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SYSTEMATIC REVIEW AND META-ANALYSIS

Intravenous Thrombolysis Before Mechanical Thrombectomy for Acute Ischemic Stroke: A Meta-Analysis

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BACKGROUND: Whether intravenous thrombolysis before mechanical thrombectomy provides additional benefit for functional outcome in acute ischemic stroke remains uncertain. We performed a meta-analysis to compare the outcomes of direct mechanical thrombectomy (dMT) to mechanical thrombectomy with bridging using intravenous thrombolysis (bridging therapy [BT]) in patients with acute ischemic stroke.

METHODS AND RESULTS: We performed a literature search in the PubMed, Excerpta Medica database, and Cochrane Central Register of Controlled Trials from January 1, 2003, to April 26, 2021. We included randomized clinical trials and observational studies that reported the 90-day functional outcome in patients with acute ischemic stroke undergoing dMT compared with BT. The 12 included studies (3 randomized controlled trials and 9 observational studies) yielded 3924 participants (mean age, 68.0 years [SD, 13.1 years]; women, 44.2%; 1887 participants who received dMT and 2037 participants who received BT). A meta-analysis of randomized controlled trial and observational data revealed similar 90-day functional independence (odds ratio [OR], 1.04; 95% CI, 0.90–1.19), mortality (OR, 1.03; 95% CI, 0.78–1.36), and successful recanalization (OR, 0.93; 95% CI, 0.76–1.14) for patients treated with dMT or BT. Compared with those in the BT group, patients in the dMT group were less likely to experience symptomatic intracranial hemorrhage (OR, 0.68; 95% CI, 0.51–0.91; P=0.008) or any intracranial hemorrhage (OR, 0.71; 95% CI, 0.61–0.84; P<0.001).

CONCLUSIONS: In this meta-analysis of patients with acute ischemic stroke, we found no significant differences in 90-day functional outcome or mortality between dMT and BT, but a lower rate of symptomatic intracranial hemorrhage for dMT. These findings support the use of dMT without intravenous thrombolysis bridging therapy.

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Key Words: functional independence ■ ischemic stroke ■ thrombectomy ■ thrombolysis

Intravenous thrombolysis (IVT) administered within 4.5 hours is the first-line treatment for acute ischemic stroke.[1] However, only about one third of patients with acute ischemic stroke have improved functional recovery using IVT.[2,3] Endovascular intervention using mechanical thrombectomy (MT) has been increasingly used over the past 2 decades based on previous randomized controlled trials (RCTs) and meta-analyses showing efficacy for acute ischemic stroke caused by proximal occlusion in the intracranial anterior circulation.[4,5] The current American Heart Association/American Stroke Association guidelines recommend IVT before MT for eligible patients, evidenced by the fact that all patients in the

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CLINICAL PERSPECTIVE

What Is New?

- In this meta-analysis of patients with acute ischemic stroke eligible for intravenous thrombolysis, there were no significant differences in 90-day functional outcome or mortality between direct mechanical thrombectomy and bridging therapy, but a lower rate of symptomatic intracranial hemorrhage for direct mechanical thrombectomy.

What Are the Clinical Implications?

- Current available evidence suggests that direct mechanical thrombectomy is effective and safe compared with bridging therapy, supporting the use of direct mechanical thrombectomy without intravenous thrombolysis bridging therapy.

Nonstandard Abbreviations and Acronyms

BT	bridging therapy
dMT	direct mechanical thrombectomy
ICH	intracranial hemorrhage
IVT	intravenous thrombolysis
MT	mechanical thrombectomy
sICH	symptomatic intracranial hemorrhage

trials received intravenous alteplase treatment if they did not have contraindications.[6] However, whether IVT provides additional clinical benefits (above "direct" MT [dMT] alone) on functional outcome remains uncertain. Although several recent meta-analyses suggested potential beneficial effects of IVT pretreatment,[7–9] some observational analyses yielded conflicting results about the additional benefit in terms of 90-day favorable functional outcome[10–15] or mortality.[10,14] IVT pretreatment might facilitate MT by facilitating clot detachment, enhancing collateral circulation, or lysing distal thrombi not accessible to endovascular devices.[16–18] But these hypotheses were not supported by 3 recently published RCTs[19–21] and a prospective cohort study,[22] suggesting that dMT was noninferior but not superior in acute ischemic stroke attributable to large-vessel occlusion. However, the aforementioned RCTs were heterogeneous in statistical design. We therefore aimed to synthesize all available evidence (from RCTs and observational studies) on the efficacy and safety of IVT before MT in IVT-eligible patients compared with dMT.

METHODS

The data sets used and analyzed for the current study are available from the corresponding author on reasonable request.

Study Design

We prospectively registered this meta-analysis in the international prospective register of systematic reviews (PROSPERO CRD: 42021234664) in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines and applying the methods recommended in the Meta-Analysis of Observational Studies in Epidemiology proposal.[23,24] Any modification to this protocol will be updated in PROSPERO.

Data Source and Search Strategy

We performed a literature search up to April 26, 2021, for relevant publications in PubMed, Excerpta Medica database, and Cochrane Central Register of Controlled Trials database. Our search strategy included the following set of terms: (stroke) AND (thrombolysis OR tPA OR plasminogen OR alteplase OR tenectplase) AND (thrombectomy OR endovascular OR bridging treatment). We also manually screened references for additional studies.

Study Selection

Randomized clinical trials and observational studies were eligible if they met the following criteria: (1) original published studies involving human participants regardless of language; (2) patients with acute ischemic stroke eligible for IVT, according to the current US guidelines,[6] aged ≥18 years, regardless of sex, race, and area; and (3) the intervention arm is dMT, and the control arm is MT with bridging using intravenous thrombolysis (bridging therapy [BT]). We applied the following exclusion criteria: (1) patients with IVT contraindications; (2) patients who ultimately did not undergo any endovascular treatment; (3) insufficient data information provided; (4) study with <10 participants in each arm; (5) case reports or case series with <10 eligible patients; (6) review articles, meta-analyses, literature reviews, and commentaries; and (7) abstracts or posters from conference proceedings before the full-text article was formally published in a peer-reviewed journal. Disagreements about inclusion or exclusion criteria were settled by team discussion.

Screening and Data Extraction

Two trained authors (H.L. and S.F.) blindly assessed study inclusion and study quality, and extracted data on study characteristics (ie, authors, date of publication,

setting, sample size, and study design), participants' characteristics (ie, mean/median age and sex), inclusion and exclusion criteria, follow-up time points, and outcome measures using standardized data collection sheets. Articles were imported to a citation manager (Endnote X 8.2; Thompson Reuters, Philadelphia, PA) to automatically exclude most duplicate records at the article importing stage. These 2 reviewers (H.L. and S.F.) then compared studies based on their research teams (eg, authors list), study setting (ie, nation, city, and hospital), and reported study period, to further exclude the potential duplicates from the selected studies. When multiple published literatures were from the same study or center, only data for each outcome from the largest reported sample were extracted to avoid overlap. Data extractions were checked for accuracy by 2 authors (R.H. and H.D.). We extracted the frequency counts and measures of association for main outcomes when reported. When both unadjusted and adjusted odds ratios (ORs) were available, we recorded the adjusted ORs and the variables used in the adjustment. We contacted the corresponding authors to obtain the data needed to quantify the measures of association in case relevant information was not provided in a publication. Disagreements and missing data were settled by team discussion.

Outcomes

The primary outcome was functional independence, defined as a modified Rankin Scale score of 0 to 2 at 3 months. Secondary outcomes included the occurrence of mortality at follow-up, successful recanalization (defined as Thrombolysis in Cerebral Infarction scores of 2b–3 after the end of MT), and symptomatic or any intracranial hemorrhage (ICH). The differences in onset to artery puncture time between dMT and BT groups were reported in the form of standardized mean differences.

Statistical Analysis

Studies with data available for the main outcomes in the dMT group and comparator (BT) group were included in the quantitative meta-analysis. We analyzed data separately for RCTs and observational study designs to calculate summary estimates from the individual studies using a random-effects (DerSimonian-Laird) approach[25] and a fixed-effects model, and displayed the results using forest plots. Dichotomous outcomes of interests were summarized as ORs. We evaluated heterogeneity by inspecting forest plots, and with tests for heterogeneity after calculating the Q statistic and I^2 values. We considered the I^2 statistic using thresholds of 25%, 50%, and 75% as a low, moderate, and high heterogeneity, respectively.[26] To minimize possible imbalances in baseline characteristics, we statistically combined the adjusted OR resulting from multiple regression or multivariate matching analyses (propensity score matching) when reported. In addition, we compared the pooled ORs from RCTs and observational data using a test of interaction before performing overall analyses.[27] We performed preplanned subgroup analyses stratified by participant region (East Asia and Western countries) of the main outcomes to further understand heterogeneity. We conducted 2 sensitivity analyses by limiting the studies to those on acute ischemic stroke attributable to anterior circulation occlusion, and by including only RCTs and high-quality observational studies according to the Newcastle-Ottawa Scale. We additionally combined the RCTs and observational propensity score matching data in another sensitivity analysis. We also performed a separate analysis limited to studies with a full dose of alteplase. All analyses were performed using the STATA 15.0 (StataCorp LP, College Station, TX) and the Cochrane Collaboration's Review Manager (Rev Man 5.3) Software Package (2014; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Statistical significance was set at $\alpha=0.05$ for all analyses.

Assessment of Publication Bias and Study Quality Assessment (Risk of Bias)

Publication bias tests for funnel plot asymmetry and the Egger test were performed for associations described in >10 studies. Two authors (H.L. and S.F.) independently evaluated the quality of the included RCT studies using the Cochrane Collaboration risk of bias tool on the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result.[26] The Newcastle-Ottawa Scale was adapted for observational studies, and studies with <5 stars were considered of low quality, studies with 5 to 7 stars were considered of moderate quality, and studies with >7 stars were considered of high quality.[28]

RESULTS

Identified Studies

We included 12 eligible studies (3 RCTs[19–21] and 9 observational studies[22,29–36]) for the final quantitative analysis (Figure 1).

Study Characteristics

Table 1 summarizes the key characteristics of the included studies. The sample size of eligible participants in all included studies ranged from 42 to 1148 (median, 190 [interquartile range, 105–561]). The median baseline National Institutes of Health Stroke Scale score ranged from 14 to

18 points (moderate to severe severity) across studies. The 12 included studies yielded 3924 participants (mean age, 68.0 years [SD, 13.1 years]; women, 44.2%; 1887 participants in the dMT arm and 2037 in the BT arm). Most studies only included patients with acute ischemic stroke involving the anterior circulation, except 2 studies[22,29] that included patients involving both anterior and posterior circulation occlusion. Among 9 observational studies, 5 studies[22,30,31,33–35] provided propensity score matching analysis results. One study[29] included patients within a 3-hour time window. For thrombectomy devices, 1 study[29] only applied the first-generation devices (Merci retrieval system/Penumbra system). All 12 studies provided the primary outcome (modified Rankin Scale score 0–2 at 90 days), the results of mortality and successful recanalization, and 10 studies reported the outcome for ICH.

RCT Evidence

Table 2 summarizes the pooled estimated effect sizes for the RCT and observational evidence using a random-effects approach. RCT data showed there were no statistically significant differences for functional independence (OR, 1.08; 95% CI, 0.84–1.38; Figure 2A), mortality (OR, 0.93; 95% CI, 0.66–1.31; Figure 2B), successful recanalization (OR, 0.77; 95% CI, 0.54–1.10; Figure 2C), and symptomatic ICH (sICH) (OR, 0.72; 95% CI, 0.43–1.22; Figure 2D). However, patients treated with dMT had significantly lower odds of any ICH (OR, 0.68; 95% CI, 0.50–0.92; Figure 2E). Only 1 study reported that patients in the dMT group had a shorter delay in onset to artery puncture time (–0.21; 95% CI, –0.47 to 0.05).[21] We also performed a separate analysis for RCTs using a fixed-effects model because of similar treatments and populations. The results were similar to those derived from the random-effects model (Figure 3A through 3F).

Observational Evidence

Compared with BT participants, there were no statistically significant differences for dMT in 90-day

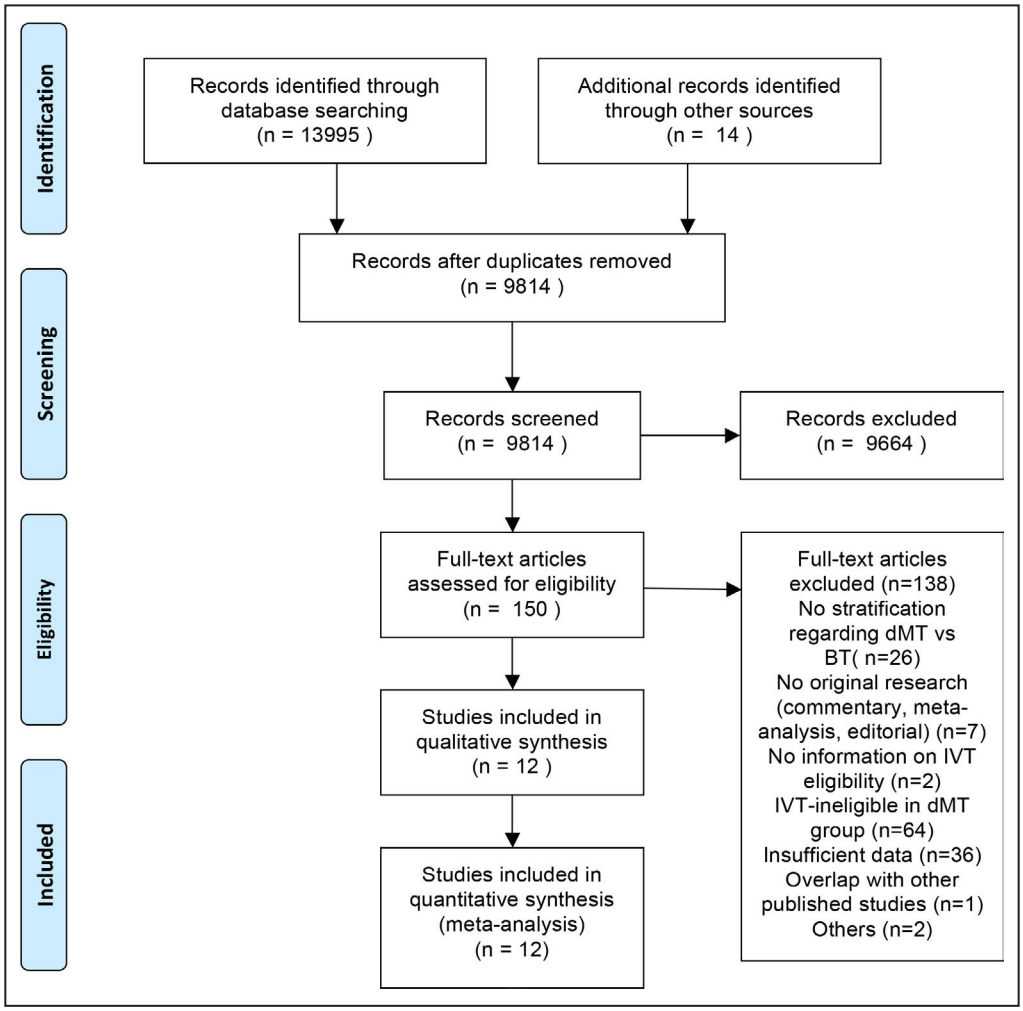

Figure 1. Flowchart of study selection.
BT indicates bridging therapy; dMT, direct mechanical thrombectomy; and IVT, intravenous thrombolysis.

functional independence (OR, 1.02; 95% CI, 0.86–1.21; Figure 2A), mortality (OR, 1.03; 95% CI, 0.70–1.53; Figure 2B), or successful recanalization (OR, 1.03; 95% CI, 0.79–1.35; Figure 2C). However, patients receiving dMT had lower odds of sICH (OR, 0.66; 95% CI, 0.47–0.93; Figure 2D) or any ICH (OR, 0.72; 95% CI, 0.57–0.90; Figure 2E); those receiving dMT had a shorter delay in onset to artery puncture time (−0.50; 95% CI, −0.94 to −0.07; Figure 2F). A separate analysis for observational studies using a fixed-effects model yielded similar results to those derived from the random-effects model (Figure 3A through 3F).

Overall Analysis

A test of interaction showed no significant differences between pooled ORs derived from RCTs and observational studies for 90-day functional independence (Z=0.146; *P*=0.884), mortality (Z=0.385; *P*=0.700), successful recanalization (Z=0.227; *P*=0.820), sICH (Z=0.318; *P*=0.751), or any ICH (Z=0.194; *P*=0.846). A combination of RCTs and observational data using a random-effects approach showed no significant differences for 90-day functional independence (OR, 1.04; 95% CI, 0.90–1.19; Figure 2A), mortality (OR, 1.03; 95% CI, 0.78–1.36; Figure 2B), or successful recanalization (OR, 0.93; 95% CI, 0.76–1.14; Figure 2C) between dMT and BT. However, dMT was associated with lower odds of sICH (OR, 0.68; 95% CI, 0.51–0.91; *P*=0.008; Figure 2D), lower odds of any ICH (OR, 0.71; 95% CI, 0.60–0.84; *P*<0.001; Figure 2E), and a shorter delay in onset to artery puncture time (−0.46; 95% CI, −0.81 to −0.10; Figure 2F). The results derived from the fixed-effects model were similar to those derived from the random-effect model (Figure 3A through 3F).

Subgroup Analysis

Our predetermined subgroup analysis, stratified by participant region (East Asia and Western countries), yielded results consistent with the overall analyses for 90-day functional independence (for the East Asian population: OR, 1.08; 95% CI, 0.91–1.29; for the Western population: OR, 0.96; 95% CI, 0.73–1.26; Figure 4A), mortality (for the East Asian population: pooled OR, 1.04; 95% CI, 0.83–1.30; for the Western population: OR, 0.78; 95% CI, 0.35–1.73; Figure 4B), and successful recanalization (for the East Asian population: OR, 1.01; 95% CI, 0.70–1.43; for the Western population: OR, 0.88; 95% CI, 0.68–1.15; Figure 4C). dMT was associated with significantly lower odds of sICH (OR, 0.70; 95% CI, 0.51–0.95; *P*=0.024; Figure 4D) and any ICH (OR, 0.69; 95% CI, 0.58–0.82; *P*<0.001; Figure 4E) in the East Asian patients. Similarly, Western patients with stroke in dMT group were at lower odds of experiencing an sICH (OR, 0.59; 95% CI, 0.29–1.21; Figure 4D) and any ICH (OR,

Table 1. Baseline Characteristics

Study	Study type	Country	Sample size		Age, mean/median, y		Women, n (%)		Baseline NIHSS score, median (IQR)		ASPECTS, median (IQR)		Onset to groin puncture time, median (IQR), min	
			dMT	BT	dMT	BT	dMT	BT	dMT	BT	dMT	BT	dMT	BT
Suzuki et al, 2021[19]	RCT	Japan	101	103	74 (67–80)	76 (67–80)	45 (45)	31 (30)	19 (13–23)	17 (12–22)	7 (6–9)	8 (6–9)	N/A	N/A
Yang et al, 2020[20]	RCT	China	327	329	69 (61–71)	69 (61–76)	138 (42.2)	148 (45)	17 (12–21)	17 (14–22)	9 (7–10)	9 (7–10)	N/A	N/A
Zi et al, 2021[21]	RCT	China	116	118	70 (60–77)	70 (60–78)	50 (43.1)	52 (44.1)	16 (12–20)	16 (13–20)	8 (7–9)	8 (7–9)	200 (155–247)	210 (179–255)
Broeg-Morva et al, 2016[30]	Retrospective	Germany	40	40	77 (14)	78 (12)	15 (37.5)	15 (37.5)	17 (4–38)	17 (4–36)	N/A	N/A	228.6 (78.6)	262.2 (85.2)
Casetta et al, 2019[31]	Retrospective	Italy	513	635	68.8 (13.1)	67.6 (14.6)	262 (51.1)	322 (50.7)	18 (14–22)	18 (14–21)	N/A	N/A	210 (170–270)	230 (185–275)
Du et al, 2021[32]	Retrospective	China	57	54	66.9 (11.9)	65.2 (12.2)	25 (43.9)	26 (48.1)	18 (13–22)	18 (16–23)	9 (8–10)	9 (7–10)	198 (156–252)	218 (175–294)
Gong et al, 2019[33]	Retrospective	China	21	21	71 (10)	70 (11)	10 (48)	9 (43)	15 (6–22)	14 (7–21)	N/A	N/A	216.5 (57.8)	172.2 (29.81)
Kass-Hout et al, 2014[29]	Retrospective	United States	62	42	69.3 (15.8)	67.6 (14.9)	33 (53.2)	22 (52.4)	16.0 (5.3)	14.8 (4.7)	N/A	N/A	121.9 (36.78)	227.8 (88)
Pienimäki et al, 2021[34]	Retrospective	Finland	48	58	72 (11)	69 (12)	18 (38)	21 (36)	14 (9)	16.5 (8)	10 (2)	9.5 (2)	N/A	N/A
Tong et al, 2021[22]	Prospective	China	394	394	65 (55–73)	65 (55–73)	139 (35.3)	147 (37.3)	17 (12–21)	16 (11–21)	9 (7–10)	10 (7–10)	N/A	N/A
Wang et al, 2017[35]	Retrospective	China	138	138	67 (58.75–75)	67 (58.75–73)	62 (44.9)	60 (43.5)	16 (13–21)	17 (13–21.25)	9 (8–10)	9 (8–10)	N/A	N/A
Weber et al, 2017[36]	Retrospective	Switzerland	70	105	70.7 (17.1)	70.2 (12.6)	32 (45.7)	53 (50.5)	15 (10–18)	15.5 (12–20)	N/A	N/A	183 (132–225)	233 (198–295)

(*Continued*)

Table 1. Continued

Study	sICH definition	Mortality definition	SR definition	FI definition	Adjustment method	Rescue therapy	Occlusion vessel	rtPA dose, mg/kg	MT devices
Suzuki et al, 2021[19]	NINDS	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	N/A	Yes	AC	0.6	Penumbra/stent retriever
Yang et al, 2020[20]	Heidelberg criteria	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	N/A	Yes	AC	0.9	Stent retriever/aspiration
Zi et al, 2021[21]	ECASS II	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	N/A	Yes	AC	0.9	Stent retriever/aspiration
Broeg-Morvayet al, 2016[30]	PROACT II	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	Multivariable PS matching	Yes	AC	0.9 or 0.6	Stent retriever/aspiration
Casetta et al, 2019[31]	ECASS II	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	PS matching	N/A	AC	0.9	Stent retriever/aspiration
Du et al, 2021[32]	ECASS II	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	Multivariable	Yes	AC	0.9	Stent retriever
Gong, et al, 2019[33]	NA	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	PS matching	N/A	AC	N/A	Stent retriever
Kass-Hout et al, 2014[29]	ECASS III	All cause (in hospital)	mTICI score 2B/3	mRS score 0–2 (discharge)	N/A	Yes	AC/PC	0.9 or 0.6	Merci retrieval system/ Penumbra system
Pienimäki et al, 2021[34]	NA	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	Multivariable	Yes	AC	0.9	Stent retriever/aspiration
Tong et al, 2021[22]	Heidelberg	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	PS matching	Yes	AC/PC	0.9	Stent retriever/aspiration
Wang et al, 2017[35]	Heidelberg Bleeding Classification	All cause (90 d)	mTICI score 2B/3	mRS score 0–2 (90 d)	PS matching	Yes	AC	Not mentioned	Stent retriever
Weber et al, 2017[36]	ECASS III	All cause (5.7 mo)	mTICI score 2B/3	mRS score 0–2 (5.7 mo)	N/A	N/A	AC	Not mentioned	Stent retriever

Data are generally displayed as mean (SD) or median (IQR) if not otherwise specified. AC indicates anterior circulation; ASPECTS, Alberta Stroke Program Early CT [Computed Tomography] Score; BT, bridging therapy; dMT, direct mechanical thrombectomy; ECASS, Europe cooperative acute stroke study; FI, functional independence; IQR, interquartile range; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Ischemia; NA, not available; NIHSS, National Institutes of Health Stroke Scale; NINDS, national institute of neurological disease and stroke; PC, posterior circulation; PROACT, prolyse in acute cerebral thromboembolism; PS, propensity score; RCT, randomized controlled trial; rtPA, recombinant tissue plasminogen activator; sICH, symptomatic intracranial hemorrhage; and SR, successful recanalization.

Table 2. Summary Pooled OR (95% CI) Values for Main Outcomes

Variable	90-d mRS score 0–2	Mortality	Recanalization	sICH	Any ICH
RCTs	1.08 (0.84–1.38), I^2=0.0%, *P*=0.538	0.93 (0.66–1.31), I^2=0.0%, *P*=0.690	0.77 (0.54–1.10), I^2=0.0%, *P*=0.152	0.72 (0.43–1.22), I^2=0.0%, *P*=0.222	0.68 (0.50–0.92), I^2=23.3%, *P*=0.014
Observational studies	1.02 (0.86–1.21), I^2=0.0%, *P*=0.854	1.03 (0.70–1.53), I^2=57.5%, *P*=0.866	1.03 (0.79–1.35), I^2=20.2%, *P*=0.837	0.66 (0.47–0.93), I^2=0.0%, *P*=0.018	0.72 (0.57–0.90), I^2=21.2%, *P*=0.004
Overall analysis	1.04 (0.90–1.19), I^2=0.0%, *P*=0.615	1.03 (0.78–1.36), I^2=45.8%, *P*=0.832	0.93 (0.76–1.14), I^2=10.1%, *P*=0.486	0.68 (0.51–0.91), I^2=0.0%, *P*=0.008	0.71 (0.60–0.84), I^2=13.9%, *P*<0.001
East Asia	1.08 (0.91– 1.29), I^2=0.0%, *P*=0.358	1.04 (0.83–1.30), I^2=0.0%, *P*=0.762	1.01 (0.70–1.43), I^2=40.4%, *P*=0.977	0.70 (0.51–0.95), I^2=0.0%, *P*=0.024	0.69 (0.58–0.82), I^2=0.0%, *P*<0.001
Western countries	0.96 (0.73–1.26), I^2=6.0%, *P*=0.776	0.78 (0.35–1.73), I^2=76.6%, *P*=0.534	0.88 (0.68–1.15), I^2=0.0%, *P*=0.359	0.59 (0.29–1.21), I^2=0.0%, *P*=0.148	0.80 (0.50–1.26), I^2=33.0%, *P*=0.335
RCT+PSM	0.97 (0.84–1.13), I^2=0.0%, *P*=0.723	1.07 (0.87–1.32), I^2=0.0%, *P*=0.510	0.85 (0.66–1.09), I^2=23.0%, *P*=0.201	0.66 (0.51–0.85), I^2=0.0%, *P*=0.001	0.82 (0.68–0.98), I^2=17.2%, *P*=0.030
RCT+observational studies with an NOS score >7	1.03 (0.89–1.20), I^2=0.9%, *P*=0.665	1.04 (0.79–1.36), I^2=42.6%, *P*=0.785	0.94 (0.73–1.20), I^2=29.8%, *P*=0.611	0.68 (0.50–0.91), I^2=0.0%, *P*=0.010	0.72 (0.62–0.85), I^2=6.0%, *P*<0.001
Anterior circulation occlusion	1.01 (0.85–1.19), I^2=0.0%, *P*=0.945	0.96 (0.67–1.37), I^2=54.0%, *P*=0.810	1.00 (0.76–1.32), I^2=24.8%, *P*=0.983	0.74 (0.52–1.07), I^2=0.0%, *P*=0.110	0.68 (0.55–0.84), I^2=20.0%, *P*<0.001

ICH indicates intracranial hemorrhage; mRS, modified Rankin Scale; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PSM, propensity score matching; RCT, randomized controlled trial; and sICH, symptomatic ICH.

0.80; 95% CI, 0.50–1.26; Figure 4E), although these results were not statistically different (Table 2).

Sensitivity Analyses

A sensitivity analysis in studies on acute ischemic stroke attributable to anterior circulation occlusion yielded similar findings to the overall analyses for most main outcomes except sICH (Figure 5A through 5E). Another sensitivity analysis, by including RCTs and high-quality observational studies, showed the stability of our overall analyses results for 90-day functional independence, mortality, successful recanalization, sICH, and any ICH (Figure 6A through 6E). Additional sensitivity analysis, by including RCTs and observational studies with propensity score matching data, confirmed the results derived from the overall analyses (Figure 7A through 7E). A separate analysis limited to studies with a full dose of alteplase (0.9 mg/kg) yielded similar results to the primary analysis (Figure 8A through 8E).

Study Quality Evaluation and Publication Bias Assessment

All 3 RCTs in this meta-analysis were investigator initiated, using web-based randomization, and complying with reported open-label treatment with blinded end point evaluation (Prospective randomized open blinded end-point [PROBE] design) with low risks of reporting bias assessed by the Cochrane collaboration's tool (Figure 9). The overall score on the Newcastle–Ottawa scale was 67 of 81 (82.7%), representing overall high quality (Table 3). The reporting bias risk of included observational studies was generally regarded low because of appropriate adjustments for potential confounders in 7 studies (Table 4). There was low evidence of publication bias on the basis of minimal asymmetry in the visual inspection of the funnel plot for 90-day functional independence, mortality, successful recanalization, sICH, and any ICH (Figure 10A through 10E). The Egger test showed no significant evidence of small study effect (*P*=0.732 for 90-day functional independence, *P*=0.150 for mortality, *P*=0.537 for recanalization, *P*=0.350 for sICH, and *P*=0.592 for any ICH).

DISCUSSION

Our present meta-analysis of moderate to high quality RCT and observational evidence showed similar 3-month functional outcome and successful recanalization after dMT compared with dMT and intravenous thrombolysis bridging therapy (BT) in acute ischemic stroke. Our findings also suggest that dMT is associated with a lower odds of symptomatic ICH and a shorter onset to artery puncture time.

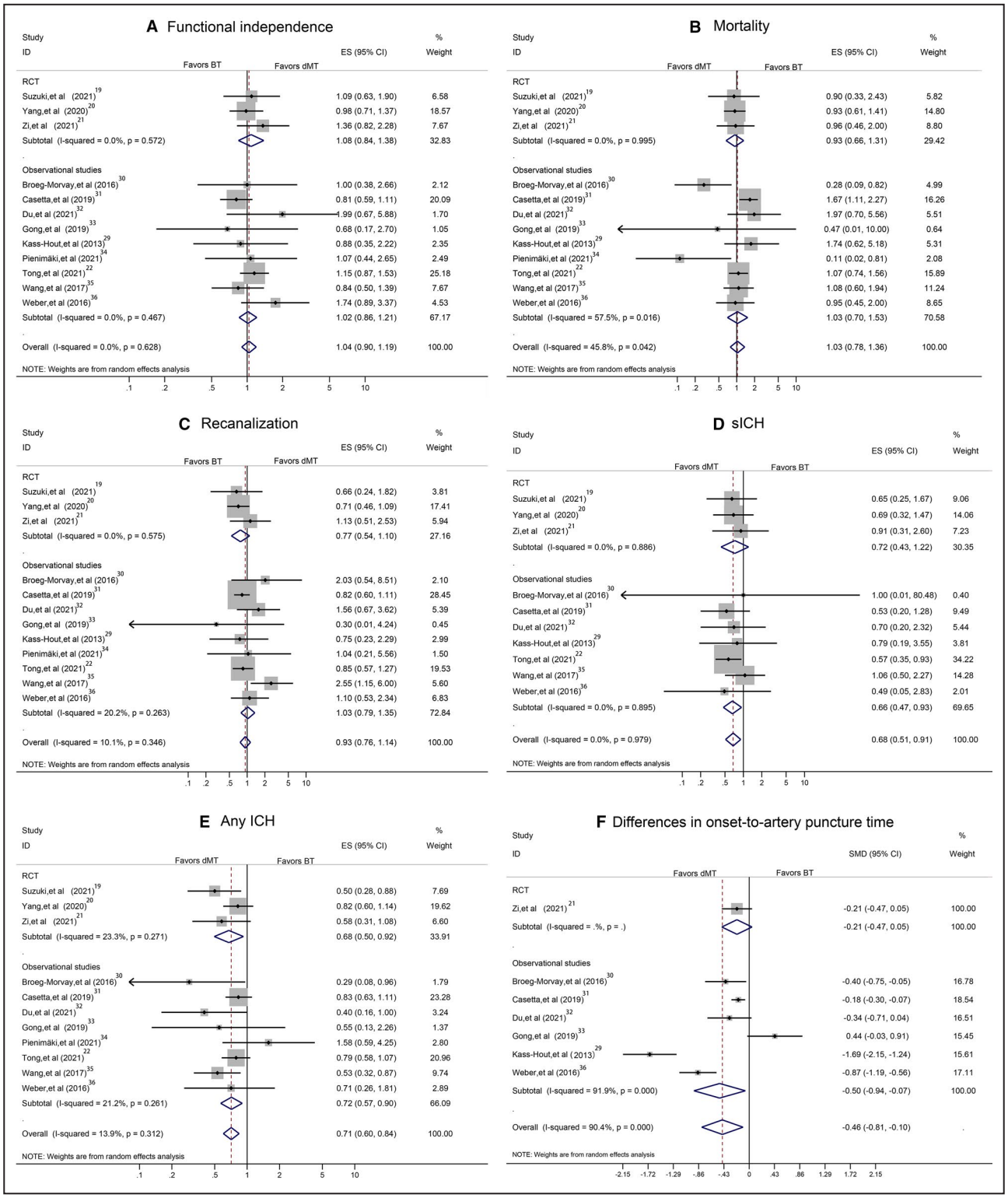

Figure 2. Overall pooled estimate effect size by combining randomized controlled trials (RCTs) and observational studies using a random-effects model.

A, The 90-day functional independence. **B**, Mortality. **C**, Successful recanalization. **D**, Symptomatic intracranial hemorrhage (sICH). **E**, Any intracranial hemorrhage (ICH). **F**, Onset to artery puncture time. BT indicates bridging therapy; dMT, direct mechanical thrombectomy; ES, effect size; and ID, identifier.

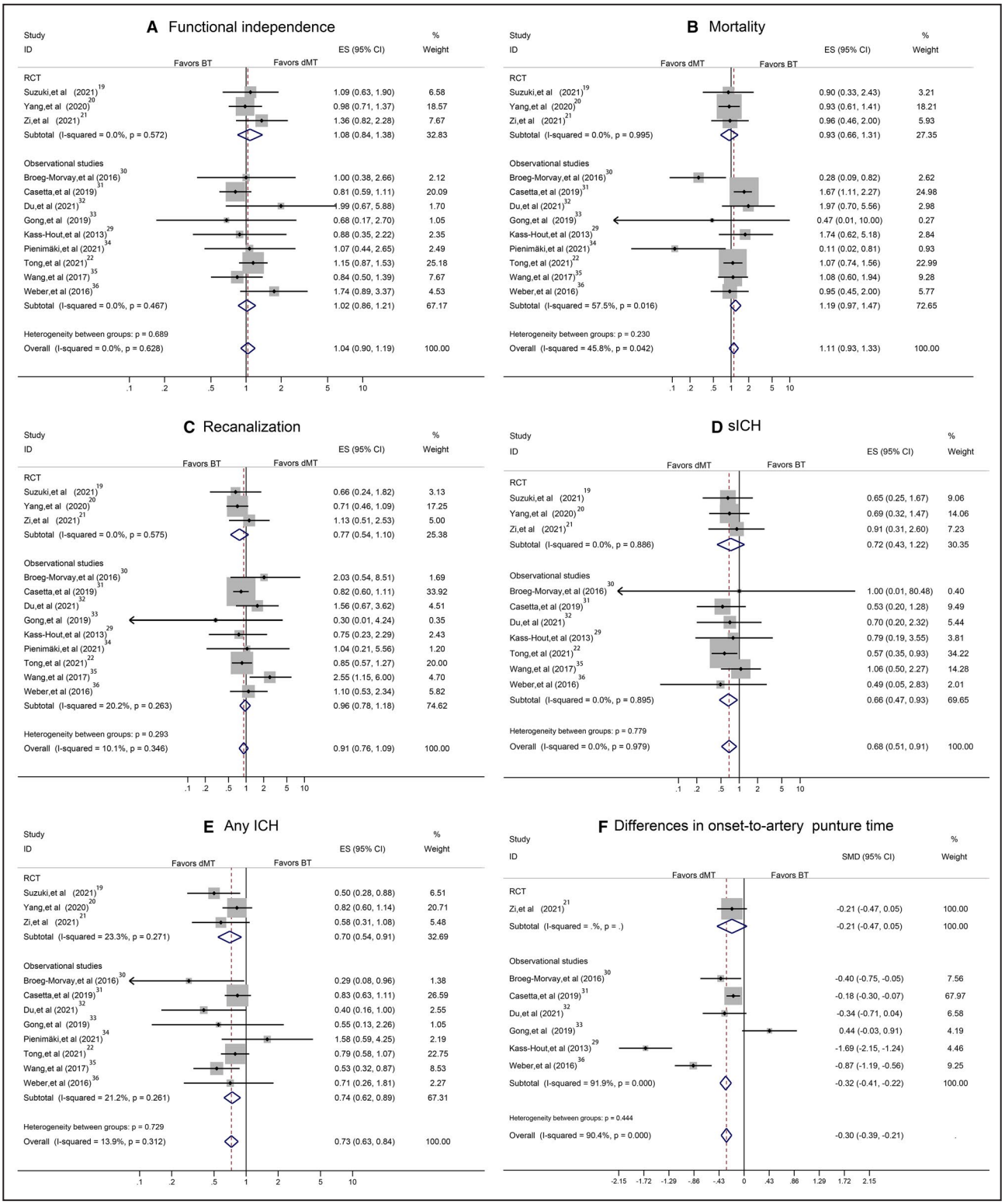

Figure 3. Overall pooled estimate effect size by combining randomized controlled trials (RCTs) and observational studies using a fixed-effects model.

A, The 90-day functional independence. **B**, Mortality. **C**, Successful recanalization. **D**, Symptomatic intracranial hemorrhage (sICH). **E**, Any intracranial hemorrhage (ICH). **F**, Onset to artery puncture time. BT indicates bridging therapy; dMT, direct mechanical thrombectomy; ES, effect size; and ID, identifier.

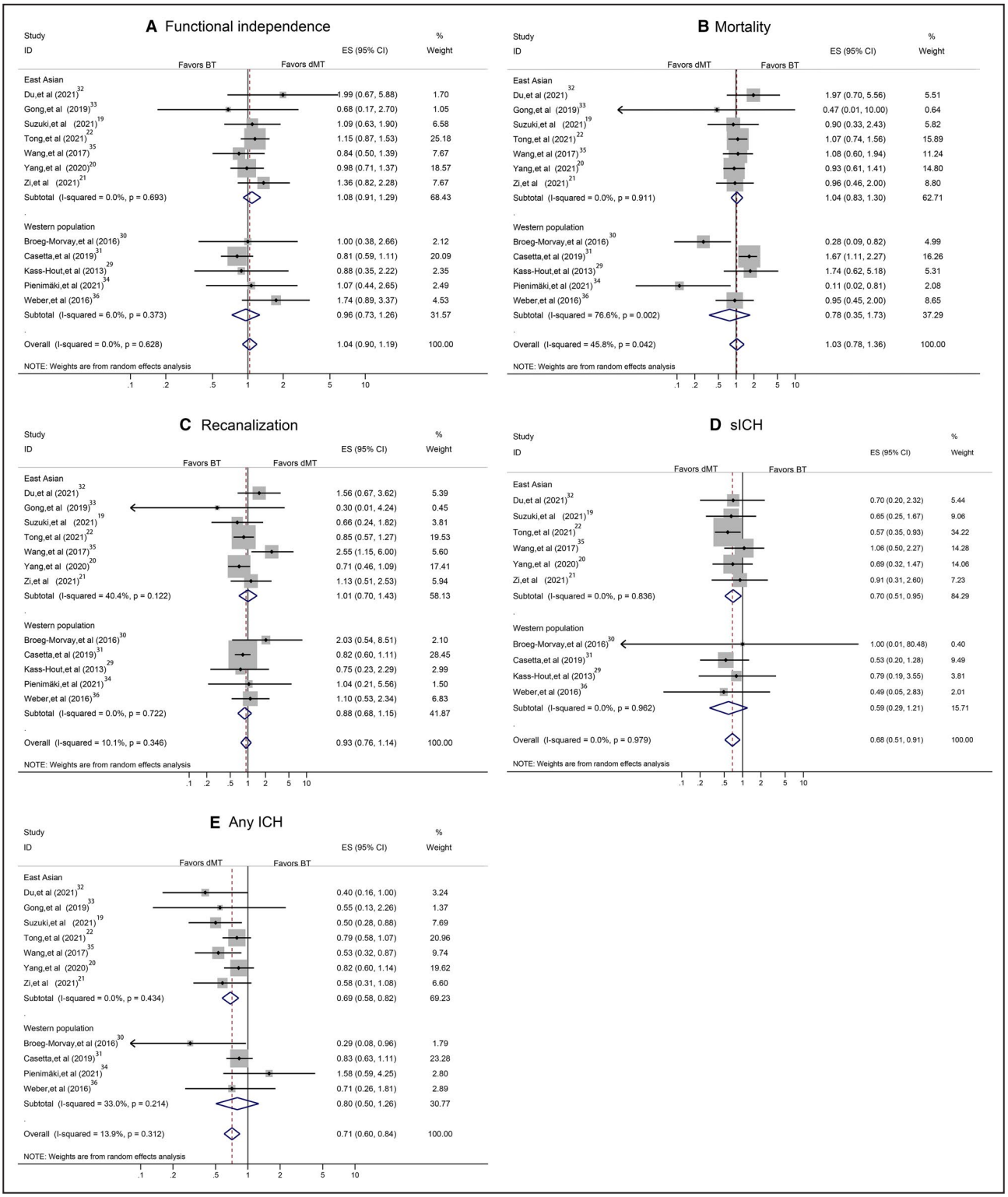

Figure 4. Pooled odds ratio, stratified by participant region.
A, The 90-day functional independence. **B**, Mortality. **C**, Successful recanalization. **D**, Symptomatic intracranial hemorrhage (sICH). **E**, Any intracranial hemorrhage (ICH). BT indicates bridging therapy; dMT, direct mechanical thrombectomy; ES, effect size; ID, identifier; and RCT, randomized controlled trial.

Several previous meta-analyses showed that BT was superior to dMT in achieving a favorable outcome at 90 days,[7–9,37,38] whereas others showed that outcomes were not significantly different for dMT and BT.[39,40] However, most previous meta-analyses included both IVT-eligible and IVT-ineligible patients in the MT group

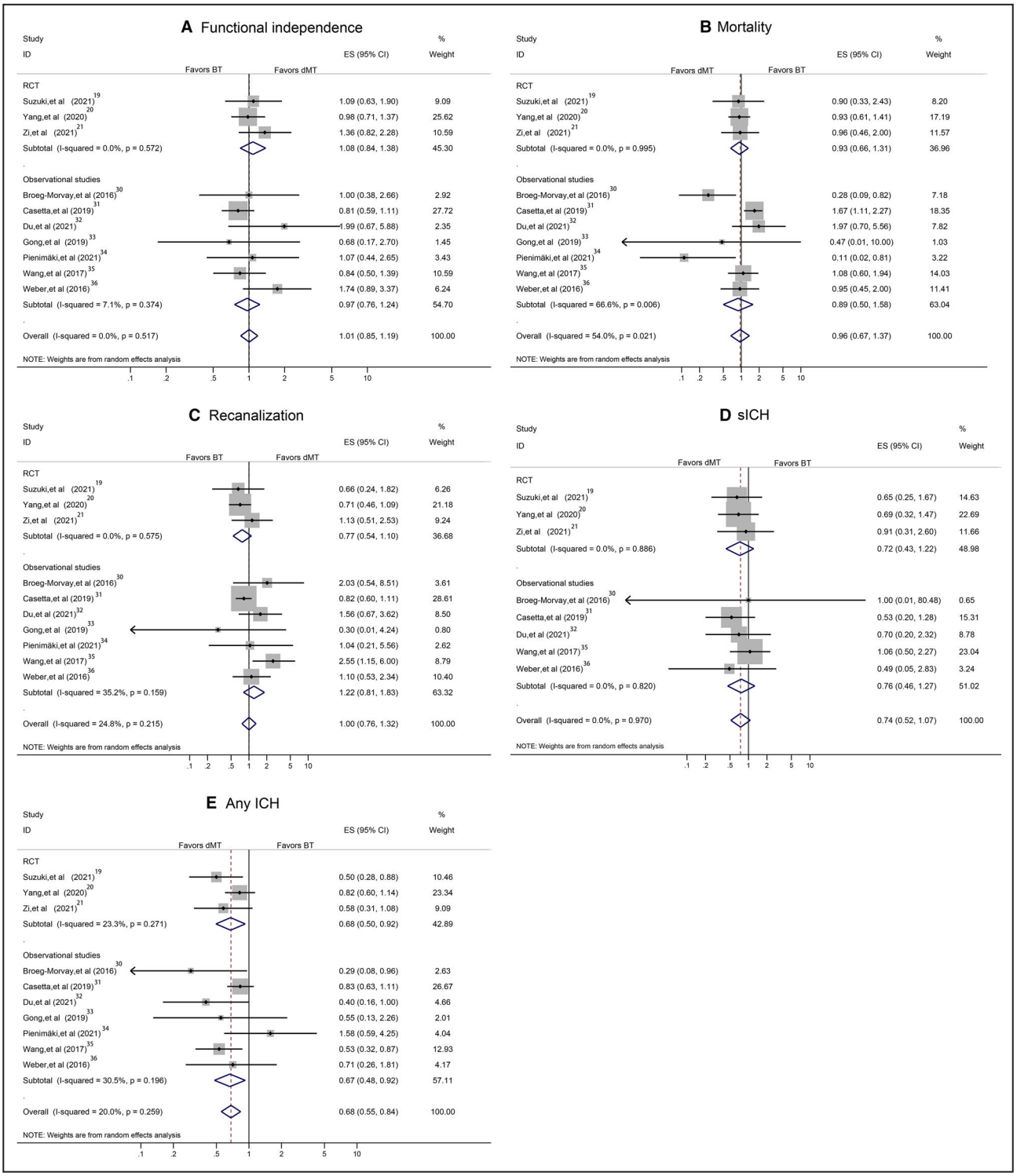

Figure 5. Pooled odds ratio limited to anterior circulation occlusion.
A, The 90-day functional independence. **B**, Mortality. **C**, Successful recanalization. **D**, Symptomatic intracranial hemorrhage (sICH). **E**, Any intracranial hemorrhage (ICH). BT indicates bridging therapy; dMT, direct mechanical thrombectomy; ES, effect size; ID, identifier; and RCT, randomized controlled trial.

or compared IVT-eligible patients (undergoing BT) with IVT-ineligible patients (undergoing dMT).[7–9,39,40] Only a few meta-analyses provided pooled effect sizes in IVT-eligible participants based on observational data.[9,37,38] Our meta-analysis adds to previous studies by including the most recently published RCTs and large-sample prospective cohort data, allowing direct and indirect comparison. In addition, to our knowledge, our study

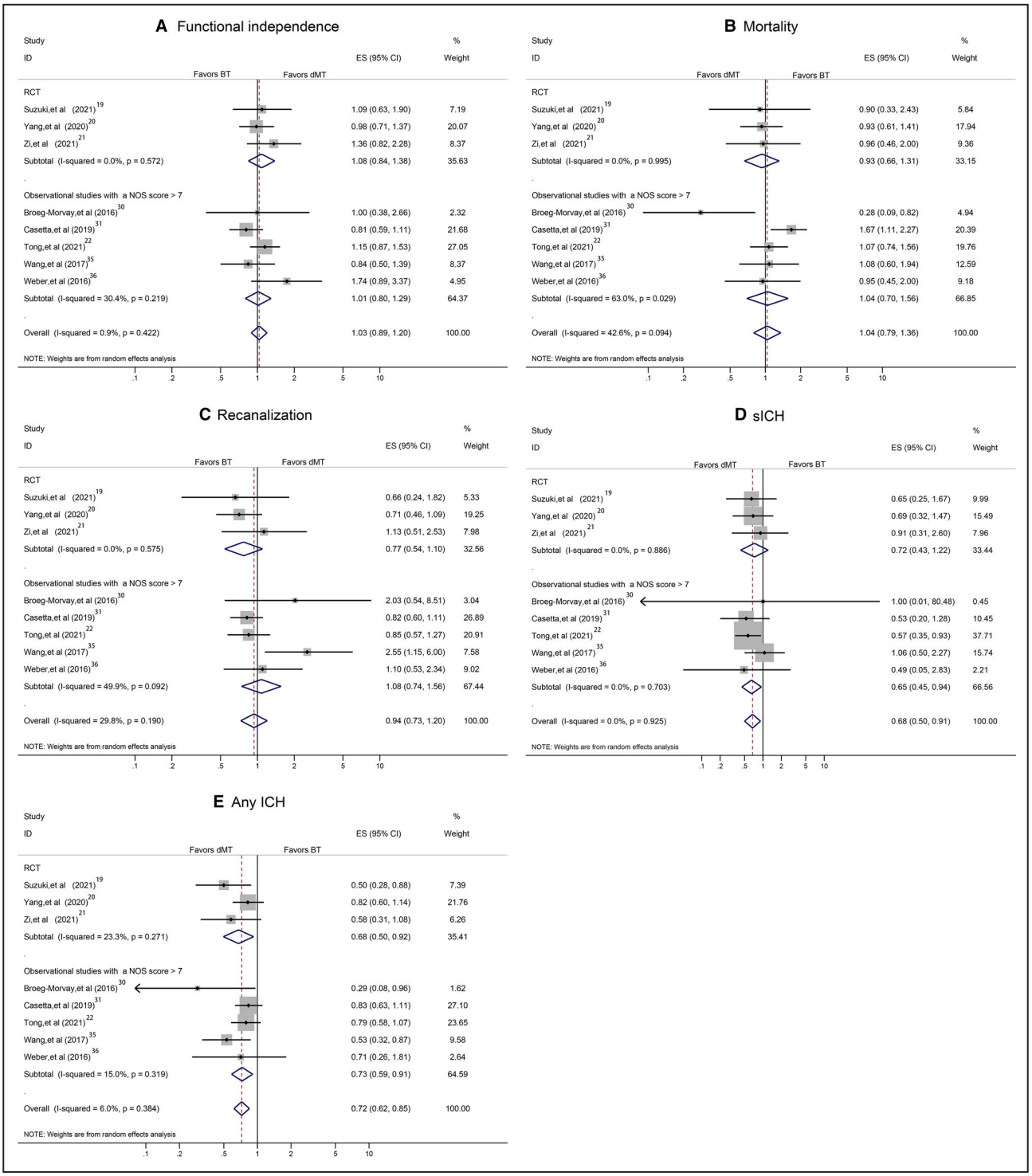

Figure 6. Pooled odds ratio by including high-quality studies.
A, The 90-day functional independence. **B**, Mortality. **C**, Successful recanalization. **D**, Symptomatic intracranial hemorrhage (sICH). **E**, Any intracranial hemorrhage (ICH). BT indicates bridging therapy; dMT, direct mechanical thrombectomy; ES, effect size; ID, identifier; and RCT, randomized controlled trial.

includes the highest number of IVT-eligible patients, minimizing the risk of selection bias.

Notably, heterogeneity was driven by differences in study method (design and sample) and clinical characteristics across the included studies. We therefore look at the results of the 3 RCTs and observational studies separately. The 3 RCTs are all open-blinded end point designed, allowing greater similarities with

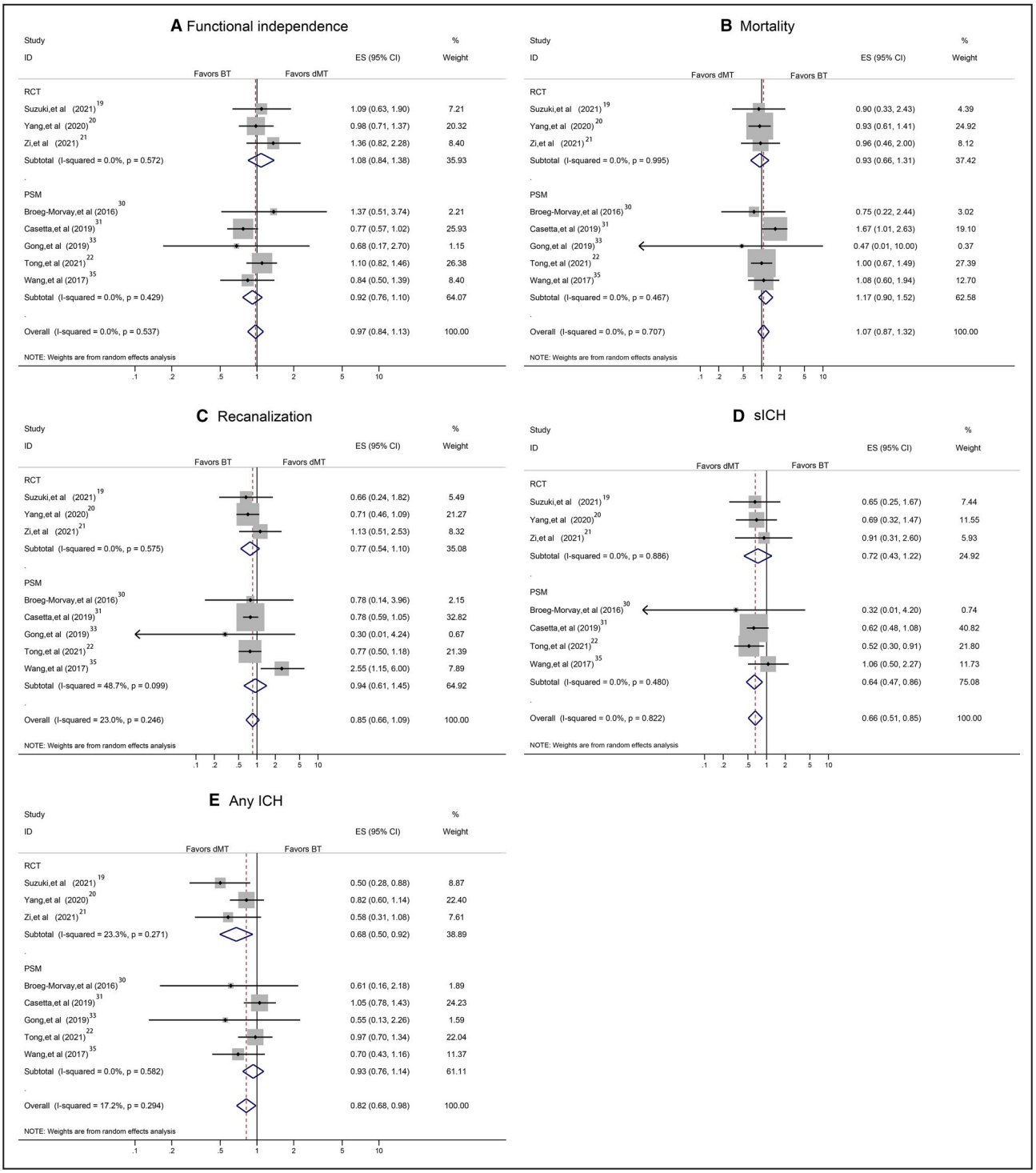

Figure 7. Pooled odds ratio by including randomized controlled trials (RCTs) and observational propensity score matching data.

A, The 90-day functional independence. **B**, Mortality. **C**, Successful recanalization. **D**, Symptomatic intracranial hemorrhage (sICH). **E**, Any intracranial hemorrhage (ICH). BT indicates bridging therapy; dMT, direct mechanical thrombectomy; ES, effect size; and ID, identifier.

real-world clinical practice. However, information from the 3 RCTs in the present meta-analysis is not adequately powered to assess the safety of dMT versus BT. Our observational studies contributed a larger sample of IVT-eligible participants than RCTs (2830 versus 1094), providing more adequate power to evaluate

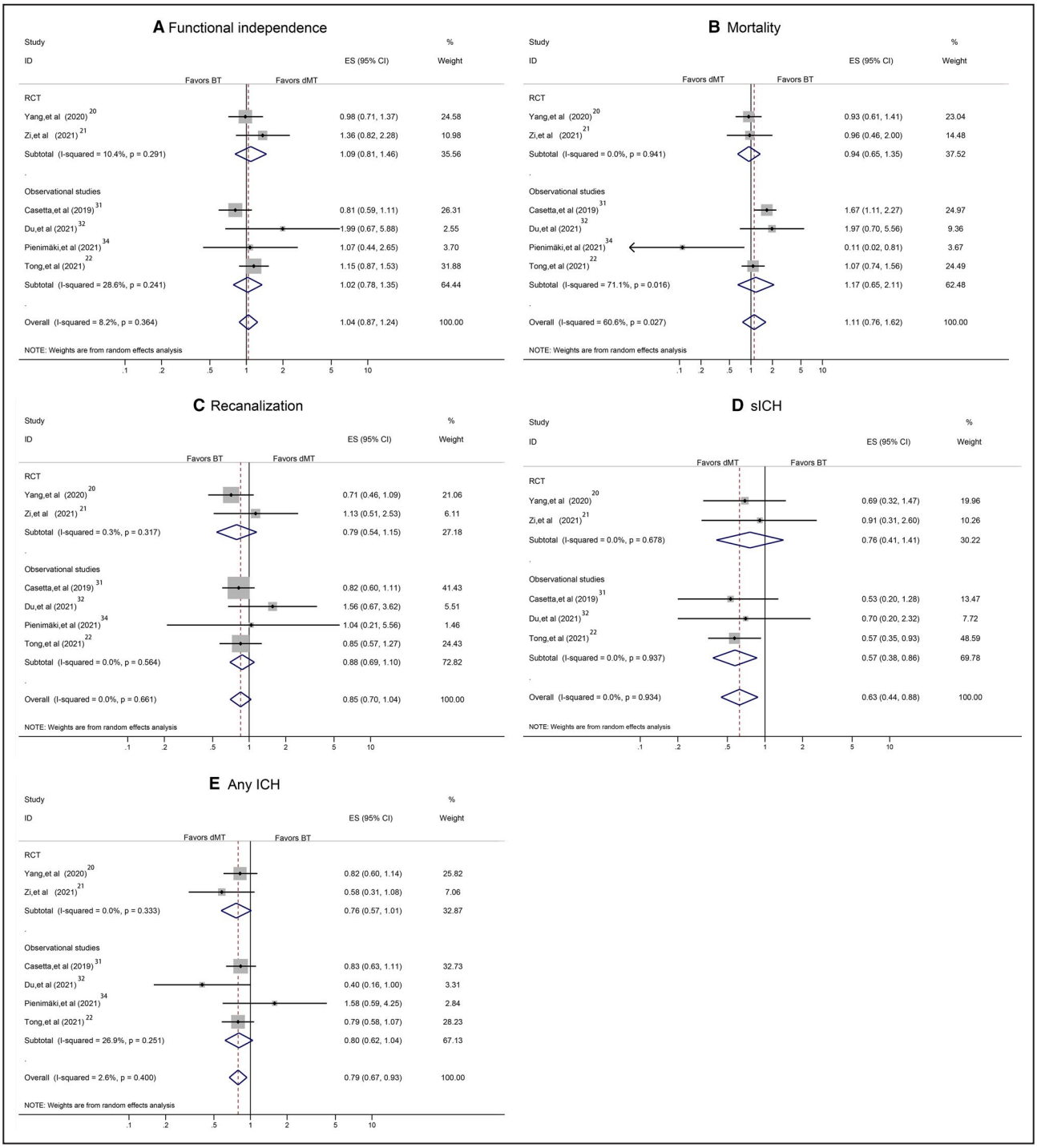

Figure 8. Pooled odds ratio limited to studies with a full dose of alteplase.
A, The 90-day functional independence. **B**, Mortality. **C**, Successful recanalization. **D**, Symptomatic intracranial hemorrhage (sICH). **E**, Any intracranial hemorrhage (ICH). BT indicates bridging therapy; dMT, direct mechanical thrombectomy; ES, effect size; ID, identifier; and RCT, randomized controlled trial.

safety outcomes. Notably, our findings should be interpreted with caution because in observational studies, the decision on whether IVT was initiated before MT was based on arbitrary decisions rather than predefined protocol. However, the consistency between RCTs and observational studies for 90-day functional outcomes may provide evidence that skipping IVT should be considered in a specific population with acute ischemic stroke, particularly in East Asians with large-vessel occlusion (class of recommendation=I, level of evidence=A in both US and European stroke guidelines).[6,41] Moreover, we assessed the estimated

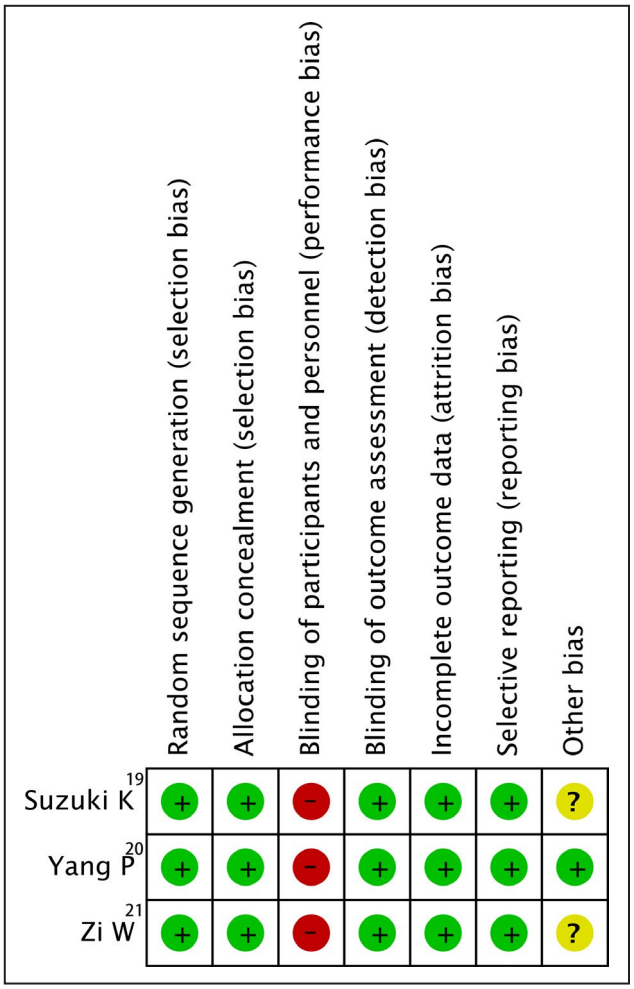

Figure 9. Reporting bias of randomized controlled trials (RCTs), assessing by Cochrane Collaboration's tool. ES, effect size.

effect sizes that have been adjusted for potential confounders and/or minimized for baseline characteristics with propensity score matching analyses (multivariate matched comparison) in observational studies.

The largest study population in the present meta-analysis was East Asian. Clinicians therefore need to note the differences in clinical features between the Asian and Western population with ischemic stroke as well as stroke care systems. For example, because East Asian populations with acute ischemic stroke have been shown to be more likely to experience ICH after IVT with alteplase, the bleeding risk of IVT before MT may also be higher than for dMT.[22,42] Moreover, there might be differences in the prevalence of intracranial stenosis and atrial fibrillation between the East Asian and Western populations with ischemic stroke.[22,43] Asian patients were more likely to harbor intracranial arterial stenosis,

Table 4. Overview of Confounders That Were Used for Adjustment in Eligible Studies

Study name, y	Confounder adjustment
Broeg-Morvay et al, 2016[30]	Age, NIHSS score, time from symptom onset to diagnosis, hypertension, and thrombus location (internal carotid artery or middle cerebral artery)
Casetta et al, 2019[31]	Age, sex, history of diabetes, atrial fibrillation, hypertension, previous stroke, or transient ischemic attack in the previous 3 mo, the presence of carotid stenosis >70%, baseline NIHSS score, baseline ASPECTS, onset to ECC arrival time, onset to groin puncture time, and site of occlusion
Du et al, 2021[32]	Age, NIHSS score on admission, ASPECTS on admission and onset to imaging time, clot burden score, successful recanalization, ICH, and collateral status
Gong et al, 2019[33]	Age, sex, NIHSS score, vascular risk factors, and laboratory parameters based on a multiple logistic regression model that accounted for additional explanatory variables
Pienimäki et al, 2021[34]	Age, onset-reperfusion time, NIHSS score, atrial fibrillation, mTICI score 2b-3
Tong et al, 2021[22]	Age, sex, NIHSS score, and the baseline and procedural variables with a significant difference of $P<0.05$
Wang et al, 2017[35]	Age, sex, previous stroke, premorbid mRS score, time from onset to door, stroke cause, occlusion site, baseline ASPECTS, baseline NIHSS score, and collateral status

ASPECTS indicates Alberta Stroke Program Early CT [Computed Tomography] Score; ECC, endovascular-capable center; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Ischemia; and NIHSS, National Institutes of Health Stroke Scale.

Table 3. Quality Assessment of Observational Studies Using the Newcastle-Ottawa Scale

Study name, y	Selection	Comparability	Outcome	Overall score
Broeg-Morvay et al, 2016[30]	3*	2*	3*	8/9
Casetta et al, 2019[31]	3*	2*	3*	8/9
Du et al, 2021[32]	3*	2*	2*	7/9
Gong et al, 2019[33]	3*	2*	2*	7/9
Kass-Hout et al, 2014[29]	3*	0*	2*	5/9
Pienimäki et al, 2021[34]	3*	2*	2*	7/9
Tong et al, 2021[22]	3*	2*	3*	8/9
Wang et al, 2017[35]	4*	2*	3*	9/9
Weber et al, 2017[36]	3*	2*	3*	8/9

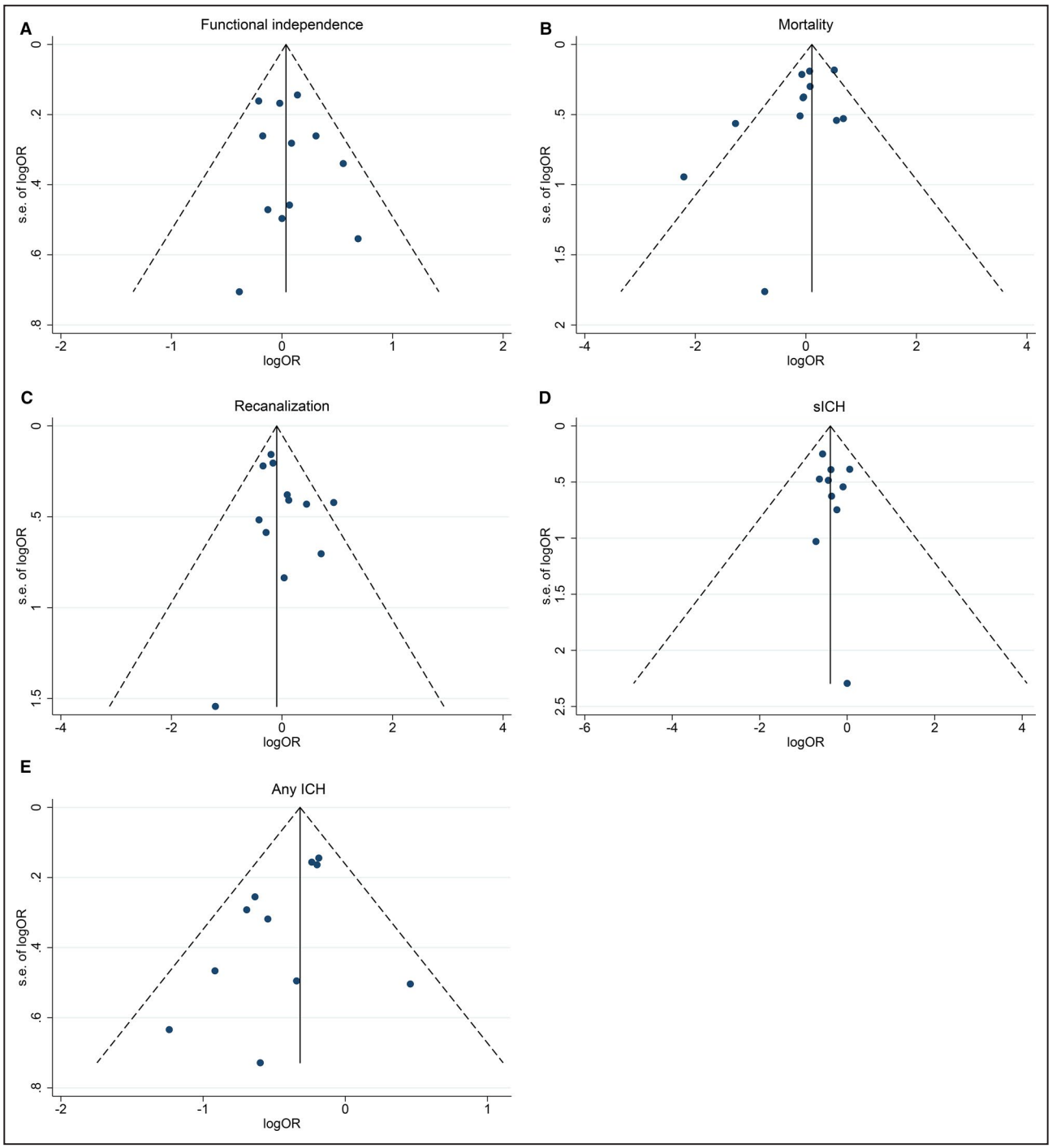

Figure 10. Funnel plot for publication bias. **A**, The 90-day functional independence. **B**, Mortality. **C**, Successful recanalization. **D**, Symptomatic intracerebral hemorrhage (sICH). **E**, Any intracranial hemorrhage (ICH).

which frequently requires stent implantation and additional powerful antiplatelets.[44,45] A sensitivity analysis of the ANGEL-ACT (Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke) study showed that rescue stenting was associated with a higher probability of 90-day functional independence, but was not associated with an increased risk of sICH, any ICH, or mortality (ANGEL-ACT study group, unpublished data, 2021), supporting the safety and efficacy of rescue stenting in selected patients after thrombectomy. Moreover, data from a subgroup study of ANGEL-ACT registry showed no statistically significant differences in safety outcomes, efficacy outcomes on successful recanalization, dramatic clinical improvement, or 3-month modified Rankin

Scale score between the tirofiban and nontirofiban groups.[46] These results need to be validated in future large multicenter studies.

All 5 studies performed in Western countries in this meta-analysis were retrospectively designed.[29–31,34,36] We therefore could not provide clear evidence which therapy approach (dMT versus BT) might be more beneficial for Western patients with ischemic stroke. The results driven from the ongoing studies (MR CLEAN-NO IV [Multicenter Randomised Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands], ISRCTN80619088; SWIFT-DIRECT [Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus Direct Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke], NCT03192332; and DIRECT-SAFE [Direct Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval], NCT03494920) permitting direct comparison of dMT to BT will provide more data on this issue.

Previous studies showed that the response to IVT might be partly determined by the site of occlusion (whether internal carotid artery, middle cerebral artery, or basilar artery).[22,47] One study showed that the median 90-day modified Rankin Scale score in anterior circulation occlusion was lower than in posterior circulation occlusion (3 versus 4; P=0.06).[22] Our subgroup analysis, including only patients with anterior circulation occlusion, showed that patients receiving dMT had a similar likelihood of achieving functional independence, mortality, and successful recanalization, but lower rates of sICH and any ICH compared with those in the BT arm. The evidence in the present meta-analysis supports dMT as a treatment of choice in health systems with rapid access to comprehensive stroke centers. Comparable efficacy for dMT and BT might also raise questions about cost-effectiveness.

We acknowledge limitations. First, there is selection bias between the dMT and BT groups. Even RCTs and observational studies with propensity score matching data unavoidably introduced selection bias; further studies need to address the factors that might account for the inconsistencies, such as microbleed burden, the sites of occlusion, admission mode (drip-and-ship versus mother ship), and procedure parameters (time to start endovascular treatment, anesthetic factors, and thrombectomy devices). Second, our findings were not generalized to the Western population because most included studies were performed in East Asia. Third, because all participants with BT used alteplase in the present meta-analysis, our findings are not generalized to those who underwent IVT with tenecteplase. Some recent published studies indicated that patients with acute ischemic stroke treated with tenecteplase were superior to those treated with alteplase,[48,49] raising concerns about the efficacy of BT using tenecteplase. Fourth, because of limited available information, we could not draw a conclusion in acute ischemic stroke with posterior circulation occlusion. Last, our study only evaluated the 90-day outcome, so future research with longer follow-up times is required to better understand longer-term functional outcome.

CONCLUSIONS

Current available evidence suggests that dMT is effective and safe in comparison to BT. The risk of ICH appears to be lower for patients treated with dMT than BT; sensitivity analyses suggest that the lower ICH risk is more pronounced in the East Asian populations.

ARTICLE INFORMATION

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Author Contributions: Concept and design: Drs Du, Werring, and Liu. Acquisition, analysis, or interpretation of data: Drs Du, Lei, Fang, Ambler, Liu, and Werring. Drafting of the manuscript: Drs Du, Lei, and Fang. Critical revision of the manuscript for important intellectual content: Drs He, Yuan, Ambler, Liu, and Werring. Statistical analysis: Drs Du, Lei, and Ambler. Drs Du and Liu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

None.

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