPA treatment in AIS patients with renal dysfunction. No significant statistical interactions between categories of eGFR and variables of interests were found in the stratified analysis.

Previous studies that aimed to assess the association of renal dysfunction with in-hospital outcomes are inconsistent. The inconsistency among study results might be attributable to the difference in sample sizes and the method of categorizing eGFR levels. For instance, 3 studies found associations between renal dysfunction and in-hospital death. A study conducted in Japan that included 578 patients revealed that renal dysfunction was significantly associated with poor outcome and mortality.[9] Another study involving 740 patients showed that only severe renal impairment (eGFR <30 mL/min) was related to sICH.[10] A cohort study of 232 236 patients revealed that renal dysfunction was associated with increased risk of in-hospital mortality, even though the study included the general AIS population rather than only AIS patients who received t-PA.[25] It has also been suggested that renal impairment reduces the efficacy of tPA therapy in AIS.[11] However, 3 other studies did not find that renal dysfunction was associated with death, ICH, or poor outcomes, suggesting that renal dysfunction does not influence the safety and efficacy of tPA thrombolysis in AIS patients.[12–14] In our study, the insignificant association of renal function and sICH might be explained by a decreasing effect after adjusting for confounding variables. Thrombolysis with tPA is an effective early treatment for AIS if the treatment is given within 4.5 hours after symptom onset. The presence of renal dysfunction independently portends a worse prognosis after stroke. Thus, our study has critical implications for the safety

Outcomes	No. of patients	No. of events (%)	Odds ratio (95% CI) Crude	Odds ratio (95% CI) Adjusted
In-hospital mortality				
eGFR <45	601	40(6.7)	7.64(5.09-11.47)	3.59(2.18-5.91)
eGFR 45-59	625	25(4.0)	4.47(2.85-7.00)	2.00(1.18-3.38)
eGFR 60-89	3679	93(2.5)	2.78(2.10-3.68)	1.67(1.20-2.34)
eGFR ≥90	13415	124(0.9)	Ref.	Ref.
In-hospital sICH				
eGFR <45	601	48(8.0)	1.78(1.31-2.43)	0.86(0.59-1.24)
eGFR 45-59	625	59(9.4)	2.14(1.60-2.86)	1.08(0.79-1.48)
eGFR 60-89	3679	249(6.8)	1.49(1.28-1.73)	0.90(0.76-1.07)
eGFR ≥90	13415	623(4.6)	Ref.	Ref.

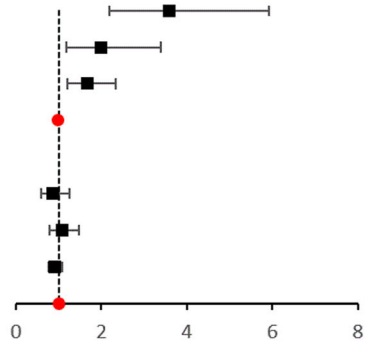


Figure 2. Associations Between eGFR and Outcomes in AIS Patients Treated With tPA, Including In-Hospital Mortality or sICH. CI indicates confidence interval; sICH, symptomatic intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; Adjusted variables include age, gender, BMI, previous hypertension, diabetes mellitus, previous stroke or TIA, coronary artery disease/previous myocardial infarction, dyslipidemia, previous smoking, pneumonia during index hospitalization, NIHSS score, antihypertensive drug use, glucose-lowering drug use, antiplatelet therapy, tPA dose, OTT and hospital level when appropriate.

and efficacy of tPA treatment and showed that renal dysfunction should not be viewed as a limitation when making decisions on whether to provide tPA treatment for AIS patients. This finding needs to be verified in future studies with other populations.

In our study, analyses stratified by age, tPA dose, OTT, and NIHSS presented similar results across strata; that is, a lower eGFR was associated with a higher risk of death, but no significant interaction with the variables of interest was noted for any eGFR category. The findings indicated that the associations between eGFR and outcomes did not significantly differ by age, tPA dose, OTT, or NIHSS score. Some previous evidence indicates that older age and NIHSS scores are the most notable predictors of ischemic stroke, and age is the risk factor for both ischemic stroke and kidney disease.[26,27] However, few studies have evaluated whether these factors change the relation between in-hospital outcomes and renal dysfunction. A current study showed no significant influence of the interaction between eGFR and age or other risk factors on mortality.[28] In addition, the latest guidelines recommend that AIS patients should be treated with thrombolytic therapy within 3 to 4.5 hours after symptom onset, except for those with severe contraindications. Because intravenous alteplase is still recommended for end-stage renal disease,[29] interactions between eGFR and risk factors for in-hospital outcomes may be less significant. This result should be verified, and other risk factors related to renal function need to be studied in larger populations in the future. Our study involved 18 320 patients

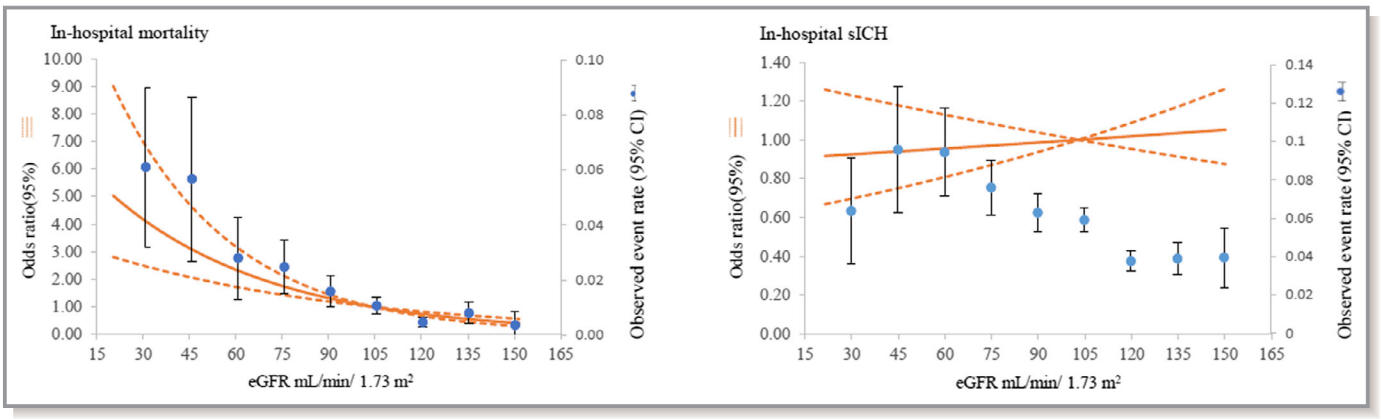


Figure 3. Relationship between estimated glomerular filtration rate (eGFR) and in-hospital death (left) and in-hospital symptomatic intracerebral hemorrhage (sICH) (right) in patients with ischemic stroke after treatment with tissue plasminogen activator. The adjusted odds ratios and 95% CIs are shown for each 15 mL/min per 1.73 m^2 change from the reference value (eGFR=104 mL/min per 1.73 m^2).

Table 2. Adjusted Odds Ratios of eGFR Status for In-Hospital Mortality and sICH Stratified by Age, Dose, OTT, and NIHSS

Outcomes	Odds Ratios With 95% CI				*P* for Interaction
	eGFR <45	eGFR 45 to 59	eGFR 60 to 89	eGFR ≥90	
In-hospital mortality					
Age, y					
<65	3.49 (1.15–10.58)	1.16 (0.14–9.91)	2.01 (0.98–4.13)	1.00 (reference)	0.90
≥65	4.09 (2.42–6.93)	2.04 (1.18–3.54)	1.73 (1.19–2.50)	1.00 (reference)	
Dose of tPA, mg/kg					
<0.89	3.72 (1.97–7.04)	1.46 (0.76–2.83)	1.47 (0.94–2.31)	1.00 (reference)	0.99
≥0.89	3.36 (1.65–6.85)	2.95 (1.28–6.77)	1.99 (1.25–3.18)	1.00 (reference)	
OTT, h					
0–3	3.59 (2.02–6.39)	1.92 (1.03–3.58)	1.47 (0.95–2.28)	1.00 (reference)	0.89
>3	3.56 (1.53–8.29)	1.77 (0.66–4.78)	2.02 (1.19–3.43)	1.00 (reference)	
NIHSS score					
<15	2.17 (1.04–4.55)	2.12 (0.94–4.74)	1.55 (1.04–2.33)	1.00 (reference)	0.55
>15	4.78 (2.67–8.56)	1.42 (0.76–2.68)	1.60 (1.05–2.44)	1.00 (reference)	
In-hospital sICH					
Age, y					
<65	0.41 (0.12–1.40)	1.66 (0.71–3.84)	0.98 (0.65–1.49)	1.00 (reference)	0.65
≥65	1.03 (0.70–1.52)	1.11 (0.80–1.55)	0.93 (0.77–1.13)	1.00 (reference)	
Dose of tPA, mg/kg					
<0.89	0.72 (0.44–1.20)	1.07 (0.73–1.58)	0.87 (0.69–1.09)	1.00 (reference)	0.14
≥0.89	1.03 (0.62–1.76)	1.08 (0.67–1.75)	0.94 (0.71–1.26)	1.00 (reference)	
OTT, h					
0–3	0.79 (0.48–1.29)	1.12 (0.77–1.63)	0.81 (0.63–1.02)	1.00 (reference)	0.57
>3	0.97 (0.56–1.66)	0.92 (0.52–1.63)	1.04 (0.80–1.34)	1.00 (reference)	
NIHSS score					
<15	0.96 (0.63–1.49)	1.01 (0.68–1.51)	0.99 (0.81–1.22)	1.00 (reference)	0.09
≥15	1.04 (0.62–1.72)	1.12 (0.71–1.77)	0.89 (0.68–1.16)	1.00 (reference)	

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale; OTT, symptom onset-to-treatment time; sICH, symptomatic intracerebral hemorrhage; TIA, transient ischemic attack; tPA, tissue plasminogen activator.
All the models adjusted for age, sex, BMI, previous hypertension, diabetes mellitus, previous stroke or TIA, coronary artery disease/previous myocardial infarction, dyslipidemia, previous smoking, pneumonia during index hospitalization, NIHSS score, antihypertensive drug use, glucose-lowering drug use, antiplatelet therapy, tPA dose, OTT, and hospital level when appropriate.

from 1092 hospitals, by far the largest to date to assess the relationship of specific levels of CKD to in-hospital outcomes including mortality and sICH, in Chinese AIS patients. In addition, the new Chronic Kidney Disease Epidemiology Collaboration equation was applied to provide more accurate measurement than the Modification of Diet in Renal Disease equation to calculate eGFR in our study.[30]

Some limitations of this study should be considered. First, because our cohort included only Chinese adult patients with AIS, the results might not be representative of other races and ethnicities. Second, clinical outcomes were measured only in hospitals, and follow-up information was not included in our study. Thus, we were not able to observe whether renal function status affects long-term outcomes. Third, our study data were abstracted from a voluntary registry program, which may have led to overreporting by high-quality hospitals, resulting in selection bias. In addition, we were unable to detect a same patient admitted in different hospitals since data were stripped of all identifiers before their use in our study. Thus, correlation among observations cannot be accounted for or adjusted for, which means that the precision and significance of these tests is affected and the significance levels may be inflated. Fourth, the low rate of patients included per hospital and year may translate to a noncomprehensive inclusion of patients in the registry, a fact that endangers the external validity. Fifth, only 0.7% of the

total patients had an eGFR <15. Information on dialysis was not available in the study; thus, how dialysis or very low eGFR affects outcomes is unknown. Data on thrombectomy were also not collected, and it would have been useful to assess the effect of interaction between renal dysfunction and endovascular thrombectomy after stroke onset. Information on dialysis was not available; thus, how dialysis or very low eGFR affects outcomes is unknown. Finally, information on other reperfusion therapies, pretreatment glucose levels, extent of ischemic damage in pretreatment computed tomography scan (ASPECTS score), and occlusion location were not collected. Some of these variables are used in risk scores for sICH that have been published in the past few years.

Conclusions

Among AIS patients treated with tPA, in-hospital mortality increased across all categories of eGFR and was highest in those with eGFR <45. Furthermore, eGFR was not found to be associated with increased in-hospital sICH. These findings suggest that tPA treatment should not be withheld on the basis of renal dysfunction.

Acknowledgments

We thank all participating hospitals, colleagues, nurses, and imaging and laboratory technicians and the Chinese Stroke Center Alliance Steering Committee members.

Sources of Funding

This work was supported by grants from the National Key R&D Program of China (2017YFC1310901, 2016YFC0901001, and 2016YFC0901002), the Beijing Municipal Committee of Science and Technology (D151100002015003), and the Beijing Municipal Administration of Hospitals' Mission Plan (SML20150502).

Disclosures

None.

References

1. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545–1602.
2. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, Wan X, Yu S, Jiang Y, Naghavi M, Vos T, Wang H, Lopez AD, Murray CJ. Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;381:1987–2015.
3. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet*. 2017;389:1238–1252.
4. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, Chen M, He Q, Liao Y, Yu X, Chen N, Zhang JE, Hu Z, Liu F, Hong D, Ma L, Liu H, Zhou X, Chen J, Pan L, Chen W, Wang W, Li X, Wang H. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet*. 2012;379:815–822.
5. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*. 2010;341:c4249.
6. Holzmann MJ, Aastveit A, Hammar N, Jungner I, Walldius G, Holme I. Renal dysfunction increases the risk of ischemic and hemorrhagic stroke in the general population. *Ann Med*. 2012;44:607–615.
7. Gensicke H, Zinkstok SM, Roos YB, Seiffge DJ, Ringleb P, Artto V, Putaala J, Haapaniemi E, Leys D, Bordet R, Michel P, Odier C, Berrouschot J, Arnold M, Heldner MR, Zini A, Bigliardi G, Padjen V, Peters N, Pezzini A, Schindler C, Sarikaya H, Bonati LH, Tatlisumak T, Lyrer PA, Nederkoorn PJ, Engelter ST. IV thrombolysis and renal function. *Neurology*. 2013;81:1780–1788.
8. Ovbiagele B, Smith EE, Schwamm LH, Grau-Sepulveda MV, Saver JL, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Chronic kidney disease and bleeding complications after intravenous thrombolytic therapy for acute ischemic stroke. *Circ Cardiovasc Qual Outcomes*. 2014;7:929–935.
9. Naganuma M, Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K, Toyoda K. Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: the stroke acute management with urgent risk-factor assessment and improvement (SAMURAI) rt-PA registry. *Cerebrovasc Dis*. 2011;31:123–129.
10. Tutuncu S, Ziegler AM, Scheitz JF, Slowinski T, Rocco A, Endres M, Nolte CH. Severe renal impairment is associated with symptomatic intracerebral hemorrhage after thrombolysis for ischemic stroke. *Stroke*. 2013;44:3217–3219.
11. Power A, Epstein D, Cohen D, Bathula R, Devine J, Kar A, Taube D, Duncan N, Ames D. Renal impairment reduces the efficacy of thrombolytic therapy in acute ischemic stroke. *Cerebrovasc Dis*. 2013;35:45–52.
12. Sobolewski P, Kozera G, Kazmierski R, Michalak S, Szczuchniak W, Sledzinska-Dzwigal M, Nyka WM. Intravenous rt-PA in patients with ischaemic stroke and renal dysfunction. *Clin Neurol Neurosurg*. 2013;115:1770–1774.
13. Hsieh CY, Lin HJ, Sung SF, Hsieh HC, Lai EC, Chen CH. Is renal dysfunction associated with adverse stroke outcome after thrombolytic therapy? *Cerebrovasc Dis*. 2014;37:51–56.
14. Agrawal V, Rai B, Fellows J, McCullough PA. In-hospital outcomes with thrombolytic therapy in patients with renal dysfunction presenting with acute ischaemic stroke. *Nephrol Dial Transplant*. 2010;25:1150–1157.
15. Hao Z, Yang C, Liu M, Wu B. Renal dysfunction and thrombolytic therapy in patients with acute ischemic stroke: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2014;93:e286.
16. Wang Y, Li Z, Wang Y, Zhao X, Liu L, Yang X, Wang C, Gu H, Zhang F, Wang C, Xian Y, Wang DZ, Dong Q, Xu A, Zhao J. Chinese Stroke Center Alliance: a national effort to improve healthcare quality for acute stroke and transient ischaemic attack: rationale, design and preliminary findings. *Stroke Vasc Neurol*. 2018;3:256–262. DOI: 10.1136/svn-2018-000154.
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; Ckd EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
18. Teo BW, Xu H, Wang D, Li J, Sinha AK, Shuter B, Sethi S, Lee EJ. GFR estimating equations in a multiethnic Asian population. *Am J Kidney Dis*. 2011;58:56–63.
19. Wang X, Wang Y, Wang C, Zhao X, Xian Y, Wang D, Liu L, Luo Y, Liu G, Wang Y. Association between estimated glomerular filtration rate and clinical outcomes in patients with acute ischaemic stroke: results from China National Stroke Registry. *Age Ageing*. 2014;43:839–845.
20. Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD. Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. *Am Heart J*. 2011;162:548–554.
21. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney F. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137–147.
22. Group TNIoNDaSr-PSS. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
23. McDonald JH. *Handbook of Biological Statistics*. 3rd ed. Baltimore, MD: Sparky House Publishing; 2014.
24. Hardin JW. Generalized estimating equations (GEE). *Encyclopedia of statistics in behavioral science*. Hoboken, NJ, USA: John Wiley & Sons; 2005.
25. El Husseini N, Fonarow GC, Smith EE, Ju C, Schwamm LH, Hernandez AF, Schulte PJ, Xian Y, Goldstein LB. Renal dysfunction is associated with poststroke discharge disposition and in-hospital mortality: findings from get with the guidelines-stroke. *Stroke*. 2017;48:327–334.

26. Dad T, Weiner DE. Stroke and chronic kidney disease: epidemiology, pathogenesis, and management across kidney disease stages. *Semin Nephrol*. 2015;35:311–322.

27. Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. *Lancet Neurol*. 2014;13:823–833.

28. Fox CS, Matsushita K, Woodward M, Bilo HJG, Chalmers J, Heerspink HJL, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen C-P, Nelson RG. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380:1662–1673.

29. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e99.

30. Wang X, Luo Y, Wang Y, Wang C, Zhao X, Wang D, Liu L, Liu G, Wang Y. Comparison of associations of outcomes after stroke with estimated GFR using Chinese modifications of the MDRD study and CKD-EPI creatinine equations: results from the China National Stroke Registry. *Am J Kidney Dis*. 2014;63:59–67.

SUPPLEMENTAL MATERIAL

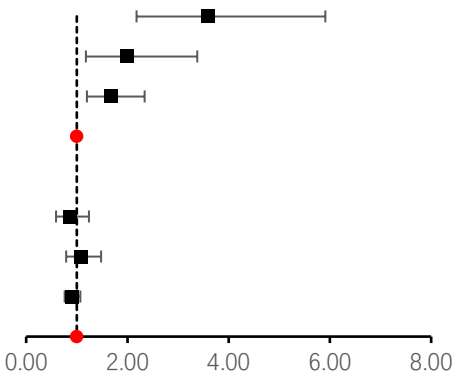
Appendix

The Chinese Stroke Center Alliance investigators

Jizong Zhao, Qiang Dong, Caiyun Wang, Fuying Zhang, Anding Xu

Table S1. Associations between eGFR and outcomes in all AIS patients, including in-hospital mortality or sICH.

Outcomes	No. of patients	No. of events (%)	Odds ratio (95% CI)	
			Crude	Adjusted
In-hospital mortality				
eGFR <45	16473	382(2.3)	7.30(6.31-8.45)	3.59(2.18-5.91)
eGFR 45-59	17474	228(1.3)	4.07(3.50-4.73)	2.00(1.18-3.38)
eGFR 60-89	92669	664(0.7)	2.22(1.98-2.49)	1.67(1.20-2.34)
eGFR ≥90	287083	930(0.3)	Ref.	Ref.
In-hospital sICH				
eGFR <45	16473	386(2.3)	1.48(1.30-1.68)	0.86(0.59-1.24)
eGFR 45-59	17474	396(2.3)	1.43(1.29-1.58)	1.08(0.79-1.48)
eGFR 60-89	92669	1807(2.0)	1.22(1.15-1.30)	0.90(0.76-1.07)
eGFR ≥90	287083	4590(1.6)	Ref.	Ref.



CI, confidence interval; sICH, symptomatic intracerebral hemorrhage; *Adjusted variables include age, sex, BMI, previous hypertension, diabetes mellitus, previous stroke or TIA, coronary artery disease/previous myocardial infarction, dyslipidemia, previous smoking, pneumonia, NIHSS score, antihypertensive drug use, glucose-lowering drug use, antiplatelet therapy, dose of tPA, OTT and hospital level when appropriate.

Figure S1. Flow chart of study patient selection.