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Systematic Review

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Endovascular Treatment Versus Medical Management in Patients with Large Vessel Occlusion and Pre-Stroke Disability: A Systematic Review and Meta-Analysis

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ABSTRACT

AIM: To assess the effectiveness and safety of endovascular treatment (EVT) versus medical management (MM) in stroke patients with premorbid disabilities.

MATERIAL and METHODS: A systematic search was conducted in PubMed, Embase, and the Cochrane Library for studies on EVT in large vessel occlusion (LVO) patients with pre-stroke modified Rankin Scale (mRS) score of 2-4. The primary outcome was functional recovery, defined as returning to at least the pre-stroke mRS score within 90 days. The secondary outcomes included symptomatic intracranial hemorrhage (sICH) and 90-day mortality. The meta-analyses were conducted via random effects models.

RESULTS: Six cohort studies involving 2,106 patients were included. Compared with MM, EVT was associated with a higher likelihood of functional recovery (adjusted odds ratio [aOR], 3.26; 95% confidence interval [CI], 2.26-4.70; p<0.001) and lower risk of mortality (aOR, 0.40; 95% CI, 0.20-0.83; p=0.01). EVT was also associated with a potentially increased risk of sICH, although the difference did not reach statistical significance (aOR 2.47, 95% CI 0.81-7.52; p=0.11).

CONCLUSION: Although EVT may be associated with a higher potential risk of sICH, it improves the likelihood of functional recovery and reduces mortality in LVO patients with pre-stroke disability. Therefore, denying EVT solely on the basis of premorbid disability may be unjustified. Further high-quality randomized controlled trials are warranted to validate these findings.

KEYWORDS: Ischemic stroke, Disabled persons, Thrombectomy, Outcomes

ABBREVIATIONS: AIS: Acute ischemic stroke, **LVO:** Large vessel occlusion, **EVT:** Endovascular treatment, **BMM:** Best medical management, **mRS:** Modified rankin scale, **sICH:** Symptomatic intracranial hemorrhage, **CI:** Confidence interval, **RR:** Risk ratio, **NIHSS:** National institutes of health stroke scale

INTRODUCTION

Large vessel occlusion (LVO) leading to acute ischemic stroke (AIS) is a significant cause of disability worldwide (11). Endovascular treatment (EVT) has become the standard of care for reducing disability associated with LVO-related AIS (1). However, a significant proportion of LVO-AIS patients have pre-existing disabilities, known as pre-stroke disabilities, with nearly one-third of those undergoing EVT in clinical practice having baseline pre-stroke disabilities (4,12). Unfortunately, these patients are often excluded from randomized controlled trials (RCTs) because their prestroke modified Rankin Scale (mRS) scores (≥2) pose challenges to the traditional definition of favorable outcomes, which rely on

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binary measures in clinical trials (9). Existing guidelines for treating patients with mRS scores ≥2 lack explicit strategies, and there is significant variability in EVT practices for this population, with decisions often being based on clinical judgment. This creates a therapeutic dilemma for stroke physicians managing patients with mRS scores ≥2 (5,7). Therefore, stroke physicians face a therapeutic dilemma when managing patients with mRS scores ≥2. Therefore, it is imperative to select the optimal treatment to ensure timely, successful vascular reperfusion and improve clinical outcomes for these patients.

While previous systematic reviews have provided insights, they did not include a control group receiving medical management (MM), limiting the ability to determine differences in outcomes related to the intervention. This study aims to evaluate whether EVT is superior to MM in terms of safety and effectiveness in patients with pre-stroke disabilities, providing clinicians with guidance for acute stroke treatment in this specific population.

MATERIAL and METHODS

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (1). The study protocol was prospectively registered in the international prospective register of systematic reviews (PROSPERO) with registration number CRD42023443307.

Selection Criteria

Comparative studies with English texts that met the following PICO (Patient, Intervention, Comparator, and Outcome) criteria were considered eligible for inclusion (2).

Patients: Individuals aged ≥18 years with pre-stroke disability of LVO-AIS who had pre-stroke, defined as an mRS score of 2-4.

Intervention: Receiving EVT.

Comparison: Receiving MM.

Outcomes: The primary outcome was functional recovery, which was defined as a return to at least the pre-stroke mRS score at 90 days. The secondary outcomes included symptomatic intracranial hemorrhage (sICH) and mortality at 90 days.

Search Strategy

Our search was last updated on 1 July 2023 to ensure that there were no new studies meeting the eligibility criteria. The search keywords used were as follows: (“prestroke” or “pre-stroke” or (“stroke” and (“premorbid” or “premorbid” or “pre-existing” or “preexisting” or “previous” or “baseline”))); (“morbidity” or “mobility impairment” or “disability” or “disabilities” or “dependence” or “dependent” or “dependency”); and (“reperfusion therapies” or “reperfusion treatments” or “endovascular therapy” or “endovascular treatment” or “intra-arterial therapy” or “intra-arterial treatment” or “endovascular thrombectomy” or “mechanical thrombectomy” or “intra-arterial thrombectomy” or “MT” or “EVT” or “IAT”).

Data Extraction

Two authors (T.-Y.Z. and D.L.) independently extracted information on study characteristics (first author, year of publication, study period, country, study design, number of institutions, population included, and number of patients), patient characteristics (age, sex, National Institutes of Health Stroke Scale), and clinical outcomes. When duplicate reports of the same study were found, the data were analyzed from the most complete dataset. Objections were adjudicated by the senior author (H.-Z. Z.).

Risk of Bias Assessment

The quality of the included studies was assessed via the Newcastle-Ottawa Scale (NOS) research checklist, which evaluates the selection, comparability, and outcomes of both case-control and cohort studies (3). Each study was reviewed and scored in three categories: selection of study groups (0-4 points), comparability (0-2 points), and assessment of outcomes (0-3 points), with a maximum possible score of 9 points. A score of ≥8 indicates a low risk of bias, a score of 6-7 indicates a moderate risk of bias, and a score of ≤5 indicates a high risk of bias. Potential discrepancies were resolved through discussions with the senior author (H.Z.Z.). Both reviewers (T.Y.Z. and D.L.) independently assessed the quality of all included studies, and any differences were resolved by consensus. See Table I for details.

Statistical Analysis

To derive the odds ratio (OR) from reported binary outcomes comparing EVT and BMM, we performed a meta-analysis via the Mantel-Haenszel method. The results were presented as relative risks with corresponding 95% confidence intervals (CIs). To account for variability both within and between studies, we used a random effects model for this meta-analysis. Heterogeneity among studies was assessed via Cochran’s Q statistic and the I^2 statistic. I^2 values exceeding 50% were interpreted as indicating significant heterogeneity, whereas values over 75% were considered indicative of considerable heterogeneity. A sensitivity analysis was conducted for all outcomes after adjusting for potential confounding factors. Owing to the inclusion of fewer than 10 studies in our analysis, we did not perform a publication bias assessment or meta-regression analysis. All the statistical analyses were conducted via Review Manager (RevMan) version 5.3, which was developed by the Cochrane Collaboration and is located at the Nordic Cochrane Centre in Copenhagen.

RESULTS

Overview of Included Studies

The initial search identified 1,495 records, with 357 duplicates. After reviewing the titles and abstracts, 1,120 records were excluded. A detailed examination of the remaining 18 full-text articles led to the inclusion of 6 studies in this systematic review and meta-analysis. These studies involved a total of 2,106 AIS stroke patients and compared MM with EVT (Figure 1).

Table I: Quality Assessment of the Included Studies

Article	Selection				Comparability	Outcome			Scores
	Representati-veness of the exposed cohort	Selecting of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control on the basis of the design or analysis	Asssessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Kastrup et al., (6)	★	★	★	★	★	★		★	7
Sprugel et al., (11)	★	★	★	★	★★	★	★	★	9
Sykora et al., (13)	★	★	★	★	★★	★	★	★	9
Tanaka et al., (14)	★	★	★	★	★★	★	★	★	9
Siegler et al., (10)	★	★	★	★	★★	★	★	★	9
Miyake et al., (8)	★	★	★	★	★	★	★	★	8

Newcastle-Ottawa Scale for assessing the quality of studies in meta-analysis.

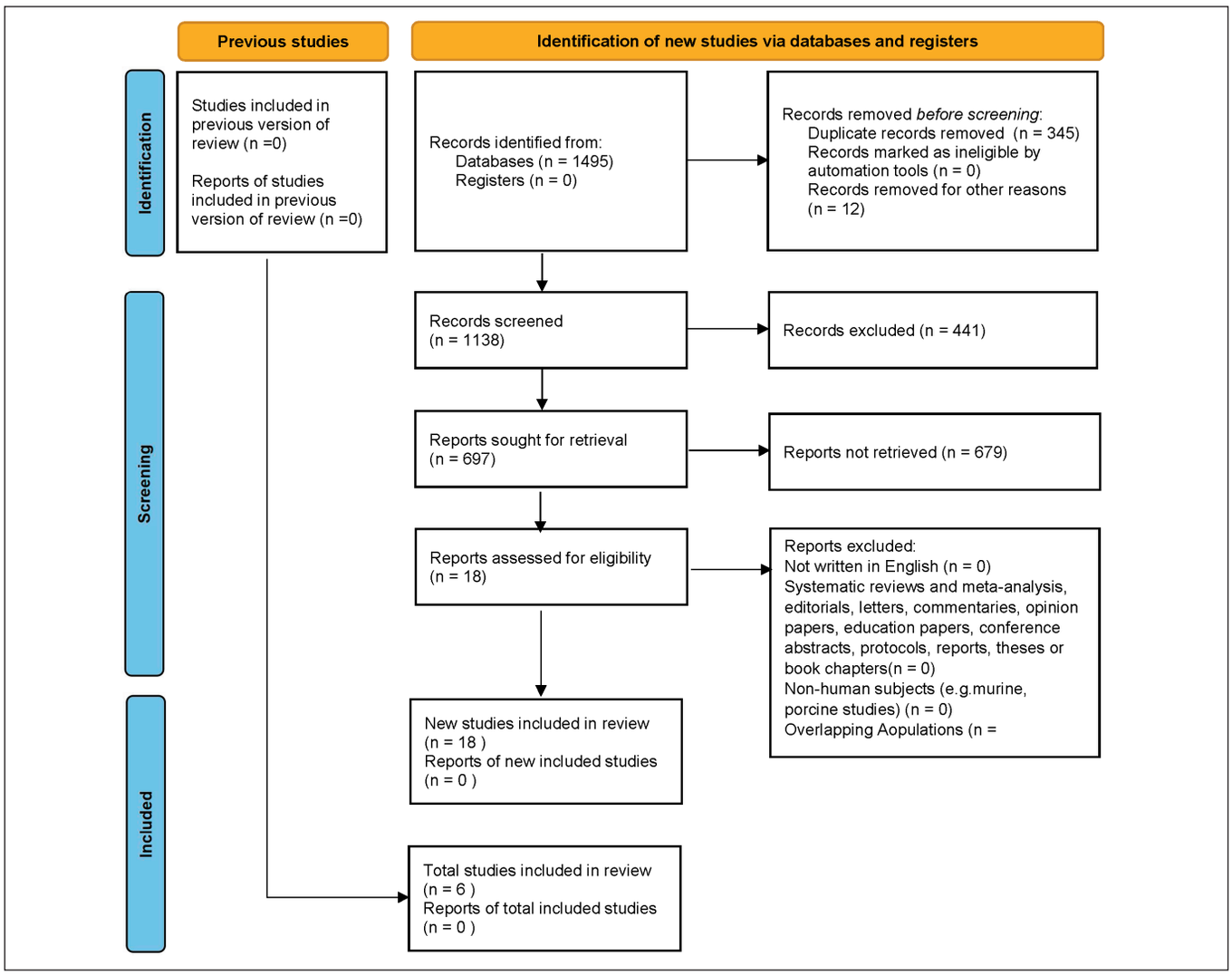

Figure 1: Study selection.

All studies included in this analysis were non-randomized, multicenter, retrospective cohort studies, with data collected from high-volume neurointerventional centers across five countries: Germany, Japan, Austria, Switzerland, and the United States. The risk of bias was evaluated via the Newcastle-Ottawa Scale (Table I), and all six studies achieved a score of 7 or higher, indicating generally good quality.

Study Characteristics and Patient Demographics

The study included 2,106 acute stroke patients aged 18 years or older, all of whom had been treated for previous proximal LAO involving the intracranial proximal internal carotid artery and/or the M1 and/or M2 segments of the middle cerebral artery, accompanied by disabling symptoms. Among these patients, 1,300 received MM, while 806 were receiving drug treatment. Table II provides a comprehensive description of the baseline characteristics of these patients. The management of each patient followed the BAO International Ischemic Stroke Management Guidelines. The control group consisted of patients who did not undergo thrombectomy during hospitalization and who received only medical treatment, whereas the intervention group included patients who underwent standard thrombectomy during their hospital stay.

The Primary Outcome was a Return to at Least the Pre-Stroke mRS Score

Among the six studies, four reported functional recovery outcomes and were included in the meta-analysis, involving 1560 pre-stroke disabled patients (with 900 receiving EVT and 660 receiving MM) (10,11,13,14). The pooled analysis for this group of AIS patients indicated that, compared with MM, EVT may be a higher likelihood of functional recovery at 90 days (OR=2.62; 95% CI, 1.53-4.49; p<0.001; Figure 2A), with a significant level of study heterogeneity and statistical significance (I^2=65%, p=0.04). The sensitivity analysis, adjusted for potential confounding factors, indicated the robustness of the

Table II: Pooled Baseline Characteristics of Included Patients

Author	Year	Definition of premorbid disability and control groups		Patients (n)	Age (median) (years)	Female, %	Return to baseline mRS, n (%)	sICH, n (%)	90-day mortality, n (%)
Tanaka et al., (14)	2021	EVT	2	70	82	65.1	49 (28.0)	6 (3.0)	31 (18.0)
			3	54					
			4	51					
		BMM	2	42	87	75.0	18 (11.0)	2 (1.0)	44 (27.0)
			3	54					
			4	68					
Sykora et al., (13)	2022	EVT	3	136	79.4±12.2	62.3	47 (27.0)	7 (4.0)	76 (43.0)
			4	33					
			5	6					
		BMM	3	185	85.2±8.8	65.2	58 (20.0)	6 (2.0)	180 (63.0)
			4	83					
			5	19					
Sprugel et al., (11)	2022	EVT	3	82	82	72.5	20 (20.0)	6 (6.0)	54 (53.0)
			4	20					
		BMM	3	80	81	72.8	8 (8.0)	1 (1.0)	76 (74.0)
			4	23					
Siegler et al., (10)	2022	EVT	2~4	448	82	66.3	118 (26.0)	31 (7.0)	170 (38.0)
		BMM	2~4	106		/	8 (8.0)	0 (0.0)	48 (45.0)
Kastrup et al., (6)	2021	EVT	3~4	142	83 ± 8	/	/	12 (8.0)	31 (22.0)
		BMM	3~4	89	86 ± 7	/	/	7 (8.0)	22 (25.0)
Miyake et al., (8)	2023	EVT	2~3	258	82.2 ± 0.7	60.1	/	/	55 (21.3)
		BMM	2~3	57	83.4 ± 1.4	68.4	/	/	9 (15.8)

EVT: *Endovascular treatment,* ***BMM:*** *Best medical management.*

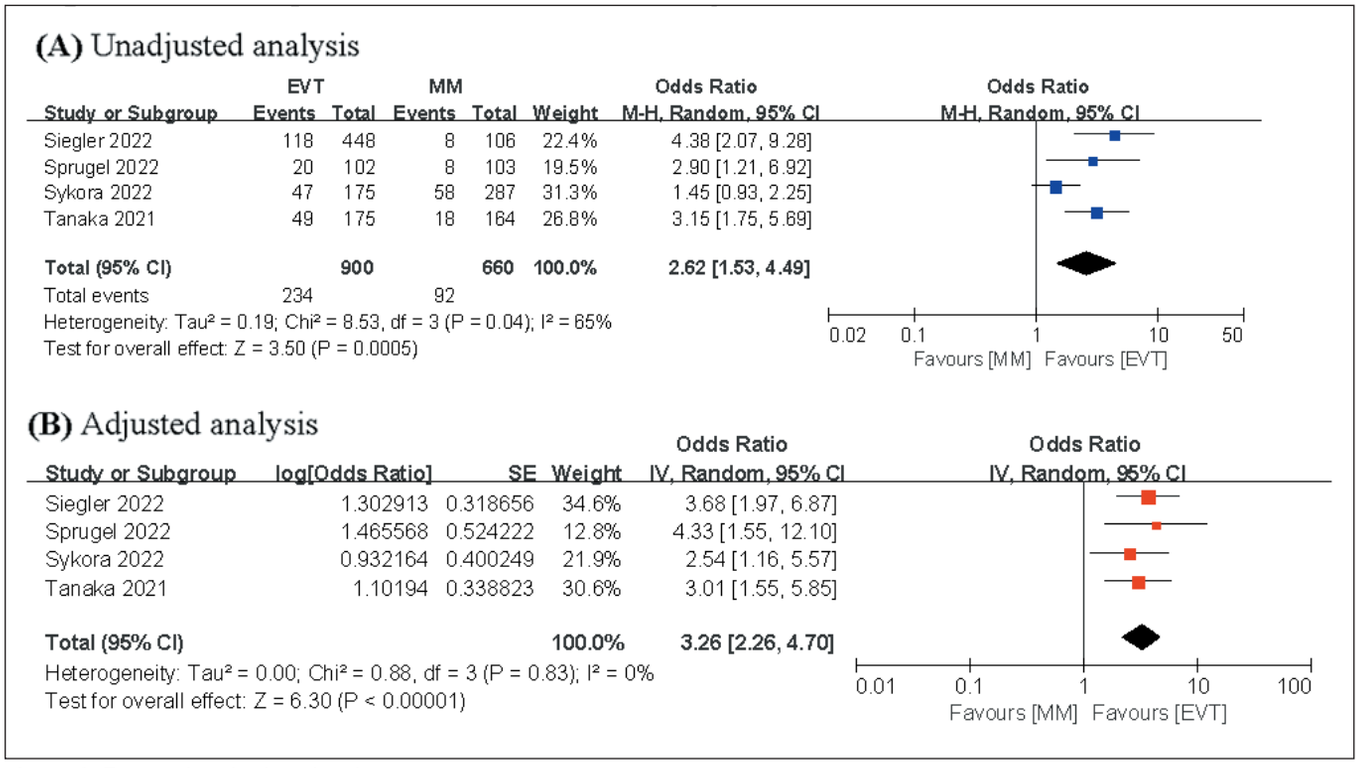

Figure 2: Forest plots for functional recovery.

outcome related to functional recovery (4 studies; adjusted OR [aOR]=3.26; 95% CI, 2.26-4.70; p<0.001; I^2 =0%; Figure 2B).

Secondary Outcomes: 90-Day Mortality and sICH Outcomes

All six studies, comprising a total of 2106 patients (1300 receiving EVT and 806 receiving MM), provided data on the 90-day mortality rate for pre-stroke disabled patients (6,8,10, 11,13,14). Specifically, the EVT group presented a lower 90-day mortality rate (OR=0.64; 95% CI, 0.47-0.88; p=0.006; Figure 3A). Notably, there was minimal heterogeneity and relatively significant statistical significance between the studies (I^2=54%, p=0.05). The sensitivity analysis indicated the robustness of the outcome related to the 90-day mortality rate (4 studies; aOR=0.40; 95% CI, 0.20-0.83; p=0.01; I^2 =62%; Figure 3B).

Among the five studies involving 1791 pre-stroke disabled patients (with 1042 receiving EVT and 749 receiving MM), data were available to assess the occurrence of sICH (6, 10,11,13,14). In terms of the rate of sICH, the EVT group demonstrated a higher risk than the MM group did (OR=2.28; 95% CI, 1.03-5.01; p=0.04), as illustrated in Figure 4A. In this case, heterogeneity was also relatively low (I^2= 29%, p=0.23). In contrast, the sensitivity analysis adjusted for confounding factors suggested a potentially higher incidence of sICH in the EVT group than in the MM group. However, the difference did not reach statistical significance (2 studies; aOR=2.47; 95% CI, 0.81-7.52; p=0.11; I^2 =4%; Figure 4B).

DISCUSSION

Our meta-analysis focused exclusively on cohort studies retrieved from databases that included patients with pre-stroke disability. The aim was to provide evidence-based treatment data specifically for this patient population. These findings suggest that, compared with MM, EVT may be associated with a higher likelihood of functional recovery and lower mortality. No significant difference was observed in the incidence of sICH after adjusting for potential confounders.

After the search, we systematically reviewed six studies involving a total of 2106 patients. The controlled studies in this review indicated that, for acute ischemic strokes caused by AIS-LVO, patients who received EVT had a better prognosis in terms of recovering baseline functionality than did those who received MM. Notably, EVT demonstrated superior efficacy in achieving a reduction in mRS scores for pre-stroke disabled patients within 90 days compared with conventional drug therapy, leading to a lower mortality rate. Additionally, the EVT group also presented a greater probability of intracranial hemorrhage within 90 days. A prior observational study by Ganesh et al. also suggested that a significant proportion of pre-stroke disabled patients may recover to their pre-stroke state after surgery, without indicating a higher incidence of treatment-related complications or supporting the routine exclusion of these patients from thrombectomy procedures (4). The study by Bala et al. yielded similar results, but in comparison with the two included studies, our study had a larger sample size, conducted a systematic review and data analysis of EVT versus MM, and provided more comprehensive data, thereby enhancing the persuasiveness of the results (1).

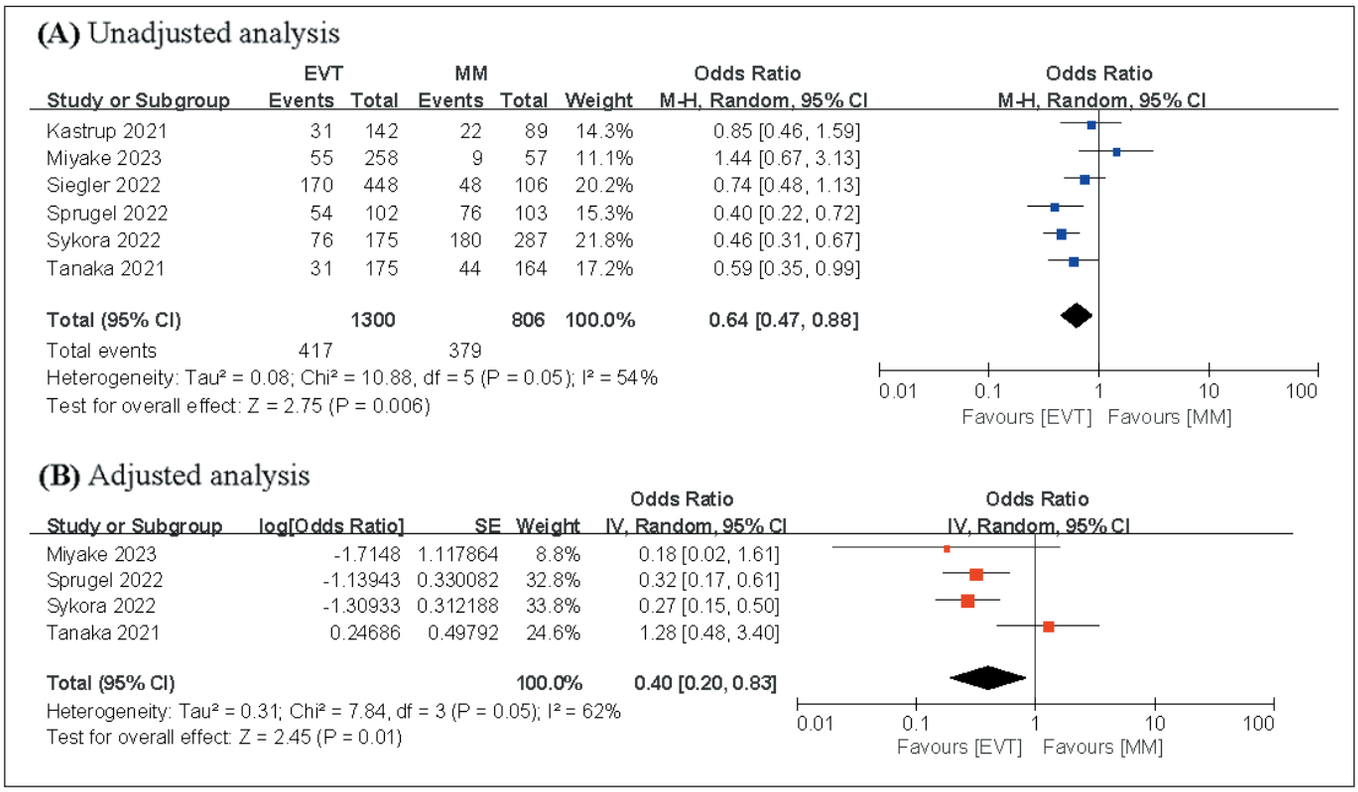

Figure 3: Forest plots for mortality.

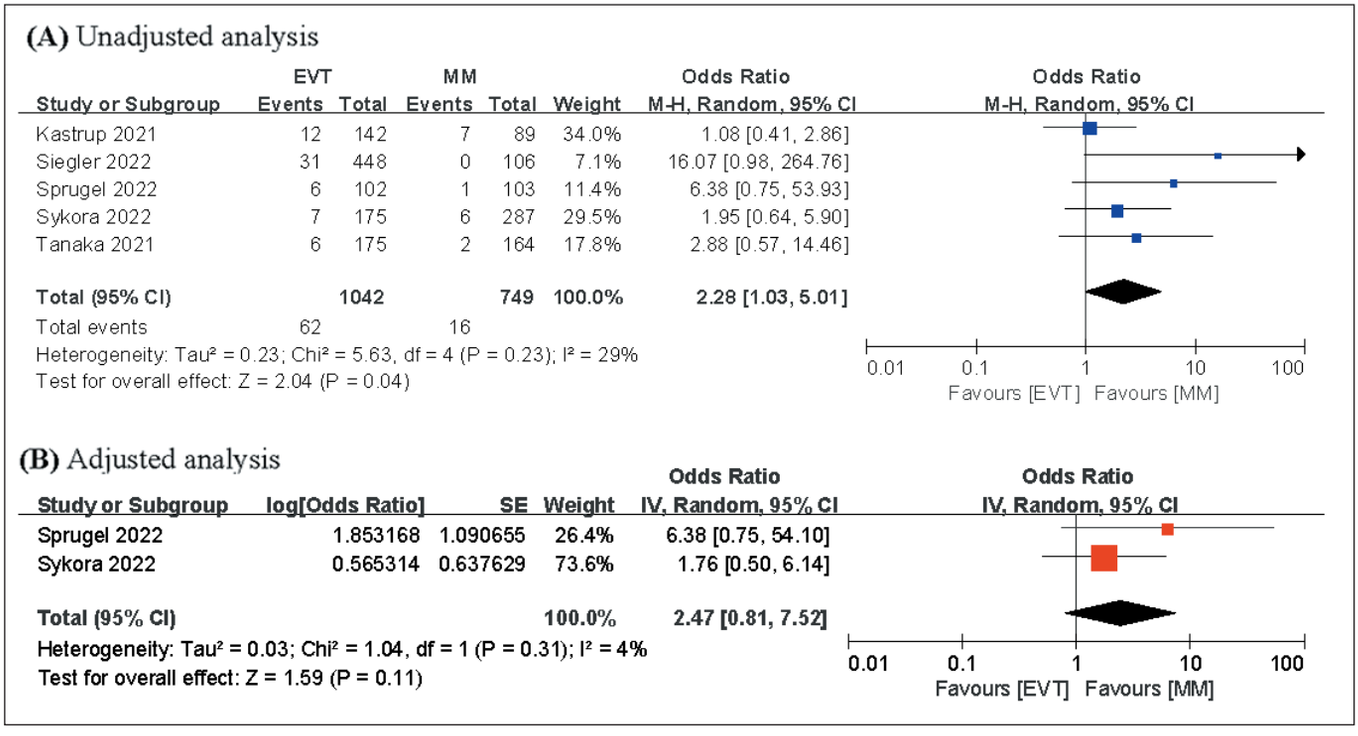

Figure 4: Forest plots for symptomatic intracranial hemorrhage.

However, the proportion of pre-stroke disabled patients within the stroke patient population is relatively small, hindering research efforts directed at this subset. Given that disability and stroke risks often increase in disabled patients, addressing this subset is crucial. With further research in this field, we anticipate a more precise assessment of the impact of endovascular treatment on pre-stroke disabled patients, facilitating the formulation of more accurate treatment strategies.

Our meta-analysis has certain inherent limitations. The included studies were essentially retrospective and observational, introducing inherent limitations. There were some differences in the baseline characteristics between groups, preventing deeper subgroup analysis and matching studies. Patients usually receive medication therapy to maintain vascular patency before undergoing EVT. Unfortunately, details regarding the type and dosage of medication remain unclear, which could influence our research results. Furthermore, after a systematic literature search, only six studies met the inclusion criteria, yielding a moderately sized overall sample. The absence of primary outcome data in one report led to slightly larger discrepancies in the results. Owing to the limited sample size, further analyses exploring confounding factors, such as meta-regression and subgroup analyses, were not feasible, potentially affecting the reliability and generalizability of the study results. On the other hand, although interdisciplinary collaboration is crucial for the rehabilitation of stroke-disabled patients, current research largely focuses on specific disciplines and lacks a comprehensive perspective and approach to interdisciplinary cooperation.

In the coming years, research on stroke treatment, whether involving endovascular treatment or drug intervention, is expected to expand. Medical institutions may increasingly emphasize stroke treatment. This study offers a new approach for researching stroke treatment in specific patient populations, ultimately leading to more personalized and detailed interventions. As healthcare professionals draw experiences from clinical guidelines and the latest research findings, treatment prospects will become more refined, thereby improving patient outcomes. We also look forward to clinicians paying more attention to such special patients. Through in-depth research and precise intervention, significant improvements in treatment outcomes for pre-stroke disabled patients are anticipated, allowing more patients to return to normal life.

CONCLUSION

This meta-analysis demonstrated that EVT may be associated with a higher likelihood of functional recovery and lower risk of mortality in AIS patients with pre-stroke disabilities, challenging the traditional hesitation to treat this population aggressively. Our findings suggest that premorbid disability alone should not preclude consideration for EVT. These results have the potential to inform more inclusive treatment guidelines. However, the conclusions are limited by the small number of eligible studies and inherent confounding biases of observational designs. Future high-quality RCTs are urgently needed to strengthen the evidence base and guide optimal therapeutic strategies in this underserved subgroup of stroke patients.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: TYZ, YQH, HZZ
Data collection: TYZ, DL
Analysis and interpretation of results: TYZ, YQH, HZZ
Draft manuscript preparation: TYZ, YQH, HZZ
Critical revision of the article: TYZ, DL, YQH, HZZ
Other (study supervision, fundings, materials, etc...): TYZ, HZZ
All authors (TYZ, DL, YQH, HZZ) reviewed the results and approved the final version of the manuscript.

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