CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF

PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

http://doi.org/10.5281/zenodo.4658054

Avalable online at: http://www.iajps.com *Review Article*

COMPARISON OF CAROTID DOPPLER ULTRASOUND AND COMPUTERIZED TOMOGRAPHIC ANGIOGRAPHY IN THE EVALUATION OF CAROTID ARTERY STENOSIS: A SYSTEMIC REVIEW AND META-ANALYSIS

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Article Received: February 2021 **Accepted:** February 2021 **Published:** March 2021

Abstract:

Introduction: *Accurate non-invasive carotid imaging is important for effective secondary stroke prevention. We conducted a systematic review and meta-analysis to compare DUS and CTA accuracy for diagnosing (70-99%) carotid artery stenosis.* ***Methodology:*** *A systematic search was conducted in PubMed and Embase from February, 2021, to March, 2021, to compare diagnostic test accuracy of DUS and CTA. The stated method for determining the degree of stenosis (e.g., NASCET or ECST)* ***Results:*** *In 23 included studies with 3229 participants, the pooled sensitivity for CTA test is 0.79 [0.72, 0.85], and the pooled specificity is 0.93 [0.84, 0.97]. We also found that the pooled sensitivity for DUS test is 0.90 [0.80, 0.95], and the pooled specificity is 0.87 [0.75, 0.94]. Regarding the CTA test, most of the points gathered around the top left of the graph, with the area under the curve of 0.87 [0.84-0.90], indicate the test's good accuracy. For the DUS test, most of the points clustered around the top left of the graph, with area under the curve of 0.95 [0.92-0.95], indicating high accuracy of the test.* ***Conclusion:*** *We found relatively high sensitivity and specificity of both CTA and DUS tests. However, the DUS test's accuracy in diagnosing (70-99%) carotid artery stenosis was greater than CTA.*

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Please cite this article in press Maisa ali altarouti et al., ***Comparison Of Carotid Doppler Ultrasound And Computerized Tomographic Angiography In The Evaluation Of Carotid Artery Stenosis: A Systemic Review And Meta-Analysis.,*** *Indo Am. J. P. Sci, 2021; 08(03).*

INTRODUCTION:

Extra-cranial carotid atherosclerosis is a known cause of acute ischemic attacks and stroke, resulting in substantial morbidity and mortality in the population. The degree of stenosis in carotid artery disease can be associated with a stroke [1, 2]. The first observation of atherosclerotic stenosis was Fisher's original report in 1951 [3], which demonstrated that atherosclerotic stenosis is a principal cause of cerebral infarction.

The degree of stenosis, measured as the highest percentage reduction in the diameter of the related carotid artery, may be mild (less than 30%), moderate (30-69%), or extreme (more than 70%). (70-99%) [4]. The burden of cardiovascular disease has increased disproportionally in low- and middle-income countries in the past few decades. Nearly 80% of cardiovascular disease death occur now [5, 6], and by 2030 almost 23.6 million people are expected to die from cardiovascular diseases per year [7].

Doppler ultrasound (DUS) is a non-invasive test that uses the doppler effect (high-frequency sound waves) to produce imagining of the movement of blood flow through blood vessels [8]. Since the discovery of DUS in the 1950s, the Spectral Doppler waveform analysis and color doppler imaging have become commonly used in medical diagnosis and imaging [9].

Diagnostic Doppler works by calculating the discrepancy in the frequency of the original incident acoustic sound wave and the returning echoes' frequency. The returning echoes will have a lower Doppler-shifted frequency if the reflector moves away from the acoustic source (sonographic transducer). However, echoes reflecting by flowing blood that moves towards the transducer would have a greater Doppler-shifted frequency than the incident sonographic beam [10].

DUS is the most prevalent imaging study implemented for diagnosing carotid disease. The extra-cranial carotid arteries with their superficial location are indefectible for color and duplex Doppler sonography (CDDS) [11]. Color Doppler sonography permits simultaneous real-time visualization of vascular lesions and related flow abnormalities. It guides cursor location on potential stenosis areas and helps determine critical stenosis and occlusion [12].

Computed tomographic angiography (CTA)is a non-invasive vascular imaging technique in which angiographic images are generated by viewing or reconstructing vessel structure in three dimensions (3D) as portrayed on overlapping helical CT images [13]. In 1984, ***Heinz* et al. [14]** demonstrated the use of thin-section dynamic CT to enable direct visualization of carotid atheroma and thrombi and 3D reconstructions of the carotid artery. CTA has progressed in tandem with developments in CT hardware and applications. Modern CTA represents carotid disease correctly and consistently and allows for immediate quantification of carotid stenosis in millimeters when done with multidetector high-speed CT hardware and tested with 3D reformatting software [15, 16].

We conducted a systematic review and meta-analysis to detect and compare the accuracy (sensitivity and specificity) of DUS and CTA tests in diagnosing (70-99%) carotid artery stenosis.

METHODOLOGY:

Search strategy

We conducted an electronic systematic search in PubMed and EMBASE from February, 2021, to March, 2021 with a strategy established through initiating appropriate process for diagnostic tests in accordance with the QUADAS-2 quality assessment tool [17]. To validate the quest, we hand-searched core publications from 1990 to 2020 (Radiology, Neuroradiology, American Journal of Neuroradiology, American Journal of Roentgenology, Stroke, and European Journal of Vascular and Endovascular Surgery).

Inclusion and exclusion criteria

Two reviewers independently evaluated the papers with predetermined STARD criteria [18]. Disagreements were discussed and resolved through. We were no capable of assessing every non-English language study, because of a lack of resources for translation. We excluded all studies except those that: included patients with carotid artery stenosis or minor stroke; using DUS or CTA as a diagnostic test; stated that patients had received the reference test; included data for true positives and negatives, false positives and negatives; stated that the index (i.e., non-invasive) test had been assessed blind to the reference test; stated the method for determining the degree of stenosis (e.g., NASCET or ECST); included at least 70 images; stated that the index (i.e., non-invasive) test had been assessed blind to the reference test; stated that the index. We took special care not to use data from redundant publications. We excluded studies articles of carotid imaging in trauma, tumours, healthy volunteers, infants, animals, or test phantoms (plastic tubes with pulsatile flow generators that simulate stenosed vessels) and instead looked at technological advances.

Statistical analysis

Some studies used the number of patients correctly diagnosed as a sample, while others used the number of arteries correctly diagnosed (i.e., two arteries per patient), and even others combined the interpretations of many experts, inflating the sample size as compared to the real number of patients. To obtain the number of patients and arteries per sample, we modified the raw values of true and false positives and negatives as needed. The main research was done on a patient-by-patient basis.

For the primary meta-analysis, we used a random effects model [18] to get an overview estimation of sensitivity and specificity with 95% confidence intervals for each non-invasive imaging technique relative to IAA by stenosis band. We used Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark) for data extraction and STATA 16 software for conducting the diagnostic test accuracy meta-analysis, and creating the forest plots and summary receiver-operator characteristic (SROC) plots for each test. Deek's funnel plots were used to detect publication bias where a p-value < 0.05 was considered significant.

RESULTS:

Search results

A total of 497 study articles were retrieved from the systematic search, with additional 18 articles identified from other sources. 133 duplicate records were identified and removed. After title and abstract screening, 198 articles were excluded. 139 records were excluded after full-text assessment. Eventually, 23 eligible study articles were included in this meta-analysis. The summary of the study selection process is illustrated in PRISMA chart **Figure (1).** The summary of the study characteristics of the included studies is shown in **Table (1).** A total of 3229 participants were included in this meta-analysis. Of the 23 included studies, one study was conducted is in Finland [17], 4 studies are in Germany [18, 21, 25, 31], one study in Boston and Israel [19], 2 studies in Netherlands [20, 34], 2 studies in the USA [22, 20], 2 studies in Spain [23, 28], 3 studies in France [24, 29, 32], 4 studies in Italy [27, 30, 37, 39], 1 study in Japan, 2 studies in Canada [35, 38] and 1 study in North Carolina.

Pooled diagnostic accuracy for CTA and DUS tests

Summary of performance estimates among studies with CTA diagnostic test for carotid artery stenosis (70-99%) is shown in **Figure (2).** The pooled sensitivity for CTA test is 0.79 [0.72, 0.85], while the pooled specificity is 0.93 [0.84, 0.97]. Summary of performance estimates among studies with DUS diagnostic test for carotid artery stenosis (70-99%) is shown in **Figure (3).** We found that the pooled sensitivity for DUS test is 0.90 [0.80, 0.95], and the pooled specificity is 0.87 [0.75, 0.94].

Illustrated diagnostic accuracy for CTA and DUS tests

A graphical display of the previous results, with sensitivity on the vertical axis and specificity on the horizontal axis, is indicated in **Figure (4) and figure (5).** The graphical results of the CTA test's sensitivity and specificity are illustrated in the summary receiver operating characteristic (SROC) plot in **Figure (4).** Most of the points gathered around the top left of the graph, with the area under the curve of 0.87 [0.84-0.90], indicate the test's good accuracy. The graphical results of the DUS test's sensitivity and specificity are illustrated in the SROC plot in **Figure (5).** Most of the points clustered around the top left of the graph, with the area under the curve of 0.95 [0.92-0.95], indicating the test's high accuracy.

Publication bias

Deeks' funnel plot was demonstrated to estimate the publication bias. There was no publication bias detected for the CTA test (P=0.13) (**Figure 6).** However, we detected publication bias for DUS tests (P=0.05) **(Figure 7).**

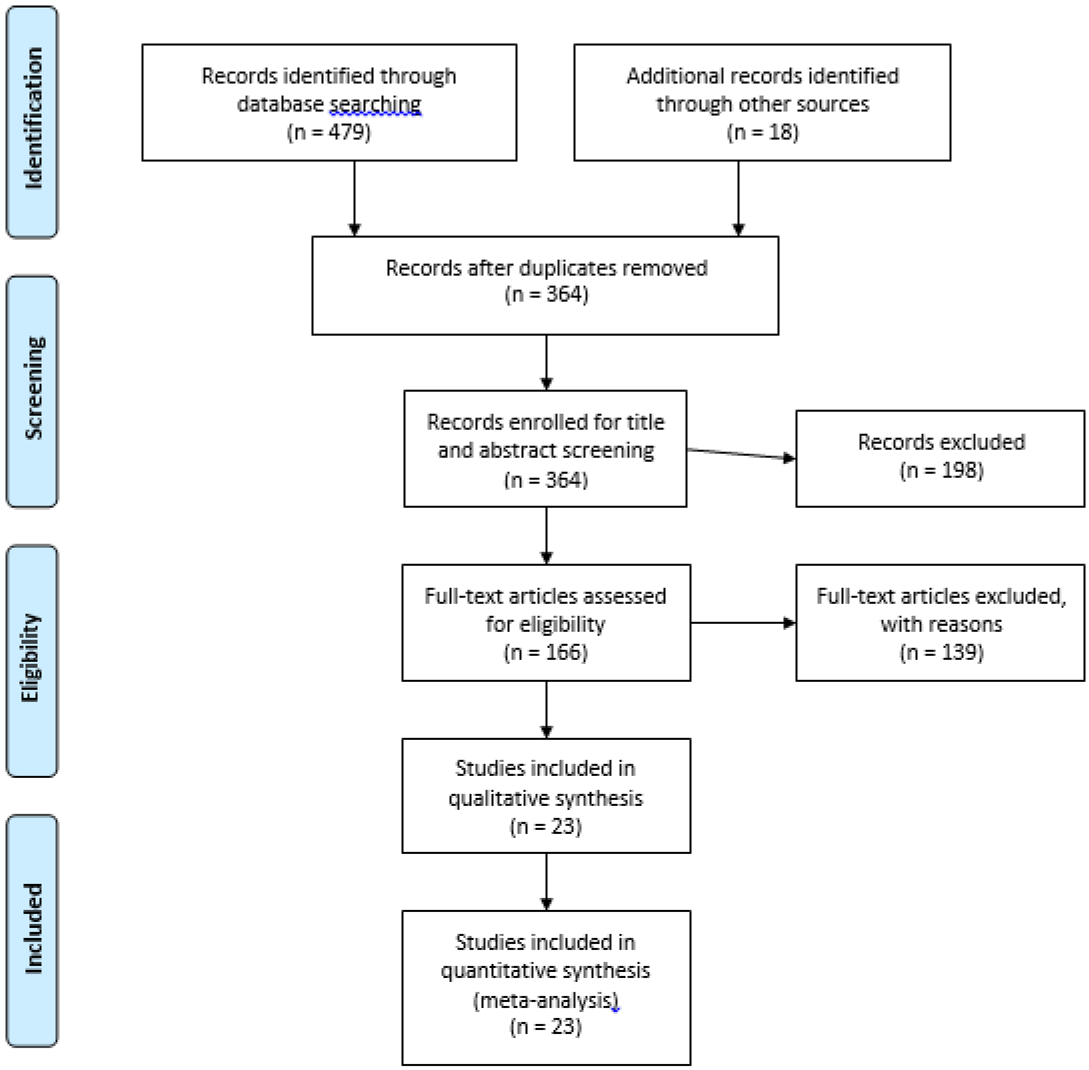

Figure (1). PRISMA flow chart shows the summary of the study selection.

Study (Author, year) [Ref]	Mean age (range)	Number of patients (arteries)	Country	Type of non-invasive imaging	Disease spectrum	Cut-off at 70 NASCET
Vanninen R, 1995 [21]	59 (34–72)	45 (90)	Finland	MRA, DUS	0-100%	Yes
Sitzer M, 1993 [22]	Median 60 (39–80)	56 (111)	Germany	MRA	≥70% by DUS	Yes
Patel MR, 1995 [23]	70 (48–87)	88 (167)	Boston and Israel	DUS, MRA	0-100%	Yes
Nederkoorn PJ, 2002 [24]	67 (39–88)	313 (313)	Netherlands	MRA, DUS	0-100%	Yes
Link J, 1997 [25]	63 (46–77)	28 (56)	Germany	CTA, DUS	0-100%	Yes
Knudsen L, 2002 [26]	-	65 (129)	USA	DUS	0-100%	Yes

de la Cruz Cosme, 2019 [27]	66±13	228	Spain	DUS	0-100%	Yes
Chappell FM, 2009 [28]	67 (26–91)	1456	France	DUS, MRA, CTA	0-100%	Yes
Borisch I, 2003 [29]	67·4 (41–80)	39 (71)	Germany	MRA, DUS	0-100%	Yes
Bönig L, 2000 [30]	66·3 (40–80)	79 (158)	USA	CTA, DUS	0-100%	Yes
Simeone A, 1997 [31]	(35–75)	40 (80)	Italy	CTA	0-100%	Yes
Santos AL, 2001 [32]	Median 68 (14-83)	428	Spain	CTA	0-100%	Yes
Randoux B, 2001 [33]	Median 70 (59-83)	22 (44)	France	CTA, MRA	0-100%	Yes
Magarelli N, 1998 [34]	65	20 (40)	Italy	MRA, CTA	0-100%	Yes
Link J, 1996 [35]	63 (42–80)	64 (92)	Germany	CTA	0-100%	Yes
Leclerc X, 1999 [36]	Median 61 (42–84)	22 (44)	France	CTA	0-100%	Yes
Hirai T, 2001 [37],	68 (52-82)	21 (42)	Japan	CTA, DSA	0-100%	Yes
Dillon EH, 1993 [38]	62·5 (37–79)	27 (50)	Netherlan ds	CTA	Screened by DUS	Yes
Cumming MJ, 1994 [39]	75 (51–85)	35 (70)	Canada	CTA	0-100%	Yes
Castillo M, 1993 [40]	(40-76)	20 (40)	North Carolina	CTA	0-100%	Yes
Bozzao A, 1998 [41]	-	53 (106)	Italy	Angio-spiral CTA	0-100%	Yes
Anderson GB, 2000 [42]	(44-83)	40 (80)	Canada	CTA	≥50% by DUS	Yes
Alvarez-Linera J, 2003 [43]	61·5 (42–80)	40 (80)	Italy	MRA, CTA	≥70% by DUS	Yes

Table (1): shows the study characteristics of the included studies.

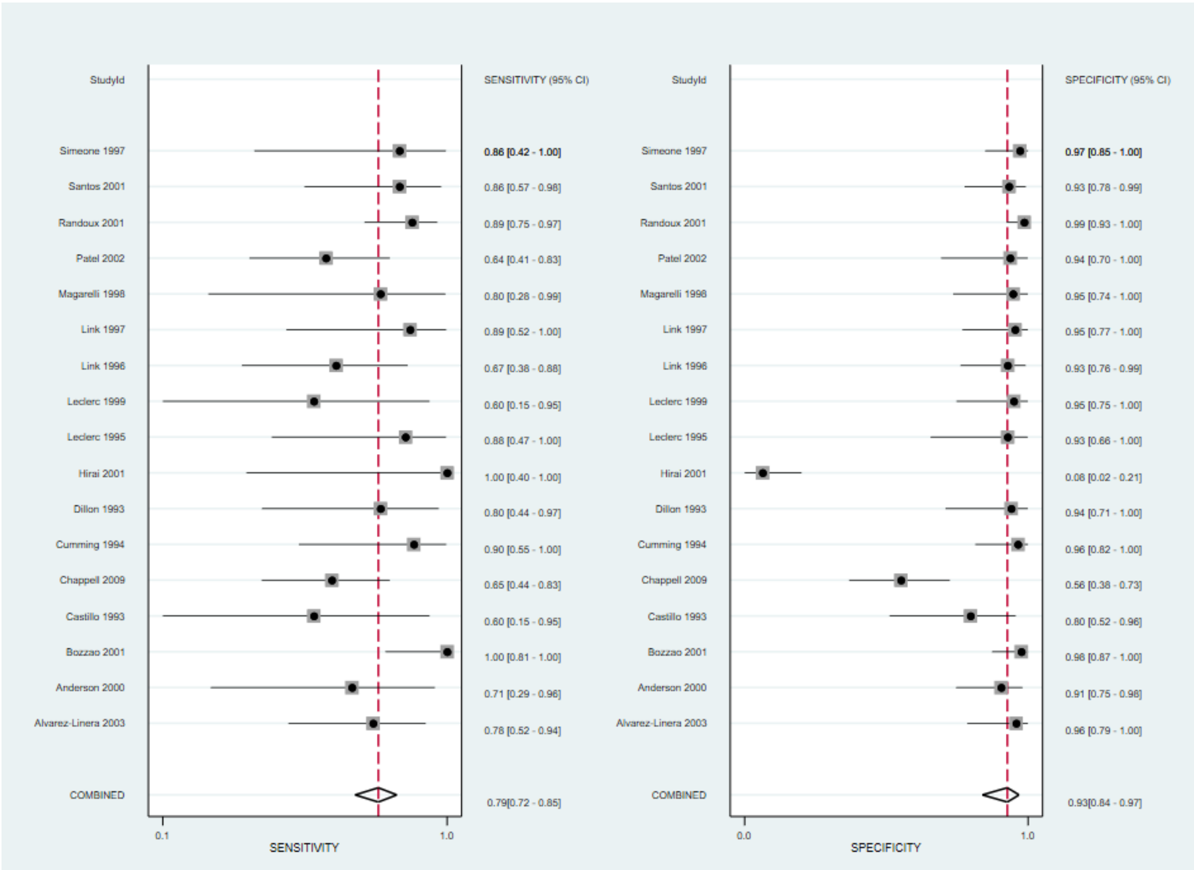

Figure (2): Forest plot of sensitivity and specificity of studies used CTA in the diagnosis of carotid artery stenosis (70-99%).

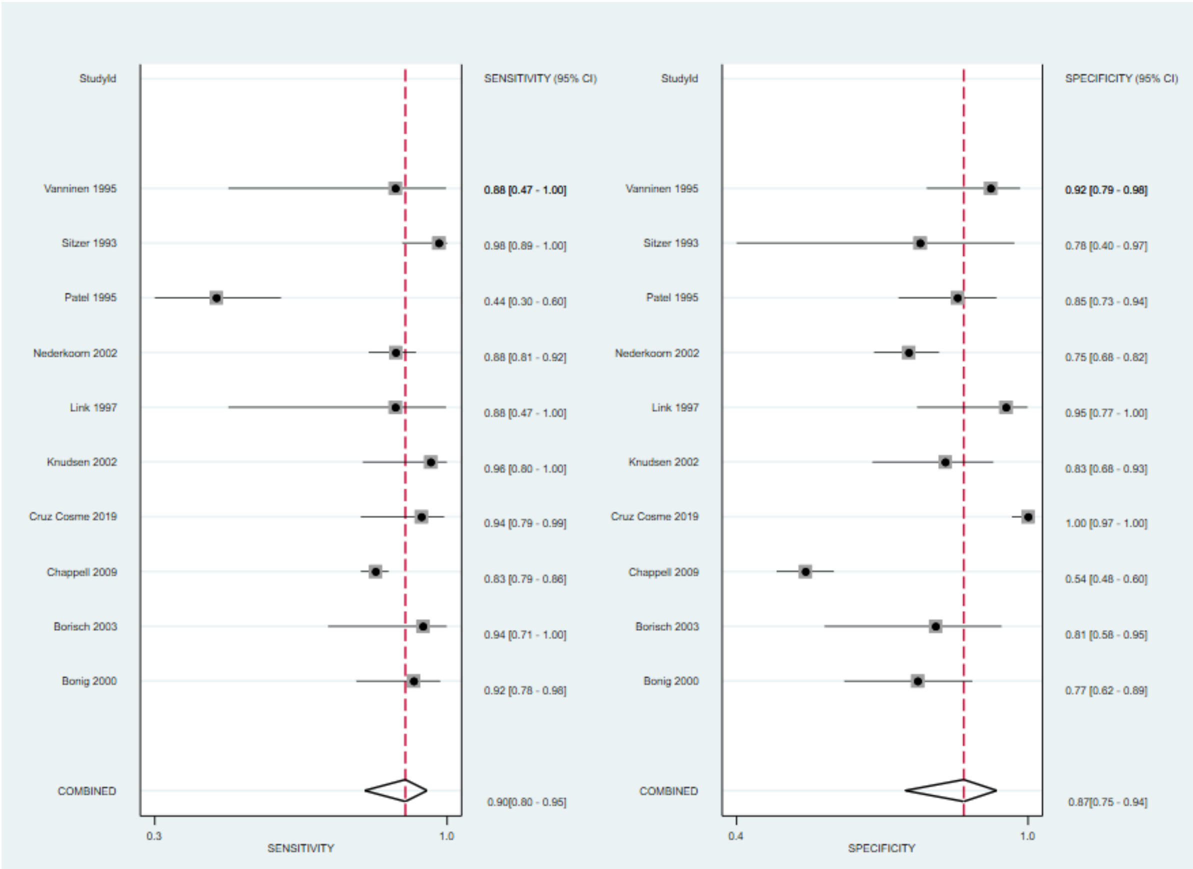

Figure (3): Forest plot of sensitivity and specificity of studies used DUS in the diagnosis of carotid artery stenosis (70-99%).

(70-99%) stenosis	**CTA**	**DUS**
Sensitivity (95% CI)	0.79 [0.72-0.85]	0.90 [0.80-0.95]
Specificity (95% CI)	0.93 [0.84-0.97]	0.87 [0.75-0.94]
Positive Likelihood Ratio	10.9 [4.6-25.8]	6.8 [3.3-13.8]
Negative Likelihood Ratio	0.22 [0.16-0.31]	0.12 [0.06-0.24]
Diagnostic Odds Ratio	49 [16-148]	58 [17-197]

Table (2): Meta-analysis of sensitivity and specificity of carotid artery stenosis (70-99%) and imaging techniques.

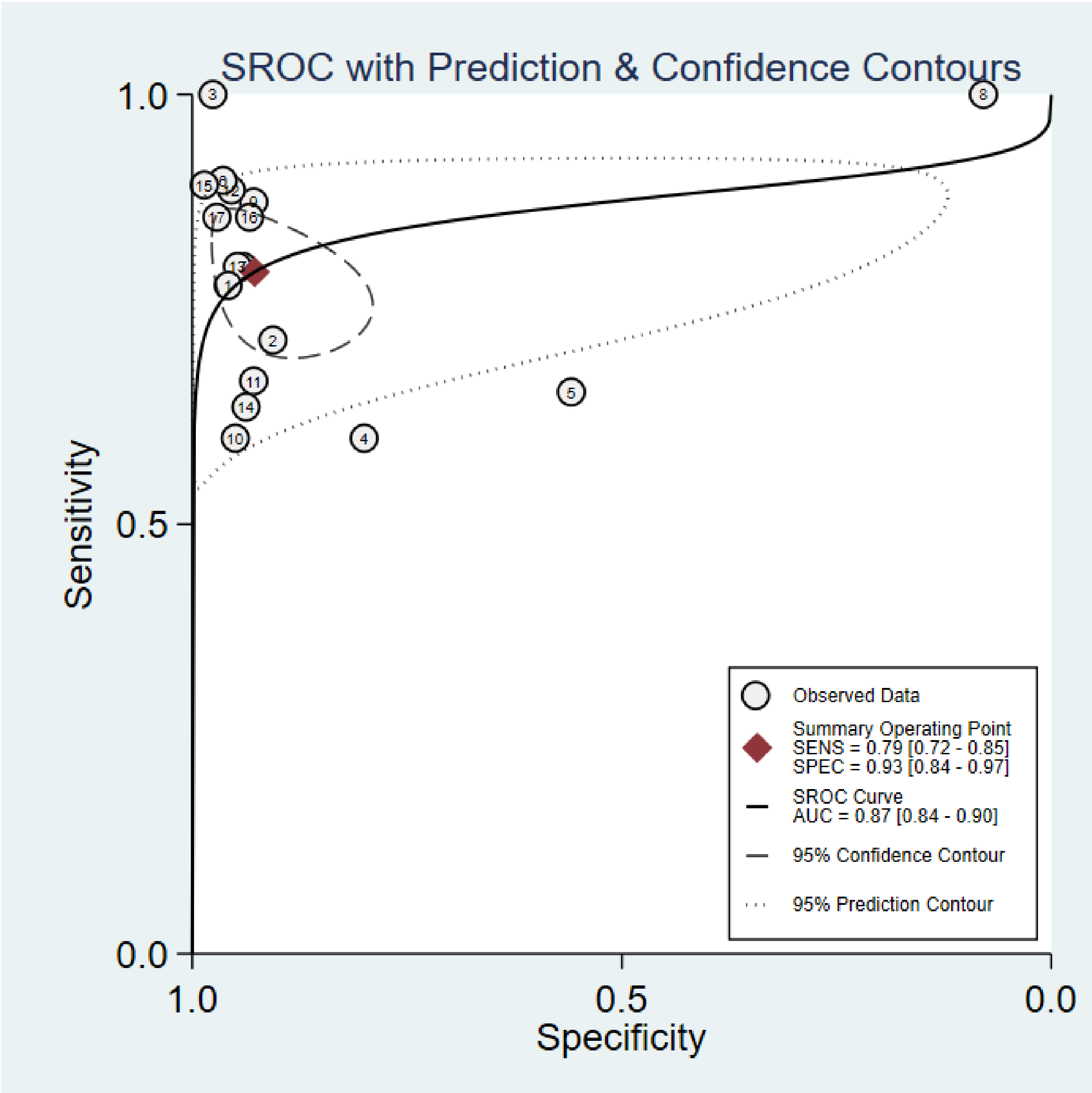

Figure (4): SROC plot of sensitivity and specificity of CTA in carotid arterial stenosis diagnosis (70-99%).

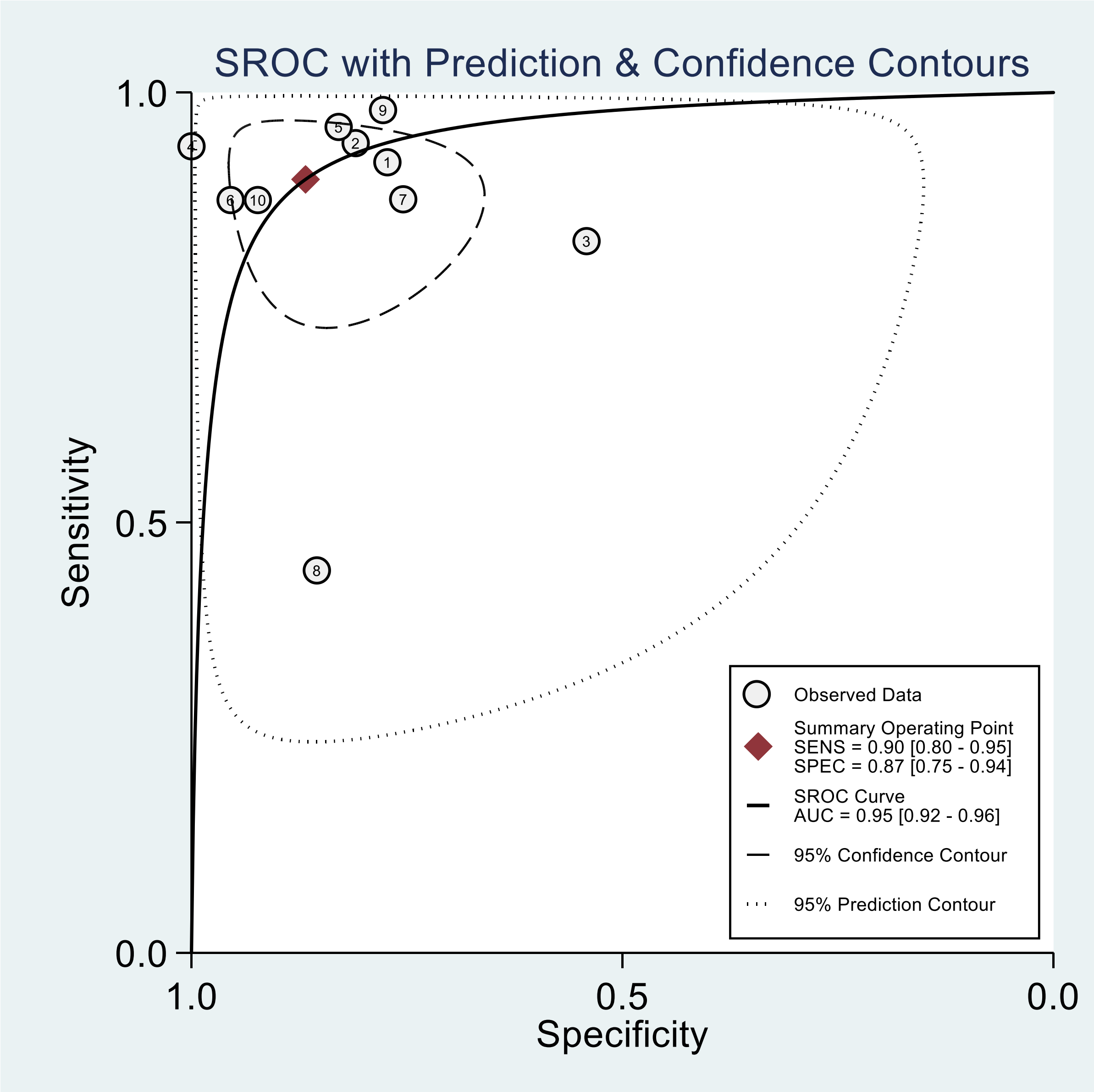

Figure (5): SROC plot of sensitivity and specificity of DUS in the diagnosis of carotid arterial stenosis (70-99%).

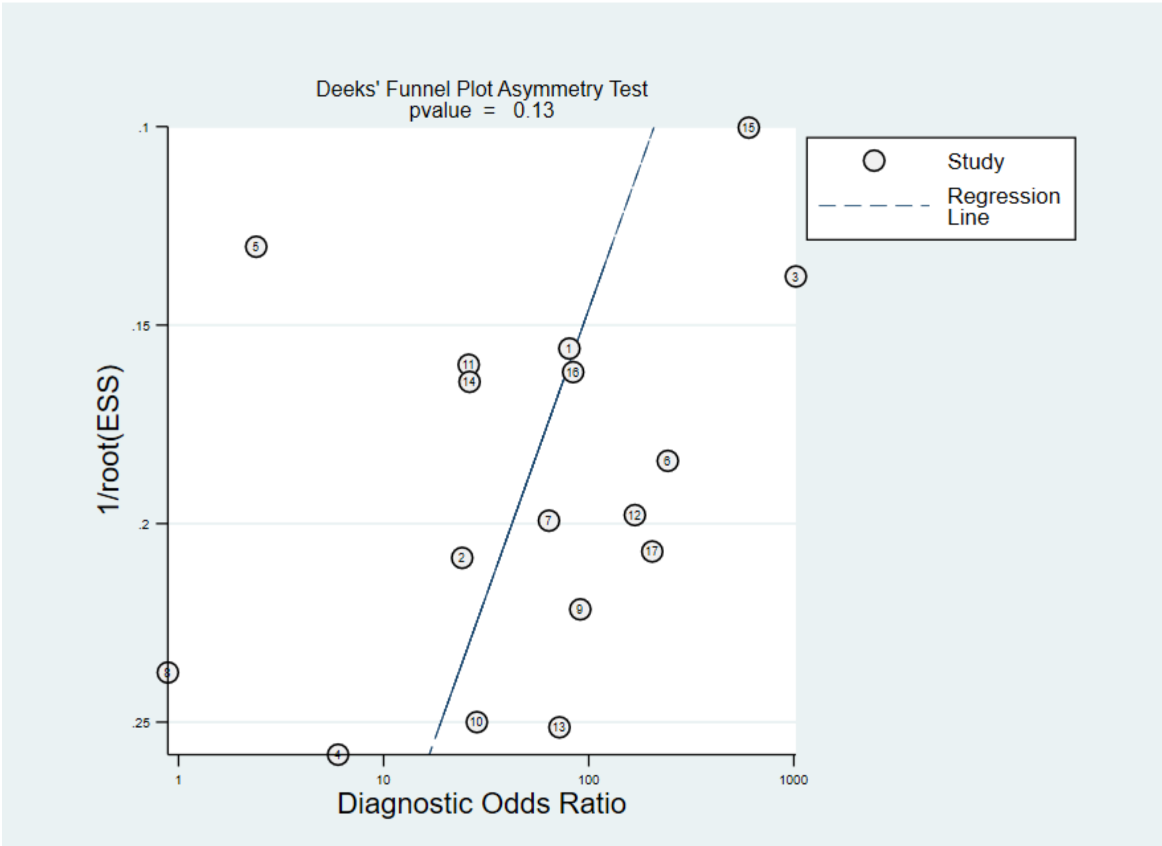

Figure (6): Deeks' funnel plot for publication bias of CTA diagnostic odds ratio.

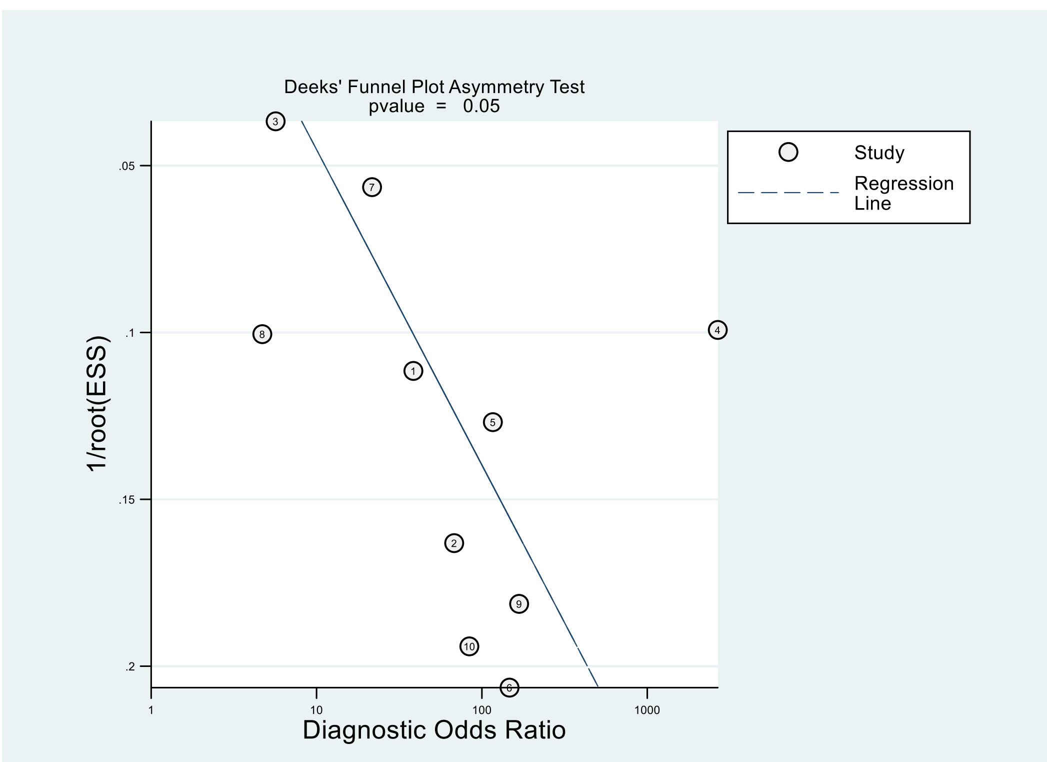

Figure (7): Deeks' funnel plot for publication bias of DUS diagnostic odds ratio.

DISCUSSION:

Proper management and diagnosis of carotid artery stenosis require a multifaceted approach [44]. This systematic review and meta-analysis were conducted to compare the accuracy (sensitivity and specificity) of CTA and DUS tests in diagnosing (70-99%) carotid artery stenosis.

This study found that the pooled sensitivity CTA test was 0.79 [0.72-0.85], and the pooled specificity is 0.93 [0.84-0.97]. We found that the pooled accuracy of the CTA test was 0.87 [0.84-0.90], indicating good accuracy of the test. A meta-analysis conducted by ***Wardlaw*** **et al. [45]** also reported similar results to ours with a sensitivity of 0.77 [0.68-0.84] and specificity of 0.95 [0.91-0.97].

Our records were more conservative than a similar meta-analysis that estimated the accuracy of CTA and reported a pooled sensitivity of 91.6% and a pooled specificity of 97.4% for diagnosing (70-99%) stenosis [46]. This difference could be explained as they included many studies to evaluate different post-processing techniques more than once. A retrospective review compared CTA and ultrasonography (US) for the stented carotid artery found that CTA provided better image quality than the US [47].

DUS is usually the only diagnostic method utilized to determine the degree of stenosis [48]. Our results reported that the pooled sensitivity for DUS test is 0.90 [0.80, 0.95], and the pooled specificity is 0.87 [0.75, 0.94]. We also found that the DUS test's pooled accuracy was 0.95 [0.92-0.95], indicating the test's high accuracy. ***Wardlaw*** **et al. [45]** also reported similar results to ours with a sensitivity of 0.89 (0.85–0.92) and specificity of 0.84 (0.77–0.89).
Another meta-analysis conducted by ***Chappell*** **et al. [28],** based on literature and reported that the sensitivity of DUS in diagnosing (70-99%) carotid stenosis 0.89 [0.85-92]and specificity of 0.84 [0.77-0.89].

Moreover, only Doppler US had higher audit proportions than the other modalities, which may be one explanation for the disparity in diagnostic precision between contrast-enhanced MR angiography and Doppler US, despite Doppler US performing as well as CT angiography and MR angiography. MR angiography precision is considered to differ with the proportion of diseased arteries, at least in theory [49]. ***Sameshima*** **et al.** [50] compared CTA MIP images with DSA in the largest sequence to date (128 arteries). They discovered a 0.987 correlation overall. For full occlusions, they had absolute consensus, and for 70% –99% stenoses, they had sensitivity, reliability, and consistency of 93%, 100%, and 98%, respectively. They discovered as we did that CTA was less accurate in identifying intermediate degrees of stenosis.

While researchers have reported that the average doppler velocity increases in direct proportion to the degree of stenosis as determined by angiography [51], the ranges of Doppler values across those measures are extremely broad, making it difficult to classify lesions into gradations as narrow as 10% [51, 52]. Also, when assessing the capacity of DUS to help measure the degree of stenosis by using more extended strata (e.g., 50%, 50%–69%, and 70% stenosis), the results have been frustrating. When lesions are categorized as being above or below a single stage, such as 60% stenosis or 70% stenosis, US is most reliable [51].

Limitations

Locating and collecting data sets was time-consuming and resource-intensive compared to a detailed analysis of published data. The absence of data sets that aren't visible may be a source of prejudice. A lack of evidence plagued some studies. We were also unable to make firm recommendations on which test should be used, as this would be contingent on availability, expense, and other factors. The nature of this research did not allow for a total cost-effectiveness review.

CONCLUSION:

This systematic review and meta-analysis reported relatively high sensitivity and specificity of both CTA and DUS tests. However, the DUS test's accuracy in diagnosing (70-99%) carotid artery stenosis was greater than CTA.

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