Systematic Reviews

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Endovascular thrombectomy after anterior circulation large vessel ischemic stroke: an updated meta-analysis

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Abstract

Background Endovascular thrombectomy (EVT) has emerged as the established standard of care for the treatment of anterior circulation large-vessel occlusion (LVO). However, its benefits remain unclear in specific patient populations. Herein, we present an updated systematic review and meta-analysis aimed at thoroughly assessing the effectiveness and safety of combining EVT with medical treatment (MT) compared with MT alone.

Methods This systematic review was performed in accordance with the PRISMA guideline. The MEDLINE, Embase, and Cochrane databases were systematically searched to identify relevant articles published until December 30, 2023. The inclusion criteria restricted articles to randomized clinical trials (RCTs). We pooled odds ratios (OR) and their respective 95% confidence intervals (CIs).

Results Fifteen RCTs involving 3897 patients were included in the study. EVT plus MT was associated with a significant reduction in disability at 90 days (*OR* = 1.91, [1.61–2.26]), improved functional independence (modified Rankin Scale [mRS] 0–2) (*OR* = 2.19 [1.81–2.64]), excellent functional outcomes (*mRS* 0–1) (*OR* = 2.37, [1.45–3.87]), improved independent ambulation (*mRS* 0–3) (*OR* = 2.17, [1.75–2.69]), and higher rates of partial/complete recanalization (*OR* = 2.18, [1.66–2.87] compared with EVT. Efficacy outcomes for both large and small infarct cores were statistically favorable following EVT. Safety outcomes showed comparable rates, except for intracerebral and subarachnoid hemorrhage, which favored MT alone.

Conclusion This meta-analysis supports the use of EVT plus MT as the standard of care for acute ischemic stroke patients with LVO of any infarct core size, as it offers substantial improvements in functional outcomes and recanalization. Safety considerations, particularly the risk of hemorrhage, warrant careful patient selection. These findings provide valuable insights for optimizing stroke management protocols and enhancing patient outcomes.

Keywords Large vessel ischemic stroke, Endovascular thrombectomy, Meta-analysis, Anterior circulation

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Introduction

Acute ischemic stroke (AIS) is a severe neurological emergency with significant global health implications, primarily due to associated large-vessel occlusion (LVO) [1]. While intravenous thrombolysis (tPA) has been considered the standard treatment for AIS, its efficacy in LVO cases is limited, and it has a narrow treatment window [2, 3]. As such, there is an urgent need to explore more effective therapies, including the best medical treatments for this high-risk patient group. Endovascular thrombectomy (EVT) has recently emerged as a groundbreaking intervention for AIS with LVO in the context of optimal medical treatment [3]. This technique involves the mechanical removal of thrombi from blocked brain vessels, the restoration of blood flow, and the preservation of ischemic brain tissue. Advancements in stent retrieval and imaging technologies have revolutionized stroke management [4]. Numerous randomized clinical trials (RCTs) have previously investigated the efficacy and safety of EVT in patients with AIS LVO [5–15], reporting promising functional outcomes and overall improvements in patient prognosis with a combination of the best medical treatment (MT) and EVT. However, despite the growing evidence supporting EVT, there remains a critical need for a comprehensive analysis of the collective data from these trials to draw robust conclusions regarding its efficacy and safety.

A systematic review and meta-analysis on this topic would provide a more comprehensive understanding of the impact of treatment on functional outcomes, safety profiles, and other relevant measures associated with AIS due to LVO in the context of the best medical treatment. The findings of the present meta-analysis could thus potentially affect stroke care practices, leading to improved patient outcomes and reduced long-term disability in this high-risk population. By offering a comprehensive evaluation of the available evidence, this meta-analysis seeks to inform stroke care guidelines and ultimately benefit numerous patients with AIS and their families. The results of this study will help to consolidate evidence supporting the efficacy and safety of EVT, strengthening its establishment as a standard of care for AIS with LVO, thus transforming stroke management and improving patient outcomes.

Methods

This study was registered in the PROSPERO (CRD42023423020) database prior to the preliminary search and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Furthermore, this study did not require ethical approval as the data have been published previously. All data are available in this article.

Eligibility criteria

This systematic review and meta-analysis included only RCTs that used vessel imaging to include patients with vessel occlusion in one of the following locations: the internal carotid artery (ICA), middle cerebral artery segment 1 (M1), or middle cerebral artery segment 2 (M2). In all the included studies, patients were randomized to receive either EVT plus MT or MT alone.

Search strategy

We systematically searched the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from database initiation until December 30, 2023, without any restrictions on date or language. All databases were searched with keywords including "ischemic stroke" OR "stroke" OR "acute ischemic stroke" AND "Endovascular treatment" OR "mechanical thrombectomy" OR "thrombectomy" AND "large vessel occlusion" OR "Large vessel ischemia" OR "large artery occlusion" AND "thrombolytics" OR "thrombolysis" AND "randomized clinical trials." Manual searches of the reference lists from recent systematic reviews and published studies were also performed to identify any eligible studies missed during screening.

Study selection and data extraction

After excluding duplicates, two authors independently screened the articles by title, abstract, and full-text evaluation to identify articles eligible for inclusion based on the criteria. Disagreements at both stages were clarified by a consensus or by a third author. Data were extracted using a predetermined Excel spreadsheet. Data were extracted according to the following protocol variables: study characteristics, design, number of subjects, inclusion and exclusion criteria, demographic data of participants, baseline characteristics, imaging and treatment details of interest, efficacy, and safety outcomes.

Study outcomes

The efficacy outcomes of this meta-analysis included the overall ordinal shift across the range of degree of disability on the modified Rankin Scale (mRS) at 90 days, which categorizes patient disability on scores ranging from 0 (no symptoms) to 6 (death). The mRS is a widely used measure of functional outcome following stroke, with established reliability and validity [16]. We further assessed functional independence (defined as mRS score of 0–2 at 90 days), excellent functional outcome (defined as mRS score 0–1 at 90 days), independent ambulation (defined as mRS score of 0–3 at 90 days), early neurological improvement (ENI) as defined for each study (Supplementary Table 1), Barthel Index score of 95–100 at 90 days, and partial/complete recanalization as defined for each study (Supplementary Table 1). The safety outcomes included any intracerebral hemorrhage (ICH), symptomatic intracranial hemorrhage (sICH) (Supplementary Table 1), mortality at 90 days, early neurological worsening (ENW) as defined in each study (Supplementary Table 1), parenchymal hematoma type 1, parenchymal hematoma type 2, and subarachnoid hemorrhage.

Risk of bias and quality assessment

Two reviewers used the Revised Cochrane Risk-of-Bias 2 tool (RoB2) to independently evaluate the risk of bias in all eligible RCTs. Any disagreements were resolved by discussion with a third author.

Statistical analysis

Data from the included trials were analyzed using RevMan (Review Manager) version 5.4.1 (Cochrane Collaboration). The effect sizes for the intended outcomes were combined using the inverse variance method for generic variance or dichotomous data, as appropriate, with a random effects model to calculate the overall effect size. The threshold for statistical significance was set at a 95% confidence level or $P < 0.05$. Statistical heterogeneity was assessed using the I^2 and P-values of the chi-squared test. When I^2 was > 50%, sensitivity analysis was conducted by excluding each study at a time, and the highest change was reported. Subgroup analysis was further performed based on the infarct core size to identify the effect of the intervention on functional independence, partial/complete recanalization, sICH, rates of any ICH, and mortality. Furthermore, a subgroup analysis was performed based on age to observe the change in mRS scores at 90 days. Publication bias was further assessed based on a visual inspection of the symmetrical distribution of the included studies. For the asymmetrical distributions, Egger's regression and Begg's rank correlation tests were conducted to confirm the results.

Results

Search result and study selection

The initial database search using the aforementioned keywords yielded 3695 articles, which decreased to 2915 articles after removing duplicates. After completing the title and abstract screening, 29 studies were included in the full-text screening. Eight articles were included in this study, with an additional seven identified by screening the citations of the included articles. Finally, 15 RCTs were included in the meta-analysis (Fig. 1).

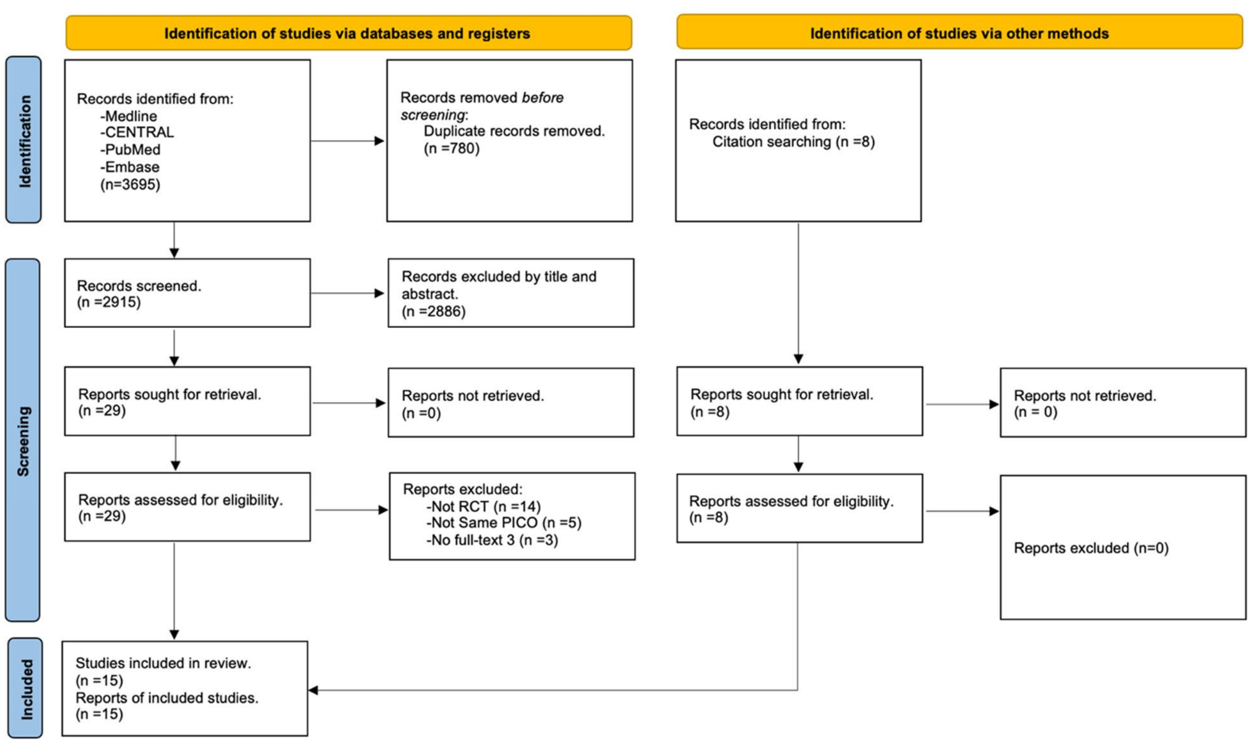

Fig. 1 PRISMA flowchart

Study baseline characteristics

Fifteen RCTs with 3897 patients met the inclusion criteria and were included in the meta-analysis. Of the patient cohort, 1939 were allocated to the intervention group (EVT + MT) and 1958 to the control group (MT alone). Thirteen RCTs were multicenter studies, whereas that by Khoury was a single-center study [4]. Table 1, Supplementary Table 2, and Supplementary Table 3 show the demographic characteristics, reported comorbidities, definition of the infarct core for each study, and baseline characteristics for all 16 included RCTs. A summary of the results of risk-of-bias assessment is shown in Supplementary Fig. 1.

mRS ordinal shift distribution at 90 days

Thirteen RCTs reported an ordinal shift analysis of the mRS distribution. After pooling the results of the ordinal shift distribution, EVT plus MT was associated with a significant reduction in disability at 90 days over MT alone (*OR* = 1.91, 95% *CI* [1.61–2.26]), $P < 0.00001$, $I^2 = 54\%$) (Fig. 2A). In sensitivity analysis, removing the study of Goyal et al. [11] resulted in a significant decrease in heterogeneity (*OR* = 1.79, 95% *CI* [1.53–2.10]), $P < 0.00001$, $I^2 = 42\%$) (Supplementary Fig. 2). A sub-group analysis of four RCTs based on age, both with groups patients less than 70 years old and 70 years or older, demonstrated significant difference favoring intervention with homogenous effects (*OR* = 1.72, 95% *CI* [1.40–2.11], $P < 0.00001$, $I^2 = 0\%$) and (*OR* = 1.40, 95% *CI* [1.11–31.77], $P = 0.004$, $I^2 = 0\%$), respectively (Supplementary Fig. 3).

Excellent functional outcome (mRS 0–1) at 90 days

Four RCTs reported excellent functional outcomes between the two groups. EVT plus MT was found to be significantly associated with excellent functional outcome with homogenous effects (*OR* = 2.37, 95% *CI* [1.45–3.87], $P = 0.0006$, $I^2 = 0\%$) (Fig. 2B).

Functional independence (mRS 0–2) at 90 days

All RCTs investigated the differences between EVT plus MT and EVT alone. The pooled analysis showed that EVT plus MT was significantly associated with functional independence (*OR* = 2.19, 95% *CI* [1.81–2.64], $P < 0.00001$, $I^2 = 46\%$) (Fig. 2C). Visual inspection revealed that the studies were skewed to the right, resulting in an asymmetrical distribution in the funnel plot (Supplementary Fig. 4). Egger's regression test for funnel plot asymmetry yielded a *t*-statistic of 2.3625, with a *p*-value of 0.0359, presenting evidence of asymmetry. Begg's rank correlation test revealed a *z*-statistic of 1.92 with a *P*-value of 0.0554, indicating borderline evidence of funnel plot asymmetry (Supplementary Fig. 5). Infarct core-based analysis was further performed. Patients with both large and small infarct cores treated with EVT plus MT showed significant improvement in functional independence at 90 days (*OR* = 2.50, 95% *CI* [1.76–3.54], $P < 0.00001$, $I^2 = 26\%$) and (*OR* = 2.27, 95% *CI* [1.67–3.08], $P < 0.00001$, $I^2 = 57\%$), respectively (Fig. 3).

Independent ambulation (mRS 0–3) at 90 days

Five RCTs reported differences in independent ambulation at 90 days between the two groups. EVT plus MT was significantly associated with independent ambulation with a homogenous effect (*OR* = 2.17, 95% *CI* [1.75–2.69], $P < 0.00001$, $I^2 = 6\%$) (Fig. 2D).

Early neurological improvement (ENI)

A pooled analysis of nine RCTs comparing the two groups showed that EVT plus MT was significantly associated with ENI compared with MT alone (*OR* = 3.28, 95% *CI* [2.47–4.34], $P < 0.00001$, $I^2 = 39\%$) (Fig. 2E).

A pooled analysis of three RCTs comparing the two groups showed that EVT plus MT was significantly associated with a Barthel Index score of 95–100 at 90 days compared with MT alone, with a homogeneous effect (*OR* = 2.53, 95% *CI* [1.83–3.52], $P < 0.00001$, $I^2 = 29\%$) (Fig. 2F).

Barthel Index score of 95–100 at 90 days

A pooled analysis of three RCTs comparing the two groups showed that EVT plus MT was significantly associated with a Barthel Index score of 95–100 at 90 days compared with MT alone, with a homogeneous effect (*OR* = 2.53, 95% *CI* [1.83–3.52], $P < 0.00001$, $I^2 = 29\%$) (Fig. 2F).

Partial/complete recanalization

Six RCTs encompassing 1401 patients reported differences in partial and complete recanalization. EVT plus MT demonstrated statistically significant higher rates in achieving partial/complete recanalization of occluded vessels (*OR* = 2.18, 95% *CI* [1.66–2.87], $P < 0.00001$, $I^2 = 84\%$) (Supplementary Fig. 6). In the sensitivity analysis, removing Brekhemer et al. [13] resulted in the most significant change in heterogeneity, which was deemed as moderate heterogeneity (*OR* = 2.37, 95% *CI* [1.92–2.93], $P < 0.00001$, $I^2 = 54\%$) (Supplementary Fig. 7). Infarct core-based analysis was further performed. Large infarct core and small infarct core patients who treated with EVT plus MT showed higher rates of partial/complete recanalization (*OR* = 2.47, 95% [1.99–3.06], $P < 0.00001$) and (*OR* = 2.37, 95% [1.76–3.21], $P < 0.00001$, $I^2 = 64\%$), respectively (Fig. 4).

Table 1 Baseline patient characteristics of included studies

Studies (author, publication year)	Country	Study design	No. of patients	Gender		Median age (IQR), mean ± SD	Baseline NIHSS score mean (SD)	ASPECTS on baseline CT mean (SD)	Internal carotid artery occlusion [*n* (%)]	M1 segment middle cerebral artery occlusion [*n* (%)]	M2 segment middle cerebral artery occlusion [*n* (%)]
				Male [*n* (%)]	Female [*n* (%)]						
Huo (2023) [15]	China	RCT	MM: 225 EVT + MM: 230	MM: 144 (64.0) EVT + MM: 135 (58.7)	MM: 81 (36) EVT + MM: 95 (41.3)	MM: 67 (59–73) EVT + MM: 68 (61–73)	MM: 15 (12–19) EVT + MM: 16 (13–20)	MM: 3 (3–4) EVT + MM: 3 (3–4)	MM: 81 (36.0) EVT + MM: 83 (36.1)	MM: 142 (63.1) EVT + MM: 145 (63.0)	MM: 2 (0.9) EVT + MM: 2 (0.9)
Sarraj (2023) [5]	USA	RCT	MM: 174 EVT + MM: 178	MM: 98 (57.0) EVT + MM: 109 (60.6)	MM: 74 (42.5) EVT + MM: 71 (39.9)	MM: 67 (58–75) EVT + MM: 66 (58–75)	MM: 19 (15–22) EVT + MM: 19 (15–23)	MM: 4 (4–5) EVT + MM: 4 (3–5)	MM: 66 (38.4) EVT + MM: 80 (44.4)	MM: 98 (57.0) EVT + MM: 93 (51.7)	MM: 8 (4.7) EVT + MM: 7 (3.9)
Bendszus (2023) [17]	Worldwide	RCT	MM: 128 EVT + MM: 125	MM: 51 (48.0) EVT + MM: 59 (55)	MM: 67 (52) EVT + MM: 56 (45)	MM: 74 (64–80) EVT + MM: 73 (65–81)	MM: 18 (15–22) EVT + MM: 19 (16–22)	NR	MM: 37 (29) EVT + MM: 41 (33)	MM: 88 (69) EVT + MM: 83 (66)	MM: 7 (5) EVT + MM: 0 (0)
Albers (2018) [18]	USA	RCT	MM: 90 EVT + MM: 92	NR	MM: 46 (51) EVT + MM: 46 (50)	MM: 71 (95–80) EVT + MM: 70 (59–79)	MM: 16 (12–21) EVT + MM: 16 (10–20)	MM:8 (7–9) EVT + MM: 8 (7–9)	MM: 36 (40) EVT + MM: 32 (35)	MM: 54 (60) EVT + MM: 60 (65)[a]	
Nogueria (2018) [19]	Worldwide	RCT	MM:99 EVT + MM: 107	MM: 51 (52) EVT + MM: 42 (39)	NR	MM: 70.7 (13.2) EVT + MM: 69.4 (14.1)	MM: 17 (13–21) EVT + MM: 17 (14–21)	NR	MM: 19 (19) EVT + MM: 22 (21)	MM: 77 (78) EVT + MM: 83 (78)	MM: 2 (2) EVT + MM: 3 (3)
Yoshimura (2022) [14]	Japan	RCT	MM: 102 EVT + MM: 101	MM: 58 (56.9) EVT + MM: 55 (54.5)	MM: 44 (43.1) EVT + MM: 46 (45.5)	MM: 75.7 ± 10.2 EVT + MM: 76.6 ± 10.0	MM: 22 (17–26) EVT + MM: 22 (18–26)	MM: 4 (3–4) EVT + MM: 3 (3–4)	MM: 49 (48.0) EVT + MM: 47 (46.5)	MM: 70 (68.6) EVT + MM: 74 (73.3)	MM: 3 (2.9) EVT + MM: 0
Khoury (2017) [7]	Canada	RCT	MM: 37 EVT + MM: 40	MM: 20 (54.1) EVT + MM: 18 (45)	MM: 17 (45.9) EVT + MM: 22 (55.0)	MM: 71 (59–79) EVT + MM: 74 (62.7–80)	MM: 20 (12.00–23.00) EVT + MM: 18 (13.00–21.75)	MM: 9 (8–9) EVT + MM: 8 (7–9)	MM: 2 (5.4) EVT + MM: 6 (15.0)	MM: 24 (64.9) EVT + MM: 17 (42.5)	MM: 6 (16.2) EVT + MM: 12 (30.0)
Mocco (2016) [9]	USA	RCT	MM: 62 EVT + MM: 43	MM: 23 (43) EVT + MM: 34 (62)	MM: 30/53 (57) EVT + MM: 21/55 (38)	MM: 70 (10) EVT + MM: 67 (11)	MM: 18 [14.22] EVT + MM: 17 [13.22]	MM: 8.0 (7–9) EVT + MM: 7.5 (6–9)	MM: 23% (12/53) EVT + MM: 33% (18/55)	MM: 68% (36/53) EVT + MM: 56% (31/55)	MM: 9.4% (5/53) EVT + MM: 11% (6/55)
Muir (2017) [6]	UK	RCT	MM: 32 EVT + MM: 33	MM: 16 (50) EVT + MM: 13 (39)	MM: 16 (50) EVT + MM: 20 (61)	MM: 64 ± 16 EVT + MM: 67 ± 17	MM: 14 (6–29) EVT + MM: 18 (6–24)	MM: 9 (2–10) EVT + MM: 9 (4–10)	MM: 6 (19) EVT + MM: 4 (14)	MM: 21 (65) EVT + MM: 22 (76)	MM: 5 (16) EVT + MM: 3 (10)

Table 1 (continued)

Studies (author, publication year)	Country	Study design	No. of patients	Gender		Median age (IQR), mean ± SD	Baseline NIHSS score mean (SD)	ASPECTS on baseline CT mean (SD)	Internal carotid artery occlusion [n (%)]	M1 segment middle cerebral artery occlusion [n (%)]	M2 segment middle cerebral artery occlusion [n (%)]
				Male [n (%)]	Female [n (%)]						
Berkhermer (2015) [13]	Netherlands	RCT	MM: 267 EVT + MM: 233	MM: 157 (58.8) EVT + MM: 135 (57.9)	MM: 110 (41.2) EVT + MM: 98 (42.1)	MM: 65.7 EVT + MM: 65.8	MM: 18 (14–22) EVT + MM: 17 (14–21)	MM: 9 (8–10) EVT + MM: 9 (7–10)	MM: 75/266 (28.2) EVT + MM: 59/233 (25.3)	MM: 165/266 (62.0) EVT + MM: 154/233 (66.1)	MM: 21/266 (7.9) EVT + MM: 18/233 (7.7)
Bracard (2016) [8]	France	RCT	MM: 208 EVT + MM: 204	MM: 104 (50) EVT + MM: 116 (57)	MM: 104 (50) EVT + MM: 88 (43)	MM: 68 (54–75) EVT + MM: 66 (54–74)	MM: 17 (13–20) EVT + MM: 18 (15–21)	MM: 0–4 (35 [17%]), 5–7 (52 [26%]), 8–10 (115 [57%]) EVT + MM: 0–4 (22 [11%]), 5–7 (80 [41%]), 8–10 (94 [48%])	MM: 24 (12) EVT + MM: 24 (12)	MM: 164 (79) EVT + MM: 176 (86)	MM: 2 (1) EVT + MM: 0
Campbell (2015) [4]	Australia, New Zealand	RCT	MM: 35 EVT + MM: 35	MM: 17 (49) EVT + MM: 17 (49)	MM: 18 (51) EVT + MM: 18 (51)	MM: 70.2 ± 11.8 EVT + MM: 68.6 ± 12.3	MM: 13 (9–19) EVT + MM: 17 (13–20)	NR	MM: 11 (31) EVT + MM: 11 (31)	MM: 18 (51) EVT + MM: 20 (57)	MM: 6 (17) EVT + MM: 4 (11)
Goyal (2015) [11]	Worldwide	RCT	MM: 150 EVT + MM: 165	MM: 71 (47.3) EVT + MM: 79 (47.9)	MM: 79 (52.7) EVT + MM: 86 (52.1)	MM: 70 EVT + MM: 71	MM:17 EVT + MM: 16	MM: 9 (8–10) EVT + MM: 9 (8–10)	MM: 39/147 (26.5) EVT + MM: 45/163 (27.6)	MM: 105/147 (71.4) EVT + MM: 111/163 (68.1)	MM: 3/147 (2.0) EVT + MM: 6/163 (3.7)
Jovin (2015) [10]	Spain	RCT	MM: 103 EVT + MM: 103	MM: 54 (52.4) EVT + MM: 55 (53.4)	MM: 49 (47.6) EVT + MM: 48 (46.6)	MM: 67.2 ± 9.5 EVT + MM: 65.7 ± 11.3	MM: 17.0 (12.0–19.0) EVT + MM: 17.0 (14.0–20.0)	MM: 8.0 (6.0–9.0) EVT + MM: 7.0 (6.0–9.0)	MM: 27/101 (26.7) EVT + MM: 26/102 (25.5)	MM: 26/102 (25.5) EVT + MM: 66/102 (64.7)	MM: 8/101 (7.9) EVT + MM: 10/102 (9.8)
Saver (2015) [12]	Worldwide	RCT	MM: 98 EVT + MM: 98	MM: 45/96 (47) EVT + MM: 54/98 (55)	MM: 51/96 (53) EVT + MM: 44/98 (45)	MM: 66.3 ± 11.3 EVT + MM: 65.0 ± 12.5	MM: 17 EVT + MM: 17	MM: 9 EVT + MM: 9	MM: 15/94 (16) EVT + MM: 17/93 (18)	MM: 72/94 (77) EVT + MM: 62/93 (67)	MM: 6/94 (6) EVT + MM: 13/93 (14)

NR Not reported, *ASPECT* Alberta stroke programme early CT score, *RCT* Randomized controlled trial, *USA* United States of America, *UK* United Kingdom, *EVT + MM* endovascular thrombectomy plus medical treatment, *MM* Medical treatment, *IQR* Interquartile range, *NIHSS* National institute health stroke scale, *SD* Standard deviation

[a] All middle-cerebral-artery occlusions involved the M1 segment, except in one patient in the medical-therapy group who had an occlusion involving the M2 segment

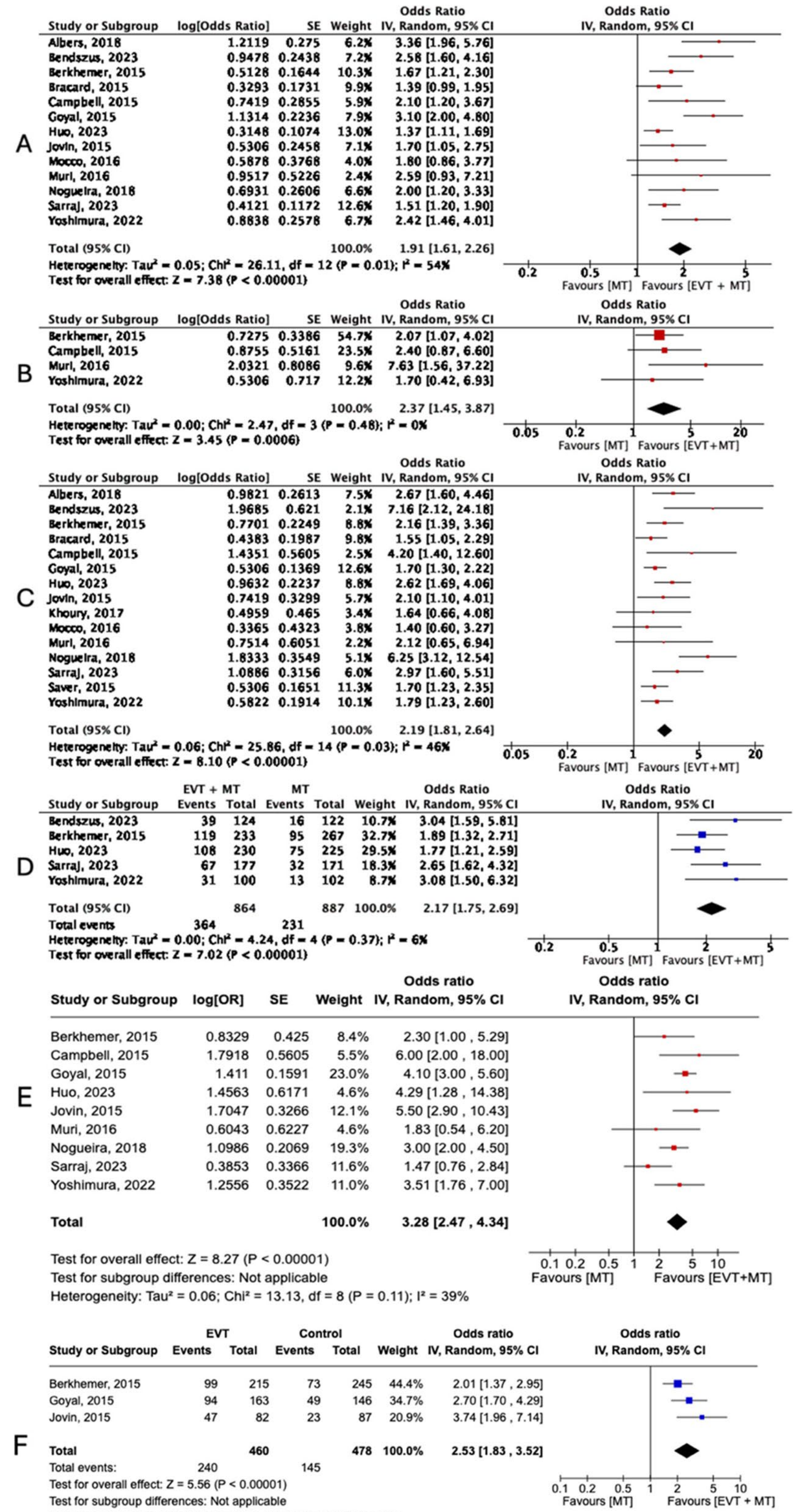

Fig. 2 Efficacy outcomes. **A** mRS ordinal shift distribution at 90 days. **B** mRS 0–1. **C** mRS 0–2. **D** mRS 0–3. **E** ENI. **F** Barthel Index score

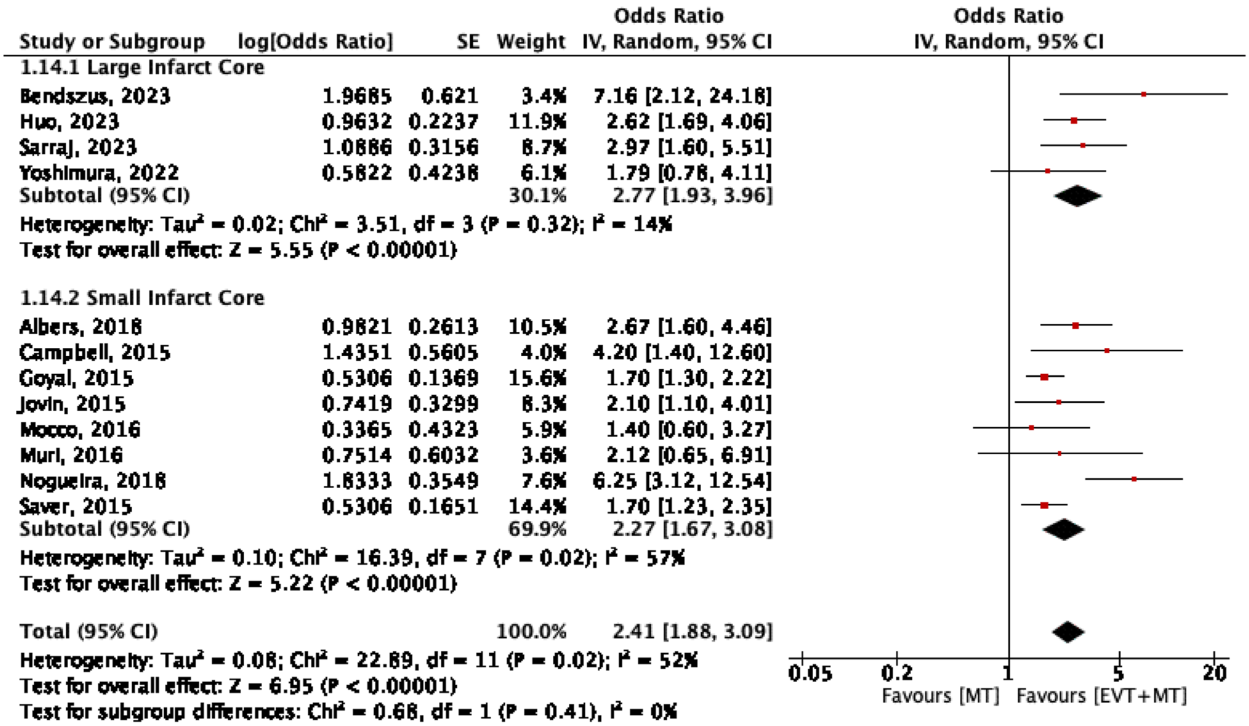

Fig. 3 Forest plot of sub-group analysis based on infarct core size showing the odds of functional independence (mRS 0–2)

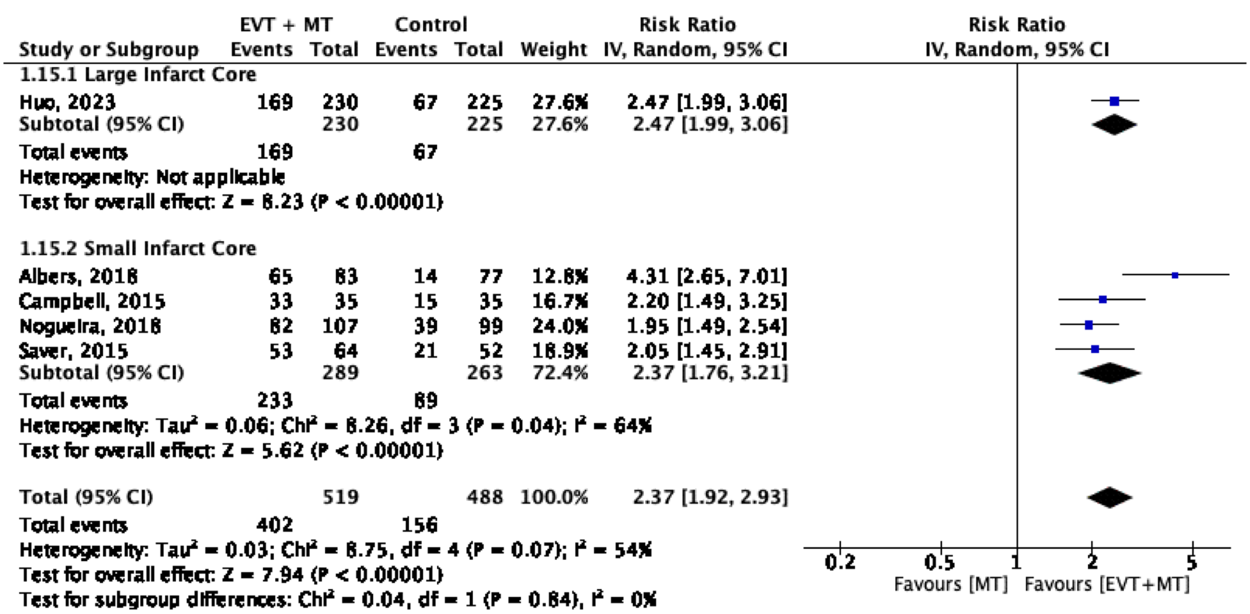

Fig. 4 Forest plot of sub-group analysis based on infarct core size showing the rates of partial/complete recanalization

Any intracerebral hemorrhage

Five RCTs enrolling a total of 1305 patients investigated the incidence of any ICH. The pooled analysis showed a statistically significant effect favoring MT alone ($OR = 1.77$, 95% CI [1.30–2.42], $P = 0.007$, $I^2 = 72\%$) (Fig. 5A). In the sensitivity analysis, removing Khoury et al. [7] yielded statistically significant and homogenous effect ($OR = 2.06$, 95% CI [1.46–2.92], $P < 0.0001$, $I^2 = 47\%$) (Supplementary Fig. 8). Infarct core-based analysis was subsequently performed, with analysis showing that

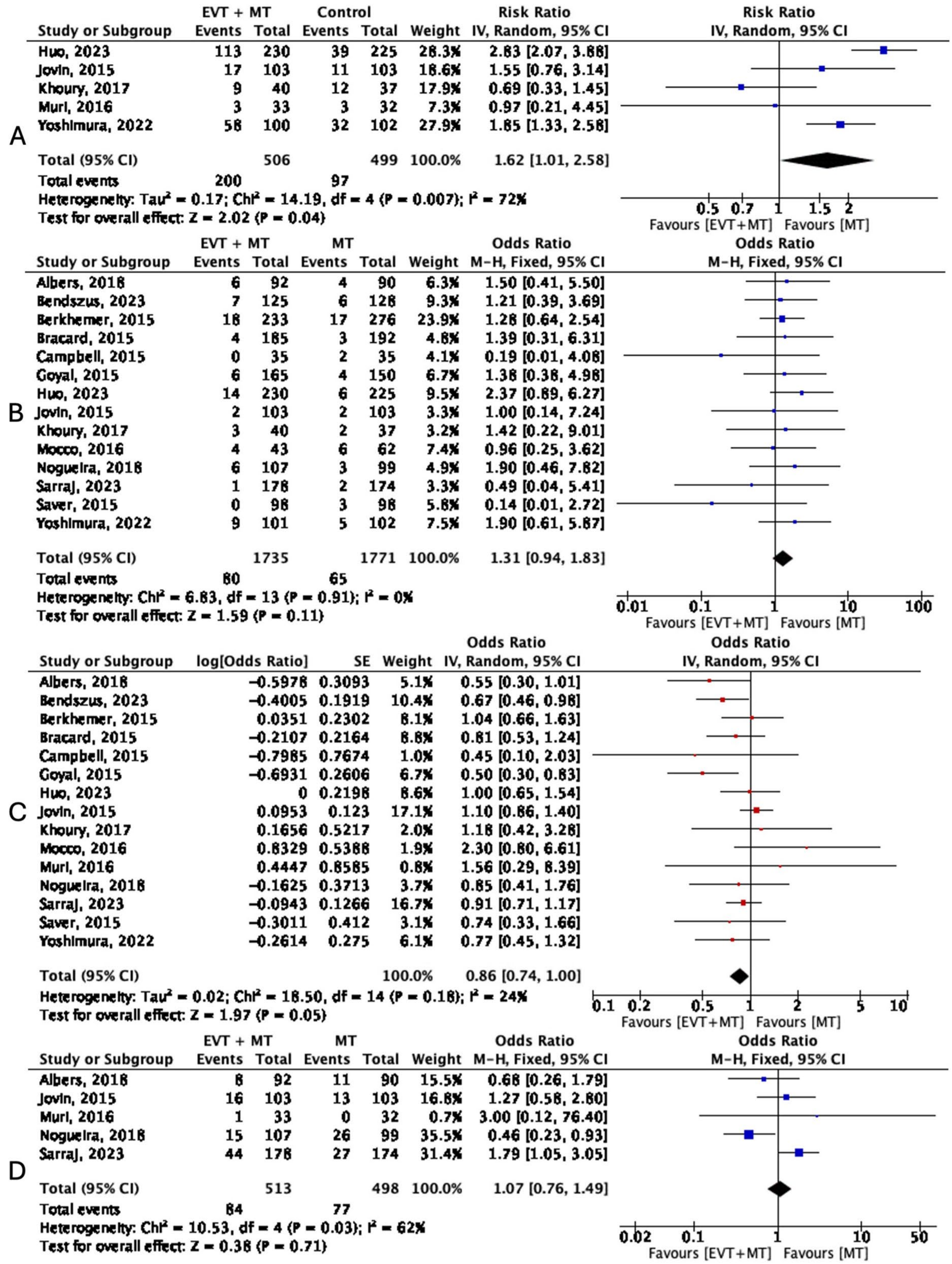

Fig. 5 Safety outcomes. **A** Any intracerebral hemorrhage. **B** Symptomatic intracranial hemorrhage (sICH). **C** Mortality at 90 days. **D** Early neurological worsening (ENW)

patients with both large and small infarct cores had insignificant differences between the two groups, although MT alone has lower rates of any ICH (*OR* = 2.93, 95% [1.08–7.95], $P = 0.03$, $I^2 = 79\%$) and (*OR* = 2.27, 95% [0.86–5.98], $P = 0.10$, $I^2 = 37\%$), respectively (Supplementary Fig. 9).

Symptomatic intracranial hemorrhage (sICH)

Fourteen RCTs enrolling 3806 patients assessed the differences in sICH between the two groups. There was no significant difference between the two arms, with a homogeneous effect (*OR* = 1.31, 95% [0.94–1.83], $P = 0.11$, $I^2 = 0\%$) (Fig. 5B). Infarct core-based analysis was subsequently performed. Analysis of patients with both large and small infarct cores showed insignificant difference between the two groups (*OR* = 1.67, 95% [0.93–3.00], $P = 0.09$, $I^2 = 0\%$) and (*OR* = 1.04, 95% [0.59–1.84], $P = 0.90$, $I^2 = 0\%$), respectively (Supplementary Fig. 10).

Mortality at 90 days

All RCTs assessed the association between mortality at 90 days between the two groups. The pooled estimate revealed that there was no significant difference between the two groups (*OR* = 0.86, 95% [0.74–1.00], $P = 0.05$, $I^2 = 23\%$) (Fig. 5C). Visual inspection revealed that the studies were skewed to the right, showing an asymmetrical distribution in the funnel plot (Supplementary Fig. 11). Egger's regression test for funnel plot asymmetry yielded a *t*-statistic of − 0.9419 with a *P*-value of 0.3634, indicating no significant evidence of asymmetry. Begg's rank correlation test showed a *z*-statistic of 0.15 with a *P*-value of 0.8820, further suggesting no significant evidence of funnel plot asymmetry (Supplementary Fig. 12). Infarct core-based analysis was performed. Large infarct core and small infarct core patients showed insignificant difference between the two groups (*OR* = 0.85, 95% [0.71–1.01], $P = 0.07$, $I^2 = 0\%$) and (*OR* = 0.82, 95% [0.57–1.17], $P = 0.26$, $I^2 = 53\%$), respectively (Supplementary Fig. 13).

Early neurological worsening (ENW)

Five RCTs with 1011 patients assessed ENW. The pooled analysis showed insignificant difference between the two groups *(OR* = 1.07, 95% *CI* [0.76–1.49], $P = 0.71$, $I^2 = 62\%$) (Fig. 5D). In a sensitivity analysis, the largest change in heterogeneity occurred when the study by Nogueira et al. [16] was removed, resulting in low heterogeneity (*OR* = 1.40, 95% *CI* [0.95–2.08], $P = 0.09$, $I^2 = 7\%$) (Supplementary Fig. 14).

Parenchymal hematoma

Four RCTs comprising 1297 patients investigated the differences in parenchymal hematoma type 1 between the two arms. There was no statistically significant difference between the two groups, with a homogeneous effect (*OR* = 1.03, 95% [0.55–1.93], $P = 0.93$, $I^2 = 0\%$) (Supplementary Fig. 15). Seven RCTs comprising 1789 patients assessed the rates of parenchymal hematoma type 2. There was no statistically significant difference between the two groups, with a homogeneous effect (*OR* = 1.31, 95% [0.87–1.97], $P = 0.20$, $I^2 = 0\%$) (Supplementary Fig. 16).

Subarachnoid hemorrhage

Four RCTs with a total of 1297 patients assessed the SAH rates of subarachnoid hemorrhage between the two groups. The pooled analysis further demonstrated that MT alone was significantly associated with lower rates of subarachnoid hemorrhage (*OR* = 3.75, 95% [1.44–9.73], $P = 0.007$, $I^2 = 0\%$) (Supplementary Fig. 17).

Discussion

This systematic review and meta-analysis focusing on acute large-vessel ischemic stroke revealed notable improvements in functional outcomes, ENI, Barthel Index score, and partial/complete recanalization when employing EVT in conjunction with medical treatment compared to medical treatment alone. Safety outcome analysis further indicated comparable rates between the two cohorts in terms of mortality, sICH, ENW, and parenchymal hematoma types 1 and 2. Nevertheless, statistically significant differences were observed in the incidences of ICH treatment in terms of the administration of any ICH and subarachnoid treatment. Subgroup analysis based on infarct core size revealed significant improvements in functional independence and recanalization in patients with large or small infarct cores. Moreover, no statistically significant associations were discerned between sICH and mortality at the 90-day mark in either infarct core subgroup.

The homogeneous effects observed in both age groups indicate that EVT consistently improves outcomes in terms of the mRS ordinal shift analysis, regardless of whether the patients are younger or older than 70 years. Clinically, this finding indicates that EVT could be confidently applied across a broad age range, supporting its use as a standard treatment for acute ischemic stroke in both younger and older patients. These results further highlight that age alone should not be a limiting factor when considering EVT, as the benefits extend across different age demographics, potentially including better overall recovery and reduced disability in stroke survivors.

In recent years, endovascular thrombectomy has arisen as the primary standard of care for patients with ischemic stroke with LVO. Many studies have consistently highlighted the advantageous effects of this intervention on functional outcomes and mortality rates. Nonetheless, research regarding the effectiveness and safety of endovascular thrombectomy remains ongoing within specific patient cohorts, such as those with large and small core infarcts, as well as consideration of demographic features [2, 3].

Our meta-analysis focusing on efficacy outcomes, including the reduction of disability scale score at 90 days, excellent functional outcome, functional independence, independent ambulation, ENI, and partial/complete recanalization, revealed statistically significant improvements, providing robust evidence to support the use of EVT in the management of large-vessel ischemic strokes. Notably, these findings align with previous meta-analyses [2, 20–22]. Consistent outcomes across these analyses underscore the efficacy of endovascular thrombectomy in enhancing functional outcomes after large-vessel ischemic stroke, reinforcing the current imperative for its integration into clinical stroke management practice. Improved functional outcomes, extending beyond the clinical realm, further have a profound impact on the quality of life of stroke survivors. This empowerment enabled them to regain mastery of their daily activities, engage in social interactions, and experience a renewed sense of autonomy. Our meta-analysis establishes a foundational perspective endorsing the efficacy of endovascular thrombectomy in managing both large- and small-infarct core patients, resulting in improved functional outcomes. This observation aligns with earlier meta-analytic findings [23]. The ongoing discourse regarding the efficacy of EVT has been constrained by stringent selection criteria in previous RCTs [24]. Furthermore, our results underscore the efficacy of EVT in improving recanalization across both infarct core groups, although caution is warranted because of the significant heterogeneity. These findings open up avenues for further research, particularly in regards to the appropriateness of EVT for patients with both infarct core types.

Our analysis of safety outcomes revealed no statistically significant differences in terms of sICH, ENW, parenchymal hematoma types 1 and 2, or mortality between the two groups. However, EVT combined with medical treatment was associated with elevated ICH and subarachnoid hemorrhage rates. These findings are consistent with those of Campbell et al. [4], Sarraj et al. [5], Saver et al. [12], and Goyal et al. [2]. The incorporation of EVT in the management of large-vessel ischemic stroke, notwithstanding the associated hemorrhagic risks, was rationalized by the substantial benefits that often outweigh the inherent risks [25]. The results of this subgroup analysis based on infarct core size further support this rationale, particularly among patients with small infarcts, where the benefits of EVT appear to outweigh the risks. However, in patients with large infarcts, the higher incidence of any ICH indicates the need for more in-depth long-term safety trials to fully understand the impact of EVT in this group. This is crucial for optimizing treatment strategies, as well as ensuring the best possible outcomes for all patients. Furthermore, our analysis of patients stratified by infarct core size revealed diminished rates of mortality at the 90-day in both infarct core groups, thus favoring the use of EVT in conjunction with medical treatment. This outcome suggests that EVT may be judiciously applied in a more inclusive manner, extending its consideration to patients with larger infarct cores than those conventionally treated in typical clinical practice.

The heterogeneity observed in the different outcome analyses likely stemmed from key differences in how the studies were designed as well as the patient populations they included. For example, the study by Goyal et al. [11] included patients up to 12 h after stroke onset, compared to the more common 4.5- to 6-h window, likely resulting in better outcomes because these patients may have had stronger collateral circulation and smaller infarcts. The study of Brekhemer et al. [13] further contributed to the variability in recanalization outcomes by including the less common anterior cerebral artery (ACA) occlusions, which behave differently from the more frequently studied MCA and ICA occlusions. Khoury et al. [7] also included patients within 5 h of symptom onset or those with a clinical imaging mismatch, thus possibly including individuals with more severe ischemia and thereby increasing the risk of intracerebral hemorrhage. Finally, Nogueira et al. [19] focused on patients who had either failed IV tPA therapy or were on anticoagulants, groups typically excluded from other studies. These patients likely had more complex strokes, increasing the chances of early neurological worsening. These variations in patient selection, treatment timing, and inclusion criteria explain the observed heterogeneity across the outcomes.

This meta-analysis has several limitations. First, it was conducted using aggregate level data, rather than individual patient data, thus introducing potential constraints on the precision of our findings. Secondly, the presence of heterogeneity among the pooled RCTs presents a substantial challenge in formulating definitive conclusions regarding the efficacy of EVT in a large infarct core population. Potential sources of heterogeneity include variations in patient selection criteria, definition of the infarct core, diverse imaging modalities employed for patient identification, and disparities in the thrombectomy devices and techniques utilized across the studies. Third, the variability in the definitions of sICH may have affected the results despite the I^2 statistic suggesting no substantial heterogeneity. Fourth, the reliance on unmasked neurologists for the estimation of mRS in the study by Bracard et al. [8] further introduced the possibility of bias, potentially influencing the accuracy of functional outcome assessment in the study results. Fifth, potential publication bias was identified, as indicated by the funnel plot asymmetry observed through visual inspection, and further supported by Egger's regression test and Begg's rank correlation test, both of which indicated evidence or borderline evidence of asymmetry. Finally, inadequate reporting of recanalization outcomes in certain studies may have introduced bias, underscoring the importance of interpreting recanalization results with caution and from a multifactorial perspective.

Conclusion

Overall, our meta-analysis demonstrated that EVT plus medical treatment was associated with significant improvements in functional outcomes, ENI, overall disability reduction at 3 months, and recanalization among patients with large-vessel acute ischemic stroke. Physicians should consider EVT as a standard of care for eligible patients with large vessel occlusion to optimize treatment outcomes and improve overall stroke prognosis and recovery. In addition, EVT plus medical treatment may be considered for patients with a large infarct core. Nevertheless, further studies are warranted to investigate the role of EVT in patients with large infarct cores.

Abbreviations

EVT	Endovascular thrombectomy
LVO	Large vessel occlusion
MM	Medical treatment
RCTs	Randomized clinical trials
OR	Odds ratios
CIs	Confidence intervals
mRS	Modified Rankin Scale
AIS	Acute ischemic stroke
tPA	Intravenous thrombolysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
ICA	Internal carotid artery
M1	Middle cerebral artery segment 1
M2	Middle cerebral artery segment 2
CENTRAL	Cochrane Central Register of Controlled Trials
ENI	Early neurological improvement
ICH	Any intracerebral hemorrhage
sICH	Symptomatic intracranial hemorrhage
ENW	Early neurologic worsening
RoB2	Revised Cochrane risk of bias tool
RevMan	Review Manager

Supplementary Information

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Supplementary Material 1. Table S1: Outcomes Definitions. Table S2: Studies Clinical history. Table S3: Infarct Core Definitions. Fig. S1. Risk of Bias assessment summary. Fig. S2. mRS Ordinal Shift Distribution at 90 Days after Sensitivity analysis. Fig. S3. Sub-group analysis of mRS Ordinal Shift Distribution at 90 Days based on age. Fig. S4. Funnel Plot of Functional Independence (mRS 0–2) at 90 Days. Fig. S5. Egger's Regression Test and Begger's Rank Correlation Test of Functional Independence (mRS 0–2) at 90 Days. Fig. S6. Partial/Complete recanalization. Fig. S7. Partial/Complete recanalization after sensitivity analysis. Fig. S8. Any Intracerebral Hemorrhage after sensitivity analysis. Fig. S9. Forest plot of sub-group analysis based on infarct core size showing the rates of Any Intracerebral Hemorrhage. Fig. S10. Forest plot of sub-group analysis based on infarct core size showing the rates of Symptomatic Intracranial Hemorrhage (sICH). Fig. S11. Funnel Plot of mortality at 90 Days. Fig. S12. Egger's Regression Test and Begger's Rank Correlation Test of Mortality at 90 Days. Fig. S13. Forest plot of sub-group analysis based on infarct core size showing the rates of mortality at 90 days. Fig. S14. Early Neurological Worsening (ENW) after sensitivity analysis. Fig. S15. Parenchymal hematoma type 1. Fig. S16. Parenchymal hematoma type 2. Fig. S17. Subarachnoid Hemorrhage.

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Authors' contributions
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Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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