

Risk assessment of mechanic thrombectomy on post-stroke seizures: a systematical review and meta-analysis

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Purpose: We conducted a systematic review and meta-analysis to evaluate the risk of early and late onset seizures following stroke mechanic thrombectomy (MT) compared with other systematic thrombolytic strategies. **Methods:** A literature search was conducted to identify articles covering databases (PubMed, Embase, and Cochrane Library) published from 2000 to 2022. The primary outcome was the incidence of post-stroke epilepsy or seizures following MT or in combination with intravenous thrombolytics therapy. Risk of bias was assessed by recording study characteristics. The study was conducted according to the PRISMA guidelines. **Results:** There were 1346 papers in the search results, and 13 papers were included in the final review. We identified 29,793 patients with stroke, of which 695 had seizures. Pooled incidence of post-stroke seizures had no significant difference between mechanic thrombolytic group and other thrombolytic strategy group (OR=0.95 (95%CI= 0.75-1.21); Z=0.43; p=0.67). In subgroup analysis, mechanic group have a lower risk of post-stroke early onset of seizures (OR=0.59 (95%CI=0.36-0.95); Z=2.18; p<0.05) but showed no significant difference in post-stroke late onset of seizures (OR=0.95 (95%CI= 0.68-1.32); Z=0.32; p=0.75). **Conclusions:** MT may be associated with a lower risk of post-stroke early onset of seizures, despite MT does not affect the pooled incidence of post-stroke seizures compared with other systematic thrombolytic strategies.

Keywords: mechanic thrombectomy—meta-analysis—reperfusion—seizures—thrombolysis

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Introduction

Acute ischemic stroke is a leading cause of disability, with over a third of survivors developing new post-stroke disabilities around the world.¹ Many post-stroke patients have a significant higher risk of developing post-stroke

seizures of which the incidence has also been increasing over the past decades.² Cerebrovascular disease is the leading cause of seizures in adults over 60-year-old, which has been shown to account for nearly 50% of newly diagnosed epilepsy in this age group.³

Abbreviations: MT, mechanic thrombectomy; rtPA, recombinant tissue plasminogen activator; EEG, electroencephalograph; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; NOS, Newcastle–Ottawa Scale; ES, early onset of seizures; LS, late onset of seizures; ORs, Odds ratios; CIs, confidence intervals

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The current gold standard for treating the onset of stroke symptoms is recombinant tissue plasminogen activator (rtPA), which is also the sole drug approved for the treatment of acute ischemic stroke.⁴ Limitations of rtPA therapy include lack of reversibility and a 4-6.4% risk of hemorrhagic transformation, resulting in death from intracranial hemorrhage in 40% of patients treated with this therapy.^{5,6} In patients with large vessel occlusion, MT has shown higher recanalization rates and restoration outcomes, making it the method of choice for acute treatment.⁷⁻¹⁰

However, the seizures have become a latent complication of reperfusion therapies in acute ischemic stroke.¹¹ Reperfusion therapy alters long-term survival, with outcomes associated with clinically acute symptomatic seizures and development of epileptiform activity on electroencephalograph (EEG) in stroke patients.^{12,13} Additionally, the impact and risk assessment of post stroke seizures after MT is currently controversial in recent reports. Some studies have pointed to a lower incidence of PSE after MT, and others have suggested that ischemic stroke patients treated with MT have a higher risk of seizures.¹⁴⁻¹⁹

Hence, a systematic review and meta-analysis were performed to investigate the occurrence and association of MT with seizures in patients with ischemic strokes, aiming to provide prophylactic guidance of treatment-related seizures.

Methods

Data source

Articles searched were performed in PubMed, Embase, and Cochrane Library, using search terms provided in the Supplementary material. This study was conducted following the standards of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The reference list of a previous systematic review of thrombolysis or MT was reviewed, and Google Scholar and Web of Science was searched for interventional studies of ischemic stroke using the keyword MT and post stroke seizures or epilepsy.

Study selection and quality assessment

Inclusion criteria :1) Studies published from 2000 to 2022 reporting the occurrence of seizures in ischemic stroke patients treated with MT, regardless of additional intra-arterial thrombolysis. 2) Studies without separate data on intravenous thrombolysis and MT were also included. Exclusion criteria: 1) Studies with seizures before or during acute reperfusion therapy were excluded. 2) Likewise, studies that did not determine whether epilepsy occurred during or after thrombectomy were excluded. 3) Duplicate publications, studies not published in English, review articles, studies conducted only

in the pediatric population, animal studies, case series and case reports were excluded. Data extraction was conducted by two independent reviewers.

Extracted data included study setting, design, population characteristics, diagnostic criteria for stroke and seizures, disease occurrence (incidence or prevalence), seizure type (focal versus generalized), and association of MT with post-stroke seizures effect size. Epilepsy occurred within 7 days of stroke was defined as acute symptomatic epilepsy, and unprovoked epilepsy occurred more than 7 days after stroke was defined as post-stroke epilepsy. Consistent with clinical definitions of acute symptomatic and post-stroke epilepsy from the current International League Against Epilepsy (ILAE).^{20,21} The Newcastle–Ottawa Scale (NOS) tool was used to evaluate the risk of bias for selected studies.²²

Statistical analysis

The primary outcome was the estimation of the pooled incidence of post-stroke seizure following MT and other thrombolytic therapy. Subgroup analyses were conducted to assess differences between early onset of seizures (ES) and late onset of seizures (LS): definition of ES as occurring within seven days post-stroke, while LS occurring after seven days. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare events of incident seizures between the thrombectomy and the control groups. Heterogeneity among studies was quantitatively assessed with the I^2 index (presence of heterogeneity when $I^2 \geq 50\%$).²³ Both fixed and random-effect models were used. Meta analyses were performed with RevMan software, version 5.4 (Cochrane, Oxford, UK).

Results

Overview

A total of 1,346 articles was retrieved, of which 13 records were carefully investigated and considered (Fig. 1). The full-text review confirmed 13 eligible articles from the following countries: United States,^{17,24,25} Germany,^{25,26} Qatar,²⁷ Switzerland,¹⁹ Spain¹⁸, Sweden,¹⁴ Australia,²⁸⁻³⁰ Italy,³¹ and China.²⁸ Nine studies were retrospective analyses and four were prospective cohort studies. Study characteristics such as participants, mean age, follow-up time, thrombolytic strategy, and primary clinical outcome were presented in Table 1. Ischemic stroke was diagnosed based on clinical symptoms, and associated imagological examination (brain magnetic resonance imaging, computerized tomography angiography, or computerized tomography perfusion) described in each included study.

Meta-analysis outcome

Totally, 29,793 stroke patients experienced reperfusion therapy were included. Among them, 695 patients

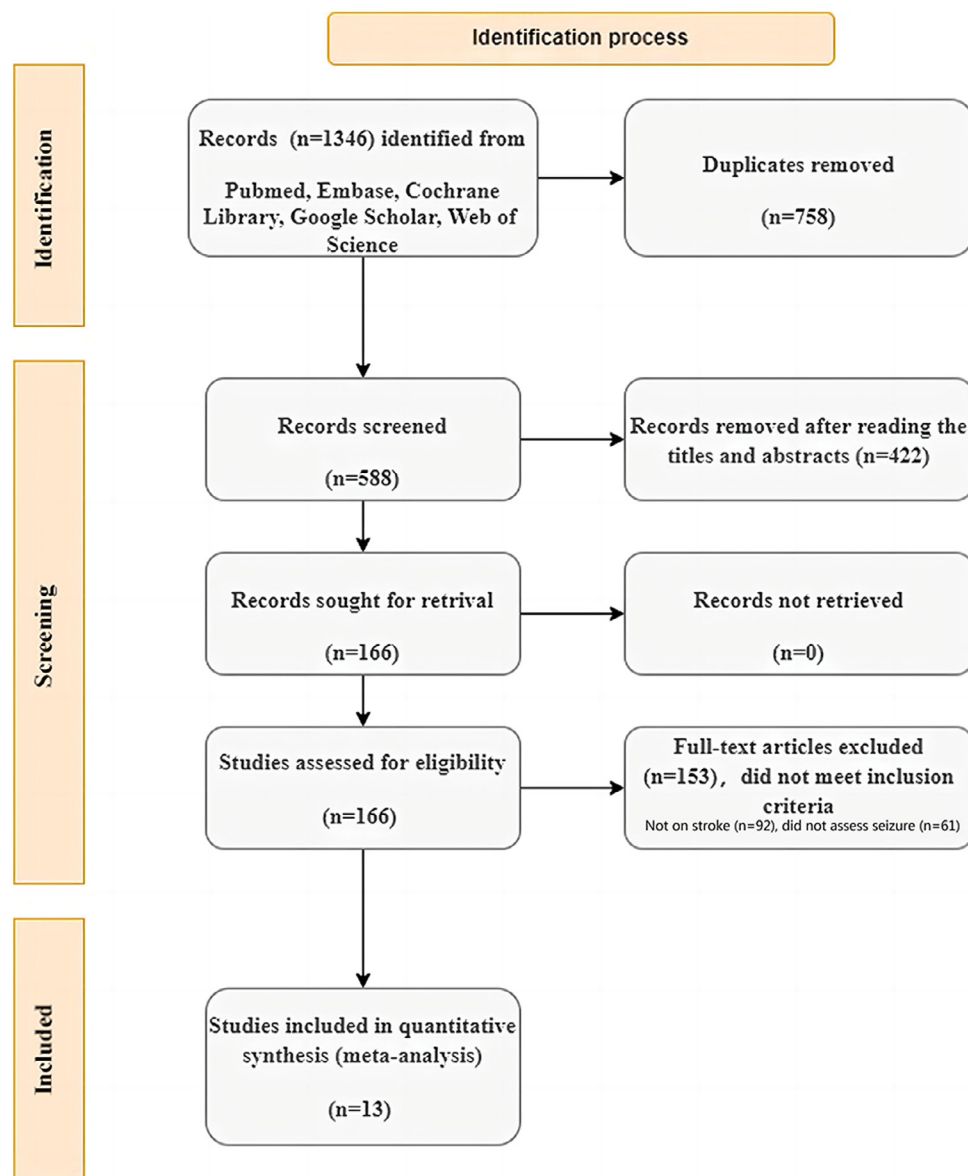


Fig. 1. Flow Chart of Identification Process.

occurred in symptomatic seizures after starting reperfusion treatment in participants with acute ischemic stroke. Risk of bias of each study were assessed by NOS and scored by a reviewer (Table 2).

Post stroke seizures

Thirteen cohort studies were first analyzed (Fig. 2). LS and ES were not different in comparison. Due to the low overall heterogeneity ($\chi^2=14.9$; $df=12$; $I^2=16\%$), fixed-effects model was used to evaluate the risk of post-stroke seizures after MT compared with other systemic thrombolysis modalities. Results indicated that MT may not have a significant impact on incident rate of post-stroke seizures compared with other systematic thrombolytic strategies, especially intravenous thrombolysis (OR=0.95

(95% CI=0.75-1.21); $Z=0.43$; $p=0.67$). Although there were some differences in the ORs (OR=0.59 (95% CI=0.32-1.09) and OR=1.10 (95% CI=0.64-1.89) respectively) of the two cohorts^{19,25} with a larger weight (22.8% and 17.4%, respectively), the majority of the included studies had no evidence to indicate that MT affects the occurrence of epilepsy after stroke.

ES and LS

Post-stroke seizures were classified into LS and ES according to the ILAE criteria and the description of the clinical outcome measures in the research paper, then a subgroup analysis was performed (Fig. 3), five studies were included in LS^{19,25,28-30} and five were included in ES^{17,18,27,31,32}. In the LS group, the results of the analysis

Table 1. Characteristics of included studies.

Article	Study Design	Participants	Mean Age	Follow-Up Time	Thrombolytic Strategy	Clinical Outcome	Country
Lindsey R Kuohn et al. 2022 [22]	RS	595,545	74	6 years	IV-tPA; MT	PSS; ASS	United States
Konstantin Kohlhasse et al. 2022 [23]	RS	987	None	4 years	MT; ST	PSS	Germany
Tasnim Mushannen et al. 2021 [25]	RS	508	53.3	4 years	IV-tPA; MT	PSS	Qatar
Carolina Ferreira-Atuesta et al. 2021 [16]	PS	4,229	None	4 years	MT; IVT; IAT	PSS; ASS	Switzerland
M Alemany et al. 2021 [15]	RS	344	69	5 years	MT; IVT	PSS; ASS	Spain
Johann Philipp Zöllner et al. 2020 [24]	RS	14,369	73.7	None	MT; IVT	PSS; ASS	Germany
Hanna Eriksson et al. 2020 [11]	PS	90	72	4 years	MT; IVT	PSS	Sweden
Francesco Brigo et al. 2020 [29]	RS	680	75	7 years	MT; IVT	PSS	Italy
Mohammad Anadani et al. 2019 [14]	PS	459	67.5	5 years	IV-tPA; MT	PSS	United States
Jillian Naylor et al. 2018 [26]	RS	1,375	70/74	8 years	MT; IVT; IAT	PSS	Australia; China
Ziyi Chen et al. 2018 [27]	RS	409	75	None	IV-tPA; MT	PSS; ASS	Australia
Simon Jung et al. 2012 [21]	PS	805	61.7	3 months	MT; IVT	PSS; ASS	United States
Ziyuan Chen et al. 2017 [28]	RS	348	73	6 years	MT; IVT	PSS; ASS	Australia

ASS, acute symptomatic seizures; IV-tPA, intravenous recombinant tissue plasminogen activator; IVT, intravenous thrombolysis; IAT, intra-arterial thrombolysis; MT, mechanic thrombectomy; PS, prospective study; PSS, post-stroke seizures; RS, Retrospective study

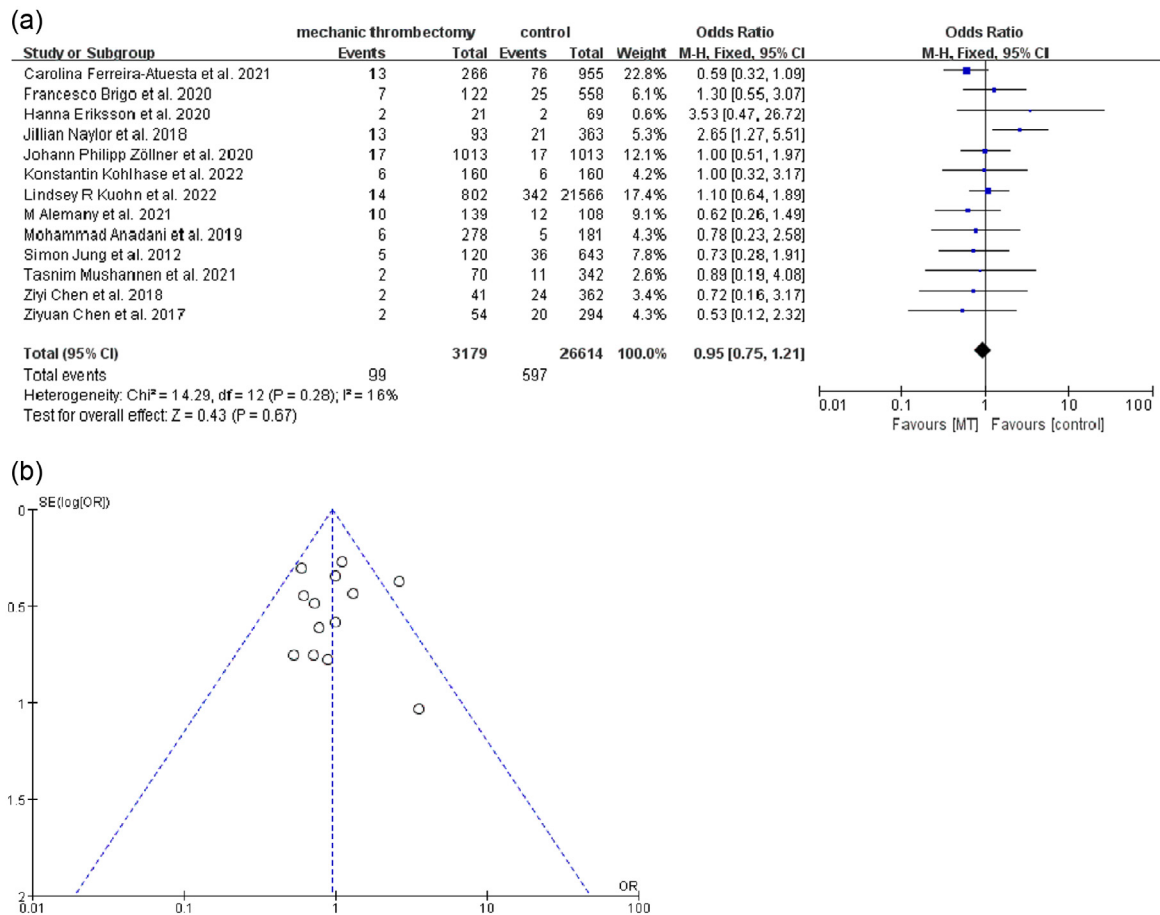
**Fig. 2.** Forest plot and corresponding funnel plot: post-stroke seizures after mechanistic thrombectomy versus other systematic thrombolytic strategies.

Table 2. The Newcastle–Ottawa Scale (NOS) score of included studies.

Author	Is the case definition adequate?	Representativeness of cases	Control Selection	Control Definition	Comparability of cases and controls upon design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Total Score
Lindsey R Kuohn et al. 2022 [22]	★	★	★	☆	★	★	★	☆	6
Konstantin Kohlhase et al. 2022 [23]	★	★	★	★	★	★	★	☆	7
Tasnim Mushannen et al. 2021 [25]	★	★	☆	★	★	★	★	☆	7
Carolina Ferreira-Atuesta et al. 2021 [16]	★	★	★	★	★	★	★	☆	8
M Alemany et al. 2021 [15]	★	★	★	★	☆☆	★	★	☆	6
Johann Philipp Zöllner et al. 2020 [24]	★	★	☆	★	★	★	★	☆	7
Hanna Eriksson et al. 2020 [11]	☆	★	★	★	★	★	★	☆	5
Francesco Brigo et al. 2020 [29]	★	★	☆	★	★	★	★	☆	7
Mohammad Anadani et al. 2019 [14]	★	☆	★	★	★	★	★	☆	7
Jillian Naylor et al. 2018 [26]	★	★	★	★	★	★	★	☆	7
Ziyi Chen et al. 2018 [27]	★	★	★	★	★	★	★	☆	8
Simon Jung et al. 2012 [21]	★	★	★	★	★	★	★	☆	8
Ziyuan Chen et al. 2017 [28]	★	★	★	★	★	★	★	☆	8

★ the item had not been scored; ☆ the item had not been scored. Total score of the Newcastle–Ottawa Scale (NOS) is 9.

showed that MT had no significant effect on the overall incidence of LS (OR=0.95 (95%CI= 0.68-1.32); Z=0.32; p=0.75), in which J. Naylor et al. showed that MT caused an increase in the pooled incidence of LS (OR=2.41 (95%CI=1.14-5.10)). In the analysis of the ES group, MT reduced the overall incidence of ES after stroke (OR=0.59 (95%CI=0.36-0.95); Z=2.18; p<0.05), and there was no significant heterogeneity among the five studies ($\chi^2=0.97$, df=4, I²=0%).

Discussion

This meta-analysis revealed that MT had a lower pooled incidence of post-stroke ES. However, the difference of overall post-stroke seizures and LS between MT and other intravenous thrombolytic administration did not reach significant difference. We think that the difference in outcomes between ES and LS might be caused by different pathophysiological mechanisms. Because the mechanism of ES may involve transient release of neurotransmitters or redistribution of other metabolites in ischemic conditions, etc.³³

MT was recommended as a complementary treatment with intravenous thrombolysis for the management of ischemic stroke related to proximal occlusion of the anterior arterial circulation.³⁴ But thrombolysis might be associated with the occurrence of acute symptomatic seizures according to other clinical studies.³⁵ Recent studies have identified post-stroke ES in 2.4 to 4.4% patients after MT,¹⁴ suggesting that the application of different thrombolysis methods may have an impact on the prognosis of stroke patients during clinical practice.

There are many factors that affect the incidence of epilepsy after stroke. For example, in the meta-analysis of Richard S Chang et al.³⁶, the prophylactic use of antiepileptic drugs has a significant impact on post stroke seizures patients. In addition, according to a report, the post-stroke seizures rate was 6.1% for intravenous thrombolysis, 5.9% for MT, and 5.8% for combination therapy, meaning that specific reperfusion therapy may be independently associated with post-stroke seizures.³⁷ The post-stroke seizure incidence estimated in our study compared with other systematic thrombolytic strategies is similar to the largest post stroke seizures meta-analysis (without considering any acute treatment), which included more than 150,000 patients with ischemic stroke and an occurrence rate of 5.86%.³⁸

Some included studies also described and differentiated post-stroke ES and LS during statistical analysis.²⁴ This analysis also found that MT was associated with a lower incidence of epilepsy compared with other thrombolytic modalities. This might be due to the strategy of thrombectomy-assisted thrombolysis which can achieve better therapeutic effect within the thrombolysis window.

This study also has some limitations. First, the ethnicity selected for the included studies is relatively single, which

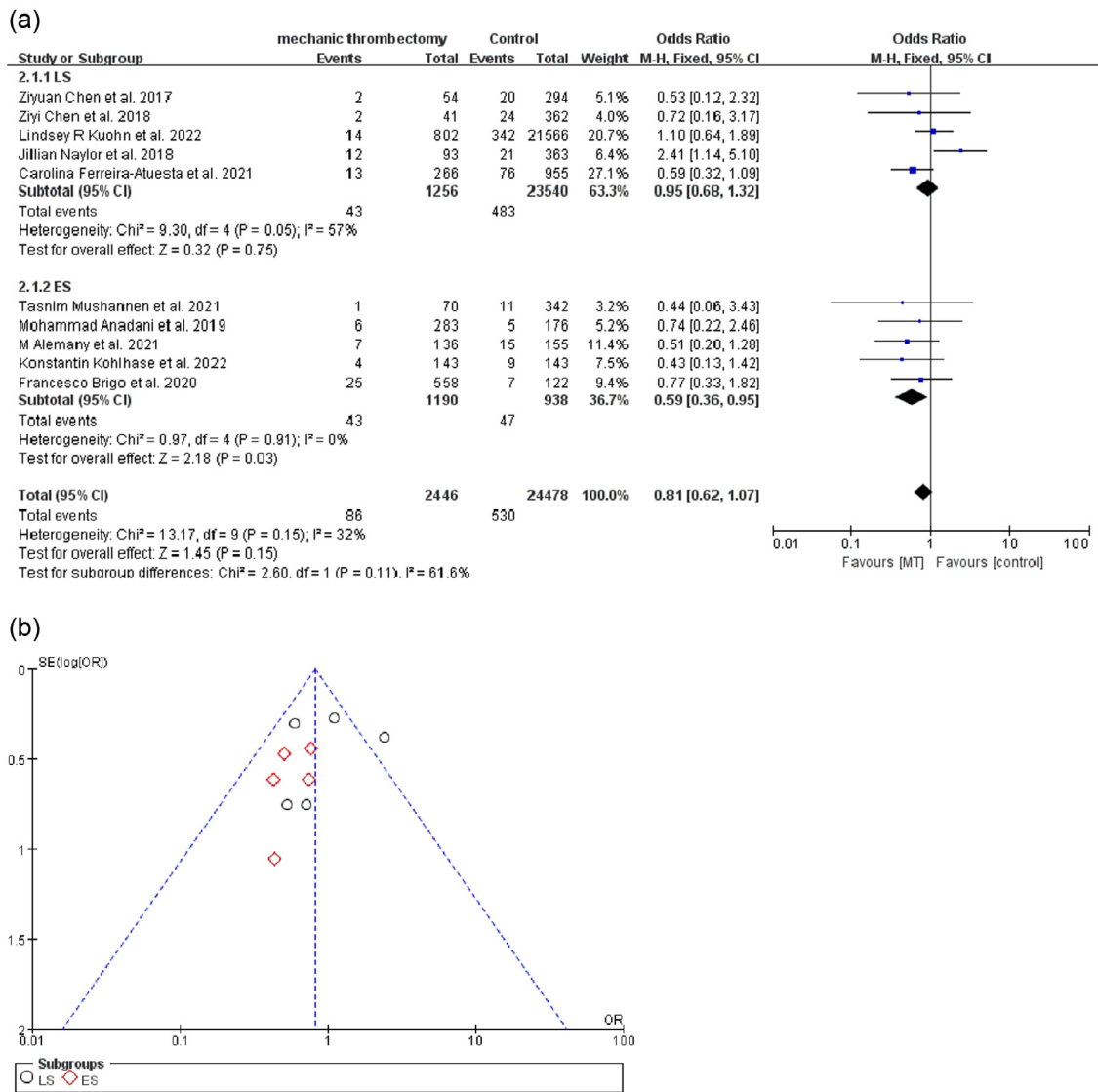


Fig. 3. Forest plot and corresponding funnel plot: early onset of seizures (ES) and late onset of seizures (LS) after mechanistic thrombectomy versus other systematic thrombolytic strategies.

may be difficult to generalize. Secondly, in many studies, intravenous thrombolysis and mechanical thrombolysis have not been compared separately, which makes it challenging to describe the specific effects of each type of thrombolysis on post-stroke epilepsy. There is a heterogeneity in the sample size of studies with the largest one being 595,545 and the smallest one being 90. There may be differences in the pathogenesis of ES in patients with different age, gender and disease status. The pathogenesis of ES involves a variety of factors, including genetic factors, changes in neuronal excitability, imbalance of neuronal network, inflammatory response, cerebrovascular disease, and so on. Therefore, heterogeneity of the sample and other factors, such as comorbidities, including diabetes, etc., may have an impact on the onset mechanism of ES. Despite these limitations, our meta-analysis results also suggest clinical practitioner that different

thrombolysis methods may have an impact on the occurrence of post-stroke epilepsy.

Overall, MT does not affect the pooled incidence of post-stroke seizures compared with other systematic thrombolytic strategies. But MT may be associated with a lower risk of post-stroke ES compared with other systematic thrombolytic strategies. Although this study has some limitations, we can still use this study to provide some valuable references for future clinical practice. First, the external validity of the study could be improved by adding a diverse ethnic sample. In addition, we can further compare different types of thrombolytic therapy to determine their specific effects on the generation of post-stroke epilepsy. Future studies are necessary to identify risk factors associated with LS and ES in patients in order to prevent such events and improve patient outcomes. By improving our understanding of the risk factors involved,

we can develop more effective prevention and treatment strategies in clinical practice.

Ethics approval and consent to participate

The study was approved by the First Affiliated Hospital of Kunming Medical University [No.(2022)L157]. Written informed consent was obtained from all individuals included in this study.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this. Further enquiries can be directed to the corresponding author.

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Author Contributions

WJ is responsible for the study concepts & design, definition of intellectual content, literature research, experimental studies, data acquisition & analysis, statistical analysis, manuscript preparation; XYZ is responsible for the literature research, data acquisition; CYL is responsible for the guarantor of integrity of the entire study, experimental studies, data analysis, statistical analysis; GLJ is responsible for the guarantor of integrity of the entire study, literature research, experimental studies; LMZ is responsible for the data acquisition & analysis, statistical analysis; SM and LMZ are responsible for the manuscript editing & review. All authors read and approved the final manuscript.

Declaration of Competing Interest

There are no potential conflicts of interest to disclose.

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