



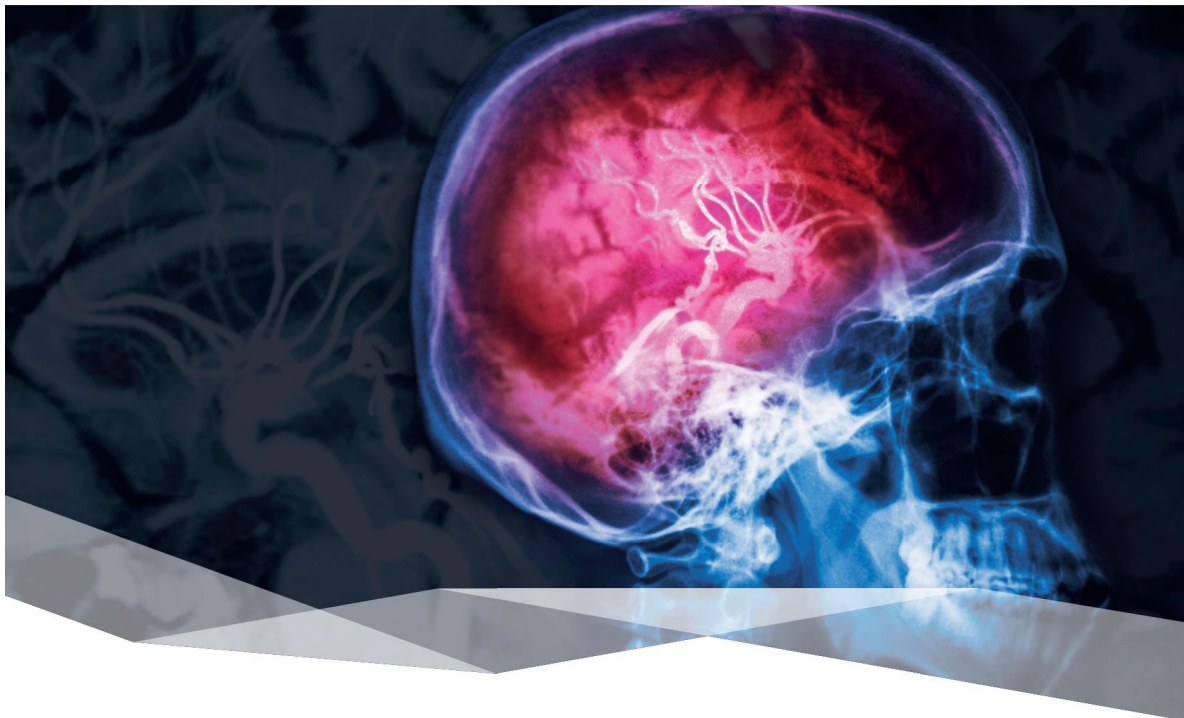
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695 Erratum

Mechanical Thrombectomy for Mild Acute Ischemic Stroke with Large-Vessel Occlusion: A Systematic Review and Meta-Analysis

Xiaowen Hou Xu Feng Huixin Wang Qian Li

School of Public Health, Shenyang Medical College, Shenyang, China

Keywords

Functional prognosis · Mechanical thrombectomy · Mild acute ischemic stroke · Large-vessel occlusion · Meta-analysis

Abstract

Background: The functional prognosis of mechanical thrombectomy (MT) for mild acute ischemic stroke (AIS) with large-vessel occlusion (LVO) is controversial. To explore a more precise estimation, a meta-analysis was conducted. **Methods:** The relevant studies were identified by searching PubMed, Embase, Web of Science, and Cochrane Collaboration Database until October 2021. The pooled analysis, subgroup analysis, sensitivity analysis, and publication bias examination were all conducted. The meta-analysis was performed by using Stata 12.0. **Results:** Eleven studies were included with a total of 1,929 subjects, including 794 patients receiving MT and 1,135 patients receiving medical management. The pooled analysis showed that MT might be not associated with functional prognosis among mild AIS with LVO (excellent functional prognosis: risk ratio (RR) = 1.07, 95% confidence interval (CI) = 0.94–1.21, $p = 0.294$; favorable functional prognosis: RR = 1.01, 95% CI = 0.96–1.06, $p = 0.823$). The statistical stability and reliability were dem-

onstrated by the sensitivity analysis and publication bias outcomes. **Conclusion:** Our meta-analysis suggests that MT may be not associated with functional prognosis of mild AIS with LVO.

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Introduction

Acute ischemic stroke (AIS) is the most common type of stroke. In general, AIS with mild symptoms (National Institutes of Health Stroke Scale [NIHSS] score ≤ 5) is associated with good functional prognosis [1]. However, when mild AIS is caused by large-vessel occlusion (LVO), patients are at higher risk of early neurological deterioration and poor functional prognosis [2]. Therefore, improving functional prognosis of mild AIS with LVO has become a hot topic in clinical research.

As we have described in our previous study, mechanical thrombectomy (MT) and intravenous thrombolysis (IVT) are both effective treatments for AIS patients [3]. Although IVT is recommended as the first choice for most patients, MT has become a standard therapy for moderate to severe AIS (NIHSS score ≥ 6) with LVO in proximal anterior circulation [4]. However, there is no

consensus on whether mild AIS with LVO can benefit from MT.

A meta-analysis was conducted to compare the functional prognosis of MT and medical management (MM) in AIS patients with an NIHSS score ≤ 8 and LVO [5]. Although two original studies were reported after that [6, 7], no meta-analysis has been reperformed. Since most studies defined mild stroke as an NIHSS score ≤ 5 [8–10], subjects in the present meta-analysis are limited to an NIHSS score ≤ 5 , which aims to evaluate the functional prognosis of MT for mild AIS with LVO.

Methods

The study was performed in accordance with the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Searching Strategy

A literature search from PubMed, Embase, Web of Science, and Cochrane Collaboration Database was conducted to identify all relevant studies up to October 2021. The following terms were used for searching: (mechanical thrombectomy OR MT OR endovascular thrombectomy OR endovascular therapy OR ET OR EVT) AND (mild stroke OR minor stroke OR minimal stroke OR NIHSS ≤ 5 OR NIHSS < 6) AND (large vessel occlusion OR LVO). No language or other restrictions were used. Meanwhile, the references used in the eligible articles were carefully reviewed to identify potential studies.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) all patients had been diagnosed with mild AIS (NIHSS score ≤ 5); (2) all patients were with LVO (anterior circulation and/or posterior circulation); (3) patients were divided into two groups, one group received MT and the other received MM; and (4) the study should provide the number of patients with excellent (or favorable) functional prognosis for each group, respectively. Functional prognosis was assessed using the modified Rankin scale (mRS) score at 90 days [11]. Furthermore, a score of 0–1 was defined as excellent functional prognosis and 0–2 as favorable. Studies were excluded when they were (1) reviews, letters, case reports, protocols, or animal studies; (2) duplicate publications of data from the same study; (3) studies providing insufficient information the meta-analysis needed.

Data Extraction

Information was extracted independently by two experienced investigators (Wang H.X. and Li Q.), and any discrepancy was resolved by the third investigator (Feng X.). Authors were contacted if studies did not provide adequate information. The following data were collected: first author's name, publication year, country of study population, mean age, male ratio, anterior circulation ratio, NIHSS score at admission, treatment in the MM group, and the number of functional prognosis of patients who received MT and MM.

Quality Assessment

The Newcastle-Ottawa quality assessment scale (NOS) was utilized to evaluate the quality of included studies [12]. All studies were assessed independently by two authors (Wang H.X. and Li Q.), and disagreement was resolved by consulting a third author (Feng X.). The assessment scale included the following aspects: selection method of the exposed group (receiving MT) and nonexposed group (receiving MM), comparability of the two groups, and assessment of functional prognosis. The study with best quality can be awarded a score of 9, and scores ≥ 6 were considered as high quality.

Statistical Analysis

The association between MT and functional prognosis of mild AIS with LVO was estimated by the risk ratio (RR) and 95% confidence interval (CI). Q and I^2 statistics were used to assess the heterogeneity between studies. When statistical heterogeneity was significant (p value of Q statistic < 0.05 or $I^2 \geq 50\%$), a random-effect model would be used; otherwise, a fixed-effect model would be used [13]. To explore sources of heterogeneity, subgroup analyses were performed by continent (Europe, Asia, or North America), mean/median NIHSS score at admission (2, 3, or 4 score), male ratio ($\geq 50\%$ or $< 50\%$), and treatment in the MM group (IVT alone or IVT combined with other treatments). Sensitivity analysis by sequentially excluding every study was performed to assess the robustness of the results. To assess the potential publication bias, Begg's correlation and Egger's regression were used [14, 15]. All the analyses were conducted using Stata 12.0 (Stata, College Station, TX, USA).

Results

Eligible Studies

A flow diagram summarizing the whole process of selection procedures is shown in Figure 1. According to our searching strategy, a total of 1,869 potentially relevant studies were identified. Of these studies, only 11 retrospective studies met all the inclusion criteria [6, 7, 16–24]. The dataset represented 794 patients receiving MT and 1,135 patients receiving MM. The quality evaluation showed reasonable study design and clear results. No study was excluded on grounds of quality. The characteristics of all the included studies are listed in Table 1. The results of quality evaluation are shown in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000523838).

Pooled Analysis

There were 11 studies concerning the functional prognosis of MT for mild AIS with LVO in the present meta-analysis. Based on the values of heterogeneity (excellent functional prognosis: $p = 0.028$, $I^2 = 52.0\%$; favorable functional prognosis: $p = 0.080$, $I^2 = 41.7\%$), correspond-

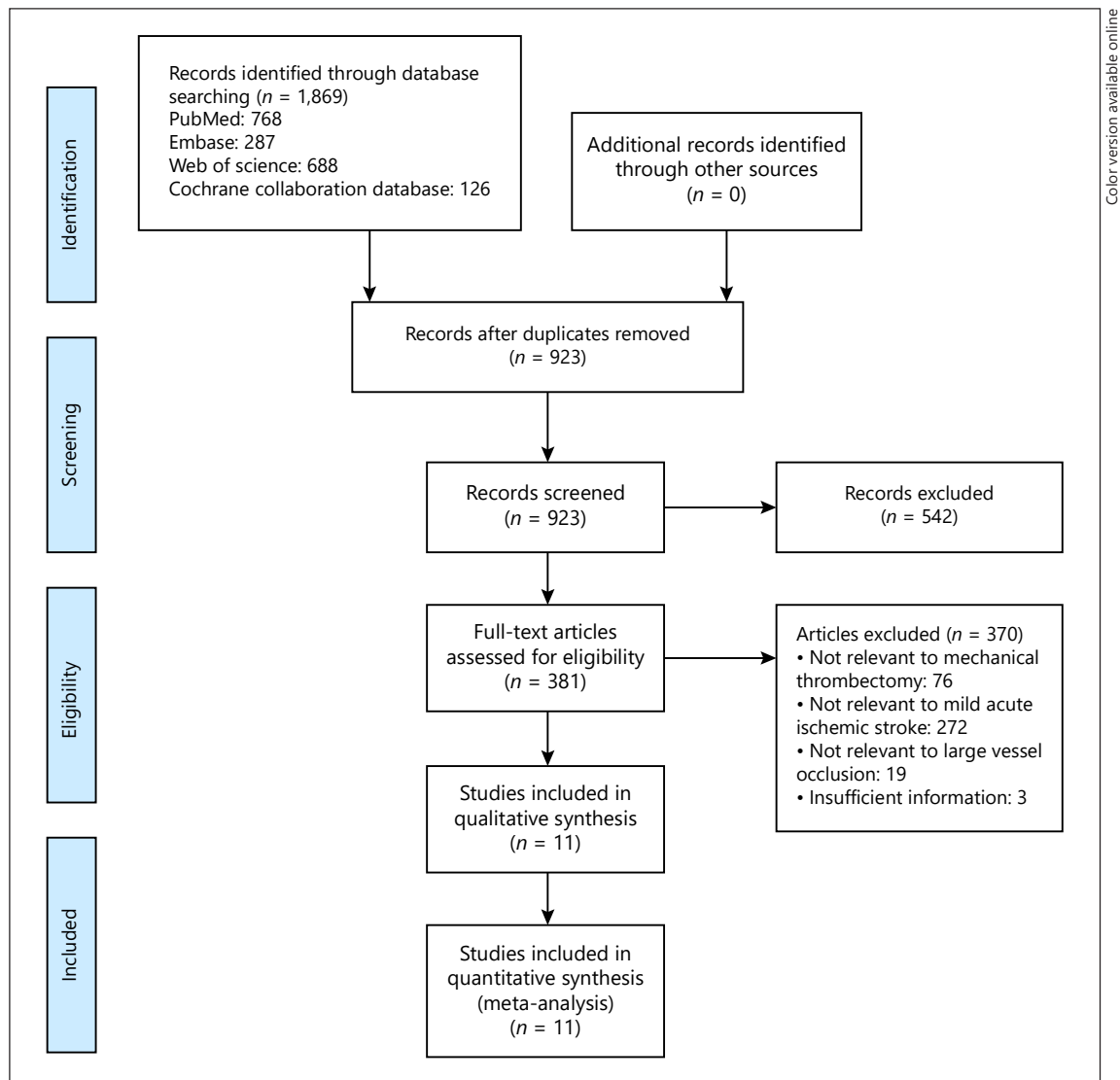


Fig. 1. Flow diagram of study selection.

ing effect models were used. Overall, the results indicated that MT might be not associated with functional prognosis of mild AIS with LVO (excellent functional prognosis: $RR = 1.07$, 95% $CI = 0.94-1.21$, $p = 0.294$; favorable functional prognosis: $RR = 1.01$, 95% $CI = 0.96-1.06$, $p = 0.823$) (Fig. 2).

Subgroup Analysis

In the subgroup analysis, studies were categorized by the continent, NIHSS score at admission, male ratio, and treatment in the MM group. The results of the subgroup analysis are shown in Table 2. In the subgroup analysis by continent, a significant association was shown between

MT and functional prognosis in the North-American population (excellent functional prognosis: $RR = 1.77$, 95% $CI = 1.18-2.66$, $p = 0.006$; favorable functional prognosis: $RR = 1.39$, 95% $CI = 1.06-1.81$, $p = 0.016$). However, no obvious association was found in the other populations. In the subgroup analysis by the NIHSS score at admission, a significant association was observed between MT and functional prognosis in the 2-score subgroup (excellent functional prognosis: $RR = 1.77$, 95% $CI = 1.18-2.66$, $p = 0.006$; favorable functional prognosis: $RR = 1.39$, 95% $CI = 1.06-1.81$, $p = 0.016$). Nevertheless, the other subgroups showed no obvious association.

Sensitivity Analysis

The sensitivity analysis was performed to evaluate the influence of each individual study on the pooled RR by omitting every single study. The analysis results reflected that the results were statistically stable and reliable (Fig. 3).

Publication Bias

No significant publication bias was found in the meta-analysis, reflected by p values from Begg's correlation (excellent functional prognosis: $p = 0.210$; favorable functional prognosis: $p = 0.190$) and Egger's regression (excellent functional prognosis: $p = 0.592$; favorable functional prognosis: $p = 0.574$). The shapes of the funnel plots did not show any strong evidence of asymmetry.

Discussion

In general, AIS with LVO has severe disability symptoms [25]. Even if the symptoms are mild, the disease also has a high risk of serious deterioration and poor prognosis without reperfusion [26, 27]. MT has been demonstrated to rapidly and effectively recanalize occluded vessels, but it increased the risk of intracranial hemorrhage, which might lead to poor prognosis [28, 29]. Therefore, MT is only recommended for moderate to severe patients (NIHSS ≥ 6) as the standard treatment for AIS with LVO under the current guidelines [4]. Whether MT should be used for mild AIS with LVO is still controversial.

A meta-analysis has been performed to compare the efficacy and safety between MT and IVT alone for patients with distal LVOs regardless of the severity of AIS in 2021 [30]. The results of that showed no significant difference between MT and IVT alone in favorable outcome, occurrence of sICH, or 90-day mortality [30]. Meta-analyses have been conducted to identify whether MT was associated with functional prognosis of AIS patients with an NIHSS score ≤ 8 and LVO [5, 31], while subjects of the present paper were limited to an NIHSS score ≤ 5 . Furthermore, we have conducted subgroup analysis, sensitivity analysis, and publication bias test, which were not performed in the previous meta-analyses.

In the present study, 11 retrospective studies were included with a total of 1,929 subjects, comprising 794 patients receiving MT and 1,135 patients receiving MM. The pooled analysis showed MT might be not associated with functional prognosis of mild AIS with LVO, which was almost consistent with the previous meta-analysis [5]. In the subgroup analysis, MT was shown to be correlated with functional prognosis in the North-American

Table 1. Characteristics of all studies included in the meta-analysis

Author	Country of study population	Mean age, years	Male ratio, %	Anterior circulation, %	Mean/median NIHSS at admission	MT group, n			MM group, n			Treatment in MM NOS scale	group
						excellent functional prognosis	favorable functional prognosis	total	excellent functional prognosis	favorable functional prognosis	total		
Wang et al. [6]	China	61.9	72.3	70.2	3	14	16	23	16	18	24	IVT alone	7
Seners et al. [16]	France	68.9	46.5	100.0	3	160	178	214	285	320	384	IVT alone	8
Saito et al. [7]	Japan	NA	65.8	65.1	3	NA	44	54	NA	164	218	IVT + other treatments	7
Nagel et al. [17]	Germany	70.4	53.2	87.2	4	21	22	30	48	56	64	IVT alone	7
Goyal et al. [18]	NA	65.0	46.2	100.0	4	84	102	138	62	75	113	IVT + other treatments	8
Da Ros et al. [19]	Italy	69.1	52.8	100.0	4	27	27	29	11	19	24	IVT alone	7
Manno et al. [20]	Switzerland	69.2	47.7	100.0	4	68	86	108	71	93	108	IVT alone	7
Sarraj et al. [21]	Spain, USA	65.6	57.5	100.0	4	69	79	124	49	61	90	IVT + other treatments	7
Hausen et al. [22]	USA	NA	51.9	80.8	2	23	25	26	13	18	26	IVT + other treatments	8
Messer et al. [23]	Germany	NA	NA	100.0	NA	8	NA	14	22	NA	40	IVT alone	6
Urra et al. [24]	Spain	67.9	64.1	69.2	3	20	26	34	30	37	44	IVT + other treatments	7

IVT, intravenous thrombolysis; MM, medical management; MT, mechanical thrombectomy; NA, not available; NIHSS, National Institutes of Health Stroke Scale; NOS, Newcastle-Ottawa quality assessment Scale.

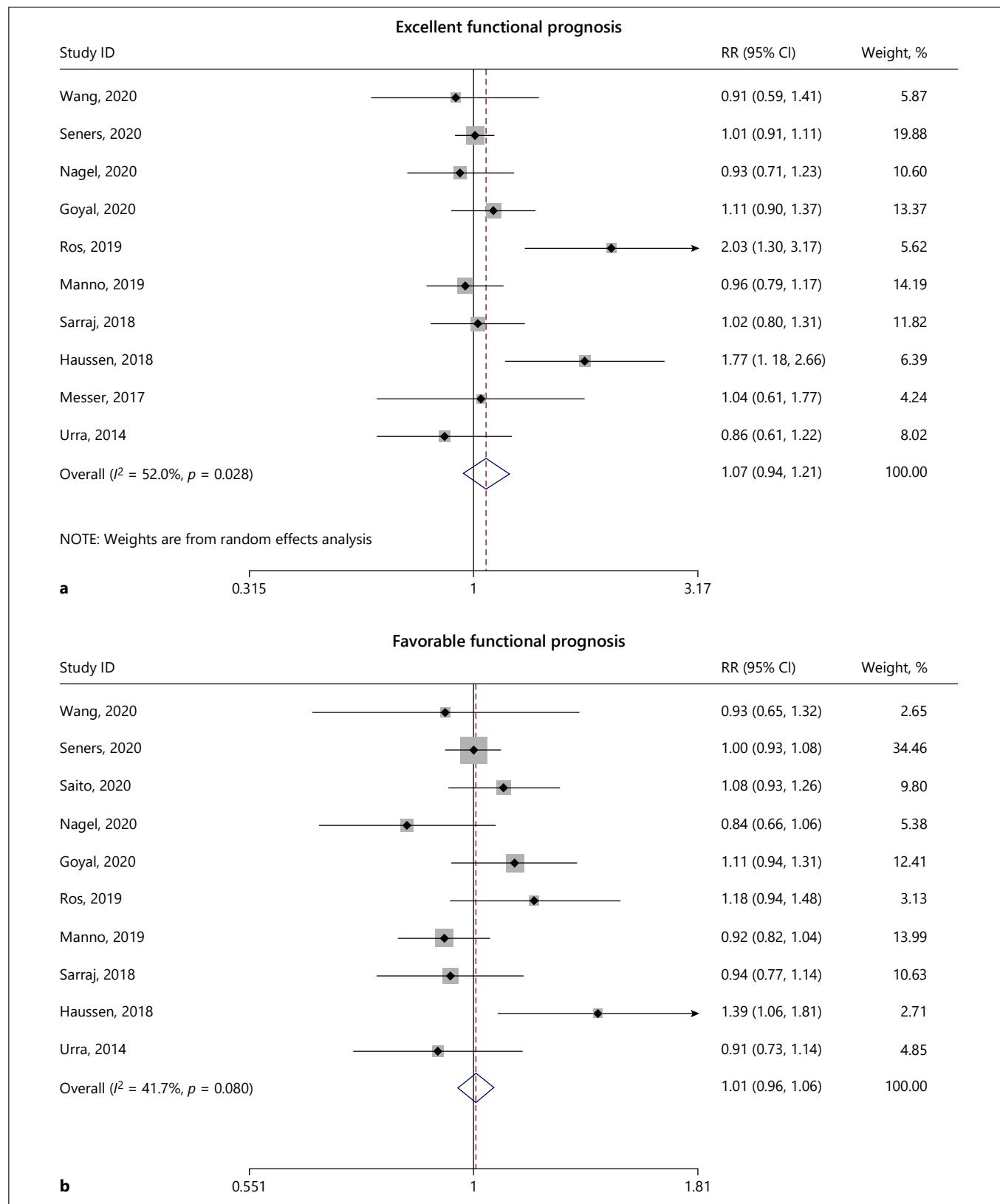


Fig. 2. a, b Forest plot of the RR of functional prognosis associated with MT for mild AIS with LVO.

Table 2. Results of subgroup analysis

Subgroup	Excellent functional prognosis				Favorable functional prognosis			
	study, <i>n</i>	RR (95% CI)	<i>p</i> heterogeneity	<i>I</i> ² , %	study, <i>n</i>	RR (95% CI)	<i>p</i> heterogeneity	<i>I</i> ² , %
Continent								
Europe	6	1.03 (0.88, 1.20)	0.055	53.8	5	0.97 (0.92, 1.03)	0.223	29.8
Asia	1	0.91 (0.59, 1.41)	NA	NA	2	1.05 (0.91, 1.21)	0.425	0
North America	1	1.77** (1.18, 2.66)	NA	NA	1	1.39** (1.06, 1.81)	NA	NA
Mean/median NIHSS score at admission (score)								
2	1	1.77** (1.18, 2.66)	NA	NA	1	1.39** (1.06, 1.81)	NA	NA
3	3	0.99 (0.91, 1.09)	0.650	0	4	1.00 (0.94, 1.07)	0.582	0
4	5	1.09 (0.91, 1.31)	0.037	60.9	5	0.99 (0.91, 1.07)	0.110	47.0
Male ratio, %								
≥50	6	1.15 (0.89, 1.49)	0.005	70.2	7	1.01 (0.93, 1.10)	0.060	50.3
<50	3	1.01 (0.93, 1.10)	0.603	0	3	1.00 (0.95, 1.07)	0.190	39.7
Treatment in the MM group								
IVT alone	6	1.04 (0.89, 1.22)	0.069	51.2	5	0.97 (0.92, 1.03)	0.249	25.9
IVT + other treatments	4	1.12 (0.89, 1.40)	0.059	59.6	5	1.05 (0.97, 1.15)	0.107	47.4

RR, risk ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; MM, medical management; IVT, intravenous thrombolysis; NA, not available. RR*: $p < 0.05$; RR**: $p < 0.01$.

population, but no association was found in other populations. One possible explanation for the result was that a large number of trials had been carried out in North America, and the technology of the experts there was better. Furthermore, the association between MT and functional prognosis was shown in the patients with a mean/median NIHSS score of 2 at admission, but no association was found in the patients with other scores at admission. The reason for that might be a statistically significant association reported by Haussen et al. [22], and their subjects were from USA with a mean/median NIHSS score of 2 at admission. Therefore, the subgroup variability is worth further studying in the future. The statistical stability and reliability were demonstrated by the sensitivity analysis and publication bias results.

Multiple studies have shown that recanalization was associated with improving functional prognosis in mild AIS patients [32–34]. In a recent study, Lau et al. [35] proposed that patients with mild AIS who were unlikely to recanalize without reperfusion therapies might be the ideal population for acute therapy. In theory, patients with severe perfusion deficit and failure of collaterals are more likely to benefit from MT, even if the NIHSS score is similar. As a result, it is crucial to identify the target population of MT by multimodal perfusion imaging.

Some limitations and shortages should be addressed. First, insufficient data from the eligible studies limited our subgroup analysis by other baseline characteristics, such

as occlusion site, onset to treatment time, and recanalization rate. Second, the lack of original data on patients receiving bridging therapy limited our further evaluation of the functional prognosis of bridging therapy and MT alone. Third, since all the studies included in the meta-analysis are retrospective, the lack of randomization and potential confounding should be considered when interpreting the results. Finally, sample size is still relatively small in the meta-analysis, especially in the subgroup analysis. Therefore, studies with larger sample size are needed in the future. Despite the limitations, our meta-analysis significantly increased the statistical power based on substantial data from different studies. Sensitivity analysis and publication bias outcomes both demonstrated that our results were statistically stable and reliable.

In conclusion, this study suggests that MT may be not associated with functional prognosis of mild AIS with LVO. This finding indicates that the use of MT in mild AIS with LVO should be considered carefully. Furthermore, multimodal perfusion imaging may play an important role in identifying the target population of MT. More studies with larger sample size are needed to reach a more definitive conclusion.

Acknowledgments

We thank all the participants in this study.

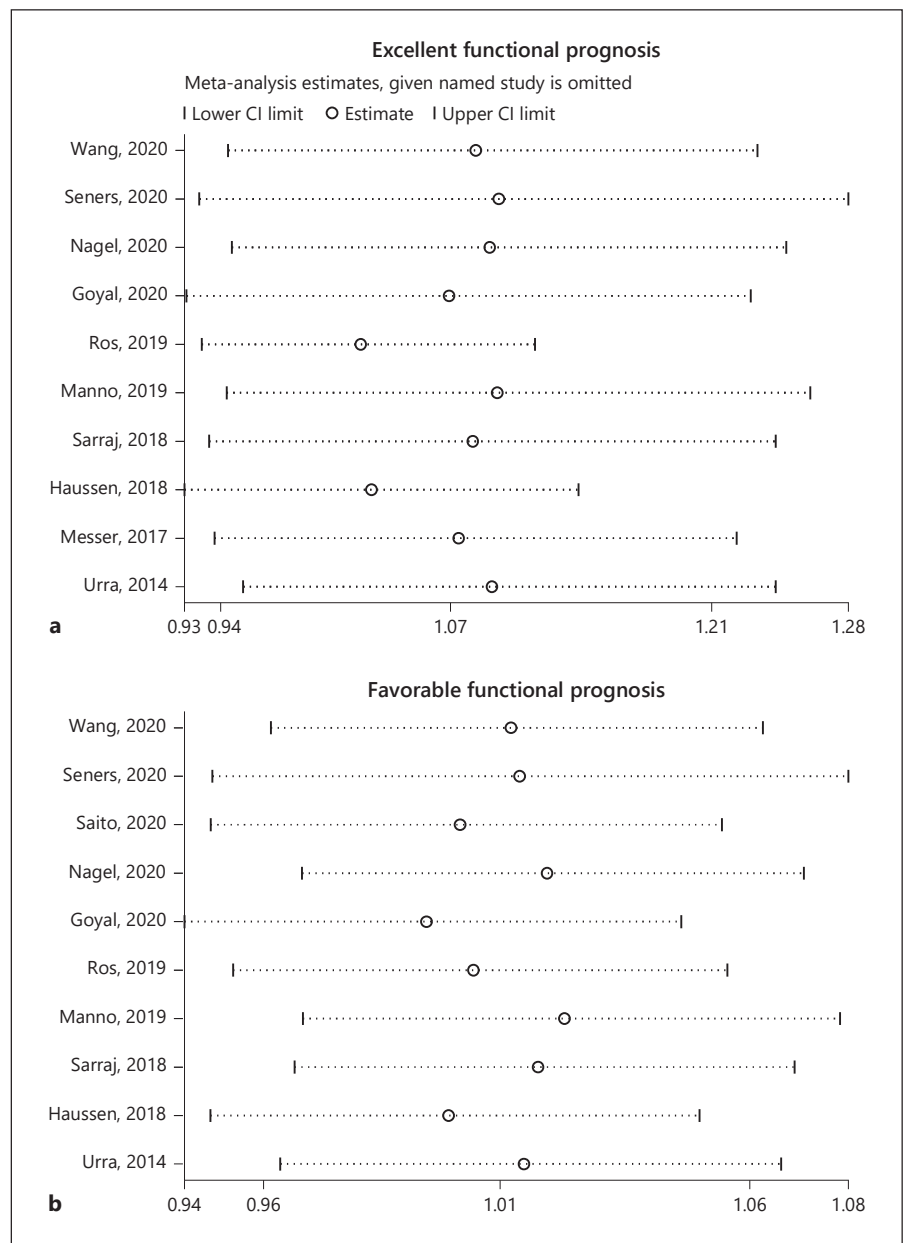


Fig. 3. a, b Sensitivity analysis of the RR of functional prognosis associated with MT for mild AIS with LVO.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The paper has no funder.

Author Contributions

Xiaowen Hou designed the study, wrote the first draft, and revised the manuscript. Xu Feng, Huixin Wang, and Qian Li searched the literature and conducted the data analysis.

Data Availability Statement

The data that support the findings of the study are available from the corresponding author.

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