

BMJ Open Sex differences in outcomes after mechanical thrombectomy for acute ischemic stroke in the 'real world': protocol for a systematic review and meta-analysis study

Lixin Xu ^{1,2}, Binglong Li,^{1,3} Xiao Zhang,¹ Xuesong Bai,¹ Adam Andrew Dmytriw ⁴, Tao Wang ¹, Xue Wang,⁵ Kun Yang ⁶, Xiaoli Min,^{1,7} Liqun Jiao ^{1,8}

To cite: Xu L, Li B, Zhang X, *et al.* Sex differences in outcomes after mechanical thrombectomy for acute ischemic stroke in the 'real world': protocol for a systematic review and meta-analysis study. *BMJ Open* 2022;**12**:e056025. doi:10.1136/bmjopen-2021-056025

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-056025>).

LX, BL and XZ contributed equally.

LX, BL and XZ are joint first authors.

Received 05 August 2021
Accepted 04 March 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Liqun Jiao; liqunjiao@sina.cn

ABSTRACT

Introduction Mechanical thrombectomy (MT) had been regarded as the first-line therapy for acute ischaemic stroke patients. The sex differences in post-MT treatment outcomes were analysed by randomised controlled trial (RCT) studies with inconsistent conclusions. We suggest the results from the real-world data may differ from RCT containing studies. Therefore, the sex difference in non-clinical trial populations needs to be clarified.

Methods and analysis In order to obtain relative studies comprehensively, we will search the main document databases, consisting of Web of Science, Medline in Ovid, Embase in Ovid and Cochrane Library, and trials registers, including Clinical Trails register. The clinical outcomes of real-world studies published between January 2015 and March 2022 will be included. The assessment methods of bias risk will be performed according to study type. The inclusion of studies, evaluation of risk and publication bias, data extraction will be implemented by two reviewers, respectively. The primary outcomes include successful recanalisation and 90-day favourable outcome. Secondary outcomes include vascular complication, hospital-related complications, death during hospital stay and follow-up, and intracerebral haemorrhage. The risk bias of observational studies will be evaluated by Newcastle-Ottawa Scale. I^2 statistic will be used to perform the assessment of study heterogeneity.

Ethics and dissemination With no need of ethics approval in this review, results in this review ground on public data. The results of the study will be eventually presented at international conferences or in a related journal.

PROSPERO registration number CRD42021242597.

BACKGROUND

Acute ischaemic stroke (AIS) has been a major concern of public health worldwide due to its high mortality and morbidity. Mechanical thrombectomy (MT) has been recommended as the first-line therapy for AIS patients with large vessel occlusion.¹ Whether sex influences the outcomes of MT remains uncertain. Sex

Strengths and limitations of this study

- The objective of the review study is exploring outcome differences between females and males in acute ischaemic stroke (AIS) patients receiving mechanical thrombectomy (MT) in the real-world setting.
- This study will provide the re-evaluation of sex differences for eligible AIS patients with a therapy of MT in non-clinical trial population, as randomised controlled trial based meta-analysis is limited by the strict inclusion/exclusion criteria.
- The outcomes with significant heterogeneity will be explored by subgroup analysis and sensitivity analysis.
- Applying meta-analytical methods of different outcomes will bring an inherent risk of uncertainty.

differences in outcomes after MT for acute large-vessel ischaemic stroke was analysed in several studies from randomised controlled trials (RCTs), showing either statistically insignificant treatment effects or mutually inconsistent results. For example, in the Multicentre Randomised Clinical Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR CLEAN), the analysis of sex-specific outcome demonstrated the superiority of endovascular thrombectomy over best medical management. There were no statistically significant treatment effects of EVT for women in terms of 90-day functional outcomes in MR CLEAN trial.² Previous subgroup analysis recruiting seven RCTs by Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) collaborators showed no influence of sex on clinical outcome after MT.³

While, in the 'real-world' populations, studies exploring sex differences in functional

outcomes after MT for large vessel occlusion strokes have controversial results. Some studies showed consistent results with the study of HERMES,⁴⁻⁶ but others demonstrated females are less likely to benefit from MT than males.^{7,8} A previous meta-analysis suggests that females have inferior 90-day clinical outcomes compared with males when undergoing endovascular thrombectomy for large-vessel occlusions, but both RCTs and observational studies were included.⁹ However, as results from the real-world data may differ from the RCTs, the sex difference in MT effectiveness in non-clinical trial populations needs to be clarified. Also, it could further assist clinicians and neuroradiologists worldwide identifying potential modifiable factors optimising poststroke outcomes of acute interventions during clinical practice.⁸ Thus, this systematic review and meta-analysis will explore sex differences in functional outcomes following MT in non-clinical trial AIS populations, hoping to provide a comprehensive view of MT outcomes in both males and females.

METHODS AND ANALYSIS

The protocol was drafted strictly abide by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (see online supplemental file 1, PRISMA-P Checklist). The review will be performed and reported following Meta-analyses of Observational Studies in Epidemiology.

Inclusion criteria for study selection

1. Real-world data contains observational study and pilot study. Observational study includes cohort study, case-control study, cross-sectional study and case series report.
2. All studies must be published in English.
3. Studies with the outcomes comparing sex (men vs women) and studies that outcome data can be extracted across men and women.

Participants

AIS patients due to acute anterior circulation stroke and aged ≥ 18 years old will be included. Cerebrovascular occlusion will be assessed using various imaging tests, including ultrasound, CT, CT angiography, MRI or MR angiography.

Intervention

MT treatment including stent retrieval, aspiration thrombectomy or combined approach will be included.

Outcomes

Any information associated with postintervention condition will be documented.

Primary outcomes consist of successful recanalisation and 90-day favourable outcome. Successful recanalisation can be graded by modified Thrombolysis in Cerebral Infarction scale (mTICI). An mTICI score of 2b-3 is considered as successful recanalisation. A 90-day

favourable outcome is defined as modified Rankin score ≤ 2 or equivalent to pre-morbid value.

Secondary outcomes include vascular complications (perforation, dissection and vasospasm), hospital-related complications, death during hospital stay and follow-up, and intracerebral haemorrhage. Intracerebral haemorrhage was evaluated by European Cooperative Acute Stroke Study classification. The symptomatic intracerebral haemorrhage was confirmed if National Institutes of Health Stroke Scale score increased four points at least during 24 hours before intervention,

Studies

All studies included in this systematic review will be non-RCT studies, including case-control study, cohort study and registry study. Only studies originally published in English will be considered. The inclusion criteria of literatures for this review will be studies with the outcomes comparing sex (men vs women) and studies that outcome data can be extracted across men and women.

Exclusion criteria for study selection

1. Studies published before 1 January 2015 will be excluded to obtain the clinical outcomes of modern thrombectomy devices.
2. Studies that fail to report the above outcomes and with outcome data that cannot be extracted or are not available will be excluded.
3. If the sample size of real-world study is less than 5, the study will be excluded.
4. Conference reports, abstracts, case reports, editorials, comments and reviews will also be excluded.

Search strategy

This meta-analysis will be conducted in accordance with the search strategies. The search will be carried out to screen suitable literature in the main electronic bibliographic databases, which include PubMed, the Cochrane library, EMBASE and Web of Science. We will review all relevant articles reporting sex differences in functional outcomes following MT in real-world studies for AIS populations. All studies published before 1 October 2021 will be reviewed. We will formulate the search strategy specific to each searched database, and it will be based on terms such as “acute ischemic stroke,” “mechanical thrombectomy,” “stent retrieval thrombectomy,” “stent retriever,” “sex,” “female” and “male”. When drafting and revising this search strategy, we will meet the standards of the Peer Review of Electronic Search Strategies checklist. (online supplemental file 2, search strategy)

Data selection and analysis

Inclusion of studies

The first selection of research reports will depend mainly on the title and abstract, and two reviewers (BL and XZ) familiar with research in the field of thrombectomy will conduct it independently. Their selections will be cross-checked, and a third reviewer (XB) will be inquired in

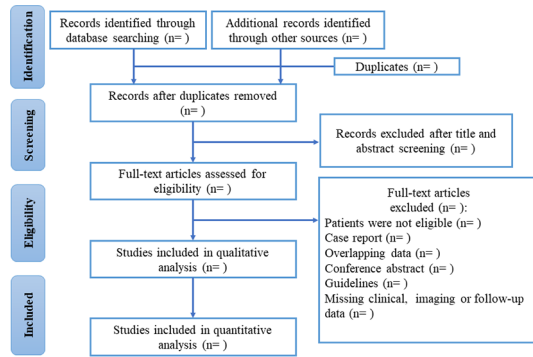


Figure 1 Flow diagram of literature for systematic review and meta-analysis.

the event of any discrepancy between two reviewers. The inclusion flow is presented in [figure 1](#).

Data selection and management

When initial selection is finished, the second stage of selection will also be performed by two independent reviewers (LX and TW). They will use EndNote V.X9 software (Clarivate Analytics, Philadelphia, Pennsylvania, USA) for processing the literature. In this stage, not only the titles and abstracts but also the full texts of reports will be reviewed. The reviewers will evaluate relevant studies on the basis of criteria such as study type, demographic characteristics, imaging characteristics, intervention techniques and outcome evaluation. Both the primary and secondary outcomes will be assessed and documented separately. A formal chart will be designed for data documentation. In the event of any disagreement between the two reviewers about study screening or data extraction, a group discussion among all team members will be held for the final decision.

Assessment of risk bias

Two independent reviewers (XW and KY) will conduct assessment of the risk bias in the studies selected during the second stage. One risk bias tool of the Newcastle-Ottawa Scale will be adopted to assess the quality of observational studies (see online supplemental file 3). The score of 5–9 points will be deemed to high-quality evidence. Any disagreement between the two reviewers will be addressed first by discussion, and may be consulted with the team for discussion when necessary.

Data analysis

Data analysis for the effect of each specific variable on thrombectomy outcomes will be practical only when at least two studies are accessible. The statistical software of Stata (V.17.0, StataCorp) will be used for analysing data. Presentation of the results will depend on the outcome variables. Continuous variables are presented as standardised mean difference, and dichotomous variables are relative risk, respectively. The reporting of final results will be accompanied by 95% CIs. For significant heterogeneity of outcomes, the random-effects model will be applied, but a fixed-effects model will be applied when

little evidence of heterogeneity ($I^2 < 20\%$) exists. The inclusion of covariates, such as age and comorbidities, could dramatically change the sex effects. Therefore, we will plan to include covariates into any of the models. If there are insufficient studies for some variables, we will consider formulating a narrative description of the particular factors. If studies have data that are unsuitable for extraction and analysis but appear to possibly offer meaningful results for a specific variable, the principal authors of relevant studies will be contacted through email in an effort to obtain the original data. If there is no response, we will try to contact again, and if there remains no response, we will document the situation. Subgroup analysis will be performed based on characteristics such as race and region, if this is practical. If there are sufficient studies for its construction and publication bias also exists, we will apply funnel plot to evaluate it.

Patient and public involvement

No patient and public involved.

DISCUSSION

A number of landmark RCTs and the HERMES meta-analysis of five RCTs proved that MT is superior than IV-tPA in treating AIS with large vessel occlusion patients. Moreover, a recent systematic review based on the background that MT plus best medical therapy (BMT) is superior over BMT alone in terms of functional outcomes in AIS patients due to large vessel occlusion.¹⁰ Under the influences of the increasing results, MT is currently considered to be the first-line treatment for AIS patients with large vessel occlusion. This systematic review clarified the benefit of MT plus BMT on 3-month mortality and presented in the meta-regression analyses that no moderating effect on the aforementioned association was detected with sex. Regarding the sex difference of MT treated patients, according to the potential cellular mechanisms of brain recovery, it has been proposed that females may exhibit worse outcome from MT treated eligible AIS patients. However, while the comparison through the subgroup analysis from seven RCTs showed no statistical differences of clinical outcomes on sex for MT treated eligible AIS patients, the past and newly published, mostly non-clinical trial researches, provided inconsistent results on this subject. Therefore, in addition to results of meta-analyses that only included RCTs, it remains necessary to analyse in the ‘real-world population’ whether the outcomes differ between females and males in MT treated eligible AIS patients. This work would clarify the outcome differences, and provide valuable evidence for clinicians and neuroradiologists worldwide for clinical decision making, treatment plan optimising and poststroke outcome predicting.

ETHICS AND DISSEMINATION

This protocol is the plan of steps to be followed for a systematic review, which aim to be presented at relatively



academic conferences and published in a peer-reviewed journal. The results of the study are based on published studies, therefore, no ethics approval is needed.

Author affiliations

¹Department of Neurosurgery, Xuanwu Hospital Capital Medical University, Beijing, People's Republic of China

²China International Neuroscience Institute (China-INI), Beijing, People's Republic of China

³Department of Emergency, The Third Hospital of Jinan, Jinan, Shandong, People's Republic of China

⁴Neuroendovascular Program, Massachusetts General Hospital, Boston, Massachusetts, USA

⁵Medical Library, Xuanwu Hospital Capital Medical University, Beijing, People's Republic of China

⁶Department of Evidence-based Medicine, Xuanwu Hospital Capital Medical University, Beijing, People's Republic of China

⁷Department of Cerebrovascular Diseases, The Second Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, People's Republic of China

⁸Department of Interventional Neuroradiology, Xuanwu Hospital Capital Medical University, Beijing, People's Republic of China

Contributors XM and LJ developed the initial idea for this study. XZ and BL developed and revised the search strategy. LX and XZ finished the study design. LJ were consulted about clinical issues. LX, XZ and BL contributed to the original draft. XW, KY and TW contributed to the methods revision. LX, AAD and XB were responsible for the revision of the draft. LX, BL and XZ contributed equally to this article. All the authors approved the final work prior to submission.

Funding The study is supported by Natural Science Foundation of China (grant number: 82171303).

Disclaimer The funder has no role in study design, data analysis and writing the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines,

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Lixin Xu <http://orcid.org/0000-0003-2208-018X>

Adam Andrew Dmytriw <http://orcid.org/0000-0003-0131-5699>

Tao Wang <http://orcid.org/0000-0003-1225-0173>

Kun Yang <http://orcid.org/0000-0002-6459-9185>

Liqun Jiao <http://orcid.org/0000-0003-4982-6295>

REFERENCES

- 1 Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2019;50:e344–418.
- 2 de Ridder IR, Franssen PSS, Beumer D, *et al*. Is intra-arterial treatment for acute ischemic stroke less effective in women than in men? *Interv Neurol* 2016;5:174–8.
- 3 Chalos V, de Ridder IR, Lingsma HF, *et al*. Does sex modify the effect of endovascular treatment for ischemic stroke? *Stroke* 2019;50:2413–9.
- 4 Deb-Chatterji M, Schlemm E, Flottmann F, *et al*. Sex differences in outcome after thrombectomy for acute ischemic stroke are explained by confounding factors. *Clin Neuroradiol* 2021;31:1101–9.
- 5 Ciardi C, Cirio JJ, Scrivano EV, *et al*. Sex-Related Differences after Endovascular Treatment of Acute Ischemic Stroke in the 'Real World'. *J Stroke Cerebrovasc Dis* 2020;29:105240.
- 6 Carvalho A, Cunha A, Gregório T, *et al*. Is the efficacy of endovascular treatment for acute ischemic stroke sex-related. *Interv Neurol* 2018;7:42–7.
- 7 Uchida K, Yoshimura S, Sakai N, *et al*. Sex differences in management and outcomes of acute ischemic stroke with large vessel occlusion. *Stroke* 2019;50:1915–8.
- 8 Madsen TE, DeCrose-Movson E, Hemendinger M, *et al*. Sex differences in 90-day outcomes after mechanical thrombectomy for acute ischemic stroke. *J Neurointerv Surg* 2019;11:221–5.
- 9 Dmytriw AA, Ku JC, Yang VXD, *et al*. Do outcomes between women and men differ after endovascular thrombectomy? A meta-analysis. *AJNR Am J Neuroradiol* 2021;42:910–5.
- 10 Katsanos AH, Malhotra K, Goyal N, *et al*. Mortality risk in acute ischemic stroke patients with large vessel occlusion treated with mechanical thrombectomy. *J Am Heart Assoc* 2019;8:e014425.