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ORIGINAL RESEARCH

Mothership Versus Drip-and-Ship Models in Acute Stroke Care: A Time-Sensitive Meta-Analysis

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BACKGROUND: Mechanical thrombectomy is the standard of care for acute ischemic stroke due to large vessel occlusion. Whether the mothership model or the drip-and-ship model provides superior outcomes remains unclear. This systematic review and meta-analysis aimed to compare functional and safety outcomes between these 2 models and assess the impact of onset-to-groin puncture delay on outcomes.

METHODS: We conducted a systematic review and meta-analysis following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD420251034209). We searched PubMed, EMBASE, and Cochrane CENTRAL up to March 9, 2025. We included randomized trials, cohort studies enrolling patients with anterior circulation large vessel occlusion treated with mechanical thrombectomy. The primary outcome was 90-day functional independence (modified Rankin Scale score, 0–2). Secondary outcomes included excellent outcome (modified Rankin Scale score 0–1), successful recanalization, symptomatic intracranial hemorrhage, any intracranial hemorrhage, and 90-day mortality. Risk of bias was assessed using Risk of Bias in Non-randomized Studies of Interventions and Risk of Bias 2.0 tools. Meta-regression was performed to evaluate the effect of onset-to-groin puncture time differences on outcomes.

RESULTS: Nineteen studies (16485 patients) were included. The mothership model and drip-and-ship model showed no significant difference in achieving 90-day functional independence (odds ratio, 1.12 [95% CI, 0.94–1.32]). Meta-regression showed that longer delays to thrombectomy in the drip-and-ship model significantly reduced the odds of functional independence (*P*<0.001). A onset-to-groin time delay of approximately 43 minutes between the two models of care was identified as the threshold beyond which the mothership model conferred superior outcomes.

CONCLUSIONS: Direct transport to a thrombectomy-capable center should be prioritized when secondary transfer is expected to delay treatment, as functional outcomes worsen significantly beyond this threshold.

Key Words: drip-and-ship ■ mothership ■ thrombectomy

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CLINICAL PERSPECTIVE

What Is New?

- In regions where the additional delay from secondary transfer exceeds ~40 minutes, direct transport to a thrombectomy-capable center may improve functional outcomes.

What Are the Clinical Implications?

- Clinical systems should prioritize the strategy that minimizes time to reperfusion, rather than assuming one pathway is uniformly superior.
- Each stroke network should evaluate its typical transport times and prehospital configuration to determine whether direct bypass is likely to be beneficial.

Nonstandard Abbreviations and Acronyms

ICH	intracranial hemorrhage
IVT	intravenous thrombolysis
LVO	large vessel occlusion
mRS	modified Rankin Scale
MT	mechanical thrombectomy
OTG	onset-to-groin (puncture) time
sICH	symptomatic intracranial hemorrhage

Acute ischemic stroke due to large vessel occlusion (LVO) represents a time-sensitive neurological emergency.[1] Mechanical thrombectomy (MT) has emerged as the standard of care for selected patients with anterior and posterior circulation LVO, significantly improving clinical outcomes when performed promptly.[2] Consequently, optimizing prehospital triage and transport strategies is crucial to minimize treatment delays and maximize therapeutic benefit. Two models of stroke care delivery are currently adopted: the mothership model, where patients are directly transported to a comprehensive stroke center capable of MT, and the drip-and-ship model, wherein patients are first evaluated at a primary stroke center and then secondarily transferred for MT.[3] Although both models are widely used across different health care systems, it remains unclear from previous meta-analysis which approach offers superior outcomes.[3] However, previous studies[3] have not used the delay to thrombectomy—specifically, onset-to-groin (OTG) time—as a systematic comparator between strategies, potentially missing a crucial determinant of clinical outcomes. Understanding how this delay affects the benefit of thrombectomy is essential for guiding prehospital triage decisions, especially in settings where both models are feasible. In this systematic review and meta-analysis, we aimed to compare functional, procedural, and safety outcomes between mothership and drip-and-ship models for patients with anterior circulation LVO treated with MT. We also conducted a meta-regression to examine the influence of OTG puncture time on treatment effect, with the aim to clarify whether and when delays inherent to the drip-and-ship model may offset its potential benefits.

METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. The protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD420251034209). The search strategy and the clinical question were formulated according to the Population-Intervention-Comparison-Outcome scheme reported in Table 1.

Data are available upon reasonable request. This study is a systematic review and meta-analysis of previously published studies and did not involve direct participation of human subjects or collection of primary data. As such, ethical approval and informed consent were not required.

We made a literature search on articles published in English language up to March 9, 2025 on PubMed, Cochrane Central, and EMBASE using a combination of four index terms: "Mothership," "Drip and Ship," "Ischemic stroke," and "Thrombectomy." The search strings are reported in Table S1.

We selected articles that fulfilled the following inclusion criteria: randomized clinical trials (RCTs) or cohort studies on patients with anterior circulation LVO treated with MT. The exclusion criteria were wrong design (not RCTs or cohort studies), wrong exposure (not treated with MT), wrong population (not anterior circulation LVO), and wrong publication type (letters, editorials, comments, narrative reviews, case reports, case series). For clarity, we used throughout the text the term "articles" referring to papers retrieved from the literature search and the terms "trial" or "study" when referring to the populations of subjects considered for quantitative synthesis (meta-analysis). As a first step, 2 authors (G.M. and L.D.) independently screened for title and abstracts all the records, using Rayyan Systematic Reviews web-based tool. Then, 4 authors (A.B., L.B., F.K., and D.R.) selected the

Table 1. Population-Intervention-Comparison-Outcome question

Population	Individuals with anterior circulation large vessel occlusion treated with MT
Intervention	Mothership prehospital model of care
Comparison	Drip-and-ship prehospital model of care
Outcome	The primary study outcome was 90-d functional independence, defined as mRS scores of 0 through 2. Secondary outcomes were 90-d excellent outcome (defined as mRS score 0–1) and rate of successful reperfusion. Safety outcomes were rate of intracranial hemorrhage and symptomatic intracranial hemorrhage post MT; mortality at 90 d post MT.

mRS indicates modified Rankin Scale; and MT, mechanical thrombectomy.

articles after examining the full text. Disagreements on eligibility were resolved by consensus among all the authors involved.

Quality Assessment

The methodological quality of the included studies was assessed using 2 distinct tools, according to study design. For observational studies, the Risk of Bias in Non-randomized Studies of Interventions tool was employed, evaluating the following 7 domains: bias due to confounding, bias in selection of participants, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. Each domain was rated as "Low," "Moderate," or "Serious" risk of bias, and an overall judgment was determined accordingly. A study was rated as low risk if all domains were low; moderate if at least 1 domain was moderate with none serious; and Serious if any domain was rated as serious. For the single RCT included, we applied the Cochrane Risk of Bias 2.0 tool, which assesses 5 domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was judged as low Risk, some concerns, or high risk, and the overall risk of bias was determined using a structured algorithm similar to the Risk of Bias in Non-randomized Studies of Interventions tool.

Data Extraction

Data extraction was conducted by 4 authors (A.B., L.B., F.K., and D.R.), independently and blinded and thereafter compared by 2 other authors (G.M. and L.D.) using an electronic spreadsheet with the following prespecified variables: first author's name, publication year, number of participants, sex proportion, mean/median age, National Institutes of Health Stroke Scale score on admission, rate of patients treated with intravenous thrombolysis (IVT), mean/median time from onset to needle, mean/median time from OTG puncture, mean/median time from onset to recanalization, and number of participants with primary, secondary, and safety outcomes.

Outcome Measures

The primary outcome measure was 90-day functional independence defined as modified Rankin Scale (mRS) scores of 0 through 2. Secondary outcomes were 90-day excellent outcome (defined as mRS score of 0–1) and rate of successful reperfusion defined as grade 2b, 2c, or 3 of recanalization by applying the modified thrombolysis in cerebral infarction classification. Safety outcomes were rate of intracranial hemorrhage (ICH), symptomatic ICH (sICH) post MT and mortality at 90 days post MT.

Statistical Analysis

Meta-analysis was performed according to random effects modeling to calculate the pooled treatment effect for mothership prehospital model of care versus drip-and-ship prehospital model of care. Heterogeneity across cohort studies was assessed with Cochrane's Q statistics ($P<0.005$) and I^2 statistics (<40% low, 40%–60% moderate, >60% substantial). Effects estimates were expressed as odds ratio (OR) with 95% CI. For outcomes where ≥1 studies included 0 events in 1 treatment arm, we applied a standard continuity correction of 0.5 to the 2×2 contingency table to avoid reliance on large-sample approximations and ensure stable estimation of the OR. For the primary outcome, we explored heterogeneity trough influence study, sequentially omitting each study ("leave-one-out" analysis). Forest plots were generated for each outcome. Our primary approach was to use a random- effects model for all the meta-analyses. We additionally computed a precision-weighted fixed-effect model for the primary outcome. To explore whether the difference in OTG puncture time between the drip-and-ship and mothership models influenced the treatment effect expressed as primary outcome (90-day mRS score 0–2), we conducted a mixed-effects meta-regression using the rma() function from the metafor*package* in R. The outcome measure was the logOR, computed for each study using a random-effects model with

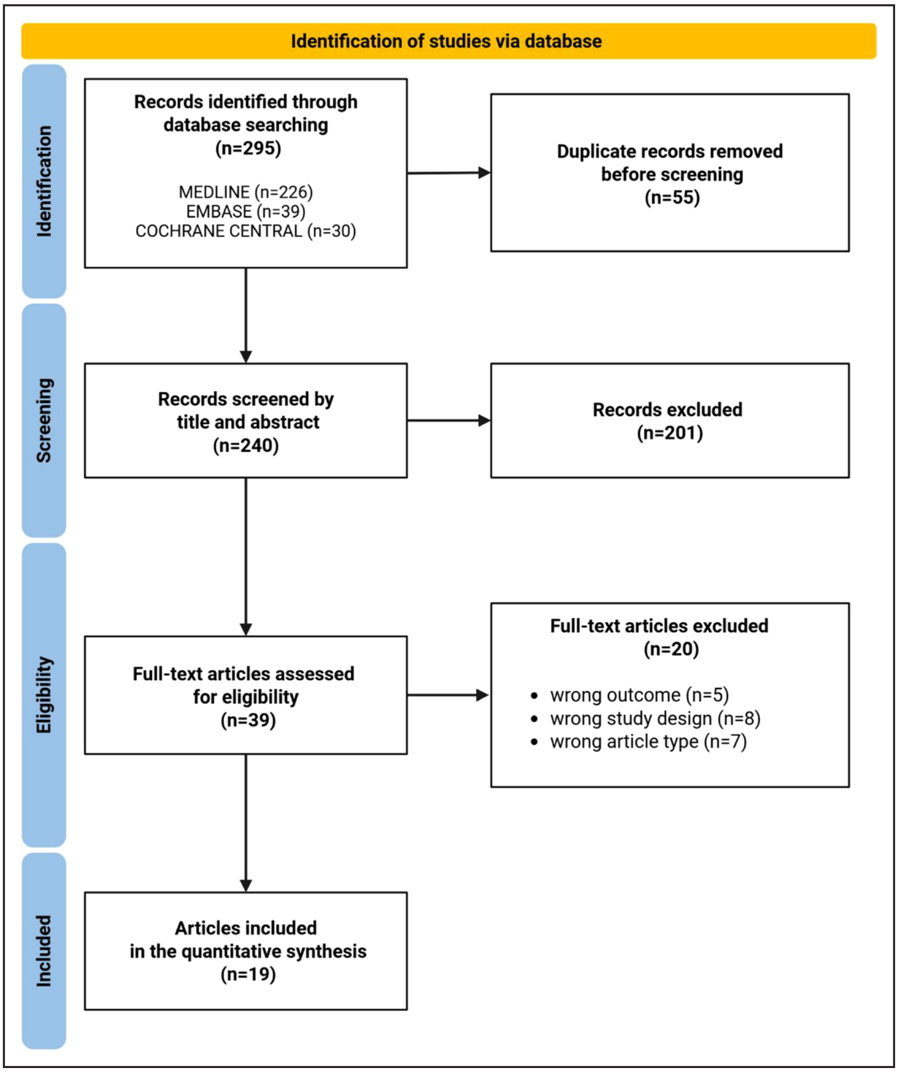

Figure 1. PRISMA flow diagram of study selection.
Flow chart depicting the identification, screening, eligibility, and inclusion process of studies for the systematic review and meta-analysis, according to PRISMA guidelines. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

restricted maximum likelihood estimation. The moderator was defined as the difference in mean OTG time between the 2 models (delay in OTG) expressed in minutes (drip-and-ship minus mothership). A positive coefficient indicates a growing benefit in favor of the mothership model as the delay introduced by the drip-and-ship strategy increases. We extracted the mean difference in OTG time in the drip-and-ship and mothership models as reported in each study. When time data were provided as medians with interquartile ranges, they were converted to estimated means and standard deviations using established methods. Finally, as part of this meta-analysis, we conducted a predefined subgroup analysis to explore whether geographical setting contributed to the primary outcome. Studies were categorized as conducted in urban, rural, or mixed areas based on the Rural Urban Classification system used in the United Kingdom (https://www.gov.uk/government/collections/rural-urban-classification). This classification distinguishes areas according to population size, density, and settlement context. Rural areas were defined as settlements with <10 000 inhabitants, including villages, hamlets, and isolated dwellings; urban areas comprised cities, towns, and conurbations with populations >10 000; mixed settings referred to studies that included participants from both rural and urban areas without a clearly predominant setting. Classification was based on descriptions provided in the original studies, supplemented by official sources (eg, Office for National Statistics, Department for Environment, Food and Rural Affairs). In cases where the classification was unclear, 2 reviewers independently assessed and resolved discrepancies through consensus. All analyses were performed using

R studio V.4.2.2 (RStudio PBC) with *Meta* and *Metafor* packages.

There was no funding source for this study.

RESULTS

Study Selection

Our search initially identified 295 titles and abstracts, of which 240 were eligible for screening after duplicates removal. Through the screening process, we excluded 201 records, resulting in 39 documents assessed for eligibility. During the full-text evaluation, we further excluded 20 documents. Finally, we included 19 studies[4–22] in the quantitative synthesis (Figure 1, Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart).

Study Characteristics

Overall, our analysis included 16 485 participants, of whom 8571 (52%) were treated with mothership prehospital model care and 7914 (48%) with drip-and-ship prehospital model of care. Table 2 summarizes the baseline characteristics of the 19 studies included in this analysis. All studies adopted a cohort design, except for 1 RCT conducted by de la Ossa et al.[19] in Spain. The studies span a diverse geographical range, encompassing Europe (Portugal, Northern Ireland, France, Germany, Italy, Poland, Belgium, Spain, England), Australia, and China, thereby offering a broad representation of health care systems and stroke networks. The total sample size per study ranged from 50 to 6632 patients. The proportion of patients managed using the mothership model varied from 28.1% (van Veenendaal et al.[6]) to 66.9% (Taschner et al.[17]), and the drip-and-ship model accounted for the remaining patients. Several studies reported a near-equal distribution between the 2 models, such as Brochado et al.[9] and de la Ossa et al.,[19] suggesting similar deployment across networks. Conversely, some studies demonstrated a predominance of one model over the other, reflecting differences in local stroke logistics and infrastructure.

Clinical Characteristics of Included Study Populations

Table S2 details the clinical characteristics of patients from the included studies, stratified by treatment model—mothership versus drip and ship. The reported variables include age, sex distribution, stroke severity on admission (as assessed by the National

Table 2. Study Characteristics

Study	Location	Type of study	Total number of patients, n	Number of patients treated with mothership model of care, n (%)	Number of patients treated with drip-and-ship model of care, n (%)
Cristina et al. 2022[4]	Portugal	Cohort study	1154	407 (35.3)	747 (64.7)
Adams et al. 2019[5]	Northern Ireland	Cohort study	214	124 (57.9)	90 (42.1)
van Veenendaal et al. 2018[6]	Australia	Cohort study	178	50 (28.1)	128 (71.9)
Mourand et al 2019[7]	France	Cohort study	179	93 (52)	86 (48)
Weiss et al 2023[8]	Germany	Cohort study	202	92 (45.5)	110 (54.5)
Brochado et al. 2022[9]	Spain	Cohort study	375	188 (50.1)	187 (49.9)
Raquin et al. 2025[10]	France	Cohort study	79	25 (31.6)	54 (68.4)
Cabaraux et al. 2024[11]	Belgium	Cohort study	366	137 (37.4)	229 (62.6)
Paolucci et al. 2021[12]	Italy	Cohort study	50	26 (52)	24 (48)
Sallustio et al. 2024[13]	Italy	Cohort study	293	113 (38.6)	180 (61.4)
Luchowski et al. 2021[14]	Poland	Cohort study	400	267 (66.8)	133 (33.2)
Seker et al. 2020[15]	Germany	Cohort study	2797	1657 (59.2)	1140 (40.8)
D'Anna et al. 2022[16]	England	Cohort study	579	216 (37.3)	363 (62.7)
Taschner et al. 2021[17]	Germany	Cohort study	332	222 (66.9)	110 (33.1)
Schaefer et al. 2022[18]	Germany	Cohort study	6632	3819 (57.6)	2813 (42.4)
de la Ossa et al. 2022[19]	Spain	Randomized clinical trial	949	482 (50.8)	467 (49.2)
Huang et al. 2021[20]	China	Cohort study	92	55 (59.8)	37 (40.2)
Weisenburger-Lile et al. 2019[21]	France	Cohort study	971	298 (30.6)	673 (69.4)
Weber et al. 2016[22]	Germany	Cohort study	643	300 (46.7)	343 (53.3)

Institutes of Health Stroke Scale), the use of IVT, and key time metrics such as onset to needle, OTG, and onset to recanalization times. Across studies, the median or mean age of patients was generally in the range of 67 to 80 years in both treatment groups. Sex distribution was relatively balanced, although several studies showed a slightly higher proportion of men in the drip-and-ship cohorts.[5,6,8,14] Stroke severity, measured by the National Institutes of Health Stroke Scale on admission, was moderately high across both groups, ranging from 13 to 18. The use of IVT was variably reported and showed wide variation between studies and treatment strategies. In some studies, such as those by Mourand et al.[7] and de la Ossa et al.,[19] a greater proportion of drip-and-ship patients received IVT. Across the included studies, onset to needle was reported in 12 studies and generally favored the drip-and-ship model. Specifically, drip-and-ship patients showed shorter onset to needle in 8 out of 12 studies.[7,8,10,12,13,16,17,19] Conversely, OTG and onset to recanalization times consistently demonstrated a significant advantage for the mothership model. In nearly all studies providing these metrics, patients directly admitted to comprehensive stroke centers (mothership) underwent groin puncture and achieved recanalization more rapidly than those managed through the drip-and-ship approach. The OTG interval was, on average, 60 to 120 minutes shorter in the mothership group across studies such as van Veenendaal et al.,[6] Mourand et al.,[7] Raquin et al.,[10] and Sallustio et al.[13] Similarly, onset to recanalization times favored the mothership model, with some studies showing differences >1 hour between groups.

Clinical Outcomes of Included Patients

Clinical outcomes were variably reported across the included studies, with most providing data on 90-day functional independence (defined as mRS score 0–2), rates of successful recanalization (thrombolysis in cerebral infarction ≥2b), sICH, any ICH, and 90-day mortality (Table S3). Functional outcomes (mRS score 0–2 at 90 days) were reported in most studies, with results varying across cohorts. In some studies, the mothership model was associated with higher proportions of patients achieving good functional outcomes, such as in van Veenendaal et al.[4,6] (63% versus 52%) and Cristina et al.[4] (41.3% versus 34.9%). However, other studies showed the opposite trend, as in Adams et al.[5] (51.6% versus 62.2%, favoring drip and ship). In several cases, outcomes were comparable between models, such as in the study by de la Ossa et al.[19] (33.4% versus 32.8%). Successful reperfusion, defined as thrombolysis in cerebral infarction ≥2b, was generally high across both groups and often >80%. In studies like Brochado et al.[9] and Cabaraux et al.,[11] rates approached or exceeded 90%, with modest differences between strategies. However, Weber et al.[22] reported a striking contrast (mothership 72.7% versus drip and ship 92.4%). The rate of sICH was generally low in both groups, typically <7%, though some variation was observed as Huang et al.[20] reported a relatively high sICH rate in the mothership group (14.5%). The 90-day mortality ranged from ~15% to 36% in the studies included. In several studies, the mothership model was associated with lower mortality (eg, Raquin et al.[10] 19% versus 33%, Weisenburger-Lile et al.[21] 16.1% versus 17.4%), whereas others found higher mortality in the mothership group (Cristina et al.[4] 21% versus 24.1%, Sallustio et al.[13] 36.3% versus 24.4%).

Primary Outcome: 90-Day mRS Score 0 to 2

A total of 18 studies involving 16 214 patients (8445 managed via the mothership strategy and 7769 via the drip-and-ship approach) were included, with 6245 patients achieving a favorable outcome, defined as mRS score of 0 to 2 at 90 days. Using a random-effects model, the pooled OR for achieving mRS score 0to 2 was 1.12 (95% CI, 0.94–1.32; P=0.199), indicating no statistically significant difference in functional outcomes at 90 days between the mothership and drip-and-ship strategies (Figure 2). The analysis revealed substantial heterogeneity across studies (I^2=82.2% [95% CI. 73.0–88.3%]), with Cochran's Q test confirming statistically significant heterogeneity (Q=95.55, df=17, P<0.0001). The between-study variance was estimated as tau^2=0.0826 (95% CI. 0.0407–0.4915) and tau=0.2875 (95% CI. 0.2018–0.7011). To aid interpretation, the estimated between-study SD (τ=0.2875) corresponds to a multiplicative factor of approximately $\exp(\tau)$=1.33. This implies that the true treatment effect may vary by ~33% across the different stroke care systems. To evaluate the robustness of the results, a leave-one-out sensitivity analysis was conducted (Figure S1). The pooled OR for mRS scores 0 to 2 remained consistent across all iterations, ranging from 1.08 to 1.16, with all P values remaining nonsignificant. Between-study heterogeneity (I^2) also remained high, ranging from 69.5% to 83.2%. Notably, omission of Schaefer et al.[18] and Seker et al.[15] led to a modest reduction in heterogeneity (I^2=69.5% and 72.7%, respectively), although the corresponding effect estimates remained nonsignificant. In addition to the random-effects analysis, we also computed a precision-weighted fixed-effect model for the primary outcome. The fixed-effect pooled OR for achieving functional independence (mRS score

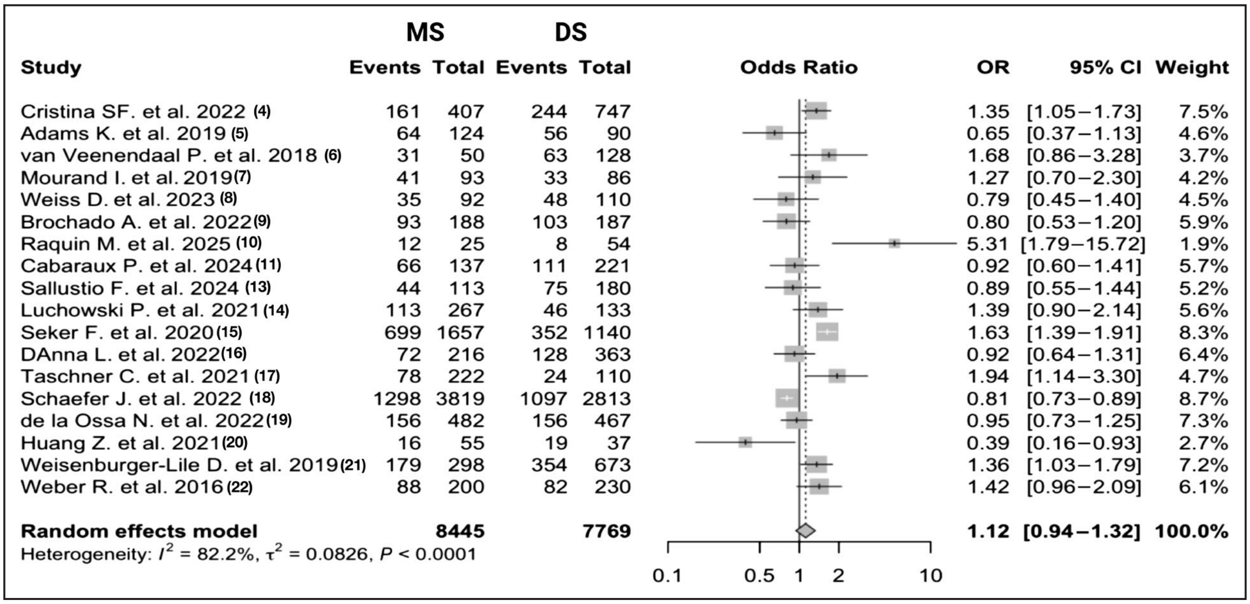

Figure 2. Forest plot of the primary outcome (90-day functional independence, mRS score 0–2).
Forest plot showing the odds ratios and 95% CIs for achieving functional independence (mRS score 0–2 at 90 d) comparing the mothership vs drip-and-ship models across included studies. DS indicates drip and ship; mRS, modified Rankin Scale; MS, mothership; and OR, odds ratio.

0–2) at 90 days was 1.04 (95% CI, 0.98–1.11), which closely mirrors the estimate obtained using the random-effects approach (Figure S2).

Secondary Outcome: 90-Day mRS Score 0 to 1 and Successful Recanalization

As regards the 90-day mRS score 0 to 1, the pooled OR was 1.07 (95% CI, 0.74–1.54; P=0.719), indicating no statistically significant difference between the mothership and drip-and-ship approaches (Figure 3A). Substantial heterogeneity was observed among the included studies (I^2=82.2% [95% CI, 67.6–90.3%]), with Cochran's Q test confirming statistically significant heterogeneity (Q=45.07, df=8, P<0.0001). The between-study variance was estimated as tau^2=0.2234 (95% CI, 0.0811–2.4604), and tau=0.4726 (95% CI, 0.2848–1.5686). To aid interpretation, this corresponds to a multiplicative factor of $\exp(\tau) \approx 1.60$, indicating that the true effect may vary by ~60% across stroke care systems.
The pooled OR for achieving successful recanalization was 0.80 (95% CI, 0.59–1.07; P=0.135) suggesting no statistically significant difference in recanalization rates between the mothership and drip-and-ship strategies (Figure 3B). Moderate to substantial heterogeneity was observed across the included studies (I^2==72.6% [95% CI, 54.0–83.6%]), with a statistically significant Cochran's Q test (Q=51.03, df=14, P<0.0001). The between-study variance was estimated as tau^2=0.2226 (95% CI, 0.0669–0.6406), and tau=0.4718 (95% CI, 0.2586–0.8004), corresponding to $\exp(\tau) \approx 1.60$, again indicating approximately 60% variation across health care systems.

Safety Outcomes and 90-Day Mortality, Symptomatic Intracranial Hemorrhage, and Intracranial Hemorrhage

As regards the 90-day mortality, the pooled OR was 1.02 (95% CI, 0.85–1.22; P=0.840) and indicated no statistically significant difference between the 2 strategies for this outcome (Figure 4A). Moderate heterogeneity was observed across studies (I^2=52.6% [95% CI, 17.6–72.7%]), with the Cochran's Q test confirming statistically significant heterogeneity (Q=33.73, df=16, P=0.0059). The estimated between-study variance was tau^2=0.0573 (95% CI, 0.0207–0.7182), and tau=0.2394 (95% CI, 0.1440–0.8474), which corresponds to a multiplicative factor of $\exp(\tau) \approx 1.27$. This suggests that the underlying treatment effect may vary by ~25% to 30% across stroke networks.
The pooled OR for the occurrence of sICH was 0.89 (95% CI, 0.66–1.20; P=0.430) (Figure 4B), indicating no statistically significant difference in the risk of sICH between the mothership and drip-and-ship strategies. Heterogeneity among studies was low (I^2=19.2% [95% CI, 0.0–59.0%]), and the Cochran's Q test did not indicate statistically significant heterogeneity (Q=12.38, df=10, P=0.260). The between-study variance was negligible (tau^2<0.0001 [95% CI, 0.0000–1.5568]), with tau=0.0008 (95% CI, 0.0000–1.2477), corresponding to a multiplicative factor of $\exp(\tau) \approx 1.00$. This suggests

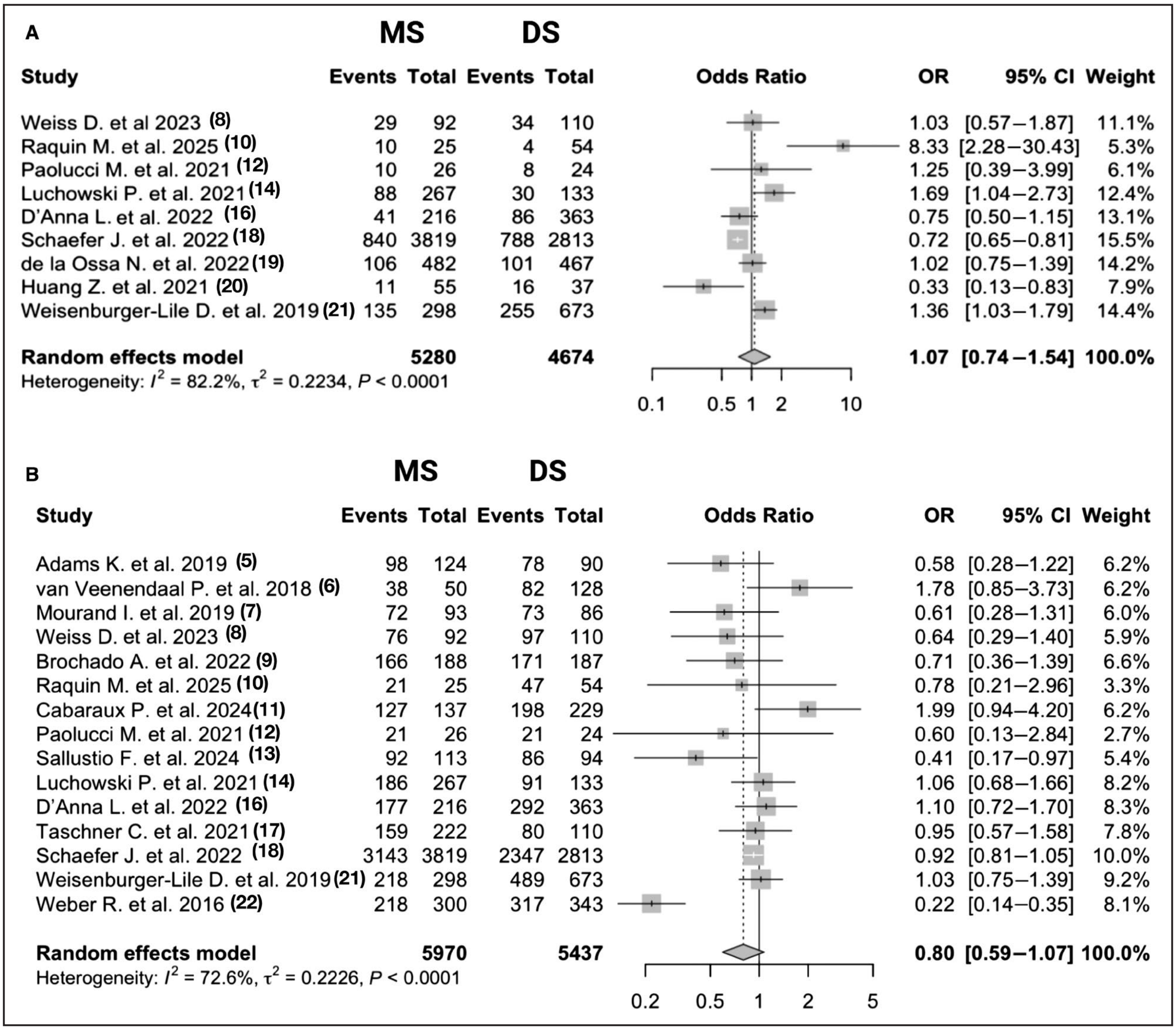

Figure 3. Forest plots of secondary outcomes.

A, Forest plot showing the odds ratios and 95% CIs for achieving excellent outcome (mRS score 0–1 at 90 d) comparing mothership vs drip-and-ship models. **B**, Forest plot showing the odds ratios and 95% CIs for achieving successful recanalization (TICI ≥2b) comparing mothership vs drip-and-ship models. DS indicates drip and ship; mRS, modified Rankin Scale; MS, mothership; OR, odds ratio; and TICI, thrombolysis in cerebral infarction.

that the estimated effect on sICH risk was essentially consistent across stroke systems. Several studies in this analysis reported 0 events in 1 arm. To ensure stable estimation in the presence of sparse data, a standard continuity correction of 0.5 was applied.

As regards the risk of ICH post MT, the pooled OR was 0.81 (95% CI, 0.63–1.03; P=0.080) (Figure 4C). Although the result did not reach statistical significance, it suggests a potential trend toward a lower risk of ICH with the mothership strategy. Moderate heterogeneity was observed among the studies (I^2=60.9% [95% CI, 10.6–82.9%]), with Cochran's Q test indicating statistically significant heterogeneity (Q=15.35, df=6, p=0.0177). The estimated between-study variance was tau^2=0.0548 (95% CI, 0.0013–0.4193), and tau=0.2341 (95% CI, 0.0354–0.6475), corresponding to a multiplicative factor of $\exp(\tau)\approx1.26$. This indicates that underlying study effects may reasonably differ by approximately 26% across stroke systems.

Risk of Bias

The risk-of-bias assessment is shown in Figure 5. As shown in the risk-of-bias summary figure, the majority of observational studies showed low to moderate risk across most domains, with some studies displaying serious concerns, particularly related to confounding

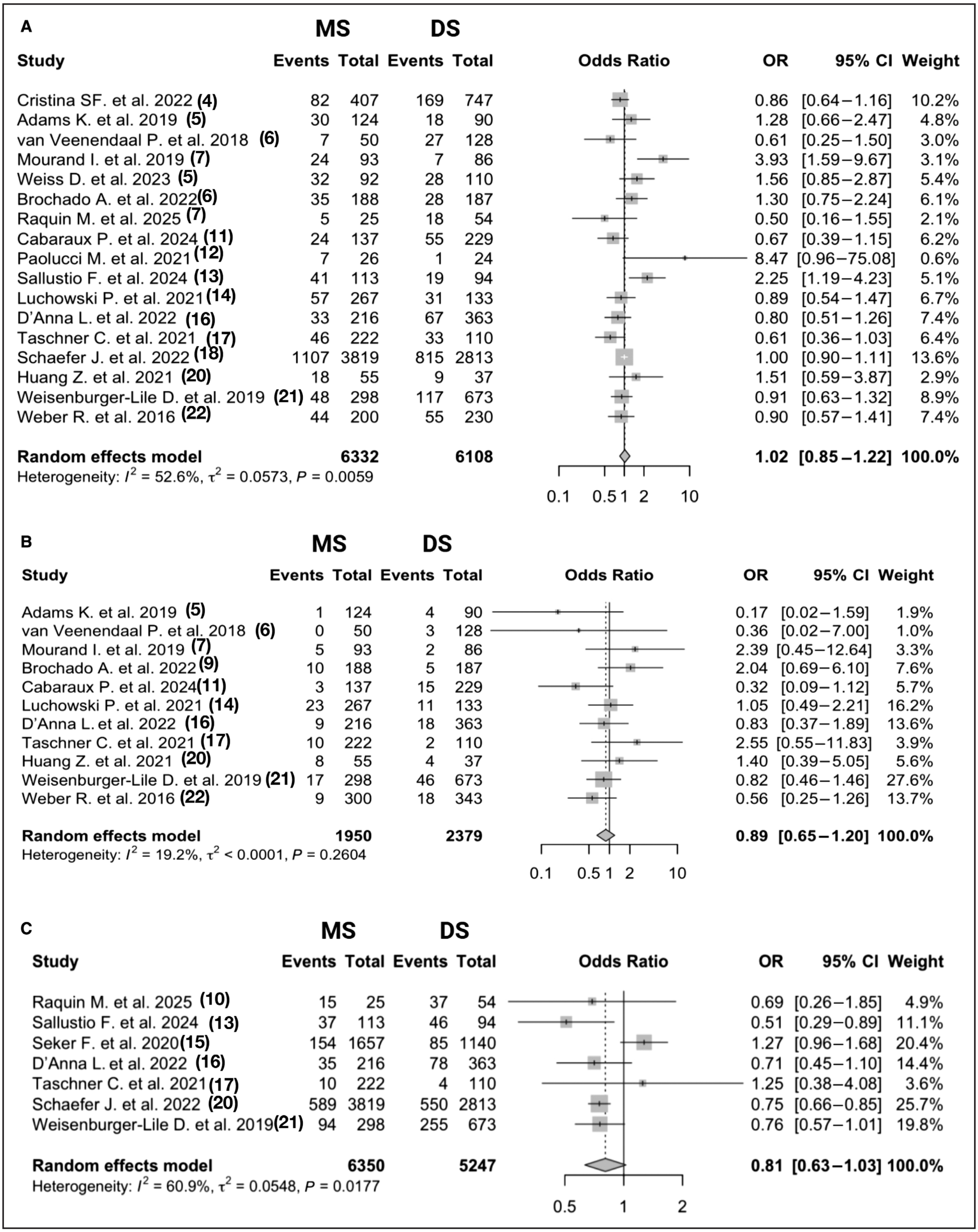

Figure 4. Forest plots of safety outcomes.

A, Forest plot showing the odds ratios and 95% CIs for 90-d mortality comparing mothership vs drip-and-ship models. **B**, Forest plot showing the odds ratios and 95% CIs for symptomatic intracranial hemorrhage after mechanical thrombectomy. **C**, Forest plot showing the odds ratios and 95% CIs for any intracranial hemorrhage after mechanical thrombectomy. DS indicates drip and ship; MS, mothership; and OR, odds ratio.

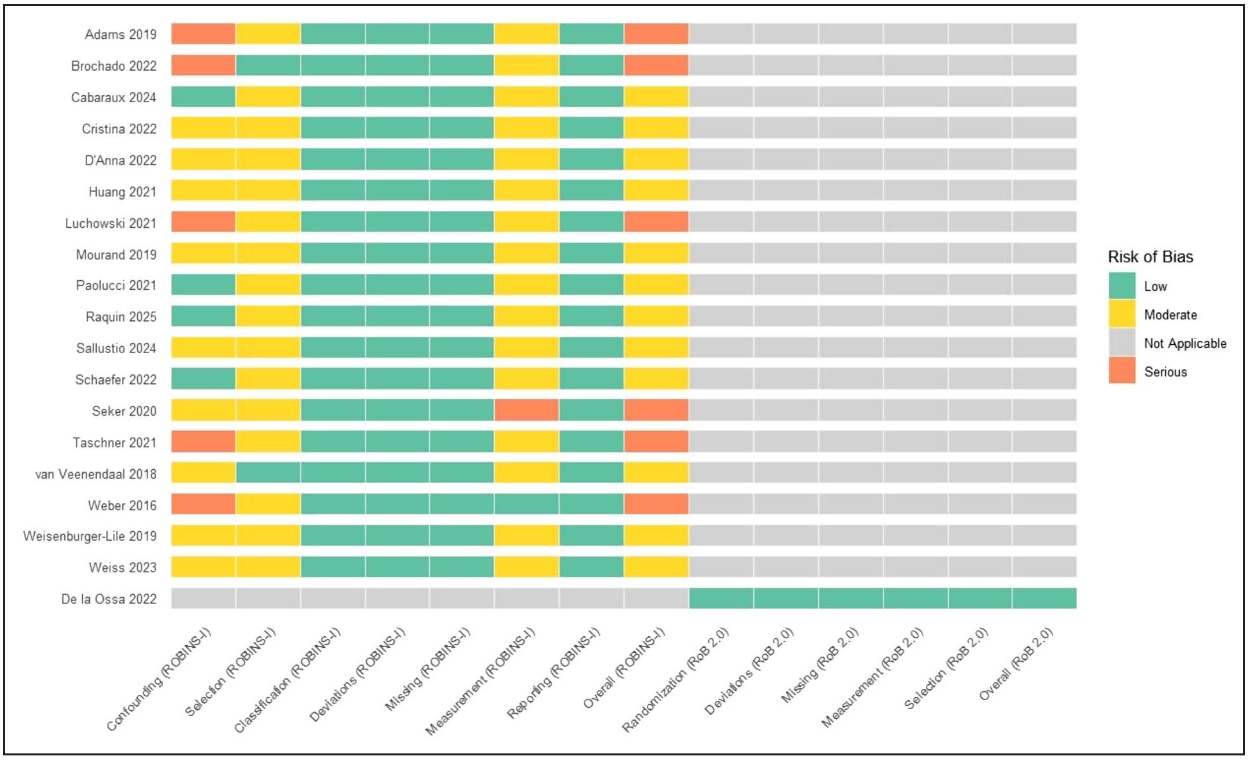

Figure 5. Risk-of-bias assessment of included studies.
Adams[5]; Brochado[9]; Cabaraux[11]; Cristina[4]; D'Anna[16]; Huang[20]; Luchowski[14]; Mourand[7]; Paolucci[12]; Raquin[10]; Sallustio[13]; Schaefer[18]; Taschner[17]; van Veenendaal[6]; Weber[22]; Weisenburger-Lile[21]; Weiss[8]; de la Ossa[19]. Summary of the risk-of-bias assessment for the included studies using ROBINS-I for observational studies and RoB 2.0 tool for the randomized controlled trial. RoB 2.0 indicates Risk of Bias 2.0; and ROBINS-I, Risk of Bias in Non-randomized Studies of Interventions.

and outcome reporting. The RCT study demonstrated low risk across all Risk of Bias 2.0 domains, indicating robust methodological quality. Visual inspection of the funnel plot for the primary outcome analysis did not reveal clear asymmetry (Figure S3). To assess for the presence of publication bias, Egger's linear regression test was performed. The test result was not statistically significant (t=1.01, df=16, P=0.328), indicating no evidence of funnel plot asymmetry or small-study effects. The estimated bias coefficient was 0.97 (SE=0.96), further supporting the absence of publication bias in this analysis.

Meta-Regression of the Primary Outcome (90-Day mRS Score 0–2) Based on Delay Between Models

Table S4 provides detailed OTG puncture times for mothership and drip-and-ship models across studies, from which the delay (drip-and-ship minus mothership) used in the meta-regression analysis was derived. The analysis revealed that the delay in OTG, expressed in minutes (drip-and-ship minus mothership), was a significant moderator of treatment effect for likelihood of achieving 90-day functional independence (QM=12.96, df=1, P=0.0003) (Figure 6). The estimated coefficient for the delay in OTG was 0.0045 (SE=0.0012 [95% CI, 0.0020–0.0069]), indicating that for every 1-minute increase in the delay associated with the drip-and-ship model, the logOR increases by 0.0045, corresponding to an ~4.6% increase in the OR every 10 minutes. The intercept of the model (logOR=−0.1945, P=0.0790) suggests no significant treatment difference when the delay is 0. The proportion of between-study heterogeneity accounted for by the difference in OTG time was very high (R^2=99.99%), indicating that most of the variability in study-level treatment effects was aligned with differences in workflow delay rather than unexplained random variation. In practical terms, once this factor was included in the model, the remaining heterogeneity was minimal ($\tau^2 \approx 0$, I^2=0.01%), suggesting that the delay in treatment time represents a major contributor to the observed differences across studies, rather than other unmeasured study characteristics. Solving the equation for log(OR)=0, the estimated time difference at which the 2 strategies become equivalent was ~43.2 minutes (95% CI, 30–70 minutes). Beyond this threshold, the mothership model was associated with a progressively greater likelihood of achieving

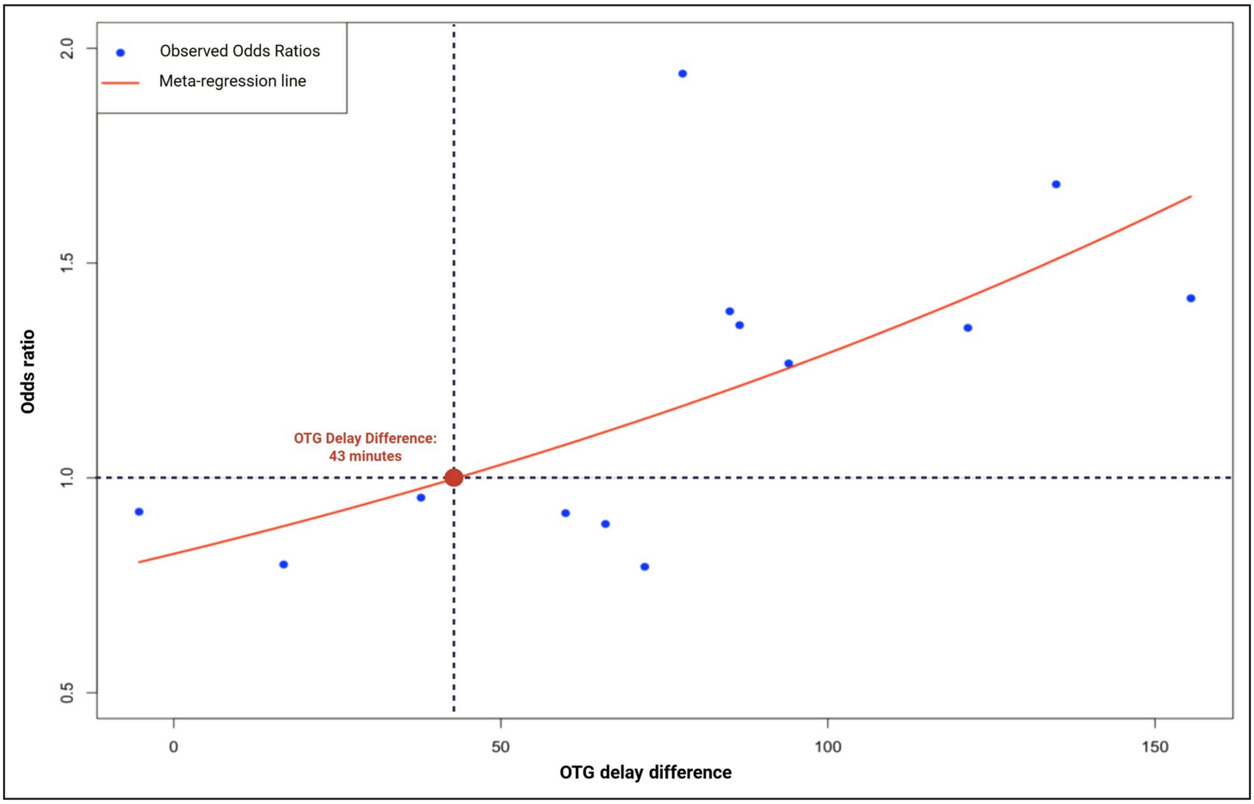

Figure 6. Meta-regression analysis of primary outcome based on onset-to-groin puncture delay.
Meta-regression plot illustrating the association between delay in OTG puncture time (min) between models and the odds ratio for achieving functional independence (mRS score 0–2) at 90 d A delay threshold of approximately 43 minutes was identified. mRS indicates modified Rankin Scale; and OTG, onset-to-groin.

90-day functional independence compared with the drip-and-ship model.

Subgroup Analysis by Rural–Urban Classification

With regard to studies conducted in an urban setting, the pooled OR for the primary outcome was 1.08 (95% CI 0.87–1.33; *P*=0.489) (Figure S4A), indicating no statistically significant difference between the 2 groups. Heterogeneity across the studies was moderate, with an I^2 value of 46.1% (95% CI, 0.0–77.3%) and a nonsignificant Cochran's Q test (Q=11.14, df=6, *P*=0.0841). The between-study variance was estimated as tau^2=0.0336 (95% CI, 0.0000–0.4644), with tau=0.1834 (95% CI, 0.0000–0.6815), corresponding to a multiplicative factor of exp(τ)≈1.20, suggesting that underlying effects in urban networks varied modestly (≈20%) across systems.

As regards to studies conducted in a rural setting Figure S4B), the pooled OR for primary outcome was 1.13 (95% CI 0.76–1.67, *P*=0.540) indicating no statistically significant difference between the two groups. Substantial heterogeneity was observed among studies (I^2=73.4% [95% CI 33.5%–89.3%]; τ^2=0.1382), and the test for heterogeneity was statistically significant (Q=15.02, df=4, *P*=0.0047), suggesting considerable between-study variability. The between-study variance was estimated as τ^2=0.1382, corresponding to a between-study SD of τ=0.37. This value reflects that the true underlying effects may differ by a multiplicative factor of approximately exp(τ)≈1.45 across rural systems, suggesting that differences across systems contribute to the observed heterogeneity.

Finally, for studies conducted in mixed settings (ie, involving populations from both rural and urban areas) (Figure S4C), the pooled OR for the primary outcome was 0.99 (95% CI 0.72–1.36, *P*=0.940), indicating no statistically significant association. There was substantial heterogeneity across studies (I^2=91.3% [95% CI 84.6%–95.1%]; τ^2=0.1440), and the test for heterogeneity was significant (Q=68.82, df=6, *P*<0.0001). The between-study variance was τ^2=0.1440, corresponding to a between-study SD of τ=0.38. This implies that the underlying treatment effects varied by a multiplicative factor of approximately exp(τ)≈1.46 across mixed settings, suggesting marked variability in the systems.

DISCUSSION

This systematic review and meta-analysis compared the effectiveness of 2 prehospital transport strategies—mothership and drip and ship—for delivering MT in patients with anterior circulation LVO. The main finding was that, when considered as a whole, neither strategy was significantly superior in terms of achieving the study outcomes of interest. However, our meta-regression analysis revealed that the delay in access to thrombectomy, quantified as OTG puncture time, significantly moderated the treatment effect. Specifically, the longer the delay associated with the drip-and-ship approach compared with the mothership model, the more likely the latter was to yield favorable functional outcomes. These findings underscore the central role of time in endovascular stroke care and provide a critical insight into the debate surrounding optimal prehospital stroke triage.

Although no statistically significant difference was observed overall between mothership and drip-and-ship for achieving functional independence at 90 days, the meta-regression demonstrated that treatment delays associated with secondary transfer strongly influence clinical outcomes. Even modest delays of 10 minutes were associated with an ~4% to 5% reduction in the odds of achieving functional independence, with the mothership strategy becoming progressively more beneficial when transfer delays exceed ~43 minutes. These findings underscore the importance of optimizing prehospital triage based on expected transfer-related delays rather than adopting a uniform approach.

Previous studies have presented conflicting evidence on which model is superior, often yielding nonsignificant or mixed results.[5,9,15,16,18–20] A previous meta-analysis made the comparison to aggregate outcomes without accounting for the variation in time metrics between models.[3] This may have contributed to inconclusive results and limited the clinical applicability of our findings. Our analysis is, to our knowledge, the first to incorporate OTG as a continuous moderator, allowing us to quantify the impact of treatment delay on clinical outcome. The results demonstrate that even modest delays in access to thrombectomy can diminish the benefit of treatment, supporting the well-established concept that "time is brain" remains highly relevant in the era of mechanical thrombectomy. Indeed, our meta-regression analysis yielded a delay threshold of approximately 43 minutes, beyond which the mothership model was significantly more likely to result in functional independence at 90 days compared with drip-and-ship model. This might have substantial implications for systems of care planning and triage algorithms. In geographic settings or network configurations where interhospital transfer is likely to add >40 minutes of delay to thrombectomy, direct transportation to a comprehensive stroke center might offer superior outcomes. Conversely, when the delay to a comprehensive stroke center is minimal, the drip-and-ship model may remain a reasonable option.

Moreover, recent advances in acute stroke logistics and pharmacological management may further influence the impact of transport delays. The increasing adoption of tenecteplase,[23] with faster and easier administration compared with alteplase, could streamline workflows and potentially mitigate some of the delays observed in drip-and-ship models. A potentially higher rate of reperfusion achieved with intravenous tenecteplase compared with intravenous alteplase in patients with LVO may also be another consideration in drip-and-ship models,[24] as the studies in our analysis were mainly of patients treated with alteplase. Additionally, reorganizing ambulance logistics, such as implementing a system where emergency vehicles remain on standby at the primary stroke center during initial evaluation and thrombolysis administration, rather than departing and returning later, may significantly reduce interhospital transfer times.[25] These optimizations warrant future investigation as they may enhance the overall efficiency of the drip-and-ship strategy and improve outcomes, particularly in regions characterized by limited accessibility to comprehensive stroke centers.

Our subgroup analysis according to geographical context (urban, rural, and mixed settings) did not identify any setting in which one model clearly outperformed the other. However, heterogeneity remained substantial in rural and mixed environments, suggesting that other unmeasured variables—such as emergency medical service availability, traffic patterns, helicopter use, and stroke network coordination—may influence outcomes. These results highlight the need for context-specific stroke systems planning, rather than adopting a uniform model across regions with differing logistical challenges.

Our findings have important implications for stroke care delivery in the United Kingdom and other settings with prolonged door-in-door-out times.[26] In the United Kingdom, data from the Sentinel Stroke National Audit Programme indicate median door-in-door-out times >120 minutes in many centers. When contrasted with our meta-regression analysis—which identified a 43-minute delay threshold beyond which functional outcomes significantly decline—this suggests a potentially substantial inequity in access to thrombectomy-related benefit. If our findings are reflective of real-world UK practice, many patients routed through the drip-and-ship model may be at a major disadvantage compared with those transported directly to a thrombectomy center. Addressing this gap may require either a systemic reduction in door-in-door-out times or a restructuring of prehospital triage to favor direct access to MT.

The heterogeneity observed across studies is best understood as a reflection of real-world differences between stroke systems rather than inconsistency in the direction of the treatment effect. Our meta-regression showed that delays introduced by the drip-and-ship pathway accounted for almost all of the between-study variability, indicating that time to reperfusion is the primary determinant of whether one model performs better than the other. Consistently, subgroup analyses demonstrated lower heterogeneity in urban networks, where transport distances and workflows are more standardized, and substantially higher heterogeneity in rural and mixed systems, where logistical constraints and referral pathways vary widely. Taken together, these findings support the interpretation that the comparative effectiveness of mothership versus drip-and-ship depends on the structural and geographical characteristics of the prehospital environment.

To realize the potential of this model without compromising care for patients without LVO, advances in prehospital triage will be critical. Emerging strategies—such as video triage, point-of-care imaging, and stroke severity scoring—may help identify patients with a high probability of LVO and prioritize them for direct MT referral, whereas patients unlikely to benefit from thrombectomy can be safely routed to the nearest IVT-capable hospital.[27,28] These findings underscore the urgent need for stroke system reconfiguration and investment in triage technology to deliver equitable and time-sensitive stroke care.

Finally, variability in IVT use across studies likely contributed to heterogeneity in our analysis. One potential advantage of the drip-and-ship model is the shorter interval from stroke onset to IVT administration, as patients are transported to the nearest primary stroke center. This rapid initiation of IVT may partially mitigate delays associated with secondary transfer, particularly within well-organized networks with optimized logistics. Moreover, evolving IVT strategies may further influence the balance between mothership and drip-and-ship models. The growing adoption of tenecteplase, with its single-bolus administration and potential for faster reperfusion, could enhance the effectiveness of initial treatment at primary stroke centers and reduce overall delays to thrombectomy centers. Future studies should reassess prehospital triage strategies in light of these evolving therapeutic options.

The strength of our review lies in its rigorous methodology, broad inclusion of international studies, and novel use of meta-regression to address a key limitation in prior research. Furthermore, the consistency of our findings across sensitivity analyses supports the robustness of the results. We also employed a prespecified rural–urban classification to better capture contextual factors often overlooked in traditional analyses. Nonetheless, several limitations warrant consideration. First, most included studies were observational in nature and thus inherently subject to confounding and selection bias. Although one high-quality RCT (RACECAT [Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion]) was included, the generalizability of its findings is limited to nonurban areas in Spain. Second, reporting of time metrics was inconsistent, and conversions from medians to means may have introduced imprecision. Third, our analysis was conducted at the study level, not the individual patient level, which precludes more granular assessment of how patient-specific factors (eg, age, baseline National Institutes of Health Stroke Scale score, collateral status) interact with treatment delay. It is worth noting that although the recent TRIAGE-STROKE (Treatment Strategy in Acute Ischemic Large Vessel Stroke: Prioritize Thrombolysis or Endovascular Treatment) RCT by Behrndtz et al.[29] addressed transport strategies in patients with suspected large vessel occlusion, it was not included in our meta-analysis. This decision was based on the fact that the study did not provide outcome data specifically stratified for patients who underwent MT. Although the trial reported some secondary analyses in patients with LVO, functional outcomes at 90 days were not clearly separated between those who did and did not receive endovascular therapy. As our analysis focused explicitly on patients treated with thrombectomy, including only those studies reporting outcome data for this subgroup was essential to preserve methodological consistency and interpretability of effect estimates. Finally, differences in local protocols, imaging selection, baseline degree of ischemic core, and thrombectomy techniques were not uniformly reported, potentially introducing additional variability.

CONCLUSIONS

In conclusion, while functional outcomes were not statistically different between the mothership and drip-and-ship models overall, our meta-regression analysis clearly demonstrated that delay in access to thrombectomy is a key modifier of treatment effect. Our results suggest that stroke systems should aim to minimize OTG time regardless of the model employed, and that pre-hospital decision-making should incorporate real-time estimates of transfer delay when deciding between transport strategies. Time to thrombectomy is a critical determinant of outcome, and the benefit of the mothership model increases with greater delay introduced by the drip-and-ship pathway.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S4

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