Renal Dysfunction Associated with Symptomatic Intracranial Hemorrhage after Intravenous Thrombolysis

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Background and Aim: Renal dysfunction (RD) is prevalent in patients with acute ischemic stroke requiring intravenous thrombolysis. The relationship between renal function and thrombolysis related intracranial hemorrhagic (ICH) complications is contradictory according to previous studies. The current study is to clarify whether RD could increase the risk of symptomatic intracranial hemorrhage (SICH) after recombinant tissue plasminogen activator (IV rtPA) in acute ischemic stroke patients. *Methods:* In this observational study, acute ischemic stroke patients who received IV rtPA within 4.5 hours of symptom onset were retrospectively analyzed. Creatinine levels on admission served to calculate glomerular filtration rate (GFR) to estimate RD. SICH was defined with National Institute of Neurological Disorder and Stroke (NINDS, $SICH_{NINDS}$) or European Cooperative Acute Stroke Study II (ECASS II, $SICH_{ECASSII}$) criteria. Association of RD with SICH was assessed using continuous GFR or binary GFR (RD defined as GFR < 90 ml/minute/1.73 m^2). *Results:* Of 312 patients included, the incidence of $SICH_{NINDS}$ was 7.69%, of $SICH_{ECASSII}$ was 5.45%. Patients with RD had higher prevalence of $SICH_{NINDS}$ (12.80% versus 2.03%, $P < .001$) and $SICH_{ECASS\ II}$ (9.15% versus 1.35%, $P = .002$). GFR as a continuous variable was associated with $SICH_{NINDS}$ ($OR_{adjust} = .97$, $P = .003$), but not with $SICH_{ECASS\ II}$. GFR less than 90 ml/minute/1.73 m^2 remained independently associated with $SICH_{NINDS}$ ($OR_{adjust} = 4.79$, $P = .016$), and $SICH_{ECASS\ II}$ ($OR_{adjust} = 2.99$, $P = .032$) in multiple logistic regression analysis. *Conclusions:* Renal function is independently associated with SICH after IV rtPA thrombolysis. RD is an independent predictor for both $SICH_{NINDS}$ and $SICHE_{CASS\ II}$. RD should be considered when evaluating the risk of intravenous thrombolysis with IV rtPA.

Keywords: Renal dysfunction—ischemic stroke—thrombolysis—symptomatic intracranial hemorrhage

Introduction

Intravenous recombinant tissue-type alteplase (IV rtPA) improves outcome in selected patients with acute ischemic stroke (AIS) when treated within 4.5 hours from onset.[1] Despite its efficacy in reducing mortality and disability, the use of alteplase is limited by the strict time

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window and the risk of bleeding complications. Symptomatic intracranial hemorrhage (SICH) is the most feared complication of IV rtPA. It is defined both on radiographic appearance of hemorrhage and the presence of associated neurological deterioration.[2] Meanwhile, the prevalence of chronic kidney disease (CKD) in the aging population was growing and the risk of stroke in patients with CKD is increasing.[3] Renal function is not included in the current predicting scores of SICH after rtPA thrombolysis.[2] In the latest guideline for early treatment of ischemic stroke that even in patients with end-edge renal disease on hemodialysis, IV rtPA is recommended if activated partial thromboplastin time (aPTT) is normal.[4] However, it should be noted that accumulating evidence suggest renal dysfunction (RD) is a risk factor of SICH after IV rtPA.[5-8] And there are also studies which varied by races, study design and sample size, that prove the irrelevance of renal impairment and SICH.[9-12] Therefore, it is worthwhile to study the association of renal function with the symptomatic hemorrhagic complication of thrombolytic treatment.

Using data from 312 patients treated with IV rtPA, we retrospectively studied whether impaired renal function regarding reduced glomerular filtration rate (GFR) was independently with increased risk of SICH.

Materials and Methods

Study Population

The current study has been approved by the First Affiliated Hospital of SooChow University Research Ethics Committee approved (no. 2019032) and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. We retrospectively reviewed the patients receiving IV rtPA (0.9 mg/kg) from August 2016 to April 2018. The included and excluded criteria of IV rtPA were strictly adhered to the current guidelines.[4,13] Patients were excluded if they went to intra-arterial lysis (mechanical thrombectomy) after IV rtPA, or IV rtPA was halted halfway if contraindication was detected, no creatine measured on admission or no CT image after thrombolysis due to early discharge. For those patients with hemorrhagic transformation, the anticoagulation and/or antiplatelet therapy was stopped at once. All the patients received the appropriate rehabilitation guidance according to the clinical condition.

Demographic variables (age, gender); medical information (history of hypertension, diabetes mellitus, atrial fibrillation (AF), chronic heart failure, current smoking, prior stroke, antiplatelets, statins, a complete blood count, glucose, coagulation test, and admission systolic blood pressure); the National Institute of Health Stroke Score (NIHSS) before and 24 hours after thrombolysis; onset-to-treatment time, systolic blood pressure before thrombolysis were collected. Serum creatine levels (mmol/L) were measured for each patient on admission. Renal function was assessed by estimated GFR using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation: $GFR = 144 \times (SCr/.7)^{-0.329} \times (.993)^{age}$ (if female and SCr $\leq$ .7 mg/dL), $GFR = 144 \times (SCr/.7)^{-1.209} \times (.993)^{age}$ (if female and SCr $>$ .7 mg/dL), $GFR = 141 \times (SCr/.9)^{-0.411} \times (.993)^{age}$ (if male and SCr $\leq$ .9 mg/dL), and $GFR = 141 \times (SCr/.9)^{-1.209} \times (.993)^{age}$ (if male and SCr $>$ .9 mg/dL).[14]

Hemorrhagic Transformation and Symptomatic Intracranial Hemorrhage

On admission, all patients underwent a CT scan within the first 4.5 hours of stroke onset. CT was repeated within 24 hours-36 hours after IV rt-PA, or performed whenever needed. Intracranial hemorrhage (ICH) was confirmed by CT. Any ICH defines as any radiographic appearance of the hemorrhage within 24 hours after thrombolysis. Parenchymal hemorrhage was defined as hemorrhage with a mass effect according to previously published criteria.[15] SICH has numerous definitions. The current study utilized those definitions of National Institute of Neurological Disorder and Stroke (NINDS) and European Cooperative Acute Stroke Study II (ECASS II). NINDS defines SICH as any ICH with a worsening in the NIHSS score of greater than or equal to 1 point or death within 24 hours-36 hours ($SICH_{NINDS}$).[16] ECASS II defines SICH as ICH with worsening in the NIHSS greater than or equal to 4 points or death within 24 hours-36 hours ($SICH_{ECASS\ II}$).[17] CT images were reviewed and determined by one neurologist blinded to patients' medical records. Any ICH and SICH were determined by 2 neurologists independently.

Statistical Analysis

Continuous variables are presented as median with interquartile range (IQR) and categorical variables are shown in percentages. Renal function as quantified by GFR was compared with SICH as a continuous variable and as a categorical variable. For the latter, patients' GRFs were divided into 2 groups using threshold consistent with the *International Classification of Disease* for RD: no RD (GFR $\geq$ 90 ml/minute/1.73 m^2) and RD (GFR $<$ 90 ml/minute/1.73 m^2). Baseline variables on demographic and clinical data were compared by Mann-Whitney *U* tests for continuous variables and chi-square test for categorical variables. Univariable logistic regression analysis was performed to find variables that were accounted for SICH. To adjust for confounding factors with *P* less than .10, multivariable logistic regression analysis was used to assess any independent factors of SICH. Statistical analysis was performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL). Two-tailed significance values were applied, and statistical significance was defined as *P* less than .05.

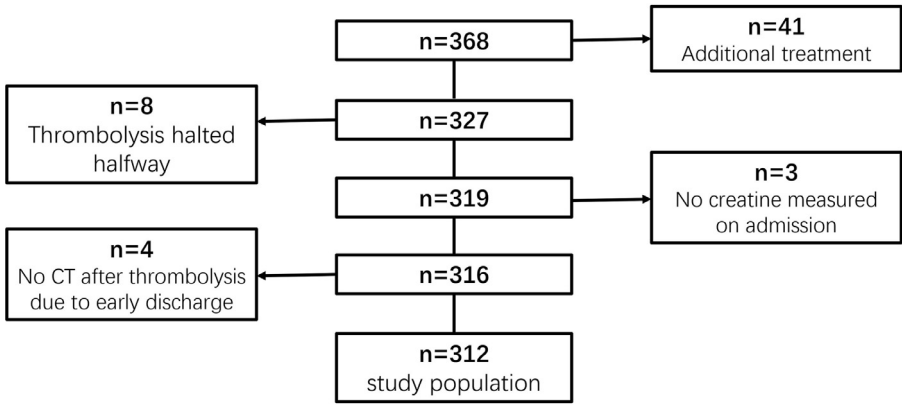

Figure 1. *The definition of the study population.*

Results

The definition of the study population is shown in Figure 1. A total of 312 patients receiving IV rtPA were enrolled. Table 1 shows the baseline demographic and clinical characteristics. The onset-to-treatment time was 170 (125-215) minutes and the initial NIHSS was 7 (3-13). Any ICH occurred in 48 (15.38%) patients. SICH rate was 7.69% (24/312) according to the criteria of NINDS and 5.45% to the criteria of ECASS II. Among 312 patients included, 164 (52.56%) presented RD (GFR < 90 ml/minute/1.73 m^2).

In relative to those who without $SICH_{NINDS}$, patients with $SICH_{NINDS}$ presented higher NIHSS on admission (13 (7-15) versus 7 (3-13), $P = .006$), higher frequency of AF (58.33% versus 23.61%, $P = .001$), lower GFR (80.84 (57.08-88.15) versus 90.21 (74.01-103.10), $P = .003$), and high prevalence of RD (87.50% versus 49.65%, $P < .001$). Furthermore, patients

Table 1. *Baseline characteristics of the study*

	Total (n = 312)	NO $SICH_{NINDS}$ (n = 288)	$SICH_{NINDS}$ (n = 24)	*P* value	NO $SICH_{ECASS\ II}$ (n = 295)	$SICH_{ECASS\ II}$ (n = 17)	*P* value
Age, y, median (IQR)	68 (60-77)	68 (60-77)	74 (65-80)	.135	68 (60-77)	73 (64-79)	.327
Male sex, n (%)	179 (57.37%)	164 (56.94%)	15 (62.50%)	.38	168 (56.95%)	11 (64.71%)	.357
NIHSS o.A, median (IQR)	7 (3-13)	7 (3-13)	13 (7-15)	**.006**	7 (3-13)	12 (7-15)	.063
Atrial fibrillation, n (%)	82 (26.28%)	68 (23.61%)	14 (58.33%)	**.001**	72 (24.41%)	10 (58.82%)	**.004**
Diabetes mellitus, n (%)	57 (18.27%)	55 (9.10%)	5 (20.83%)	.505	57 (19.32%)	3 (17.65%	.581
Hypertension, n (%)	223 (57.37%)	202 (70.14%)	21 (7.50%)	.051	209 (70.85%)	14 (82.35%)	.234
Previous stroke, n (%)	46 (14.74%)	40 (13.89%)	6 (25.00%)	.122	43 (14.58%)	3 (17.65%)	.471
Current smoking, n (%)	65 (20.83%)	59 (20.49%)	6 (25.00%)	.382	61 (20.68%)	4 (23.53%)	.488
OTT, min, median (IQR)	170 (125-215)	170 (124-215)	185 (129-249)	.205	170 (124-215)	190 (130-248)	.293
SBP, mmHg, median (IQR)	151 (137-167)	151 (136-166)	155 (140-176)	.41	152 (137-166)	150 (134-171)	.935
Glucose, mmol/L, median (IQR)	6.60 (5.64-8.08)	6.58 (5.64-7.93)	7.45 (5.63-8.85)	.135	6.60 (5.66-8.00)	6.24 (5.47-8.63)	.799
INR, median (IQR)	1.05 (.99-1.11)	1.04 (.99-1.61)	1.09 (1.03-1.15)	.059	1.04 (.99-1.11)	1.10 (1.04-1.15)	.10
Antiplatelets, n (%)	49 (15.70%)	45 (15.63%)	4 (16.67%)	.439	48 (16.27%)	1 (5.88%)	.22
Statins, n (%)	21 (6.73%)	18 (6.25%)	3 (12.50%)	.212	20 (6.78%)	1 (5.88%)	.68
Chronic heart failure, n (%)	23 (7.37%)	19 (6.60%)	4 (16.67%)	.088	20 (6.78%)	3 (17.65%)	.12
GFR, median (IQR)	88.41 (73.19-101.99)	90.21 (74.01-103.10)	80.84 (57.08-88.15)	**.003**	89.80 (73.69-102.73)	82.20 (66.76-87.69)	.068
GFR90	164 (52.56%)	143 (49.65%)	21 (87.50%)	**<.001**	149 (50.51%)	15 (88.24%)	**.002**

Abbreviations: GFR: glomerular filtration rate; GFR90: GFR < 90 ml/min/1.73 m^2; NIHSS o. A: NIH Stroke Scale on admission; OTT: onset-to-treatment time; SBP: systolic blood pressure; $SICH_{ECASS\ II}$: symptomatic intracranial hemorrhage per European Cooperative Acute Stroke Study II definition; $SICH_{NINDS}$: symptomatic intracranial hemorrhage per National Institute of Neurological Disorder and Stroke definition.

Bold value represent $P < .05$.

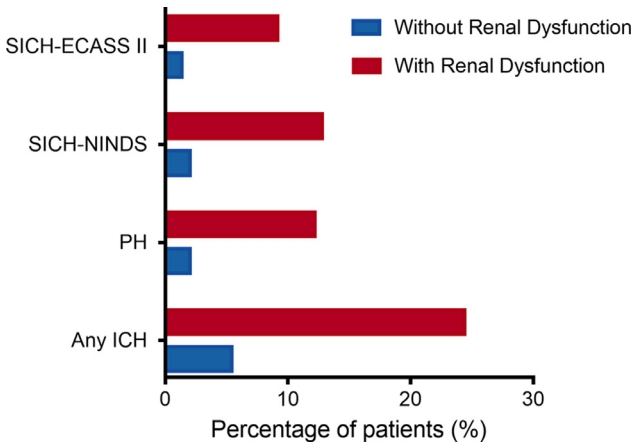

Figure 2. *Frequency of intracranial hemorrhagic complications in stroke patients after IV rtA treatment according to the categorized renal function (GFR < 90 ml/min/1.73 m^2 or not). Abbreviations: PH, parenchymal hematoma; SICH, symptomatic intracranial hemorrhage.*

with $SICH_{ECASS\ II}$ had higher prevalence of both AF (58.82% versus 24.41%, $P = .004$) and RD (88.24% versus 50.51%, $P = .002$) compared with those without.

Patients with RD developed significantly higher incidence of hemorrhage after thrombolysis both asymptomatic and symptomatic (Fig 2). RD significantly increased the incidence of any ICH (24.39% versus 5.41%, $P < .001$) and parenchymal hemorrhage (12.20% versus 2.03%, $P = .001$). The presence of $SICH_{NINDS}$ was 6.3-folds higher (12.80% versus 2.03%, $P < .001$) and that of $SICH_{ECASS\ II}$ was 6.8-folds higher (9.15% versus 1.35%, $P = .002$) in patients with RD as relative to those without RD.

In regression analysis of $SICH_{NINDS}$ (Table 2), GFR as a continuous variable ($OR_{adjust} = .98$, 95% CI = .96-.99, $P = .025$) was a predictor of $SICH_{NINDS}$ independent of the history of atrial fibrillation or baseline NIHSS before rtPA thrombolysis (Table 2, model 1). RD (GFR < 90 ml/minute/1.73 m^2) was also a significant factor ($OR_{adjust} = 4.79$, 95% CI = 1.35-17.04, $P = .016$) adjusted with history of AF and baseline NIHSS (Table 2, model 2).

In uni- and multivariate analysis for $SICH_{ECASS\ II}$ as summarized in Table 2, continuous GFR was not related to $SICH_{ECASSII}$. But RD (GFR < 90 ml/minute/1.73 m^2) was independently associated with a greater risk of $SICH_{ECASS\ II}$ with an adjusted OR of 5.36 (95% CI = 1.16-24.77, $P = .032$) with adjustment for AF. In addition, AF ($OR_{adjust} = 2.99$, 95% CI = 1.06-8.40, $P = .001$) remained significant outcome predictor for $SICH_{ECASS\ II}$.

Discussion

The present single-center study demonstrates 2 findings. First, RD increases the intracranial hemorrhagic complications of IV rtPA in patients with acute ischemic stroke. The risk of SICH increased by RD appears to be independent of history of atrial fibrillation and/or baseline NIHSS. Second, the threshold of GFR as less than 90 ml/minute/1.73 m^2 could be applied as an independent predictor of SICH after rtPA thrombolytic therapy.

Patients with RD are at an increased risk of any bleed, including SICH. This increased risk might be partially mediated by endothelial and platelet function.[18] Assumed mechanisms by which renal function affects the outcome and complications of stroke patients after thrombolysis include renal anemia, thrombocytopenia, oxidative stress, inflammation, endothelial dysfunction, and impairment of primary hemostasis.[19] Moreover, RD might worsen the

Table 2. *Univariate and multivariate analysis of clinical characteristics in patients with IV rtPA complicated with symptomatic intracranial hemorrhage*

$SICH_{NINDS}$	$OR_{unadjust}$	95% CI	*P* value	OR_{adjust}-*Model 1*	95% CI	*P* value
NIHSS o.A	1.08	1.01-1.14	.02	1.04	.97-1.11	.26
AF	4.53	1.93-10.66	.00	3.41	1.41-8.29	.007
GFR	.97	.96-.99	.003	.98	.96-.99	.03
GFR90	7.098	2.071-24.32	.002	-	-	-
$SICH_{NINDS}$	$OR_{Unadjust}$	95% CI	*P* value	OR_{adjust}-*Model2*	95% CI	*P* value
NIHSS o.A	-	-	-	1.04	.98-1.11	.241
AF	-	-	-	2.78	1.13-6.83	.026
GFR	-	-	-	-	-	-
GFR90	-	-	-	4.79	1.35-17.04	.016
$SICH_{ECASS\ II}$	$OR_{Unadjust}$	95% CI	*P* value	OR_{Adjust}	95% CI	*P* value
AF	4.425	1.625-12.048	.004*	2.99	1.06-8.40	.038
GFR90	7.349	1.651-32.705	.009*	5.36	1.16-24.77	.032

Abbreviations: AF: atrial fibrillation; GFR: glomerular filtration rate; GFR90: GFR < 90 ml/min/1.73 m^2; NIHSS o. A: NIH Stroke Scale on admission; $SICH_{ECASS\ II}$: symptomatic intracranial hemorrhage per European Cooperative Acute Stroke Study II definition; $SICH_{NINDS}$: symptomatic intracranial hemorrhage per National Institute of Neurological Disorder and Stroke definition.

*$P < .05$.

Table 3. *Summary of studies evaluating the effect of rtPA in stroke patients with and without renal dysfunction*

Studies	Definition of RD	With renal dysfunction/all	Dosage of rtPA, mg/kg	time window	Race	GFR formula	Definition of SICH	outcome assessment	Adjusted effect of renal dysfunction	SICH	REF
Lyrer et al. 2008 (n = 196)	eGFR < 90	138/196	.9	3 h	NA, from Switzerland	MDRD	NINDS	3 months	every 10 umol/l elevation in creatinine increase the odds for poorer outcomes by 12.7%	8% versus 2%, $P = .096$	9
Naganuma et al. 2011	eGFR < 60	186/578	.6	3 h	NA, from Japan	revised equation	NINDS	3 months	increased odds for SICH (OR 2.64), poor outcome (OR 1.55) and mortality (OR 2.94)	8% versus 3%, $P = .004$	21
Chao et al. 2013	eGFR < 60	65/297	.9	3 h	NA, from Taiwan	MDRD	NINDS and ECASS	1 month and 1 year	RD did not independently predict ICH.	23% versus 12.5%, $P < .05$	22
Gensicke et al. 2013	eGFR < 60	1217/4780	NA	NA	NA, from 11 European centers	CKD-EPI	ECASS II and NINDS	3 months	associated with poor 3-month outcome and SICH (OR 1.64)	OR 1.11, $P = 0{,}003$	8
Marsh et al. 2013	serum creatnine > 1.0 mg/dL	113/224	.9	4.5 h	32% American Black	MDRD	NINDS	1 day	an adjusted 5.5-fold increased odds of SICH when creatinine was >1.0 mg/dL	10.6% versus 1.8%, $P = .010$	5
Power et al. 2013	eGFR < 60	65/229	.9	4.5 h	White 66.4%, south Ascian 21.8%	CKD-EPI	ECASS II	7 days	associated with reduction to therapeutic effect of alteplase	6.2% versus 6.7%, $P = .90$	10
Tariq et al. 2013	dialysis-dependent renal failure	1072/82,142	NA	NA	White 54.6%, African-American 29%, Hispanic 9%, other 7.4%	NA	(ICH)	in-hospital	associated with higher rates of in-hospital mortality	5.2% versus 6.1%, $P = .50$	24
Tutuncu et al. 2013	any RI (eGFR < 90) and Severe RI (GFR < 30)	614/740 (any RI) and 37/740 (severe RI)	.9	4.5 h	NA, from Germany	CKD-EPI	ECASS II	in-hospital	Severe RI (OR 3.75) and GFR (centered and squared) independently associated with SICH	15% versus 4%, $P < .01$	6

(*Continued*)

Table 3 (*Continued*)

Studies	Definition of RD	With renal dysfunction/all	Dosage of rtPA, mg/kg	time window	Race	GFR formula	Definition of SICH	outcome assessment	Adjusted effect of renal dysfunction	SICH	REF
Hsieh et al. 2014	eGFR < 60	239/659	.6/.9	4.5 h	NA, from Taiwan	CKD-EPI	NINDS	3 months	No differences in SICH and poor outcome between patients with and without renal dysfunction	8% versus 7%, $P = .56$	12
Ovbiagele et al. 2014	eGFR < 60	15,191/44,410	NA	4.5 h	white 72.1%, black 14.7%, hispanic 7%	MDRD	NINDS	in-hospital	higher unadjusted odds of symptomatic intracranial hemorrahge (OR 1.0, .91-1.10) or serious systemic hermorrhage (OR .97, .80-1.18)	5.42% versus 4.21%, $P < .0001$	23
Carr et al. 2017	severe RI (eGFR < 30)	659/3220	.6/.9	4.5 h	63.51% Asian	CKD-EPI	SITS-MOST, NINDS, ECASS II et. al	90 days	severe RI associated with increased mortality but not SICH	ECASS II criteria 3.0% versus 5.0%, NINDS criteria 5.0% versus 8.0%	11
Sadeghi-Hokmabadi et al. 2017	eGFR < 45	57/403	.9	4.5 h		CKD-EPI	ECASS II	90 days	independently associated with poor outcome but not SICH	3.5% versus 7.0%, $P = .323$	25
Present Study	eGFR < 90	164/312	.9	4.5 h	Chinese	CKD-EPI	NINDS, ECASS II,	in-hospital	RD (GFR < 90) as independent risk factor for SICH	NINDS criteria: 12.80% versus 2.03%, $P < .001$	

outcome of stroke after IV rtPA through impairing endothelial release of t-PA and increasing plasminogen activator inhibitor-1 activity.[20]

Renal function was not included in the current predicting risk scores of symptomatic hemorrhage after thrombolysis.[2] The impact of renal function on hemorrhagic transformation after IV rtPA in stroke patients had not been satisfactorily investigated. We reviewed 12 studies addressing this question in Table 3. Studies consistently revealed that renal impairment independently predicted poor outcome in stroke patients after thrombolysis. As for the association between RD and SICH post IV rtPA thrombolysis in acute stroke patients, 4 studies suggested SICH occurred significantly more often in patients with RD,[5,6,8,21] 2 studies revealed nonsignificantly important tendency,[22,23] whereas 6 other studies could not find such an association.[9-12,24,25] The discrepancies might be due to the relatively small sample sizes in some studies (N = 200-600). One previous large cohort multicenter study (N = 4780) investigated the impact of renal function in IV-rtPA treated stroke patients revealed that renal function was a strong predictor for SICH. In patients with GFR, the risk of SICH occurred 1.4-1.7 fold more frequently.[8] To date, the largest description and analysis of SICH among IV rtPA patients with CKD, the US National Get With The Guidelines-Stroke (GWTG-Stroke) registry data (N = 44,410) suggested that presence of chronic kidney disease (GFR < 60 ml/minute/1.73 m^2) among stroke patients treated with IV rtPA is associated with unadjusted odds of symptomatic intracranial hemorrhage (adjusted OR 1.0, 95%CI .91-1.10) or serious systemic hemorrhage (adjusted OR .97, 95% CI .80-1.18).[23] The GWTG analysis failed to observe any independent relationships between presence of CKD and occurrence of SICH in rtPA treated patients. However, it should be noted that as for patients included in that study, 72.1% were white, 14.7% black and 7.0% Hispanic. Hence, it is questionable to transfer the results directly to an Asian population who are considered at high SICH risk.[26] Moreover, one study originated from Japan (N = 578) demonstrated that RD was independently related to any ICH, SICH, poor outcome and mortality.[21] The differences might also be attributable to variations in the methodological differences such as formula used to estimate GFR, i.e., modification of diet in renal disease (MDRD) and CKD-EPI in our study. The CKD-EPI formula has been shown to more accurately categorize the risk for mortality and end-stage renal disease than did the MDRD study equation across a broad range of population.[27]

Furthermore, we revealed that even mild RD predicted higher risk of SICH. A new cutoff point of 90 ml/minute/1.73 m^2 was reached and applied instead of 60 ml/minute/1.73 m^2 [8,21,23] or 30 ml/minute/1.73 m^2 [6,11], which had been reported in previous studies. Study by Lyrer et al also applied GFR less than 90 ml/minute/1.73 m^2 as threshold of RD. However, in that small sampled study in Switzerland, no significantly important association was reached.[9] The current study was retrospective in design; therefore, causality could not be proven. However, our evidence suggested that GFR less than 90 ml/minute/1.73 m^2 was an independent risk factor for SICH in small sample number of Chinese populations. It thereby might be considered as an important risk factor in future studies.

Certain limitations of the study have to be considered. First, it is a retrospective analysis of relatively small number of patients. The frequency of outcome event (SICH) was too low, in particular in the non-RD group. It might cause inappropriate statistical analysis. Second, this is a single-center study restricting generalization. Third, GFR was calculated on the basis of one serum creatinine recorded on the day of admission. Equations for estimating GFR do not account for potential dynamics in ongoing acute kidney injury and could not tell chronic renal disease from acute kidney injury.

Summary and Conclusion

In conclusion, the current study argues that patients with even mild degree of renal impairment (GFR < 90 ml/minute/1.73 m^2) might have an increased risk of developing SICH after IV rtPA within 4.5 hours of acute ischemic stroke onset. When calculating the risk of rtPA thrombolysis, especially in Chinese population, renal function should be taken into consideration. And still, larger, multi-centered studies are needed to verify the impact of RD and its reflection point at which the risk of SICH might outweigh its potential benefit in different races.

Author Contributions

J.Z., X.C. and Q.F. designed research and wrote the manuscript. J.Z., X.S., C.H., C.M., Y.Z. and H.W. collected the data. Y.J., and Y.K., analyzed the data.

Ethical Approval

All procedures performed in the current study involving human participants were in accordance with the ethical standards of the First Affiliated Hospital of SooChow University Research Ethics Committee (no. 2019032) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable standards.

Data Availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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