BMJ Open

Contrast extravasation and outcome of endovascular therapy in acute ischaemic 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;
haiyanl@hospital.cqmu.edu.cn

ABSTRACT

Objective Contrast extravasation (CE) after endovascular therapy (EVT) is commonly present in acute ischaemic 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 ORs with 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 1897 patients were included. Patients with CE had higher risks of poor functional outcome at discharge (2.38, 95% CI 1.45 to 3.89 p=0.001; n=545) and poor functional outcome at 90 days (OR 2.16, 95% CI 1.20 to 3.90; n=1194). We found no association between CE and in-hospital mortality (OR 0.95, 95% CI 0.27 to 3.30; n=376) or 90-day mortality (OR 1.38, 95% CI 0.81 to 2.36; n=697) after EVT. Moreover, CE was associated with higher risks of post-EVT intracranial haemorrhage (ICH) (OR 6.68, 95% CI 3.51 to 12.70; n=1721) and symptomatic ICH (OR 3.26, 95% CI 1.97 to 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 unfavourable functional outcomes and ICH. Thus, we should pay more attention to CE in patients with AIS undergoing EVT.

Strengths and limitations of the study

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

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

► 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.

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

► 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 ischaemic 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 non-enhanced CT (NECT) scan or dual-energy CT (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 guidelines.[5] The Medline and Embase databases were systematically searched using a predefined retrieval strategy (online supplemental table 1 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, MRI 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 but no high density in the corresponding areas on virtual noncontrast-enhanced (VNC) images.[3] The differential diagnosis between CE and cerebral haemorrhage 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 haemorrhage (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 haemorrhagic event, including haemorrhagic infarction, parenchymal haemorrhage or ICH-extracerebral haemorrhage[8]; sICH was defined as ICH with significant neurological aggravation and an increase in National Institutes of Health Stroke Scale score ≥4 in total.

Table 1 The assessment strategies of contrast extravasation and haemorrhage after EVT

Assessment methods	Definition of CE	Definition of haemorrhage	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 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	Haemorrhage 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	Haemorrhage 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]

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

5. Assessment of outcome: The study provided the adjusted or unadjusted OR and the corresponding 95% 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: Non-original 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 online supplemental table 2 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 recognised 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
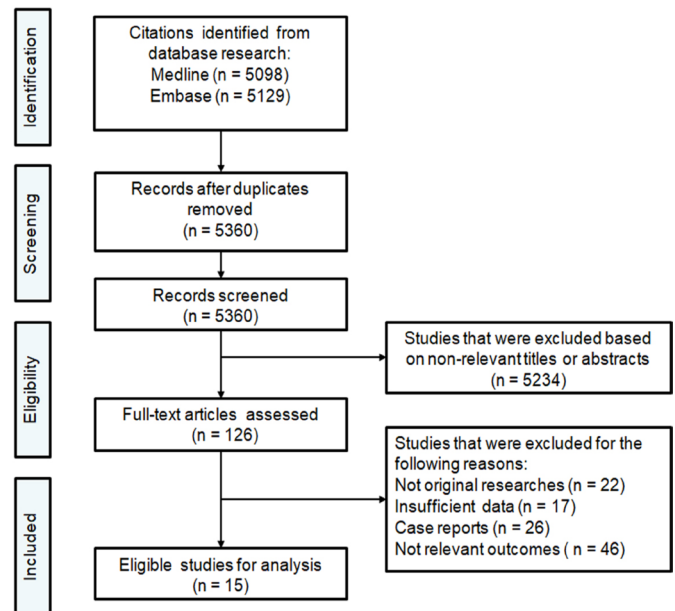

Figure 1 Flow chart of the literature search process.

also performed subgroup analyses based on predefined variables (eg, 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 V.12.0 (StataCorp) 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 5360 unduplicated records. A total of 15 articles published between 2004 and 2020 including 1897 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 four studies used DECT immediately after EVT to assess CE after EVT.[2 3 14 16] The characteristics of each included study are summarised in table 2. Of the 15 included studies, five were from China[2 3 12–14], five were from South Korea,[4 6 19–21] two were from France,[17 18] one was from the USA,[15] one was from

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

First author, year of publication	Country	Participants inclusion period	Study design	Primary methods of EVT	Vascular lesion location	Age, year/men, %/No. in cohort	Outcomes of EVT
Kim et al[4]	South Korea	2012–2019	R	SR, AT and IA	ACC	NA/54.9%/145	ICH and sICH
Chen et al[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 et al[12]	China	2014–2018	P	SR	NA	69.8%±11.7/58.6%/198	ICH
Sun et al[2]	China	2016–2018	R	SR	PCA	60.9%±10.6/82.4%/108	Poor functional outcomes at 3 months
Chen et al[13]	China	2015–2016	R	SR	ACC	NA/54.9%/82	Poor functional outcomes at 3 months; ICH and sICH
An et al[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 et al[15]	USA	NA	R	SR, AT and IA	ACC	NA/42.9%/210	Poor functional outcomes at discharge; mortality at discharge; ICH
Renú et al[16]	Spain	2010–2013	P	SR	NA	NA/47.7%/132	Poor functional outcomes at 3 months; ICH
Kim et al[6]	South Korea	2007–2014	R	SR, AT and IA	ACC	NA/50.0%/56	Poor functional outcomes at discharge; ICH and sICH
Rouchaud et al[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 et al[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 et al[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 et al[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 et al[20]	South Korea	1999–2004	R	IA	ACC	64.7%±11.5/67.0%/94	ICH
Yoon et al[21]	South Korea	1995–2002	R	IA	ACC	NA/56.5%/62	Poor functional outcomes at 3 months; ICH and sICH

ACC, anterior cerebral circulation; AP, angioplasty; AT, aspiration technique; EVT, endovascular therapy; IA, intra-arterial thrombolysis; ICH, intracranial haemorrhage; NA, not available; P, prospective; PCC, posterior cerebral circulation; R, retrospective; sICH, symptomatic intracranial haemorrhage; SR, stent retriever.
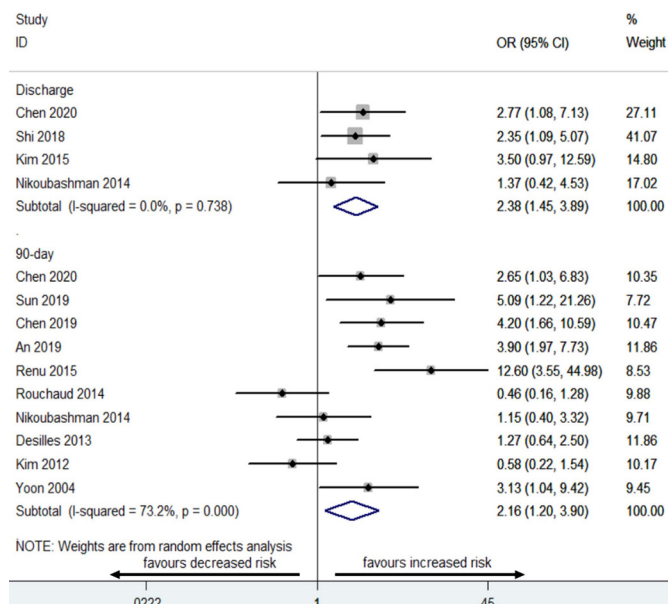
Figure 2 Summary of ORs for the relationships between contrast extravasation (CE) and poor functional outcomes at discharge and 90 days. Each diamond indicates the OR, and the horizontal line indicates the 95% CI. CE was associated with higher risks of poor functional outcome at discharge (heterogeneity test: I^2=0.0%, 95% CI 0.00 to 0.83) and poor functional outcome at 90 days (heterogeneity test: I^2=73.2%, 95% CI 0.50 to 0.86).

Spain[16] and one was from Germany.[7] Eleven studies had a retrospective design,[2–4 6 7 13 15 17 19–21] and four 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: eight studies included patients with AIS caused by LVO in the anterior cerebral circulation (ACC); three 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 summarised in online supplemental table 3 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 outcomes 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 to 3.89; p=0.001; 4 studies; n=545) and poor 90-day functional outcome (OR 2.16, 95% CI 1.20 to 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 to 3.30; p=0.934; 2 studies; n=376) or 90-day mortality (OR 1.38, 95% CI 0.81 to 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 to 12.70; p<0.001; 13 studies; n=1721) and sICH (OR 3.26, 95% CI 1.97 to 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 to 0.86) and post-EVT ICH (I^2=78.80%, 95% CI 0.64 to 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 (online supplemental table 4 in the online data supplement) and the association between CE and post-EVT ICH (online supplemental table 5 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) (online supplemental table 4 in the online data supplement).

Publication bias assessment

Asymmetric funnel plots were identified in the pooled estimates (included ≥5 studies) (online supplemental figures 1–4 in the online data supplement). However, Egger's tests indicated no significant publication bias in
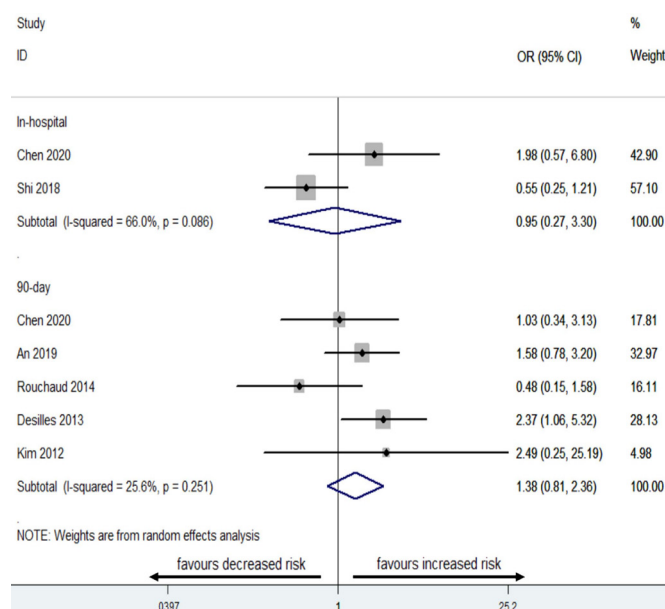

Figure 3 Summary of ORs for the relationships between contrast extravasation (CE) and in-hospital mortality and 90-day mortality. Each diamond indicates the OR, and the horizontal line indicates the 95% CI. CE was not associated with in-hospital mortality (heterogeneity test: I^2=66.0%, 95% CI −0.50 to 0.92) or 90-day mortality (heterogeneity test: I^2=25.6%, 95% CI −0.85 to 0.70).
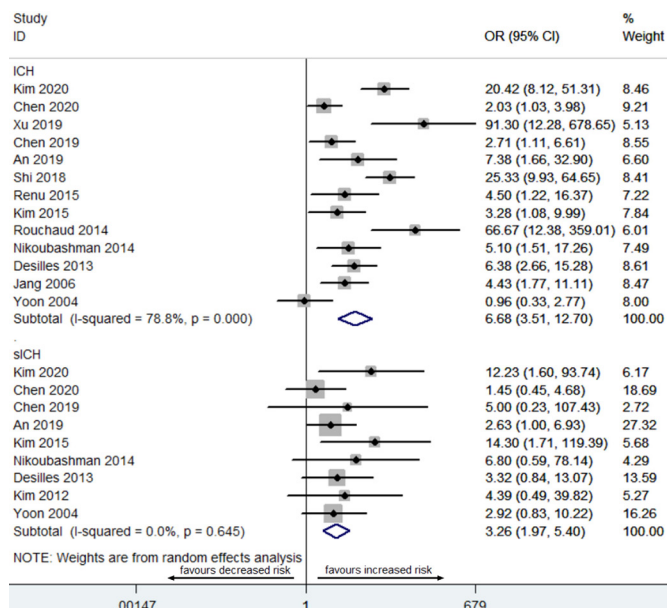
Figure 4 Summary of ORs for the relationships between contrast extravasation (CE) and risks for intracranial haemorrhage (ICH) and symptomatic ICH (sICH). Each diamond indicates the OR, and the horizontal line indicates the 95% CI. CE was related to higher risks of post-EVT ICH (heterogeneity test: I^2=78.8%, 95% CI 0.64 to 0.87) and sICH (heterogeneity test: I^2=0.0%, 95% CI −4.30 to 0.67). EVT, endovascular therapy.

the pooled estimates (online supplemental table 6 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 1897 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 unfavourable 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 ischaemia and reperfusion injury.[3 16] In patients with AIS, ischaemic 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 ischaemic time) and hyper-perfusion after revascularisation 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 recanalisation time, gentle delivery of the EVT device, and controlling blood pressure after EVT) that are able to protect and stabilise 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 haemorrhage 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 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 of the relationship between the coexistence of CE and haemorrhage 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 unfavourable 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.

ORCID iD
Haiyan Luo http://orcid.org/0000-0001-7120-5175

REFERENCES

1. Román LS, Menon BK, Blasco J, *et al*. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *Lancet Neurol* 2018;17:895–904.
2. Sun Y, Su Y, Chen Z, *et al*. Contrast extravasation after endovascular treatment in posterior circulation stroke. *World Neurosurg* 2019;130:e583–7.
3. 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.
4. Kim H, Lee S-J, Lee T-K, *et al*. Subarachnoid contrast accumulation and Alberta stroke program early computed tomography score applied to contrast accumulation after thrombectomy as predictors of symptomatic hemorrhage. *World Neurosurg* 2020;138:e847–58.
5. Stroup DF, Berlin JA, Morton SC, *et al*. Meta-Analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (moose) group. *JAMA* 2000;283:2008–12.
6. Kim JM, Park KY, Lee WJ, *et al*. The cortical contrast accumulation from brain computed tomography after endovascular treatment predicts symptomatic hemorrhage. *Eur J Neurol* 2015;22:1453–8.
7. Nikoubashman O, Reich A, Pjontek R, *et al*. Postinterventional subarachnoid haemorrhage after endovascular stroke treatment with stent retrievers. *Neuroradiology* 2014;56:1087–96.
8. von Kummer R, Broderick JP, Campbell BCV, *et al*. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* 2015;46:2981–6.
9. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
10. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. *BMC Med Res Methodol* 2015;15:35.
11. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
12. 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;40:661–7.
13. Chen W-H, Yi T-Y, Wu Y-M, *et al*. Parenchymal hyperdensity on C-arm CT images after endovascular therapy for acute ischaemic stroke predicts a poor prognosis. *Clin Radiol* 2019;74:399–404.
14. 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.
15. Shi Z-S, Duckwiler GR, Jahan R, *et al*. Early blood-brain barrier disruption after mechanical thrombectomy in acute ischemic stroke. *J Neuroimaging* 2018;28:283–8.
16. 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.
17. Rouchaud A, Pistocchi S, Blanc R, *et al*. Predictive value of flat-panel CT for haemorrhagic transformations in patients with acute stroke treated with thrombectomy. *J Neurointerv Surg* 2014;6:139–43.
18. Desilles J-P, Rouchaud A, Labreuche J, *et al*. Blood-Brain barrier disruption is associated with increased mortality after endovascular therapy. *Neurology* 2013;80:844–51.
19. Kim J-T, Heo S-H, Cho B-H, *et al*. Hyperdensity on non-contrast CT immediately after intra-arterial revascularization. *J Neurol* 2012;259:936–43.
20. Jang YM, Lee DH, Kim HS, *et al*. The fate of high-density lesions on the non-contrast CT obtained immediately after intra-arterial thrombolysis in ischemic stroke patients. *Korean J Radiol* 2006;7:221–8.
21. Yoon W, Seo JJ, Kim JK, *et al*. Contrast enhancement and contrast extravasation on computed tomography after intra-arterial thrombolysis in patients with acute ischemic stroke. *Stroke* 2004;35:876–81.
22. Shi Z-S, Liebeskind DS, Loh Y, *et al*. Predictors of subarachnoid hemorrhage in acute ischemic stroke with endovascular therapy. *Stroke* 2010;41:2775–81.

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.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

BMJ Open

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

First Author, y of publication	CE		non-CE	
	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.
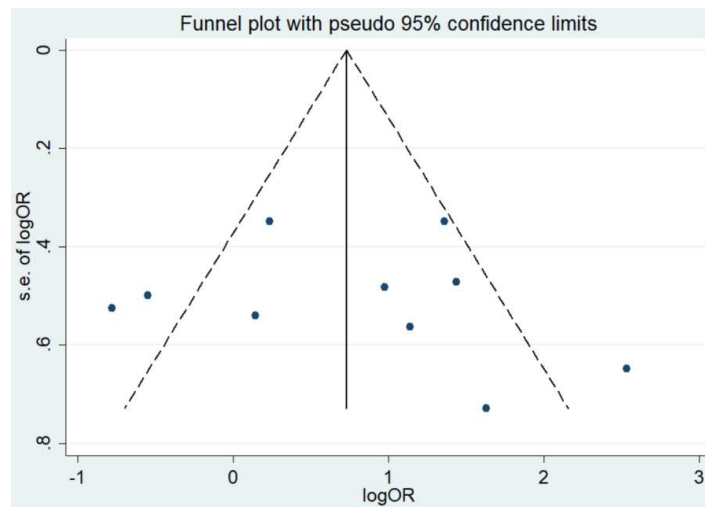
Figure S1. Funnel plot for publication bias test for the associations between contrast extravasation and poor functional outcomes at 90 days.
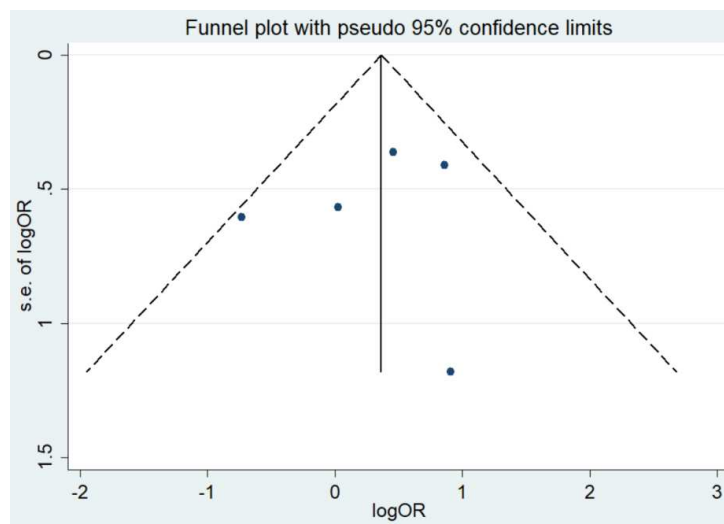

Figure S2. Funnel plot for publication bias test for the associations between contrast extravasation and mortality at 90 days.
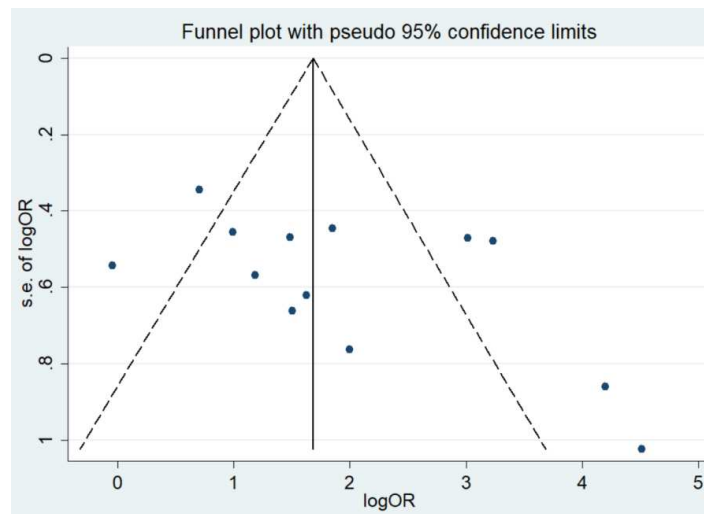
Figure S3. Funnel plot for publication bias test for the associations between contrast extravasation and intracranial haemorrhage.
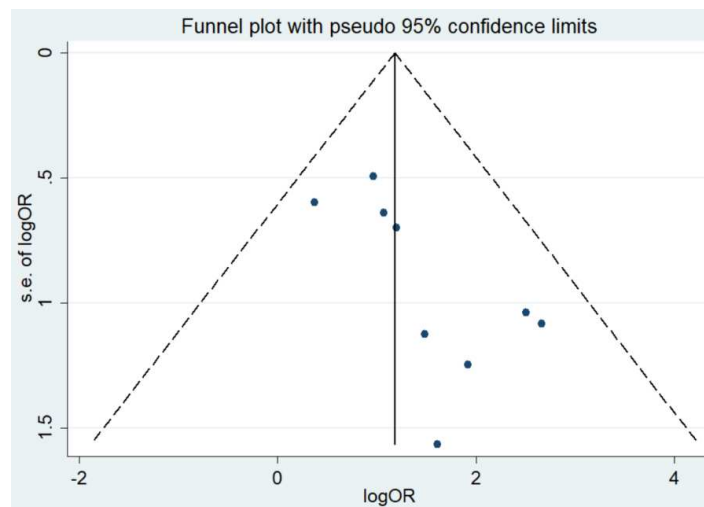

Figure S4. Funnel plot for publication bias test for the associations between contrast extravasation and symptomatic intracranial haemorrhage.

References

1. Kim H, Lee SJ, Lee TK, et al. Subarachnoid Contrast Accumulation and Alberta Stroke Program Early Computed Tomography Score Applied to Contrast Accumulation After Thrombectomy as Predictors of Symptomatic Hemorrhage. *World Neurosurg* 2020.

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.

5. Chen WH, Yi TY, Wu YM, et al. Parenchymal hyperdensity on C-arm CT images after endovascular therapy for acute ischaemic stroke predicts a poor prognosis. *Clin Radiol* 2019;**74**:399-404.

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.

9. Kim JM, Park KY, Lee WJ, et al. The cortical contrast accumulation from brain computed tomography after endovascular treatment predicts symptomatic hemorrhage. *Eur J Neurol* 2015;**22**:1453-8.

10. Rouchaud A, Pistocchi S, Blanc R, et al. Predictive value of flat-panel CT for haemorrhagic transformations in patients with acute stroke treated with thrombectomy. *J Neurointerv Surg* 2014;**6**:139-43.

11. Nikoubashman O, Reich A, Pjontek R, et al. Postinterventional subarachnoid haemorrhage after endovascular stroke treatment with stent retrievers. *Neuroradiology* 2014;**56**:1087-96.

12. Desilles JP, Rouchaud A, Labreuche J, et al. Blood-brain barrier disruption is associated with increased mortality after endovascular therapy. *Neurology* 2013;**80**:844-51.

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.

14. Jang YM, Lee DH, Kim HS, et al. The fate of high-density lesions on the non-contrast CT obtained immediately after intra-arterial thrombolysis in ischemic stroke patients. *Korean J Radiol* 2006;**7**:221-8.

15. Yoon W, Seo JJ, Kim JK, et al. Contrast enhancement and contrast extravasation on computed tomography after intra-arterial thrombolysis in patients with acute ischemic stroke. *Stroke* 2004;**35**:876-81.

16. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;**25**:603-5.