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Renal impairment and the prognosis of endovascular thrombectomy: a meta-analysis and systematic review

Rui Wang, Zechun Xie, Bo Li and Peng Zhang

***Abstract*:**
Background: The association between renal impairment (RI) and stroke outcome after endovascular thrombectomy (EVT) remains unclear, which limits the estimation of patient prognosis by clinicians involved in EVT decision-making.
Purpose: This study aimed to investigate the association between RI and acute ischemic stroke (AIS) outcomes in patients treated with EVT.
Methods: Studies involving the association between RI at admission and AIS outcomes after EVT were retrieved from the PubMed and Embase databases from their inception to 17 January 2022. A fixed-effects model was used to synthesize the data of the included studies. Sensitivity analysis was performed to identify the source of heterogeneity.
Results: Overall, 11 studies, including 5053 patients with stroke receiving EVT, were included in the full analysis. In unadjusted analyses, RI was associated with 3-month poor functional outcome and mortality; the odds ratios (ORs) were 2.13 [10 studies; 95% confidence interval (CI), 1.77–2.56; I^2 = 45%] and 2.42 (8 studies; 95% CI, 2.02–2.90; I^2 = 58%), respectively. In adjusted analyses, the above associations remained significant; the OR of the 3-month poor functional outcome was 1.49 (5 studies; 95% CI, 1.17–1.90; I^2 = 58%), and the OR of the 3-month mortality was 1.84 (6 studies; 95% CI, 1.45–2.33; I^2 = 74%). Similar results were obtained in sensitivity analyses.
Conclusion: Our results suggest that in patients with AIS who underwent EVT, RI at admission was associated with 3-month poor functional outcome and mortality.

Keywords: endovascular thrombectomy, meta-analysis, outcome, renal impairment, stroke

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Correspondence to:
Bo Li
Department of Epidemiology and Biostatistics, School of Public Health, Jilin University, 1163 Xinmin Street, Changchun 130021, China.
li_bo@jlu.edu.cn

Peng Zhang
Clinical Trial and Research Center for Stroke, Department of Neurology, The First Hospital of Jilin University, 1 Xinmin Street, Changchun 130021, China.
pengzhang14@mails.jlu.edu.cn

Rui Wang
Department of Epidemiology and Biostatistics, School of Public Health, Jilin University, Changchun, China

Department of Thoracic Surgery, The First Hospital of Jilin University, Changchun, China

Zechun Xie
Department of Epidemiology and Biostatistics, School of Public Health, Jilin University, Changchun, China

Introduction

In recent years, endovascular thrombectomy (EVT) has been identified as a primary treatment for acute ischemic stroke (AIS) with large vessel occlusion of the anterior cerebral circulation.[1–5] However, despite an 80–90% rate of successful revascularization, the functional outcome of more than 50% of the patients receiving EVT remains unsatisfactory.[6] Therefore, it is of great clinical significance to determine which factors are related to the prognosis of AIS after EVT.

Whether renal impairment (RI) is a risk factor for stroke is still in debate. Some researchers believe that RI is a biomarker rather than a risk factor for stroke.[7] However, other researchers believe that RI is a risk factor for stroke as there is a dose–response relationship between estimated glomerular filtration rate (eGFR) and stroke.[8] A recent meta-analysis and systematic review indicated that moderate to severe RI is associated with an increased risk of intracranial hemorrhage and poorer functional outcome in patients with AIS treated with intravenous thrombolysis.[9] As a result of digital subtraction angiography, patients treated with EVT are exposed to a larger volume of contrast medium than other patients with stroke, which may increase the burden of kidney metabolism, especially in patients with RI. However, the association between RI and stroke outcome after EVT remains unclear, which limits the estimation of patient prognosis by clinicians involved in EVT decision-making. Therefore, we conducted a meta-analysis and systematic review to investigate the association

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between RI at admission and stroke outcomes in patients treated with EVT.

Methods

Our meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[10] The study protocol was not registered in advance, but we strictly followed the steps of the meta-analysis.

Search strategy

We identified published studies reporting the association between RI at admission and AIS outcomes [symptomatic intracranial hemorrhage (sICH), 3-month poor functional outcome (modified Rankin Scale score $\geqslant$ 3), or mortality] after EVT by searching the PubMed and Embase databases from their inception to 17 January 2022. Two reviewers (R.W. and P.Z.) independently conducted the literature search. The following search terms were used: stroke, cerebral infarction, vessel occlusion, artery occlusion, thrombectomy, endovascular recanalization, endovascular therapy, endovascular treatment, kidney dysfunction, estimated glomerular filtration rate, eGFR, kidney injury, kidney disease, renal function, RI, and renal failure. These were combined using Boolean logical operators (such as 'AND' and 'OR') to construct the final search strategy, which is provided in the Supplementary Materials (Appendix S1). We first searched the PubMed database; then, when searching the Embase database, we limited the source of articles to those not indexed in MEDLINE. In addition, the article type was also limited to articles, articles in press, or short surveys when searching the Embase database. The reference list of each included study was also reviewed as an additional source of qualified studies.

Study selection and quality assessment

Studies were considered eligible when they met the following criteria: (1) original research; (2) reporting the unadjusted or adjusted association between RI at admission and AIS outcomes after EVT [sICH, 3-month poor functional outcome (modified Rankin Scale score $\geqslant$ 3) or mortality]; (3) including more than 100 patients with AIS; (4) reporting the odds ratios (ORs) and their 95% confidence intervals (CIs) for the relevant outcomes, or the number of events needed to calculate them. For multiple studies from the same source of cases, the research team decided which one to retain through discussion (based on the sample size or the compliance with the inclusion criteria of our study). However, if such multiple studies separately reported the outcomes of interest, they were all included in this study.

The Newcastle–Ottawa Scale was used to assess the quality of the included studies.[11] Two authors (R.W. and P.Z.) independently performed quality assessment. Disagreements were discussed and resolved by the research team.

Data extraction and statistical analysis

The following information was extracted from the included studies: first author, publication year, research location, case number, mean age, baseline National Institute of Health stroke scale (NIHSS) score, definition of RI, eGFR calculation formula, proportion of bridging therapy, types of outcome, OR with 95% CI or number of events, and covariates adjusted for in a multivariable model.

In our study, both the unadjusted and adjusted associations between RI and outcomes of patients with AIS treated with EVT were evaluated by ORs and their corresponding 95% CIs. For unadjusted associations, if the OR and its 95% CI were not reported directly in the included studies but sufficient data were available, we calculated them using a previously described method to calculate them.[12] Statistical analysis was conducted using R version 4.1.0. The *meta* package was used to calculate the pooled ORs and their 95% CI, assess the heterogeneity of the included studies (I^2), and generate forest plots. A fixed-effects model was used to synthesize the data of the included studies because the study by Rice *et al.*[13] showed that its application does not depend on the homogenization conditions between studies. Sensitivity analysis was performed to identify the source of heterogeneity. A random effects model was also used to calculate the pooled ORs and their 95% CIs to test the stability of the results.

Results

Characteristics of the included studies

A total of 251 articles were identified from PubMed, Embase, and the references of the included studies. After removing duplicates, 243 articles were eligible for title and abstract screening. At this stage, 227

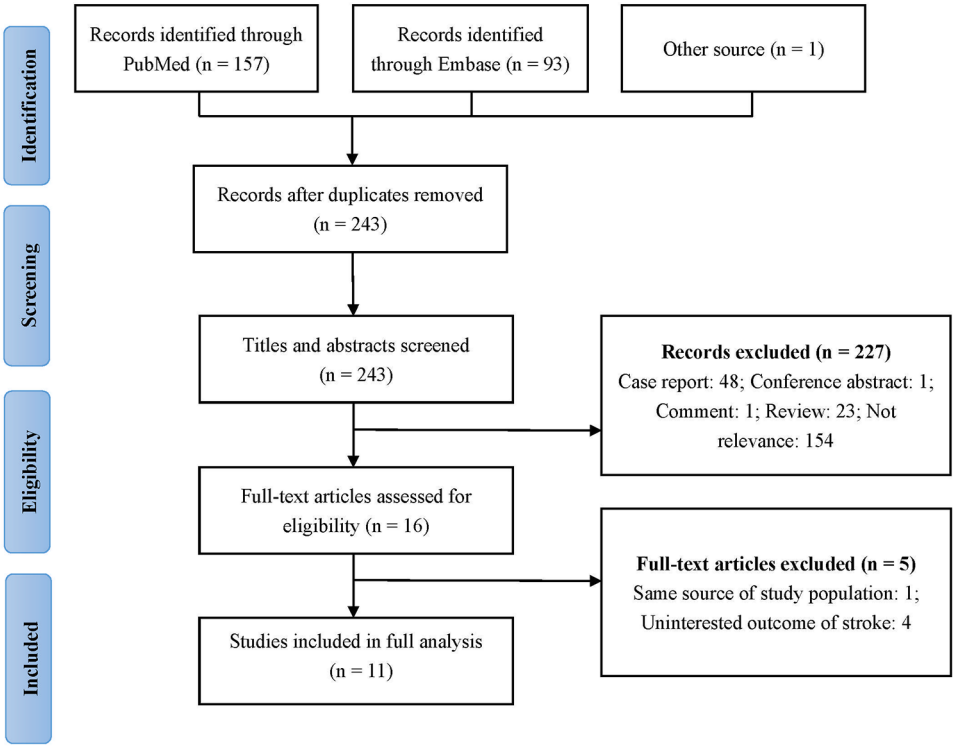

Figure 1. Summary of the study selection process.

articles were excluded [case reports (n=48), conference abstracts (n=1), comments (n=1), reviews (n=23), and not relevant (n=154)]. Of the remaining 16 articles eligible for full-text screening, 1 article was excluded for considering the same source of study population as another study, and 4 were excluded for reporting outcomes other than those relevant to our study. Finally, 11 articles,[14–24] including 5053 patients with stroke receiving EVT, were included in the full analysis. The detailed process of article screening is shown in Figure 1. The 11 articles eventually included were published between 2007 and 2021, including 8 (72.7%) published after January 2020. The proportion of bridging therapy in the 11 included studies ranged from 18.5% to 67.3%. However, 9 (81.8%) of the included studies had a clear definition of RI (eGFR$<$60 ml/min/1.73 m^2 or eGFR$\leqslant$60 ml/min/1.73 m^2). The detailed characteristics of the included articles are summarized in Table 1.

Study quality and publication bias

The Newcastle-Ottawa scale scores of the eleven included articles were all greater than 6, meaning that their quality was considered to meet the requirements for inclusion in a meta-analysis and systematic review. As most types of outcomes in this study included fewer than 10 studies, detection of publication bias was not recommended by the Cochrane Handbook because of contingency. However, funnel plots were still provided in the Supplementary Materials (Appendix S3) for reference.

Association between RI and outcomes

3-month poor functional outcome. In total, 10 studies[15–24] reported unadjusted data on the association between RI and 3-month poor functional outcomes after EVT. The risk of 3-month poor functional outcome in patients with RI was 2.13 times higher than that in patients without RI; the pooled OR was 2.13 (95% CI, 1.77–2.56; I^2=45%). Five studies[14,16,17,22,24] reported adjusted data on the association between RI and 3-month poor functional outcomes after EVT. The risk of 3-month poor functional outcome in patients with RI was higher than that in patients without RI; the pooled OR was 1.49 (95% CI, 1.17–1.90; I^2=58%). The details are presented in Figure 2.

Table 1. Main characteristics of the included studies.

Study	Country	Case no.	Mean age	Baseline NIHSS score	eGFR calculation formula	Definition of RI (ml/min/1.73 m²)	Proportion of bridging therapy (%)	Outcome[a]	NOS score
Fandler-Höfler *et al.*[15]	Austria	465	68.9 ± 13.4	15 (11, 18)	CKD-EPI	eGFR < 60	55.9	①	6
Sutherland *et al.*[17]	New Zealand	378	65 ± 15	17 (12, 21)	CKD-EPI	eGFR < 60	54.2	①②③④⑤⑥	8
Vavrova *et al.*[20]	Czech Republic	111	65.9	NR	NR	NR	26.1	①	6
Pan *et al.*[18]	China	373	NR	NR	CKD-EPI	eGFR < 60	42.6	①③⑤	6
Laible *et al.*[21]	Germany	505	70.1 ± 13.4	17 ± 6	CKD-EPI	eGFR < 60	67.3	①③⑤	6
Xiao *et al.*[16]	China	628	64.7 ± 12.5	17 (12, 21)	CKD-EPI	eGFR ⩽ 60	34.2	①②③④⑤	8
Laible *et al.*[14]	Germany	1169	76 (66, 82)	17 (11, 21)	CKD-EPI	eGFR < 60	59.6	②③④⑥	7
Wirtz *et al.*[19]	USA	156	71.5 (61, 82)	18 (14, 24)	NR	NR	40.3	①	6
Hu *et al.*[22]	China	607	Non-RI: 69 (60, 76) RI: 78 (73, 81)	Non-RI: 17 (13, 22) RI: 18 (14, 23)	CKD-EPI	eGFR < 60	50.7	①②③④⑤⑥	8
Xiao *et al.*[23]	China	551	64 (55, 73)	23 (14, 29)	CKD-EPI	eGFR < 60	18.5	①③④⑤⑥	8
Rhim *et al.*[24]	South Korea	110	Non-RI: 64.1 ± 13.1 RI: 71.5 ± 12.8	Non-RI: 10.0 (6.0, 18.0) RI: 18.0 (6.3, 22.8)	NR	eGFR < 60	47.3	①②③④	6

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; eGFR, estimated glomerular filtration rate; NIHSS, National Institute of Health stroke scale; NOS, Newcastle-Ottawa Scale; NR, not reported; RI, renal impairment.

[a]① – 3-month functional outcome (unadjusted); ② – 3-month functional outcome (adjusted); ③ – 3-month mortality (unadjusted); ④ – 3-month mortality (adjusted); ⑤ – symptomatic intracranial hemorrhage (unadjusted); ⑥ – symptomatic intracranial hemorrhage (adjusted).

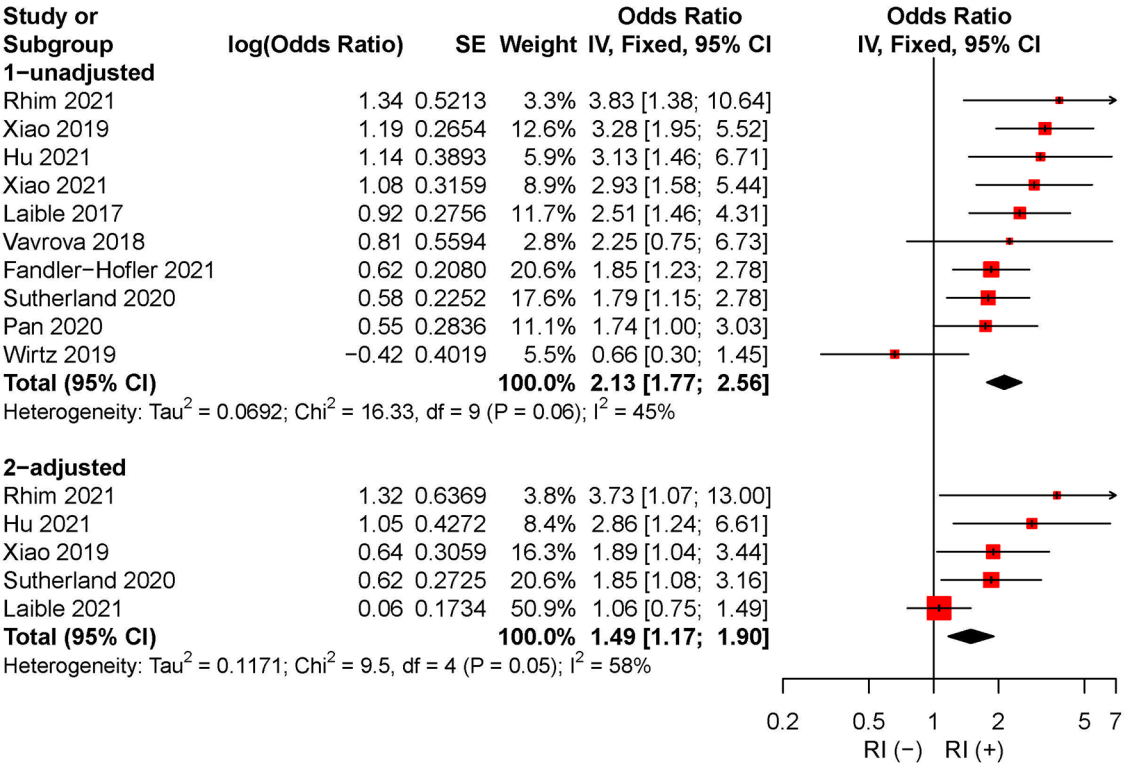

Figure 2. Association between RI and 3-month functional outcome in patients with AIS treated with EVT.

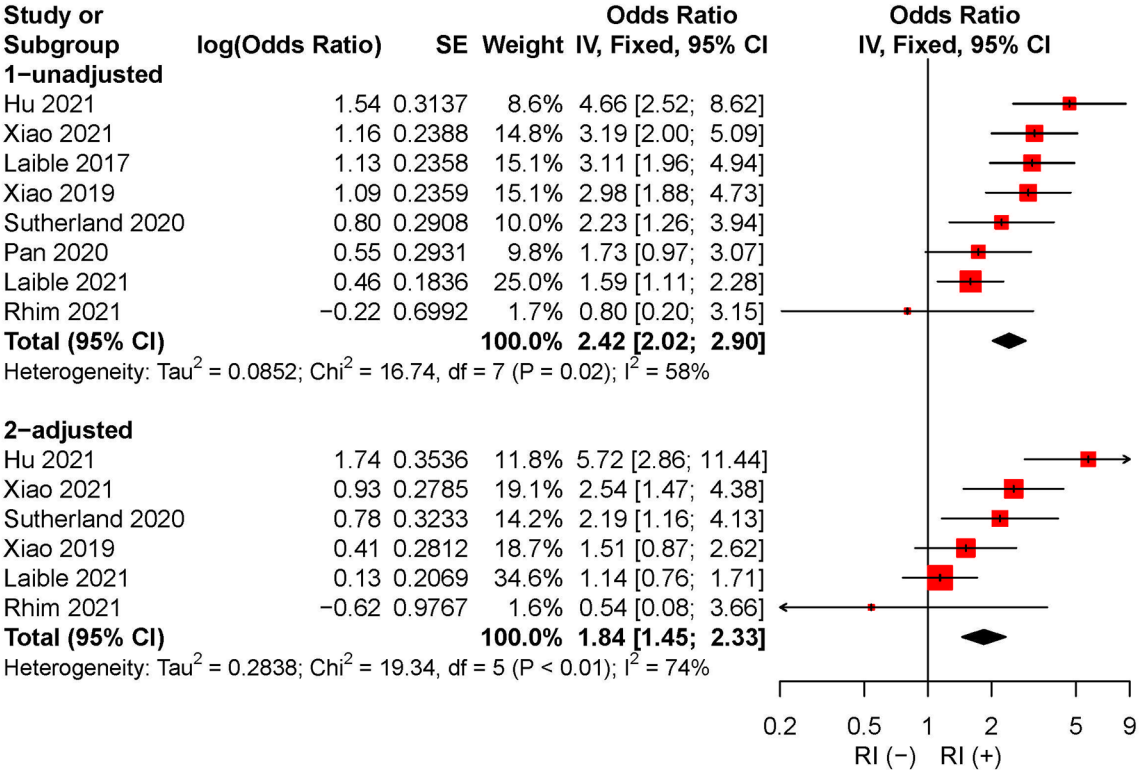

Figure 3. Association between RI and 3-month mortality in patients with AIS treated with EVT.

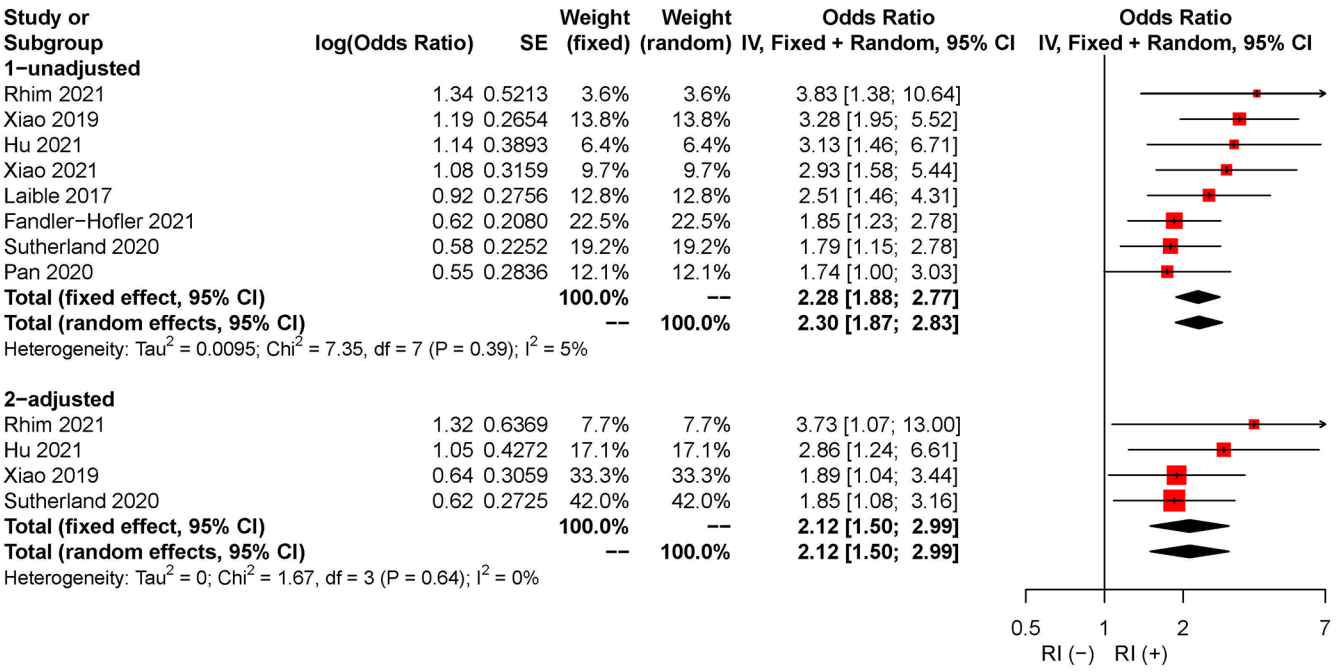

Figure 4. Sensitivity analysis of the association between RI and 3-month functional outcome in patients with AIS treated with EVT.

3-month mortality. Among patients with stroke receiving EVT, those with RI had a higher risk of 3-month mortality than those without RI based on unadjusted data (eight studies; OR, 2.42; 95% CI, 2.02–2.90; $I^2 = 58\%$).[14,16–18,21–24] The association of RI with an increased risk of 3-month mortality held also for adjusted data (six studies; OR, 1.84; 95% CI, 1.45–2.33; $I^2 = 74\%$).[14,16,17,22–24] The details are shown in Figure 3.

Symptomatic intracranial hemorrhage. Due to the different sICH diagnostic criteria used in different studies, we did not synthesize these data. A prospective registration study conducted by Sutherland *et al.*[17] found that RI (eGFR < 60 ml/min/1.73 m^2) was not associated with sICH [as defined by the Safe Implementation of Thrombolysis in Stroke-Monitoring Study definition (SITS-MOST)] in univariate or multiple logistic regression; the ORs and 95% CIs were 1.25 (0.41–3.81) and 1.18 (0.38–3.69), respectively. Similarly, a *post hoc* analysis of the DIRECT-MT study by Hu *et al.*[22] found that RI (eGFR < 60 ml/min/1.73 m^2) was not associated with sICH (according to Heidelberg Bleeding Classification); the ORs and 95% CIs were 1.16 (0.34–3.96) for unadjusted data and 1.07 (0.30–3.78) for adjusted data. However, the study by Xiao *et al.*[23] found that RI (eGFR < 60 ml/min/1.73 m^2) was associated with sICH (according to Heidelberg Bleeding Classification); the ORs and 95% CIs were 3.62 (1.78–7.35) for unadjusted data and 3.30 (1.55–7.18) for adjusted data. Based on a prospective database of patients with AIS who received EVT between 2010 and 2018, Laible *et al.*[14] showed that RI (eGFR < 60 ml/min/1.73 m^2) was not associated with sICH [according to the European Cooperative Acute Stroke Study II criteria (ECASS II)] in multiple logistic regression (OR, 1.22; 95% CI, 0.66–2.24). Three studies reached inconsistent conclusions based on unadjusted data. Laible *et al.*[21] and Xiao *et al.*[16] found that RI (eGFR < 60 ml/min/1.73 m^2 for Laible *et al.* and eGFR ⩽ 60 ml/min/1.73 m^2 for Xiao *et al.*) was not associated with sICH (ECASS II for Laible *et al.* and Heidelberg Bleeding Classification for Xiao *et al.*); the ORs (95% CIs) were 0.66 (0.25–1.76) and 1.16 (0.66–2.07), respectively. However, Pan *et al.*[18] found that RI (eGFR < 60 ml/min/1.73 m^2) was associated with an increased risk of sICH (ECASS II; OR, 2.84; 95% CI, 1.41–5.73).

Sensitivity analysis

Of the 10 studies reporting the unadjusted association between RI and 3-month poor functional

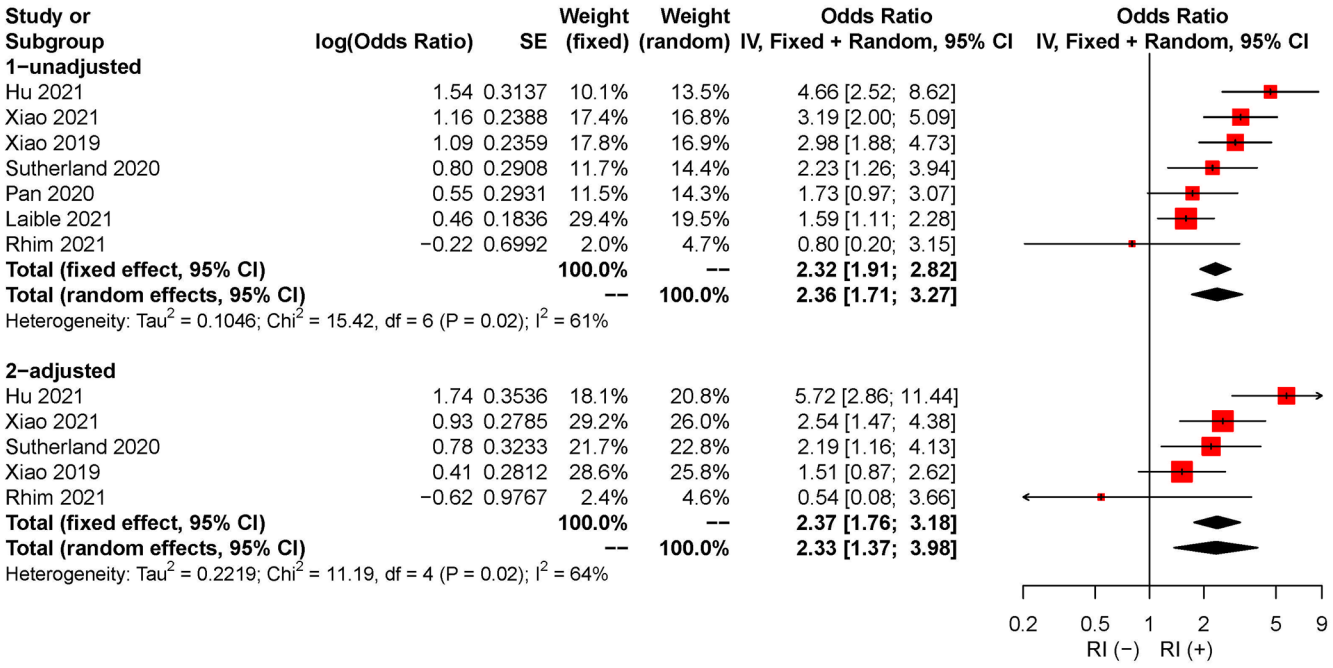

Figure 5. Sensitivity analysis of the association between RI and 3-month mortality in patients with AIS treated with EVT.

outcome, 2 (the Sutherland 2020 study[17] and the Wirtz 2019 study[19]) did not clearly report the definition of RI. Therefore, they were excluded from data synthesis in the sensitivity analysis. The I^2 decreased from 45% to 5%, and the OR (95% CI) changed from 2.13 (1.77–2.56) to 2.28 (1.88–2.77) (Figures 2 and 4). Both the Laible 2017 study[21] and the Laible 2021 study[14] reported an unadjusted association between RI and 3-month mortality, but since they shared the same data source, we only retained the study with a larger sample size (the Laible 2021 study) in the sensitivity analysis. The I^2 changed from 58% to 61%, and the OR (95% CI) changed from 2.42 (2.02–2.90) to 2.32 (1.91–2.82) (Figures 3 and 5).

Regarding the studies reporting adjusted data, the covariates included in the multiple logistic regression model of each study are listed in Supplementary Materials (Appendix S2). We noticed that when exploring the association between RI and stroke outcome (sICH, 3-month poor functional outcome, or 3-month mortality), post-contrast acute kidney injury (AKI) was considered as a confounding factor in the multiple logistic regression model of the Laible 2021 study.[14] AKI after contrast media may be an intermediate state in the relationship between RI and poor outcomes after EVT. Including it as a covariate in the regression model may mislead the true relationship between them. After excluding the Laible 2021 study,[14] RI was still associated with 3-month poor functional outcome based on adjusted data; the I^2 decreased from 58% to 0%, and the OR (95% CI) changed from 1.49 (1.17–1.90) to 2.12 (1.50–2.99) (Figures 2 and 4). Similarly, RI was associated with 3-month mortality based on adjusted data after excluding the Laible 2021 study;[14] the I^2 decreased from 74% to 64%, and the OR (95% CI) changed from 1.84 (1.45–2.33) to 2.37 (1.76–3.18) (Figures 3 and 5).

In addition, there was not much difference between the results obtained using fixed effect or random effect models in the data synthesis, indicating that the results were stable.

Discussion

In this meta-analysis and systematic review involving patients with AIS who underwent EVT, we found that RI at admission was associated with 3-month poor functional outcome and mortality based on both unadjusted and adjusted data. In the sensitivity analyses after excluding several studies, the association between RI and poor outcomes at 3 months became more significant.

Studies involving the association between RI and sICH after EVT in patients with AIS are relatively rare, and the diagnostic criteria for sICH vary among different studies. Therefore, no data were synthesized.

Many studies have demonstrated that contrast-associated AKI is associated with increased mortality.[25–27] Although the results of a meta-analysis and systematic review indicated no difference in the risk of AKI between patients with AIS undergoing computed tomography (CT) angiography or CT perfusion and those undergoing non-contrast CT, to the best of our knowledge, there is also evidence that the risk of AKI varies according to the type of clinical manifestations and imaging procedures.[28,29] It is generally believed that compared with CT, arteriography has a higher risk of AKI because arteriography delivers a higher concentration of contrast medium to the kidney.[30] The risk of AKI after taking a contrast agent is also affected by factors related to patient characteristics. Previous studies indicate that previous RI is the strongest independent risk factor for contrast-associated AKI.[31,32] Therefore, this may explain the mechanism of the relationship between RI at admission and poor prognosis in patients with AIS treated with EVT.

Although the pathophysiological mechanism of kidney injury caused by contrast agents has not been fully clarified, possible explanations include the direct and indirect effects of contrast agents and hemodynamic disorders.[33,34] The direct toxicity of contrast medium to renal tubular epithelial cells leads to loss of function, apoptosis, and necrosis, while its indirect effect is related to ischemic injury caused by vasomotor changes mediated by vasoactive substances (such as endothelin, nitric oxide, and prostaglandins). In addition, the partial pressure of oxygen in the outer renal medulla is relatively low. When the metabolic demand increases due to the intake of contrast media, the medulla is particularly susceptible to hemodynamic effects. There is a strong bidirectional relationship between RI and stroke, which may be the result of physiological interactions between brain and kidney. The kidney and the brain are similar in some structures and functions, and in their microvascular regulation.[35] Chronic renal dysfunction can easily lead to microvascular changes, leading in turn to asymptomatic lacunar infarction, leukoaraiosis, and microbleeds, which can further cause reperfusion injury and intracerebral hemorrhage in patients with AIS.[36] These baseline comorbidities in patients with RI are independently associated with worse prognosis, death, and sICH.[37]

The Laible 2021 study[14] reported the association of RI at admission with unfavorable functional outcome and mortality after adjusting for the effect of age, NIHSS score at admission, preexisting functional impairment, post-contrast AKI, posterior circulation stroke, failed recanalization, and sICH. Since RI is the strongest independent risk factor for contrast-associated AKI, the relationship between RI and stroke outcomes in patients treated with EVT will be underestimated after controlling for the influence of AKI in the same regression model. Moreover, post-contrast AKI, vascular recanalization state, and sICH are not in the same cross-section of the time series as RI at admission, but rather in an intermediate state between RI at admission and 3-month prognosis. When exploring the relationship between RI at admission and 3-month outcome of stroke, post-contrast AKI, vascular recanalization state, and sICH should not be considered as possible confounding factors. Therefore, the Laible 2021 study was excluded from the sensitivity analyses. The Wirtz 2019 study[19] and the Vavrova 2018 study[20] were also excluded from the sensitivity analyses because they did not report a detailed definition of RI. Moreover, the number of patients involved in these two studies was relatively small, which may explain why the results of the Wirtz 2019 study were quite different from those of other studies.

Recently, a systematic review and meta-analysis by Jeon *et al.*[38] came to similar conclusions to our study. They searched MEDLINE, EMBASE, and Google Scholar on 11 September 2020, and their study contained some unpublished data obtained by contacting the corresponding authors of potential studies. However, the majority of these unpublished data have been published in 2021. Our literature search was completed on 17 January 2022 and only published studies were included. In addition to those unpublished data, our study also included other newly published studies that explored the relationship between RI and EVT prognosis.

This study has several limitations. First, it could not avoid the inherent biases of the included

observational studies. Although our study reported results based on adjusted data, the effects of any other residual confounding factors could not be considered. Second, due to the small number of included studies, publication bias could not be detected, and whether our results are affected by such bias is uncertain. Moreover, the results of our study need to be verified by further meta-analyses containing a larger number of original articles. Third, our study was not registered, which might have caused slight bias; however, we strictly followed the steps of the meta-analysis. Finally, we only searched the PubMed and Embase databases, which may have led to a slight selection bias.

Conclusion

Our study suggests that RI at admission was associated with 3-month poor functional outcome and mortality in patients with AIS who underwent EVT. Further studies are needed to explore the association between RI and sICH.

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Author contributions

Rui Wang: Conceptualization; Data curation; Funding acquisition; Writing – original draft; Writing – review & editing.

Zechun Xie: Writing – original draft; Writing – review & editing.

Bo Li: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Peng Zhang: Conceptualization; Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

All analyses were based on previously published data, thus no ethical approval and patient consents are required.

ORCID iD

Peng Zhang https://orcid.org/0000-0001-5536-0255

Supplemental material

Supplemental material for this article is available online.

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