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Review Article

Diagnostic Accuracy of 64-Slice Computed Tomography Angiography in Patients with Chest Pain vs. SPECT in the Assessment of Significant Coronary Artery Disease: A Systematic Review and Meta-analysis

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Abstract

Context: This systematic review and meta-analysis intended to investigate the diagnostic accuracy of computed tomography angiography (CTA) in comparison with single-photon emission computed tomography (SPECT) for the diagnosis of coronary artery disease (CAD) in chest pain patients with no history of cardiovascular diseases (CVDs).

Methods: Invasive angiography was considered as the reference test with a stenosis threshold of $\geq$ 50%. Cochrane, Scopus, Science Direct, PubMed, and Embase databases were comprehensively searched from the time of inception of these databases to May 15, 2018. A manual search in Google Scholar, a reference review of the obtained studies, and a review of gray literature (including those presented in conferences and congresses) regarding diagnostic performances of CTA and SPECT techniques were performed independently by two researchers. A meta-analysis was performed to determine pooling estimates of sensitivity, specificity, diagnostic odds ratio, and positive as well as negative likelihood ratios in CTA and SPECT tests. According to the 2 × 2 contingency table of each study, at 0.95 confidence interval, the diagnostic accuracy of CTA and SPECT was meta-analyzed by pooling estimates of sensitivity, specificity, diagnostic odds ratio (DOR), and positive and negative likelihood ratios based on DerSimonian-Laird's random-effects model. Heterogeneity was assessed by calculating I2. Analyses were performed using MetaDiSc version 1.4 and Stata version 11. The qualities of the selected studies were assessed independently by two researchers according to the quality assessment of diagnostic accuracy studies (QUADAS) questionnaire. Sensitivity analyses were performed by the Jackknife method. Publication bias was evaluated by Deeks' funnel plot.

Results: Fourteen studies related to CTA (1206 individuals) and 15 related to SPECT (1638 individuals) were eligible for meta-analysis. The pooled sensitivity and the specificity of CTA for CAD diagnosis were 91% (95% CI, 88% - 94%) and 87% (95% CI, 84% - 98%), respectively. The pooled positive and negative likelihood ratios, the diagnostic odds ratio, and the area under the ROC curve for CTA were 7.93 (95% CI, 5.11 - 12.29), 0.1 (95% CI, 0.06 - 0.17), 95.71 (95% CI, 59.81 - 153.15), and 0.96, respectively. The pooled sensitivity and the specificity of SPECT for CAD diagnosis were 81% (95% CI, 79% - 83%) and 74% (95% CI, 71% - 78%), respectively. The pooled positive and negative likelihood ratios, the diagnostic odds ratio, and the area under the ROC curve for SPECT were 3.03 (95% CI, 2.34 - 3.91), 0.25 (95% CI, 0.21 - 0.30), 13.56 (95% CI, 10.60 - 12.34), and 0.86, respectively. According to the sensitivity analyses, the removal of any single study at a time did not change the effect size of the remaining studies. We observed symmetry in the Deeks' funnel plot, indicating that there was ignorable publication bias for CTA and SPECT studies.

Conclusions: This study demonstrated that the diagnostic accuracies of CTA and SPECT tests lie in the 'excellent' and the 'very good' ranges, respectively. CTA is stronger evidence, than SPECT, to rule out CVDs in patients with low and intermediate risks of CAD with no history of cardiovascular diseases.

Keywords: Coronary Artery Disease; Computed Tomography Angiography; Single-photon Emission Computed Tomography (SPECT); Sensitivity; Specificity

1. Context

Cardiovascular diseases (CVDs) are the leading cause of death globally. In 2016, CVDs claimed about 17.9 million lives, which accounts for about 31% of the world's total mortality (1). According to the current European and American Guidelines on Coronary Artery Disease (CAD) management, patients with an average pre-test probability (PTP) of 15% - 85% of CAD should be evaluated using non-invasive tests (2, 3).

Computed tomography angiography (CTA) is used as a non-invasive method for monitoring coronary artery status following the intravenous injection of contrast material to clearly visualize the vessels that carry blood in and out of the heart (4). Single photon emission computed tomography (SPECT) imaging is a nuclear medicine technique that is regarded as the most frequently used tool for myocardial perfusion diagnosis. In this method, following either the exercise-stress or the drug-stress test-

ing, a radiopharmaceutical agent is administered intravenously, and images are taken by a gamma camera. Heart defects, which result in reduced radiopharmaceutical uptake, are indicators of CAD (stenosis $\geq 50\%$) (5).

In recent years, several studies have investigated computed tomography angiography (CTA) in assessing diagnostic accuracy and have reported high accuracy of CTA in ruling out CAD in suspected individuals with a history of CVDs (6-19). To the best of our knowledge, no systematic study has focused on suspected individuals without a history of CVDs. In this study, we compared the diagnostic accuracy of the two aforementioned tests in chest pain patients with low or intermediate risk for CAD with no history of CVDs.

This systematic review and meta-analysis intended to evaluate the diagnostic accuracy of CTA in comparison with SPECT for diagnosis of CAD in chest pain patients with no history of CVDs. Invasive angiography was considered as the reference test with a stenosis threshold of $\geq 50\%$.

2. Methods

This study was performed following the Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guideline. Two independent researchers systematically searched Science Direct, PubMed, Cochrane, Scopus, and Embase databases to identify relevant studies. Since CTA was introduced in 2004 (20) and SPECT was introduced in 1990 (20), search periods for CTA-related and SPECT-related studies were from January 2004 to May 15, 2018, and from January 1990 to May 15, 2018, respectively. As two systematic reviews on CTA and SPECT were conducted, respectively, in April 2012 (21) and January 2012 (22), their search results were used in this study. A manual search in Google Scholar, a reference review of the obtained studies, and a review of gray literature (including those presented in conferences and congresses) were performed up until 2018. The search was limited to human studies, either in English or Persian. After removing duplicates, the titles and abstracts of all identified studies were independently reviewed by two individuals, and, in the next phase, full-text articles were screened by two individuals independently. In case of a disagreement, a consensus was reached through discussion or, if necessary, the third reviewer was consulted. If the full text of an article was not available, it was requested from its corresponding author through an email.

The inclusion criteria for CTA and SPECT were as follows:

Examining CAD in chest pain patients or in individuals with low to intermediate risk for CAD without a CVD history.

Investigating the accuracy of CTA diagnostic test with a 64-slice single-source CT scan. (Because it is the minimum slice for CAD diagnosis) (23).

Invasive coronary angiography (ICA) should be considered as the reference test with a stenosis threshold of $\geq 50\%$ (5). The study design should be cross-sectional or cohort.

The exclusion criteria for CTA and SPECT were as follows:

Study participants other than chest pain patients with a CVD history (MI, coronary care unit (CCU) admission, heart surgery, CAD, and heart failure were considered as a positive history of CVD)

Patients with an acute coronary syndrome or with a high probability of CAD.

Languages other than English or Persian.

Investigating non-human subjects.

Having a case-control design.

Not using ICA for all patients.

The CTA obtained from devices other than the 64-slice single-source CT scan.

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the quality of articles.

A sensitivity analysis was performed using the Jackknife method to find out whether a single study had undue influence on the results of the study. In the Jackknife method, one study at a time was excluded, and the repeated calculation of the pooled estimates of DOR was used as effect size for the remaining studies to find out that there was a significant change in effect size.

Data extraction forms included essential information such as the first author's surname, publication year, study location, number of cases, the mean and standard deviation of age, proportion of male participants, true positive, true negative, false positive, and false negative. The data of the included articles were extracted by two reviewers separately. Disagreements were resolved by consensus.

2.1. Statistical Analysis

According to the 2×2 contingency table of each study, at a 0.95 confidence interval, the diagnostic accuracies of CTA and SPECT were meta-analyzed by pooling estimates of sensitivity, specificity, and positive and negative likelihood ratios based on a random-effects model (DerSimonian-Laird). Heterogeneity was assessed by calculating I^2. Analyses were performed using MetaDiSc version 1.4 and Stata version 11. Publication bias and sensitivity analysis were evaluated by Deek's funnel plot and the Jackknife method, respectively.

The following tables were used to interpret the results and evaluating the associations between the area under the ROC curve, the diagnostic accuracy, and the likelihood ratios (Tables 1 and 2) (24, 25).

Table 1. Likelihood ratios (LR) interpretation

Interpretation	Negative LR	Positive LR
Generate large and often conclusive shifts in probability	< 0.1	> 10
Generate moderate conclusive shifts in probability	0.1 - 0.2	5 - 10
Generate small but sometimes important shifts in probability	0.2 - 0.5	2 - 5
Alter probability to a small and rarely important degree.	0.5 - 1	1 - 2

Table 2. The Association Between the Area Under the ROC Curve and Diagnostic Accuracy

Diagnostic Accuracy	Area Under the ROC Curve
Excellent	0.9 - 1
Very good	0.8 - 0.9
Good	0.7 - 0.8
Sufficient	0.6 - 0.7
Bad	0.5 - 0.6
Test not useful	< 0.5

3. Results

The main search resulted in 4891 articles, and 123 articles were identified by a hand search. Titles and abstracts of the articles were reviewed. After deleting duplicates, 3293 articles were left. According to the inclusion and exclusion criteria, titles and abstracts of the remaining ones were reviewed, which resulted in the removal of 2399 articles. In the next step, the full texts of 894 articles were examined in detail. Of these, 29 were included in the final analysis. Among the 29 articles, 14 were focused on investigating the diagnostic accuracy of CTA (1206 participants) and 15 on investigating the diagnostic accuracy of SPECT (1638 participants). Full specifications of all selected articles are presented in Table 3.

Table 3. Studies Characteristics [CTA (A), SPECT (B)]

	Year	Participants	TP	FP	FN	TN	Mean Age ± SD	Men, %
A. Study-ID (CTA)								
Ilic and Jankovic (26)	2016	78	29	3	2	44	64.3 ± 11	71.79
Achenbach et al. (27)	2008	51	19	5	3	24	65 ± 11	100.00
Herzog et al. (28)	2007	40	16	3	0	21	61 ± 8	55.00
Ropers et al. (29)	2006	81	25	5	1	50	58 ± 10	64.20
Sheikh et al. (30)	2009	73	51	1	2	19	60 ± 9	75.71
Budoff et al. (31)	2017	77	27	5	5	40	54 ± 10.5	64.20
Chow et al. (32)	2011	117	58	2	13	44	59.9 ± 9.9	62.96
Kerl et al. (33)	2011	113	43	4	0	66	65	82.19
Husmann et al. (34)	2008	63	23	6	3	31	64.8 ± 9.4	57.14
Ladeiras-Lopes et al. (35)	2016	95	42	22	0	31	62 ± 8.2	59.83
Budoff et al. (36)	2008	227	52	30	3	142	57 ± 10	63.33
Herzog et al. (37)	2009	29	16	1	0	12	62 ± 8.4	95.24
van Werkhoven et al. (38)	2010	61	16	5	0	40	57 ± 9	68.42
Joutsiniemi et al. (39)	2012	101	24	3	10	64	64	59.13
B. Study-ID (SPECT)								
San Roman et al. (40)	1998	92	54	9	8	21	64 ± 10	54.35
Tsougos et al. (41)	2012	359	187	24	51	97	59.8 ± 9.8	74.65
Ozguven and OztUrk (42)	1993	27	17	1	1	8	47.2 ± 8	85.19
Marwick (43)	1993	217	108	25	34	50	58 ± 10	71.89
Matzer et al. (44)	1994	51	35	2	3	11	66.8 ± 11.3	49.02
Shin et al. (45)	2009	246	140	34	19	53	61.5 ± 11.2	56.5
Bokhari et al. (46)	2008	218	116	16	27	59	62 ± 13	68.81
Ma et al. (47)	2013	46	25	6	4	11	60.08 ± 8.58	67.39
De Bello et al. (48)	1996	45	33	1	5	6	53 ± 6.8	73.33
Yao et al. (49)	2004	73	28	3	7	35	52.6 ± 10.6	75.34
Bai et al. (50)	2001	102	53	2	29	18	61.8 ± 13.8	83.33
Freeman et al. (51)	1998	72	49	3	13	7	60 ± 11	75
Mak et al. (52)	1995	49	31	2	6	10	51.3 ± 9.8	
Herbst et al. (53)	1990	20	15	3	1	1	56 ± 7	70
Chen et al. (54)	2013	21	13	3	1	4	62.1	61.9

[z]Abbreviations: FN, false negative; FP, false positive; TN, true negative; TP, true positive.

The process of selecting articles is also displayed in Figure 1 (PRISMA).

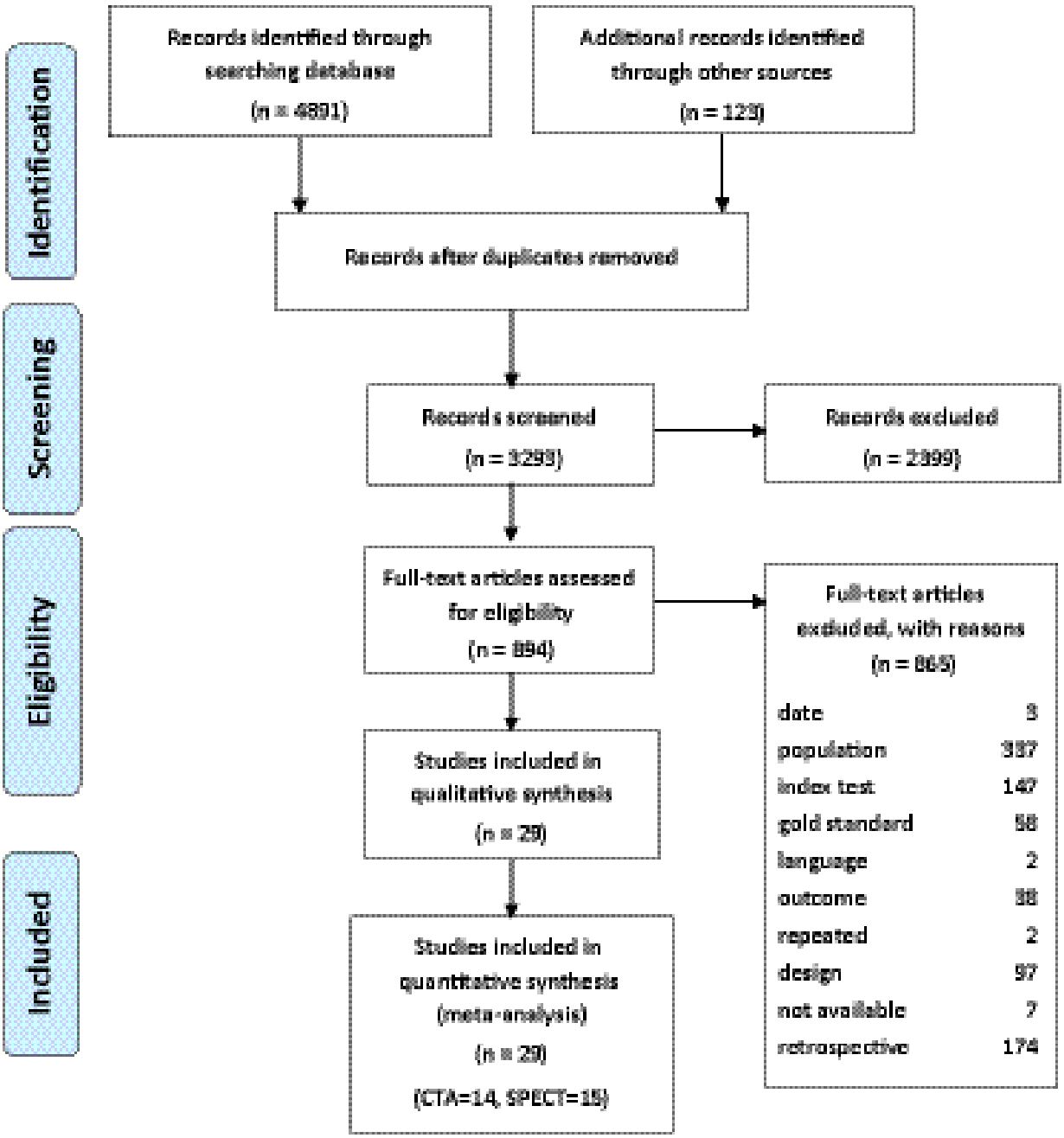

Figure 1. Flow diagram of the study (PRISMA)

4.1. Study Heterogeneity and Quality

The value of the heterogeneity index (I^2) was 0.00 and 15% in CTA and SPECT studies, respectively (Figure 2).

In general, the studies had the lowest bias in the domains of index test and reference standard, but due to uncertainty in the studied population regarding the history of CVDs, the highest bias was related to the patient selection process. In the flow and timing domain, the highest risk was found for the time interval between the index test and the reference standard test, as well as the reasons for excluding participants. Previous studies were insufficient in providing data for this assessment. The overall quality of the included studies is shown in Figure 3.

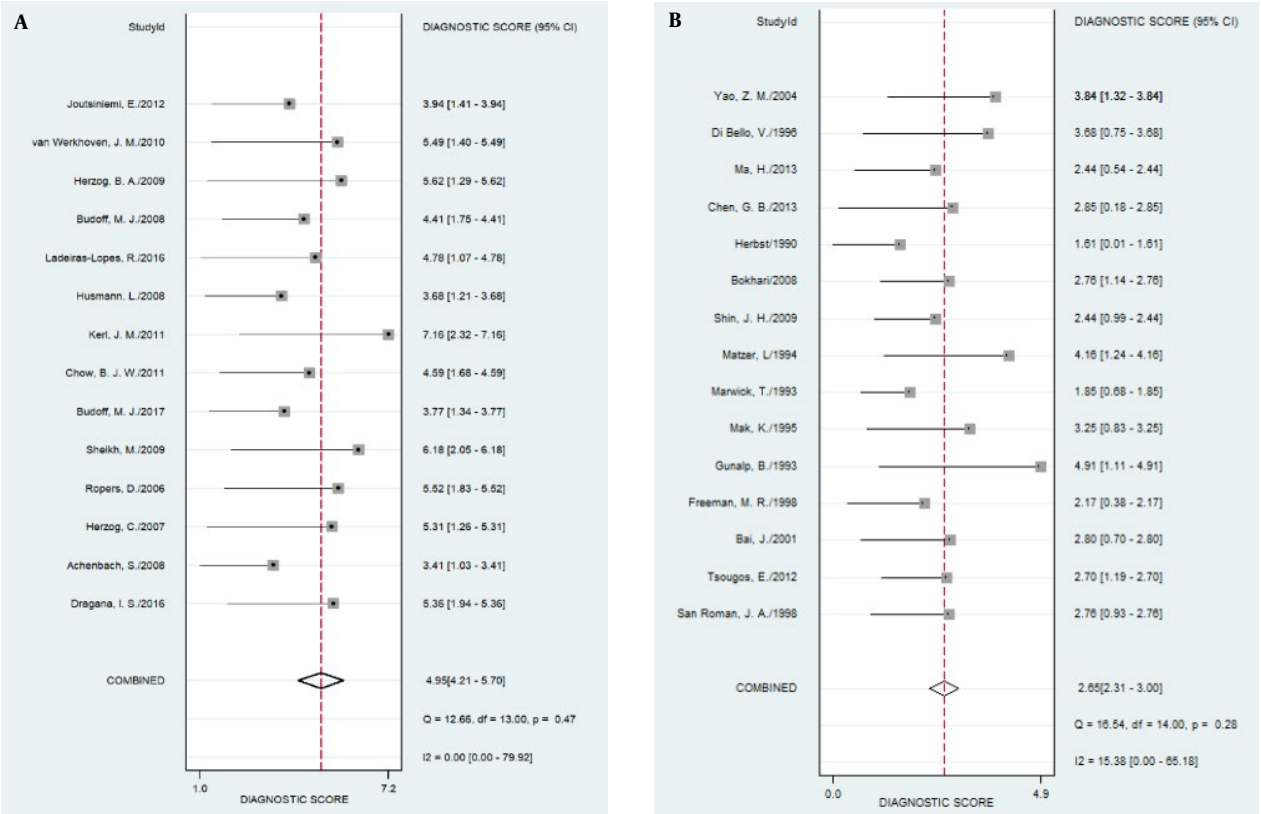

Figure 2. DOR Forest plots [CTA (A), SPECT (B)]

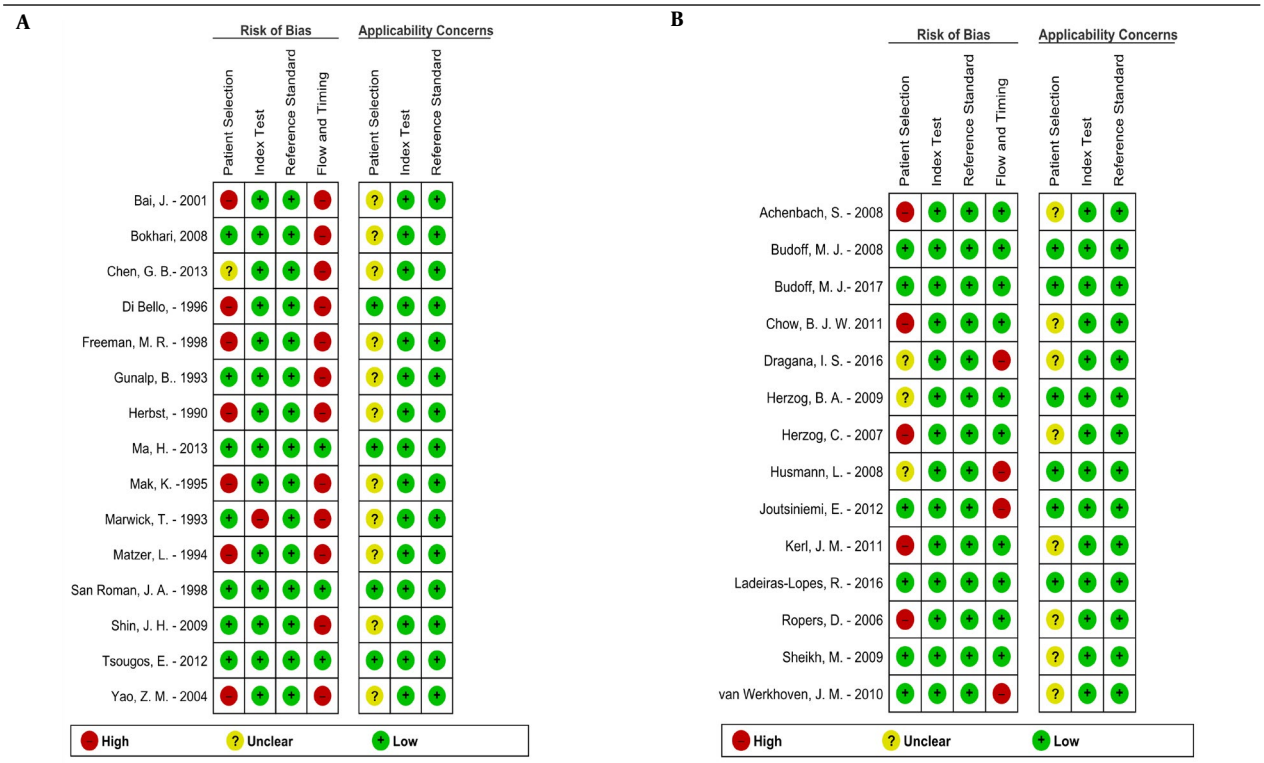

Figure 3. Quality of the studies [CTA (A), SPECT (B)]

4.2. Performance Estimates

The results of all indices are summarized in Table 4, separated by the test type.

Table 4. Summary of Results

Test	Sensitivity	Specificity	PLR	NLR	Diagnostic Odds Ratio	SROC
CTA	0.91 [0.94 0.88]; very good to excellent	0.87 [0.89 0.84]; very good	7.93 [5.11 12.29]; generate moderate to large	0.10 [0.06 0.17]; generate moderate to large	95.71 [59.81 53.15]; CTAOR > SPECTOR	0.96; excellent
SPECT	0.81 [0.83 0.79]; good to very good	0.74 [0.78 0.71]; good	3.03 [3.91 2.34]; generate small	0.25 [0.21 0.3]; generate small	13.56 [17.34 10.60]; CTAOR > SPECTOR	0.86; very good

[z]Abbreviations: NLR, negative likelihood ratio; PLR, positive likelihood ratio; ROC, receiver operating characteristic.

Forest plots of meta-analyzed sensitivity, specificity, PLR, NLR, OR, and SROC for CTA and SPECT are presented in Figures 4 to 8. The pooled sensitivity and specificity of CTA for CAD diagnosis were 91% (95% CI, 88% - 94%) and 87% (95% CI, 84% - 89%), respectively. The pooled sensitivity and specificity of SPECT for CAD diagnosis were 81% (95% CI, 79% - 83%) and 74% (95% CI, 71% - 78%), respectively.

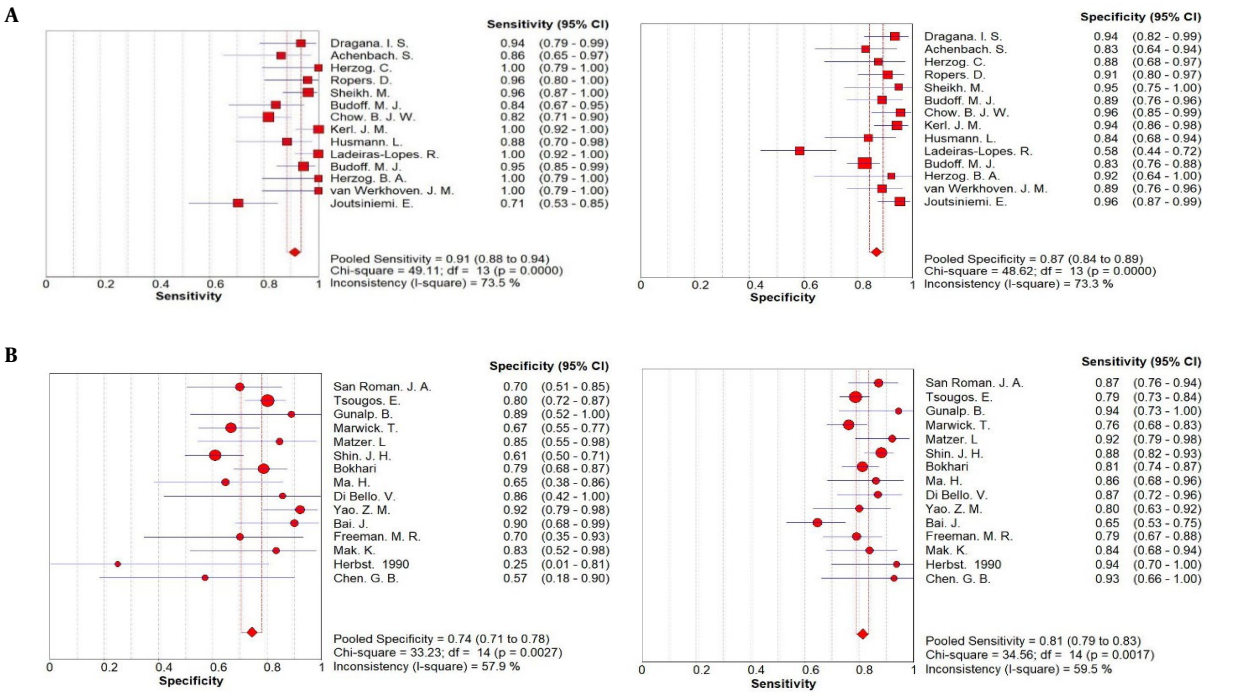

Figure 4. Sensitivity and specificity Forest plots [CTA (A), SPECT (B)]

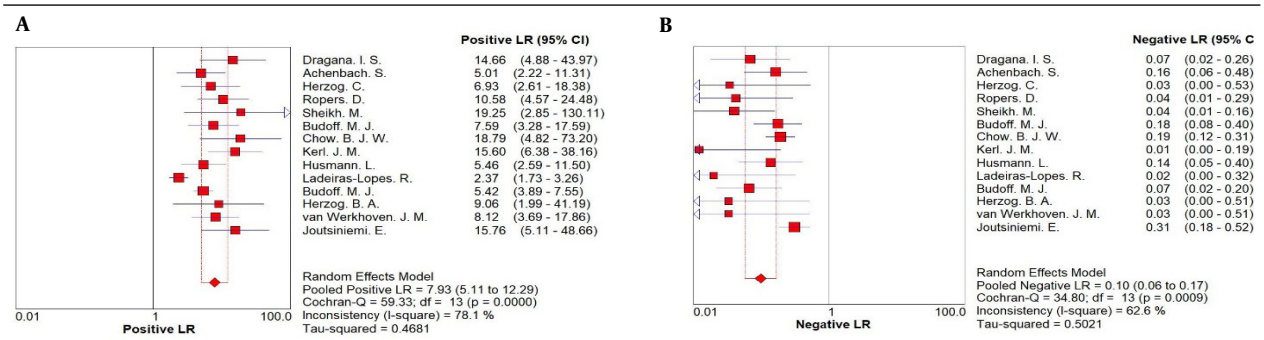

Figure 5. PLR and NLR forest plots of CTA [PLR (A), NLR (B)]

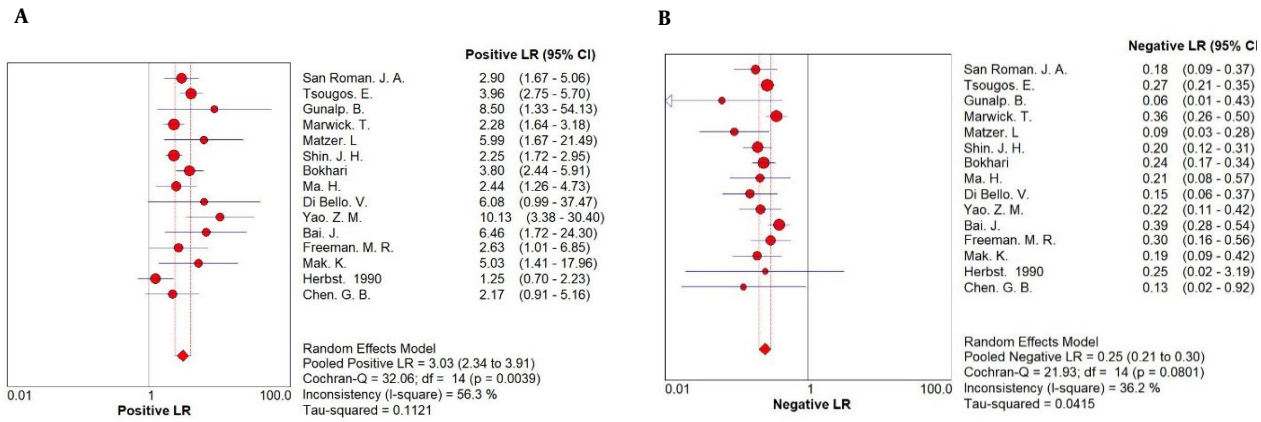

Figure 6. PLR and NLR forest plots of SPECT [PLR (A), NLR (B)]

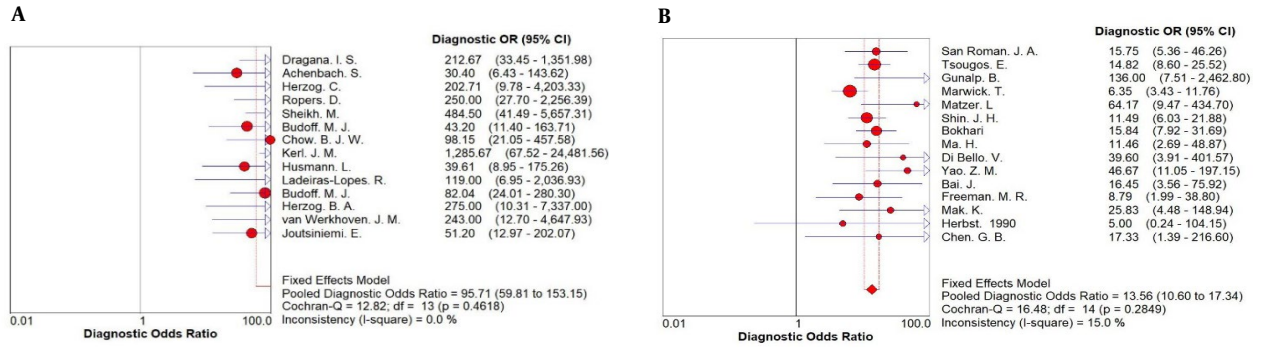

Figure 7. Forest plot showing OR for CTA (A) and SPECT (B).

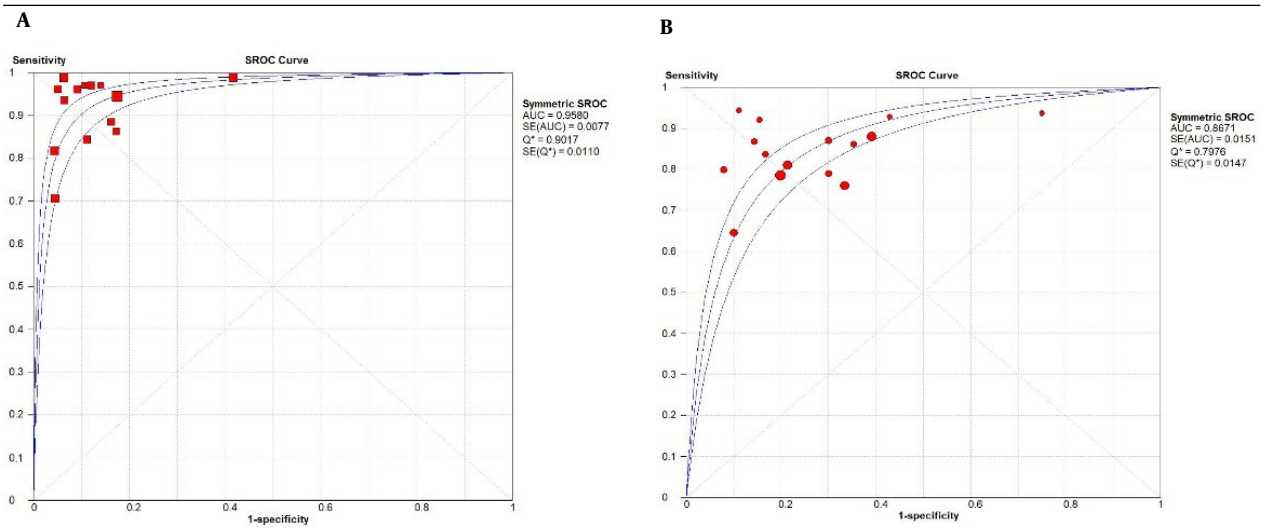

Figure 8. SROC [CTA (A), SPECT (B)]

The pooled positive likelihood ratios of CTA and SPECT were 7.93 (95% CI, 5.11 - 12.29) and 3.03 (95% CI, 2.34 - 3.91), respectively (Figures 5 and 6).

The pooled negative likelihood ratios of CTA and SPECT were 0.1 (95% CI, 0.06 - 0.17) and 0.25 (95% CI, 0.21 - 0.30), respectively (Figures 5 and 6).

The pooled diagnostic odds ratios of CTA and SPECT were 95.71 (95% CI, 58.81-153.15) and 13.56 (95% CI, 10.60 - 17.34), respectively (Figure 7).

The area under the ROC curve and the Q* for CTA were 0.96 and 0.90 and for SPECT were 0.86 and 0.79, respectively (Figure 8).

4.3. Sensitivity Analysis

According to the results of the Jackknife sensitivity analysis method, the removal of any single study did not change the effect size of the remaining studies (Figure 9). Therefore, it can be argued that no single study affected the effect size for CTA and SPECT studies.

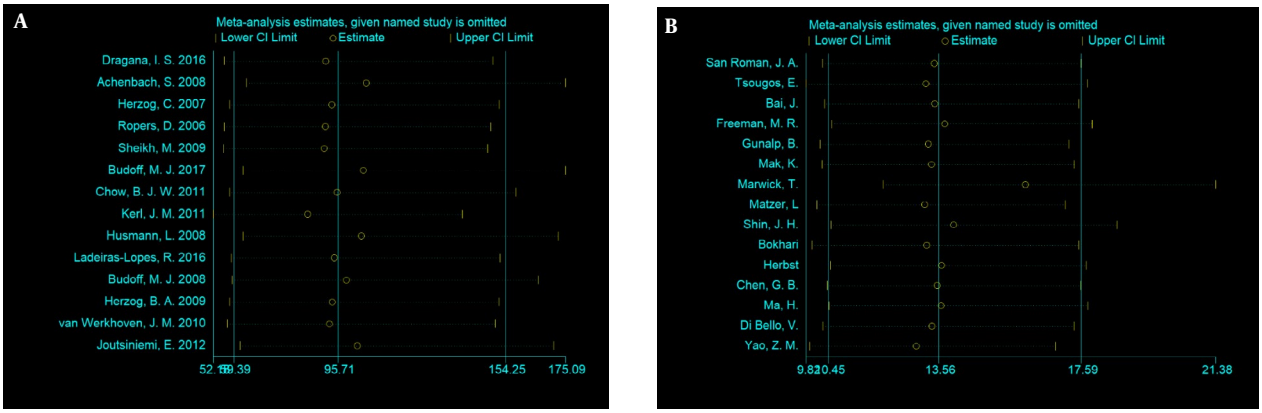

Figure 9. Sensitivity analysis [CTA (A), SPECT (B)]

4.4. Publication bias

Publication bias was evaluated using the Deeks' funnel plot. The Deeks' funnel plot revealed a symmetric pattern, which indicates that the publication bias for CTA and SPECT studies is ignorable (Figure 10).

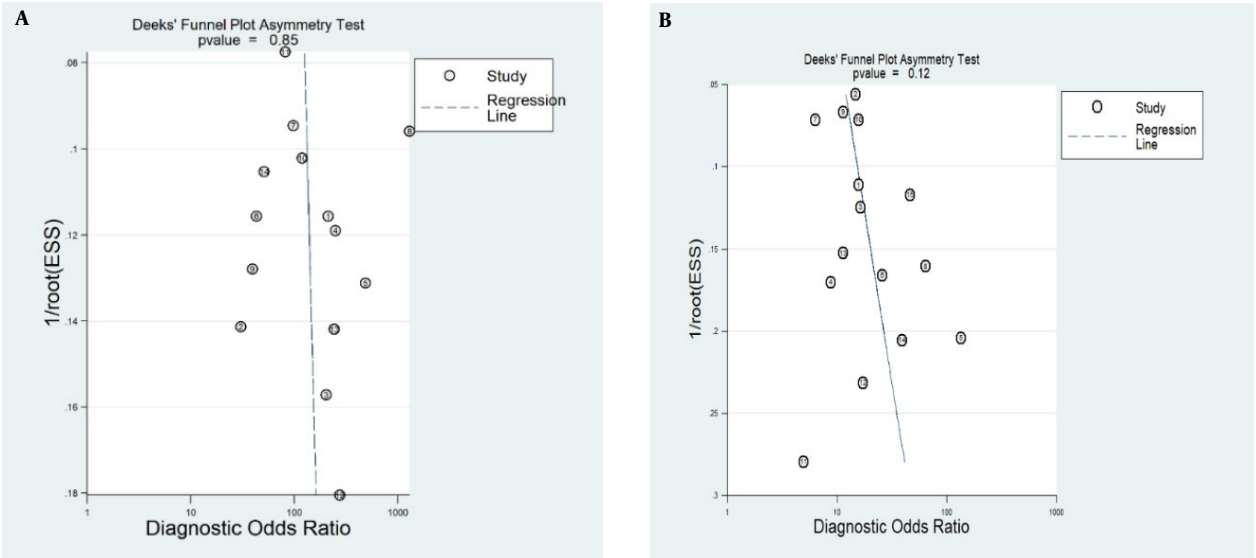

Figure 10. The Deek's funnel plots [CTA (A), SPECT (B)]

4. Discussion

As the burden of CAD has increased in the past decades, the accurate and rapid diagnosis of the disease is of high importance. In this study, we investigated the evidence regarding diagnostic performances of CTA and SPECT techniques for diagnosing coronary artery stenosis in chest pain patients with no history of CVDs, considering invasive angiography as the reference test. Some studies have investigated the diagnostic accuracy of CTA and SPECT. To the best of our knowledge, no systematic study has focused on suspected individuals without a history of CVDs.

According to the results of the meta-analysis, pooled

sensitivities of CTA and SPECT were 91% and 81%, respectively. Therefore, CTA and SPECT pooled sensitivities are in the ranges of 'very good' to 'excellent' (0.8 - 1) and "good" to "very good" (0.7 - 0.9), respectively. The higher the sensitivity of a test, the better the diagnostic accuracy of that test is in discriminating the patients.

The meta-analysis results of our study showed that pooled specificities of CTA and SPECT are 0.87 and 0.74, respectively. Therefore, CTA and SPECT pooled specificities are in the 'very good' (0.8 - 0.9) and 'good' (0.7 - 0.8) ranges, respectively. The higher the specificity of a test, the better the diagnostic accuracy of that test is in discriminating healthy individuals and ruling out the disease. Hence, the diagnostic accuracy of CTA in ruling out CAD is in the very good range (0.8 - 0.9).

The positive likelihood ratio (PLR) was considered to be strong evidence for ruling in CAD if values above 10 were produced. It was strong evidence for ruling out CAD if values below 0.1 were produced.

The higher the PLR, the better the diagnostic accuracy of CTA is in the CAD screening. The pooled PLR of CTA was 7.93 (95% CI, 5.11 - 12.29), which is considered to be in the range of intermediate to large ($\geq$ 5). That is, value-added information obtained from the positive result of CTA examination is in the range of intermediate to large ($\geq$ 5). The pooled PLR of SPECT was 3.03 (95% CI, 2.34 - 3.91), which is considered to be in the small range (2 - 5). That is, value-added information obtained from the positive result of the SPECT examination is in the small range (2 - 5).

The results also show that the pooled NLR of CTA was 0.1 (95% CI, 0.06 - 0.17), which is considered to be in the range of intermediate to large ($\leq$ 0.2). That is, value-added information obtained from the negative result of CTA examination is in the range of intermediate to large ($\leq$ 0.2). The pooled NLR of SPECT was 0.25 (95% CI, 0.21 - 0.30), which is considered to be in the small range (0.2 - 0.5). That is, value-added information obtained from the negative result of the SPECT examination is in the small range (0.2 - 0.5).

The results show that the pooled diagnostic odds ratio of CTA was 95.71 (95% CI, 59.81 - 153.15) and that of SPECT was 13.56 (95% CI, 10.60 - 17.34). The diagnostic odds ratio signifies the effectiveness of the diagnostic test. The higher this ratio is, the better the test is.

ROC charts are normally used to assess diagnostic accuracy. The closer the area under the ROC curve (AUC) is to one, the greater the diagnostic accuracy of the test is in determining the disease state for patients and the non-disease state for healthy individuals. The area under the ROC curve, which is an indicator for the diagnostic accuracy of CTA, was 0.96 with a standard deviation of 0.0077. The Q* index of CTA was 0.90 with a standard deviation of 0.011. Considering the calculated values of AUC and Q* indices, the diagnostic accuracy of CTA is in the 'excellent' range (0.9 - 1). For the SPECT test, the AUC was 0.86 with a standard deviation of 0.015, and the Q* was 0.79 with a standard deviation of 0.014. Considering the calculated values of AUC and Q* indices, the diagnostic accuracy of SPECT is in the 'very good' range (0.8 - 0.9).

In a meta-analysis, Knuuti et al. (55) reported the sensitivity, specificity, and positive and negative likelihood ratios of CTA and SPECT diagnostic tests.

Knuuti et al.'s meta-analysis (55) evaluated the diagnostic accuracy of noninvasive tests for the diagnosis of significant stenosis in patients. The difference between the current research and the mentioned study is in the study populations. So that in the study by Knuuti et al. (55), individuals with a history of CVDs and MI were included, whereas we only included those with low to intermediate probabilities of CAD with no history of CVDs. In our study, sensitivity values were lower than those reported by Knuuti et al. This difference can be attributed to differences in the study populations since patients with high risks and history of MI were also included in the study by Knuuti et al (55).

Powell and Cosson (21), in a systematic review, evaluated the diagnostic accuracy of CTA and reported that the sensitivity of CTA was in the 'very good' to the 'excellent' range, which is similar to the findings of the present study.

Parker et al. (22), in a meta-analysis, evaluated the diagnostic accuracy of SPECT and demonstrated a sensitivity for SPECT that is similar to that of our study, i.e., in the 'very good' range.

The specificity values reported in the present study are higher than those reported by Knuuti et al. (55), which is an indication of a decreased false-negative rate. Therefore, it seems that the ability of the index test of our study in discriminating healthy individuals and ruling out CAD is higher than that of the Knuuti et al.'s study (55).

Parker et al. (22) reported a specificity for SPECT that is similar to the present study (it is in the 'good' range).

Similar to our findings, the study by Powell and Cosson (21) showed that CTA is a highly sensitive and specific non-invasive test for the diagnosis of significant stenosis in patients with angina.

Comparisons of PLR and NLR of CTA in these two studies lead us to the conclusion that in the present study value-added information is higher than that of Knuuti et al. (55) Moreover, the resulting diagnostic accuracy for ruling in and ruling out the CAD is greater in our population in comparison with that of the Knuuti et al.'s study (55). Comparing the PLRs between these two studies indicate that PLR of CTA has a higher value in our study than in the Knuuti et al.'s study (55). This is probably due to including patients with a history of CVDs in the study by Knuuti et al (55).

According to current European and American guidelines on coronary artery disease (CAD) management, patients with a pre-test probability (PTP) of 15% - 85% of CAD should be evaluated using non-invasive tests. No routine testing is needed for patients with low pre-test probabilities (< 15%). Patients with high pre-test probabilities (< 85%) should undergo direct and invasive interventions (2,

3). Therefore, considering the high diagnostic accuracy of CTA for individuals with low to intermediate risks of CAD, using CTA for ruling out CVDs can reduce unnecessary invasive interventions. As these procedures are costly, a decrease in their frequency can significantly reduce costs. Besides, it would be useful for improving the quality of life of patients. Moreover, due to preoperative anxiety and stress in patients undergoing invasive angiography, a reduction in unnecessary invasive interventions will eliminate such a difficult experience (56). It should be noted that there would be a reduction in overall costs following the use of CTA if patients with low to intermediate pre-test probabilities of CAD have a low prevalence of stenosis. Otherwise, in patients with a high prevalence of stenosis who have high pre-test probabilities of CAD, the use of CTA will raise the costs, since the patients should undergo both CTA and invasive angiography.

Sedighi et al. (57) showed that of 1100 individuals who underwent invasive angiography in cardiac centers in Isfahan, only 42% received exercise testing. Other methods, such as cardiac scans and CTA, were performed in 2.7% and 0.6% of the patients, respectively. However, a normal angiography result was found in 40% of the patients. Therefore, CTA, as a non-invasive method with high diagnostic accuracy, in patients with low to intermediate risks of CAD with no history of CVDs can reduce treatment costs. In what follows, we will compare the results of cost-effectiveness analyses in other country settings with the analysis presented in this study.

The results of this meta-analysis are useful for physicians since CTA has high diagnostic accuracy in ruling out CAD, which further leads to a reduction in false negatives and an improvement in diagnosing patients. By allowing early treatments, CTA not only prevents CAD progression but also results in saving the costs for patients and health systems, mainly due to excluding more expensive treatments.

5. Conclusions

This study demonstrated that the accuracy of CTA and SPECT in diagnosing CAD lies in the 'excellent' and the 'very good' ranges, respectively. In comparison with SPECT, CTA diagnostic test had higher diagnostic accuracy in ruling out CVD in individuals with low to intermediate risks for CAD with no history of CVD.

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