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Sex differences in Outcomes After Mechanical Thrombectomy for Acute Ischemic Stroke In the 'Real World'——protocol for a systematic review and meta-analysis study

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Abstract

Introduction

Since the mechanical thrombectomy (MT) has been proved to be a superior treatment over intravenous tissue-type plasminogen activator (IV-tPA) for acute ischemic stroke (AIS) patients, it had been regarded as the first-line treatment. The analyses of sex differences in post MT treatment outcomes were analyzed by 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

This protocol was drafted using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement. Herein, major databases will be searched, including Medline, Web of Science, Embase and the Cochrane Library, and high-quality observational studies will be included. We will screen all studies published from January 2015 to October 2021. Bias risk will be evaluated using the Cochrane Collaboration criteria or Methodological Index for Non-randomised Studies criteria, depending on the study type. Two reviewers will select eligible studies and extract the data independently. The primary outcome will include stroke or death during the perioperative period and follow-up. Subgroup and sensitivity analyses will be performed to explore any potential heterogeneity. Specific results will be described in a narrative form when available eligible studies are insufficient for meta-analysis. Publication bias will be assessed using funnel plot.

Ethics and dissemination

This study will summarize and analyze the existing literature; hence, ethics approval will not be required. The results may be published at a relevant academic conference or journal.

PROSPERO registration number: CRD42021242597

Keyword: acute ischemic stroke, mechanical thrombectomy, sex differences, systematic review, meta-analysis

Article Summary

Strengths and limitations of this study

- This protocol of systematic review and meta-analysis will state the plan for analyzing the outcome differences between females and males in eligible acute ischemic stroke patients treated by mechanical thrombectomy.
- Due to the inconsistent results of published researches including clinical trials, non-clinical trial studies and meta-analysis, the re-evaluation of sex differences for eligible acute ischemic stroke patients treated by mechanical thrombectomy in non-clinical trial population is needed.
- Subgroup analysis will be used when there is significant evidence of heterogeneity.
- Polling these data is at risk of inherent uncertainty due to different outcomes and methods used.

BACKGROUND

Acute ischemic stroke (AIS), a common cause of mortality and morbidity, has been a major concern of public health worldwide. The superiority of mechanical thrombectomy (MT) over intravenous tissue-type plasminogen activator (IV-tPA) in treating AIS patients has been proved by several landmark randomized clinical trials (RCTs),[1-3] and it has been further consolidated by a meta-analysis of five RCTs by the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaborators.[4] So, MT has already been regarded as the first-line treatment for AIS.

It has been proposed males and females may exhibit sex differences in cellular mechanisms of brain recovery.[5] Also, different outcomes were observed in males and females after receiving intra-arterial thrombolysis among studies.[6 7] Compared with males, females have worse functional outcomes after stroke in some studies.[8 9] On the other hand, previous subgroup analysis recruiting 7 RCTs by HERMES collaborators showed no influence of sex on clinical outcome after MT.[10] 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,[11-13] but others demonstrated females are less likely to benefit from MT than males.[14 15] Previous meta-analysis investigating endovascular treatment outcomes between women and men included both RCTs and observational studies suggests that females have inferior 90-day clinical outcomes comparing with males when undergoing endovascular thrombectomy for large-vessel occlusions.[16] 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 optimizing post-stroke outcomes of acute interventions during clinical practice.[15] 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

This systematic review has been registered in the International Prospective Register of Systematic Reviews (CRD42021242597) and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and Meta-analyses of Observational Studies in Epidemiology (MOOSE). (see **Supplementary file 1, PRISMA-P Checklist**)

Inclusion criteria for study selection

1. Real-world data such as high-quality case–control study or cohort study.
2. All studies must be published in English.
3. Studies with the outcomes comparing sex (females versus males) or studies that outcome data can be extracted according to sex.

Participants

AIS patients due to acute anterior circulation and aged ≥ 18 years old will be included. Initiation of intra-arterial treatment had to be possible within 24 hours after stroke onset. Cerebrovascular occlusion will be assessed using various imaging tests, including ultrasound, computed tomographic angiography (CTA), magnetic resonance angiography (MRA), digital subtraction angiography (DSA).

Intervention

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

Outcomes

At least one of the following items will be reported.

Primary outcomes

1. Successful revascularization defined as a modified Thrombolysis in Cerebral Infarction scale (mTICI) of 2b, 2c and/or 3 (Any mTICI 2b or greater), which was determined by post-interventional DSA. Any mTICI of 2b or greater suggests a partial or complete revascularization in one or more operative attempts or passes.

2. Favorable outcome defined as modified Rankin score (mRS) ≤ 2 or equal to the pre-stroke score at the 3-month follow-up

3. Good outcome defined as mRS ≤ 3 or equal to the pre-stroke score at the 3-month follow-up

Secondary outcome

1. Death during hospitalization

2. Hospital-related complications including pneumonia, deep vein thrombosis, urinary tract infection, and other infections

3. Intracerebral hemorrhage (ICH) classified according to the European Cooperative Acute Stroke Study (ECASS) classification, including hemorrhagic infarction, parenchymal hemorrhage, subarachnoid hemorrhage. ICH considered symptomatic if related with a minimum increase of 4 points on the National Institutes of Health Stroke Scale (NIHSS) score within 24 hours post-intervention, according to the second European Australasian Acute Stroke Study classification or National Institute of Neurological Disorders and Stroke criteria

4. Mortality at the 3-month follow-up

5. Procedure-related and device-related serious adverse events, including:

a. vascular perforation

b. arterial dissection

c. embolization to a new territory

Studies

All studies included in this systematic review will be non-RCT studies. 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 (females versus males)

or studies that outcome data can be extracted according to sex.

Exclusion criteria for study selection

1. Studies published before January 1, 2015 will be excluded to obtain the clinical outcomes of modern thrombectomy devices.
2. Studies omitting the report of the above outcomes or studies where extraction of data for the analysis of complications was impossible will be excluded.
3. Observational studies with a sample size of less than 10, conference reports, abstracts, case reports, editorials, comments, and reviews will be excluded.

Search strategy

This meta-analysis will be performed in accordance with the search strategies. The search will be carried out to screen suitable literature in the main electronic bibliographic databases of Medline, 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 October 1 2021, will be reviewed. An explicit search strategy will be designed for each 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. (see **Supplementary file 2**, Search strategy)

Data selection and analysis

Selection of studies

The first screening of research reports will depend mainly on the titles and abstracts, and it will be conducted by two independent reviewers (B Li and X Zhang) familiar with research in the field of thrombectomy. Their selections will be cross-checked, and a third reviewer (X Bai) will be inquired in the event of any discrepancy between the two reviewers. The screening process is shown in **Figure 1.**

Data extraction and management

After the initial screening, the second stage of selection will also be performed by two independent reviewers (L Xu and T Wang). They will use EndNote X7 software (Clarivate Analytics, Philadelphia, PA, USA) to manage 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 numbers will be held for the final decision.

Assessment of risk bias

Two independent reviewers (X Wang and K Yang) will conduct assessment of the risk bias in the studies selected during the second stage. One risk bias tool, namely, the Newcastle-Ottawa Scale (NOS), will be adopted for observational studies with high quality (see **Supplementary file 3**). Studies with scores of 5-9 points will be considered as 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 data analysis will be conducted by using Stata (version 15.0, Stata Corp, College Station, TX, USA). Presentation of the results will depend on the outcome variables and will include standardized mean difference (SMD) for continuous outcomes and relative risk (RR) for dichotomous outcomes. The reporting of final results will be accompanied by 95%

confidence intervals (CIs). A random-effects model will generally be utilized for data analysis, but a fixed-effects model will be applied when there is little evidence of heterogeneity ($I^2 < 20\%$). 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, we will try to contact the authors of the relevant reports through e-mail 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. Publication bias will also be evaluated using a funnel plot of if there are sufficient studies.

Patient and public involvement

As the present study is a systematic review based on published data, patient and public are not involved in the study design, conduct, data analysis and result dissemination.

DISCUSSION

This study aims to summarize the current literature and compare outcomes of eligible AIS patients treated by MT between males and females. A number of landmark randomized clinical trials (RCTs) and the HERMES meta-analysis of five RCTs proved that MT is superior than IV-tPA in treating AIS patients. Therefore, MT is currently regarded as the first-line treatment for AIS. 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 7 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, it remains necessary to analyze 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 optimizing and post-stroke outcome predicting.

ETHICS AND DISSEMINATION

There is no need for ethical approval because primary data will not be obtained. The systematic review will be presented at international conferences and published in peer-reviewed journals.

Author Contributors

LJ and XM 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. LX and TW were responsible for the revision of the draft. LX and BL contributed equally to this article. All the authors approved the final work prior to submission.

Funding statement None declared.

Competing interests None declared.

Patient consent Not required.

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Figure Legends

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

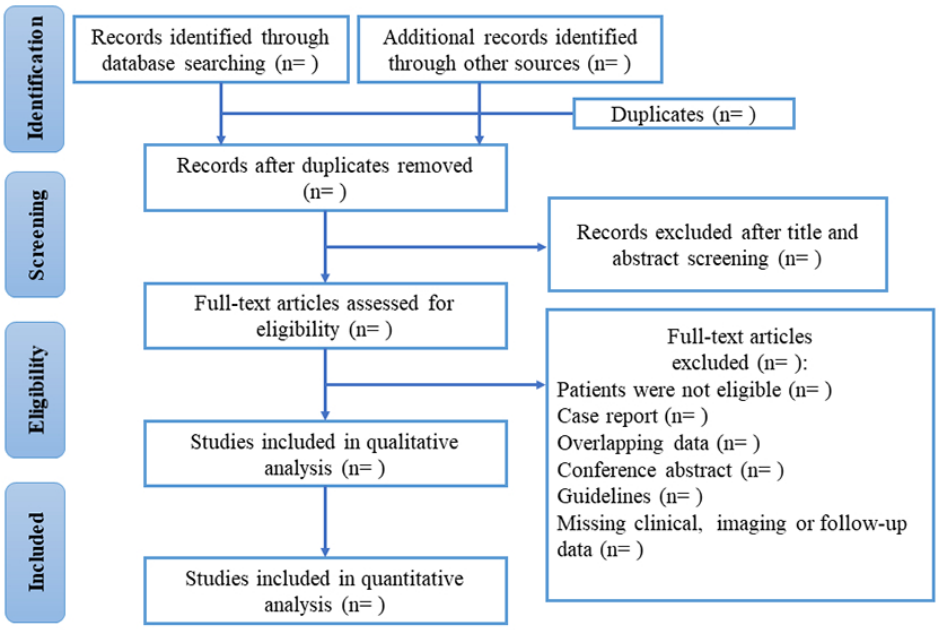

Figure 1 Flow diagram of literature for systematic review and meta-analysis.

75x56mm (300 x 300 DPI)

Supplementary file 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check results
ADMINISTRATIVE INFORMATION			
Title:			P1, L1-2
Identification	1a	Identify the report as a protocol of a systematic review	Yes
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Yes
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes P2, L24
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes P1, L4-19
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes P7, L28-32
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes
Support:			P7, L33-34
Sources	5a	Indicate sources of financial or other support for the review	Yes
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes

Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes P4, L2-33
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes P4, L33-36
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes P5, L2-36
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes P5, L39-41
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes Supplementary file 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes P6, L15
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes P6, L8-12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes P6, L16

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes P5, L21-27
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes P5, L30-36
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes P6, L27-33
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes P6, L36-37
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes P6, L37-43
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes P6, L43-P7, L1
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes P6, L40-41
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes P6, L41-43
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes P6, L28-30

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

- **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) from 1946 to July 31, 2021**

No.	Searches
1	cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp brain infarction/ or exp carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2	(isch?emi$ adj5 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or brain vasc$ or cva or attack$)).tw.
3	((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or MCA or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4	1 or 2 or 3
5	carotid artery, internal/
6	carotid artery thrombosis/ or carotid stenosis/ or arterial occlusive diseases/ or exp arteriosclerosis/ or constriction, pathologic/
7	5 and 6
8	((internal carotid or ICA or tandem) adj5 (stenos?s or occlus$ or occlud$ or thrombo$ or narrow$ or plaque$ or constrict$ or emboli$ or block$ or arteriosclero$ or atherosclero$ or atheroma$ or isch?emi$ or infarct$ or insufficien$ or obstruct$)).tw.
9	7 or 8
10	endovascular procedures/ or catheterization/ or angioplasty/ or exp angioplasty, balloon/
11	vascular surgical procedures/ or exp thrombectomy/ or exp embolectomy/
12	exp stents/
13	(angioplast$ or stent$ or pta or revasculari?ation or recanali?ation or catheter$ or dilatation or thromboaspirat$ or thrombo-aspirat$ or thrombecto$ or embolecto$).tw.
14	((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragmentation or retract$ or extract$ or obliterat$ or dispers$)).tw.
15	((mechanical or pharmacomechanical or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspirat$)).tw.
16	thrombolytic therapy/ or fibrinolytic agents/ or tissue plasminogen activator/ or exp plasminogen activators/ or fibrinolysis/

17	(thromboly$ or fibrinoly$ or recanali?ation).tw.
18	((clot or thrombus or thrombi or embol$) adj5 (lyse or lysis or dissolve$ or dissolution)).tw.
19	(tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
20	(anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or retevase).tw.
21	16 or 17 or 18 or 19 or 20
22	infusions, intra-arterial/
23	(intra arterial or intra-arterial or intraarterial or IA).tw.
24	22 or 23
25	21 and 24
26	10 or 11 or 12 or 13 or 14 or 15 or 25
27	4 and 9 and 26

Supplementary file 3

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Note: 1 ✸ means 1 point, and studies with scores of 0–4 points were identified as low quality and 5–9 points as high quality and only high-quality literature will be in our analysis.

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

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Sex differences in Outcomes After Mechanical Thrombectomy for Acute Ischemic Stroke In the 'Real World'——protocol for a systematic review and meta-analysis study

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Abstract

Introduction

Mechanical thrombectomy (MT) had been regarded as the first-line treatment for acute ischemic stroke (AIS) patients due to large vessel occlusion. The sex differences in post MT treatment outcomes were analyzed by 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

This protocol was drafted using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement. Herein, major databases will be searched, including Medline, Web of Science, Embase and the Cochrane Library, and high-quality observational studies will be included. We will screen all studies published from January 2015 to October 2021. Bias risk will be evaluated using the Cochrane Collaboration criteria or Methodological Index for Non-randomised Studies criteria, depending on the study type. Two reviewers will select eligible studies and extract the data independently. The primary outcome will include stroke or death during the perioperative period and follow-up. Subgroup and sensitivity analyses will be performed to explore any potential heterogeneity. Specific results will be described in a narrative form when available eligible studies are insufficient for meta-analysis. Publication bias will be assessed using funnel plot.

Ethics and dissemination

This study will summarize and analyze the existing literature; hence, ethics approval will not be required. The results may be published at a relevant academic conference or journal.

PROSPERO registration number: CRD42021242597

Keyword: acute ischemic stroke, mechanical thrombectomy, sex differences, systematic review, meta-analysis

Article Summary

Strengths and limitations of this study

- This protocol of systematic review and meta-analysis will state the plan for analyzing the outcome differences between females and males in eligible acute ischemic stroke patients treated by mechanical thrombectomy.
- Randomized Controlled Trial based meta-analysis is limited by the strict inclusion/exclusion criteria and that ensures the internal validity while reduces the external validity of the study.
- This study will provide the re-evaluation of sex differences for eligible acute ischemic stroke patients treated by mechanical thrombectomy in non-clinical trial population.
- Subgroup analysis will be used when there is significant evidence of heterogeneity.
- Polling these data is at risk of inherent uncertainty due to different outcomes and methods used.

BACKGROUND

Acute ischemic stroke (AIS), a common cause of mortality and morbidity, has been a major concern of public health worldwide. Sex differences in outcomes after mechanical thrombectomy (MT) for acute large-vessel ischemic stroke was analyzed in several studies including randomized clinical trials (RCTs), observational studies, as well as Meta-analysis that assessed RCTs. These studies concluded with either statistically insignificant treatment effects or mutually inconsistent results. For example, sex specific outcome analysis of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), that demonstrated the superiority of endovascular thrombectomy over best medical management, showed that there were no statistically significant treatment effects of EVT for women in terms of 90-day functional outcomes.[1]

On the other hand, different outcomes were observed in males and females after receiving intra-arterial thrombolysis among studies. Compared with males, females have worse functional outcomes after stroke in some studies.[2 3] Previous subgroup analysis recruiting 7 RCTs by HERMES collaborators showed no influence of sex on clinical outcome after MT.[4] 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,[5-7] but others demonstrated females are less likely to benefit from MT than males.[8 9] Previous meta-analysis investigating endovascular treatment outcomes between women and men included both RCTs and observational studies suggests that females have inferior 90-day clinical outcomes comparing with males when undergoing endovascular thrombectomy for large-vessel occlusions.[10] Moreover, not only studies on sex differences after intra-arterial thrombolysis, but also after intra-venous thrombolysis reveals such result.[11] 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 optimizing post-

stroke outcomes of acute interventions during clinical practice.[9] 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

This systematic review has been registered in the International Prospective Register of Systematic Reviews (CRD42021242597) and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and Meta-analyses of Observational Studies in Epidemiology (MOOSE). (see **Supplementary file 1, PRISMA-P Checklist**)

Inclusion criteria for study selection

1. Real-world data such as high-quality case–control study, cohort study or registry study.
2. All studies must be published in English.
3. Studies with the outcomes comparing sex (men versus women) and studies that outcome data can be extracted across men and women.

Participants

AIS patients due to acute anterior circulation and aged ≥ 18 years old will be included. Initiation of intra-arterial treatment had to be possible within 24 hours after stroke onset. Cerebrovascular occlusion will be assessed using various imaging tests, including ultrasound, computed tomographic angiography (CTA), magnetic resonance angiography (MRA), digital subtraction angiography (DSA).

Intervention

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

Outcomes

At least one of the following items will be reported.

Primary outcomes

1. Successful revascularization defined as a modified Thrombolysis in Cerebral Infarction scale (mTICI) of 2b, 2c and/or 3 (Any mTICI 2b or greater), which was determined by post-interventional DSA. Any mTICI of 2b or greater suggests a partial or complete revascularization in one or more operative attempts or passes.

2. Favorable outcome defined as modified Rankin score (mRS) ≤ 2 or equal to the pre-stroke score at the 3-month follow-up

3. Good outcome defined as mRS ≤ 3 or equal to the pre-stroke score at the 3-month follow-up

Secondary outcome

1. Death during hospitalization

2. Hospital-related complications including pneumonia, deep vein thrombosis, urinary tract infection, and other infections

3. Intracerebral hemorrhage (ICH) classified according to the European Cooperative Acute Stroke Study (ECASS) classification, including hemorrhagic infarction, parenchymal hemorrhage, subarachnoid hemorrhage. ICH considered symptomatic if related with a minimum increase of 4 points on the National Institutes of Health Stroke Scale (NIHSS) score within 24 hours post-intervention, according to the second European Australasian Acute Stroke Study classification or National Institute of Neurological Disorders and Stroke criteria

4. Mortality at the 3-month follow-up

5. Procedure-related and device-related serious adverse events, including:

   a. vascular perforation

   b. arterial dissection

   c. embolization to a new territory

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 versus women) and studies that outcome data can be extracted across men and women.

Exclusion criteria for study selection

1. Studies published before January 1, 2015 will be excluded to obtain the clinical outcomes of modern thrombectomy devices.
2. Studies omitting the report of the above outcomes or studies where extraction of data for the analysis of complications was impossible will be excluded.
3. Observational studies with a sample size of less than 10, conference reports, abstracts, case reports, editorials, comments, and reviews will be excluded.

Search strategy

This meta-analysis will be performed in accordance with the search strategies. The search will be carried out to screen suitable literature in the main electronic bibliographic databases of Medline, 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 October 1 2021, will be reviewed. An explicit search strategy will be designed for each 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. (see **Supplementary file 2**, Search strategy)

Data selection and analysis

Selection of studies

The first screening of research reports will depend mainly on the titles and abstracts, and it will be conducted by two independent reviewers (B Li and X Zhang) familiar with research in the field of thrombectomy. Their selections will be cross-checked, and a third reviewer (X Bai) will be inquired in the event of any discrepancy between the two reviewers. The screening process is shown in **Figure 1.**

Data extraction and management

After the initial screening, the second stage of selection will also be performed by two independent reviewers (L Xu and T Wang). They will use EndNote X7 software (Clarivate Analytics, Philadelphia, PA, USA) to manage 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 numbers will be held for the final decision.

Assessment of risk bias

Two independent reviewers (X Wang and K Yang) will conduct assessment of the risk bias in the studies selected during the second stage. One risk bias tool, namely, the Newcastle-Ottawa Scale (NOS), will be adopted for observational studies with high quality (see **Supplementary file 3**). Studies with scores of 5-9 points will be considered as 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 data analysis will be conducted by using Stata (version 15.0, Stata Corp, College Station, TX, USA). Presentation of the results will depend on the outcome variables and will include standardized mean difference (SMD) for continuous outcomes and relative risk (RR) for dichotomous outcomes. The reporting of final results will be accompanied by 95% confidence intervals (CIs). A random-effects model will generally be utilized for data analysis, but a fixed-effects model will be applied when there is little evidence of heterogeneity ($I^2 < 20\%$). 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, we will try to contact the authors of the relevant reports through e-mail 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. Publication bias will also be evaluated using a funnel plot of if there are sufficient studies.

Patient and public involvement

As the present study is a systematic review based on published data, patient and public are not involved in the study design, conduct, data analysis and result dissemination.

DISCUSSION

This study aims to summarize the current literature and compare outcomes of eligible AIS patients treated by MT between males and females. A number of landmark randomized clinical trials (RCTs) and the HERMES meta-analysis of five RCTs proved that MT is superior than IV-tPA in treating AIS patients. Therefore, MT is currently regarded as the first-line treatment for AIS. 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 7 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, it remains necessary to analyze 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 optimizing and post-stroke outcome predicting.

ETHICS AND DISSEMINATION

There is no need for ethical approval because primary data will not be obtained. The systematic review will be presented at international conferences and published in peer-reviewed journals.

Author Contributors

Liqun Jiao and Xiaoli Min developed the initial idea for this study. Xiao Zhang and Binglong Li developed and revised the search strategy. Lixin Xu and Xiao Zhang finished the study design. Liqun Jiao were consulted about clinical issues. Lixin Xu, Xiao Zhang and Binglong Li contributed to the original draft. Xue Wang, Kun Yang and Tao Wang contributed to the methods revision. Lixin Xu, Adam A. Dmytriw, and Xuesong Bai were responsible for the revision of the draft. Lixin Xu, Binglong Li and Xiao Zhang contributed equally to this article. All the authors approved the final work prior to submission.

Funding statement None declared.

Competing interests None declared.

Patient consent Not required.

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Online First: 2020/10/18]

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Figure Legends

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

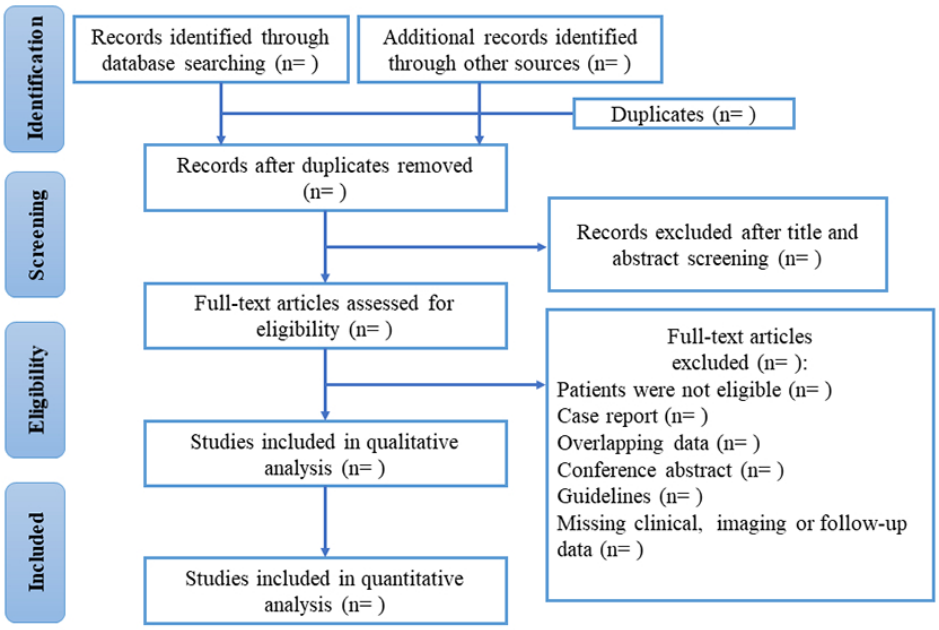

Figure 1 Flow diagram of literature for systematic review and meta-analysis.

75x56mm (300 x 300 DPI)

Supplementary file 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check results
ADMINISTRATIVE INFORMATION			
Title:			P1, L1-2
Identification	1a	Identify the report as a protocol of a systematic review	Yes
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Yes
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes P2, L24
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes P1, L4-19
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes P7, L28-32
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes
Support:			P7, L33-34
Sources	5a	Indicate sources of financial or other support for the review	Yes
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes

Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes P4, L2-33
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes P4, L33-36
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes P5, L2-36
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes P5, L39-41
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes Supplementary file 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes P6, L15
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes P6, L8-12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes P6, L16

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes P5, L21-27
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes P5, L30-36
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes P6, L27-33
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes P6, L36-37
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes P6, L37-43
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes P6, L43-P7, L1
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes P6, L40-41
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes P6, L41-43
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes P6, L28-30

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

- **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) from 1946 to July 31, 2021**

No.	Searches
1	cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp brain infarction/ or exp carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2	(isch?emi$ adj5 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or brain vasc$ or cva or attack$)).tw.
3	((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or MCA or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4	1 or 2 or 3
5	carotid artery, internal/
6	carotid artery thrombosis/ or carotid stenosis/ or arterial occlusive diseases/ or exp arteriosclerosis/ or constriction, pathologic/
7	5 and 6
8	((internal carotid or ICA or tandem) adj5 (stenos?s or occlus$ or occlud$ or thrombo$ or narrow$ or plaque$ or constrict$ or emboli$ or block$ or arteriosclero$ or atherosclero$ or atheroma$ or isch?emi$ or infarct$ or insufficien$ or obstruct$)).tw.
9	7 or 8
10	endovascular procedures/ or catheterization/ or angioplasty/ or exp angioplasty, balloon/
11	vascular surgical procedures/ or exp thrombectomy/ or exp embolectomy/
12	exp stents/
13	(angioplast$ or stent$ or pta or revasculari?ation or recanali?ation or catheter$ or dilatation or thromboaspirat$ or thrombo-aspirat$ or thrombecto$ or embolecto$).tw.
14	((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragmentation or retract$ or extract$ or obliterat$ or dispers$)).tw.
15	((mechanical or pharmacomechanical or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspirat$)).tw.
16	thrombolytic therapy/ or fibrinolytic agents/ or tissue plasminogen activator/ or exp plasminogen activators/ or fibrinolysis/

17	(thromboly$ or fibrinoly$ or recanali?ation).tw.
18	((clot or thrombus or thrombi or embol$) adj5 (lyse or lysis or dissolve$ or dissolution)).tw.
19	(tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
20	(anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or retevase).tw.
21	16 or 17 or 18 or 19 or 20
22	infusions, intra-arterial/
23	(intra arterial or intra-arterial or intraarterial or IA).tw.
24	22 or 23
25	21 and 24
26	10 or 11 or 12 or 13 or 14 or 15 or 25
27	4 and 9 and 26

Supplementary file 3

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Note: 1 ✸ means 1 point, and studies with scores of 0–4 points were identified as low quality and 5–9 points as high quality and only high-quality literature will be in our analysis.

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

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Primary Subject Heading:	Neurology
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Sex differences in Outcomes After Mechanical Thrombectomy for Acute Ischemic Stroke In the 'Real World'——protocol for a systematic review and meta-analysis study

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Abstract

Introduction

Mechanical thrombectomy (MT) had been regarded as the first-line therapy for acute ischemic stroke (AIS) patients. The sex differences in post MT treatment outcomes were analyzed by 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 outcome include successful recanalization and 90-day favorable outcome. Secondary outcomes include vascular complication, hospital-related complications, death during hospital stay and follow-up, and intracerebral hemorrhage. The risk bias of observational studies will be evaluated by Newcastle-Ottawa Scale (NOS). 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

Keyword: acute ischemic stroke, sex differences, mechanical thrombectomy,

Article Summary

Strengths and limitations of this study

- The objective of the review study is exploring outcome differences between females and males in AIS patients receiving 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 randomized 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-analytic methods of different outcomes will bring an inherent risk of uncertainty.

BACKGROUND

Acute ischemic 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 differences in outcomes after MT for acute large-vessel ischemic stroke was analyzed in several studies from randomized clinical trials (RCTs), showing either statistically insignificant treatment effects or mutually inconsistent results. For example, in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic 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 7 RCTs by 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 optimizing post-stroke 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

This systematic review has been prospectively recorded on the PROSPERO database (https://www.crd.york.ac.uk/prospero/) with a registration number is CRD42021242597. The protocol was drafted strictly abide by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) (see **Supplementary file 1, PRISMA-P Checklist**). The review will be performed and reported following Meta-analyses of Observational Studies in Epidemiology (MOOSE).

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 versus 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, computed tomography, computed tomographic angiography, magnetic resonance imaging or magnetic resonance angiography.

Intervention

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

Outcomes

Any information associated with post-intervention condition will be documented.

Primary outcomes consist of successful recanalization and 90-day favorable outcome. Successful recanalization can be graded by modified Thrombolysis in Cerebral Infarction scale (mTICI). An mTICI score of 2b-3 is considered as successful recanalization. 90-day favorable outcome is defined as modified Rankin score (mRS) ≤ 2 or equivalent to premorbid value.

Secondary outcomes include vascular complications (perforation, dissection and vasospasm), hospital-related complications, death during hospital stay and follow-up, and intracerebral hemorrhage. Intracerebral hemorrhage was evaluated by European Cooperative Acute Stroke Study classification. The symptomatic intracerebral hemorrhage was confirmed if National Institutes of Health Stroke Scale score increased 4 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 versus women) and studies that outcome data can be extracted across men and women.

Exclusion criteria for study selection

1. Studies published before January 1, 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 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 October 1 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. (**Supplementary 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 (B Li and X Zhang) familiar with research in the field of thrombectomy will conduct it independently. Their selections will be cross-checked, and a third reviewer (X Bai) will be inquired in 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 (L Xu and T Wang). They will use EndNote X9 software (Clarivate Analytics, Philadelphia, PA, 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 numbers will be held for the final

decision.

Assessment of risk bias

Two independent reviewers (X Wang and K Yang) will conduct assessment of the risk bias in the studies selected during the second stage. One risk bias tool of the NOS will be adopted to assess the quality of observational studies (see **Supplementary 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, Stata Corp, 2021) will be used for analyzing data. Presentation of the results will depend on the outcome variables. Continuous variables are presented as standardized mean difference (SMD), and dichotomous variables are relative risk (RR), respectively. The reporting of final results will be accompanied by 95% confidence intervals (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 e-mail 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 7 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 analyze 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 optimizing and post-stroke 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 Contributors

The original idea of the review was developed by Xiaoli Min and Liqun Jiao. The search strategy was developed and optimized by Xiao Zhang and Binglong Li. The study design was accomplished by Lixin Xu and Xiao Zhang. Liqun Jiao were consulted about clinical issues. Lixin Xu, Xiao Zhang and Binglong Li contributed to the original draft. Xue Wang, Kun Yang and Tao Wang contributed to the methods revision. Lixin Xu, Adam A. Dmytriw, and Xuesong Bai were responsible for the draft revision. Lixin Xu, Binglong Li and Xiao Zhang contributed equally and are co-first authors to this study. All authors reviewed and approved the submission and publication of the protocol.

Funding statement None declared.

Competing interests None declared.

Patient consent Not required.

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Figure Legends

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

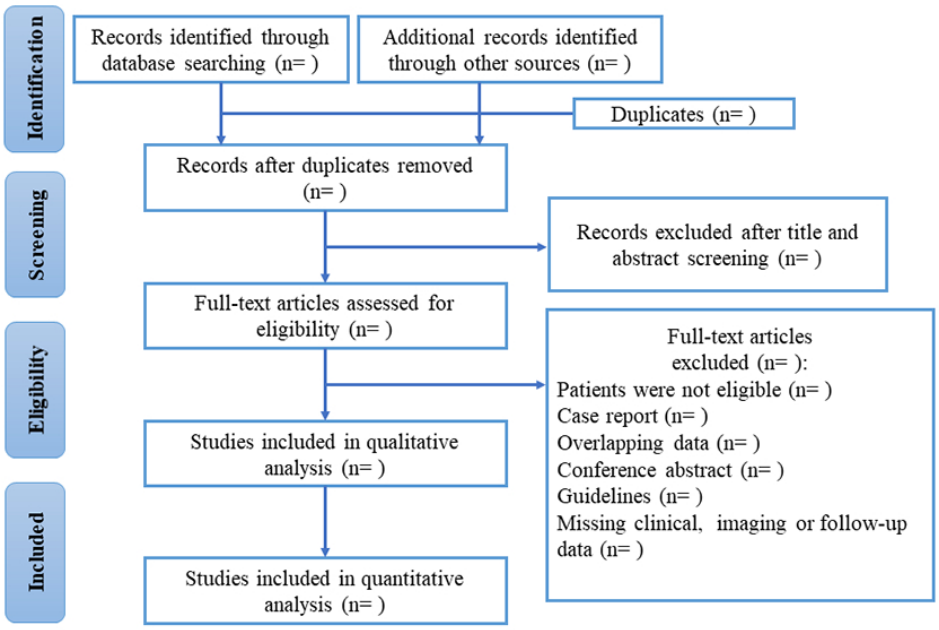

Figure 1 Flow diagram of literature for systematic review and meta-analysis.

75x56mm (300 x 300 DPI)

Supplementary file 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check results
ADMINISTRATIVE INFORMATION			
Title:			P1, L1-2
Identification	1a	Identify the report as a protocol of a systematic review	Yes
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Yes
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes P2, L24
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes P1, L4-19
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes P7, L28-32
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes
Support:			P7, L33-34
Sources	5a	Indicate sources of financial or other support for the review	Yes
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes

Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes P4, L2-33
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes P4, L33-36
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes P5, L2-36
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes P5, L39-41
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes Supplementary file 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes P6, L15
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes P6, L8-12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes P6, L16

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes P5, L21-27
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes P5, L30-36
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes P6, L27-33
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes P6, L36-37
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes P6, L37-43
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes P6, L43-P7, L1
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes P6, L40-41
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes P6, L41-43
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes P6, L28-30

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

- **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) from 1946 to July 31, 2021**

No.	Searches
1	cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp brain infarction/ or exp carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2	(isch?emi$ adj5 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or brain vasc$ or cva or attack$)).tw.
3	((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or MCA or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4	1 or 2 or 3
5	carotid artery, internal/
6	carotid artery thrombosis/ or carotid stenosis/ or arterial occlusive diseases/ or exp arteriosclerosis/ or constriction, pathologic/
7	5 and 6
8	((internal carotid or ICA or tandem) adj5 (stenos?s or occlus$ or occlud$ or thrombo$ or narrow$ or plaque$ or constrict$ or emboli$ or block$ or arteriosclero$ or atherosclero$ or atheroma$ or isch?emi$ or infarct$ or insufficien$ or obstruct$)).tw.
9	7 or 8
10	endovascular procedures/ or catheterization/ or angioplasty/ or exp angioplasty, balloon/
11	vascular surgical procedures/ or exp thrombectomy/ or exp embolectomy/
12	exp stents/
13	(angioplast$ or stent$ or pta or revasculari?ation or recanali?ation or catheter$ or dilatation or thromboaspirat$ or thrombo-aspirat$ or thrombecto$ or embolecto$).tw.
14	((clot or thrombus or thrombi or embol$) adj5 (aspirat$ or remov$ or retriev$ or fragmentation or retract$ or extract$ or obliterat$ or dispers$)).tw.
15	((mechanical or pharmacomechanical or endovascular or neurovascular) adj5 (thrombolys$ or reperfusion or fragmentation or aspirat$)).tw.
16	thrombolytic therapy/ or fibrinolytic agents/ or tissue plasminogen activator/ or exp plasminogen activators/ or fibrinolysis/

17	(thromboly$ or fibrinoly$ or recanali?ation).tw.
18	((clot or thrombus or thrombi or embol$) adj5 (lyse or lysis or dissolve$ or dissolution)).tw.
19	(tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
20	(anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or retevase).tw.
21	16 or 17 or 18 or 19 or 20
22	infusions, intra-arterial/
23	(intra arterial or intra-arterial or intraarterial or IA).tw.
24	22 or 23
25	21 and 24
26	10 or 11 or 12 or 13 or 14 or 15 or 25
27	4 and 9 and 26

Supplementary file 3

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Note: 1 ✸ means 1 point, and studies with scores of 0–4 points were identified as low quality and 5–9 points as high quality and only high-quality literature will be in our analysis.