Effects of Estimated Glomerular Filtration Rate on Clinical Outcomes in Patients with Intracerebral Hemorrhage

zhaoxia Li

Capital Medical University

Zixiao Li

Capital Medical University

Qi Zhou

Capital Medical University

Hongqiu Gu

Capital Medical University

Yongjun Wang

Capital Medical University

Xingquan Zhao (✉ zxq@vip.163.com)

Capital Medical University

Research Article

Keywords: glomerular filtration rate, chronic kidney disease, intracerebral hemorrhage, prognosis, mortality

Posted Date: September 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-844881/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at BMC Neurology on January 10th, 2022. See the published version at <https://doi.org/10.1186/s12883-022-02551-2>.

Abstract

Background: The influence of chronic kidney disease (CKD) on severity and prognosis of spontaneous intracerebral hemorrhage (ICH) is scarcely investigated. We aimed to explore the association of admission estimated glomerular filtration rate (eGFR) levels with stroke severity and outcomes in ICH patients.

Materials and Methods: The patients enrolled in this study were from the China Stroke Center Alliance study (CSCA). Patients were divided into four groups according to different admission eGFR levels (≥ 90 ; 60-89; 45-59; <45). Multivariable logistic regression analysis was used to determine the association of admission eGFR levels with stroke severity, in-hospital complications, discharge disposition, and in-hospital mortality after ICH.

Results: 85167 patients with acute ICH were included in the present analysis. Among them, 9493 (11.1%) had baseline eGFR ≥ 60 ml/min/1.73 m². Low eGFR was associated with increasing risk of in-hospital mortality [eGFR 60-89 ml/min/1.73 m², odds ratios(OR) 2.07(95% confidence interval(CI) 0.45 -9.4); eGFR 45-59, 8.43 (1.15- 61.98); eGFR ≤ 45 , 13.92 (2.22 - 87.15); *P for trend* < 0.0001]after adjusting for the confounding factors. With the declining of eGFR, the risk of non-routine disposition and hematoma evacuation increased in patients with eGFR 45 to 59 ml/min/1.73 m²(OR 8.43; 95%CI 1.15-61.98 and OR 3.36; 95% CI 1.2-9.44, respectively). No significant association between different level of eGFR at baseline and stroke severity, in-hospital complication such as pneumonia, hydrocephalus, rebleeding were observed.

Conclusions: Low eGFR at baseline was associated with increased risk of in-hospital mortality, non-routine disposition and hematoma evacuation but not with stroke severity and in-hospital complications in acute ICH patients.

Background

Chronic kidney disease(CKD), defined as reduced estimated glomerular filtration rate(eGFR) and/or presence of proteinuria, affects almost 119.5 million Chinese adults aged 18 years or older[1]. It's becoming a public health problem. Our previous study showed that CKD increased the risk of stroke including ischemic stroke and hemorrhagic stroke and all-cause mortality among Chinese general population[2, 3]. Mechanisms of CKD influencing the brain are unclear. There were several hypotheses that CKD increased the risk of ischemic stroke by enhancing the process of atherosclerosis, exacerbating the platelet dysfunction and aggregation, activating the oxidative stress[4–7]. CKD can also induce volume overload and hypertension by reacting to renin angiotensin aldosterone system, which in turn cause ischemic stroke and hemorrhagic stroke[8, 9].

Prevalence of spontaneous intracerebral hemorrhage (ICH) is high in China and carries substantial risk for disability and mortality[10, 11]. Most of the ICH are due to hypertension[11]. Renal and brain perforating arteries are both short, small arteries, mechanisms of maintaining the perfusion pressure and

blood flow are similar[8, 12]. Therefore, both of ICH and CKD can attribute to small vessel disease. Declining glomerular filtration rate (GFR) not only affects nephron arteries but also cerebral arteries[12]. CKD increase the risk of worse outcomes, stroke severity, hemorrhagic transformation among ischemic stroke has been elucidated in some studies[13–15]. While there are little studies exploring the relationship between CKD and outcomes of ICH, especially among large sample sizes from Asian population.

The aim of this study was to assess the relationship between different levels of eGFR and in-hospital mortality, stroke severity, discharge disposition, and in-hospital complications among ICH patients from the China Stroke Center Alliance.

Materials And Methods

Study Design and Participants

The data for this study were abstracted from the China Stroke Center Alliance (CSCA). Details of the study design have been described previously[16]. Briefly, the study was a national, hospital-based, multicenter, voluntary, multifaceted intervention and continuous quality improvement initiative performed in China. The study was approved by the Chinese Stroke Center Alliance, the Beijing Tiantan hospital Ethics Committee (the ethical reference number is KY 2018-061- 02) in accordance with the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations. Participating hospitals received a healthcare quality assessment and research approval to collect data in the CSCA without requiring individual patient informed consent under the common rule or a waiver of authorization and exemption from their Institutional Review Board. Patient informed consent was waived by the Beijing Tiantan hospital Ethics Committee. Patient confidentiality will be protected in the following ways:(1) data are stripped of all identifiers before their use in research and (2) the use of data for these purposes is closely overseen by the China National Clinical Research Center for Neurological Diseases analytic center. Patient confidentiality will be protected in the following ways:(1) data are stripped of all identifiers before their use in research and (2) the use of data for these purposes is closely overseen by the China National Clinical Research Center for Neurological Diseases analytic center[16]. Between August 2015 and July 2019, 1006798 consecutive patients aged 18 years or older, with acute stroke or transient ischemic attack (TIA) confirmed by brain computed tomography (CT) magnetic resonance imaging (MRI) within 7 days of symptom onset from 1312 designed hospitals in China were included. Among the trial, 85705 patients diagnosed with spontaneous ICH. 538 patients were excluded due to missing serum creatinine. Therefore, 85167 patients including 53208 men and 31959 women were included in this analysis.

Demographic and Clinical Information

Demographic characteristics, medical history and laboratory data were collected at admission. Body mass index (BMI) was calculated as kg/m^2 . Hypertension was classified as blood pressure $\geq 140/90$ mmHg, or self-reported history of hypertension, or antihypertensive medication use. Diabetes mellitus was defined by self-reported history, use of hypoglycemic medications, or fasting glucose level ≥ 7.0 mmol/l.

Hypercholesterolemia was defined as self-reported history, or use of lipid-lowering medication. Current smoking was defined as smoking more than one cigarette a day. Alcohol use was defined as drinking more than three glasses of wine (or equivalent alcohol) per day. Severity of stroke was assessed using Glasgow Coma Scale (GCS) and National Institutes of Health Stroke Scale (NIHSS). In-hospital mortality and complications (including pneumonia, pulmonary embolism, urinary tract infection, seizure, hydrocephalus, gastrointestinal bleeding, and deep vein thrombosis (DVT)), hematoma evacuation, length of hospital stay, hospital expenditure, and discharging disposition were recorded through hospitalization.

Estimation of glomerular filtration rate and Measurements of kidney function

Baseline serum creatinine (SCr) was measured by automated hematology analyzer at each research center using the enzymatic method. GFR was estimated by using a modified 4-variable Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with an adjusted coefficient of 1.1 for the Chinese population[17]: $eGFR_{CKD-EPI} = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times 1.1$, 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 divided into four categories, <45, 45 to 59, 60 to 89, and ≥ 90 ml/min/1.73 m², which were based on the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF/DOQI)[18].

Outcome

The primary outcome was in-hospital mortality. The secondary outcomes included stroke severity, discharge disposition, and in-hospital complication. Severe stroke was defined as NIHSS ≥ 11 . Discharging to home was considered to be routine disposition, while discharging to graded II or III hospital, community hospital, or rehabilitation facilities were considered as non-routine disposition. The in-hospital complications included pneumonia, urinary tract infection, hydrocephalus, gastrointestinal bleeding, and DVT[16].

Statistical Analysis

Categorical variables were presented as frequencies with percentages and were compared using Chi-square test. Continuous variables were tested for distribution using the Kolmogorov Smirnov test. Normally distributed data were described by mean $\pm$ standard deviation and were compared using one-way ANOVA. Non-normally distributed data were described by medians with interquartile ranges and were compared using the Mann-Whitney U-test. Logistic regression models were performed to calculate the odds ratios and 95% confidence intervals for the association of eGFR and in-hospital mortality, stroke severity, in-hospital complications, and discharge disposition. Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, systolic blood pressure(SBP), diastolic blood pressure(DBP), BMI, current smoking, prior stroke or TIA, prior chronic heart disease(CHD) or myocardial infarction, hypertension, dyslipidaemia, atrial fibrillation, diabetes mellitus, peripheral vascular disorder(PVD), drinking, low-density lipoprotein(LDL), glycated hemoglobin(GHb), homocysteine(HCY), blood urea nitrogen(BUN), uric acid. A

two-sided p-value < 0.05 was considered to be statistically significant. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 85705 patients diagnosed with spontaneous ICH from 1,312 designed hospitals in China were enrolled in CSCA. We excluded 538 patients without serum creatinine data. At last, 85167 patients with acute ICH were included in the analysis.

Table 1 and Table 2 show the demographic and clinical characteristics of ICH patients according to different levels of eGFR. The mean age was 62.9 years, 62.5% (n = 53208) were men. The most prevalent ICH risk factor was hypertension (72.2%, n = 61488). At hospital admission, the median serum creatinine was 67.7 $\mu\text{mol/L}$ and median eGFR was 101.4 ml/min/1.73 m², and 9493 (11.1%) patients with eGFR less than 60 ml/min/1.73 m². A total of 58418 patients (68.6%) had an eGFR ≥ 90 , 17256 (20.3%) had an eGFR 60 to 89, 3507 (4.1%) had an eGFR 45 to 59, 5986 (7.0%) had an eGFR < 45 mL/min/1.73 m². Median NIHSS at admission was 6 (interquartile range 2 to 12). 1975 (2.3%) patients died in hospital.

Table 1
Clinical characteristics among intracerebral hemorrhage patients grouped by baseline estimated glomerular filtration rate

Variables	eGFR at baseline (ml/min/1.73 m ²)					P Value
	Total (N = 85167)	≥ 90 (N = 58418)	60–89 (N = 17256)	45–59 (N = 3507)	< 45 (N = 5986)	
Demographic						
Age, y, mean(SD)	62.9 ± 12.9	60.8 ± 12.1	68.3 ± 12.9	69.5 ± 13.4	63.8 ± 13.9	< .0001
Male, n (%)	53208 (62.5)	36846 (63.1)	10680 (61.9)	2060 (58.7)	3622 (60.5)	< .0001
Physical examination, mean (SD)						
BMI, kg/m ²	23.9 ± 4.5	23.9 ± 4.1	23.6 ± 4.3	23.6 ± 3.9	24.3 ± 8.2	< .0001
SBP, mmHg	164.6 ± 28.2	163.3 ± 27.34	166.3 ± 28.9	169.0 ± 30.1	168.7 ± 32.	< .0001
DBP, mmHg	95.3 ± 16.9	95.2 ± 16.4	94.8 ± 17.4	95.7 ± 18.2	97.1 ± 19.3	< .0001
Medical history, n (%)						
Prior stroke or TIA	24472 (28.7)	16177 (27.7)	5096 (29.5)	1128 (32.2)	2071 (34.6)	< .0001
Prior CHD or myocardial infarction	4779 (5.6)	2945 (5.0)	1136 (6.6)	293 (8.4)	405 (6.8)	< .0001
Hypertension	61488 (72.2)	41188 (70.5)	12892 (74.7)	2706 (77.2)	4702 (78.5)	< .0001
Dyslipidemia	7246 (8.5)	4636 (7.9)	1613 (9.3)	370 (10.6)	627 (10.5)	< .0001
Atrial fibrillation	1304 (1.5)	644 (1.1)	425 (2.5)	111 (3.2)	124 (2.1)	< .0001
Diabetes mellitus	8335 (9.8)	5182 (8.9)	1731 (10.0)	446 (12.7)	976 (16.3)	< .0001
PVD	822 (1.0)	465 (0.8)	205 (1.2)	46 (1.3)	106 (1.8)	< .0001
Behavioral history, n (%)						
Current smoking	16767 (19.7)	12179 (20.8)	3080 (17.8)	556 (15.9)	952 (15.9)	< .0001

Variables	eGFR at baseline (ml/min/1.73 m ²)					P Value
	Total (N = 85167)	≥ 90 (N = 58418)	60–89 (N = 17256)	45–59 (N = 3507)	< 45 (N = 5986)	
Drinking	20790 (24.4)	14795 (25.3)	3812 (22.1)	705 (20.1)	1478 (24.7)	< .0001
Laboratory test, median(IQR)						
LDL cholesterol, mmol/L	2.6 (2.0–3.2)	2.6 (2.0–3.2)	2.6 (2.1–3.2)	2.7 (2.1–3.4)	2.8 (1.9–4.3)	< .0001
GHb, mmol/L	139.0 (125.0–153.0)	141.0 (128.0–154.0)	134.0 (121.0–149.0)	130.0 (120.0–143.0)	120.0 (100.0–143.0)	< .0001
Hcy, mmol/L	13.7 (10.0–20.0)	13.0 (9.5–19.0)	14.6 (10.5–20.6)	16.0 (11.3–23.1)	18.9 (10.5–31.5)	< .0001
Creatinine, μmmol/L	67.7 (55.0–85.0)	60.0 (50.1–70.0)	88.0 (77.0–98.8)	118.3 (101.6–131.0)	231.0 (159.0–440.0)	< .0001
BUN, mmol/L	5.1 (4.0–6.6)	4.8 (3.8–6.0)	5.8 (4.7–7.2)	7.1 (5.7–9.0)	9.1 (5.3–13.1)	< .0001
eGFR, ml/min/1.73 m ²	101.4 (84.0–113.6)	108.8 (100.5–118.3)	78.6 (70.9–85.0)	53.9 (49.9–57.2)	23.4 (10.4–35.0)	< .0001
Uric acid, μmmol/L	277.0 (210.0–354.0)	260.0 (200.4–329.0)	311.0 (240.7–382.5)	347.0 (263.0–432.0)	352.0 (216.0–483.0)	< .0001
SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; CHD, chronic heart disease; PVD, peripheral vascular disorder; LDL, low-density lipoprotein; GHb, glycated hemoglobin; Hcy, homocysteine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate						

Table 2
Clinical characteristics and severity and in-hospital outcome in ICH patients

Variables	eGFR at baseline (ml/min/1.73 m ²)					P Value
	Total (N = 85167)	≥ 90 (N = 58418)	60–89 (N = 17256)	45–59 (N = 3507)	< 45 (N = 5986)	
In hospital NIHSS, median(IQR)	6.0 (2.0–12.0)	5.0 (2.0–12.0)	6.0 (2.0–12.0)	7.0 (3.0–14.0)	8.0 (3.0–18.0)	< .0001
Score severity by NIHSS						< .0001
Missing	36155	24376	7144	1545	3090	
Score 0–5, n (%)	21264 (43.4)	15070 (44.3)	4463 (44.1)	757 (38.6)	974 (33.6)	
Score 6–10, n (%)	13537 (27.6)	9599 (28.2)	2740 (27.1)	495 (25.2)	703 (24.3)	
Score ≥ 11, n (%)	14211 (29.0)	9373 (27.5)	2909 (28.8)	710 (36.2)	1219 (42.1)	
GCS, median(IQR)	13.0 (8.0–15.0)	14.0 (8.0–15.0)	13.0 (8.0–15.0)	12.0 (7.0–15.0)	11.0 (6.0–15.0)	< .0001
In-hospital mortality, n(%)	1975 (2.3)	955 (1.6)	437 (2.5)	157 (4.5)	426 (7.1)	< .0001
In-hospital complication, n(%)						
Pneumonia	21795 (25.6)	13673 (23.4)	4883 (28.3)	1132 (32.3)	2107 (35.2)	< .0001
Pulmonary embolism	229 (0.3)	149 (0.3)	52 (0.3)	9 (0.3)	19 (0.3)	0.6504
Urinary tract infection	2106 (2.5)	1386 (2.4)	457 (2.6)	85 (2.4)	178 (3.0)	0.0123
Seizure	1191 (1.4)	808 (1.4)	234 (1.4)	50 (1.4)	99 (1.7)	0.3654
DVT	1125 (1.3)	761 (1.3)	242 (1.4)	45 (1.3)	77 (1.3)	0.7719
Gastrointestinal bleeding	1014 (1.2)	728 (1.2)	195 (1.1)	37 (1.1)	54 (0.9)	0.0767
Hydrocephalus	1862 (2.2)	1216 (2.1)	352 (2.0)	98 (2.8)	196 (3.3)	< .0001
Hematoma evacuation	8901 (10.5)	6258 (10.7)	1473 (8.5)	326 (9.3)	844 (14.1)	< .0001
Rebleeding	7026 (8.2)	4762 (8.2)	1381 (8.0)	316 (9.0)	567 (9.5)	0.008

Variables	eGFR at baseline (ml/min/1.73 m ²)					P Value
	Total (N = 85167)	≥ 90 (N = 58418)	60–89 (N = 17256)	45–59 (N = 3507)	< 45 (N = 5986)	
Length of hospital stay, mean(SD)	16.6 ± 11.7	17.0 ± 11.6	16.0 ± 11.3	15.5 ± 12.0	15.1 ± 12.6	< .0001
Hospital expenditure RMB, mean(SD)	18399.1 ± 17035.9	18425.3 ± 16947.2	17540.2 ± 16139.2	18435.6 ± 17117.9	20627.6 ± 19959.9	< .0001
Non-routine disposition, n (%)	4952 (5.8)	3318 (5.7)	979 (5.7)	208 (5.9)	447 (7.5)	< .0001
NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow coma scale; DVT: deep vein thrombosis						

Table 1 demonstrated that compared with those with normal eGFR, patients with decreased eGFR were older, more likely to be female, had higher prevalence of BMI, SBP and DBP, and had higher burden of vascular risk factors and comorbidities, including history of stroke or TIA, coronary artery disease or myocardial infarction, hypertension, dyslipidemia, atrial fibrillation, diabetes mellitus and PVD, but they were less likely to be current smoking and drinking($P<0.001$).

Table 2 presented that patients in the lowest category of the eGFR had higher NIHSS scores and lower Glasgow Coma Scale (GCS) scores, more likely to be severe stroke, more prone to die in hospital, more likely to have in-hospital complications including pneumonia, hydrocephalus, hematoma evacuation and rebleeding, had higher hospital expenditure, and more likely to discharged to II/III hospital, community hospital or rehabilitation facilities instead of home, but had shorter length of stay in hospital as compared with the highest category of the eGFR($P<0.001$). There were no significant differences in complications such as pulmonary embolism, urinary tract infection, seizure, DVT, and gastrointestinal bleeding among different groups(all $P>0.05$).

The association between eGFR and in-hospital mortality, discharge disposition, stroke severity and in-hospital complication were further explored using logistic regression analysis (Table 3). eGFR was inversely associated with increased risks of in-hospital mortality. The adjusted odds ratios(95%CI) for in-hospital mortality were 2.07 (95% CI, 0.45–9.4) associated with GFR 60 to 89 and 8.43 (95% CI, 1.15–61.98) associated with GFR 45 to 59 and 13.92 (95%CI, 2.22 to 87.15) associated with GFR<45 as compared with GFR ≥ 90 mL/min/1.73 m² (P for trend < 0.0001).

Table 3
Logistic regression of the eGFR levels on in-hospital mortality and discharge disposition

	Baseline eGFR (mL/min/1.73 m ²)				P for trend
	≥ 90(n = 58418)	60–89(N = 17256)	45–59(N = 3507)	< 45(N = 5986)	
In-hospital mortality(N = 1975)	N = 955	N = 437	N = 157	N = 426	
Unadjusted model OR(95% CI)	Ref.	1.56 (1.39–1.75)	2.82 (2.37–3.35)	4.62 (4.1–5.19)	< 0.001
Model 1 OR(95% CI)	Ref.	1.36 (1.21–1.53)	2.41 (2.02–2.88)	4.38 (3.89–4.93)	< 0.001
Model 2 OR(95% CI)	Ref.	2.07 (0.45–9.4)	8.43 (1.15–61.98)	13.92 (2.22–87.15)	0.0039
Non-routine disposition(N = 4952)	N = 3318	N = 979	N = 208	N = 447	
Unadjusted model OR(95% CI)	Ref.	1 (0.93–1.07)	1.11 (1.03–1.2)	2.15 (1.31–3.55)	< 0.001
Model 1 OR(95% CI)	Ref.	1.05 (0.91–1.21)	1.19 (1.03–1.38)	4.17 (1.86–9.37)	< 0.001
Model 2 OR(95% CI)	Ref.	1.34 (1.21–1.49)	1.4 (1.26–1.55)	0.73 (0.25–2.19)	0.9911
Severe stroke(N = 14211)	N = 9373	N = 2909	N = 710	N = 1219	
Unadjusted model OR(95% CI)	Ref.	1.06 (1.01–1.12)	1.49 (1.36–1.64)	1.91 (1.77–2.07)	< 0.001
Model 1 OR(95% CI)	Ref.	0.99 (0.94–1.04)	1.37 (1.24–1.51)	1.85 (1.71–2)	< 0.001
Model 2 OR(95% CI)	Ref.	1.17 (0.75–1.84)	1.09 (0.46–2.6)	0.97 (0.44–2.15)	0.3957
In-hospital complication					
Pneumonia(N = 21795)	N = 13673	N = 4883	N = 1132	N = 2107	
Unadjusted model OR(95% CI)	Ref.	1.29 (1.24–1.34)	1.56 (1.45–1.68)	1.78 (1.68–1.88)	< 0.001
Model 1 OR(95% CI)	Ref.	1.1 (1.06–1.15)	1.31 (1.21–1.41)	1.69 (1.59–1.78)	< 0.001
Model 1: Adjusted for age, gender					
Model 2: Adjusted for age, gender. SBP, DBP, BMI, current smoking, Prior stroke or TIA, Prior CHD or myocardial infarction, Hypertension, Dyslipidaemia, Atrial fibrillation, Diabetes mellitus, PVD, Drinking, LDL, GHb, HCY, BUN, Uric acid					

	Baseline eGFR (mL/min/1.73 m ²)				P for trend
	≥ 90(n = 58418)	60–89(N = 17256)	45–59(N = 3507)	< 45(N = 5986)	
Model 2 OR(95% CI)	Ref.	0.93 (0.66–1.3)	1.7 (0.93–3.13)	1.2 (0.67–2.14)	0.1702
Hydrocephalus(N = 1862)	N = 1216	N = 352	N = 98	N = 196	
Unadjusted model OR(95% CI)	Ref.	0.98 (0.87–1.1)	1.35 (1.1–1.67)	1.59 (1.37–1.86)	< 0.001
Model 1 OR(95% CI)	Ref.	0.99 (0.88–1.12)	1.37 (1.11–1.69)	1.6 (1.37–1.86)	< 0.001
Model 2 OR(95% CI)	Ref.	1.97 (0.85–4.52)	3.77 (0.96–14.85)	1.46 (0.33–6.48)	0.4785
Rebleeding(N = 7026)	N = 4762	N = 1381	N = 316	N = 567	
Unadjusted model OR(95% CI)	Ref.	0.98 (0.92–1.04)	1.12 (0.99–1.26)	1.18 (1.08–1.29)	0.001
Model 1 OR(95% CI)	Ref.	0.97 (0.91–1.03)	1.1 (0.98–1.24)	1.17 (1.07–1.29)	0.001
Model 2 OR(95% CI)	Ref.	1.08 (0.63–1.87)	0.83 (0.27–2.57)	1.66 (0.66–4.19)	0.4775
Hematoma evacuation(N = 8901)	N = 6258	N = 1473	N = 326	N = 844	
Unadjusted model OR(95% CI)	Ref.	0.78 (0.73–0.83)	0.85 (0.76–0.96)	1.37 (1.27–1.48)	< 0.001
Model 1 OR(95% CI)	Ref.	0.93 (0.88–0.99)	1.05 (0.93–1.18)	1.46 (1.35–1.58)	< 0.001
Model 2 OR(95% CI)	Ref.	1.51 (0.75–3.01)	3.36 (1.2–9.44)	1.05 (0.3–3.73)	0.4265
Model 1: Adjusted for age, gender					
Model 2: Adjusted for age, gender, SBP, DBP, BMI, current smoking, Prior stroke or TIA, Prior CHD or myocardial infarction, Hypertension, Dyslipidaemia, Atrial fibrillation, Diabetes mellitus, PVD, Drinking, LDL, GHb, HCY, BUN, Uric acid					

Compared with eGFR ≥ 90 ml/min/1.73 m², patients with eGFR 45 to 59 ml/min/1.73 m² had increased risk of non-routine disposition and hematoma evacuation (OR 8.43; 95%CI 1.15–61.98; OR 3.36; 95% CI 1.2–9.44, respectively) after adjusting for confounding factors. However, there were no statistically significance in patients with eGFR less than 45 ml/min/1.73 m² (*P for trend* >0.05).

In crude model and model 1 adjusted for age and gender, there were trends that with the declining of eGFR, the risk of severe stroke, in-hospital complications such as pneumonia, rebleeding and hematoma evacuation increased. Yet, these relationships vanished after adjustment with other confounders.

Discussion

In this study, we found that reduced eGFR at baseline was associated with increased risk of in-hospital mortality, non-routine disposition and hematoma evacuation in acute ICH patients. However, no independent relationships between decreased eGFR and stroke severity and in-hospital complications were observed.

There are few studies exploring the association between eGFR and adverse outcome among ICH patients and the results are controversial[19–22]. In a large cohort study of 113,059 patients hospitalized at 1472 united states centers, ICH patients with renal dysfunction were strongly related to inpatient mortality[19]. In a small sample size prospective study including 365 patients with ICH, after 3-month follow-up, patients with low eGFR at baseline are associated with increased risk of all-cause mortality[20]. In a study of 1758 patients with acute stroke including 566 hemorrhagic stroke admitted to a hospital in China found that decreased eGFR was an independent predictor of death/disability in patients with hemorrhagic stroke, but not for ischemic stroke[21]. Our results are in accordance with these studies. While another study from China enrolled 1909 patients with acute stroke including ICH found that low eGFR had no relationship with increased risk of death/disability at 3 months[22]. The discrepancy may be attributable to the differences of the study populations and study design.

Mechanisms of low eGFR affect ICH are unexplored. But, several explanations can be proposed for the link between CKD and adverse outcome in patients with stroke. First, declining of eGFR leads to electrolyte imbalances, which causes vasoconstriction and increases blood pressure by the action of aldosterone on sodium-water retention[8, 9]. Second, renal dysfunction has a bleeding tendency due to platelet dysfunction[23]. Third, CKD has been associated with inflammation and endothelial dysfunction, which may accelerate leukocyte infiltration and further contribute to arteriosclerosis and platelet dysfunction[7]. All those together are contributed to hematoma expansion, hemorrhagic transformation, and cerebral microbleeds and lead to adverse outcome among stroke patients. Several studies have found that patient with moderate/severe kidney impairment had larger hematoma volumes and unfavorable outcome[24–26]. In an analysis of 770 participants with ischemic stroke and found that low levels of eGFR are independently associated with a high risk of hemorrhagic transformation after ischemic stroke[27]. Association of CKD with cerebral microbleeds has been elucidated in some studies, which reinforces the notion of a link between hypertensive vasculopathy, renal impairment and stroke[28–30]. To our disappointment, in our study, there were trends that with the declining of eGFR, the risks of rebleeding, hematoma evacuation and severe stroke increased, however, those relationships disappeared after adjustment with confounders.

There were several limitations in our study. First, measurement of serum creatinine was performed locally rather than at a central laboratory and was not calibrated amongst laboratories, which may have produced substantial variability in the measured values. Second, data were ascertained from the medical record and depended on the accuracy and completeness of clinical documentation. Third, we were unable to assess the effect of proteinuria among acute ICH patients due to the lack of data, while proteinuria has been shown to be an important independent risk factor for ischemic stroke[31–33]. Fourth, although we adjusted for known confounders, there were potential sources of confounding have affected our results. Finally, due to the lack of follow-up data, we were unable to assess the long-term impact of CKD on ICH-related outcomes. Further prospective and multi-center evaluation is necessary to verify the results of this study.

Conclusions

Reduced eGFR at baseline was associated with increased risk of in-hospital mortality, non-routine disposition and hematoma evacuation but not stroke severity and in-hospital complications in acute ICH patients. Decreased eGFR was an independent factor affecting the prognosis of ICH.

Abbreviations

CKD: chronic kidney disease; ICH intracerebral hemorrhage; eGFR: estimated glomerular filtration rate; CSCA: China Stroke Center Alliance study; OR: odds ratios; CI: confidence interval; CKD: chronic kidney disease; TIA: transient ischemic attack; CT: computed tomography; MRI: magnetic resonance imaging; BMI: body mass index; GCS: Glasgow Coma Scale; NIHSS: National Institutes of Health Stroke Scale; DVT: deep vein thrombosis; SCr: serum creatinine; CKD-EPI: chronic kidney disease epidemiology collaboration; NKF/DOQI: National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; SBP: systolic blood pressure; DBP: diastolic blood pressure; CHD: chronic heart disease; PVD: peripheral vascular disorder; LDL: low-density lipoprotein; GHb: glycated hemoglobin; HCY: homocysteine; BUN: blood urea nitrogen.

Declarations

Acknowledgements

Not applicable.

Funding

This study was supported by grants from Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-029), Beijing Municipal Committee of Science and Technology (Z201100005620010), National Key R&D Program of China (2018YFC1312903), the National Natural Science Foundation of China (81870905), and Beijing Municipal Science & Technology Commission (D171100003017002).

Availability of data and materials

Due to CSCA project regulations, data that support the findings of this study is not publicly available. If someone wants to request the data, please contact the investigators of the Beijing tiantan hospital with reasonable request.

Ethics approval and consent to participate

The study was approved by the Chinese Stroke Center Alliance, the Beijing Tiantan hospital Ethics Committee (the ethical reference number is KY 2018-061- 02) in accordance with the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations. Participating hospitals received a healthcare quality assessment and research approval to collect data in the CSCA without requiring individual patient informed consent under the common rule or a waiver of authorization and exemption from their Institutional Review Board. Patient informed consent was waived by the Beijing Tiantan hospital Ethics Committee. Patient confidentiality will be protected in the following ways:(1) data are stripped of all identifiers before their use in research and (2) the use of data for these purposes is closely overseen by the China National Clinical Research Center for Neurological Diseases analytic center.

Consent for publication

Not applicable.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Author Contributions

ZhaoXL, ZiXL, YJW and XQZ planned and designed the study. HQG and QZ analyzed the data. ZhaoXL wrote the paper. ZiXL and XQZ revised the paper.

Author details

¹ Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

² China National Clinical Research Center for Neurological Diseases, Beijing, China.

³ Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China.

⁴ Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, China.

⁵ Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences, Beijing, China

List of directors of Provincial Centers of Neurological Diseases/Stroke Care Management

1安徽: Kai Wang, Department of Neurology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China.

2北京: Xunming Ji, Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China.

3重庆: Xinyue Qin, Department of Neurology, the First Affiliated hospital of Chongqing Medical University, Chongqing, China.

4福建: Ning Wang, Department of Neurology and Institute of Neurology, First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian, China.

5甘肃: Zhaoming Ge, Department of Neurology, Lanzhou University Second Hospital, Lanzhou, Gansu, China.

6广东: Jinsheng Zeng, Department of neurology, National Key Clinical Department and Key Discipline of Neurology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China.

7广西: Lvli Li, Department of Neurology, the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi, China.

8贵州: Lan Chu, Department of Neurology, Hospital Of Guizhou Medical University, Guiyang, Guizhou, China.

Hainan: Zhibin Chen, Department of Neurology, the First Affiliated Hospital of Hainan Medical University, Haikou, Hainan, China.

9河北: Li Guo, Department of Neurology, the Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China.

Heilongjiang: Guozhong Li, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China.

10河南: Yuming Xu, Department of Neurology, the First Affiliated Hospital of Zhengzhou University, Henan, China.

11湖北: Bo Hu, Department of Neurology, Union Hospital, Hua Zhong Science and Technology University, Wuhan, Hubei, China.

12湖南: Beisha Tang, Department of Neurology and Gerontology, Xiangya Hospital, Central South University, Changsha, Hunan, China.

- 13 Inner Mongolia: Guorong Liu, Department of Neurology, Baotou City Central Hospital Inner Mongolia CVD Institute, Baotou, Inner Mongolia, China.
- 14 Jiangsu: Xiaoshan Wang, Department of Neurology, Nanjing Brain Hospital, Nanjing Medical University, Nanjing, Jiangsu, China.
- 15 Jiangxi: Xiaomu Wu, Department of Neurology, Jiangxi Provincial People's Hospital, Nanchang, Jiangxi, China.
- 16 Jilin: Yi Yang, Department of Neurology, the First Hospital of Jilin University, Changchun, Jilin, China.
- 17 Liaoning: Zhiyi He, Department of Neurology, the First Affiliated Hospital of China Medical University, Shenyang, Liaoning, China.
- 18 Ningxia: Zhenhai Wang, Department of Neurology, General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China.
- 19 Qing Hai: Shizheng Wu, Department of Neurology, Qinghai Provincial People's Hospital, Xining, Qinghai, China.
- 20 Shaanxi: Gang Zhao, Department of Neurology, Xijing Hospital, the Fourth Military Medical University, Xian, Shaanxi, China.
- 21 Shandong: Meijia Zhu, Department of Neurology, Qianfoshan Hospital, Shandong University, Jinan, Shandong, China.
- 22 Shanghai: Qiang Dong, Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China.
- 23 Shanxi: Xiaoyuan Niu, Department of Neurology, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China.
- 24 Sichuan: Dong Zhou, Department of Neurology, West China Hospital of Sichuan University, Chengdu, Sichuan, China.
- 25 Tianjin: Zhongping An, Department of Neurology, Tianjin Huanhu Hospital, Tianjin, China.
- 26 Tibet: Yuhua Zhao, Department of Neurology, the People's Hospital of Tibetan Autonomous Region, Lhasa, Tibet, China.
- 27 Xinjiang: Xiaoning Zhang, Department of Neurology, the Fourth Affiliation Hospital, Xinjiang Medical University, Urumuqi, Xinjiang, China.
- 28 Yunnan: Li Ding, Department of Neurology, the First People's Hospital of Yunnan Province, Kunming, Yunnan, China.

References

1. Zhang LX, Wang F, Wang L, Wang WK, Liu BC, Liu J, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet*. 2012;379 9818:815-22; doi: Doi 10.1016/S0140-6736(12)60033-6.
2. Li Z, Wang A, Cai J, Gao X, Zhou Y, Luo Y, et al. Impact of proteinuria and glomerular filtration rate on risk of ischaemic and intracerebral hemorrhagic stroke: a result from the Kailuan study. *Eur J Neurol*. 2015;22 2:355-60; doi: 10.1111/ene.12580.
3. Wu JW, Jia JK, Li ZX, Pan H, Wang AX, Guo XH, et al. Association of estimated glomerular filtration rate and proteinuria with all-cause mortality in community-based population in China: A Result from Kailuan Study. *Sci Rep-Uk*. 2018;8; doi: Artn 215710.1038/S41598-018-20554-3.
4. Chelluboina B, Vemuganti R. Chronic kidney disease in the pathogenesis of acute ischemic stroke. *J Cerebr Blood F Met*. 2019;39 10:1893-905; doi: Artn 0271678x1986673310.1177/0271678x19866733.
5. Bulow RD, Boor P. Extracellular Matrix in Kidney Fibrosis: More Than Just a Scaffold. *J Histochem Cytochem*. 2019;67 9:643-61; doi:10.1369/0022155419849388.
6. Formanowicz D, Wanic-Kossowska M, Pawliczak E, Radom M, Formanowicz P. Usefulness of serum interleukin-18 in predicting cardiovascular mortality in patients with chronic kidney disease - systems and clinical approach. *Sci Rep-Uk*. 2015;5; doi: Artn 1833210.1038/Srep18332.
7. Shah B, Jagtap P, Sarmah D, Datta A, Raut S, Sarkar A, et al. Cerebro-renal interaction and stroke. *Eur J Neurosci*. 2020; doi: 10.1111/ejn.14983.
8. Lau WL, Huisa BN, Fisher M. The Cerebrovascular-Chronic Kidney Disease Connection: Perspectives and Mechanisms. *Transl Stroke Res*. 2017;8 1:67-76; doi: 10.1007/s12975-016-0499-x.
9. Flythe JE, Brunelli SM. Blood Pressure Variability and Dialysis: Variability May Not Always Be the Spice of Life. *J Am Soc Nephrol*. 2014;25 4:650-3; doi: 10.1681/Asn.2013111237.
10. Wang WZ, Jiang B, Sun HX, Ru XJ, Sun DL, Wang LH, et al. Prevalence, Incidence, and Mortality of Stroke in China Results from a Nationwide Population-Based Survey of 480 687 Adults. *Circulation*. 2017;135 8:759-+; doi: 10.1161/Circulationaha.116.025250.
11. Wang YJ, Li ZX, Gu HQ, Zhai Y, Jiang Y, Zhao XQ, et al. China Stroke Statistics 2019: A Report From the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. *Stroke Vasc Neurol*. 2020;5 3:211-39; doi: 10.1136/svn-2020-000457.

12. Toyoda K. Brain, Stroke and Kidney Cerebrorenal Interaction and Stroke. *Contrib Nephrol.* 2013;179:1-6.
13. Rao ZZ, Gu HQ, Wang XW, Xie XW, Yang X, Wang CJ, et al. Renal Dysfunction and In-Hospital Outcomes in Patients With Acute Ischemic Stroke After Intravenous Thrombolytic Therapy. *J Am Heart Assoc.* 2019;8 20; doi: ARTN e01205210.1161/JAHA.119.012052.
14. Sutherland LJ, Diprose WK, Wang MTM, Barber PA. Chronic Kidney Disease and Outcome Following Endovascular Thrombectomy for Acute Ischemic Stroke. *J Stroke Cerebrovasc.* 2020;29 4; doi: ARTN 10466510.1016/j.jstrokecerebrovasdis.2020.104665.
15. Castro P, Azevedo E, Rocha I, Sorond F, Serrador JM. Chronic kidney disease and poor outcomes in ischemic stroke: is impaired cerebral autoregulation the missing link? *Bmc Neurol.* 2018;18; doi: ARTN 2110.1186/s12883-018-1025-4.
16. Wang YJ, Li ZX, Wang YL, Zhao XQ, Liu LP, Yang X, et al. 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 4:256-62; doi: 10.1136/svn-2018-000154.
17. Teo BW, Xu H, Wang DH, Li JL, Sinha AK, Shuter B, et al. GFR Estimating Equations in a Multiethnic Asian Population. *Am J Kidney Dis.* 2011;58 1:56-63; doi: 10.1053/j.ajkd.2011.02.393.
18. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report (vol 80, pg 17, 2011). *Kidney Int.* 2011;80 9:1000-; doi: 10.1038/ki.2011.310.
19. Ovbiagele B, Schwamm LH, Smith EE, Grau-Sepulveda MV, Saver JL, Bhatt DL, et al. Hospitalized Hemorrhagic Stroke Patients with Renal Insufficiency: Clinical Characteristics, Care Patterns, and Outcomes. *J Stroke Cerebrovasc.* 2014;23 9:2265-73; doi: 10.1016/j.jstrokecerebrovasdis.2014.04.016.
20. You SJ, Shi LY, Zhong CK, Xu JP, Han Q, Zhang X, et al. Prognostic Significance of Estimated Glomerular Filtration Rate and Cystatin C in Patients with Acute Intracerebral Hemorrhage. *Cerebrovasc Dis.* 2016;42 5-6:455-63; doi: 10.1159/000448340.
21. Hao ZL, Wu B, Lin S, Kong FY, Tao WD, Wang DR, et al. Association between Renal Function and Clinical Outcome in Patients with Acute Stroke. *Eur Neurol.* 2010;63 4:237-42; doi: 10.1159/000285165.
22. Yang J, Arima H, Zhou J, Zhao Y, Li Q, Wu G, et al. Effects of low estimated glomerular filtration rate on outcomes after stroke: a hospital-based stroke registry in China. *Eur J Neurol.* 2014;21 8:1143-5; doi: 10.1111/ene.12311.
23. Sohal AS, Gangji AS, Crowther MA, Treleaven D. Uremic bleeding: Pathophysiology and clinical risk factors. *Thromb Res.* 2006;118 3:417-22; doi: 10.1016/j.thromres.2005.03.032.
24. Molshatzki N, Orion D, Tsabari R, Schwammenthal Y, Merzeliak O, Toashi M, et al. Chronic Kidney Disease in Patients with Acute Intracerebral Hemorrhage: Association with Large Hematoma Volume and Poor Outcome. *Cerebrovasc Dis.* 2011;31 3:271-7; doi: 10.1159/000322155.

25. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage - Reply from the authors. *Neurology*. 2007;68 6:472-.
26. Xu MM, Lei CY, Liu M, Liu JF, Tan G, Li D. Influence of End-Stage Renal Disease on Hematoma Volume and Intraventricular Hemorrhage in Patients with Intracerebral Hemorrhage: A Cohort Study and Meta-Analysis. *Eur Neurol*. 2016;75 1-2:33-40; doi: 10.1159/000442572.
27. Lee JG, Lee KB, Jang IM, Roh H, Ahn MY, Woo HY, et al. Low Glomerular Filtration Rate Increases Hemorrhagic Transformation in Acute Ischemic Stroke. *Cerebrovasc Dis*. 2013;35 1:53-9; doi: 10.1159/000345087.
28. Tsai YH, Lee M, Lin LC, Chang SW, Weng HH, Yang JT, et al. Association of Chronic Kidney Disease With Small Vessel Disease in Patients With Hypertensive Intracerebral Hemorrhage. *Front Neurol*. 2018;9; doi: Artn 28410.3389/Fneur.2018.00284.
29. Cho AH, Lee SB, Han SJ, Shon YM, Yang DW, Kim BS. Impaired kidney function and cerebral microbleeds in patients with acute ischemic stroke. *Neurology*. 2009;73 20:1645-8; doi: 10.1212/WNL.0b013e3181c1defa.
30. Ovbiagele B, Wing JJ, Menon RS, Burgess RE, Gibbons MC, Sobotka I, et al. Association of Chronic Kidney Disease With Cerebral Microbleeds in Patients With Primary Intracerebral Hemorrhage. *Stroke*. 2013;44 9:2409-13; doi: 10.1161/Strokeaha.113.001958.
31. Kumai Y, Kamouchi M, Hata J, Ago T, Kitayama J, Nakane H, et al. Proteinuria and clinical outcomes after ischemic stroke. *Neurology*. 2012;78 24:1909-15; doi: Doi 10.1212/Wnl.0b013e318259e110.
32. Kim J, Song TJ, Song D, Yoo J, Baek JH, Lee HS, et al. Prognostic value of urine dipstick proteinuria on mortality after acute ischemic stroke. *Atherosclerosis*. 2016;253:118-23; doi: 10.1016/j.atherosclerosis.2016.08.030.
33. Aguilar MI, O'Meara ES, Seliger S, Longstreth WT, Hart RG, Pergola PE, et al. Albuminuria and the risk of incident stroke and stroke types in older adults. *Neurology*. 2010;75 15:1343-50; doi: Doi 10.1212/Wnl.0b013e3181f73638.