

Low Estimated GFR Predicts Hemorrhagic Complication in Acute Ischemic Stroke: A Meta-analysis

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ABSTRACT

Introduction

Intracerebral hemorrhage (ICH) can occur in patients following acute ischemic stroke (AIS) and results in significant long-term morbidity and mortality. Patients with renal impairment have a higher risk of bleeding. Therefore, AIS patients with renal impairment may have a higher risk of such complications. We performed a meta-analysis of observational studies to determine the relationship between renal impairment and hemorrhagic complications in patients with AIS.

Methods

This meta-analysis was conducted following the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. PubMed, Google Scholar, Web of Science and China National Knowledge Infrastructure (CNKI) were searched to identify studies published between 1995 and 2020. Relative risk estimates of all the included studies were pooled to calculate pooled OR and 95% confidence intervals.

Results

Fourteen studies involving 10,033 AIS patients from Asia, Europe, and North America were included. We found that patients with renal impairment as indicated by low eGFR had a higher odds of developing any ICH (OR: 1.7; 95% CI: 1.13 to 2.57; $p=0.011$; $I^2=87.2\%$) following AIS. Similarly, we found that patients with renal impairment had a higher odds of developing symptomatic ICH (SICH) (OR: 1.7; 95% CI: 1.32 to 2.17; $p<0.001$; $I^2=37.3\%$) following AIS.

Conclusion

There is an increased odds of developing any ICH and SICH in AIS patients with renal impairment.

Keywords

Acute ischemic stroke, glomerular filtration rate, hemorrhagic transformation

INTRODUCTION

According to global burden of disease 2019 study, globally, stroke remained the second-leading cause of death and the third-leading cause of death and disability combined and acute ischemic stroke (AIS) constituted 62.4% of all incident strokes.¹ AIS is often complicated by subsequent hemorrhagic complications which occurs in 13% to 43% of patients following ischemic brain injury.² Following AIS, there is breakdown of the blood–brain barrier resulting in friable intracranial vasculature. This breakdown theoretically increases the risk of intracerebral hemorrhage (ICH), specifically into the area of ischemia. Unfortunately, little data exist to suggest how long this friability lasts or what other factors may contribute. The severity of ICH may range from subtle petechial hemorrhage within the infarcted tissue to a large parenchymal hematoma extending beyond the borders of the infarction. Thus, the patient may be symptomatic with clinical deterioration (referred to as symptomatic intracerebral hemorrhage (SICH)) or may be asymptomatic.^{2,3}

While significant advances have been made in the treatment of stroke over recent decades, these treatment options are not without risks.⁴ Identifying predictors of hemorrhagic complications could be important especially when interventional management like tissue plasminogen activator (tPA) and endovascular therapy is increasingly being used.^{2,4} While these modalities increase the recanalization rate and improve functional outcomes, they are associated with an increased risk of hemorrhagic complications.^{4,5}

Renal function is an important predictor of mortality

and other vascular events in patients with AIS.⁶ Patients with poor renal function have associated endothelial and platelet dysfunction and thus are at an increased risk for both thrombotic and hemorrhagic events.⁷ AIS patients with renal impairment might be at higher risk of hemorrhagic complications if treated with tPA, however this association is still debatable. Various studies have been conducted to establish this relationship between renal impairment and hemorrhagic complications yielding non-uniform results.^{3,8–20} Given this variation in results from prior individual studies, we conducted this meta-analysis to determine if there is an association between renal impairment as indicated by low estimated glomerular filtration rate (eGFR) and hemorrhagic complication in adult AIS patients receiving either t-PA or conventional therapy.

METHODS

This current meta-analysis was conducted following the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²¹ We searched multiple electronic bibliographic databases (PubMed, China National Knowledge Infrastructure, Google Scholar, and Web of Science) to identify studies published from 1995 to December 2020. For this purpose, we used the following search terms: (“eGFR” OR “estimated glomerular filtration rate” OR “renal dysfunction” OR “renal impairment”) AND (“hemorrhagic transformation” OR “hemorrhage” OR “intracerebral hemorrhage” OR “ICH” OR “symptomatic intracerebral hemorrhage” OR “SICH”) AND (“acute ischemic stroke” OR “AIS”). For advanced PubMed search, the medical subject headings

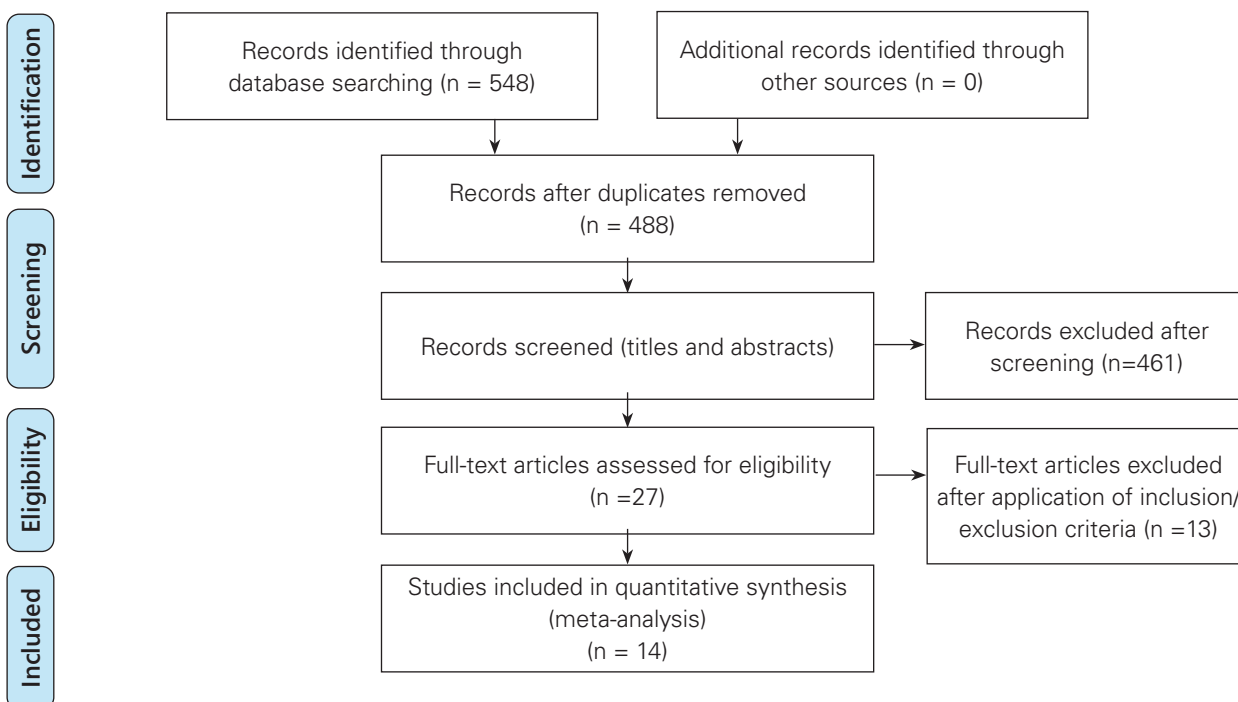


Figure 1. PRISMA flow diagram

(MeSH) database was used to find MeSH terms for the aforementioned search terms. The search was also broadened to include preprint servers and thesis repositories, hand-searching the reference lists from the selected articles for any additional references.

Eligibility criteria

The inclusion criteria were: 1) case-control or cohort studies; 2) studies that assessed the relationships between renal impairment (low eGFR) and hemorrhagic complication (any ICH or SICH) following AIS; 3) studies that reported risk estimates with 95% confidence intervals (CI) or provided information that enabled them to be calculated. The exclusion criteria were: 1) Case reports, reviews, letters, editorials, and commentaries, 2) studies that provided no relevant data to assess the association between renal impairment (low eGFR) and hemorrhagic complication following AIS.

Study Selection

All shortlisted studies were imported to Mendeley library and duplicates were removed appropriately. A subsequent manual check was done with the removal of the remaining duplicates where applicable. Two reviewers (GN and JY) independently reviewed the titles and abstracts for all the identified references. They excluded any articles that did not appear to meet the inclusion criteria. The same reviewers applied the inclusion criteria to the articles' full text, as some abstracts may have only partially presented study details or presented them incorrectly. Any discrepancies during the selection process were resolved through discussion with a third reviewer (GSS). An overall evaluation for potential overlap of the population was conducted based on authorship, hospital setting, and recruitment period. In cases of overlap, studies of higher quality or larger sample sizes were included.

Data extraction

The following information was obtained from each study: first author name, year of publication, study period, study location, study design, sample size, definition of renal impairment, eGFR calculation formula, treatment received and definitions of hemorrhagic complications. Odds ratios (ORs) with their corresponding 95% CIs were extracted for pooled analysis. In study where OR and 95% CI was not available, we calculated the OR and 95% CI from the events and total cases. Data extraction was conducted independently by two authors (GN and JY), and discrepancies were resolved by discussion with GSS.

Methodological quality

The quality of each study was independently assessed by two reviewers (GN and JY) using the Newcastle-Ottawa Quality Assessment Scale (NOS). NOS consists of three quality parameters:

selection, comparability, and outcome (cohort studies) or exposure (case-control studies). NOS allocates up to 4 points for selection, 2 points for comparability, and 3 points for exposure/outcome. Therefore, the maximum number of points is 9. Any discrepancies during data extraction and quality assessment were addressed through discussions with all other investigators.

Statistical analysis

Following the completed literature review, we summarized the methodological and clinical information from the included studies. The meta-analysis aimed to see the association between renal impairment and the occurrence of any intracerebral hemorrhage (ICH) or SICH following AIS. The meta-analysis was done by calculating the pooled ORs and 95% CIs. Heterogeneity between the included studies was determined using the I^2 test. The presence of I^2 more than 50% was considered an indicator of significant heterogeneity. If heterogeneity was determined, the DerSimonian and Laird random-effects model was used for meta-analysis. If the I^2 value was less than 50%, a fixed-effect model was used. Funnel plot, Egger's linear regression test, and Begg's test were used for the identification of publication biases. Considering the influence of various eGFR cut-off values, adjustment of variables while estimating odds ratio, and treatment received by patients on the overall effect size of the meta-analysis, subgroup analysis was performed. We divided subgroups according to eGFR cut-off value used, adjustment of variables, and treatment received by patients for meta-analysis of any ICH. However, we did not include adjustment of variables as a subgroup for meta-analysis of SICH because all studies for this outcome used multivariate analysis. A p-value of $<.05$ was considered statistically significant. All Statistical analyses were performed using Comprehensive Meta-Analysis software (CMA 3.3, Biostat, Englewood, NJ, 2014).

RESULTS

Literature search process

The results of the systematic literature search and selection are summarized in Figure 1. We identified 548 articles from database searches. After the exclusion of duplicates, 488 articles remained and after screening titles and abstracts, 27 relevant abstracts remained. After the application of inclusion and exclusion criteria, 14 studies were chosen for final analysis, and the data was extracted. The details of each study included are listed in Table 1.

Characteristics of included studies

This meta-analysis included 14 observational studies conducted among 10,033 AIS patients from Asia, Europe and North America. The year of publication

Table 1. Key methodological characteristics of studies included in this systematic review and meta-analysis

Study	Country	Renal impairment criteria	Treatment groups	Adjustment	Outcome	Definition of ICH/SICH	Estimation of GFR	NOS
Agrawal 2010	USA	eGFR<60	Thrombolysis	Multivariate	ICH	N/A	MDRD formula	7
Naganuma 2011	Japan	eGFR<60	Thrombolysis	Multivariate	ICH/SICH	N/A	MDRD formula	9
Lee 2013	Korea	eGFR<30	Both thrombolysis and non-thrombolysis	Multivariate	ICH/SICH	ECASS I and ECASS II	Cockcroft-Gault formula	7
Marsh 2013	USA	eGFR<60	Both thrombolysis and non-thrombolysis	Unadjusted	ICH	N/A	MDRD formula	9
Micozkadioglu 2013	Turkey	eGFR<60	Both thrombolysis and non-thrombolysis	Unadjusted	ICH	N/A	MDRD formula	8
Zhang 2013	Australia	eGFR<60	Thrombolysis	Multivariate	ICH	N/A	MDRD formula	8
Sobolewski 2013	Poland	eGFR<60	Thrombolysis	Multivariate	ICH	ECASS II	MDRD formula	8
Tutuncu 2013	Germany	eGFR<30	Thrombolysis	Unadjusted	ICH/SICH	ECASS II	CKD-EPI formula	9
Gensicke 2013	11 European countries	eGFR<60	Thrombolysis	Multivariate	ICH/SICH	ECASS II	CKD-EPI formula	9
Hsieh 2013	Taiwan	eGFR<60	Thrombolysis	Multivariate	ICH/SICH	NINDS	MDRD formula	9
Chao 2013	Taiwan	eGFR<60	Thrombolysis	Multivariate	ICH	NINDS and ECASS I	MDRD formula	8
Balian 2017	Argentina	eGFR<60	Non-thrombolysis	Multivariate	ICH	N/A	N/A	7
Purrucker 2017	Germany	eGFR<60	Non-thrombolysis	Unadjusted	ICH	ECASS I	N/A	7
Liu 2018	China	eGFR<60	Non-thrombolysis	Multivariate	ICH	N/A	MDRD formula	8

ranged from 2010 to 2018. Six of the included studies had prospective design while the rest had retrospective design. The majority of studies calculated estimated GFR using the Modification of Diet in Renal Disease (MDRD) formula and included subjects who had undergone thrombolysis. Renal impairment was defined as eGFR< 60 mL/min/1.73 m² in the majority of studies, while some used eGFR<30 mL/min/1.73 m² as criteria for renal impairment. Risk estimates were multivariate-adjusted in the majority of studies. Definitions of ICH and SICH used by various studies are provided in Table 1. According to the quality assessment tool

described in the methods section, quality scores for individual studies are given in Table 1.

Any intracerebral hemorrhage

For the outcome of any ICH occurrence, there was significant heterogeneity and so a random-effects model was used to estimate pooled ORs and 95% CIs. The meta-analysis found that patients with poor renal function as indicated by low eGFR had a higher odds of developing any ICH (OR: 1.7; 95% CI: 1.13 to 2.57; p= 0.011; I²=87.2%) following AIS (figure 2). There was no evidence of publication bias based on Egger's test (p=0.50), Begg's test

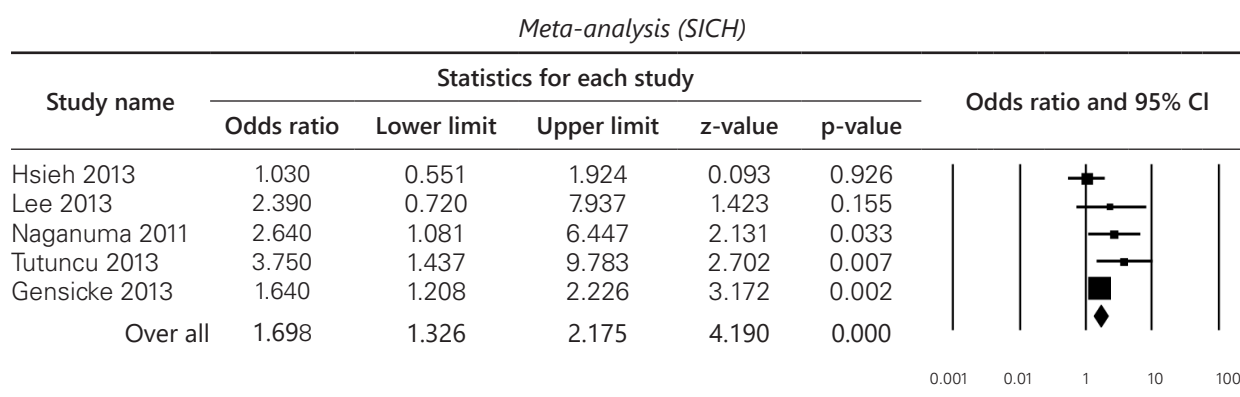
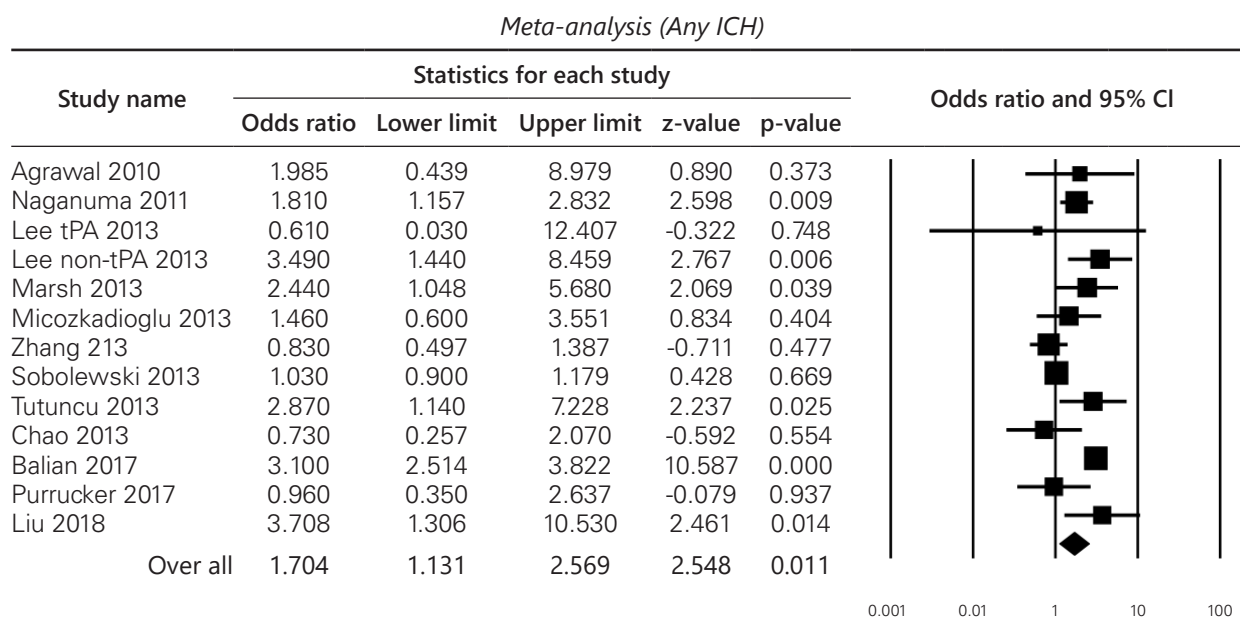


Figure 2. Forest plots for meta-analysis of association between renal impairment and hemorrhagic transformation (any ICH and SICH) following AIS. The area of each square is proportional to the study's weight in the meta-analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval. The width of the diamond serves the same purpose. The overall meta-analyzed measure of effect is an imaginary vertical line passing through the diamond.

($p=0.95$), and visual inspection of the funnel plot (figure 3a). In sensitivity analyses, sequentially omitting one study at a time from the meta-analysis produced consistent results, indicating the stability of analysis.

Symptomatic intracerebral hemorrhage

For SICH, there was no heterogeneity so a fixed-effects model was used. The meta-analysis found that patients with poor renal function as indicated by low eGFR had a higher odds of developing SICH (OR: 1.7; 95% CI: 1.32 to 2.17; $p=0.000$; $I^2=37.3\%$) following AIS (figure 2). There was no evidence of publication bias based on Egger's test ($p=0.40$), Begg's test ($p=0.46$), and visual inspection of the funnel plot (figure 3b). In sensitivity analyses, sequentially omitting one study at a time from the meta-analysis produced consistent results,

indicating the stability of analysis.

Subgroup analysis for any intracerebral hemorrhage

The detailed results of subgroup analyses for meta-analyses of any ICH are tabulated in Table 2. We found that patients with poor renal function in both multivariate-adjusted studies and unadjusted studies had a significantly higher odds of developing any ICH. Patients with very poor renal function (eGFR<30) had a significantly higher odds of developing any ICH. There was a trend among patients with poor renal function (eGFR< 60) toward an increased odds of developing any ICH, but this association was not statistically significant. We found that non-thrombolysis patients with poor renal function had a significantly higher odds of developing any ICH. There was a trend among thrombolysis patients with poor renal function

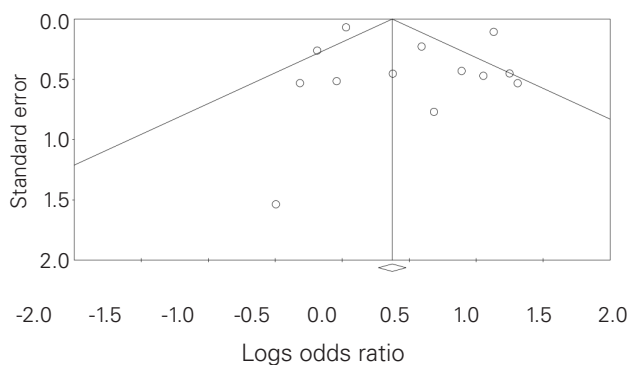


Fig 3a. Funnel Plot of Standard Error by Log odds ratio (Any ICH)

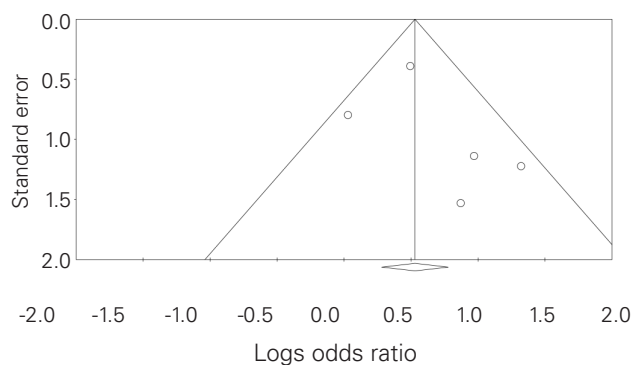


Fig 3b. Funnel Plot of Standard Error by Log odds ratio (SICH)

towards an increased odds of developing any ICH, but the association was not statistically significant.

Subgroup analysis for symptomatic intracerebral hemorrhage

The detailed results of subgroup analyses for meta-analyses of SICH are tabulated in Table 3. Patients with poor renal function (either eGFR<30 or eGFR<60) had a significantly higher odds of developing SICH. We found that subgroup of patients with poor renal function who underwent thrombolysis had a significantly higher odds of developing SICH. There was no data available to explore whether non-thrombolysis patients with poor renal function had the odds of developing SICH.

DISCUSSION

Our meta-analysis found that there is an increased odds of developing any ICH and SICH in AIS patients with renal impairment. The odds was more evident in patients with eGFR<30 and who underwent thrombolysis.

With the onset of AIS, there is a reduction in ATP and subsequent cessation of Na⁺-K⁺ ATPase activity within seconds to minutes. This leads to a wide array of cellular and metabolic derangements which disrupt the blood-brain barrier (BBB), the severity of which is dependent on the duration of ischemia. The resulting disruption of the BBB and impairment of autoregulatory capacity of the cerebral vasculature predispose to blood extravasation when the tissue is reperfused.^{22,23} Furthermore, patients with impaired renal function have pre-existing altered cerebral autoregulation.¹³ This may thus increase the risk of hemorrhage.

Patients with renal impairment (low eGFR) have an increased risk of bleeding due to impairment of the intrinsic function of platelets and their interaction with vessel walls (also referred to as "uremic platelets"), increased use of antiplatelet agents, and reduced hematocrit levels associated with anemia of chronic kidney disease, whereby platelets tend to travel closer to the vascular lumen and are less likely to interact with endothelium and

form a clot.²⁴ Further, the presence of cardiovascular risk factors and chronic microvascular damage to cerebral blood vessels in renal impairment may predispose to increased risk of hemorrhagic complication in the setting of acute ischemic stroke after thrombolysis. Studies have reported increased risk for hemorrhagic microangiopathy which may predispose to hemorrhagic complications.^{25,26} Regrettably, the underlying mechanism of the failure is poorly known, and data on milder forms of renal insufficiency are scarce.

Apart from hemorrhagic complications, poor renal function is associated with other outcomes as well. Mostofsky et al. have shown that among patients with AIS, a reduced or highly elevated eGFR at hospital admission is associated with a higher mortality rate compared to patients with moderate levels of eGFR.²⁷ Similarly, Dong et al. reported that low baseline eGFR predicted a high mortality and newly ischemic events at 3 months in AIS patients.²⁸ In another similar study, Kim et al. showed that a low baseline eGFR was strongly predictive of both poor functional outcome at 3 months after AIS and neurological deterioration/mortality during hospitalization.²⁹ Wang et al. also found that a low eGFR was associated with increased risks of all-cause mortality and recurrent stroke independent of the traditional vascular risk factors in AIS patients.³⁰ Together with the aforementioned research, our data imply that eGFR may be a useful biomarker for predicting prognosis following AIS. Further research should be conducted to develop and validate a prediction model that incorporates additional known risk factors such as patient age, increased baseline glucose, hypertension, congestive heart failure, diabetes mellitus, ischemic heart disease, atrial fibrillation, baseline antiplatelet use, leukoaraiosis, visible acute infarction, increased baseline National Institutes of Health Stroke Scale (NIHSS) score, and estimated infarct volume in addition to eGFR.^{3,31}

Our research has some limitations. First, patients with low eGFR often have multiple comorbidities, including diabetes, dyslipidemia, high blood pressure, heart disease, and the use of antiplatelet and antithrombotic drugs which may increase the

Table 2. Subgroup analysis for meta-analysis of any Intracranial Hemorrhage

Subgroups	Number of studies	OR	LL	UL	P	I ²
Overall	13	1.7	1.13	2.57	0.011	87.2%
Studies with Multivariate adjusted outcome	9	1.6	1	2.7	0.05	91%
Studies with unadjusted outcome	4	1.83	1.14	2.9	0.011	5.4%
Renal dysfunction defined by eGFR<30	3	2.96	1.58	5.53	0.001	0%
Renal dysfunction defined by eGFR<60	10	1.55	0.9	2.4	0.056	89.7%
Studies including Thrombolysis patients	7	1.23	0.88	1.72	0.229	50.8%
Studies including Non thrombolysis patients	4	2.712	1.69	4.3	0.000	42.8%
Studies including Mixed patents	2	1.912	1.036	3.528	0.038	0%

Table 3. Subgroup analysis for meta-analysis of Symptomatic Intracranial Hemorrhage

Subgroups	Number of studies	OR	LL	UL	P	I ²
Overall	5	1.698	1.326	2.175	0.000	37.3%
Renal dysfunction defined by eGFR<30	2	3.146	1.488	6.655	0.003	0%
Renal dysfunction defined by eGFR<60	3	1.56	1.048	2.32	0.03	36%
Studies including Thrombolysis patients	4	1.79	1.14	2.817	0.011	50%
Studies including Mixed patents	1	2.39	0.72	7.93	0.155	0%

risk of bleeding.³² Therefore, it may be misleading to suggest that the increased risk of hemorrhage is merely due to low eGFR. Secondly, included studies lacked information regarding stroke severity as measured by the NIHSS score at admission, which is a strong predictor of hemorrhagic complications after thrombolysis.³¹ Third, we could not include patients who underwent mechanical thrombectomy. Therefore, our results cannot be extended to those patients. Patients receiving mechanical thrombectomy require contrast administration, which can contribute to renal dysfunction. Finally, included papers lacked data on blood pressure maintenance during AIS treatment. Because poor blood pressure control during AIS treatment could be associated with hemorrhage, it may be an important confounding factor in our analysis.³¹

CONCLUSION

Our meta-analysis found that there is an increased odds of any ICH and SICH in AIS patients with renal impairment. This odds is highest in those with severe renal impairment (eGFR< 30) and those undergoing thrombolysis. Clinicians should exercise caution while administering thrombolytic therapy to

patients with severe renal impairment. The effects of renal impairment on hemorrhagic complications in patients undergoing mechanical thrombectomy should be further investigated, especially since contrast agents used in mechanical thrombectomy can further aggravate renal impairment.

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CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

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