

Renal Dysfunction and Thrombolytic Therapy in Patients With Acute Ischemic Stroke

A Systematic Review and Meta-Analysis

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Abstract: Renal dysfunction is a prevalent comorbidity in acute ischemic stroke patients requiring thrombolytic therapy. However, the effect of renal dysfunction on the clinical outcome of this population remains controversial.

This study aimed to evaluate the safety and effectiveness of thrombolytic therapy in acute stroke patients with renal dysfunction using a meta-analysis.

We systematically searched PubMed and EMBASE for studies that evaluated the relationship between renal dysfunction and intravenous tissue plasminogen activator (tPA) in patients with acute ischemic stroke. Poor outcome (modified Rankin Scale ≥ 2), mortality, and symptomatic intracranial hemorrhage (ICH) and any ICH were analyzed.

Fourteen studies were included (N = 53,553 patients). The mean age ranged from 66 to 75 years. The proportion of male participants was 49% to 74%. The proportion of renal dysfunction varied from 21.9% to 83% according to different definitions. Based on 9 studies with a total of 7796 patients, the meta-analysis did not identify a significant difference in the odds of poor outcome (odds ratio [OR] = 1.06; 95% confidence interval [CI]: 0.96–1.16; $I^2 = 44.5$) between patients with renal dysfunction and those without renal dysfunction. Patients with renal dysfunction were more likely to die after intravenous thrombolysis (OR = 1.13; 95% CI: 1.05–1.21; $I^2 = 70.3$). No association was observed between symptomatic ICH (OR = 1.02; 95% CI: 0.94–1.10; $I^2 = 0$) and any ICH (OR = 1.07; 95% CI: 0.96–1.18; $I^2 = 25.8$).

Renal dysfunction does not increase the risk of poor outcome and ICH after stroke thrombolysis. Renal dysfunction should not be a

contraindication for administration of intravenous thrombolysis to eligible patients.

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Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, mRS = modified Rankin Scale, NG = not given, NOS = Newcastle-Ottawa Scale, OR = Odds Ratio, sICH = symptomatic intracerebral hemorrhage, tPA = tissue plasminogen activator.

INTRODUCTION

Thrombolytic therapy with intravenous tissue plasminogen activator (tPA) is an effective treatment of acute ischemic stroke in patients presenting within 3 or 4.5 hours of onset of symptoms.^{1,2} More than one third of acute stroke patients have comorbidity of chronic kidney disease (CKD), defined as the presence of reduced estimated glomerular filtration rate (eGFR) or kidney injury.³ Stroke patients with renal dysfunction are more likely to have a poor outcome in the natural course.^{3–5} Although current guidelines do not include renal dysfunction as a contraindication to tPA therapy, some clinicians hesitate to administer tPA because of a tendency of bleeding in these patients.^{6,7} The real risk and benefit of thrombolytic therapy in this high-risk population are unknown. Reports on the relationship between renal dysfunction and the risk of poor outcome and symptomatic intracerebral hemorrhage (sICH) are contradictory.^{8–11} The effectiveness and safety of thrombolysis in patients with renal dysfunction has not been clearly determined.

Therefore, we aimed to perform a systematic review to evaluate the evidence of the safety and effectiveness of thrombolytic therapy in acute stroke patients with renal dysfunction.

METHODS

Search Strategy and Eligibility Studies

We systematically searched PubMed and EMBASE (from its earliest date to August 2014) for studies that evaluated the relationship between renal dysfunction and intravenous tPA in patients with acute ischemic stroke. The terms “renal dysfunction,” “kidney dysfunction,” “renal impairment,” “eGFR,” “creatinine,” “urea,” “estimated glomerular filtration rate,” “thrombolysis,” “recombinant tissue plasminogen activator,” and “rt-PA” (recombinant tissue plasminogen activator) were combined using “and” or “or” for searching relevant studies. The bibliographies of relevant articles were screened. Only studies that met the following criteria were included: (1) they

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ZH and ML designed the study. ZH and CY performed the literature searches and data extraction. ZH wrote the first draft of the manuscript. All authors helped to organize the information, and wrote and edited subsequent drafts of the manuscript.

The authors have no competing interests to declare.

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evaluated the association between renal dysfunction and the outcome of intravenous thrombolysis; (2) at least one of following outcomes was reported: modified Rankin Scale (mRS), mortality, or intracerebral hemorrhage (ICH); and (3) results were reported in a manner that allowed calculation of the odds ratio (OR) for outcomes. Articles were excluded if they were case reports. In case of multiple publications from the same study population, only the report with the most complete data was included. Our study was a systematic review of published studies. Therefore ethical approval was not required.

Selection of Studies and Extraction of Data

One reviewer independently screened the titles and abstracts of every record. The full articles were obtained when the information provided in the title or abstracts conformed to the selection criteria outlined above. Two reviewers independently performed extraction of data and compared the results. The following data were extracted: (1) general characteristics of the studies and participants, (2) sample size, (3) the diagnostic criteria for renal dysfunction, and (4) outcome measurements (eg, mRS, mortality, and ICH). Articles that met all of the inclusion criteria, but specific data extraction was not possible, were defined as “NG” (not given). Discrepancies were resolved by consensus.

Quality Assessment and Statistical Methods

We performed quality assessment using the Newcastle–Ottawa Scale (NOS) for cohort studies.¹² The NOS uses a “star” rating system to judge quality based on 3 aspects of the study: selection of participants, comparability of study groups, and outcome of interest. The maximum number of stars that a study may receive in each of these 3 categories is 4, 2, and 3, respectively. The highest-quality study receives 9 stars. We extracted adjusted ORs from logistic regression models reporting the association between renal dysfunction and outcomes after intravenous thrombolysis treatment or calculated the ORs for outcomes. We evaluated heterogeneity among included studies using the I^2 test. We considered a value greater than 50% to indicate substantial heterogeneity. Regardless of the size of heterogeneity, the random effects model was used for statistical analysis. We conducted the meta-analysis using STATA 11.0.

RESULTS

Identified Studies

The selection of studies is shown in Figure 1. The initial literature search identified 1328 relevant articles. After reading the titles and abstracts, we retained 26 studies for further assessment. Of these, we excluded 13 studies.^{13–25} A recently published study was included.²⁶ Ultimately, 14 studies, containing 53,553 patients, were included in this systematic review.^{8–11,27–35}

Characteristics of the Included Studies

Five studies were performed in Europe, 5 in Asia, 3 in the United States, and 1 in Australia. The number of participants ranged from 74 to 44410. The mean age of participants ranged from 66 to 75 years. The proportion of male participants was 49% to 74% among these trials. The proportion of renal dysfunction varied from 21.9% to 83% according to different

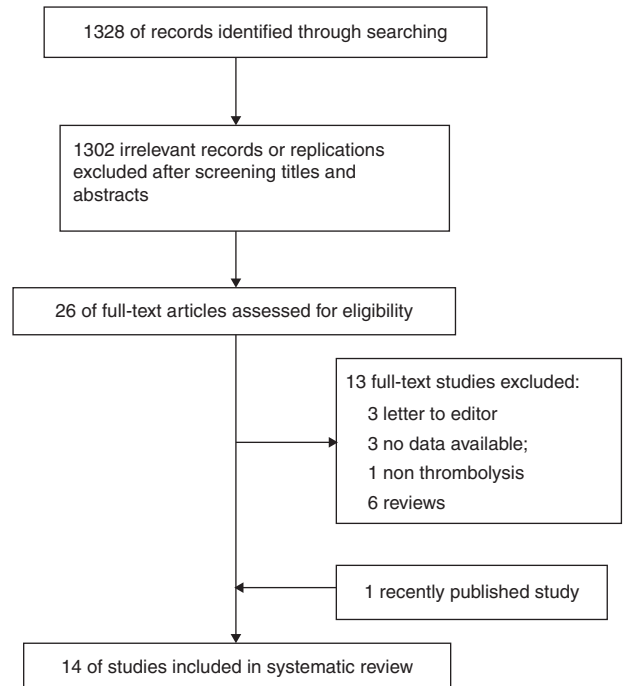


FIGURE 1. Flow chart of literature screening and selection process.

definitions, including eGFR, creatinine, proteinuria, and micro- and macro-albuminuria. Further details are summarized in Table 1. The number of stars of studies as assessed by the NOS was more than 7.

Poor Outcome at the End of the Follow-Up Period

Nine studies reported a poor outcome at the end of the follow-up period (Table 2). The cut-off to define a poor outcome was an mRS ≥ 2 (3 studies), 3 (4 studies), and 4 (2 studies). Based on 9 studies with a total of 7796 patients, the meta-analysis did not identify a significant difference in the odds of a poor outcome (OR = 1.06; 95% confidence interval [CI]: 0.96–1.16; $I^2 = 44.5$) between patients with renal dysfunction and those without renal dysfunction (Figure 2).

Mortality

Nine studies (N = 51476 patients) reported the mortality in hospital or at the end of the follow-up period (Table 2). Meta-analysis showed that patients with renal dysfunction were more likely to die after intravenous thrombolysis (OR = 1.13; 95% CI: 1.05–1.210; $I^2 = 70.3$) (Figure 3).

Occurrence of sICH and any ICH

Twelve studies (N = 53175 patients) reported the occurrence of sICH (Table 2). The definition of sICH varied among the different studies (Table 3). Meta-analysis showed that there was no association of sICH (OR = 1.02; 95% CI: 0.94–1.10; $I^2 = 0$) between patients with renal dysfunction and those without renal dysfunction (Figure 4). There was also no association of any ICH (OR = 1.07; 95% CI: 0.96–1.18; $I^2 = 25.8$) between patients with renal dysfunction and those without renal dysfunction.

TABLE 1. Characteristics of Studies on Intravenous tPA-Treated Patients With Renal Dysfunction

Study	Study type	N	Site	Time (hours)	Age	Male, %	Renal dysfunction	Proportion of renal dysfunction	Dose of t-PA (mg/Kg)	Outcome assessment
Sobolewski ⁹	Retrospective multicenter study	404	Poland	4.5	70.2 (12.0)	216, 53.5%	eGFR < 60 ml/min/1.73 m ²	117, 29.0%	0.9	3 months
Chao ²⁷	Retrospective study	297	Taiwan	3	70 (118)	45, 69%	eGFR < 60 ml/min/1.73 m ²	65/297, 21.9%	0.9	1 year
Hsieh ²⁸	Prospective multicenter study	657	Taiwan	4.5	62.8 (12.9)	146, 63%	eGFR < 60 ml/min/1.73 m ²	239/657, 36.4%	0.6–0.9	3 months
Agrawal ⁸	Retrospective single study	74	US	3	71 (10)	64%	eGFR < 60 ml/min/1.73 m ²	20/74, 27%	0.9	In hospital
Power ^{23,29}	Retrospective multicenter study	229	UK	4.5	65 (13)	61%	eGFR < 60 ml/min/1.73 m ²	65/229, 28.4%	0.9	In hospital
Naganuma ³⁰	Retrospective multicenter study	578	Japan	3	70 (13)	135/229, 59%	eGFR < 60 ml/min/1.73 m ²	186/578, 32.2%	0.6	3 months
Tüüncü ³¹	Retrospective study	740	Germany	4.5	71.4 (11.7)	372/578, 64.6%	eGFR < 90 ml/min/1.73 m ²	83%	0.9	In hospital
Gensicke ¹¹	Multicenter Cohort study	4780	European	3	75 (66–83)	391/740, 53%	eGFR < 30 ml/min/1.73 m ²	1217/4780, 25.5%	0.9	3 months
Marsh ³²	Retrospective study	224	US	4.5	71 (60–79)	2657/4780, 55.6%	eGFR < 60 ml/min/1.73 m ²	113/224, 50.4%	0.9	In hospital
Zhang ³³	Retrospective study	378	Australia	NG	66.8	49%	Creatinine > 1.0 mg/dL	157/378, 41.5%	0.9	3 months
Lyster ¹⁰	Retrospective study	196	Switzerland	3	72 (62–81)	54.2%	eGFR < 60 ml/min/1.73 m ²	138/196, 70.4%	0.9	3 months
Chen ³⁴	Multicenter cohort study	432	Taiwan	4.5	66.7 (15.2)	58%	eGFR < 90 ml/min/1.73 m ²	155/432, 35.9%	0.6–0.9	3 months
Cho ³⁵	Retrospective study	154	Korea	3.0	67.2 (12.2)	263/42, 60.9%	eGFR < 60 ml/min/1.73 m ²	132/404, 32.7%	0.9	In hospital
Ovbiagele ²⁶	Multicenter cohort study	44410	US	4.5	69.6 (12.32)	114/154, 74.3%	Micro- and macroalbuminuria, which are defined as urinary albumin-to-creatinine ratios (UACRs) of 30–300 mg/g and over 300 mg/g	15191/44410, 34.2%	0.9	In hospital

eGFR = estimated glomerular filtration rate, NG = not given, tPA = tissue plasminogen activator.

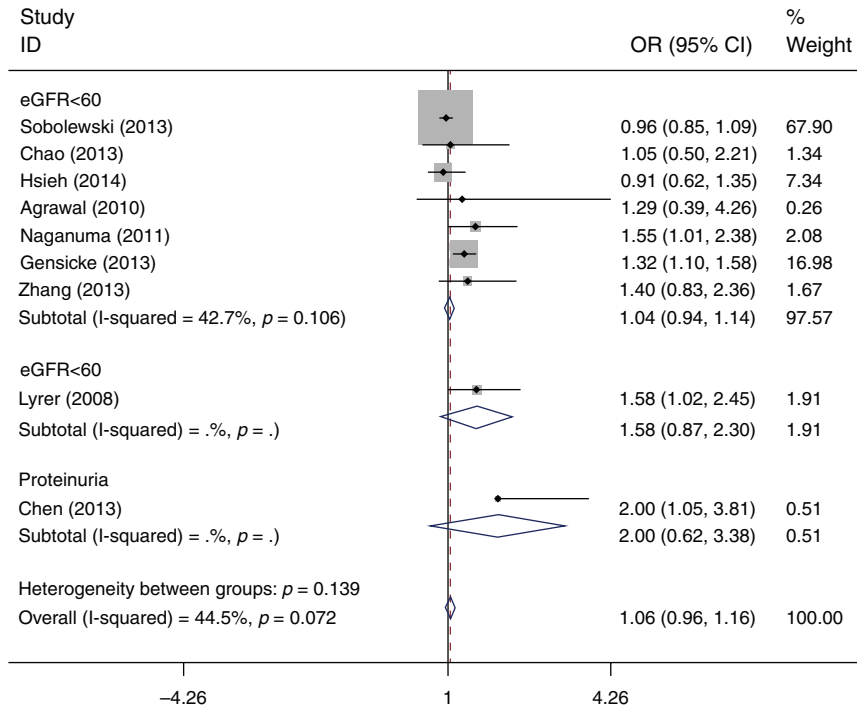


FIGURE 2. Odds ratio for poor outcome of intravenous rtPA-treated patients with renal function compared with those without renal dysfunction.

DISCUSSION

This systematic review showed that the prevalence of renal dysfunction in acute ischemic stroke varied from 21.9% to 83% according to different definitions. Meta-analysis showed that renal dysfunction did not increase the risk of a poor outcome and ICH after stroke thrombolysis. However, patients with renal dysfunction were more likely to die after intravenous thrombolysis.

The quality of reporting in general was good. The main problem was that most of the studies did not represent the population well. The statistical heterogeneity in outcome measurements was probably related to different baseline characteristics of the participants, different methods of evaluating renal function, and different classifications of renal dysfunction.

The prevalence of CKD is increasing. Studies have shown that the incidence of CKD in people with cardiovascular disease is higher than that in healthy people, and it is an independent risk factor for recurrence of cardiovascular disease and death.³⁶ Several studies have recently found that renal dysfunction increases the risk of stroke.^{37,38} Renal dysfunction can also predict short-term and long-term case fatality rates in patients with stroke.⁴ Impairment in small vessel vasculature, atherosclerotic changes in large vessels, and coagulation abnormalities in CKD probably underlie the specific characteristics of stroke in these patients.^{10,16} Therefore, we speculate that CKD patients probably have worse bleeding complications compared with those without CKD, thus increasing poor outcomes. Lyrer et al¹⁰ found that impaired renal function before thrombolysis is associated with an increased odds for a poor outcome and there is a trend for more sICH

compared with stroke patients with normal renal function. A retrospective, multicenter, observational study that was conducted in Japan also showed that reduced eGFR was associated with early ICH and a 3-month unfavorable outcome in stroke patients receiving intravenous tPA.³⁰ In contrast, another study showed that the presence of an eGFR <60 ml/min/1.73 m² was not associated with increased ICH, poor functional outcome, or death.⁸ Recently, Ovbiagele et al²⁶ showed that there was no independent relationship between the presence of CKD and occurrence of sICH in patients with intravenous rt-PA. However, they found that patients with CKD were more likely to die in the hospital because of the presence of other harmful conditions, such as anemia, oxidative stress, electrolyte imbalances, and chronic inflammation.²⁶ Our results on studies of the association between renal dysfunction and outcomes in patients with acute ischemic stroke receiving intravenous tPA showed that the presence of renal dysfunction was not associated with increased ICH or a poor functional outcome. Patients with renal dysfunction were more likely to die after intravenous thrombolysis. Notably, more than 50% of the data from our analysis including 44,410 participants and with the greater proportion of patients had CKD stages 3 to 4 versus stage 5.

The main limitation of the study is that most of the included studies were retrospective and causality cannot be proved. Second, renal function, represented by eGFR, was estimated using the Modification of Diet in Renal Disease (MDRD) formula instead of direct laboratory measurements. This difference between true GFR and eGFR may have led to misclassification of some of the subjects. However, eGFR was easily obtained before thrombolysis and served as a practical reference of renal function.

TABLE 2. Outcomes of Studies on Intravenous tPA-Treated Patients With Renal Dysfunction

Study	Quality NOS	mRS					Death	Any ICH	sICH
		2-6	3-6	4-6	4-6	4-6			
Sobolewski ⁹	4/2/2, 8	NG	61/117, 52.1% 119/287, 41.5%	NG	35/117, 29.9% 41/287, 14.3%	NG	NG	5/117, 4.3% 17/287, 5.9%	
Chao ²⁷	4/2/2, 8	NG	0.96, 0.85-1.09 1.05, 0.5-2.21	NG	0.91, 0.78-1.06 NG	NG	NG	0.72, 0.27-1.91 5/65, 7.7% 9/232, 3.9%	
Hsieh ²⁸	4/1/2, 7	NG	NG	0.91, 0.62-1.35	NG	NG	NG	1.98, 0.69-5.71 8% vs 7% 1.03, 0.55-1.92 0/20	
Agrawal ⁸	4/1/2, 7	2.356, 0.540-10.271	14/20, 70% 31/54, 57.4% 1.29, 0.39-4.26*	NG	1.55, 0.23-10.53	NG	NG	0.52, 0.03-10.46 3/65, 1.8% 6/164, 3.7%	
Powet ^{23,29}	4/1/3, 8	NG	NG	NG	NG	NG	4/65, 6.2% 11/164, 6.7%	2/54, 3.7%	
Naganuma ³⁰	4/2/2, 8	NG	NG	89/186, 47.9% 136/392, 34.7%	25/186, 13.4% 15/392, 3.8%	NG	0.92, 0.30-2.78	15/186, 8.1% 10/392, 2.6%	
Tütüncü ³¹	4/1/2, 7	NG	NG	1.55, 1.01-2.38 NG	2.94, 1.38-6.42 NG	NG	1.81, 1.16-2.84 6/48, 12.5% 33/696, 4.7%	2.64, 1.10-6.56 6/34, 17.5% 33/710, 4.6%	
Gensicke ¹¹	4/2/3, 9	NG	1.32, 1.10-1.58	NG	1.73, 1.39-2.14	NG	For <30, P=0.02	For <30, P < 0.01	
Marsh ³²	4/2/2, 8	NG	NG	NG	11/113, 9.7% 3/111, 2.7%	NG	42/48, 87.5% 574/696, 82.3%	29/34, 85.3% 587/710, 82.7%	
Zhang ³³	4/1/2, 7	1.40, 0.83-2.36	NG	NG	3.60, 1.03-12.56	NG	For <90, P=0.74	For <90, P=0.74	
Lyrer ¹⁰	4/1/2, 7	NG	64/138, 46.4% 17/58, 29.3% 1.58, 1.02-2.45	NG	2.57, 1.33-4.97 22/138, 15.9% 4/58, 6.9%	NG	1.06, 0.95-1.19	1.03, 0.89-1.19 1.64, 1.21-2.23 12/113, 10.6% 2/111, 1.8%	
Chen ³⁴	4/1/2, 7	2.0 (1.05-3.81)	NG	NG	2.31, 0.83-6.41 12/132, 9.1% 15/272, 5.5%	NG	0.83, 0.50-1.38	5.89, 1.35-25.73 NG 11/138, 8.0% 1/58, 1.7%	
Cho ³⁵	4/2/2, 8	NG	NG	NG	1.65, 0.79-3.42	NG	1.95 (1.10-3.46)	4.62, 0.61-34.99 1.07 (0.37-3.08)	
Ovbiagele ²⁶	4/1/2, 7	NG	NG	NG	1.19 (1.09-1.30)	NG	NG	5.867 (1.050-32.785) 0.99 (0.89-1.09)	

mRS = modified Rankin Scale, NG = not given, NOS = Newcastle-Ottawa Scale, sICH = symptomatic intracerebral hemorrhage.

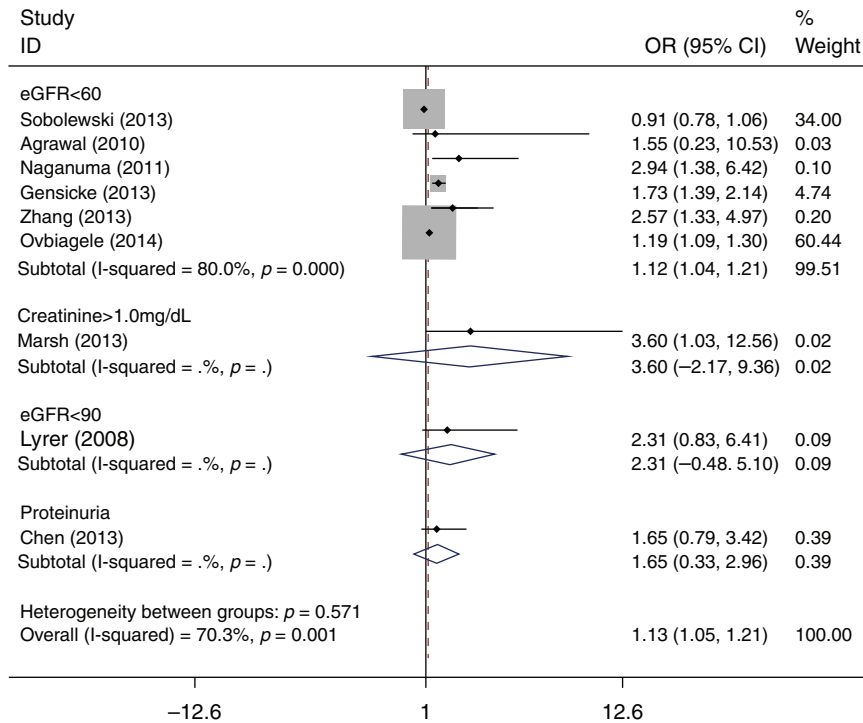


FIGURE 3. Odds ratio for mortality of intravenous rTPA-treated patients with renal function compared with those without renal dysfunction.

TABLE 3. The Definition of sICH in Included Studies

Study	Definition
Sobolewski ⁹	ECASS II criteria
Chao ²⁷	ECASS criteria (any ICH ≥ 36 hours and NIHSS worsening by ≥4) and radiologically detected type 1 and type 2 parenchymal hemorrhage (any pH) within 36 hours after thrombolysis
Hsieh ²⁸	NINDS criteria (any neurological deterioration and hemorrhage in follow-up imaging)
Agrawal ⁸	NINDS criteria
Power ^{23,29}	ICH was classified as symptomatic if there was concurrent neurological deterioration as documented in the note of the ordering physician
Naganuma ³⁰	Defined by a deterioration in NIHSS score ≥4
Tütüncü ³¹	NINDS criteria
Gensicke ¹¹	ECASS criteria
Marsh ³²	ECASS II criteria
Lyrer ¹⁰	a patient was determined to have a symptomatic hemorrhage if he or she had subjective clinical deterioration (documented by the primary neurology team) and hemorrhage on neuroimaging that was felt to be the most likely cause
Chen ³⁴	NINDS criteria
Cho ³⁵	Symptomatic hemorrhage was defined as a neurological deterioration (NIHSS ≥ 4 points) within 36 hours with no radiological findings that might have been responsible for this deterioration other than a hemorrhage
Ovbiagele ²⁶	NINDS criteria
	ECASS criteria
	SITS-MOST trials (PH grade 2 and increase in NIHSS scores by 4 or more)
	sICH was defined as neurological worsening within 36 hours of tPA administration that is attributed to ICH verified by computed tomography or MRI, as documented in the chart by the treating physician.

ECASS=European Cooperative Acute Stroke Study, NIHSS=National Institutes of Health Stroke Scale, NINDS=National Institute of Neurological Disorders and Stroke, PT=Parenchymal hemorrhage, sICH=symptomatic intracerebral hemorrhage, SITS-MOST=safe implementation of thrombolysis in stroke-monitoring.

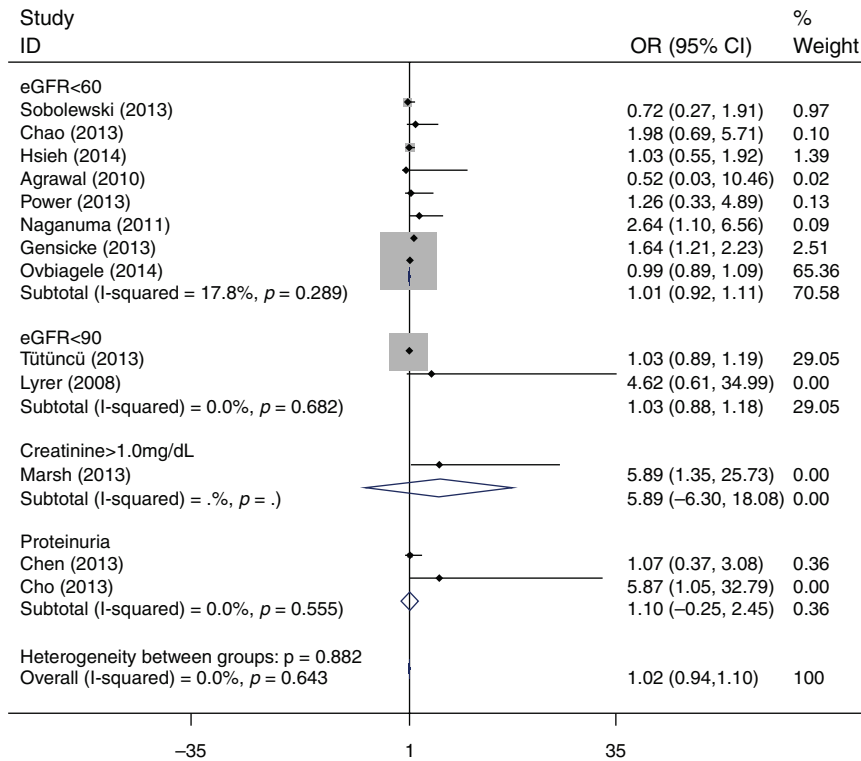


FIGURE 4. Odds ratio for sICH of intravenous rtPA-treated patients with renal function compared with those without renal dysfunction.

Third, there was lack of adjustment for baseline differences. Fourth, there was no consensus definition of renal dysfunction and sICH. Finally, there was a lack of individual patient data and a limited number of trials. Therefore, we were not able to assess whether there were significant differences in treatment effects in important subgroups, such as patients treated within 3 hours compared with those treated later.

CONCLUSIONS

Renal dysfunction does not increase the risk of poor outcome and ICH after stroke thrombolysis. Renal dysfunction should not be a contraindication for administration of intravenous thrombolysis to eligible patients.

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