Diagnostic accuracy of superb microvascular imaging (SMI) in detecting intraplaque neovascularization (IPN): A systematic review and meta-analyses protocol

Introduction

The atherosclerotic disease (e.g., myocardial infarction and stroke) has become the top killer worldwide [1, 2]. For instance, the atherosclerotic plaques can cause carotid artery stenosis and "vulnerable plaques" can even lead to ischemic stroke due to the rupture of the plaques and the formation of thrombi [3]. Therefore, to optimize the management of atherosclerotic disease, evaluation of atherosclerotic plaque vulnerability is vital.

The intraplaque neovascularization (IPN) has been proven as a risk factor to evaluate atherosclerotic plaque vulnerability [4]. Ultrasound imaging techniques, including contrast-enhanced carotid ultrasonography (CEUS) and superb microvascular imaging (SMI), can effectively indicate IPN features in patients with carotid stenosis. However, the SMI has the advantage of being less invasive compared to the CEUS, because the SMI does not use contrast agents as CEUS but uses adaptive principles to display low-velocity blood flow signals [5]. Recent published meta-analysis has shown that SMI and CEUS display an excellent agreement in detecting carotid IPN [6, 7]. However, the accuracy of SMI was inconsistent due to the small sample sizes for each study [6, 7]. To our best knowledge, there was no synthesized data on the accuracy of SMI in detection of the IPN in existing evidence.

The primary objective of this study was to assess the accuracy of SMI in the

detection of carotid IPN in patients with atherosclerotic plaque(s). Secondary objectives included 1) to investigate the correlation between histopathological intraplaque vessel density and SMI plaque neovascularization, and 2) to investigate relationship between SMI results and clinical symptoms or events.

Methods

This systematic review and meta-analysis do not need the Research Ethics Board approval because we will use the published evidence to do the data synthesis. The reporting of the present project will follow the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement [8].

Eligibility criteria

The inclusion criteria for the included studies included 1) original studies (e.g., randomized controlled trials (RCT), cohort studies, cross-sectional studies, and case-control studies), 2) patients with carotid plaque(s), 3) having information of the diagnostic accuracy of SMI in the evaluation of IPN, and 4) having information of pathologic evaluations or CEUS as the reference test. The exclusion criteria included: 1) duplicate publications, 2) study design as systematic review, meta-analysis, editorial, protocol, letters, or case reports, 3) papers' full text not available, and 3) studies without sufficient data to perform the accuracy assessment of the SMI.

Literature search

We searched databases of Cochrane Library, Embase, Medline, Wanfang database, and China National Knowledge Infrastructure (CNKI) until January 17, 2023. The

detailed search strategies were described in **Appendix 1**. Language restriction was applied as English. The key search terms included "carotid," "plaque," "fatty streak," "Fibroatheroma," "neovascularization," and "superb microvascular imaging." The bibliographies of the related papers (reviews, meta-analysis, and potential eligible studies) will be checked to find other potential articles. Besides, we will check published and conference proceedings for eligible data or references.

Study selection

Two independent reviewers will perform the title and abstract screening to generate the potentially relevant study list according to the eligibility criteria. Then, the full texts of the papers of the potential eligible study list will be extracted to do the full-text review to further confirm the eligibility of the studies. The inconsistent between the two reviewers will be resolved by discussion or refer to the third authority. The workflow of the study selection can be found in **Figure 1**.

Data collection

Two study team members will independently perform the data extraction using a pre-test data collection form. Discrepancies were resolved by discussion or by referral to a third authority. The data collection will include information of authors, publication year, study country, study design, patient demographics, SMI related data, and index test information.

Outcomes

The primary outcome of the study was the accuracy of SMI in the detection of carotid IPN in patients with atherosclerotic plaques, which was measured using sensitivity,

specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic odds ratio (DOR) analyses. Sensitivity refers to the probability of the positive results of SMI given that the patients with IPN. The equation of the sensitivity = the positive (TP)/ (the false positive (FP) + TP). The specificity refers to the probability of the negative results of SMI given that the patients without IPN. The equation of the specificity = true negative (TN)/ (false negative (FN) + TN).

We prefer the reference test to pathologic evaluations first. However, if pathologic evaluation results are not available, the CEUS results were performed as the reference test. The target condition was carotid IPN. In different category of the carotid IPN for SMI, CEUS, and pathologic evaluation results, we will count moderate (linear IPN) and severe diagnosis (multiple linear IPNs) as a positive result, and the no IPN or spot IPN as negative results due to the difference of their following clinical treatments.

The secondary outcomes include the intraplaque vessel density, intraplaque bleeding, and transient ischemic attack (TIA) or stroke.

Study risk of bias assessment

Two study team members will independently perform the risk of bias the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria [9]. There are four key domains in the QUADAS-2 tool, including patients' selection, index test, reference standards and follow and timing assess methodological quality. The quality is graded as "no" for low quality, "yes" for high quality or "unclear" if the information was not available.

Synthesis methods

We will perform the statistical analysis of the SMI accuracy according to Cochrane guidelines for diagnostic test accuracy (DTA) reviews [10]. We will apply forest plots and in receiver-operating characteristic plots to visually explore the variation between the included studies on the sensitivity and specificity of SMI their 95% confidence intervals (CI) for detection IPN. We used the bivariate random effects model to summarize sensitivity and specificity. All data analysis will be performed by using the STATA software, version 16.0 (Stata Corp., College Station, TX, USA) [11]. We calculated post-test probabilities of occurrence of the IPN following positive and negative MIS outcomes for in the included studies. We applied Cochran's Q-statistic and I^2 test to evaluate potential heterogeneity between studies. The random effects model was applied if it indicated significant heterogeneity ($P< 0.1$ for Q test or I^2 test exceeded 50%) or fixed effects model was used. Sensitivity analysis will be performed to evaluate the influence of each individual study on the overall estimate. Begg's funnel plot and Egger's test will be used to assess publication bias [9].

Subgroup analyses will be performed to explore variation in test performance according to different reference indexes (CEUS and pathologic evaluation). The meta-regression will be applied to investigate the potential heterogeneity by including the variables of age, percentage of male, percentage of having hypertension, percentage of having diabetes mellitus, percentage of having diabetes mellitus, dyslipidemia, and machine type.

Certainty assessment

105 We will apply the Grading of Recommendations, Assessment, Development, and

Evaluation (GRADE) rating system to assess certainty in the body of evidence for accuracy [12]. Detailed GRADE guidance was applied to assess the risk of bias, imprecision, inconsistency, indirectness, and publication bias. We will describe the GRADE assessment results with a summary table.

Discussion

The results of the present study will be useful for the practice. We plan to share the final results in national and international conferences and submitted it to a peer-reviewed academic journal.

References

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161 **Table 1.** The characteristics of XXXX of the 5 included studies.

First author (publication year), country	Study Design	Total sample size (experimental arm/control arm), n	Age (years), mean±SD or specified	Infertility duration (experimental arm/control arm)	Surgery procedures	The number of IVF cycles (experimental arm/control arm)	Primary outcome(s)
Bianchi et al. (2009), Brazil	Prospective cohort study	169 (64/105)	32.0±3.0	29.0±20.0 months /35.0±18.0 months	Extensive laparoscopic excision of DIE before IVF	86/153	The number of mature oocytes retrieved
Capelle et al. (2015), France	Retrospective cohort study	177 (112/65)	31.0 (mean)	3.2 years/3.4-3.5 years	Incomplete operations and complete surgical mass removal of DIE lesions.	Not specified	Pregnancy rates
Bendifallah et al. (2017), France	Retrospective cohort study	110 (55/55)	32.0 (mean)	3.0 years/3.0 years	Extensive laparoscopic excision of DIE before IVF	80/82	Live birth rates
Mounsambote et al. (2017), France	Retrospective cohort study	72 (35/37)	32.6±4.0	Not specified	Adhesion lysis, fallopian tube resection, uterosacral ligament lesion resection, ureter and intestinal surface lesion removal.	58/54	Pregnancy rates
Maignien et al. (2020), France	Retrospective cohort study	222 (155/67)	33.0±3.9	4.0±2.0 years /4.0±2.4 years	Ovarian cyst stripping and excision of DIE before IVF	311/129	The number of mature oocytes retrieved

162 Abbreviation: SD, standard deviation; DIE, deep infiltrative endometriosis; IVF, in vitro fertilization;

Figure Legends

Figure 1. PRISMA flow diagram for article selection for meta-analysis.

Figure 2. Forest plot of XXXX.

Figure 3. Forest plot of XXX.

Figure 4. Funnel plots of XXX.

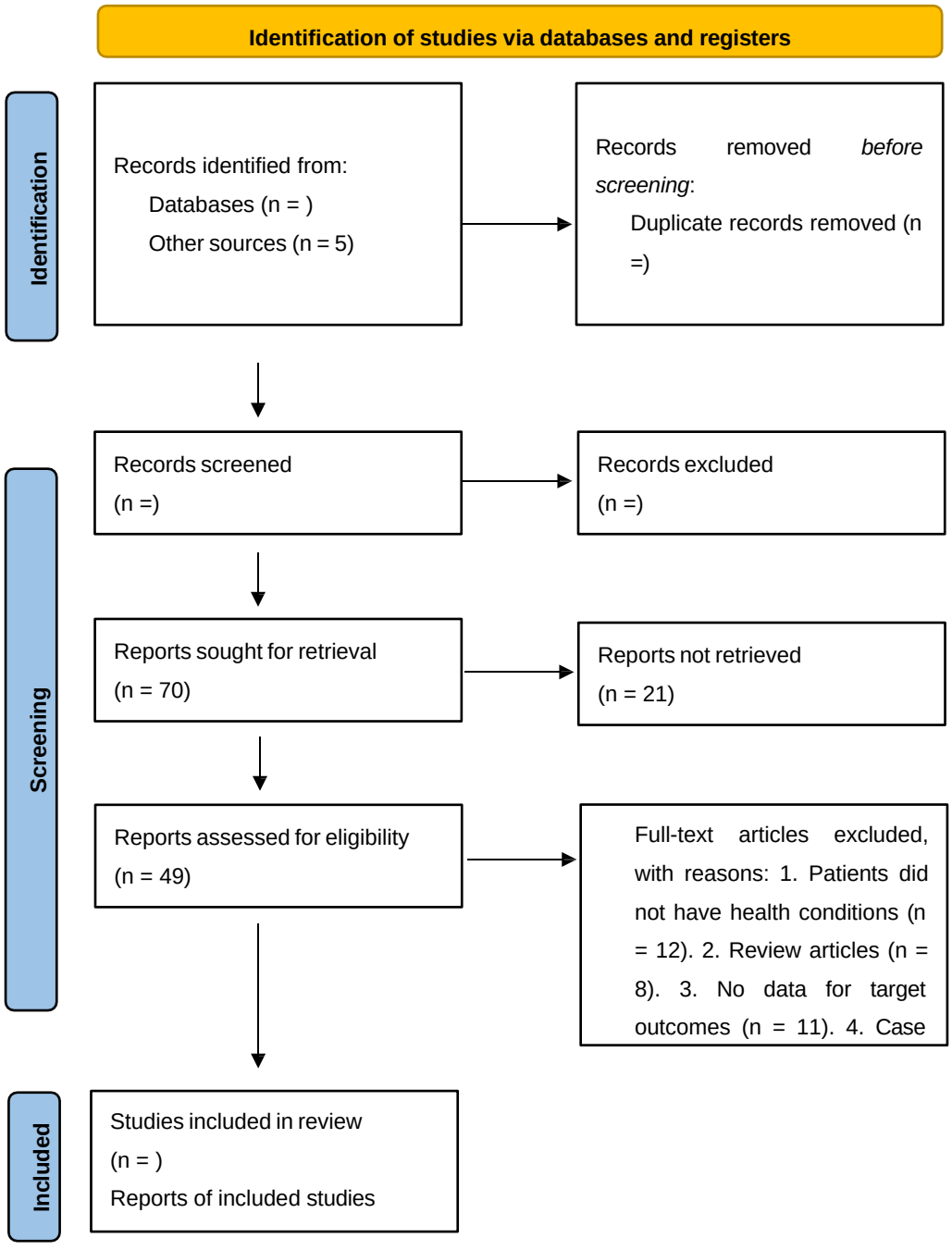

Figure 1. PRISMA flow diagram for article selection for meta-analysis [13].

Appendix 1. Literature search strategies.

Cochrane Library CENTRAL search strategy
Search Name:

Date Run: 18/01/2023 00:49:26

Comment:

ID Search Hits

#1 (Superb microvascular imaging):ti,ab,kw 15

#2 (SMI):ti,ab,kw 924

#3 (neovascularization of carotid plaque):ti,ab,kw 5

#4 #1 Or #2 927

#5 #3 and #4 1

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to present

Database: Ovid MEDLINE(R) ALL <1946 to January 13, 2023>

Search Strategy:

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1 carotid.mp. (152391)

2 ("plaque*" or "fatty streak" or "fibroatheroma").mp. (164774)

3 ("vulnerability" or "stability" or "neovascularization").mp. (754458)

4 superb microvascular imaging.mp. (277)

5 1 and 2 and 3 and 4 (23)

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Database: Embase <1974 to 2021 December 17>

Database: Embase Classic+Embase <1947 to 2023 January 13>

Search Strategy:

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1 carotid.mp. (239439)

2 ("plaque*" or "fatty streak" or "fibroatheroma").mp. (238344)

3 ("vulnerability" or "stability" or "neovascularization").mp. (885705)

4 superb microvascular imaging.mp. (393)

5 1 and 2 and 3 and 4 (37)

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