Systematic Review and Meta-Analysis

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Comparative efficacy and safety of bridging strategies with direct mechanical thrombectomy in large vessel occlusion

A systematic review and meta-analysis

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Abstract

Background: Whether bridging strategies[intravenous thrombolysis (IVT) + mechanical thrombectomy (MT)] are superior to mechanical thrombectomy alone for large vessel occlusion(LVO) is still uncertain. A systematic review and meta-analysis was conducted to investigate and evaluate comparative efficacy and safety of bridging strategies vs direct MT in patients with LVO.

Methods: The PubMed, EMBASE and Cochrane library databases were searched to evaluate the efficacy and safety of bridging strategies with direct MT in LVO. Functional independence, mortality, symptomatic intracranial hemorrhage (sICH) and successful recanalization were assessed. The risk ratio (RR) and its 95% confidence interval (CI) were calculated.

Results: The proportion of patients who received MT+IVT was significantly higher in functional independence and successful recanalization rate than MT alone patients. However, pooled results showed that the mortality of patients who received MT+IVT was significantly lower than that of MT alone patients. Moreover, no significant differences were observed in the incidence of sICH between the 2 groups.

Conclusion: The findings of our meta-analysis confirmed that bridging strategies improved functional outcomes, successful recanalization rate and reduced mortality rates. Moreover, the incidence of sICH showed no differences between the bridging strategies and MT alone treatments. However, the conduct of high-quality randomized clinical trials that directly compare both strategies is warranted.

Abbreviations: AIS = acute ischemic stroke, CI = confidence interval, ET = endovascular thrombectomy, IVT = intravenous thrombolysis, LVO = large vessel occlusion, MT = mechanical thrombectomy, RCT = randomized controlled trials, RR = risk ratio, sICH = symptomatic intracranial hemorrhage, tPA = tissue plasminogen activator.

Keywords: bridging strategies, intravenous thrombolysis, mechanical thrombectomy, meta-analysis, systematic review

1. Introduction

With the development of stroke units and progression of reperfusion therapies, the management of acute ischemic stroke (AIS) has been significantly developed over the past 20 years. Until recently, reperfusion mainly consisted of intravenous thrombolysis (IVT), and the application of IVT within 4.5 hours after symptom onset is shown to be effective.[1,2] Mechanical thrombectomy (MT) is limited to patients with basilar artery occlusion and contraindication to IVT.[3,4] Since December 2014,[5] bridging therapy, which consists of the application of IVT in 4.5 hours and MT in 6 hours of symptom onset, showed advantages when compared with MT alone in AIS with large vessel occlusion (LVO) patients.

On the other hand, observational trials from single-center series, as well as pooled and meta-analyses suggested that direct endovascular thrombectomy (ET) might demonstrated similar effectiveness to bridging therapy (IVT + ET) in LVO patients.[6–8] In contrast, another recent meta-analysis showed that patients with IVT+MT had better functional outcomes, lower mortality rates, higher rates of successful recanalization, and similar probability of symptomatic intracerebral hemorrhage (sICH) compared with patients treated with direct MT.[9] Moreover, a recent Swiss study highlighted that intravenous injection of tissue plasminogen activator (tPA) pretreatment in patients with LVO is associated with potential side effects, including high risk of cerebral hemorrhage, delayed onset of endovascular treatment and preclusion to the use of antiplatelets and heparin after tPA infusion.[6]

In view of these former considerations, a systematic review and meta-analysis of the available studies was performed to evaluate the comparative efficacy and safety between direct MT and bridging therapy (IVT and MT) in patients with LVO.

Editor: Massimo Tusconi.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2019) 98:14(e14956)

Received: 2 December 2018 / Received in final form: 28 February 2019 / Accepted: 1 March 2019

http://dx.doi.org/10.1097/MD.0000000000014956

2. Materials and methods

2.1. Search strategy

The electronic databases including PubMed, Embase, and Cochrane Library were searched by using the keywords "bridging therapy", "intravenous thrombolysis", "mechanical thrombectomy", and "large vessel occlusion/stroke". The last research was updated on October 15, 2018.

2.2. Selection criteria

The following major criteria should be met by the included studies:

1. Patients undergoing acute stroke due to LVO;
2. Comparison: one group should receive bridging therapy (IVT pretreatment followed by MT), and another group should receive alone MT;
3. primary outcomes: functional independence, mortality, successful reperfusion, and symptomatic intracerebral hemorrhage;
4. studies published in English language; and
5. the type of study design was not restricted, where both randomized controlled trials (RCT) and observational studies were included.

2.3. Data extraction and quality assessment

Two investigators independently extracted data and reached a consensus on all the items. Any disagreement was resolved by discussing with the third expert. Data retrieved from the reports included baseline data (first author, publication year, country, mean age, intervention, follow-up time), and primary outcomes (functional independence, mortality, successful reperfusion, and symptomatic intracerebral hemorrhage) assessment. We evaluated the quality of studies using the Cochrane Collaboration's tool for assessing risk of bias.[10]

2.4. Statistical analysis

The pooled relative ratio (RR) with corresponding 95% confidence interval (95% CI) was estimated. Heterogeneity in this meta-analysis was checked by using the I^2 statistic. When I^2 was <50%, then the pooled RR of each study was calculated by

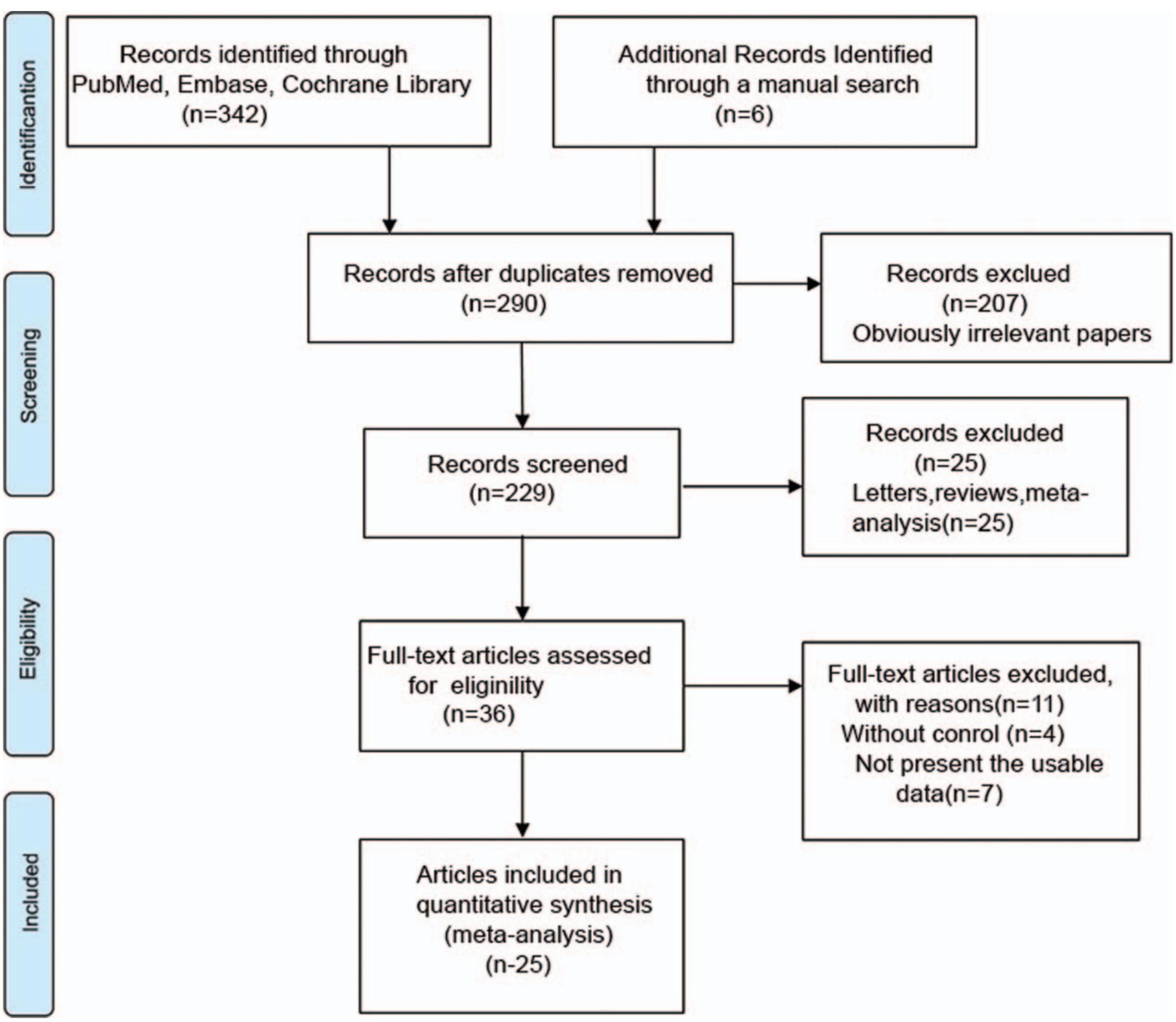

Figure 1. Flow diagram of study selection process.

using the fixed-effects model (the Mantel-Haenszel method); otherwise, random-effects model (the DerSimonian and Laird method) was used. Publication bias was evaluated by visual inspection of symmetry of funnel plot and assessment of Begg and Egger tests ($P<.05$ was regarded as representative of statistical significance). Trim-and-fill method was used to determine the effect of potential publication bias on the pooled estimates. All analyses were performed using STATA 12.0 (STATA Corp., College Station, TX), using 2-sided significance tests at 5% significance level.

3. Results

3.1. Characteristics of the studies

As shown in Figure 1, 348 potentially eligible studies were screened out in the preliminary search. Of these, 232 articles were

Table 1

Characteristics of the studies included in this meta-analysis.

Authors/year of publication	Country	Females (%)	Mean age	Intervention MT+IVT	Intervention MT	Follow-up	Study design	Outcomes assessed
Davalos/2012	Spain	MT+IVT:39%; MT:49%	MT+IVT: 62.2±12.7Y; MT: 66.4±13.6Y	74	67	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Pfefferkorn/2012	Germany	MT+IVT:38%; MT:61%	MT+IVT: 62.1±14.4Y; MT: 64.6±12.9Y	35	30	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Sallustio/2013	Italy	MT+IVT:59%; MT:41%	MT+IVT: 68.2±13.4Y; MT: 63.9±12.6Y	51	46	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Kass-Hout/2014	USA	MT+IVT:52%; MT:53%	MT+IVT: 67.64±14.85Y; MT: 69.26±15.76Y	42	62	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Goyal/2015	Canada	MT+IVT:52.1%; MT:52.7%	MT+IVT: 71±3.5Y; MT: 70±3.5Y	165	150	3M	RCT	Functional independence, mortality, sICH and successful recanalization
Guedin/2015	France	MT+IVT:60.7%; MT:62.5%	MT+IVT: 69.2±13.5Y; MT: 64.6±15.3Y	28	40	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Leker/2015	Israel	MT+IVT:67%; MT:55%	MT+IVT: 66.8±13.7Y; MT: 64.4±14.7Y	24	33	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Behme/2016	Germany	MT+IVT:48%; MT:67%	MT+IVT: 74±14.8Y; MT: 74±10.8Y	66	27	3M	Non-randomized	Successful recanalization
Broeg-Morvay/2016	Switzerland	MT+IVT:47.4%; MT:37.5%	MT+IVT: 73±14Y; MT: 77±14Y	156	40	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Kaesmacher/2016	Germany	MT+IVT:54.4%; MT:54.4%	MT+IVT: 69.8±15.5Y; MT: 73.3±12.4Y	160	79	NA	Non-randomized	Mortality, sICH and successful recanalization
mulder/2016	Netherlands	MT+IVT:42%; MT:36%	MT+IVT: 65.4±3.6Y; MT: 67.5±4.1Y	445	55	3M	Non-randomized	sICH and successful recanalization
abilleira/2017	Spain	MT+IVT:46%; MT:48.4%	MT+IVT: 68.6±12.8Y; MT: 68.1±13.5Y	567	599	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Coutinho/2017	Canada	MT+IVT:60.6%; MT:55.7%	MT+IVT: 67±13Y; MT: 69±12Y	160	131	3M	RCT	Functional independence, mortality, sICH and successful recanalization
Gerschenfeld/2017	France	MT+IVT:43%; MT:50.8%	MT+IVT: 73±3.5Y; MT: 70±6Y	100	59	3M	Non-randomized	Functional independence, and successful recanalization
Merlino/2017	Italy	MT+IVT:45.5%; MT:57.6%	MT+IVT: 69.6±12.7Y; MT: 70.8±12.2Y	33	33	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Mistry/2017	USA	54.4%	65.8±14.3Y	119	109	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Rai/2017	USA	MT+IVT:47%; MT:61%	MT+IVT: 63±19Y; MT: 69±18Y	38	52	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Wang/2017	China	MT+IVT:43.5%; MT:44.9%	MT+IVT: 67±2.4Y; MT: 67±2.7Y	138	138	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Weber/2017	Germany	MT+IVT:50.5%; MT:46.2%	MT+IVT: 70.2±12.6Y; MT: 69.3±14.9Y	105	145	3M	Non-randomized	Functional independence, mortality, and sICH
Wee/2017	Singapore	MT+IVT:62%; MT:45%	MT+IVT: 73±16Y; MT: 71±14Y	21	29	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Balodis/2018	UK	MT+IVT:54.8%; MT:54.8%	MT+IVT: 72±12.5Y; MT: 72±9.9Y	84	62	3M	Non-randomized	Functional independence, mortality, and sICH
Choi/2018	Korea	MT+IVT:32.6%; MT:55.3%	MT+IVT: 68.9±12.8Y; MT: 72.6±14.1Y	43	38	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Goyal/2018	Greece	MT+IVT:52.4%; MT:47.3%	MT+IVT: 62.5±17Y; MT: 61±19.8Y	292	277	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Maingard/2018	Ireland	MT+IVT:45%; MT:44%	MT+IVT: 66±14Y; MT: 68±14Y	210	145	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization
Sallustio/2018	Italy	MT+IVT:37.5%; MT:56%	MT+IVT: 71.8±14Y; MT: 70.3±12.9Y	193	132	3M	Non-randomized	Functional independence, mortality, sICH and successful recanalization

IVT=intravenous thrombolysis, M=months, MT=mechanical thrombectomy, NA=Not available, RCT=randomized controlled trial, sICH=symptomatic intracranial hemorrhage, UK=the United Kingdom, USA=United States of America, Y=years.

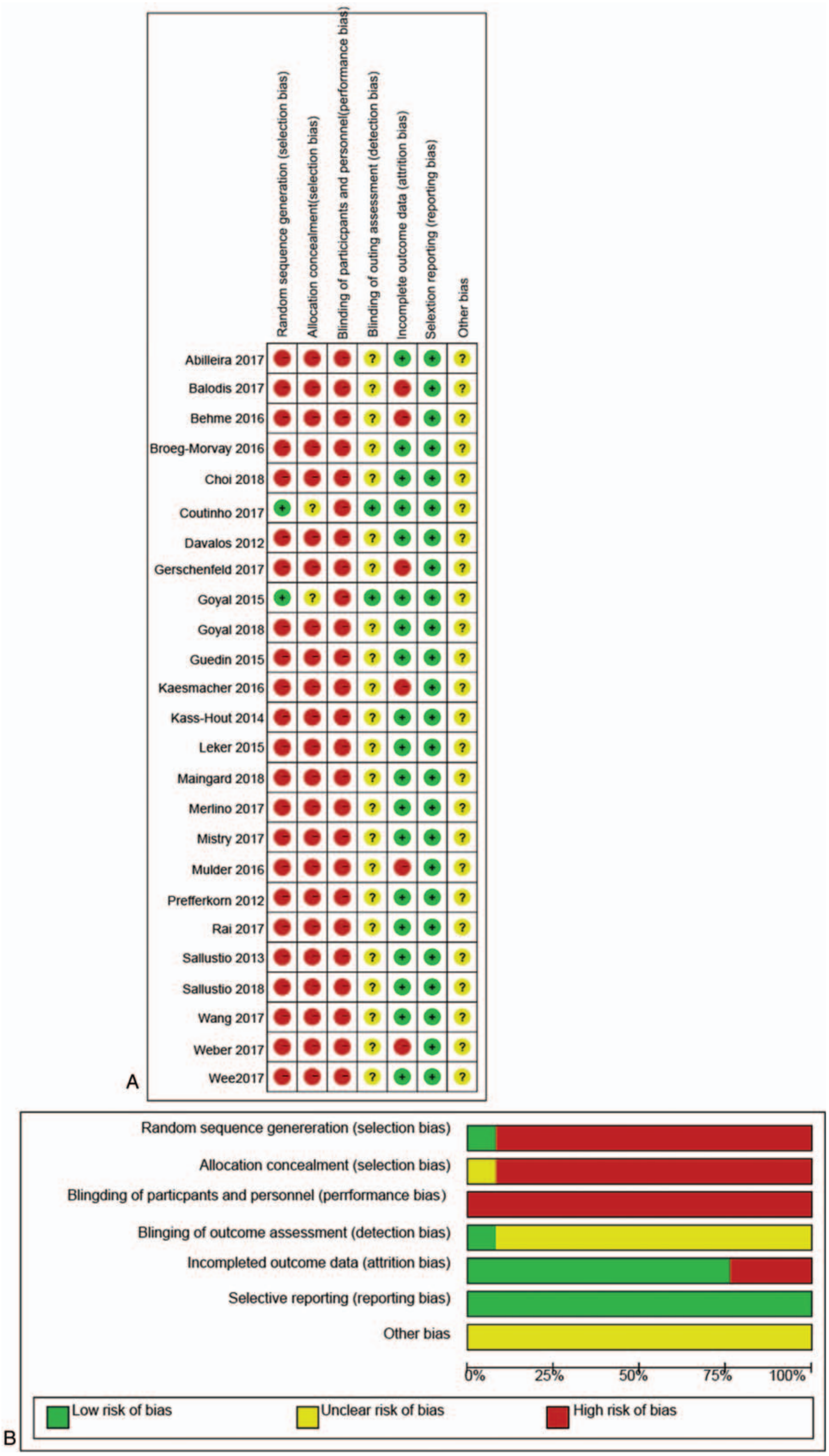

Figure 2. Risk of bias assessments for the clinical trials included in the meta-analysis. (A) Risk of bias summary; (B) Risk of bias graph. *Symbols*. (+): low risk of bias; (?): unclear risk of bias; (−): high risk of bias.

excluded due to improper titles and abstracts and 36 articles were captured after reviewing full texts for relevance with the discussed topic. Of the 36 articles, 11 studies were excluded due to lack of control and available data. Finally, 25 studies[5–7,11–32] with more detailed and sufficient evaluation meeting our entry criteria were retrieved for further analysis. The flow diagram of study selection procedure was depicted in Figure 1. The related clinical data of the 25 enrolled studies with a total of 5927 patients are depicted in Table 1. The included studies were published between 2012 and 2018. The number of participants per study ranged from 50 to 1166, with a total sample number of 5927. The mean age of patients in each study varied between 62.1 to 77 years old. All 25 studies were qualitatively assessed using tools recommended by the Cochrane Collaboration for the risk of bias. A graph and summary of selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases were identified for individual study as shown in Figure 2A and B. The risk of bias was observed in all studies, and the most common source was non-randomized allocation to treatment groups.

3.2. Quantitative synthesis

Twenty-five studies regarding the efficacy and safety of bridging strategies with direct MT in LVO were included in this meta-analysis.

3.2.1. Functional independence. This outcome was reported in 22 trials, which compared MT+IVT to MT alone. There was low heterogeneity observed between the studies ($I^2=41.2\%$, $P=.024$), and hence fixed effects model was used. Pooled results showed that the proportion of patients who received MT+IVT that achieved functional independence was significantly higher than MT alone patients (RR=1.21, 95% CI=1.13–1.30), as shown in Figure 3A.

3.2.2. Mortality. This outcome was reported by 22 trials, and all compared MT+IVT to MT alone. The results showed low heterogeneity between the studies ($I^2=0\%$, $P=.507$), and hence fixed effects model was used. The pooled results showed that the mortality of patients who received MT+IVT was significantly lower than that of MT alone patients (RR=0.74, 95% CI=0.66–0.83), (Fig. 3B).

3.2.3. Successful recanalization. This outcome was reported in 23 trials, and all compared MT+IVT to MT alone. There was significant heterogeneity between the studies ($I^2=71.1\%$, $P<.001$), and hence random effects model was used. As shown in Figure 3C, the pooled results showed that the proportion of patients who received MT+IVT with successful recanalization was significantly higher than MT alone patients (RR=1.09, 95% CI=1.02–1.15).

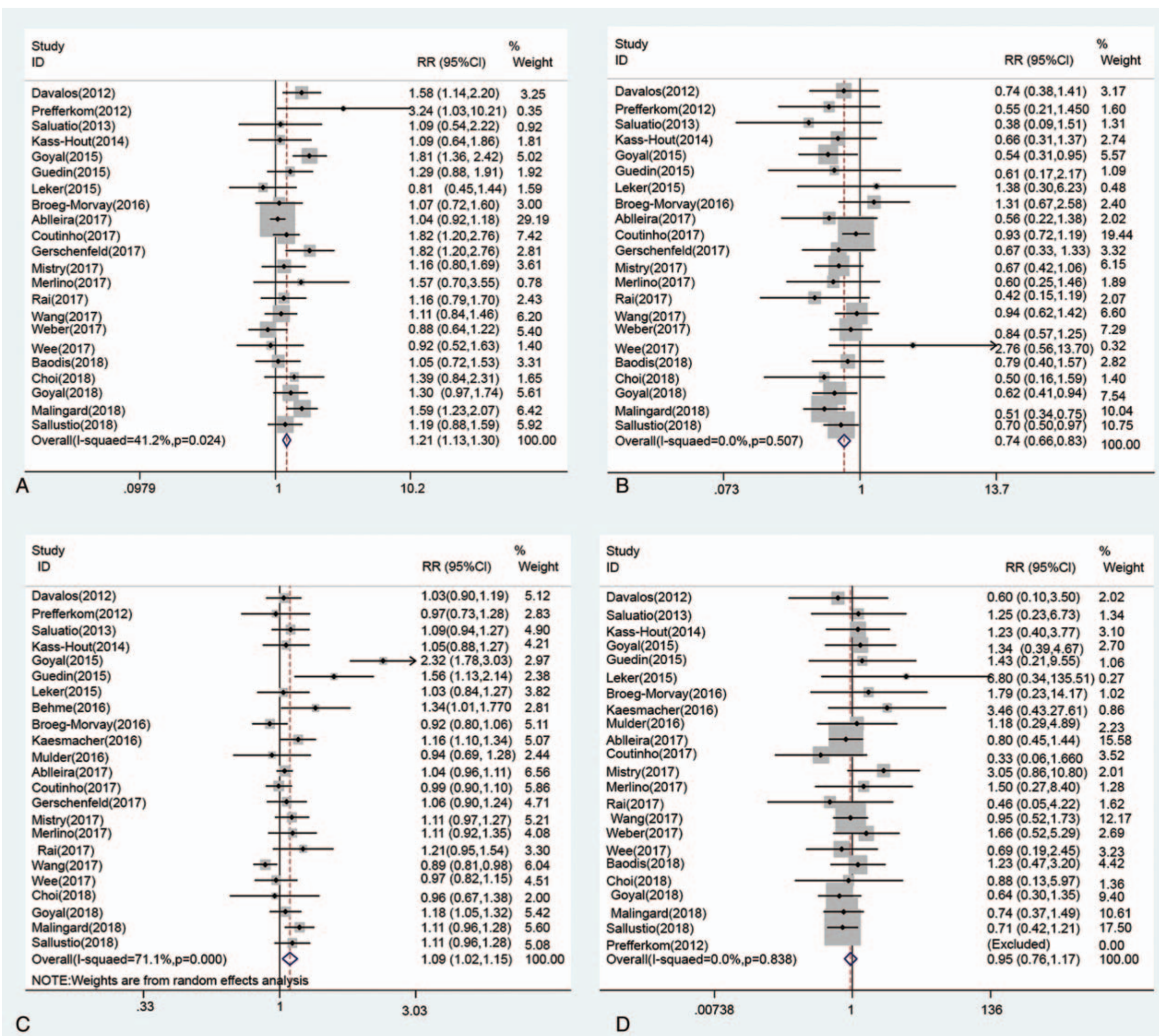

Figure 3. Outcomes of bridging strategies versus mechanical thrombectomy in patients with large vessel occlusion. (A) Functional independence; (B) Mortality; (C) Successful recanalization; (D) sICH.

3.2.4. Symptomatic intracranial hemorrhage (sICH). This outcome was reported in 23 trials, and all compared MT+IVT to MT alone. There was no heterogeneity between the studies (I^2= 0%, P=.838), and hence the fixed effects model was used. As shown in Figure 3D, the pooled results showed that the incidence of sICH was not significantly different between the 2 groups (RR=0.95, 95% CI=0.76–1.17).

3.3. Publication bias

Funnel plot, Begg and Egger tests were performed to assess publication bias among the literatures. As shown in Figure 4, there was no evidence of publication bias for functional independence (Begg test P=.866; Egger test P=.208), mortality (Begg test P=.573; Egger test P=.389) and successful recanalization (Begg test P=.224; Egger test P=.064). However, there was evidence for significant publication bias for sICH (Begg test P=.102; Egger test P=.031). Using the trim-and-fill method, 5 additional artificial studies were included into the meta-analysis to generate a symmetric funnel plot (Fig. 5). The adjusted fixed-effects pooled OR of -0.193 (95% CI: -0.401–0.015, P=.069) calculated using the trim-and-fill method was consistent with that of the original analysis (OR=-0.083, 95% CI: -0.302–0.136, P=.456).

4. Discussion

In this study, we evaluated the efficacy and safety of bridging strategies with direct MT in patients with acute stroke due to LVO. Twenty-five studies (23 cohort studies, and 2 randomized controlled trials) were included. This is the largest and most comprehensive examination conducted to evaluate the efficacy and safety of bridging strategies in patients with LVO. Our meta-analysis showed that bridging strategies improved functional outcomes, successful recanalization rate, and reduced mortality. Moreover, the incidence of symptomatic intracranial hemorrhage showed no significant differences between the MT+IVT and MT alone groups.

The efficacy and safety of bridging strategies for patients with LVO have been investigated by previous meta-analysis study. Recently, Mistry et al[9] conducted a meta-analysis on whether prior IVT provides any additional benefits to patients undergoing MT for AIS. The results demonstrated that MT+IVT patients have better functional independence, higher rate of successful recanalization, lower mortality, and equal odds of sICH compared with MT alone patients. These results are in line with our research findings. Compared with Mistry work, our study identified more eligible studies. The study carried out by Mistry et al consisted of only 13 studies, while our study analyzed data from 25 trials.

Our results showed that bridging thrombolysis prior to endovascular thrombectomy (EVT) was beneficial for LVO patients, which significantly reduced the mortality rates and improved functional independence without additional major complications such as sICH. These results can be partially explained by the effect of tPA on clot lysis during cerebral

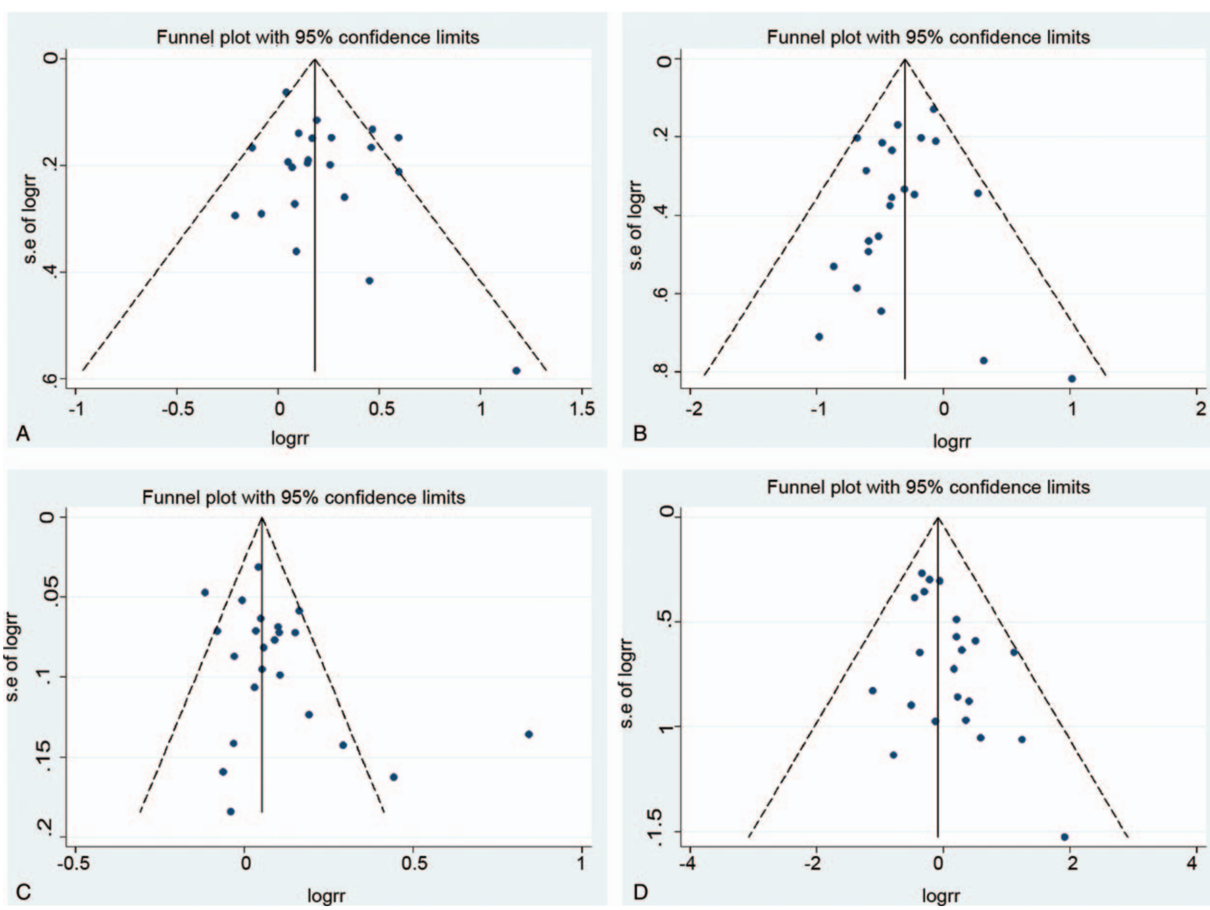

Figure 4. Funnel plot for publication bias test. Each point represents a separate study for the indicated association. (A) Functional independence; (B) Mortality; (C) Successful recanalization; (D) sICH.

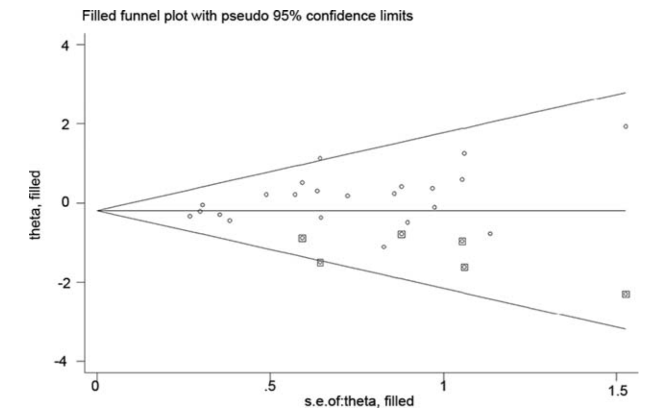

Figure 5. Funnel plot including artificial studies generated using the “trim and fill” method.

ischemia-reperfusion. Tissue plasmin factor has been shown to play a role in the coagulation cascade by converting plasminogen to plasmin. Therefore, it seems that intravenous (IV) thrombolysis induces thrombolytic effect to some extent before EVT, if not completely thrombolysis.[33] Intravenous thrombolysis can lead to thrombolysis before EVT or partial thrombolysis before EVT to allow some reperfusion, thus reducing the time of cerebral hypoxia and reducing irreversible nerve damage. In addition, some clot dissolution may permit more successful reperfusion of EVT.[31]

The present meta-analysis has several limitations. Firstly, there is publication bias in our research. Although we included all the data in the full study and summary and even used trim and fill method to confirm the results, some of the negative data that have been omitted may have influenced the results. Secondly, language can create prejudice. As we have specifically chose English language, and there might be other qualified studies in other languages that are excluded. Thirdly, our results are based on unadjusted RRs assessment, which may influence the outcomes. Finally, patients were not randomized for the use of IVT. Patients who received MT alone often had a contraindication for IVT, which may affect their outcomes. Based on the above limitations, the results should be carefully considered.

In summary, our results demonstrated that bridging strategies improved functional outcomes, successful recanalization rate and reduced mortality. Moreover, the incidence of symptomatic intracranial hemorrhage showed no significant differences between the bridging strategies and MT alone. However, the conduct of RCTs that directly compare both the strategies is warranted in future.

Author contributions

Conceptualization: Xiaohua Pan.
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Formal analysis: Xiaohua Pan, Guorong Liu, Xiuzhen Liu, Yong Fang, Bo Wu.
Writing – original draft: Xiaohua Pan, Yong Fang, Bo Wu.

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