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Efficacy and safety of endovascular thrombectomy in acute ischemic stroke with large ischemic cores: A meta-analysis of randomized controlled trials and cohort studies

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Abstract

Background: The efficacy and safety of endovascular thrombectomy (EVT) in patients with large ischemic infarcts have been the focus of recent research, yet discrepancies persist between studies. This meta-analysis evaluates the efficacy and safety of EVT using data from randomized controlled trials (RCTs) and real-world cohort studies. *Methods:* A systematic search of PubMed, Web of Science, and Embase from January 1, 2010, to June 17, 2024, identified studies reporting favorable functional outcome (FFO), moderate functional outcome (MFO), symptomatic intracranial hemorrhage (sICH), mortality, early neurologic improvement (ENI), and other outcomes. *Results:* Six RCTs and 21 cohort studies with 5,919 patients were analyzed. EVT significantly improved FFO (RR 2.49, 95% CI 1.89–3.29), MFO (RR 1.92, 95% CI 1.50–2.44), ENI (RR 2.34, 95% CI 1.77–3.09), and mRS shift (Generalized OR 1.45, 95% CI 1.32–1.61; Common OR 2.03, 95% CI 1.49–2.75) at 90 days compared to best medical treatment. EVT did not significantly increase sICH risk (RR 1.68, 95% CI 0.99–2.84; RR 1.61, 95% CI 0.80–3.23) or mortality (RR 0.86, 95% CI 0.72–1.02) but was associated with a higher incidence of any intracranial hemorrhage (ICH) (RR 1.74, 95% CI 1.28–2.36). Rates of early neurological worsening and decompressive craniectomy were similar between groups. Findings from RCTs and real-world cohort studies were consistent, reinforcing the robustness of the results. *Conclusion:* EVT improves functional outcomes in patients with large ischemic cores without increasing the risk of sICH or mortality, though it is associated with a higher incidence of ICH. Further studies are necessary to refine patient selection and confirm long-term benefits.

Keywords: Acute ischemic stroke, endovascular thrombectomy, endovascular treatment, large ischemic core, ASPECTS, meta-analysis

INTRODUCTION

Endovascular thrombectomy (EVT) has become the standard of care for patients with acute ischemic stroke (AIS) caused by large vessel occlusion (LVO) in the anterior circulation.[1] Current guidelines for the treatment of AIS state that patients are only eligible for EVT if they have an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ≥ 6 (on a scale of 0 to 10, where lower scores reflect a higher ischemic burden).[1,2] Patients with ASPECTS ≤ 5 or an ischemic core volume ≥ 70 ml have been excluded from most EVT trials due to concerns about hemorrhagic complications from reperfusion.[3,4] despite these strokes accounting for approximately 20% of all LVO strokes.[5] However, these criteria exclude a significant proportion of patients who might benefit from EVT. Notably, recent studies indicate that such patients may still benefit from EVT[5,6], challenging the existing eligibility criteria.

In light of this emerging evidence, six randomized controlled trials (RCTs) have evaluated the efficacy and safety of EVT compared with the best medical treatment (BMT) alone in AIS patients with a large ischemic core over the past few years.[7-12] These studies have demonstrated the benefits of EVT in acute stroke patients with large anterior circulation artery occlusions and a

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large infarct core. However, inconsistencies in the findings remain, and a complete consensus has not been established. Several meta-analyses have sought to address this issue by pooling and analyzing data from these six RCTs.[13-15] Nonetheless, as the results of the LASTE and TESLA trials were only recently published[11,12], these meta-analyses do not yet include all available data. Moreover, real-world data were not incorporated.

Given the rapid evolution of research in this field, we conducted a systematic review and meta-analysis to compare the efficacy and safety of EVT versus BMT in AIS patients with a large ischemic core. We incorporated both RCTs and cohort studies to comprehensively evaluate the current evidence on this issue and compared the results of RCTs with real-world evidence to enhance the broad applicability of the findings.

METHODS

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the study protocol was registered with PROSPERO (registration number CRD42022366394).

Search strategy

PubMed, Embase, and Web of Science were searched from January 1, 2010, to June 17, 2024. The language of publication was limited to English. The literature search employed a combination of Medical Subject Headings (MeSH) terms and keywords. The keywords and MeSH terms included: "Endovascular thrombectomy", "Mechanical thrombectomy", "Endovascular treatment", "Endovascular therapy", "Reperfusion therapy", "Thrombectomy", "Stroke", "Brain infarction", "Cerebral infarction", "Ischemic stroke", "Acute ischemic stroke", "ASPECT", "ASPECTS", "Alberta Stroke Program Early Computed Tomography Score", "Alberta Stroke Program Early Computed Tomographic Score", "Alberta Stroke Program Early CT Score", "Thrombectomy", "Large core", "Large region", "Large infarct", "Large ischemic". The PubMed search strategy is detailed in Supplemental Table S1. In addition, the reference lists of included studies and recent reviews were manually screened.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: (1) AIS patients with large vessel occlusion in the anterior circulation; (2) ASPECTS ≤ 5 or ischemic core volume ≥ 50 ml; (3) Intervention group: patients treated with EVT in addition to BMT; (4) Control group: patients treated with BMT alone; (5) Study design: RCTs or cohort studies (either prospective or retrospective); (6) The outcome measures of interest included: favorable functional outcome (FFO) at 90 days (mRS 0–2), moderate functional outcome (MFO) at 90 days (mRS 0–3), any intracranial hemorrhage (ICH), symptomatic intracranial hemorrhage (sICH) based on the Heidelberg Bleeding Classification (HBC) and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria, all-cause mortality at 90 days, decompressive craniectomy (DC), mRS shift analysis, early neurologic improvement (ENI), and early neurologic worsening (ENW); (7) Availability of the full text. Studies were excluded if they met any of the following criteria: (1) Single-arm studies lacking a control group; (2) Articles in formats such as abstract, letter, meta-analysis, review, comment, case report, or editorial; (3) Designated outcome not reported; (4) Duplicate publications. In cases of duplicate reports, the study with the largest sample size was selected.

Study selection and data extraction

Two investigators independently assessed the titles and abstracts of the retrieved articles, excluding those not meeting the eligibility criteria. Subsequently, the same two reviewers independently screened the full texts of potentially relevant articles and extracted the pertinent data. The following information was extracted from each eligible study: first author, year of publication, study country, study duration, study design, sample size, number of males, age, occlusion location, percentage of intravenous thrombolysis administered, study time window, prestroke mRS score, baseline NIHSS score, definition of large core, imaging modality, baseline ASPECTS, baseline infarct volume, number of modified Thrombolysis in Cerebral Infarction (mTICI) scale grade 2b to 3 after EVT, study outcome, definition of sICH, and quality of research.

Quality assessment

The quality of the included cohort studies was assessed using the Newcastle-Ottawa Scale (NOS), with scores ranging from 0 to 9, with

scores ≥ 7 indicating high quality. The quality of the included RCTs was evaluated using the Cochrane risk of bias version 2 (RoB2) tool[16], which categorizes bias criteria as low risk, some concerns, or high risk. Any disagreements regarding data extraction and quality assessment were resolved through consensus discussions, with consultation from a third reviewer.

Statistical analysis

For binary outcomes, unadjusted relative risks (RRs) with 95% confidence intervals (CIs) were calculated for RCTs, while unadjusted odds ratios (ORs) with 95% CIs were computed for cohort studies to compare outcome events in patients receiving EVT versus BMT. Pooled ORs with 95% CIs were calculated to assess the association of EVT with lower mRS scores, which indicate better functional outcomes. A stratified analysis was conducted based on varying sICH classification criteria. The I^2 statistic was used to assess statistical heterogeneity among the studies, with $I^2 \geq 50\%$ denoting significant heterogeneity. Given the observed heterogeneity among the included studies, the random effects model (DerSimonian-Laird) was employed to calculate pooled effect sizes and corresponding 95% CIs. Sensitivity analyses were conducted to test the robustness of the results by sequentially excluding each study ($n \geq 10$). All statistical tests were two-tailed, with P-values < 0.05 considered statistically significant. All statistical analyses were performed using Stata 17.0 software (Stata Corporation).

RESULTS

Study selection and characteristics

The literature search initially identified 19,595 potentially relevant articles. One additional study was identified through citation tracking. After removing duplicate results, 9,474 publications were rescreened for titles and abstracts. Of these, 9,405 studies were excluded. The full text of the remaining 69 articles was reviewed, and ultimately, 27 articles (5,919 patients) were included in our analysis. The article selection process is illustrated in Figure 1.

Table 1 presents the characteristics and quality assessments of the included studies. The selected studies were published between 2014 and 2024. Of the included papers, 6 were RCTs[7-12] and 21 were cohort studies.[17-37] The sample sizes of the included studies ranged from 34 to 745 participants. In the EVT group, the percentage of patients achieving successful revascularization (mTICI score 2b to 3) ranged from 69.7% to 93.9%. All six RCTs were rated as having a low risk of bias. The 21 cohort studies were rated as moderate to high quality, with scores ranging from 5 to 8.

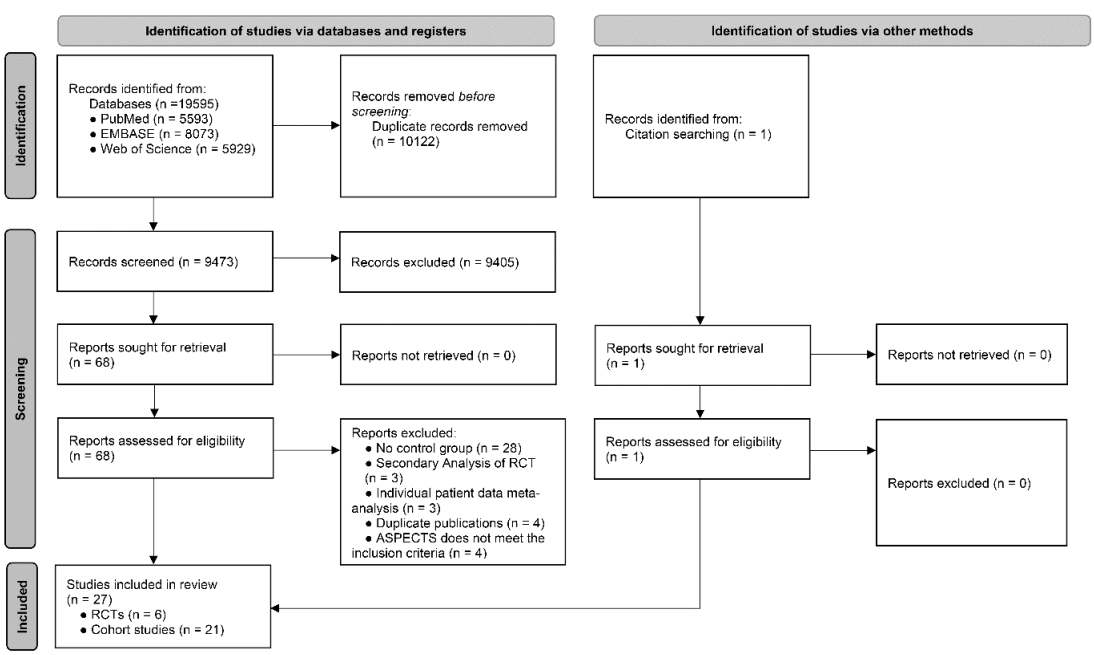

Figure1. Flow diagram of the study search and selection process.

Table 1: Basic characteristics of the studies included in the meta-analysis

ID	Author	Publication year	Country	Duration	Study design	Sample size	Male (%)	Age, y	Occlusion location	Intravenous thrombolysis administered (%)	Time window	Prestroke mRS	Baseline NIHSS	Large core definition	Imaging modality (%)	Baseline ASPECTS	Baseline Infarct volume, ml	EVT mTICI (2b–3) (%)	Study outcome	sICH definition	Quality of research
1	Costalat V, *et al.*	2024	France Spain	2019 – 2022	RCT (M)	EVT: 159 BMT: 165	EVT: 82 (51.6) BMT: 88 (53.3)	EVT: 73 (66–79) BMT: 74 (65–80)	ICA Proximal, or M1, segment of MCA	EVT: 55 (34.6) BMT: 58 (35.2)	< 6.5 h	EVT: 0 (81.8%); 1 (17.0%) BMT: 0 (78.2%); 1 (20.6%)	EVT: 21 (18–24) BMT: 21 (18–24)	ASPECTS ≤ 5	NCCT (16.4) MRI (83.6)	EVT: 2 (1–3) BMT: 2 (1–3)	EVT: 132 (104–185) BMT: 137 (106–187)	130 (86.1)	mRS shift analysis; FFO; MFO; sICH; Mortality; ICH; ENI; ENW; DC	HBC SITS-MOST	Low risk
2	Bendszus M, *et al.*	2023	Europe Canada	2018 – 2023	RCT (M)	EVT: 125 BMT: 128	EVT: 59 (55.0) BMT: 51 (48.0)	EVT: 73 (65–81) BMT: 74 (64–80)	ICA M1 M2 MCA+ACA	EVT: 49 (39.0) BMT: 44 (34.0)	< 11 h	EVT: 0 (0–1) BMT: 0 (0–1)	EVT: 19 (16–22) BMT: 18 (15–22)	ASPECTS (3–5)	NCCT (82.0) MRI (18.0)	EVT: 3 (29%); 4 (36%); 5 (35%) BMT: 3 (38%); 4 (30%); 5 (32%)	EVT: 205.8 ± 139.1 BMT: 227.7 ± 107.2	104 (83.0)	mRS shift analysis; FFO; MFO; sICH; Mortality; DC	HBC	Low risk
3	Sarraj A, *et al.*	2023	United States Canada Europe Australia New Zealand	2019 – 2022	RCT (M)	EVT: 178 BMT: 174	EVT: 107 (60.1) BMT: 100 (57.5)	EVT: 66 (58–75) BMT: 67 (58–75)	ICA M1 M2	EVT: 37 (20.8) BMT: 30 (17.3)	< 24 h	EVT: NA BMT: NA	EVT: 19 (15–23) BMT: 19 (15–22)	ASPECTS (3–5) or core ≥ 50 mL	CTP (97.7) MRI (2.3)	EVT: 4 (3–5) BMT: 4 (4–5)	EVT: 74 (50–111.5) BMT: 77 (50.3–105)	142 (79.8)	mRS shift analysis; FFO; MFO; sICH; Mortality; ENI; ENW	SITS-MOST	Low risk
4	Huo X, *et al.*	2023	China	2020 – 2022	RCT (M)	EVT: 230 BMT: 225	EVT: 135 (58.7) BMT: 144 (64.0)	EVT: 68 (61–73) BMT: 67 (59–73)	ICA M1 M2	EVT: 66 (28.7) BMT: 63 (28.0)	< 24 h	EVT: 0 (0–0) BMT: 0 (0–0)	EVT: 16 (13–20) BMT: 15 (12–19)	ASPECTS (3–5) ASPECTS (0–2) and core (70–100 mL) ASPECTS (> 5) and core (70–100 mL)	NCCT (100.0)	EVT: 3 (3–4) BMT: 3 (3–4)	EVT: 60.5 (29–86) BMT: 63 (31–86)	187 (81.3)	mRS shift analysis; FFO; MFO; sICH; Mortality; ICH; ENI; DC	HBC	Low risk
5	Yoshimura S, *et al.*	2022	Japan	2018 – 2021	RCT (M)	EVT: 101 BMT: 102	EVT: 55 (54.5) BMT: 58 (56.9)	EVT: 76.6 ± 10.0 BMT: 75.7 ± 10.2	ICA M1 M2 Tandem occlusion	EVT: 27 (26.7) BMT: 29 (28.4)	< 24 h	EVT: 0 (0–1) BMT: 0 (0–1)	EVT: 22 (18–26) BMT: 22 (17–26)	ASPECTS (3–5)	NCCT (13.8) MRI (86.2)	EVT: 3 (3–4) BMT: 4 (3–4)	EVT: 94 (66–152) BMT: 110 (74–140)	86 (86.0)	mRS shift analysis; FFO; MFO; sICH; Mortality; ICH; ENI; DC	SITS-MOST	Low risk
6	Yoo AJ, *et al.*	2024	United States	2019 – 2022	RCT (M)	EVT: 152 BMT: 148	EVT: 76 (50.0) BMT: 84 (56.8)	EVT: 66 (54–74) BMT: 67.5 (57.5–73.5)	ICA M1	EVT: 31 (20.4) BMT: 30 (20.3)	< 24 h	EVT: 0 (0–1) BMT: 0 (0–1)	EVT: 19 (15–23) BMT: 18 (14.5–21)	ASPECTS (2–5)	NCCT (100.0)	EVT: 4 (3–5) BMT: 4 (3–5)	EVT: 166 (103–261.5) BMT: 171 (93.5–235)	107 (73.3)	mRS shift analysis; FFO; MFO; sICH; Mortality; ENI; ENW; DC	SITS-MOST	Low risk
7	Zeng H, *et al.*	2024	China	2022 – 2023	R (M)	EVT: 47 BMT: 57	EVT: 31 (66.0) BMT: 33 (57.9)	EVT: 65.8 ± 11.3 BMT: 68.6 ± 11.6	ICA M1 M2	EVT: 18 (38.3) BMT: 14 (24.6)	≤ 24 h	EVT: NA BMT: NA	EVT: 21 (17–23) BMT: 20 (16–22)	ASPECTS ≤ 5	NCCT (94.2) MRI (5.8)	EVT: 4 (2–5) BMT: 3 (2–5)	EVT: NA BMT: NA	40 (85.1)	MFO; sICH; ICH; Mortality; DC	HBC	8
8	Han N, *et al.*	2024	China	2018 – 2023	R (S)	EVT: 75 BMT: 56	EVT: 42 (56.0) BMT: 31 (55.4)	EVT: 67.2 ± 14.2 BMT: 73.5 ± 12.4	ICA M1 M2	EVT: 25 (33.3) BMT: 8 (14.3)	< 24 h	EVT: NA BMT: NA	EVT: 18 (14–21) BMT: 17 (15–24)	core > 70ml	MRI (100.0)	EVT: NA BMT: NA	EVT: 121.6 (95.7–164.9) BMT: 148.5 (101.5–224.2)	68 (90.7)	FFO; MFO; ICH; Mortality	NA	6
9	Mujanovic A, *et al.*	2024	Europe North America	2014 – 2022	R (M)	EVT: 209 BMT: 101	EVT: 103 (49.3) BMT: 41 (40.6)	EVT: 68 (55–79) BMT: 80 (68–85)	ICA M1 M2 M3	EVT: 41 (19.6) BMT: 4 (4.0)	6–24 h	EVT: 0 (0–1) BMT: 1 (0–3)	EVT: 18 (15–22) BMT: 19 (16–24)	ASPECTS (0–5)	NCCT (40.9) CTP (31.5) MRI (27.6)	EVT: 5 (4–5) BMT: 4 (2–5)	EVT: NA BMT: NA	NA	mRS shift analysis; FFO; MFO; sICH; Mortality	ECASS	7
10	Guo C, *et al.*	2024	China	2021 – 2023	P (S)	EVT: 490 BMT: 255	EVT: 281 (57.3) BMT: 133 (52.2)	EVT: 69 (59–78) BMT: 72 (65–79)	ICA M1 M2 Tandem occlusion	EVT: 122 (24.9) BMT: 79 (31.0)	< 24 h	EVT: NA BMT: NA	EVT: 17 (14–20) BMT: 17 (13–22)	ASPECTS (0–5)	NCCT (100.0)	EVT: 4 (2–5) BMT: 3 (1–5)	EVT : NA BMT : NA	423 (86.3)	mRS shift analysis; FFO; MFO; sICH; ICH; Mortality; DC	HBC	8
11	Liu Q, *et al.*	2023	China	2016 – 2022	R (S)	EVT: 120 BMT: 62	EVT: 45 (37.5) BMT: 31 (50.0)	EVT: 77 (74–83) BMT: 81 (74–87)	ICA M1 M2	EVT: 33 (27.5) BMT: 25 (40.3)	< 24 h	EVT: 0 (0–0) BMT: 0 (0–1)	EVT: 17.7 ± 5.6 BMT: 17.7 ± 6.8	ASPECTS ≤ 5 or core ≥ 70 mL	NNCT (NA) CTP (NA)	EVT: 3 (2–5) BMT: 3 (1–5)	EVT: 98 (50–140) BMT: 87.5 (49.3–145)	99 (82.5)	FFO; MFO; sICH; ICH; Mortality	ECASS II	7
12	Garcia-Esperon C, *et al.*	2022	Australia China Canada	2012 – 2020	R (M)	EVT: 121 BMT: 148	EVT: 81 (66.9) BMT: 75 (50.7)	EVT: 69 (61–77) BMT: 75 (61–82.5)	ICA ACA M1 M2	EVT: 60 (49.6) BMT: 74 (50.0)	< 24 h	EVT: 0 (0–0) BMT: 0 (0–1)	EVT: 19 (16–21) BMT: 19 (17–22)	core ≥ 70 mL	CTP (100.0)	EVT: 7 (4-9) BMT: 5 (3-7)	EVT: 92 (79–116.5) BMT: 105.5 (85.7–138)	93 (76.9)	FFO; MFO; sICH	ECASS II	8

13	Karam-chandani RR, *et al.*	2022	United States	2017–2020	R (S)	EVT: 66 BMT: 38	EVT: 44 (66.7) BMT: 16 (42.1)	EVT: 58 (52–73) BMT: 72 (63–86)	ICA MCA	EVT: 40 (60.6) BMT: 17 (44.7)	< 6 h	EVT: 0 (0–0) BMT: 0 (0–2)	EVT: 19 (15–24) BMT: 20 (18–23)	core ≥ 50 mL	CTP (100.0)	EVT: 10 (9–10) BMT: 9.5 (8–10)	EVT: 72 (59–112) BMT: 104 (71–144)	62 (93.9)	MFO; sICH	ECASS II	7
14	Yoshi-moto T, *et al.*	2021	Japan	2014–2019	R (S)	EVT: 49 BMT: 108	EVT: 27 (55.1) BMT: 39 (36.1)	81 (71–86)	ICA M1 M2 Tandem occlusion	22 (14.0)	< 24 h	0 (0–2)	21 (14–27)	core ≥ 70 mL & core ≤ 300 mL	MRI (100.0)	3 (1–5)	128 (89–189)	41 (84.0)	FFO; sICH; ICH; Mor-tality; DC	ECASS II SITS-MOST	7
15	Meyer L, *et al.*	2021	Germany Singapore	2015–2018	R (M)	EVT: 168 BMT: 264	EVT: 99 (58.9) BMT: 146 (55.3)	EVT: 73 (63–80) BMT: 73 (61–81)	ICA M1 M2	EVT: 90 (53.6) BMT: 202 (76.5)	NA	EVT: NA BMT: NA	EVT: 18 (15–21) BMT: 19 (16–23)	ASPECTS (0–5)	NCCT (100.0)	EVT: 5 (4–5) BMT: 4 (2–4)	EVT: NA BMT: NA	121 (72.0)	MFO; sICH; Mortality	ECASS II	6
16	Seners P, *et al.*	2021	France	EVT: 2017–2019 BMT: 2006 – 2014	R (M)	EVT: 56 BMT: 51	EVT: 32 (57.0) BMT: 34 (67.0)	EVT: 73 (61–80) BMT: 69 (57–80)	ICA M1 M2	EVT: 32 (57) BMT: 46 (90)	< 6 h	EVT: NA BMT: NA	EVT: 20 (16–25) BMT: 19 (16–23)	core > 50 mL	CTP (2.0) MRI (98.0)	EVT: NA BMT: NA	EVT: 105 (76–133) BMT: 97 (65–124)	46 (82.0)	FFO; MFO	ECASS II	6
17	Broocks G, *et al.*	2020	Germany	2015–2019	R (S)	EVT: 99 BMT: 71	99 (58.0)	72.3 ± 13.3	ICA M1	EVT: 49 (49.5) BMT: 32 (45.0)	< 12 h	EVT: NA BMT: NA	17.4 ± 4.6	ASPECTS (0–5)	NCCT (NA) CTP (NA)	4 (3–5)	EVT: NA BMT: NA	69 (69.7)	FFO; MFO	NA	7
18	Kerler-oux B, *et al.*	2020	France Switzer-land	EVT: 2015–2018 BMT: Before 2015	R (M)	EVT: 130 BMT: 42	EVT: 77 (59.2) BMT: 33 (78.6)	EVT: 66.2 ± 15 BMT: 77.7 ± 13.5	ICA M1	EVT: 63 (48.5) BMT: 42 (100)	NA	EVT: NA BMT: NA	EVT: 18.7 ± 4.2 BMT: 18.0 ± 5.1	core ≥ 70 mL	MRI (100.0)	EVT: NA BMT: NA	EVT: 104 ± 37.7 BMT: 96.7 ± 33.0	111 (79.3)	FFO; MFO; sICH; Mortality	ECASS II	7
19	Sarraj A, *et al.*	2019	United States	2016–2018	R (M)	EVT: 62 BMT: 43	EVT: 37 (60.0) BMT: 23 (53.0)	EVT: 66 (59–74) BMT: 66 (60–81)	ICA M1 M2	EVT: 43 (69.0) BMT: 26 (60.0)	≤ 24 h	EVT: NA BMT: NA	EVT: 20 (16–23) BMT: 21 (17–23)	ASPECTS ≤ 5 or core ≥70 mL	NCCT (NA) CTP (NA)	EVT: 5 (4–7) BMT: 4 (3–5)	EVT: 60.0 (37.0–87.4) BMT: 86.6 (64.7–118.0)	50 (81.0)	FFO; MFO; sICH; Mortality; ENW	SITS-MOST	7
20	Kakita H, *et al.*	2019	Japan	2014–2016	R (M)	EVT: 172 BMT: 332	EVT: 98 (57.0) BMT: 122 (36.8)	EVT: 74.6 (10.8) BMT: 80.4 (11.3)	ICA M1	EVT: 67 (39.0) BMT: 41 (12.4)	≤ 24 h	EVT : 0 (0–1) BMT : 0 (0–3)	EVT: 21 (16–24) BMT: 22 (18–27)	ASPECTS ≤ 5	NCCT (9.5) MRI (90.5)	EVT: 5 (4–5) BMT: 3 (2–4)	EVT: NA BMT: NA	144 (83.7)	mRS shift analysis; FFO; MFO; sICH; Mortality; ICH; ENI	SITS-MOST	8
21	Jiang S, *et al.*	2018	China	2010–2015	R (M)	EVT: 36 BMT: 53	EVT: 19 (53.0) BMT: 28 (52.8)	EVT: 60.83 ± 14.22 BMT: 66.19 ± 6.79 63.13 ± 12.30	ICA M1 M2 Tandem occlusion	EVT: NA BMT: 21 (39.6)	NA	EVT: NA BMT: NA	EVT: 19.67 ± 3.41 BMT: 15.38 ± 3.88 17.91 ± 6.60	ASPECTS ≤ 5	NCCT (100.0)	EVT: 3.06 ± 1.47 BMT: 4.10 ± 1.09 3.13 ± 1.70	EVT: NA BMT: NA	NA	FFO; sICH; Mortality; ENI	ECASS II	8
22	Mourand I, *et al.*	2018	France	2009–2014	R (S)	EVT: 60 BMT: 48	EVT: 40 (66.7) BMT: 30 (62.5)	EVT: 66 (22–86) BMT: 67 (41–87)	M1 MCA distal Tandem occlusion ICA	EVT: 34 (56.7%) BMT: NA	NA	EVT: NA BMT: NA	EVT: 20 (9–28) BMT: 22 (5–40)	ASPECTS ≤ 5	MRI (100.0)	EVT: 5 (2–5) BMT: 3 (0–5)	EVT: NA BMT: NA	45 (75.0)	FFO; MFO; sICH; Mor-tality; DC	ECASS II	5
23	Chen Z, *et al.*	2018	China	2010–2017	R (S)	EVT: 28 BMT: 76	EVT: 22 (78.6) BMT: 50 (65.8)	EVT: 68.4 ± 14.0 BMT: 73.8 ± 11.8	ICA MCA	EVT: NA BMT: 76 (100.0)	< 6 h	EVT: NA BMT: NA	EVT: 16 (12–18) BMT: 16 (13–19)	core ≥ 70 mL	CTP (87.5) MRI (12.5)	EVT: NA BMT: NA	EVT: 97.8 (80.8–115.7) BMT: 114.6 (85.4–143.9)	21 (84.0)	FFO; MFO; sICH; Mortality;	ECASS II	8
24	Rebello LC, *et al.*	2016	United States	2011–2015	R (S)	EVT: 28 BMT: 28	EVT: 13 (46.0) BMT: 14 (50.0)	EVT: 62.25 ± 13.92 BMT: 58.32 ± 14.79	ICA M1 M2 Tandem occlusion	EVT: 9 (32.0) BMT: 15 (54.0)	< 12 h	EVT : NA BMT : NA	EVT: 19.5 (15.2–24.0) BMT: 18.0 (15.0–23.0)	core > 50 mL	CTP (100.0)	EVT: 6.0 (5.0–7.2) BMT: 6.0 (4.0–7.0)	EVT: 76.87 ± 23.80 BMT: 86.60 ± 22.59	22 (79.0)	FFO; MFO; Mortality; DC	ECASS II	6
25	Bracard S, *et al.*	2016	France	2010–2015	R (M)	EVT: 22 BMT: 35	EVT: NA BMT: NA	EVT: NA BMT: NA	NA	EVT: NA BMT: 35 (100.0)	< 5 h	EVT: NA BMT: NA	EVT: NA BMT: NA	ASPECTS ≤ 4	CTP (1.8) MRI (98.2)	EVT: NA BMT: NA	EVT: NA BMT: NA	NA	FFO	ECASS II	8
26	Borst J, *et al.*	2015	Nether-lands	2010–2014	R (M)	EVT: 13 BMT: 21	EVT: NA BMT: NA	EVT: NA BMT: NA	NA	EVT: NA BMT: NA	< 6 h	EVT: NA BMT: NA	EVT: NA BMT: NA	core ≥70 mL	CTP (100.0)	EVT: NA BMT: NA	EVT: NA BMT: NA	NA	FFO; MFO	ECASS II	6
27	Hill MD, *et al.*	2014	United States Canada Australia Europe	2006–2012	R (M)	EVT: 57 BMT: 35	EVT: NA BMT: NA	EVT: NA BMT: NA	ICA M1 M2 M3	EVT: NA BMT: NA	< 3 h	EVT: NA BMT: NA	EVT: NA BMT: NA	ASPECTS ≤ 4	NA	EVT : NA BMT: NA	EVT: NA BMT: NA	NA	FFO	ECASS II	6

Abbreviations: NIHSS, National Institute of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage; FFO, poor functional outcome; MFO, moderate functional outcome; ICH, intracranial hemorrhage; DC, decompressive craniectomy; ENI, early neurologic improvement; ENW, early neurologic worsening; ECASS, European Cooperative Acute Stroke Studies; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; HBC, Heidelberg Bleeding Classification; RCT, randomized control trial; R, retrospective cohort; P, prospective cohort; S, single-center; M, multi-center; NA, not available; BMT, best medical treatment; EVT, endovascular thrombectomy; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; M1, M1 segment of the middle cerebral artery; M2, M2 segment of the middle cerebral artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; mTICI, modified Thrombolysis in Cerebral Infarction; NCCT, noncontrast computed tomography; CTP, CT perfusion imaging; MRI, magnetic resonance imaging.

Favorable functional outcome (mRS 0–2 at 90 days)

Six RCTs and 18 cohort studies reported data on 3-month FFO. Among the six RCTs, EVT was associated with a significant improvement in 3-month FFO compared with BMT (19.5% vs. 7.5%, RR 2.49, 95% CI 1.89–3.29, $P < 0.01$, $I^2 = 7.5\%$) (Figure 2A). Similarly, the 18 cohort studies demonstrated that EVT was associated with improved 3-month FFO compared to BMT (26.5% vs. 9.0%, OR 3.46, 95% CI 2.29–5.22, $P < 0.01$, $I^2 = 62.27\%$) (Figure 2B). Egger's test indicated a possible publication bias in cohort studies ($P = 0.013$). Moreover, sensitivity analyses conducted on the cohort studies confirmed that the cumulative results remained consistent after the sequential exclusion of each study (Supplemental Figure S5A).

Moderate functional outcome (mRS 0–3 at 90 days)

Six RCTs and 17 cohort studies reported 3-month MFO. Among the six RCTs, EVT was significantly associated with improved 3-month MFO compared to BMT (36.5% vs. 19.9%, RR 1.92, 95% CI 1.50–2.44, $P < 0.01$, $I^2 = 53.6\%$) (Fig. 3A). Similarly, the 17 cohort studies indicated that EVT was associated with improved

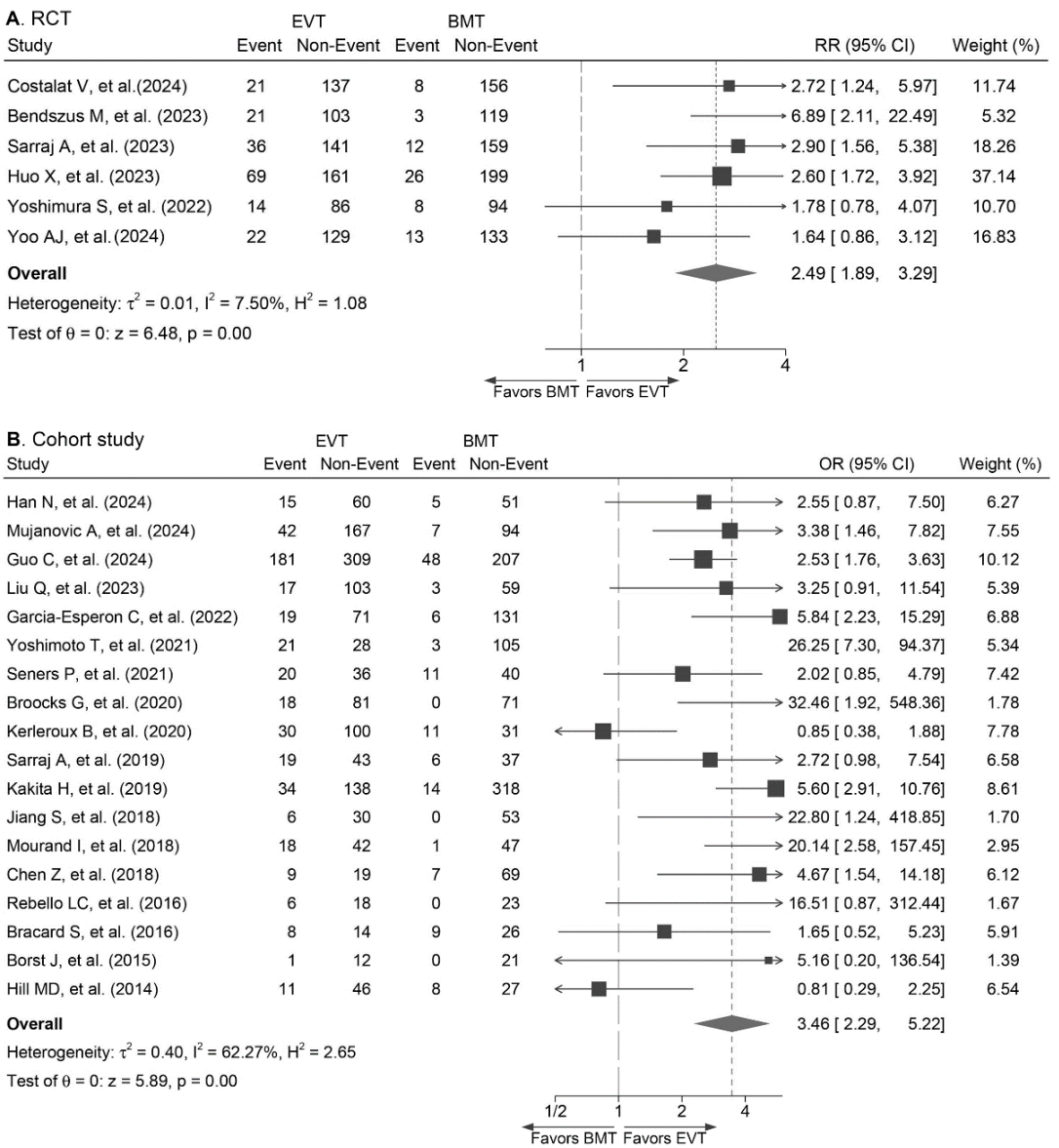

Figure 2. Forest plot showing the effect of EVT versus BMT on FFO; A. RCT; B. Cohort study.

3-month MFO compared to BMT (36.9% vs. 16.6%, OR 2.72, 95% CI 2.02–3.66, $P < 0.01$, $I^2 = 61.96\%$) (Figure 3B). Egger's test ($P = 0.37$) indicated no evidence of publication bias in the cohort studies. Sensitivity analyses in the cohort studies demonstrated that excluding individual studies did not significantly affect the results (Supplemental Figure S5B).

Symptomatic intracranial hemorrhage

Six RCTs and 14 cohort studies compared the effects of EVT versus BMT on sICH. In the RCTs, EVT did not significantly increase the risk of sICH compared to BMT according to the HBC criteria (7.0% vs. 4.1%, RR 1.68, 95% CI 0.99–2.84, $P = 0.05$, $I^2 = 0.0\%$, 3 studies) (Figure 4A) and SITS-MOST criteria for sICH (3.6% vs. 2.2%, RR 1.61, 95% CI 0.80–3.23, $P = 0.18$, $I^2 = 0.0\%$, 4 studies) (Figure 4B). Similarly, in the cohort studies, EVT did not significantly increase the incidence of sICH compared with BMT according to the HBC criteria (12.5% vs. 2.6%, OR 3.61, 95% CI 0.78–16.70, $P = 0.10$, $I^2 = 54.72\%$, 2 studies) (Figure 4C) and the SITS-MOST criteria for sICH (5.5% vs. 5.3%, OR 0.91, 95% CI 0.42–1.97, $P = 0.80$, $I^2 = 4.82\%$, 3 studies) (Figure 4D).

Mortality at 90 days

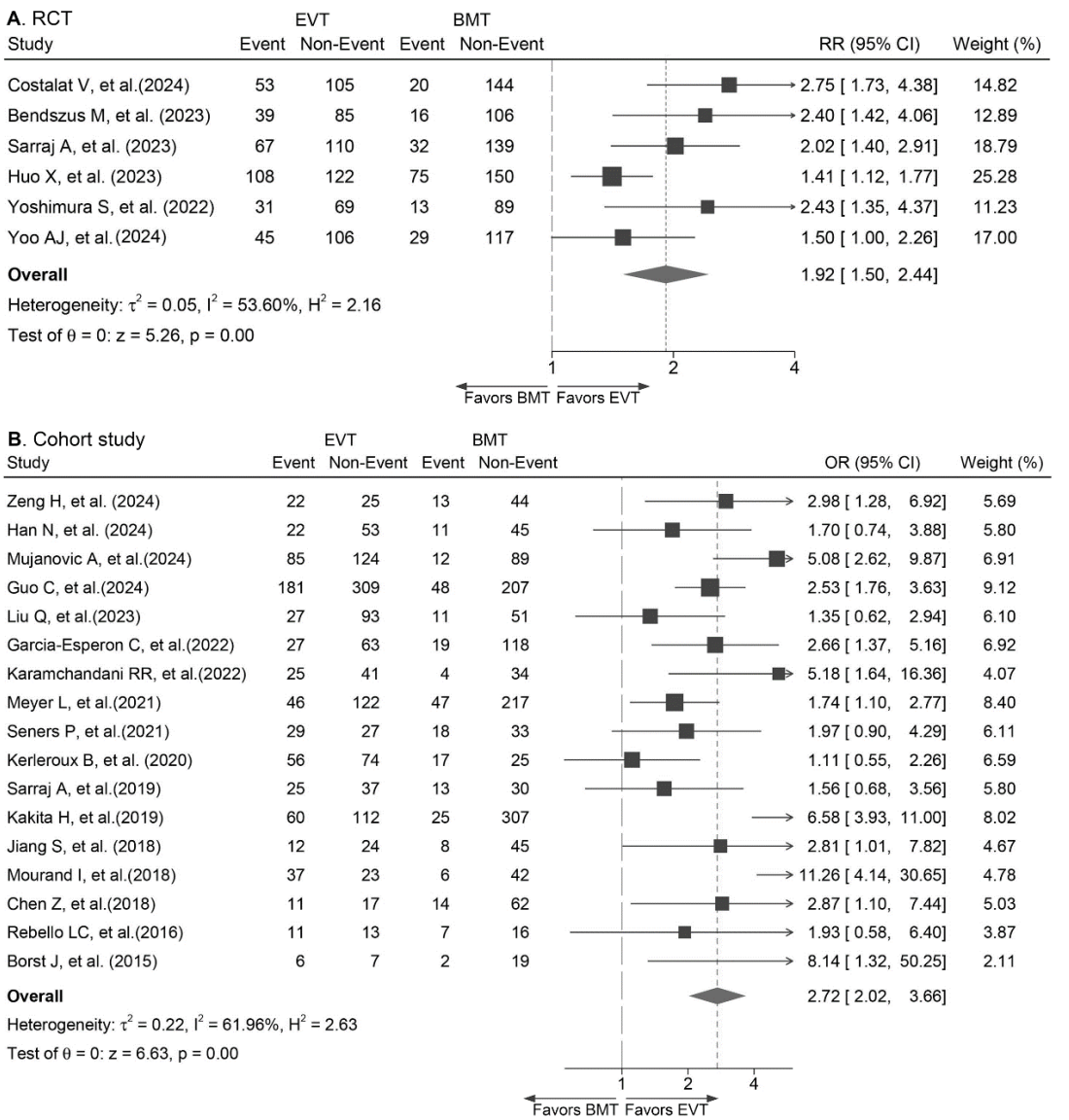

Figure 3. Forest plot showing the effect of EVT versus BMT on MFO; A. RCT; B. Cohort study.

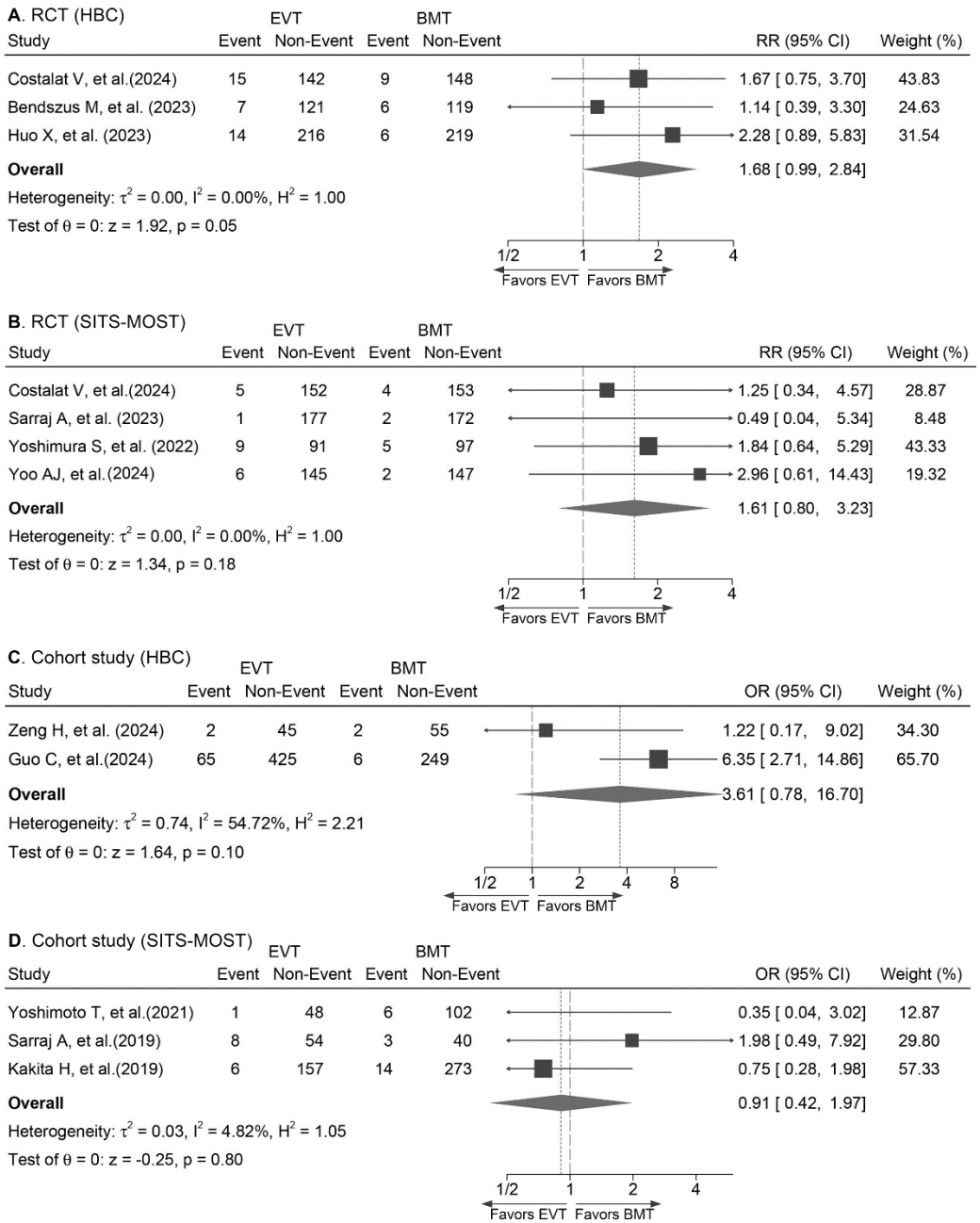

Figure 4. Forest plot showing the effect of EVT versus BMT on sICH according to different classification criteria; A, B. RCT; C, D. Cohort study.

Six RCTs and 14 cohort studies reported data on 3-month mortality. In the RCTs, EVT did not significantly increase the incidence of 3-month mortality compared to BMT, but the results showed a trend toward risk reduction (31.5% vs. 36.8%, RR 0.86, 95% CI 0.72–1.02, $P = 0.08$, $I^2 = 44.67\%$) (Figure 5A). Similarly, an analysis of 14 cohort studies revealed reduced 3-month mortality in the EVT group compared with the BMT group (34.6% vs. 39.1%, OR 0.62, 95% CI 0.47–0.82, $P < 0.01$, $I^2 = 61.12\%$) (Figure 5B). Egger's test detected no publication bias in the cohort studies ($P = 0.26$). Sensitivity analyses of the cohort studies indicated that no individual study had a significant impact on the overall results (Supplementary Figure S5C).

mRS shift analysis

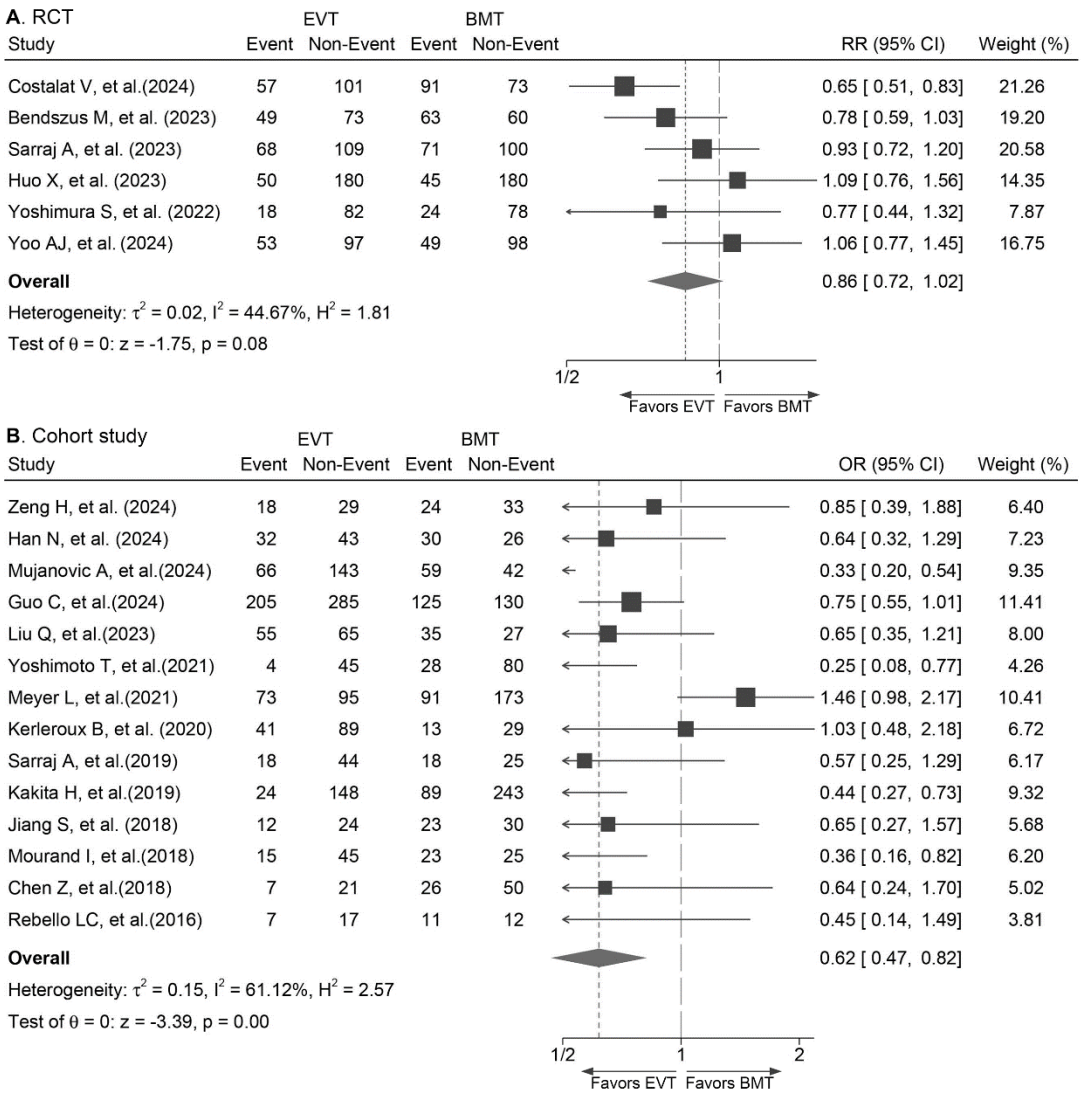

Figure 5. Forest plot showing the effect of EVT versus BMT on 3-month mortality; A. RCT; B. Cohort study.

Six RCTs and three cohort studies reported generalized or common ORs for the ordinal shift in the distribution of the mRS toward better functional outcomes (favoring EVT) at 90 days. The overall generalized OR was 1.45 (95% CI 1.32–1.61, $P < 0.01$) (Figure 6A), with low heterogeneity ($I^2 = 0\%$). Subgroup analysis by study type showed consistent results (3 RCTs, OR 1.49, 95% CI 1.31–1.69, $P < 0.01$, $I^2 = 0.00\%$; 1 cohort study, OR 1.40, 95% CI 1.19–1.64, $P < 0.01$). The overall common OR was 2.03 (95% CI 1.49–2.75, $P < 0.01$) (Fig. 6B), with substantial heterogeneity ($I^2 = 72.89\%$). Subgroup analysis by study type demonstrated consistent results (3 RCTs, OR 2.03, 95% CI 1.37–3.02, $P < 0.01$, $I^2 = 53.04\%$; 3 cohort studies, OR 2.06, 95% CI 1.22–3.48, $P = 0.01$, $I^2 = 83.27\%$).

Intracranial hemorrhage

Five RCTs and nine cohort studies compared the effects of EVT versus BMT on ICH. In the five RCTs, EVT was potentially associated with a higher rate of ICH compared to BMT (60.9% vs. 35.8%, RR 1.74, 95% CI 1.28–2.36, $P < 0.01$, $I^2 = 86.65\%$) (Supplemental Figure S1A). Similarly, in the cohort studies, EVT was associated with a higher rate of ICH compared to BMT (40.2% vs. 25.5%, OR 2.28, 95% CI 1.41–3.68, $P < 0.01$, $I^2 = 76.91\%$) (Supplemental Figure S1B).

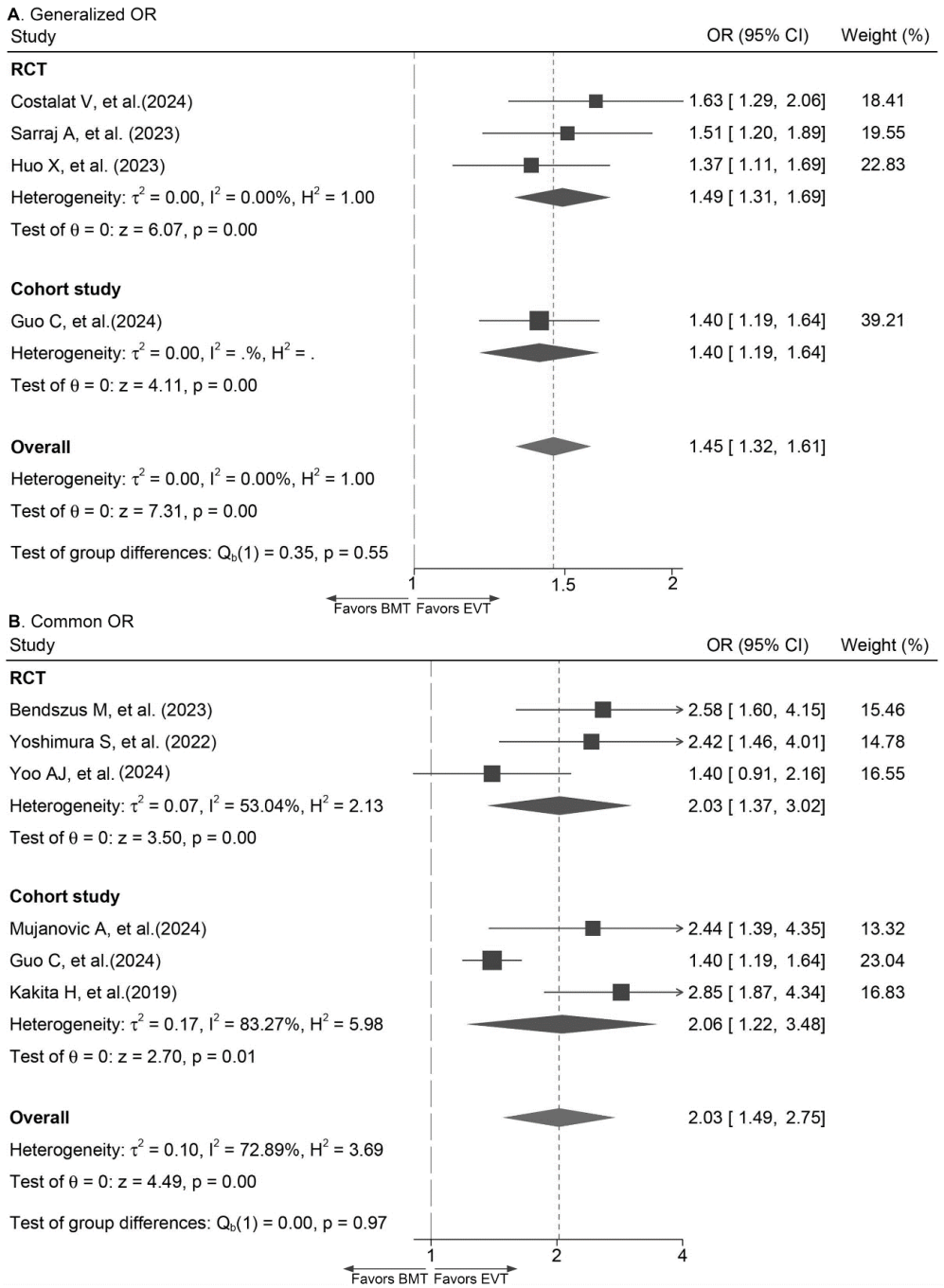

Figure 6. Forest plot showing the effect of EVT versus BMT on mRS shift; A. Generalized OR; B. Common OR.

Early neurologic improvement

Five RCTs and two cohort studies reported on ENI. In the five RCTs, EVT significantly increased the rate of ENI compared to BMT (18.4% vs. 7.8%, RR 2.34, 95% CI 1.77–3.09, $P < 0.01$, $I^2 = 1.76\%$) (Supplemental Fig. S2A). Similar findings were observed in the two cohort studies (30.2% vs. 5.2%, OR 7.72, 95% CI 4.37–13.65, $P < 0.01$, $I^2 = 0.00\%$) (Supplemental Figure S2B).

Early neurologic worsening

Three RCTs and one cohort study reported on ENW. In the three RCTs, the likelihood of ENW in the EVT group was similar to that in the BMT

group (24.1% vs. 22.5%, RR 1.09, 95% CI 0.75–1.59, P = 0.65, I^2 = 58.87%) (Supplemental Figure S3A). Similar findings were observed in the one cohort study (21.0% vs. 18.6%, OR 1.16, 95% CI 0.43–3.10) (Supplemental Figure S3B).

Decompressive craniectomy

Five RCTs and five cohort studies reported on DC. In the five RCTs, the probability of undergoing DC was similar between the EVT and BMT groups (11.1% vs. 9.4%, RR 1.17, 95% CI 0.80–1.70, P = 0.42, I^2 = 32.1%) (Supplemental Figure S4A). Similar findings were noted in the five cohort studies (8.6% vs. 9.1%, OR 0.51, 95% CI 0.15–1.75, P = 0.29, I^2 = 78.29%) (Supplemental Figure 4B).

DISCUSSION

This meta-analysis included six RCTs and 21 cohort studies to compare the impact of EVT and BMT on outcomes in patients with large core acute ischemic stroke. The pooled results showed that EVT significantly improved functional outcomes compared with BMT. The EVT group exhibited a better distribution of mRS scores compared to the BMT group. EVT was not associated with a higher incidence of sICH compared to BMT, but it was linked to a higher risk of ICH. While the 90-day mortality rate was lower in the EVT group compared to the BMT group, the difference was not statistically significant. The rates of ENW and DC were similar between EVT and BMT. Results from RCTs and real-world population-based cohort studies were consistent, further reinforcing the robustness of our findings.

The same topic has been addressed in several prior meta-analyses.[13-15] The key distinctions between this meta-analysis and previous analyses are as follows: First, the results of the LASTE and TESLA studies were published in the last few months. As a result, the data in our study was more accurate and complete compared to previous studies. As the most recent and comprehensive meta-analysis, this study confirms previous findings while offering new insights. Second, this meta-analysis included numerous real-world cohort studies to further validate the relevant findings from the RCTs. Third, in contrast to previous meta-analyses, we performed data synthesis and analysis according to different definitions of sICH. This distinction is important, as the classification criteria for sICH can influence result interpretation. Fourth, to improve the clinical applicability of our findings, we separately combined generalized and common ORs from different studies for better mRS scores. Therefore, the conclusions of this study may be more applicable to clinical practice. The present meta-analysis showed that EVT resulted in better functional outcomes compared to BMT. These findings are consistent with the results of recently published meta-analyses by Morsi *et al*.[14] and Ravipati *et al*.[15] As the LASTE study has only recently been peer-reviewed for publication, we extracted the 90-day MRS score data more accurately (EVT: 158, BMT: 164). Although the findings remain consistent with previous research, the results of this study are presented with greater rigor. In addition, in a meta-analysis of four studies, Ravipati *et al*.[15] found that EVT increased the incidence of ENI. We included the latest published data and the pooled result confirmed this finding. The findings of cohort studies also confirmed the robustness of the results obtained.

Our study observed a shift in the distribution of mRS scores at 90 days, favoring EVT over BMT in terms of better outcomes. Chen *et al*. also suggested that EVT was associated with significantly higher odds of better mRS score.[13] However, Chen *et al*. pooled common ORs and generalized ORs together.[13] Given that qualitative synthesis of different statistics may yield varying results, our meta-analysis separately pooled common ORs and generalized ORs. Additionally, subgroup analyses were conducted based on study type. Therefore, the conclusions drawn from this study may be more robust and applicable to clinical practice.

In our study, EVT did not increase the risk of sICH compared to BMT according to both HBC and SITS-MOST criteria. Similar results were observed in the real-world cohort study. This finding appears to contradict the results of previous meta-analyses.[14,15] The primary reason for this discrepancy is that we analyzed and synthesized data based on different sICH classifications. Previous research has shown that the sICH rate is slightly different according to the definition used.[38,39] Therefore, synthesizing data based on different sICH criteria may provide a more comprehensive reflection of the actual study outcomes. Therefore, we recommend that future RCTs report as much information as possible according to different standards of sICH. Our analysis also indicated that EVT increased the risk of ICH compared to BMT in both RCTs and cohort studies. The results are consistent with the reports in the literature.[15] However, in contrast

to the previous meta-analysis[15], which included four RCTs, our study included five RCTs with a larger patient population and could thus provide more information.

This study showed that EVT did not significantly increase mortality at 90 days and DC. These results are consistent with previous studies.[13-15] However, we observed a decreasing trend in mortality with EVT compared to BMT. The results of cohort studies confirmed the findings. In addition, previous studies have not reported the effect of EVT versus BMT on ENW. In our meta-analysis, which included three RCTs, EVT did not increase the rate of ENW compared with BMT.

Our study has several limitations. First, only six RCTs and 21 cohort studies met the inclusion criteria, and there were significant methodological differences among these studies. Therefore, the results should be interpreted and generalized cautiously. Second, the population in the RCTs and cohort studies was not homogeneous. However, it reflects the diversity of patient characteristics seen in clinical practice, which may enhance the external validity of the findings. Third, the definition of a large ischemic core remains contentious, and although ASPECTS can estimate infarct size, it does not reliably predict the size of the ischemic core. There may be a subset of patients with a small ischemic core in patients with ASPECTS ≤ 5. Therefore, the combined use of multiple imaging modalities (e.g., diffusion-weighted MRI, CT perfusion, and non-contrast CT) to identify patients with large ischemic core may improve treatment outcomes with EVT. Fourth, the pooled estimates were not adjusted for potential confounders, as most studies did not report adjusted RR or OR. Therefore, the current results should be interpreted with caution. Finally, our meta-analysis was conducted using aggregate data rather than individual patient data. Future meta-analyses based on individual-level participant data are needed to more precisely evaluate EVT's safety and efficacy, particularly in patients with ASPECTS scores of 0–2 or ischemic core volumes ≥ 100 ml.

In conclusion, our meta-analysis demonstrates that EVT significantly improves 90-day functional outcomes without increasing the risk of sICH or 3-month mortality compared to BMT. However, EVT is associated with a higher incidence of ICH. These findings underscore the importance of careful patient selection in clinical practice to maximize benefits and minimize risks.

DISCLOSURE

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Conflict of interest: None

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