Review

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Diagnostic accuracy of transcranial ultrasonography for detecting stenosis in patients with acute ischaemic stroke: a systematic review and meta-analysis

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Abstract

Aim: Transcranial ultrasonography, including transcranial doppler (TCD) and transcranial colour-coded duplex/sonography (TCCD/TCCS), offers potential benefits in the evaluation of cerebrovascular patency, but its accuracy remains under scrutiny. Hence, this study aims to investigate the diagnostic accuracy of transcranial ultrasonography for detecting stenosis in acute ischaemic stroke patients. **Material and methods**: We systematically reviewed the databases such as CINAHL, SCOPUS, EMBASE, MEDLINE, Cochrane Library, Google Scholar, and ScienceDirect from inception till June 2023. Studies were eligible if they compared the diagnostic role of transcranial ultrasonography with established techniques, and reported accuracy parameters such as sensitivity, specificity, positive and negative likelihood ratios. Subgroup analysis was performed for TCD and TCCD/TCCS. **Results**: Seventeen studies involving 1496 participants were included. The pooled sensitivity and specificity of transcranial ultrasonography were 90% and 95% respectively. For TCD, the sensitivity and specificity were 87% and 93% respectively. TCCD/TCCS showed sensitivity 98% and specificity 97%. High clinical value was evident in both TCD and TCCD/TCCS, with heterogeneity across studies but no observable publication bias. **Conclusion**: Transcranial ultrasonography, including both TCD and TCCD/TCCS, demonstrates high diagnostic accuracy in detecting stenosis in patients with acute ischaemic stroke. These findings support the utility of these methods as reliable, non-invasive tools for cerebrovascular assessment.

Keywords: meta-analysis; stroke; transcranial doppler ultrasonography; ultrasonography

Introduction

Stroke is a leading cause of morbidity and mortality globally, and acute ischaemic stroke, resulting from a thrombotic or embolic occlusion of a cerebral artery, accounts for approximately 85% of all stroke cases [1]. Central to the prevention, diagnosis, and management of acute ischaemic stroke is the evaluation of cerebrovascular patency [2]. Detecting and quantifying the degree of arterial stenosis (narrowing) or occlusion (blockage) can influence the therapeutic approach, predict patient outcomes, and monitor disease progression or the effectiveness of therapeutic interventions [3].

A variety of imaging modalities are employed in the assessment of acute ischaemic stroke, including computed tomography (CT), magnetic resonance imaging (MRI), and various forms of angiography [4]. These modalities provide a wealth of information about brain tissue integrity, blood flow, and the presence and extent of arterial stenosis or occlusion. However, they may also be associated with limitations such as cost, limited availability, the use of ionizing radiation or nephrotoxic contrast agents, and the requirement for patient transportation, which can be problematic in the acute setting [5].

Transcranial ultrasonography (in form of transcranial Doppler (TCD) or transcranial colour-coded sonography (TCCS) or transcranial colour coded duplex (TCCD) sonography), are non-invasive ultrasound-based methods that measure cerebral blood flow velocities and present an alternative or adjunctive approach to these imaging

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modalities [6,7]. TCD is used to measure the velocity of blood flow through the brain's major arteries. It uses a low-frequency (2 MHz) probe that can penetrate the skull and assess the speed and direction of blood flow. The data is usually presented as a waveform, and the absence, reduction, or change in the blood flow velocity can indicate various pathological conditions such as stenosis, occlusion, or vasospasm [6].

TCCD/TCCS refer to a type of ultrasound technology used to visualize and measure blood flow in the vessels of the brain. It is a more recent development in transcranial ultrasound technology. It provides Doppler information like TCD but also adds color-coded, real-time imaging of the brain's blood vessels. This additional imaging component provides spatial orientation, making it easier to locate specific vessels and pathologies, such as stenosis or occlusions, which can be seen directly on the images. Moreover, TCCD/TCCS provides the opportunity to use duplex scanning, allowing simultaneous B-mode imaging and Doppler flow evaluation. This further increases the diagnostic value of the examination [7].

These methods offer several potential advantages, including bedside availability, repeatability, and the absence of ionizing radiation or contrast media. Notably, it has demonstrated utility in detecting and monitoring cerebral arterial stenosis, with increased blood flow velocity often indicating the presence of stenosis.

Nevertheless, while these methods have been extensively studied, its accuracy in detecting stenosis in the setting of acute ischaemic stroke is a matter of ongoing investigation. Previous research has produced a spectrum of results, with some studies reporting high sensitivity and specificity for each of these methods in detecting stenosis, while others suggest that its performance may be less reliable or variable based on the operator's experience and the anatomical location of the stenosis [8-10]. Moreover, the diagnostic performance of transcranial ultrasonography is often compared to that of other imaging modalities, most commonly CT angiography (CTA) and MR angiography (MRA), which are typically considered the reference standards but have their own limitations and potential inaccuracies. The need for reliable, non-invasive, and readily available methods for detecting and evaluating cerebral arterial stenosis in patients with acute ischaemic stroke is crucial. Given the promise but also the debated diagnostic accuracy of transcranial ultrasonography, a comprehensive, updated review of the evidence is warranted.

The rapid evaluation and accurate diagnosis of acute ischaemic stroke are of paramount importance to reduce the risk of disability and improve patient outcomes [11]. In this light, the present investigation into the effectiveness and reliability of transcranial ultrasonography as a diagnostic tool in acute ischaemic stroke is of significant clinical and scientific interest. The anticipation is that this analysis will help to clarify the potential and limitations of transcranial ultrasonography in the management of acute ischaemic stroke, supporting the continuing development of optimal diagnostic and therapeutic approaches for this common and potentially devastating condition. This systematic review and meta-analysis aim to evaluate the current body of literature on the diagnostic accuracy of transcranial ultrasonography for detecting stenosis in patients with acute ischaemic stroke.

Material and methods

PROSPERO Registration number: CRD42023447405

Inclusion criteria

Study design

Eligible randomized controlled trials (RCTs), observational studies, including cohort (prospective/retrospective), case-control, and cross-sectional designs, were considered for inclusion. We incorporated full-text studies that met the eligibility criteria, while case reports/series and unpublished grey literature were excluded from the analysis.

Study participants

Studies done amongst the patients with acute ischaemic stroke and undergoing transcranial ultrasonography imaging were included.

Index test and reference standard

Studies comparing the diagnostic role of transcranial ultrasonography in the form of either TCD/TCCD/TCCS with the gold standard techniques (magnetic resonance angiography (MRA), computed tomography angiography (CTA), cerebral or intra-arterial angiography, real time diagnosis at hospital discharge) through the follow-up of patients either through records or in-person were included.

Outcomes

Detection of stenosis amongst acute ischaemic stroke patients using accuracy parameters such as sensitivity, specificity, positive and negative likelihood ratios

Search strategy

The search was conducted in multiple databases, including "CINAHL, SCOPUS, EMBASE, MEDLINE, Cochrane Library, Google Scholar, and ScienceDirect". Our search strategy incorporated medical subject headings (MeSH) and free-text terms. We employed appropriate Boolean operators ("AND," "OR," and "NOT") to combine predefined search terms. The search period spanned from January 1964 to June 2023, without any language restrictions (Supplementary File 1).

Study selection

A pair of independent researchers conducted the initial stage of the study selection process by examining the titles, keywords, and abstracts. Both investigators obtained full-text studies and narrowed them down for the second phase of screening according to the eligibility criteria. In the second step, the researchers evaluated the retrieved full-texts, and those that met the eligibility criteria were ultimately included for further analysis. The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist of diagnostic test accuracy studies (PRISMA-DTA)" was employed to report this review (supplementary file) [12].

Data extraction

Upon determining the full-text articles eligible for inclusion, both researchers participated in the manual data extraction procedure, utilizing a predefined semi-structured data collection form. The data collection form contained the following information: author details, publication year, setting, country, study design, participants, sample size, TCD details, reference standards, and accuracy parameters. Data was entered by the first author and verified by the second author.

Risk of bias assessment

A pair of investigators took on the task of evaluating the quality of the included studies. They employed the QUADAS ("Quality Assessment of Diagnostic Accuracy Studies") for assessing included studies [13]. The QUADAS tool encompasses "patient selection, index test, reference standard, and flow of patients and timing of index test domains". Based on the responses, each study was categorized as having good/poor quality.

Statistical analysis

By calculating the combined values of sensitivity, specificity, likelihood ratios for positive and negative outcomes as well as the overall diagnostic odds ratio for TCD, diagnostic accuracy was evaluated. Area under the ROC was provided as the result, which was used to produce "Summary Receiver Operator Characteristic curves (sROC)" (AUROC) [14]. Fagan's nomogram and likelihood ratio (LR) scattergram was generated to determine the clinical value of the TCD for detecting stenosis. I^2, chi square of heterogeneity and bivariate box plot were used to measure heterogeneity. Publication bias assessment was assessed using Deek's test and funnel plot. Subgroup analysis and meta-regression was examined using potential covariates. STATA version 14.2 was used for the analysis.

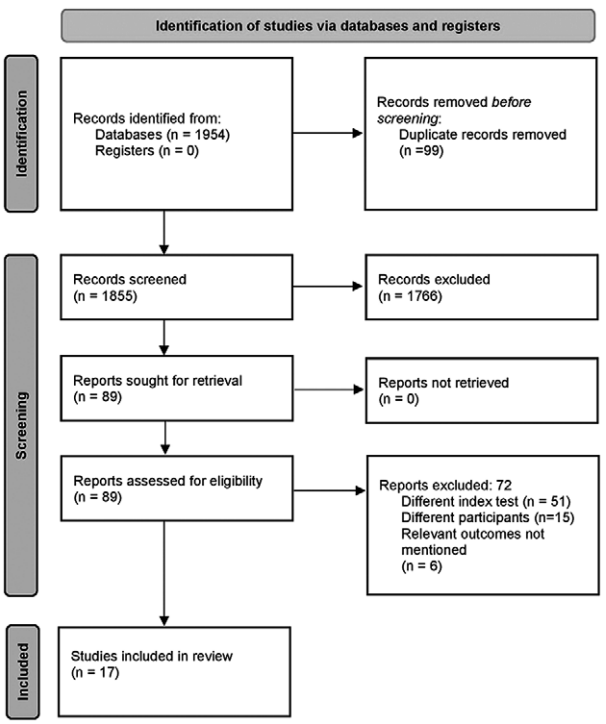

Fig 1. PRISMA flowchart

Results

Studies selection

Search identified 1954 studies. Ninety-nine were eliminated after the duplicate removal. During the initial screening, a total of 89 full-text papers considered for retrieval. Of them, 72 were excluded as not meeting eligibility criteria. Eventually, 17 studies met the eligibility criteria and were included (fig 1) [8-10,15-28].

Characteristics of the included studies

Most studies (14/17) were prospective. Almost half of them were performed in Europe (Italy, United Kingdom, Spain, Czech Republic). The rest were done in Asia (Singapore, China, India). Average age of participants was 52.7 to 74.8 years. To assess the transcranial ultrasonography for detecting stenosis, we looked at the data from 1496 participants. Most studies (14/17 studies) were conducted using TCD. Only 2 studies used the transabdominal approach, while the rest of the studies used a transvaginal approach. Most studies (11/17 studies) had utilized CTA or MRA as the reference standard. Most studies (11/17 studies) had lower risk of bias (Table I).

Diagnostic accuracy of transcranial ultrasonography

In total, 17 studies reported the utility of transcranial ultrasonography for detecting stenosis in acute ischaemic stroke patients. The diagnostic accuracy is visually reported in figure 2a. The diagnostic OR was 186 (95%CI: 61-564), the sensitivity and specificity were 90% (95%CI: 82 - 95%) and 95% (95%CI: 91 - 98%),

and the positive and negative likelihood ratios were 18.7 (95%CI: 9.3-37.6) and 0.10 (95%CI: 0.05-0.19). The AUROC was 0.98 (fig 3a).

Clinical value of the transcranial ultrasonography was high, as indicated by the Fagan's nomogram (positive=93%; negative=6%), which differed significantly

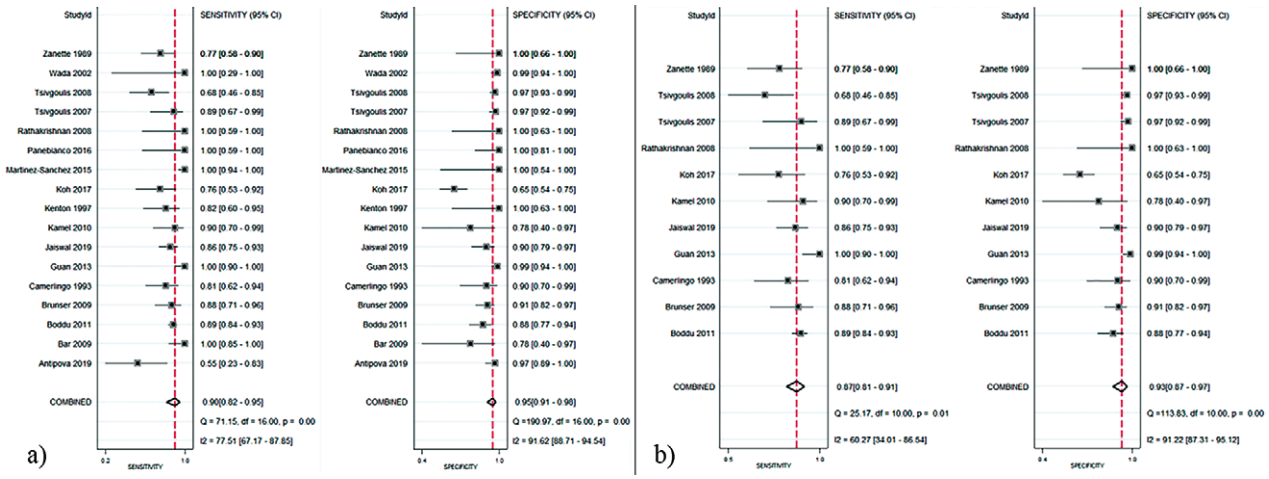

Fig 2. a) Forest plot showing a) the sensitivity and specificity of transcranial ultrasonography; b) the sensitivity and specificity of transcranial Doppler ultrasonography.

Table I. Characteristics of the included studies (N=17)

Author, year	Study design	Country	Artery	Type of ultrasonography	Reference standard	Mean age (in years)	Sample size	Risk of bias
Antipova 2019	Retrospective	UK	Large vessel occlusion	TCCS - Duplex	Hospital discharge	73	75	Low risk
Bar 2009	Prospective	Czech Republic	Any artery	TCCS - Duplex	CTA	64.5	31	Low risk
Boddu 2011	Prospective	India	MCA	TCD - Doppler	MRA	52.7	256	Low risk
Brunser 2009	Prospective	Chile	Any artery	TCD - Doppler	CTA	69.9	100	High risk
Camerlingo 1993	Prospective	Italy	MCA	TCD - Doppler	Cerebral angiography	68.1	48	Low risk
Guan 2013	Prospective	China	MCA	TCD - Doppler	CTA	61.4	128	High risk
Jaiswal 2019	Retrospective	China	anterior circulation stenosis	TCD - Doppler	MRA	68.3	115	Low risk
Kamel 2010	Prospective	Egypt	MCA	TCD - Doppler	MRA		30	Low risk
Kenton 1997	Prospective	UK	MCA	TCCD - Doppler	MRA	74.8	30	High risk
Koh 2017	Retrospective	Germany	basilar artery stenosis	TCD - Doppler	Cerebral angiography	68.6	104	High risk
Martinez-Sanchez 2015	Prospective	Spain	MCA	TCCD - Doppler	CTA	63.8	65	Low risk
Panebianco 2016	Prospective	Italy	MCA	TCCD - Doppler	CTA	60.7	25	Low risk
Rathakrishnan 2008	Prospective	Singapore	MCA	TCD - Doppler	CTA	61	15	Low risk
Tsivgoulis 2007	Prospective	Singapore	MCA	TCD - Doppler	CTA	63	132	High risk
Tsivgoulis 2008	Prospective	Singapore	PCS	TCD - Doppler	CA	65	213	High risk
Wada 2002	Prospective	Japan	MCA	TCCS - Duplex	CA	63	90	Low risk
Zanette 1989	Prospective	Italy	MCA	TCD - Doppler	IAC	66.2	39	Low risk

NR – Not reported; UK – United Kindgom; MCA – Middle Cerebral Artery; TCCS – Transcranial colour coded sonography; TCD – Transcranial Doppler sonography; CTA – Computed Tomography Angiography; MRA – Magnetic Resonance Angiography; PCS – Posterior Circulation Stenosis, CA – Cerebral Angiography, IAC – Intra-arterial Angiography

from the pre-test probability of 40% (fig 4a). Figure 5a shows that LRP and LRN was exactly in between the left upper and right upper quadrant of LR scattergram, indicating the possibility that the test can be applied for the confirmation and exclusion. $I^2 > 75\%$, chi-square p-value of 0.001 and a bivariate box plot (fig 6a) showed significant heterogeneity. Symmetrically formed funnel plot and non-significant p-value (p=0.73) of the Deek's test (fig 7a) indicated the lack of publication bias. Figure 8a shows the meta-regression results, indicating that none of

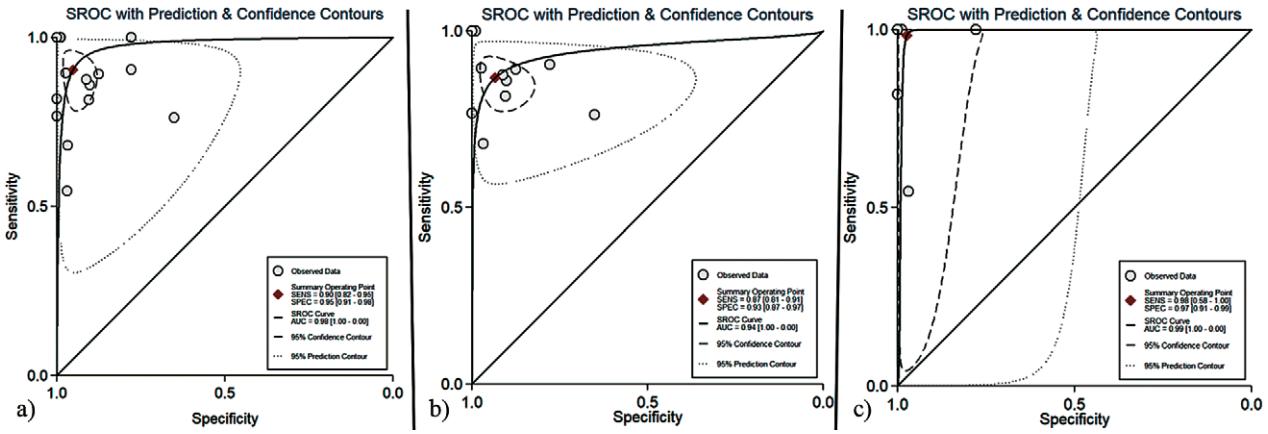

Fig 3. Summary receiver operator characteristics curve for a) transcranial ultrasonography; b) transcranial Doppler ultrasonography; c) transcranial colour-coded or transcranial colour coded duplex ultrasonography.

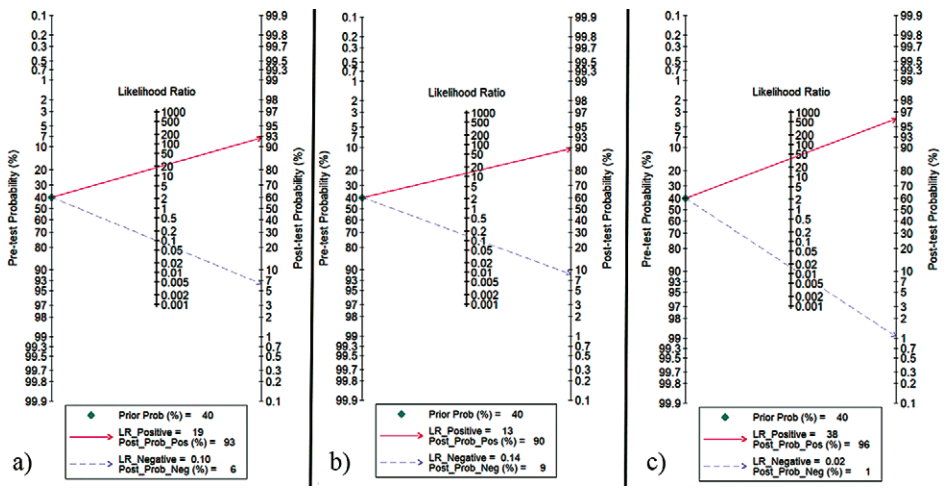

Fig 4. Fagan's nomogram of a) transcranial ultrasonography; b) transcranial Doppler ultrasonography; c) transcranial colour-coded or transcranial colour coded duplex ultrasonography.

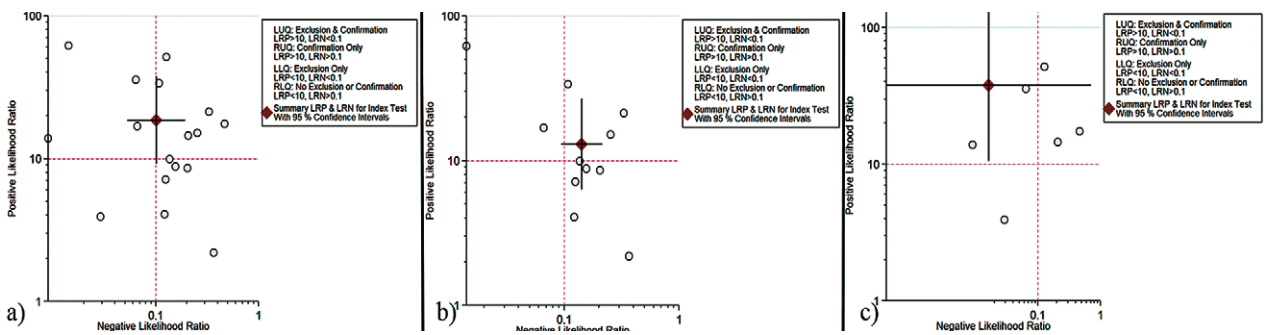

Fig 5. Likelihood ratio scattergram for a) transcranial ultrasonography; b) transcranial Doppler ultrasonography; c) transcranial colour-coded or transcranial colour coded duplex ultrasonography.

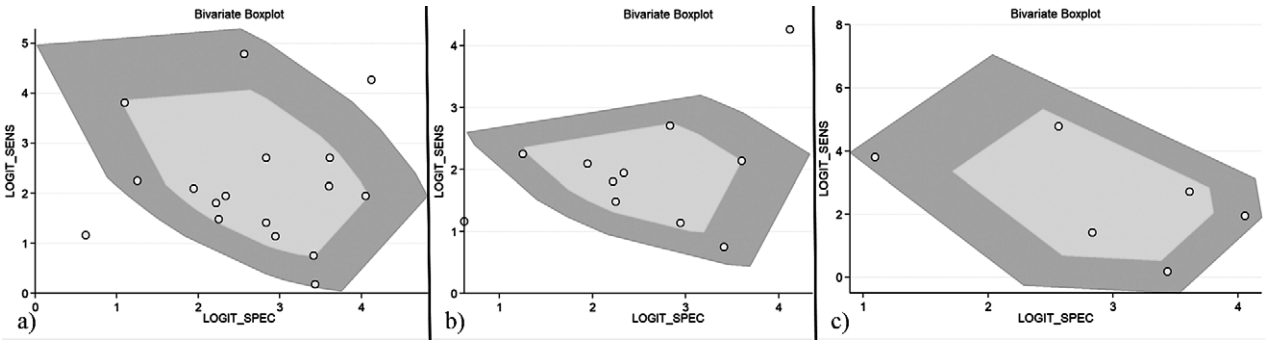

Fig 6. Bivariate boxplot for a) transcranial ultrasonography; b) transcranial Doppler ultrasonography; c) transcranial colour-coded or transcranial colour coded duplex ultrasonography.

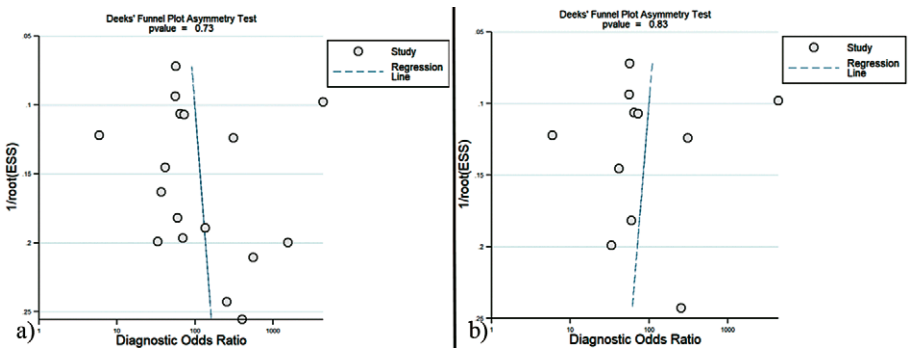

Fig 7. Deek's plot for a) transcranial ultrasonography; b) transcranial Doppler ultrasonography.

the variables were identified as a source of heterogeneity in sensitivity and specificity model. However, mean age was identified as a source of heterogeneity in the joint model ($p<0.001$).

Diagnostic accuracy of TCD

In total, 11 studies reported the utility of TCD for detecting stenosis in acute ischaemic stroke patients. The diagnostic accuracy is visually reported in fig 2b. The diagnostic OR was 92 (95%CI: 35-245), the sensitivity and specificity were 87% (95%CI: 81 - 91%) and 93% (95%CI: 87 - 97%), and the positive and negative likelihood ratios were 13 (95%CI: 6.3-26.8) and 0.14 (95%CI: 0.09-0.21). The AUROC was 0.94 (fig 3b).

Clinical value of the TCD was high, as indicated by the Fagan's nomogram (positive=90%; negative=9%), which differed significantly from the pre-test probability of 40% (fig 4b). Figure 5b shows that LRP and LRN was in the right upper quadrant of LR scattergram, indicating the possibility that the imaging can be applied for the confirmation of stenosis. $I^2 > 75\%$, chi-square p-value of 0.001 and a bivariate box plot (fig 6b) showed significant heterogeneity. The symmetrically formed funnel plot and non-significant p-value (p=0.83) of the Deek's test (fig 7b) indicated the lack of publication bias. Figure 8b shows the meta-regression results, indicating that none of the variables were identified as a source of heterogeneity in the sensitivity model, while study design and country were identified in the specificity model. In the joint model, the mean age was identified as a source of heterogeneity ($p<0.001$).

Diagnostic accuracy of TCCD/TCCS

In total, six studies have reported the utility of TCCD/TCCS for detecting stenosis in acute ischaemic stroke patients. The diagnostic accuracy is visually reported in fig 9. The diagnostic OR was 2357 (95%CI: 45-124085), the

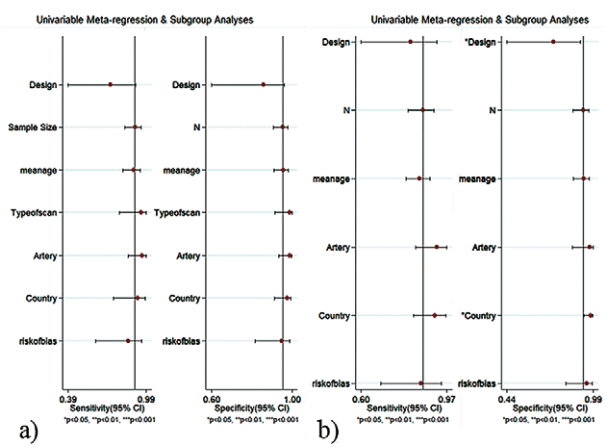

Fig 8. Meta-regression for a) transcranial ultrasonography; b) transcranial Doppler ultrasonography

sensitivity and specificity were 98% (95%CI: 58 - 100%) and 97% (95%CI: 91 - 99%), and the positive and negative likelihood ratios were 37.8 (95%CI: 10.7-134.3) and 0.02 (95%CI: 0-0.69). The AUROC was 0.99 (fig 3c).

The clinical value of the TCCD/TCCS was high, as indicated by the Fagan's nomogram (positive=96%; negative=1%), which differed significantly from the pre-test probability of 40% (fig 4c). Figure 5c shows that LRP and LRN was in the left upper quadrant of the LR scattergram, indicating the possibility that the imaging can be applied for both confirmation and exclusion of stenosis. I^2 >75%, chi-square p-value of 0.001 and a bivariate box plot (fig 6c) showed significant heterogeneity. Publication bias assessment and meta-regression could not be performed due to the limited number of included studies.

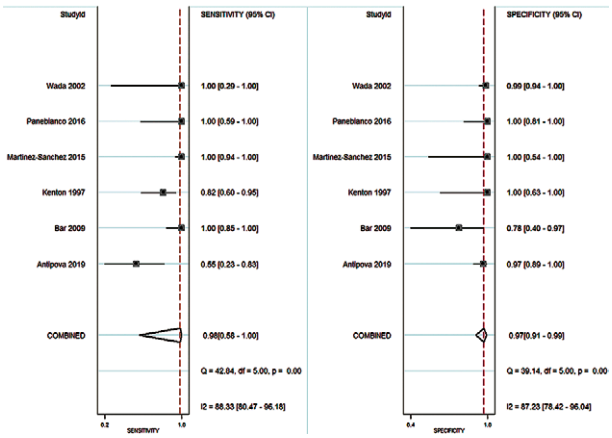

Fig 9. Forest plot showing the sensitivity and specificity of transcranial colour-coded or transcranial colour coded duplex ultrasonography.

Discussion

This systematic review and meta-analysis illuminate the potential of transcranial ultrasonography techniques - TCD, TCCD, and TCCS - in the detection of stenosis in patients with acute ischemic stroke. As ischaemic strokes account for approximately 85% of all stroke occurrences globally, this research has profound implications for the diagnostic approach and management [1].

Given that acute ischaemic stroke's primary etiology is often an occlusion of cerebral arteries, the detection and quantification of arterial stenosis or occlusion are paramount [2]. These findings not only influence the therapeutic intervention but can also predict patient outcomes and monitor disease progression. Our analysis reveals a compelling case for the inclusion of transcranial ultrasonography as an efficient, non-invasive, and cost-effective tool in managing acute ischaemic stroke.

The study's overall findings display a high diagnostic accuracy for transcranial ultrasonography in detecting stenosis in patients with acute ischaemic stroke. The overall diagnostic OR was 186, the sensitivity and specificity were 90% and 95%, respectively, with the AUROC at 0.98. This indicates a high probability that patients diagnosed with stenosis via transcranial ultrasonography are indeed positive for the condition. The high sensitivity further suggests that this technique might be valuable in ruling out stenosis in stroke patients. Comparatively, these findings align with previous studies suggesting the high diagnostic accuracy of transcranial ultrasonography [29,30]. Previous research has pointed towards the potential of these techniques, particularly TCCD/TCCS, in detecting stenosis in acute ischaemic stroke patients. Our meta-analysis, pooling data from multiple studies, provides more robust evidence for this claim, supporting and extending the existing literature.

The diagnostic accuracy of the individual techniques, TCD and TCCD/TCCS, was further examined. TCD demonstrated a diagnostic OR of 92, a sensitivity of 87%, and a specificity of 93%. Despite the slightly lower sensitivity and specificity compared to the overall analysis, the results indicate that TCD is a reliable tool for detecting stenosis in patients with acute ischaemic stroke. TCCD/TCCS, on the other hand, yielded a sensitivity of 98%, and a specificity of 97%. These results suggest that TCCD/TCCS might be even more effective at detecting stenosis than TCD, and therefore should be considered in the clinical decision-making process.

Despite the high sensitivity shown by TCCD/TCCS, there was a wide confidence interval associated with it, suggesting potential variability in its performance across different studies. This could be attributed to variations in operator experience, patient characteristics, or even the precise methodology of the procedure itself. These factors could influence the quality of the images acquired and thus the diagnostic accuracy. Considering this variability, further studies should focus on standardizing the TCCD/TCCS procedure to ensure more consistent and reliable results across different settings and operators.

The high diagnostic accuracy observed for transcranial ultrasonography and its subtypes might be attributed to the inherent properties of these techniques. Transcranial ultrasonography, specifically TCCD/TCCS, offers real-time, high-resolution imaging of intracranial vessels. This allows for the detection of subtle changes in blood flow or vessel morphology, which might be indicative of stenosis. Furthermore, the repeatability of these techniques enables continuous monitoring, improving the likelihood of capturing relevant pathological changes. Yet, these hypotheses require empirical substantiation.

However, it is crucial to contextualize these findings within the limitations of the study. Despite the high diagnostic accuracy, the presence of heterogeneity in the results should not be overlooked. It suggests that other underlying variables, such as study design, country of the study, and average patient age, might have influenced the results. This urges caution in the interpretation and generalization of the findings.

Key strengths of this study include the large sample size achieved through the pooling of data from several studies, enhancing the reliability and generalizability of the results. Moreover, the inclusion of different transcranial ultrasonography techniques and comparison of their diagnostic accuracy allows for a comprehensive evaluation of their potential roles in clinical practice. Additionally, our study adopted rigorous methodological standards, including predefined inclusion and exclusion criteria and quality assessment, contributing to the robustness of the findings.

Transcranial ultrasonography's diagnostic performance was often compared to CT angiography (CTA) and MR angiography (MRA), the currently accepted reference standards. While these modalities may have their limitations, they have been established as the gold standard for a reason. Transcranial ultrasonography does provide several advantages over these traditional methods – bedside availability, repeatability, lack of ionizing radiation, or contrast media. Yet, more robust, comparative studies are required to establish transcranial ultrasonography as an equally reliable or even superior method.

In terms of clinical implications, the high diagnostic accuracy of transcranial ultrasonography signals its potential as a primary screening tool for detecting stenosis in acute ischaemic stroke. This could expedite the diagnosis process, guiding quicker therapeutic decisions, which is vital in acute ischaemic stroke management. Moreover, as a non-invasive and cost-effective method, it could democratize stroke diagnostics, making it more accessible, particularly in low-resource settings.

Conclusion

This review demonstrates the promise of transcranial ultrasonography as a potent tool in detecting stenosis in patients with acute ischemic stroke. Yet, the heterogeneity in the results, coupled with the need for comparative studies, necessitates further research. Nonetheless, the findings underscore the need for a more nuanced discussion on integrating this technique into standard clinical practice for acute ischaemic stroke management.

Conflict of interest: none

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