International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Comparison of the diagnostic value of Contrast-Enhanced Transthoracic Echocardiography and Contrast-Enhanced Transcranial Doppler for Patent Foramen Ovale: a systematic review and meta-analysis protocol

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Zhu, LL; Ding, Y; Zhang, CQ.

Corresponding author:
Zhang Chunquan

jxzcq@163.com

Author Affiliation:
Department of Ultrasound, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 September 2025 and was last updated on 13 September 2025.

INTRODUCTION

Review question / Objective The primary objective of this systematic review and meta-analysis is to compare the diagnostic accuracy of contrast-enhanced transcranial Doppler (c-TCD) and contrast-enhanced transthoracic echocardiography (c-TTE) for detecting patent foramen ovale (PFO), using transesophageal echocardiography (TEE) as the reference standard.

The research question is defined using the PICOS framework as follows:

Population : Patients at high risk for patent foramen ovale (PFO) (e.g., patients with cryptogenic stroke, transient ischemic attack, or migraine).

Index test: Contrast-enhanced transcranial Doppler bubble study (c-TCD) and contrast-enhanced transthoracic echocardiography (c-TTE).

Comparator/Reference standard : Transesophageal echocardiography (TEE).

Outcomes : The primary outcomes are the sensitivity and specificity of c-TCD and c-TTE in diagnosing PFO, using TEE as the reference standard. Secondary outcomes include the positive likelihood ratio (+LR), negative likelihood ratio (-LR), diagnostic odds ratio (DOR), and the area under the summary receiver operating characteristic curve (AUC).

Study design: Diagnostic test accuracy studies comparing the diagnostic value of c-TCD and c-TTE for PFO.

Condition being studied Patent foramen ovale (PFO) is a common cardiac anomaly characterized by the failure of the foramen ovale to close completely after birth. The foramen ovale is a normal interatrial channel during fetal circulation that allows blood to bypass the lungs. In approximately 75% of the population, it closes

functionally within the first year of life. However, in about 25% of adults, it remains patent, making it the most prevalent congenital heart defect in adults. Most individuals with a PFO are asymptomatic. However, it can become clinically significant when a right-to-left shunt occurs, allowing venous thrombi, gas bubbles, or other emboli to bypass the pulmonary filter and enter the systemic arterial circulation directly. This paradoxical embolism is a well-established mechanism underlying cryptogenic ischemic stroke, particularly in young adults (<55 years old), transient ischemic attack (TIA), migraine with aura, and other systemic embolic events. Accurate diagnosis of PFO is therefore crucial for identifying the etiology of these conditions and guiding subsequent management decisions, such as considering PFO closure in selected patients to prevent stroke recurrence.

METHODS

Participant or population Patients at high risk for patent foramen ovale (PFO), specifically those presenting with clinical conditions such as cryptogenic ischemic stroke, transient ischemic attack (TIA), or migraine. Studies involving patients with known alternative cardiac shunts (e.g., atrial septal defects) or prior PFO closure will be excluded.

Intervention The index tests are contrast-enhanced transcranial Doppler bubble study (c-TCD) and contrast-enhanced transthoracic echocardiography (c-TTE).

Comparator The reference standard is Transesophageal echocardiography (TEE).

Study designs to be included Diagnostic test accuracy studies that directly compare the index tests (c-TCD and c-TTE) against the reference standard (TEE) for the diagnosis of PFO. Case reports, reviews and conference abstracts will be excluded.

Eligibility criteria (1) Studies must report sufficient data to construct a 2x2 contingency table (true positive, false positive, true negative, false negative values) for the index tests against the reference standard. (2) Only full-text articles published in peer-reviewed journals are included; conference abstracts, reviews, and case reports are excluded. (3) Studies published in either English or Chinese are eligible. (4) If multiple publications report on the same patient population, only the most complete or recent study is included.

Information sources We will systematically search the following electronic bibliographic databases from their inception to September 30, 2024:
English databases: PubMed, Embase, Web of Science Core Collection; Chinese databases: China National Knowledge Infrastructure (CNKI), WanFang Data, Chinese Biomedical Literature Database (CBM).

Main outcome(s) The primary outcomes of this review are the pooled estimates of the following measures of diagnostic accuracy for both c-TCD and c-TTE, using TEE as the reference standard:
Sensitivity (SEN)
Specificity (SPE)
Diagnostic odds ratio (DOR)
Positive likelihood ratio (+LR)
Negative likelihood ratio (-LR)
These measures will be presented as point estimates with their corresponding 95% confidence intervals (CIs).
Additionally, the overall diagnostic performance will be evaluated by plotting a summary receiver operating characteristic (SROC) curve and calculating the area under the curve (AUC).

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included diagnostic test accuracy studies will be assessed independently by two reviewers using the validated QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool, alongside the QUADAS-C tool for comparative studies.
The QUADAS-2 tool evaluates four key domains: (1) patient selection, (2) index test (c-TCD and c-TTE), (3) reference standard (TEE), and (4) flow and timing. The QUADAS-C tool will be used to assess concerns regarding the comparative design of the review. Each domain is rated in terms of the risk of bias as 'high', 'low', or 'unclear'.
Any disagreements between the two reviewers will be resolved through discussion or, if necessary, by consulting a third reviewer to reach a consensus. The results of the assessment will be presented in both a table and a graph.

Strategy of data synthesis All statistical analyses will be performed using Meta-DiSc software (version 1.4) and R software (version 4.4.3).
The diagnostic accuracy measures for each index test (c-TCD and c-TTE) will be pooled separately. We will calculate the pooled estimates of sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR), along with their 95% confidence intervals (CIs).
Heterogeneity will be assessed using the Cochran-Q test and the I^2 statistic. A fixed-effect model will

be used if $I^2 < 50\%$; otherwise, a random-effects model will be employed. Threshold effects will be investigated by calculating the Spearman correlation coefficient and visually inspecting the summary receiver operating characteristic (SROC) curve. The bivariate model will be used to synthesize the data and plot the SROC curves, calculating the area under the curve (AUC).
Sensitivity analysis will be conducted using the leave-one-out method. Publication bias will be assessed using Egger's regression test and the trim-and-fill method. If substantial heterogeneity is detected, meta-regression analyses will be performed to explore potential sources.

Subgroup analysis No subgroup analyses are planned in this systematic review. The primary analysis will focus on the overall pooled diagnostic accuracy of c-TCD and c-TTE in the entire study population.

Sensitivity analysis A sensitivity analysis will be performed using the leave-one-out method. This involves iteratively removing each individual study from the meta-analysis and recalculating the pooled estimates of sensitivity and specificity for the remaining studies. The purpose is to assess whether any single study exerts a disproportionate influence on the overall results. The results will be considered robust if the recalculated estimates do not differ significantly from the original pooled estimates.

Country(ies) involved China.

Keywords Right heart contrast echocardiography; Transcranial Doppler foam test; Patent foramen ovale; Meta-analysis; Diagnostic test.

Contributions of each author

Author 1 - Zhu Linli.
Email: zhulinli1987@163.com
Author 2 - Ding Yan.
Email: sqdqsh@126.com
Author 3 - Zhang Chunquan.
Email: jxzcq@163.com