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

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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 m²) 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
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.

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 1,624 hospitals participating in the CSCA. The details of the CSCA program have been previously published. The new Chronic Kidney Disease Epidemiology Collaboration (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 1,092 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. Thus, eGFR = 141 × min(SCr/κ, 1) × max(SCr/κ, 1) − 1.209 × 0.993 Age × 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. 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 (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. eGFR was stratified into 4 categories, including <45, 45 to 59, 60 to 89, and ≥90 mL/min per 1.73 m², with reference to the classifications of the National Kidney Foundation. 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.
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 continuous variables and proportions for categorical variables. eGFR groups using medians with interquartile ranges for the interaction.

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 m², 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).
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).

**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/m² | 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 m² 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 m²) 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
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
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Table 1. 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.

| Outcomes          | No. of patients | No. of events (%) | Odds ratio (95% CI) |
|-------------------|-----------------|-------------------|---------------------|
| 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.

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 m² change from the reference value (eGFR=104 mL/min per 1.73 m²).

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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

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

| Outcomes                  | eGFR <45 CI               | eGFR 45 to 59 CI          | eGFR 60 to 89 CI          | eGFR ≥90 CI            | P for Interaction |
|---------------------------|---------------------------|---------------------------|---------------------------|------------------------|-------------------|
| 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.
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.

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Disclosures
None.

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SUPPLEMENTAL MATERIAL
Appendix

The Chinese Stroke Center Alliance investigators

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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.

511,036 patients enrolled in CSCA program
- 418,282 IS patients
  - 92,754 non-IS were excluded
    - 35,167 TIA
    - 47,742 ICH
    - 6,258 SAH
    - 3,261 SNC
    - 326 without diagnosis information
- 35,167 TIA
- 47,742 ICH
- 6,258 SAH
- 3,261 SNC
- 326 without diagnosis information

418,282 IS patients
- 35,167 TIA
- 47,742 ICH
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- 3,261 SNC
- 326 without diagnosis information

18,678 AIS patients treated with tPA
- 390,100 patients with non-tPA treatment
- 9,504 patients with missing tPA treatment status

18,320 AIS patients stratified by eGFR were included in our study
- 1 patient with missing death information
- 2 patients with missing value of age
- 355 patients with missing value of serum Cr or serum Cr=0

eGFR< 45 (3.3%)
45 <=eGFR<60 (3.4%)
60 <=eGFR<90 (20.1%)
eGFR>=90 (73.2%)