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Mechanical thrombectomy first versus direct angioplasty or stenting for the treatment of intracranial atherosclerotic stenosis-related large vessel occlusion: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Mechanical thrombectomy (MT) using stent retrievers or a direct aspiration first-pass technique has proven to yield better results over intravenous thrombolysis in treating acute ischaemic stroke caused by large vessel occlusion (LVO). However, the treatment of intracranial atherosclerotic stenosis-related LVO remains unclear and has been a critical problem in daily clinical practice, as it can cause a relatively high failure rate for MT. Whether direct angioplasty and/or stenting is clinically feasible and shows advantage in reducing delay to revascularisation with better functional outcome compared with MT with rescue angioplasty and/or stenting remains unclear. This study seeks to provide direct and practical clinical evidence for clinicians.

Methods and analysis The main databases of PubMed, the Cochrane library, Embase and Web of Science will be screened for related studies published after1 January 2015. Primary outcomes include successful recanalisation and 90-day favourable outcome. Secondary outcomes include puncture to revascularisation time, vascular complication (perforation, dissection and vasospasm), intracerebral haemorrhage, hospital-related complications and 90-day mortality. The Newcastle-Ottawa Scale will be adopted to assess risk bias of observational studies. The I^2 statistic will be used to assess heterogeneity.

Ethics and dissemination No primary data of patients are needed. Therefore, ethics approval is unnecessary. The results of this systematic review and meta-analysis will be published in a peer-reviewed journal.

PROSPERO registration number CRD42021268061.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study focuses on the comparison between angioplasty and/or stenting as a rescue therapy in mechanical thrombectomy with direct angioplasty and/or stenting in the treatment of intracranial atherosclerotic stenosis-related large vessel occlusion.
⇒ The types of included studies in this meta-analysis includes non-randomised clinical trials, which increases heterogeneity at the advantage of generalisability.
⇒ Stringent rules will be kept when assessing the study risk of bias and data extraction to minimise the unfavourable impact on final results.

INTRODUCTION

Acute ischaemic stroke (AIS) caused by large vessel occlusion (LVO) is a global concern, with high mortality and morbidity. Several randomised clinical trials (RCTs) have proven the superiority of mechanical thrombectomy (MT), using stent retrievers or a direct aspiration first-pass technique, over intravenous thrombolysis.[1 2] However, severe intracranial atherosclerotic stenosis (ICAS) can account for approximately 5%–6% of all strokes due to LVO in European countries and up to 12%–30% in Asian and Hispanic populations.[3] However, treatment of ICAS-related LVO remains unclear and is a critical problem in daily clinical practice, as it has a relatively high rate of failed MT.[3 4] Thus, rescue therapy using angioplasty and/or stenting is often required and can at times effectively resolve the stenosis and achieve successful reperfusion in these patients.[3 5]

Recently, several studies proposed direct angioplasty or direct stenting in ICAS-related AIS rather than rescue after failed MT.[6–8] These propose that rescue therapy may prolong the total procedure time and contribute to poor outcomes. Additionally, less intravascular manipulation may hypothetically reduce complications such as vascular

injury, dissection or vasospasm.[8] In addition, tortuous and resistant vascular systems may increase the difficulty performing MT in patients with ICAS. Compared with MT with rescue stenting, direct stenting shortens puncture-to-recanalisation time and is suggested to be related to a higher rate of favourable functional outcome.[6 8] Thus, a comprehensive literature review and meta-analysis is warranted to update clinical evidence of the safety and effectiveness of this proposed new strategy using direct angioplasty or stenting for ICAS-related AIS.

METHODS AND ANALYSIS

This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021268061). The planned start date of the study is 1 October 2022, and the planned end date is 25 December 2022. Currently, the search strategy has been made (online supplemental file 1). Any amendment made to this study will be reflected on the PROSPERO database. This protocol was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (online supplemental file 2).

Inclusion criteria for study selection

Participants

Patients aged ≥18 with AIS due to ICAS will be included. Markers suggesting ICAS-related LVO have been described previously.[9]

Intervention

Direct stenting and/or angioplasty approach. Direct stenting or angioplasty approach includes multiple manipulations, such as stenting with stent retrievers, balloon angioplasty with a percutaneous transluminal angioplasty (PTA) balloon catheter, and balloon angioplasty and stenting with a Wingspan stent system. In our meta-analysis, we will analyse these procedures together.

Comparator

MT with/without rescue therapy with stenting and/or angioplasty will be used.

Outcomes

Any information associated with postprocedural condition will be documented.

Primary outcomes include successful recanalisation and 90-day favourable outcome. The definition of successful recanalisation is a modified Thrombolysis in Cerebral Infarction score of 2b-3, and 90-day favourable outcome is accepted to be a modified Rankin Scale (mRS) score of 0–2 or equal to preprocedural mRS score.

Secondary outcomes include puncture to revascularisation time, vascular complication (perforation, dissection and vasospasm), intracerebral haemorrhage (ICH), hospital-related complications and 90-day mortality. ICH was assessed by European Cooperative Acute Stroke Study classification. The symptomatic ICH was confirmed if National Institutes of Health Stroke Scale score increased at least 4 points in 24 hours before intervention.

Studies

Studies included in this systematic review will be both RCTs and non-RCTs. The inclusion criteria for this review will be studies with outcomes comparing the aforementioned two treatment strategies. Search dates are identified according to a preliminary search in database. To assess the modern thrombectomy results and include enough qualified studies for analysis, we included studies published later than 2015 only, as little relevant information was mentioned in articles before 2015. Exclusion criteria are the following: (1) studies published before 1 January 2015 (ie, not modern thrombectomy devices); (2) studies that fail to report the aforementioned outcomes; (3) studies with outcome data that cannot extracted or are not available; and (4) observational studies with a sample size of less than 5, conference reports, abstracts, case reports, editorials, comments and reviews.

Search strategy

This meta-analysis will be performed in accordance with contemporary systematic search strategies to screen suitable literature in the main databases of PubMed, the Cochrane library, Embase and Web of Science. We will review all relevant articles comparing the functional outcomes of the two aforementioned approaches for ICAS-related AIS populations. All studies published after 1 January 2015 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 retriever thrombectomy”, “stent retriever”, “ICAS”, “direct angioplasty” and “direct stenting”. When drafting and revising this search strategy, we will aim to meet the standards of the Peer Review of Electronic Search Strategies checklist.

Selection of studies

The first screening of research reports will depend mainly on titles and abstracts and will be conducted by two independent reviewers familiar with research in the field of thrombectomy. Second, full articles will be reviewed and screened. We will keep extremely rigorous rules when screening evidence of ICAS-related AIS to minimise the potential inclusion bias since patients with LVO and underlying occlusions could not be correctly identified at the moment of the procedure in some special cases. Selections will be cross-checked, and a third reviewer will be solicited in the event of any discrepancy or disagreement. Reasons for exclusion of articles will be recorded. The screening process is shown in figure 1.

Data selection

After the initial screening, the second stage of selection will also be performed by two independent reviewers using EndNote V.X8 (Clarivate Analytics, Philadelphia, Pennsylvania, USA) to manage literature. At this stage, the full texts will be reviewed. Data for each eligible study

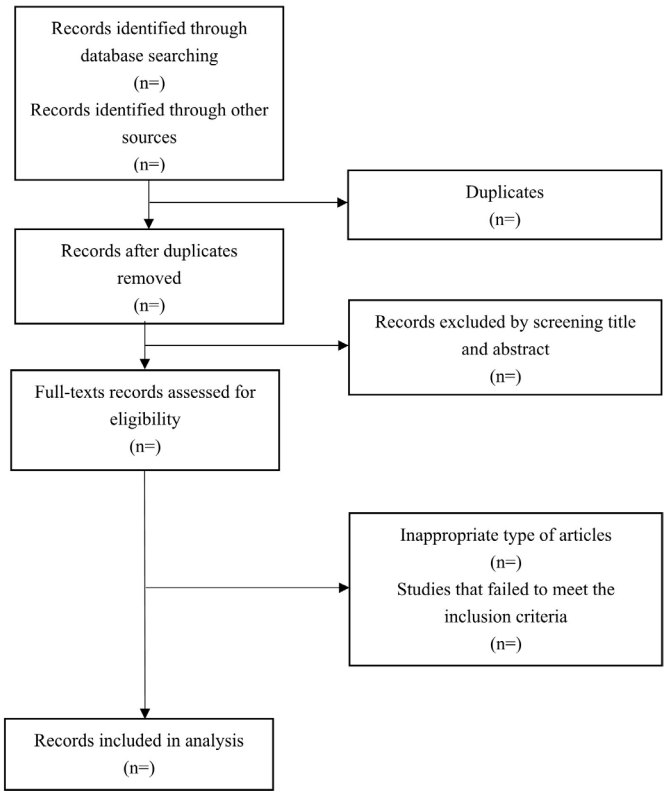

Figure 1 Flow diagram showing the study selection.

will be extracted and evaluated independently by two reviewers. Included information is listed as follows:

- Basic information, such as authors, time of publication, type of study, countries where the study was conducted, number of included patients and a Newcastle-Ottawa Scale (NOS) score for each study.
- Patient characteristics. These include demographic characteristics (age and gender) and medical history (hypertension, diabetes mellitus, dyslipidaemia, stroke history and other related information). Medication taken before the stroke including anticoagulants and antiplatelet agents will be recorded. Data regarding alcohol consumption, smoking, interventions, location of the occlusion and onset time will be extracted and recorded.
- Primary outcomes and secondary outcomes are mentioned previously. Both the primary and secondary outcomes will be assessed and documented separately.

A formal spreadsheet 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 with possible arbitration by a third reviewer as needed.

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 V.15.0. Presentation of the results will depend on the outcome variables and will include standardised mean difference for continuous outcomes and relative risk (RR) for dichotomous outcomes. The reporting of final results will be accompanied by 95% CIs. A random-effects model will generally be used for data analysis, but a fixed-effects model will be applied when there is little evidence of heterogeneity (I^2 <20%). Statistical significance is defined at p<0.05. 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 offer the possibility of meaningful results for a specific variable, we will attempt to contact the authors of the relevant reports through email in an effort to obtain the original data. Heterogeneity will be measured with the I^2 statistic before any outcome is pooled. The heterogeneity of mild (<40%), moderate (40%–60%) or substantial (>60%) will be graded, depending on the pooled results. On condition that the results have substantial heterogeneity and sufficient number of included trials, we will use subgroup analysis to examine the reasonable origins of heterogeneity. Subgroup analysis will be performed based on characteristics such as race and region, even based on different procedures regarding direct angioplasty or stenting, if practicable. Publication bias will also be evaluated using a funnel plot if there are sufficient studies for its construction.

Assessment of risk bias

Two independent reviewers will conduct assessment of bias risk in the studies selected during the second stage. The NOS will be adopted for observational studies with high quality (online supplemental file 3). Studies with scores of 5–9 points will be considered high-quality evidence. Any disagreement will be discussed and may be arbitrated by a third reviewer as necessary.

Patient and public involvement

No patients were involved in this study.

DISCUSSION

The optimal treatment strategy for ICAS-related AIS is an important area of research, especially in Asian countries where the prevalence can be particularly high. Whether direct angioplasty or stenting is clinically feasible and shows advantage in reducing delay to revascularisation while achieving better functional outcomes remains to be clarified. Thus, an updated and high-quality systematic review and meta-analysis of this distinct group of AIS patients are needed. We will apply stringent rules when assessing the risk of bias and data extraction to minimise the final trends when selecting observational studies. In addition, series with untreated patients should be also considered, since certain specialists believe that treatment of patients in this subgroup seems not to be useful, as LVOs with underlying atherosclerotic plaques represent

an acute condition of a chronic pathology with the development of a solid and stable collateral circulation. This is another important question that will be further discussed as a new topic in our next review.

ETHICS AND DISSEMINATION

No primary patient data are needed. Therefore, ethics approval is unnecessary. The results of this systematic review and meta-analysis will be published in a peer-reviewed journal.

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Contributors XB and LJ contributed to the initial idea. YF, XW and QZ developed and revised the search strategy. LJ was consulted about the clinical issues. XM, WL and HZ contributed to the original draft. QC, XZ and JZ finished the study design. XM, WL, HZ, XB, AAD, ABP, WC and LJ were responsible for the revision of the draft. XM, WL and HZ contributed equally to this article. All the authors approved the final work before submission.

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Competing interests None declared.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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PubMed from 2015 to June 01, 2022

#No.	Results	Searches
1	1,550,609	Brain Ischemia OR Stroke OR Cerebral Ischemic Stroke OR Cerebral Infarction OR cerebrovascular disease OR cerebr* stroke OR cerebr* Ischemia OR cerebr* Infarct* OR "CIS"[tw] OR "CI"[tw] OR ("Ischemic Stroke"[Mesh])
2	7172	((("Cerebrovascular Disorders"[Mesh]) OR ("Intracranial Arteriosclerosis"[Mesh])) AND ("Atherosclerosis"[Mesh])) OR (intracranial atherosclerotic stenosis OR "ICAS"[tw] OR atherosclerotic intracranial arterial stenosis OR (intracranial artery stenosis AND intracranial artery atherosclerosis))
3	1,551,138	1 OR 2
4	134,368	(Stent* OR stent* retrieval thrombectomy OR stent* retriever OR direct* stent* OR stent* implantation OR "PTAS"[tw]) OR ("Stents"[Mesh])
5	89,095	(direct* angioplasty OR percutaneous transluminal angioplasty OR "PTA"[tw]) OR ("Angioplasty"[Mesh])
6	190,105	4 OR 5
7	49,719	mechanical thrombectomy OR Mechanical* thrombectom* OR "MT"[TW] OR Mechanical Thrombolysis
8	1522	3 AND 6 AND 7
9	5,035,618	animals [mh] NOT humans [mh]
10	1498	8 NOT 9
11	9,411,185	((Chinese[Language]) OR (English[Language])) AND (("2015/01/01"[Date - Publication] : "2022/06/01"[Date - Publication]))
12	10,995,396	“Clinical Trial”[pt] OR “Clinical Trials as Topic”[Mesh] OR “Random Allocation”[Mesh] OR “Case-Control Studies”[Mesh] OR “Cohort Studies”[Mesh] OR “Comparative study”[pt] OR” Comparative Effectiveness Research”[Mesh] OR random*[tw] OR

		placebo[tw] OR groups[tw] OR trail[tw] OR cohort*[tw] OR follow up*[tw] OR case control*[tw] OR compar*[tw] OR “comparative study”[filter] OR “clinical trial”[filter] OR “multicenter study”[filter]
13	761	10 AND 11 AND 12

Cochrane Central Register of Controlled Trials (CENTRAL) from 2015 to 2022

#No.	Results	Searches
1	78875	MeSH descriptor: [Ischemic Stroke] explode all trees
2	17426	MeSH descriptor: [Cerebrovascular Disorders] explode all trees
3	122	(intracranial atherosclerotic stenosis):ti,ab,kw
4	103	(ICAS):ti,ab,kw
5	36	(atherosclerotic intracranial arterial stenosis):ti,ab,kw
6	337	(intracranial artery stenosis):ti,ab,kw
7	131	(intracranial artery atherosclerosis):ti,ab,kw
8	228	#3 or #4 or #5 or (#6 and #7)
9	17567	#8 or #2 or #1
10	4567	MeSH descriptor: [Stents] explode all trees
11	17062	(Stent*):ti,ab,kw
12	21	(stent* retrieval thrombectomy):ti,ab,kw
13	233	(stent* retriever):ti,ab,kw
14	1017	(direct* stent*):ti,ab,kw
15	3650	(stent* implantation):ti,ab,kw
16	60	(PTAS):ti,ab,kw
17	17096	#10 or #11 or #12 or #13 or #14 or #15 or #16
18	4538	MeSH descriptor: [Angioplasty] explode all trees
19	661	(direct* angioplasty):ti,ab,kw
20	2565	(percutaneous transluminal angioplasty):ti,ab,kw
21	1253	(PTA):ti,ab,kw
22	21309	#17 or #18 or #19 or #20 or #21

23	671	(mechanical thrombectomy):ti,ab,kw
24	676	(Mechanical* thrombectom*):ti,ab,kw
25	3130	(MT):ti,ab,kw
26	459	(Mechanical Thrombolysis):ti,ab,kw
27	3798	#23 or #24 or #25 or #26
28	68	#9 and #22 and #27
29	56	#28 with Publication Year from 2015 to 2022, in Trials

Web of Science from 2015 to June 01, 2022

#No.	Results	Searches
1	692,739	TS=(acute ischemic stroke OR Brain Ischemia OR Stroke OR Cerebral Ischemic Stroke OR Cerebral Infarction OR cerebrovascular disease OR cerebr* stroke OR cerebr* Ischemia OR cerebr* Infarct*) OR AB=(CIS OR CI)
2	4,567	TS=(Cerebrovascular Disorders OR intracranial atherosclerotic stenosis OR atherosclerotic intracranial arterial stenosis) OR TS=(intracranial artery stenosis AND intracranial artery atherosclerosis) OR TS=(Intracranial Arteriosclerosis AND Atherosclerosis)
3	693,292	#2 OR #1
4	14,393	TS=(Stent*OR stent* retrieval thrombectomy OR stent* retriever OR direct* stent* OR stent* implantation) OR AB=PTAS
5	17,922	TS=(Angioplasty OR direct* angioplasty OR percutaneous transluminal angioplasty) OR AB=PTA
6	29,815	#5 OR #4
7	33,841	TS=(mechanical thrombectomy OR Mechanical* thrombectom* OR Mechanical Thrombolysis) OR AB= MT
8	1,149	#7 AND #6 AND #3

Embase from 2015 to June 01, 2022

#No.	Results	Searches
1	5,407	'acute ischemic stroke'/exp
2	852,109	'cerebrovascular disease'/exp
3	7,092	'atherosclerosis'/exp AND 'brain atherosclerosis'/exp
4	179,049	((((((brain AND ischemia OR stroke OR cerebral) AND ischemic AND stroke OR cerebral) AND infarction OR cerebrovascular) AND disease OR cerebr*) AND stroke OR cerebr*) AND ischemia OR cerebr*) AND infarct*
5	1,891	((intracranial AND atherosclerotic AND stenosis OR atherosclerotic) AND intracranial AND arterial AND stenosis OR intracranial) AND stenosis AND intracranial AND artery AND atherosclerosis
6	866,656	#1 OR #2 OR #3 OR #4 OR #5
7	203,012	'stent'/exp
8	99,033	'angioplasty'/exp
9	38,923	(((stent* AND retrieval AND thrombectomy OR stent*) AND retriever OR direct*) AND stent* OR stent*) AND implantation OR 'ptas'
10	65,156	(direct* AND angioplasty OR percutaneous) AND transluminal AND angioplasty OR 'pta'
11	285,580	#7 OR #8 OR #9 OR #10
12	7,274	((mechanical AND thrombectomy OR mechanical*) AND thrombectom* OR 'mt' OR mechanical) AND thrombolysis
13	1,408	#6 AND #11 AND #12
14	859	#13 AND ([chinese]/lim OR [english]/lim) AND [2015-2022]/py

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the	7

		guarantor of the review	
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	4
Support			
Sources	#5a	Indicate sources of financial or other support for the review	n/a
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
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	4
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	4
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	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records -	#11b	State the process that will be used for selecting studies (such	5

selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - 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	5
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	5
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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	6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	6
Data synthesis	#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 I2, Kendall's τ)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

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.