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Complete List of Authors:	Xu, Tao; Chongqing Medical University Affiliated Second Hospital Wang, You; Chongqing Medical University Affiliated Second Hospital Yuan, Jinxian; Chongqing Medical University Affiliated Second Hospital Chen, Yang-Mei; Chongqing Medical University Affiliated Second Hospital Luo, Haiyan; Chongqing Medical University Affiliated Second Hospital,
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Contrast extravasation and outcome of endovascular therapy in acute ischemic stroke: a systematic review and meta-analysis

Tao Xu, You Wang, Jinxian, Yuan, Yangmei Chen, Haiyan Luo*

Department of Neurology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China.

***Correspondence to:** Haiyan Luo, e-mail: haiyanl@hospital.cqmu.edu.cn, Department of Neurology, the Second Affiliated Hospital of Chongqing Medical University, Yuzhong District, Chongqing, 400010, China. Tel: +8623 63693088. Fax: +8623 63693086.

Keywords: contrast extravasation, endovascular therapy, ischemic stroke, meta-analysis.

Word count: 3505; **Tables:** 2; **Figures:** 4.

ABSTRACT

Objective

Contrast extravasation (CE) after EVT is commonly present in acute ischemic stroke (AIS) patients after endovascular therapy (EVT). Substantial uncertainties remain about the relationship between CE and the outcomes of EVT in patients with AIS. Therefore, we aimed to evaluate this association.

Design

Systematic review and meta-analysis.

Data source

We systematically searched the Medline and Embase databases for relevant clinical studies. The last search was conducted in June 2020.

Methods

We performed a meta-analysis to assess the association between CE and outcome of EVT in AIS. The odds ratios (ORs) with confidence intervals (CIs) were pooled using random-effect meta-analysis to calculate the association between CE and outcomes of EVT in patients with AIS. The main outcome was poor functional outcome, which was defined as a modified Rankin Scale score (mRS) ≥ 3 at 90 days after EVT.

Results

Fifteen studies that enrolled 1,897 patients were included. CE was associated with increased risks of poor functional outcome at 90 days (OR 2.16, 95% CI 1.20–3.90) and poor functional outcome at discharge (OR 2.24, 95% CI 1.38–3.62). Moreover, CE was associated with elevated risks of post-EVT intracranial haemorrhage (OR

6.68, 95% CI 3.51–12.70) and symptomatic intracranial haemorrhage (OR 3.26, 95% CI 1.97–5.40). We found no association between CE and mortality at 90 days (OR 1.38, 95% CI 0.81–2.36) and in-hospital mortality (OR 0.95, 95% CI 0.27–3.30) after EVT.

Conclusions

This meta-analysis suggests that CE was associated with elevated risks of unfavourable functional outcomes and intracranial haemorrhage in patients with AIS undergoing EVT.

Keywords: contrast extravasation, endovascular therapy, ischemic stroke, meta-analysis.

Strengths and limitations of the study

1. This is a systematic review and meta-analysis to assess the association between contrast extravasation and outcome of endovascular therapy (EVT) in acute ischemic stroke.

2. Dual-energy computerized tomography (DECT) was considered to be more accurate for early differentiation between contrast extravasation (CE) and haemorrhage than nonenhanced computed tomography (NECT); however, of the included studies, only four included studies used DECT, which may reduce its diagnostic accuracy for CE, further weakening our results.

3. Most of the included studies made a strict distinction between CE and intracranial haemorrhage (ICH); thus, the clinical relevance between the coexistence of CE and ICH and the outcomes of EVT remains unclear.

4. Most of the included studies were small in size, which may reduce the strengths of this meta-analysis.

5. The location of CE is a key confounder affecting the association between CE and the outcomes of EVT; however, most of the included studies did not report and discuss this important information.

INTRODUCTION

Over the past several years, the efficacy and safety of endovascular therapy (EVT) in the treatment of acute ischemic stroke (AIS) caused by cerebral large vessel occlusion have been confirmed by clinical studies.[1] Thus, EVT is considered a standard therapy for AIS caused by cerebral large vessel occlusion in clinical practice.[1] Contrast extravasation (CE) after EVT is commonly present in patients with AIS after EVT.[2] CE is usually assessed with a nonenhanced computed tomography (NECT) scan or a dual-energy computerized tomography (DECT) immediately after EVT, which progressively resolves within 24 hours after EVT.[3 4] CE is considered a manifestation of early blood-brain barrier (BBB) disruption after EVT, which has been reported to be predictive of poor outcome in patients undergoing EVT for AIS.[3] However, to date, among the studies focusing on the prognosis of patients eligible for EVT with CE, some have indicated that patients with CE had a higher risk for impaired functional outcomes, while others found no association between CE and the outcomes of EVT. Thus, substantial uncertainties remain about this association. Therefore, we aimed to perform a systematic review and meta-analysis to evaluate the association between CE and the outcomes of EVT in patients with AIS.

METHODS

Search strategy and inclusion criteria

This systematic review and meta-analysis was conducted according to the meta-analysis of observational studies in epidemiology (MOOSE) guidelines.[5] We

searched the Medline and Embase databases using a predefined search strategy **(table S1 in the online data supplement)**. Studies were included if they met all of the following inclusion criteria: (1) exposure and outcome: the study explored the associations between CE and the outcomes of EVT (ie. stent retriever, aspiration technique, and intra-arterial thrombolysis) in patients with AIS undergoing EVT; and (2) outcome assessment: the study reported the adjusted or unadjusted odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the magnitude of association between CE and the outcomes of EVT or provided raw data that could be used to calculate the ORs and 95% CIs. The literature search was conducted independently by two authors. We also examined the reference lists of the included articles to obtain additional relevant studies. There was no limitation on publication time. We resolved disagreements about the inclusion of a study by discussion until a consensus was reached. The last search was conducted in June 2020. Institutional ethics committee approval did not apply to this study.

Data extraction and qualitative assessment

We extracted the following data from each article: first author, publication year, territory, study period and design, methods of EVT, vascular lesion sites, population demographics, assessment strategies of EVT, and outcomes. We extracted the ORs and 95% CIs or raw data to calculate the ORs for the association between CE and the outcomes of EVT. The Newcastle-Ottawa scale was used to assess the quality of the included studies.[6] The full score was 9 stars, and a high-quality study was defined as a study awarded ≥8 stars.[6]

Exposure assessments and outcome definitions

CE was detected with NECT immediately after EVT, and follow-up NECT, magnetic resonance imaging T2-weighted gradient-recall echo imaging (MRI-GRE), or MRI susceptibility-weighted imaging (MRI-SWI) were conducted 24 hours after EVT.[7 8] CE was defined as the presence of high density on NECT immediately after EVT but with no discernible high density on the 24-hour follow-up NECT after EVT or no hypointensity on the 24-hour follow-up MRI-GRE and MRI-SWI after EVT.[7 8] Moreover, CE was also detected with DECT. For DECT, CE was defined as high density on mixed energy (MIX) images and iodine overlay maps (IOMs) but no high density in the corresponding areas on virtual non-contrast-enhanced (VNC) images.[3] The differential diagnosis between CE and cerebral haemorrhage based on neuroimaging is available in **table 1**.

The primary outcome was poor functional outcome, which was defined as a modified Rankin Scale score (mRS) ≥ 3 at 90 days after EVT. The secondary outcomes included poor functional outcome at discharge, mortality at 90 days, in-hospital mortality, intracranial haemorrhage (ICH) and symptomatic ICH (sICH) after EVT.

Statistical analysis

The pooled OR was used to evaluate the association between CE and each outcome of EVT. We quantified the magnitude of heterogeneity between estimates with the I^2 heterogeneity test statistic in this meta-analysis. The pooled estimates and 95% CIs were calculated with a random-effects model. To examine the sources of

heterogeneity, we also performed sensitivity analyses restricted to predefined variables (e.g. study design, sample size, assessment strategy of CE, and study quality). Publication bias was investigated statistically with Egger's tests[9] when a pooled estimate included ≥ 5 studies. STATA version 12.0 (StataCorp, College Station, TX, USA) was used for the statistical analyses.

Patient and public involvement:

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

RESULTS

Characteristics and quality assessment of included studies

The initial literature search provided 5,098 unduplicated records. A total of 15 articles including 1,897 patients met our inclusion criteria and were finally included in this meta-analysis [2-4 7 8 10-19] **(figure 1)**. The study characteristics are summarized in **table 2**. The CE assessment strategies of the included studies are summarized in **table 1**. The quality assessment of the included studies is summarized in **table S2 in the online data supplement**, and the median score of the included studies was 7.00 (range: 6–9).

The relationship between CE and outcome of EVT in AIS

We found that CE was associated with higher risks for poor functional outcome at 90 days (OR 2.16, 95% CI 1.20–3.90; p = 0.010; 10 studies) and poor functional outcome at discharge (OR 2.24, 95% CI 1.38–3.62; p = 0.001; 4 studies) **(figure 2)**.

However, CE was not associated with 90-day mortality (OR 1.38, 95% CI 0.81–2.36; p = 0.232; 5 studies) and in-hospital mortality (OR 0.95, 95% CI 0.27–3.30; p = 0.934; 2 studies) **(figure 3)**. CE was associated with higher risks for post-EVT ICH (OR 6.68, 95% CI 3.51–12.70; p <0.001; 13 studies) and sICH (OR 3.26, 95% CI 1.97–5.40; p < 0.001; 9 studies) **(figure 4)**.

Heterogeneity assessment

Significant heterogeneity was found in the pooled estimates of poor functional outcome at 90 days (I^2 = 73.2%) and post-EVT ICH (I^2 = 78.80%). Omitting each study in turn did not significantly change the results or heterogeneity. The results with significant heterogeneity remained stable in the sensitivity analyses restricted to predefined variables (**table S3 and S4 in the online data supplement**). Egger's tests showed no publication bias in the pooled estimates (**table S5 in the online data supplement**).

DISCUSSION

Main findings

We performed a systematic review and meta-analysis of the results provided by the 15 eligible studies including 1,897 patients with AIS undergoing EVT[2-4 7 8 10-19]. The results showed that the presence of CE immediately after EVT was associated with an increased risk for an unfavourable functional outcome at 90 days, which indicated that patients with CE undergoing EVT may be at a higher risk for experiencing poor functional recovery. Moreover, we found that patients with CE had higher risks of

experiencing post-EVT ICH and sICH.

Implication and strength

The mechanism underlying the clinical relevance between CE and the outcomes of EVT remains unclear. The pathophysiology of CE after EVT is considered a disruption of the BBB due to initial ischemia and reperfusion injury.[3 14] In patients with AIS, ischemic insults can injure the vascular endothelial cell junctions and cause damage to the endothelial extracellular matrix, which may promote the permeability of the BBB, further allowing for the leakage of contrast media into the extravascular space.[3] Thus, the degree of CE has been reported to be associated with the severity of BBB disruption. In patients undergoing EVT, a delayed reperfusion time (indicating a prolonged ischemic time) and hyperperfusion after revascularization may cause greater injury to the vascular and BBB, further causing obvious CE after EVT.[14] Moreover, procedure-related vascular lesions due to the frequent use of EVT devices and inappropriate operations during EVT may promote BBB disruption.[20] Additionally, extravasated contrast media may exert direct toxic effects on local brain tissue, which might damage the brain tissue.[3 14] Thus, CE is considered to be associated with poor outcomes after EVT and may have prognostic value in predicting the outcomes of EVT. Thus, therapeutic strategies (such as shortening the recanalization time, gentle delivery of EVT device, and controlling blood pressure after EVT) that are able to protect and stabilize the BBB in perioperative period of EVT may improve the clinical outcomes of patients with EVT-related CE.

Limitations

Nonetheless, this meta-analysis has several limitations. First, DECT was considered to be more accurate for early differentiation between CE and haemorrhage than NECT. However, of the included studies, only four included studies used DECT,[2 3 12 14] which may reduce its diagnostic accuracy for CE, further weakening our results. Second, we also noticed the coexistence of CE and haemorrhage immediately after EVT in patients undergoing EVT in clinical practice. However, most of the included studies made a strict distinction between CE and haemorrhage. Thus, the clinical relevance between the coexistence of CE and haemorrhage and the outcomes of EVT remains unclear. Third, most of the included studies were small in size. Fourth, the location of CE is a key confounder affecting the association between CE and the outcomes of EVT. However, most of the included studies did not report this information; only two reported that subarachnoid and cortical CE were associated with an elevated risk of ICH.[4 7] The effect of CE location on the relationship between CE and the outcomes of EVT remains unclear.

CONCLUSIONS

Taken together, in patients with AIS undergoing EVT, CE was associated with elevated risks for unfavourable functional outcomes and ICH after EVT. Our findings highlight the need to pay careful attention to CE in patients with AIS undergoing MT.

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Contributors: HL and YC performed study design**;** TX and YW performed literature search and selection; TX, YW, and JY data acquisition, analysis, and interpretation;

TX and YW performed statistical analysis; TX and HL drafting of the manuscript.

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Patient consent: Not required

Ethics approval: Institutional ethics committee approval did not apply to this study.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: Data are available on reasonable request. The data that support the findings of this study are available from the corresponding author.

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Table 1. The assessment strategy of contrast extravasation after EVT.

Assessment methods	Definition of CE	Definition of hemorrhage	Included studies
NECT immediately after EVT, and a follow-up NECT, MRI-GRE or MRI-SWI at 24 hours after EVT	CE was defined as the presence of high density on NECT immediately after EVT, but with no longer discernible high density on 24 hours follow-up NECT after EVT or with no hyposignal on 24 hours follow-up MRI-GRE and MRI-SWI after EVT	Hemorrhage was defined as the presence of high density on NECT immediately after EVT, with high density on 24 hours follow-up NECT after EVT or with hyposignal on 24 hours follow-up MRI-GRE and MRI-SWI after EVT	Ref[4 7 8 10 11 13 15-19]
Dual-energy CT immediately after EVT	CE was defined as the high density on MIX and IOM, but with no high density of corresponding areas on VNC	CE was defined as the high density on MIX and VNC, but with no high density of corresponding areas on IOM	Ref [2 3 12 14]

Abbreviations: NECT, non-enhanced computed tomography; MRI , magnetic resonance imaging; GRE, T2-weighted gradient-recall echo imaging; SWI, susceptibility weighted imaging; EVT, endovascular therapy; MIX, mixed energy images; IOM, iodine overlay maps; VNC, virtual unenhanced non-contrast images; CE, contrast extravasation.

Table 2. Characteristics of the studies included in the meta-analysis.

First Author, y of publication	Country	Study period	Study design	Primary methods of EVT	Vascular lesion location	Age, y/Men, %/No. in Cohort	Outcomes of EVT
Kim 2020[4]	South Korea	2012-2019	R	SR, AT, and IA	ACC	NA/54.9%/145	ICH and sICH
Chen 2020[3]	China	2016-2019	R	SR, AP, and IA	ACC (ICA and MCA)	63.1±11.7/75.9%/166	Poor functional outcomes at discharge and at 3 months; mortality at discharge and at 3 months; ICH and sICH
Xu 2019[10]	China	2014-2018	P	SR	NA	69.8±11.7/58.6%/198	ICH
Sun 2019[2]	China	2016-2018	R	SR	PCA	60.9±10.6/82.4%/108	Poor functional outcomes at 3 months
Chen 2019[11]	China	2015-2016	R	SR	ACC	NA/54.9%/82	Poor functional outcomes at 3 months; ICH and sICH
An 2019[12]	China	2013-2017	P	SR	ACC and PCC	61.3±12.8/72%/180	Poor functional outcomes at 3 months; mortality at 3 months; ICH

							and sICH
Shi 2018[13]	USA	NA	R	SR, AT, and IA	ACC	NA/42.9%/210	Poor functional outcomes at discharge; mortality at discharge; ICH
Renú 2015[14]	Spain	2010-2013	P	SR	NA	NA/47.7%/132	Poor functional outcomes at 3 months; ICH
Kim 2015[7]	South Korea	2007-2014	R	SR, AT, and IA	ACC	NA/50.0%/56	Poor functional outcomes at discharge; ICH and sICH
Rouchaud 2014[15]	France	2009-2011	R	SR	ACC and PCC	63.0 (31.0–90.0)/58.7%/63	Poor functional outcomes at 3 months; mortality at 3 months; ICH
Nikoubashman 2014[8]	Germany	2010-2013	R	SR, AT, and IA	ACC	71.2±15.4/52.2%/113	Poor functional outcomes at discharge and at 3 months; ICH and sICH
Desilles 2013[16]	France	2007-2011	P	SR	NA	63.0/51.8%/220	Poor functional outcomes at 3 months; mortality at 3 months; ICH and sICH

Kim 2012[17]	South Korea	2007-2010	R	SR, AT, and IA	ACC and PCC	64.9±14.43/55.9%/68	Poor functional outcomes at 3 months; mortality at 3 months; sICH
Jang 2006[18]	South Korea	1999-2004	R	IA	ACC	64.7±11.5/67.0%/94	ICH
Yoon 2004[19]	South Korea	1995-2002	R	IA	ACC	NA/56.5%/62	Poor functional outcomes at 3 months; ICH and sICH

Abbreviations: EVT, endovascular therapy; SR, stent retriever; P, prospective; R, retrospective; AT, aspiration technique; AP, angioplasty; IA, intra-arterial thrombolysis; ACC, anterior cerebral circulation; PCC, posterior cerebral circulation; ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage; NA, not available.

Figure legends

Figure 1. Flowchart of the literature search process.

Figure 2. Summary of the odds ratios for the associations between contrast extravasation and poor functional outcomes at 90 days and discharge. Each diamond indicates the OR, and the horizontal line indicates the 95% CI.

Figure 3. Summary of the odds ratios for the associations between contrast extravasation and 90-day mortality and in-hospital mortality. Each diamond indicates the OR, and the horizontal line indicates the 95% CI.

Figure 4. Summary of the odds ratios for the associations between contrast extravasation and risks for intracranial haemorrhage (ICH) and symptomatic intracranial haemorrhage (sICH). Each diamond indicates the OR, and the horizontal line indicates the 95% CI.

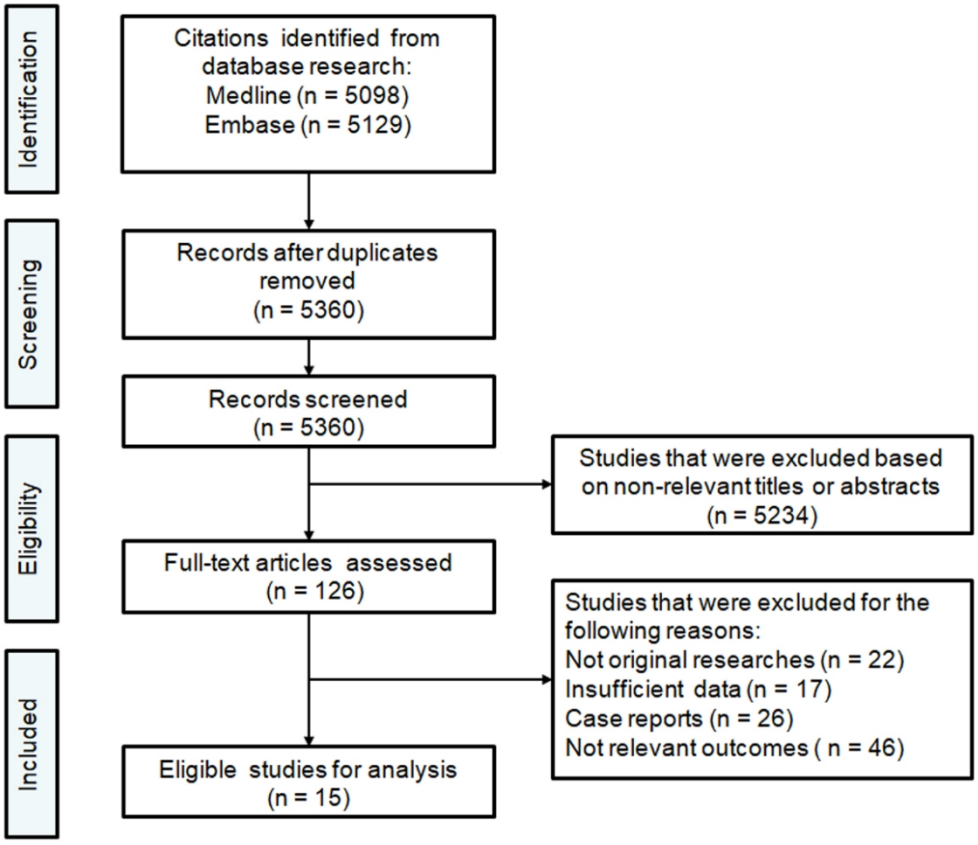

Figure 1.Flowchart of the literature search process.

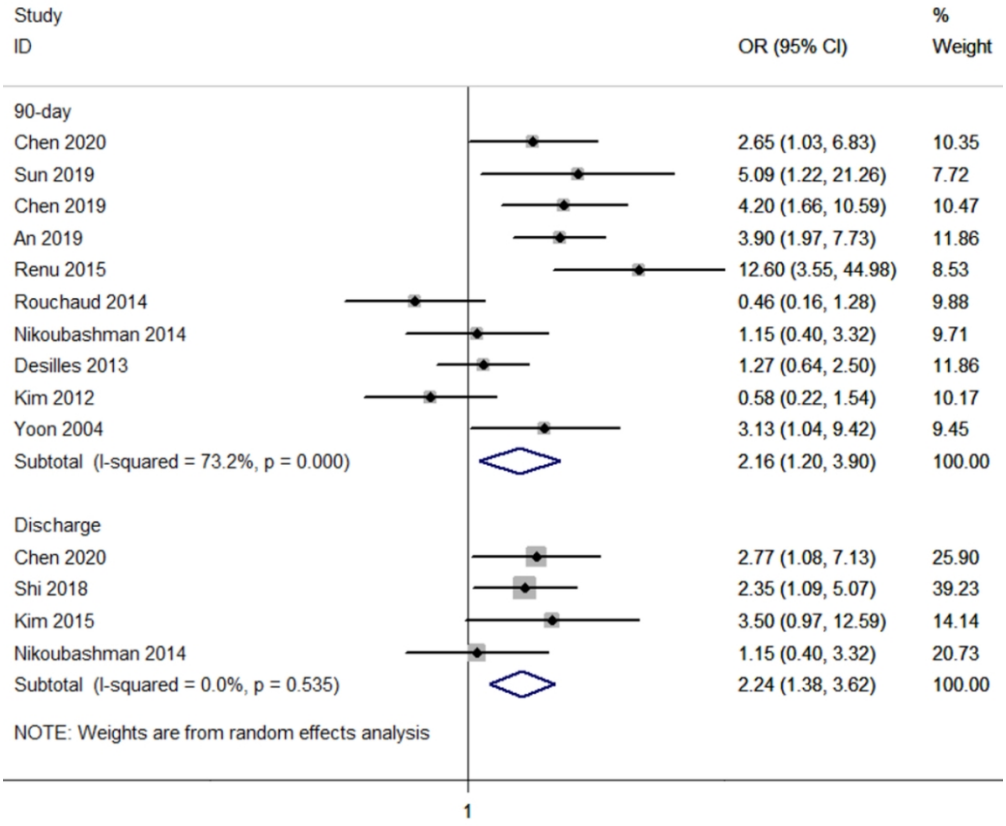

Figure 2.Summary of the odds ratios for the associations between contrast extravasation and poor functional outcomes at 90 days and discharge. Each diamond indicates the OR, and the horizontal line indicates the 95% CI.

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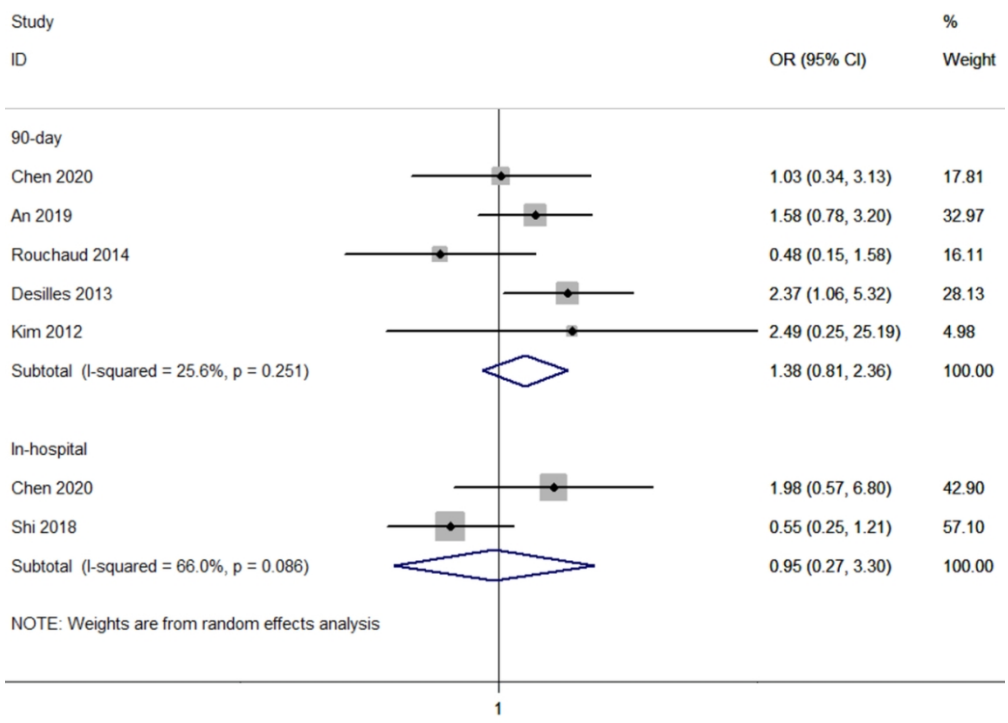

Figure 3. Summary of the odds ratios for the associations between contrast extravasation and 90-day mortality and in-hospital mortality. Each diamond indicates the OR, and the horizontal line indicates the 95% CI.

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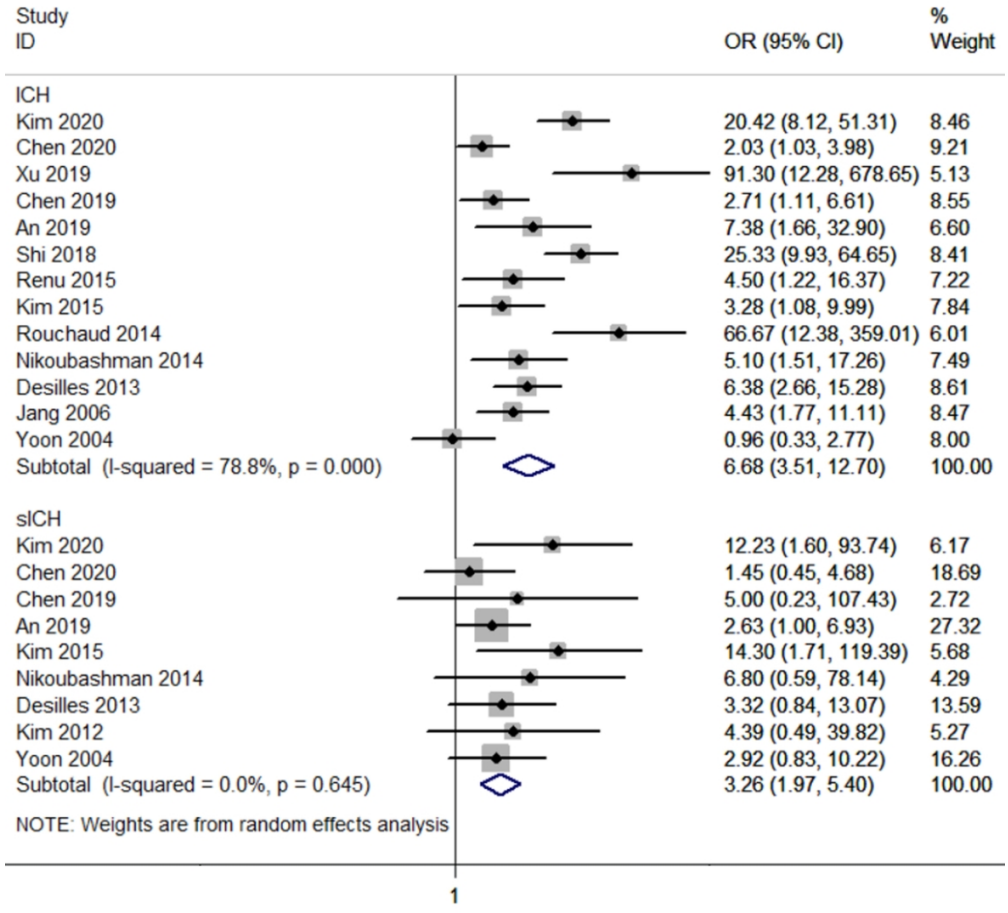

Figure 4. Summary of the odds ratios for the associations between contrast extravasation and risks for intracranial haemorrhage (ICH) and symptomatic intracranial haemorrhage (sICH). Each diamond indicates the OR, and the horizontal line indicates the 95% CI.

99x93mm (300 x 300 DPI)

Online Supplementary Materials

Table S1. Search strategy in the Medline database.

Steps*	Queries	Number of studies
#1	Search: (((((((Thrombectomy) OR (Endovascular)) OR (reperfusion)) OR (Recanalization)) OR (Aspiration)) OR (retriever)) OR (intra-arterial)) OR (revascularization)	368,970
#2	Search: (((((Blood Brain Barrier[Title/Abstract]) OR (Contrast Staining[Title/Abstract])) OR (Barrier[Title/Abstract])) OR (Contrast[Title/Abstract])) OR (Hyperdensity[Title/Abstract])) OR (high-density[Title/Abstract])	1,250,079
#3	Search: (patients[Title/Abstract]) OR (patient[Title/Abstract])	6,646,483
#4	Search: ((((((Occlusion) OR (Occlusions)) OR (Cerebral Infarction)) OR (Infarction)) OR (stroke)) OR (ischemic)) OR (ischaemia)	1,007,464
#1 and #2 and #3 and #4 and #5	Search: (((((((((Occlusion) OR (Occlusions)) OR (Cerebral Infarction)) OR (Infarction)) OR (stroke)) OR (ischemic)) OR (ischaemia)) AND ((patients[Title/Abstract]) OR (patient[Title/Abstract]))) AND ((((((Blood Brain Barrier[Title/Abstract]) OR (Contrast Staining[Title/Abstract])) OR (Barrier[Title/Abstract])) OR (Contrast[Title/Abstract])) OR (Hyperdensity[Title/Abstract])) OR (high-density[Title/Abstract]))) AND (((((((Thrombectomy) OR (Endovascular)) OR (reperfusion)) OR (Recanalization)) OR (Aspiration)) OR (retriever)) OR (intra-arterial)) OR (revascularization))	5,098

*The search strategy for the Embase and the Cochrane Library database was similar to that used for the Medline database. We also examined the reference lists of the included articles to obtain additional relevant studies. There was no limitation on literature language or publication type or time.

Table S2. Quality assessment of the included studies*

Reference#	Is the exposed cohort representativ	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of important factors†	Assessment of outcome	Follow up period	Adequacy of follow up of cohorts	Total quality scores
Kim 2020[1]	☆	☆	☆	☆	☆☆	☆	—	—	7
Chen 2020[2]	☆	☆	☆	☆	☆☆	☆	—	—	7
Xu 2019[3]	☆	☆	☆	☆	☆	☆	☆	☆	8
Sun 2019[4]	☆	☆	☆	☆	☆☆	☆	—	—	7
Chen 2019[5]	☆	☆	☆	☆	☆	☆	—	—	6
An 2019[6]	☆	☆	☆	☆	—	☆	☆	☆	7
Shi 2018[7]	☆	☆	☆	☆	☆	☆	—	—	6
Renú 2015[8]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Kim 2015[9]	☆	☆	☆	☆	☆	☆	—	—	6
Rouchaud 2014[10]	☆	☆	☆	☆	☆	☆	—	—	6
Nikoubashman 2014[11]	☆	☆	☆	☆	☆	☆	—	—	6
Desilles 2013[12]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Kim 2012[13]	☆	☆	☆	☆	☆	☆	—	—	6
Jang 2006[14]	☆	☆	☆	☆	☆	☆	—	—	6
Yoon 2004[15]	☆	☆	☆	☆	☆☆	☆	—	—	7

*Newcastle-Ottawa Scale was used to assess the study quality in this meta-analysis.[16] The full score was 9 stars, and the high-quality study was defined as a study with 8 awarded stars.

†A maximum of two stars could be awarded for this item. One star with adjustment for age, two stars if there were additional population demographics or comorbidities.

Table S3. Sensitivity analyses for the pooled analysis of poor functional outcome at 90 days restricted to predefined variables.

Variable	No. of Studies	OR	95% CI	p value	I^2
Study design					
Retrospective	7	1.67	1.13-2.47	0.011	69.0
Prospective	3	2.77	1.76-4.35	< 0.001	82.6
Sample size					
≥100	6	2.88	1.48-5.60	0.002	65.9
<100	4	1.37	0.44-4.23	0.587	80.2
Assessment strategy of CE					
Dual-energy CT	4	4.45	2.51-7.87	< 0.001	22.8
NECT and a follow-up NECT or MRI at 24 hours after EVT	6	1.31	0.67-2.57	0.429	67.2
Study quality					
<8	8	1.94	1.02-3.69	0.044	70.6
≥8	2	3.74	0.40-35.46	0.250	89.7

Abbreviations: CE = contrast extravasation; EVT = endovascular therapy; NECT = non-enhanced computed tomography; MRI = magnetic resonance imaging; OR = odds ratio.

Table S4. Sensitivity analyses for the pooled analysis of post-EVT ICH restricted to predefined variables.

Variable	No. of Studies	OR	95% CI	p-values	I^2
Study design					
Retrospective	9	5.80	2.58-13.03	< 0.001	83.4
Prospective	4	9.29	3.40-25.35	< 0.001	55.1
Sample size					
≥100	8	9.03	4.00-20.38	< 0.001	78.4
<100	5	4.15	1.48-11.66	0.007	77.8
Assessment strategy of CE					
Dual-energy CT	3	3.24	1.50-6.99	0.003	33.6
NECT and a follow-up NECT or MRI at 24 hours after EVT	10	8.02	3.69-17.43	< 0.001	80.6
Study quality					
<8	10	5.90	2.78-12.51	< 0.001	81.4
≥8	3	10.84	2.67-44.05	0.001	70.0

Abbreviations: CE = contrast extravasation; NECT = non-enhanced computed tomography; MRI = magnetic resonance imaging; OR = odds ratio.

Table S5. Egger's tests for publication bias.

Variables	Egger's tests	
	p-values	**95% CIs**
Association between CE and poor functional outcome at 90 days	0.68	-5.36-7.85
Association between CE and mortality at 90 days	0.65	-6.37-4.65
Association between CE and post-EVT ICH	0.10	-0.83-8.36
Association between CE and post-EVT sICH	0.05	-0.04-2.96

Abbreviations: CE = contrast extravasation; EVT = endovascular therapy; ICH = intracranial hemorrhage; sICH = symptomatic intracranial hemorrhage.

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MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	6
2	Hypothesis statement	6
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6,7
5	Type of study designs used	7
6	Study population	6,7
Reporting of search strategy should include		
7	Qualifications of searchers (e.g, librarians and investigators)	6,7
8	Search strategy, including time period included in the synthesis and key words	6,7 Supplementary Materials
9	Effort to include all available studies, including contact with authors	Supplementary Materials
10	Databases and registries searched	6,7 Supplementary Materials
11	Search software used, name and version, including special features used (eg, explosion)	6,7
12	Use of hand searching (eg, reference lists of obtained articles)	Supplementary Materials
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	NA
15	Method of handling abstracts and unpublished studies	6,7
16	Description of any contact with authors	NA
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7,8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7,8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Supplementary Materials
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7
22	Assessment of heterogeneity	8,9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8,9
24	Provision of appropriate tables and graphics	8,9
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig.2-Fig.4
26	Table giving descriptive information for each study included	Supplementary Materials
27	Results of sensitivity testing (eg, subgroup analysis)	Supplementary Materials

28	Indication of statistical uncertainty of findings	9,10

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10
30	Justification for exclusion (eg, exclusion of non-English language citations)	NA
31	Assessment of quality of included studies	9 Supplementary Materials
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11,12
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	11,12
34	Guidelines for future research	12
35	Disclosure of funding source	Yes

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Contrast extravasation and outcome of endovascular therapy in acute ischemic stroke: a systematic review and meta-analysis

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Contrast extravasation and outcome of endovascular therapy in acute ischemic stroke: a systematic review and meta-analysis

Tao Xu, You Wang, Jinxian Yuan, Yangmei Chen, Haiyan Luo*

Department of Neurology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China.

***Correspondence to:** Haiyan Luo, e-mail: haiyanl@hospital.cqmu.edu.cn, Department of Neurology, the Second Affiliated Hospital of Chongqing Medical University, Yuzhong District, Chongqing, 400010, China. Tel: +8623 63693088. Fax: +8623 63693086.

Keywords: contrast extravasation, endovascular therapy, ischemic stroke, meta-analysis.

Word count: 3827; **Tables:** 2; **Figures:** 4.

ABSTRACT

Objective

Contrast extravasation (CE) after endovascular therapy (EVT) is commonly present in acute ischemic stroke (AIS) patients. Substantial uncertainties remain about the relationship between CE and the outcomes of EVT in patients with AIS. Therefore, we aimed to evaluate this association.

Design

A systematic review and meta-analysis of published studies were performed.

Data source

We systematically searched the Medline and Embase databases for relevant clinical studies. The last literature search in databases was performed in June 2020.

Eligibility criteria for study selection

We included studies exploring the associations between CE and the outcomes of EVT in patients with AIS undergoing EVT.

Data extraction and synthesis

Two reviewers extracted relevant information and data from each article independently. We pooled odds ratios (ORs) with confidence intervals (CIs) using a random-effects meta-analysis to calculate the associations between CE and outcomes of EVT. The magnitude of heterogeneity between estimates was quantified with the I^2 statistic with 95% CIs.

Results

Fifteen observational studies that enrolled 1,897 patients were included. Patients with

CE had higher risks of poor functional outcome at discharge (2.38, 95% CI 1.45–3.89 p = 0.001; n = 545) and poor functional outcome at 90 days (OR 2.16, 95% CI 1.20–3.90; n = 1194). We found no association between CE and in-hospital mortality (OR 0.95, 95% CI 0.27–3.30; n = 376) or 90-day mortality (OR 1.38, 95% CI 0.81–2.36; n = 697) after EVT. Moreover, CE was associated with higher risks of post-EVT intracranial hemorrhage (ICH) (OR 6.68, 95% CI 3.51–12.70; n = 1721) and symptomatic ICH (OR 3.26, 95% CI 1.97–5.40; n = 1092).

Conclusions

This systematic review and meta-analysis indicates that in patients with AIS undergoing EVT, CE is associated with higher risks of unfavorable functional outcomes and intracranial hemorrhage. Thus, we should pay more attention to CE in patients with AIS undergoing EVT.

Strengths and limitations of the study

1. This study assessed the associations between contrast extravasation (CE) and the clinical outcomes of endovascular therapy (EVT) in patients with acute ischemic stroke.

2. Dual-energy computerized tomography (DECT) was considered to be more effective for early differentiation between CE and hemorrhage than nonenhanced computed tomography (NECT); however, of the included studies, only four included studies used DECT, which may reduce its diagnostic accuracy for CE, further weakening our results.

3. Most of the included studies made a strict distinction between CE and intracranial hemorrhage (ICH); thus, the clinical relevance between the coexistence of CE and ICH and the outcomes of EVT remains unclear.

4. Most of the included studies included a limited number of subjects, which reduced the strength of this systematic review and meta-analysis.

5. The location and volume of CE is an important confounding factor affecting the association between CE and EVT outcomes; however, most of the included studies did not report this key information.

INTRODUCTION

Over the past several years, clinical studies have confirmed the efficacy and safety of

endovascular therapy (EVT) for treating acute ischemic stroke (AIS) caused by large vessel occlusion (LVO).[1] In recent clinical practice, EVT has been a standard therapy for patients with AIS caused by LVO.[1] Intravascular injection of iodinated contrast media is commonly administered in EVT. Contrast extravasation (CE) after EVT occurs in some patients with AIS receiving EVT treatment.[2] CE is usually assessed by a nonenhanced computed tomography (NECT) scan or dual-energy computerized tomography (DECT) immediately after EVT and progressively resolves within 24 hours after EVT.[3 4] CE is considered a manifestation of early blood-brain barrier (BBB) disruption after EVT, which has been reported to be predictive of poor outcome in patients undergoing EVT for AIS.[3] However, among the studies focusing on the prognosis of patients eligible for EVT with CE, some have indicated that patients with CE had a higher risk for impaired functional outcomes, while others found no association between CE and the outcomes of EVT. Thus, this association remains unclear and has substantial uncertainties. Therefore, we aimed to evaluate the association between CE and the outcomes of EVT in AIS by performing a systematic review and meta-analysis.

METHODS

Search strategy

We performed this systematic review and meta-analysis based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[5] The Medline and Embase databases were systematically searched using a predefined retrieval strategy

(Table S1 in the online data supplement).

Inclusion criteria

We included a study if it met all of the following inclusion criteria:

(1) Exposure and outcome: The study investigated the associations between CE and the outcomes of EVT for the treatment of AIS.

(2) Definition of EVT: EVT was considered endovascular interventional therapy using aspiration techniques, stent retrievers, or intra-arterial thrombolysis for the treatment of AIS.

(3) Definition of CE: CE was detected with NECT immediately after EVT, and follow-up NECT, magnetic resonance imaging T2-weighted gradient-recall echo imaging (MRI-GRE), or MRI susceptibility-weighted-imaging (MRI-SWI) were conducted 24 hours after EVT[6 7]; CE was defined as the presence of high density on NECT immediately after EVT but with no discernible high density on 24-hour follow-up NECT after EVT or no hypointensity on 24-hour follow-up MRI-GRE and MRI-SWI after EVT.[6 7] Moreover, CE could also be detected with DECT. For DECT, CE was defined as exhibiting high density on mixed energy (MIX) images and iodine overlay maps (IOMs) but no high density in the corresponding areas on virtual noncontrast-enhanced (VNC) images.[3] The differential diagnosis between CE and cerebral hemorrhage based on neuroimaging is available in **Table 1**.

(4) Outcome definitions: The following outcomes were recorded: poor functional outcome at 90 days (defined as a modified Rankin Scale score (mRS) ≥ 3 at 90 days after EVT), poor functional outcome at discharge (defined as an mRS ≥ 3 at discharge

after EVT), in-hospital mortality, 90-day mortality, intracranial hemorrhage (ICH), and symptomatic ICH (sICH) after EVT. Post-EVT ICH was detected with CT or MRI scans after CE assessment and was defined as any hemorrhagic event, including hemorrhagic infarction, parenchymal hemorrhage, or intracranial-extracerebral hemorrhage[8]; sICH was defined as ICH with significant neurological aggravation and an increase in National Institutes of Health Stroke Scale (NIHSS) score ≥ 4 in total.

(5) Assessment of outcome: The study provided the adjusted or unadjusted odds ratio (OR) and the corresponding 95% confidence interval (CI) for the magnitude of the association between CE and each outcome of EVT or provided raw data that could be used to calculate the OR and 95% CI.

Exclusion criteria: Nonoriginal articles, articles with irrelevant outcomes or insufficient data, or case reports were excluded. A study that did not investigate the associations between CE and the outcomes of EVT was considered to have irrelevant outcomes. One study without any data regarding outcome assessment after EVT was considered to have insufficient data (did not meet the fifth inclusion criterion). Two authors (TX and YW) performed the literature search independently. Moreover, the reference lists of the included articles were also examined to obtain relevant studies. A disagreement about the inclusion of a study was resolved by us via our discussion until a consensus was reached. We performed last literature search in June 2020. In this meta-analysis, if there was a significant sample overlap among multiple studies, we included the study with the largest sample size or longest follow-up time.

Data extraction and qualitative assessment

Two reviewers (TX and JY) independently extracted the following data from each article: first author, publication year, territory, study period and design, methods of EVT, demographics of population, sites of vascular lesions, strategies of EVT, and outcomes of EVT. The ORs with 95% CIs or raw data were extracted to calculate pooled ORs. When a study reported both unadjusted and adjusted ORs, the OR from the most fully adjusted model was extracted. When the effect estimates were not provided directly, the ORs and 95% CIs were calculated based on raw data (extracted raw data are listed in **Table S2 in the online data supplement**). We assessed the quality of the included studies according to the Newcastle-Ottawa scale (NOS).[9] The full NOS score was 9 stars; if a study awarded ≥8 stars, it was defined as a high-quality study.[9]

Outcome definitions

The primary outcome of this meta-analysis was poor functional outcome at 90 days after EVT. The secondary outcomes included poor functional outcome at discharge, 90-day mortality, in-hospital mortality, ICH, and sICH after EVT.

Statistical analysis

We used pooled OR to evaluate the magnitude of the association between CE and each outcome of EVT. The magnitude of heterogeneity between estimates was quantified with the I^2 heterogeneity test statistic. We also estimated 95% CIs to assess the magnitude of heterogeneity between estimates.[10] We recognized the potential heterogeneity and varied underlying effect sizes between the included studies; thus, we used a random effects model to pool the estimates. To examine the sources of

heterogeneity, we also performed subgroup analyses based on predefined variables (e.g., study design, sample size, CE assessment strategy, study quality, and adjustments for confounders). We also performed meta-regression analyses to assess the influence of predefined variables on the heterogeneity among studies; $P_{interaction}$ from meta-regression analyses was used to assess the sources of heterogeneity. We investigated publication bias visually with funnel plots and statistically with Egger's tests[11] when a pooled estimate included ≥ 5 studies. STATA version 12.0 (StataCorp, College Station, TX, USA) was used for the statistical analyses.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

RESULTS

Characteristics and quality assessment of the included studies

The initial literature search provided 5,098 unduplicated records. A total of 15 articles published between 2004 and 2020 including 1,897 patients met our inclusion criteria and were finally included in this meta-analysis[2-4 6 7 12-21] **(figure 1)**. **Table 1** demonstrates the CE assessment strategies of the included studies. Of the 15 included studies, 11 conducted NECT immediately after EVT and further conducted follow-up NECT, MRI-GRE or MRI-SWI at 24 hours after EVT to assess whether CE had occurred after EVT[4 6 7 12 13 15 17-21]; only 4 studies used DECT immediately after EVT to assess CE after EVT[2 3 14 16]. The characteristics of each included study are summarized

in **Table 2**. Of the 15 included studies, 5 were from China [2 3 12-14], 5 were from South Korea [4 6 19-21], 2 were from France [17 18], 1 was from the USA[15], 1 was from Spain [16], and 1 was from Germany [7]. Eleven studies had a retrospective design [2-4 6 7 13 15 17 19-21], and 4 had a prospective design [12 14 16 18]. All studies reported that EVT was used for treating AIS, including stent retrievers, aspiration techniques, and intra-arterial thrombolysis. Twelve studies reported information on vascular lesion sites: 8 studies included patients with AIS caused by LVO in the anterior cerebral circulation (ACC); 3 studies included patients with AIS caused by LVO in the ACC or posterior cerebral circulation (PCC); and only one study included patients with AIS caused by LVO in the PCC. Most of the included studies had relatively small sample sizes, which ranged from 56 to 220 subjects. The quality assessment of the included studies is summarized in **Table S3 in the online data supplement**, and the median score of the included studies was 7.00 (range: 6–9).

The relationship between CE and the outcome of EVT after AIS

Regarding the functional outcome after EVT, CE was found to be associated with higher risks of poor functional outcome at discharge (OR 2.38, 95% CI 1.45–3.89; p = 0.001; 4 studies; n = 545) and poor 90-day functional outcome (OR 2.16, 95% CI 1.20–3.90; p = 0.010; 10 studies; n = 1194) **(figure 2)**. However, CE was not related to in-hospital mortality (OR 0.95, 95% CI 0.27–3.30; p = 0.934; 2 studies; n = 376) or 90-day mortality (OR 1.38, 95% CI 0.81–2.36; p = 0.232; 5 studies; n = 697) **(figure 3)**. Furthermore, CE was found to be associated with higher risks for post-EVT ICH (OR 6.68, 95% CI 3.51–12.70; p <0.001; 13 studies; n = 1721) and sICH (OR 3.26, 95% CI

1.97–5.40; p < 0.001; 9 studies; n = 1092) **(figure 4)**.

Heterogeneity assessment

Heterogeneity assessments of pooled estimates were conducted, and the I^2 and 95% CIs are listed in the figure legends. Significant heterogeneity was found in the pooled estimates of poor functional outcome at 90 days (I^2 = 73.2%, 95% CI 0.50–0.86) and post-EVT ICH (I^2 = 78.80%, 95% CI 0.64–0.87). Omitting each study in turn did not alter the significance of pooled estimates and their heterogeneity estimates. Subgroup analyses were performed to assess the relationship between CE and poor 90-day functional outcome (**Table S4 in the online data supplement**) and the association between CE and post-EVT ICH (**Table S5 in the online data supplement**). The results with significant heterogeneity remained stable in subgroup analyses that were restricted to predefined variables. Based on meta-regression analyses, we found that varied assessment strategies of CE among the included studies accounted for the main between-study heterogeneity ($P_{interaction}$= 0.039) (**Table S4 in the online data supplement**).

Publication bias assessment

Asymmetric funnel plots were identified in the pooled estimates (included ≥ 5 studies) (**figure S1-S4 in the online data supplement**). However, Egger's tests indicated no significant publication bias in the pooled estimates (**Table S6 in the online data supplement**).

DISCUSSION

Main findings

We performed a systematic review and meta-analysis of the results provided by the 15 included studies having 1,897 subjects with EVT for treating AIS caused by LVO. [2-4 6 7 12-21] Our findings based on this meta-analysis indicated that the presence of CE immediately after EVT was related to a higher risk of an unfavorable 90-day functional outcome, indicating that patients with CE after EVT may have a higher risk of poor functional recovery. Moreover, we found that patients with CE had higher risks of experiencing ICH and sICH after EVT.

Implications and strength

The mechanism underlying the clinical relevance of the relationship between CE and the outcomes of EVT remains unclear. The pathophysiology of CE after EVT is considered to involve a disruption of the BBB due to initial ischemia and reperfusion injury. [3 16] In patients with AIS, ischemic insults can injure vascular endothelial cell junctions and cause damage to the endothelial extracellular matrix, which may promote permeability of the BBB, further allowing for leakage of contrast media into the extravascular space.[3] Thus, the degree of CE has been reported to be associated with the severity of BBB disruption. In patients undergoing EVT, a delayed reperfusion time (indicating a prolonged ischemic time) and hyperperfusion after revascularization may cause greater injury to the vasculature and BBB, further leading to obvious CE after EVT.[16] Moreover, procedure-related vascular lesions due to the frequent use of EVT devices and inappropriate operations during EVT may promote BBB disruption. [22] Additionally, extravasated contrast media may exert direct toxic effects on local brain tissue, which might damage the tissue.[3 16] Thus, CE is considered to be associated with

poor outcomes after EVT and may have prognostic value in predicting the outcomes of EVT. Thus, therapeutic strategies (such as shortening the recanalization time, gentle delivery of the EVT device, and controlling blood pressure after EVT) that are able to protect and stabilize the BBB in the perioperative period of EVT may improve the clinical outcomes of patients with EVT-related CE.

Limitations

This meta-analysis has several limitations. First, DECT is considered to be more accurate for early differentiation between CE and hemorrhage than NECT. However, of the included studies, only four used DECT, [2 3 14 16] which may reduce its diagnostic accuracy for CE, further weakening our results. Second, we also noticed the coexistence of CE and hemorrhage immediately after EVT in patients undergoing EVT in clinical practice. However, most of the included studies made a strict distinction between CE and hemorrhage. Thus, the clinical relevance of the relationship between the coexistence of CE and hemorrhage and the outcomes of EVT remains unclear. Third, most of the included studies had small sample sizes. Fourth, the location and volume of CE are key confounders influencing the relationship between CE and the outcomes of EVT in patients with AIS. Most of the included studies, however, did not provide this key information; only two included studies reported that subarachnoid and cortical CE were associated with an elevated risk of ICH.[4 6] The effects of CE location and volume on the relationship between CE and the outcomes of EVT remain unclear.

CONCLUSIONS

In summary, in patients undergoing EVT for treating AIS due to LVO, CE was related

to elevated risks for unfavorable functional outcomes and ICH events after EVT. Our findings highlight that we should pay careful and increased attention to CE in patients undergoing EVT for treating AIS due to LVO. Future studies exploring the association between CE and the outcomes of EVT should take the location and volume of CE into account, which may influence the outcomes of EVT. In this meta-analysis, most eligible studies had retrospective designs; thus, future high-quality prospective studies are needed to explore the association between CE and the outcomes of EVT.

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Contributors: study concept and design: HL and YC**;** literature search and selection: TX and YW; data extraction, analysis, and interpretation: TX and JY; statistical analysis: TX and YW; drafting of the manuscript: TX and HL.

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Data availability statement: Data are available on reasonable request. The data that support the findings of this study are available from the corresponding author.

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Table 1. The assessment strategies of contrast extravasation and hemorrhage after EVT.

Assessment methods	Definition of CE	Definition of hemorrhage	Included studies
NECT immediately after EVT, and a follow-up NECT, MRI-GRE or MRI-SWI at 24 hours after EVT	CE was defined as the presence of high density on NECT immediately after EVT, but with no longer discernible high density on 24 hours follow-up NECT after EVT or with no hyposignal on 24 hours follow-up MRI-GRE and MRI-SWI after EVT	Hemorrhage was defined as the presence of high density on NECT immediately after EVT, with high density on 24 hours follow-up NECT after EVT or with hyposignal on 24 hours follow-up MRI-GRE and MRI-SWI after EVT	Ref [4 6 7 12 13 15 17-21]
Dual-energy CT immediately after EVT	CE was defined as the high density on MIX and IOM, but with no high density of corresponding areas on VNC	Hemorrhage was defined as the high density on MIX and VNC, but with no high density of corresponding areas on IOM	Ref [2 3 14 16]

Abbreviations: NECT, non-enhanced computed tomography; MRI , magnetic resonance imaging; GRE, T2-weighted gradient-recall echo imaging; SWI, susceptibility weighted imaging; EVT, endovascular therapy; MIX, mixed energy images; IOM, iodine overlay maps; VNC, virtual non-contrast-enhanced; CE, contrast extravasation.

Table 2. Characteristics of the studies included in the meta-analysis.

First Author, y of publication	Country	Participants inclusion period	Study design	Primary methods of EVT	Vascular lesion location	Age, y/Men, %/No. in Cohort	Outcomes of EVT
Kim 2020[4]	South Korea	2012-2019	R	SR, AT, and IA	ACC	NA/54.9%/145	ICH and sICH
Chen 2020[3]	China	2016-2019	R	SR, AP, and IA	ACC (ICA and MCA)	63.1±11.7/75.9%/166	Poor functional outcomes at discharge and at 3 months; mortality at discharge and at 3 months; ICH and sICH
Xu 2019[12]	China	2014-2018	P	SR	NA	69.8±11.7/58.6%/198	ICH
Sun 2019[2]	China	2016-2018	R	SR	PCA	60.9±10.6/82.4%/108	Poor functional outcomes at 3 months
Chen 2019[13]	China	2015-2016	R	SR	ACC	NA/54.9%/82	Poor functional outcomes at 3 months; ICH and sICH
An 2019[14]	China	2013-2017	P	SR	ACC and PCC	61.3±12.8/72%/180	Poor functional outcomes at 3 months; mortality at 3 months; ICH and sICH
Shi 2018[15]	USA	NA	R	SR, AT, and IA	ACC	NA/42.9%/210	Poor functional outcomes at discharge; mortality at discharge; ICH

Renú 2015[16]	Spain	2010-2013	P	SR	NA	NA/47.7%/132	Poor functional outcomes at 3 months; ICH
Kim 2015[6]	South Korea	2007-2014	R	SR, AT, and IA	ACC	NA/50.0%/56	Poor functional outcomes at discharge; ICH and sICH
Rouchaud 2014[17]	France	2009-2011	R	SR	ACC and PCC	63.0 (31.0–90.0)/58.7%/63	Poor functional outcomes at 3 months; mortality at 3 months; ICH
Nikoubashman 2014[7]	Germany	2010-2013	R	SR, AT, and IA	ACC	71.2±15.4/52.2%/113	Poor functional outcomes at discharge and at 3 months; ICH and sICH
Desilles 2013[18]	France	2007-2011	P	SR	NA	63.0/51.8%/220	Poor functional outcomes at 3 months; mortality at 3 months; ICH and sICH
Kim 2012[19]	South Korea	2007-2010	R	SR, AT, and IA	ACC and PCC	64.9±14.43/55.9%/68	Poor functional outcomes at 3 months; mortality at 3 months; sICH
Jang 2006[20]	South Korea	1999-2004	R	IA	ACC	64.7±11.5/67.0%/94	ICH
Yoon 2004[21]	South Korea	1995-2002	R	IA	ACC	NA/56.5%/62	Poor functional outcomes at 3 months; ICH and sICH

Abbreviations: EVT, endovascular therapy; SR, stent retriever; P, prospective; R, retrospective; AT, aspiration technique; AP, angioplasty; IA, intra-arterial thrombolysis; ACC, anterior cerebral circulation; PCC, posterior cerebral circulation; ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage; NA, not available.

Figure legends

Figure 1. Flowchart of the literature search process.

Figure 2. Summary of odds ratios (ORs) for the relationships between contrast extravasation (CE) and poor functional outcomes at discharge and 90 days. Each diamond indicates the OR, and the horizontal line indicates the 95% confidence interval (CI). CE was associated with higher risks of poor functional outcome at discharge (heterogeneity test: I^2 = 0.0%, 95% CI 0.00–0.83) and poor functional outcome at 90 days (heterogeneity test: I^2 = 73.2%, 95% CI 0.50–0.86).

Figure 3. Summary of odds ratios (ORs) for the relationships between contrast extravasation (CE) and in-hospital mortality and 90-day mortality. Each diamond indicates the OR, and the horizontal line indicates the 95% confidence interval (CI). CE was not associated with in-hospital mortality (heterogeneity test: I^2 = 66.0%, 95% CI -0.50-0.92) or 90-day mortality (heterogeneity test: I^2 = 25.6%, 95% CI -0.85-0.70).

Figure 4. Summary of odds ratios (ORs) for the relationships between contrast extravasation (CE) and risks for intracranial hemorrhage (ICH) and symptomatic intracranial hemorrhage (sICH). Each diamond indicates the OR, and the horizontal line indicates the 95% confidence interval (CI). CE was related to higher risks of post-EVT ICH (heterogeneity test: I^2 = 78.8%, 95% CI 0.64–0.87) and sICH (heterogeneity test: I^2 = 0.0%, 95% CI -4.30–0.67)**.**

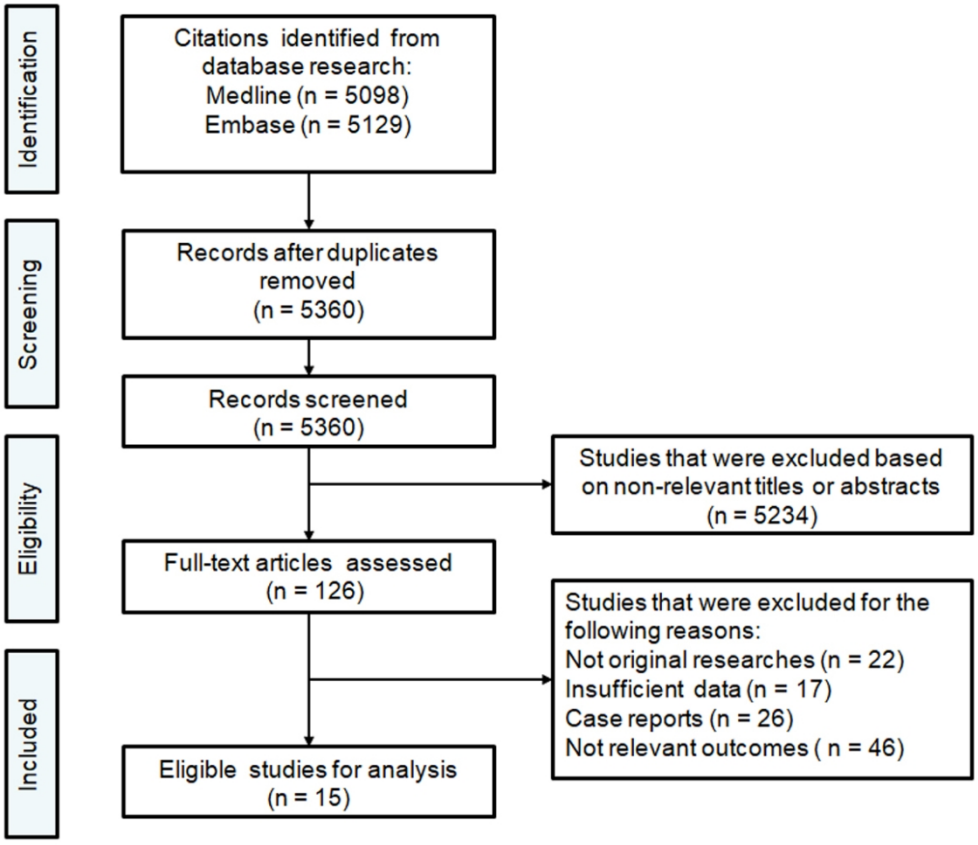

Figure 1. Flowchart of the literature search process.

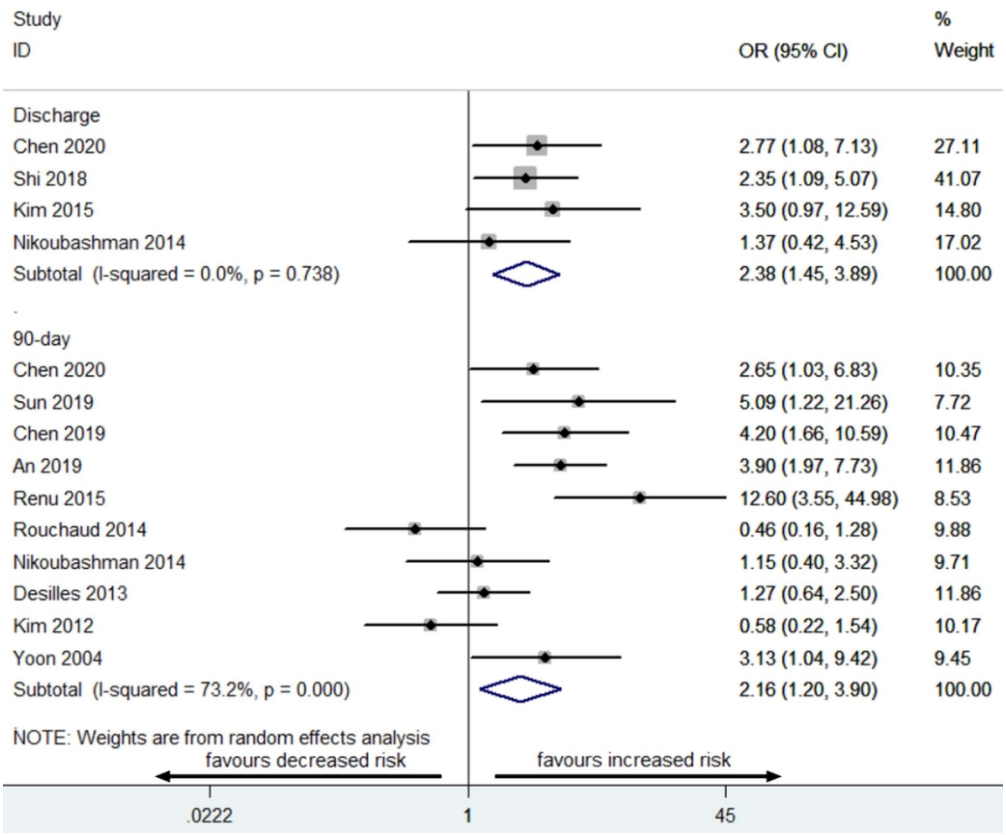

Figure 2. Summary of the odds ratios (ORs) for the associations between contrast extravasation (CE) and poor functional outcomes at discharge and 90 days. Each diamond indicates the OR, and the horizontal line indicates the 95% confidence interval (CI). CE was associated with higher risks of poor functional outcome at discharge (heterogeneity test: I2 = 0.0%, 95% CI 0.00–0.83) and poor functional outcome at 90 days (heterogeneity test: I2 = 73.2%, 95% CI 0.50–0.86).

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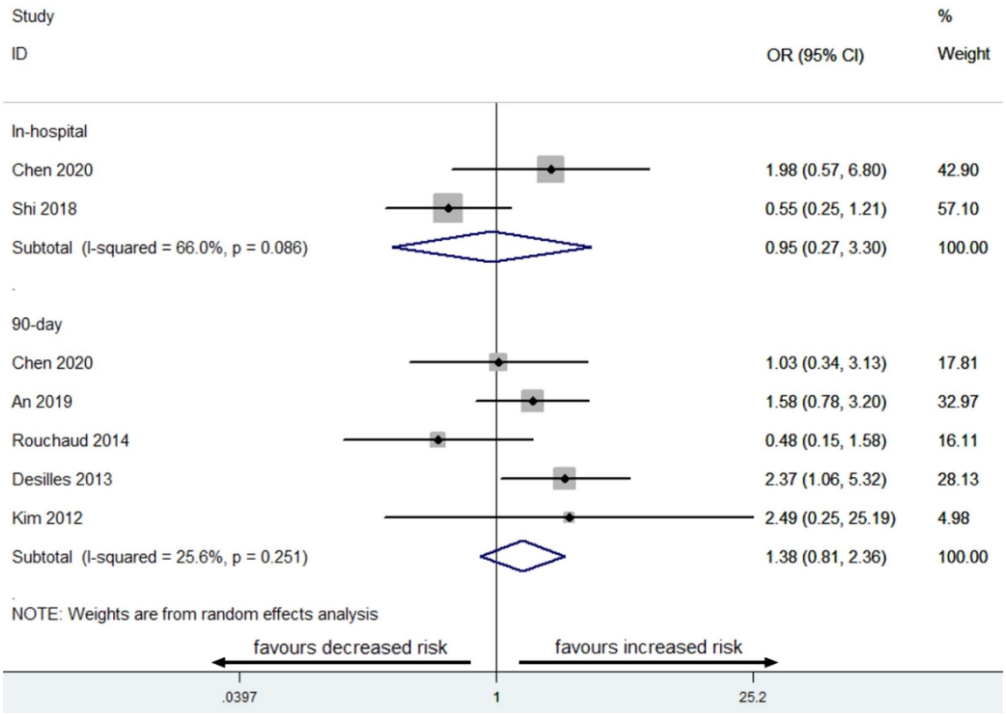

Figure 3. Summary of the odds ratios (ORs) for the associations between contrast extravasation (CE) and in-hospital mortality and 90-day mortality. Each diamond indicates the OR, and the horizontal line indicates the 95% confidence interval (CI). CE was not associated with in-hospital mortality (heterogeneity test: I2 = 66.0%, 95% CI -0.50-0.92) or 90-day mortality (heterogeneity test: I2 = 25.6%, 95% CI -0.85-0.70).

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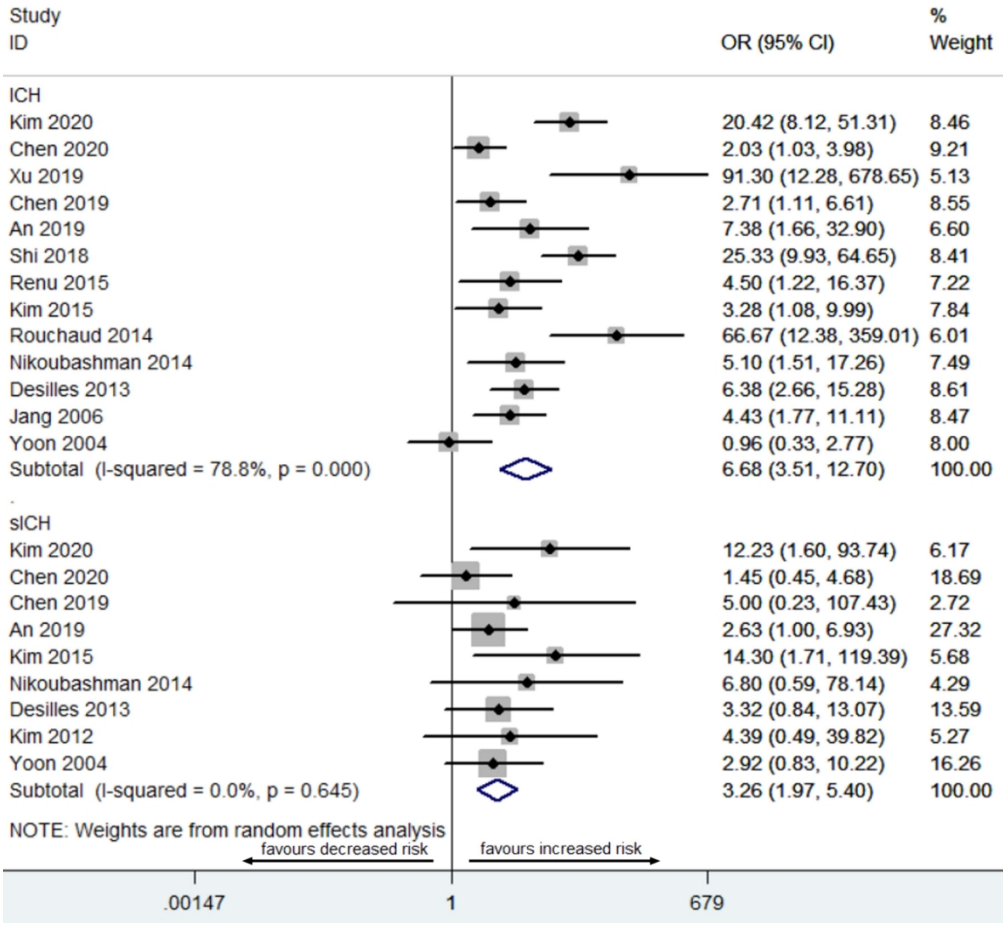

Figure 4. Summary of the odds ratios (ORs) for the associations between contrast extravasation (CE) and risks for intracranial hemorrhage (ICH) and symptomatic intracranial hemorrhage (sICH). Each diamond indicates the OR, and the horizontal line indicates the 95% confidence interval (CI). CE was associated with higher risks of post-EVT ICH (heterogeneity test: I2 = 78.8%, 95% CI 0.64–0.87) and sICH (heterogeneity test: I2 = 0.0%, 95% CI -4.30–0.67).

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Online Supplementary Materials

Title: contrast extravasation and outcome of endovascular therapy in acute ischemic stroke: a systematic review and meta-analysis

Tao Xu, You Wang, JinxianYuan, Yangmei Chen, Haiyan Luo*

Department of Neurology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China.

***Correspondence to:** Haiyan Luo, e-mail: haiyanl@hospital.cqmu.edu.cn, Department of Neurology, the Second Affiliated Hospital of Chongqing Medical University, Yuzhong District, Chongqing, 400010, China. Tel: +8623 63693088. Fax: +8623 63693086.

Table S1. Search strategy in the Medline database.

Steps*	Queries	Number of studies
#1	Search: (((((((Thrombectomy) OR (Endovascular)) OR (reperfusion)) OR (Recanalization)) OR (Aspiration)) OR (retriever)) OR (intra-arterial)) OR (revascularization)	368,970
#2	Search: (((((Blood Brain Barrier[Title/Abstract]) OR (Contrast Staining[Title/Abstract])) OR (Barrier[Title/Abstract])) OR (Contrast[Title/Abstract])) OR (Hyperdensity[Title/Abstract])) OR (high-density[Title/Abstract])	1,250,079
#3	Search: (patients[Title/Abstract]) OR (patient[Title/Abstract])	6,646,483
#4	Search: ((((((Occlusion) OR (Occlusions)) OR (Cerebral Infarction)) OR (Infarction)) OR (stroke)) OR (ischemic)) OR (ischaemia)	1,007,464
#1 and #2 and #3 and #4 and #5	Search: (((((((((Occlusion) OR (Occlusions)) OR (Cerebral Infarction)) OR (Infarction)) OR (stroke)) OR (ischemic)) OR (ischaemia)) AND ((patients[Title/Abstract]) OR (patient[Title/Abstract]))) AND ((((((Blood Brain Barrier[Title/Abstract]) OR (Contrast Staining[Title/Abstract])) OR (Barrier[Title/Abstract])) OR (Contrast[Title/Abstract])) OR (Hyperdensity[Title/Abstract])) OR (high-density[Title/Abstract]))) AND (((((((Thrombectomy) OR (Endovascular)) OR (reperfusion)) OR (Recanalization)) OR (Aspiration)) OR (retriever)) OR (intra-arterial)) OR (revascularization))	5,098

*The search strategy for the Embase and the Cochrane Library database was similar to that used for the Medline database. We also examined the reference lists of the included articles to obtain additional relevant studies. There was no limitation on literature language or publication type or time.

Table S2. The raw data to calculate ORs for the association between CE and the outcomes of EVT.

	CE		non-CE	
First Author, y of publication	**case**	**non-case**	**case**	**non-case**
90 day poor functional outcomes				
Chen 2020		Adjusted OR		
Sun 2019		Adjusted OR		
Chen 2019	27	15	12	28
An 2019	29	21	34	96
Renu 2015		Adjusted		
Rouchaud 2014	11	14	24	14
Nikoubashman 2014	18	6	52	20
Desilles 2013		Adjusted OR		
Kim 2012	19	19	19	11
Yoon 2004	14	7	16	25
Discharge poor functional outcomes				
Chen 2020	45	6	84	31
Shi 2018		Adjusted OR		
Kim 2015	14	19	4	19
Nikoubashman 2014	23	4	67	16
90 day mortality				
Chen 2020	5	46	11	104
An 2019	17	33	32	98
Rouchaud 2014	5	20	13	25
Desilles 2013		Adjusted OR		
Kim 2012	3	35	1	29
Discharge mortality				
Chen 2020	5	46	6	109
Shi 2018	20	134	12	44

ICH				
Kim 2020	84	18	8	35
Chen 2020	25	26	37	78
Xu 2019	58	1	54	85
Chen 2019	26	16	15	25
An 2019		Adjusted OR		
Shi 2018		Adjusted OR		
Renu 2015		Adjusted OR		
Kim 2015	21	12	8	15
Rouchaud 2014	32	6	2	25
Nikoubashman 2014	7	16	6	70
Desilles 2013		Adjusted OR		
Jang 2006	18	13	15	48
Yoon 2004	9	12	18	23
sICH				
Kim 2020	23	79	1	42
Chen 2020	5	46	8	107
Chen 2019	2	40	0	40
An 2019	9	41	10	120
Kim 2015	13	20	1	22
Nikoubashman 2014	2	25	1	85
Desilles 2013		Adjusted OR		
Kim 2012	5	33	1	29
Yoon 2004	7	14	6	35

Abbreviations: CE = contrast extravasation; EVT = endovascular therapy; OR = odds ratio; ICH = intracranial hemorrhage; sICH = symptomatic intracranial hemorrhage.

Table S3. Quality assessment of the included studies*

Reference#	Is the exposed cohort representativ	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of important factors†	Assessment of outcome	Follow up period	Adequacy of follow up of cohorts	Total quality scores
Kim 2020[1]	☆	☆	☆	☆	☆☆	☆	—	—	7
Chen 2020[2]	☆	☆	☆	☆	☆☆	☆	—	—	7
Xu 2019[3]	☆	☆	☆	☆	☆	☆	☆	☆	8
Sun 2019[4]	☆	☆	☆	☆	☆☆	☆	—	—	7
Chen 2019[5]	☆	☆	☆	☆	☆	☆	—	—	6
An 2019[6]	☆	☆	☆	☆	—	☆	☆	☆	7
Shi 2018[7]	☆	☆	☆	☆	☆	☆	—	—	6
Renú 2015[8]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Kim 2015[9]	☆	☆	☆	☆	☆	☆	—	—	6
Rouchaud 2014[10]	☆	☆	☆	☆	☆	☆	—	—	6
Nikoubashman 2014[11]	☆	☆	☆	☆	☆	☆	—	—	6
Desilles 2013[12]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Kim 2012[13]	☆	☆	☆	☆	☆	☆	—	—	6
Jang 2006[14]	☆	☆	☆	☆	☆	☆	—	—	6
Yoon 2004[15]	☆	☆	☆	☆	☆	☆	—	—	6

*Newcastle-Ottawa Scale was used to assess the study quality in this meta-analysis.[16] The full score was 9 stars, and the high-quality study was defined as a study with 8 awarded stars.

†A maximum of two stars could be awarded for this item. One star with adjustment for age, two stars if there were additional population demographics or comorbidities.

Table S4. Sensitivity analyses for the pooled analysis of poor functional outcome at 90 days restricted to predefined variables.

Variable	No. of Studies	OR	95% CI	p value	I^2	PI
Study design						0.317
Retrospective	7	1.67	1.13-2.47	0.011	69.0	
Prospective	3	2.77	1.76-4.35	< 0.001	82.6	
Sample size						0.262
≥100	6	2.88	1.48-5.60	0.002	65.9	
<100	4	1.37	0.44-4.23	0.587	80.2	
Assessment strategy of CE						0.039
Dual-energy CT	4	4.45	2.51-7.87	< 0.001	22.8	
NECT and a follow-up NECT or MRI at 24 hours after EVT	6	1.31	0.67-2.57	0.429	67.2	
Study quality						0.510
<8	8	1.94	1.02-3.69	0.044	70.6	
≥8	2	3.74	0.40-35.46	0.250	89.7	
Adjusted for confounders						0.282
No	6	1.62	0.73-3.63	0.238	77.0	
Yes	4	3,43	1.27-9.25	0.015	72.7	

Abbreviations: CE = contrast extravasation; EVT = endovascular therapy; NECT = non-enhanced computed tomography; MRI = magnetic resonance imaging; OR = odds ratio.

Table S5. Sensitivity analyses for the pooled analysis of post-EVT ICH restricted to predefined variables.

Variable	No. of Studies	OR	95% CI	p-values	I^2	PI
Study design						0.511
Retrospective	9	5.80	2.58-13.03	< 0.001	83.4	
Prospective	4	9.29	3.40-25.35	< 0.001	55.1	
Sample size						0.305
≥100	8	9.03	4.00-20.38	< 0.001	78.4	
<100	5	4.15	1.48-11.66	0.007	77.8	
Assessment strategy of CE						0.400
Dual-energy CT	3	3.24	1.50-6.99	0.003	33.6	
NECT and a follow-up NECT or MRI at 24 hours after EVT	10	8.02	3.69-17.43	< 0.001	80.6	
Study quality						0.494
<8	10	5.90	2.78-12.51	< 0.001	81.4	
≥8	3	10.84	2.67-44.05	0.001	70.0	
Adjusted for confounders						0.641
No	9	6.01	2.63-13.73	< 0.001	81.8	
Yes	4	9.10	4.04-20.50	< 0.001	53.0	

Abbreviations: CE = contrast extravasation; NECT = non-enhanced computed tomography; MRI = magnetic resonance imaging; OR = odds ratio; PI, P interaction.

Table S6. Egger's tests for publication bias.

Variables	Egger's tests	
	p-values	**95% CIs**
Association between CE and poor functional outcome at 90 days	0.68	-5.36-7.85
Association between CE and mortality at 90 days	0.65	-6.37-4.65
Association between CE and post-EVT ICH	0.10	-0.83-8.36
Association between CE and post-EVT sICH	0.05	-0.04-2.96

Abbreviations: CE = contrast extravasation; EVT = endovascular therapy; ICH = intracranial hemorrhage; sICH = symptomatic intracranial hemorrhage; PI, P interaction.

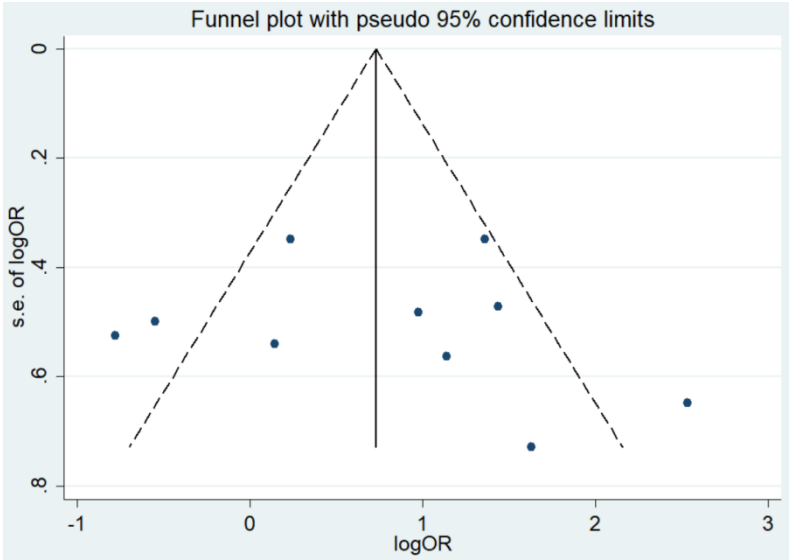

Figure S1. Funnel plot for publication bias test for the associations between contrast extravasation and poor functional outcomes at 90 days.

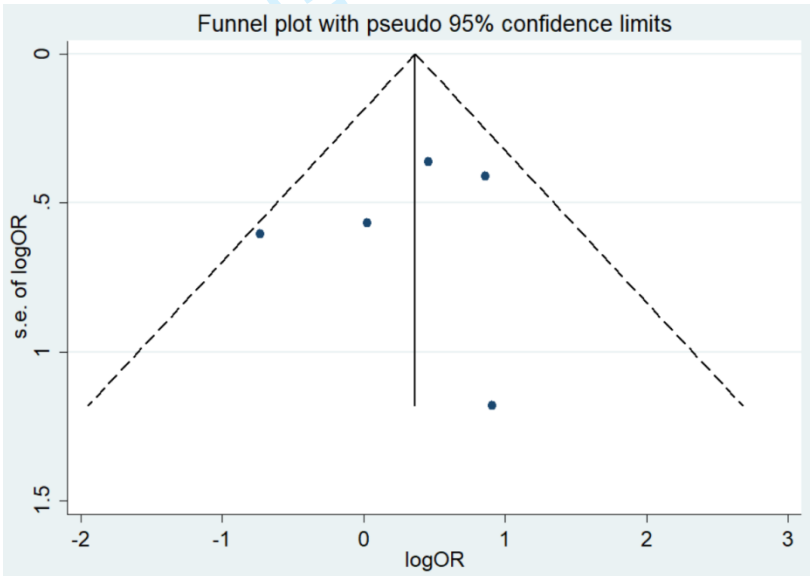

Figure S2. Funnel plot for publication bias test for the associations between contrast extravasation and mortality at 90 days.

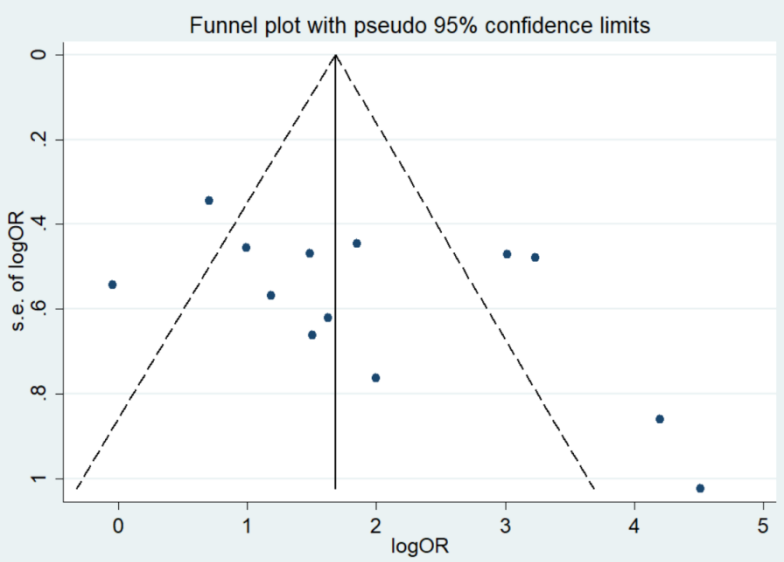

Figure S3. Funnel plot for publication bias test for the associations between contrast extravasation and intracranial haemorrhage.

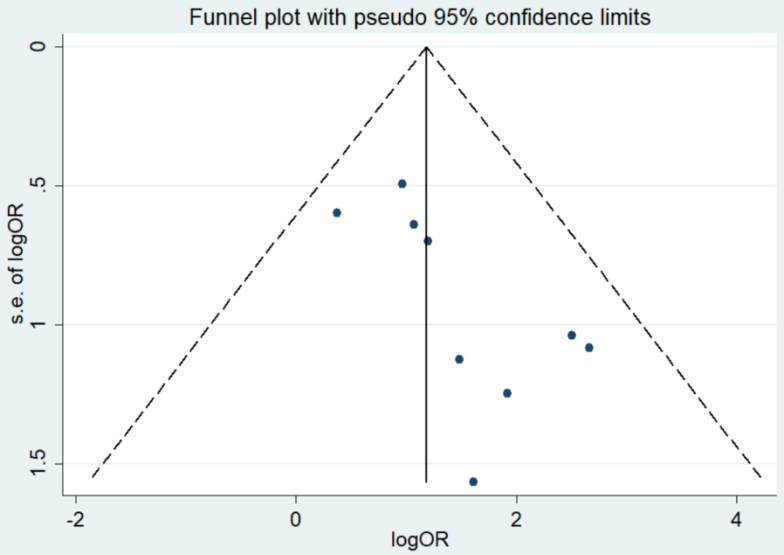

Figure S4. Funnel plot for publication bias test for the associations between contrast extravasation and symptomatic intracranial haemorrhage.

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2. Chen Z, Zhang Y, Su Y, et al. Contrast Extravasation is Predictive of Poor Clinical Outcomes in Patients Undergoing Endovascular Therapy for Acute Ischemic Stroke in the Anterior Circulation. *J Stroke Cerebrovasc Dis* 2020;**29**:104494.
3. Xu C, Zhou Y, Zhang R, et al. Metallic Hyperdensity Sign on Noncontrast CT Immediately after Mechanical Thrombectomy Predicts Parenchymal Hemorrhage in Patients with Acute Large-Artery Occlusion. *AJNR Am J Neuroradiol* 2019;**40**:661-67.
4. Sun Y, Su Y, Chen Z, et al. Contrast Extravasation After Endovascular Treatment in Posterior Circulation Stroke. *World Neurosurg* 2019;**130**:e583-e87.
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6. An H, Zhao W, Wang J, et al. Contrast Staining may be Associated with Intracerebral Hemorrhage but Not Functional Outcome in Acute Ischemic Stroke Patients Treated with Endovascular Thrombectomy. *Aging Dis* 2019;**10**:784-92.
7. Shi ZS, Duckwiler GR, Jahan R, et al. Early Blood-Brain Barrier Disruption after Mechanical Thrombectomy in Acute Ischemic Stroke. *J Neuroimaging* 2018;**28**:283-88.
8. Renú A, Amaro S, Laredo C, et al. Relevance of blood-brain barrier disruption after endovascular treatment of ischemic stroke: dual-energy computed tomographic study. *Stroke* 2015;**46**:673-9.
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11. Nikoubashman O, Reich A, Pjontek R, et al. Postinterventional subarachnoid haemorrhage after endovascular stroke treatment with stent retrievers. *Neuroradiology* 2014;**56**:1087-96.
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13. Kim JT, Heo SH, Cho BH, et al. Hyperdensity on non-contrast CT immediately after intra-arterial revascularization. *J Neurol* 2012;**259**:936-43.
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MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5
2	Hypothesis statement	5
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5,6
5	Type of study designs used	6
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (e.g, librarians and investigators)	6,7
8	Search strategy, including time period included in the synthesis and key words	6,7 Supplementary Materials
9	Effort to include all available studies, including contact with authors	Supplementary Materials
10	Databases and registries searched	6,7 Supplementary Materials
11	Search software used, name and version, including special features used (eg, explosion)	6,7
12	Use of hand searching (eg, reference lists of obtained articles)	Supplementary Materials
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	NA
15	Method of handling abstracts and unpublished studies	6-8
16	Description of any contact with authors	NA
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6,7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7,8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Supplementary Materials
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8
22	Assessment of heterogeneity	8,9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8,9
24	Provision of appropriate tables and graphics	8,9
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig.2-Fig.4
26	Table giving descriptive information for each study included	Table 1and 2
27	Results of sensitivity testing (eg, subgroup analysis)	11, Supplementary

		Materials
28	Indication of statistical uncertainty of findings	9-11

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	11-12
30	Justification for exclusion (eg, exclusion of non-English language citations)	7
31	Assessment of quality of included studies	8 Supplementary Materials
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12-14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	14
34	Guidelines for future research	14
35	Disclosure of funding source	14

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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