Diagnostic Performance of Attenuation Corrected Myocardial Perfusion Imaging for Coronary Artery Disease: A Systematic Review and Meta-analysis

Short title: Attenuation corrected MPI for CAD

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ABSTRACT

Myocardial perfusion imaging (MPI) with single photon emission computer tomography (SPECT) is a well-established tool for the diagnosis of coronary artery disease (CAD). However, soft tissue attenuation is a common artifact which limits the diagnostic accuracy of MPI. The aim of this study was to determine whether attenuation correction (AC) improved diagnostic performance of MPI, using coronary angiography as reference standard. **Methods:** MEDLINE and EMBASE were searched until March 2015 for studies evaluating AC MPI for the diagnosis of CAD. Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool. For each study, the sensitivity, specificity, and diagnostic odds ratio, along with 95% confidence intervals (CIs), were calculated to determine the diagnostic accuracy of AC vs. non-attenuation corrected (NAC) MPI. A bivariate mixed-effect model was applied for pooling the data. **Results:** Out of 201 articles, 17 studies (1,701 patients) were identified including five studies which used computed tomography AC (CTAC), 12 studies which used radionuclide source AC (RAC), and 15 studies which reported NAC results. The pooled sensitivities across studies were 0.80 (95%CI, 0.64-0.91), 0.85 (0.81-0.88), 0.84 (0.79-0.88) and 0.80 (0.75-0.85) for CTAC, RAC, all AC, and NAC, respectively; and pooled specificities were 0.83 (0.71-0.91), 0.81 (0.73-0.86), 0.80 (0.74-0.85) and 0.68 (0.61-0.74). This resulted in a
pooled diagnostic odds ratios of 20 (95%CI, 12-34), 24 (13- 43), 22 (13-35) and 9 (7-11).

Significant differences in specificity and diagnostic odds ratios were noted when comparing AC (including CTAC, RAC and all AC) vs. NAC. **Conclusion:** The results from this study suggested that attenuation correction should be applied to myocardial perfusion imaging to improve the diagnosis of CAD, especially the specificity.
INTRODUCTION

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality throughout the world (1-3). In order to select those patients who will receive the greatest benefit from revascularization, accurate diagnosis and risk stratification of CAD, using non-invasive testing, is crucial (4). Myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is a well-established tool for the diagnosis of CAD. Since it has good prognostic and net risk classification value, MPI is usually used as the gatekeeper for invasive coronary angiography (CAG) and evaluation of therapy effectiveness. (5). However, artifacts degrade image quality and increase the risk of misinterpretation and soft tissue attenuation is one of the most common artifacts (6). An external radionuclide source has been used for attenuation correction (AC), which improved sensitivity and specificity from around seventy percent to above eighty percent (7-10). But routine AC plus image reconstruction is time-consuming. The development of hybrid SPECT/computed tomography (SPECT/CT) involves the use of CT for AC by converting Hounsfield units into attenuation coefficients (11,12). Computed tomography AC using hybrid SPECT/CT has significantly reduced scan time, however, registration errors between CT and SPECT images and radiation dose are still concerns (11).
Most MPI studies were heterogeneous with small sample size. Several meta-analyses evaluated the diagnostic performance of SPECT-MPI (13-16), but did not focus on the specific role of AC in the diagnosis of CAD. Therefore, the aim of this study was to compare the diagnostic performance of AC vs. non-attenuation corrected (NAC) MPI, using CAG as the reference standard. In addition, subgroup analyses [considering radionuclide source AC (RAC) vs. computed tomography AC (CTAC)] were performed.

MATERIALS AND METHODS

Search strategy

MEDLINE and EMBASE were searched for English-language literature published until March 2015. Keywords included myocardial perfusion, SPECT, and attenuation correction. Conference articles were excluded as most conference articles lacked precise data (i.e., true positive, false positive, false negative, and true negative). Medical Subject Headings terms were used to maximize the sensitivity of the search.

Study selection
Article titles and abstracts were reviewed for eligibility. A study was included if it met the following criteria: (1) it assessed attenuation corrected MPI as a diagnostic tool to evaluate patients for the presence of CAD; (2) CAD was defined as at least \( \geq 50\% \) diameter stenosis on CAG; (3) CAG was used as the reference test; (4) absolute numbers of true positive, false positive, true negative and false negative were available or these data were derivable from the results presented. A study was excluded if it was: (1) a conference article; (2) a review or meta-analysis; (3) a study of risk stratification; (4) used a reference test other than CAG; (5) a technology or image quality studies; (6) without diagnostic performance at the patient level.

**Data extraction**

Two researchers (J.-Y.H. and C.-K.H.) independently performed data extraction. Extracted information included author, journal, year of publication and country; details of study design; patient demographic features (such as numbers of patients, mean age, percentage of males, and indication for MPI); imaging technique (such as type of AC, type of perfusion radiotracer, stress type); imaging protocol (scatter correction, gated); brand of imaging device and interpretation method; CAD definition and numbers of true positive, false positive, true negative and false negative. Data were recorded at the patient level. If a study reported > 1 pair of sensitivities and
specificities at different cut-off points, different imaging techniques, different CAD definitions or different experienced observers, the pair reported in the abstract (17) and the pair with the highest sensitivity (9,17-19) were extracted. One study (20) reported pairs of sensitivity and specificity by three independent operators with 4, 7 and 11 years of experience, respectively, and data from the most experienced physician were used in our analysis. Disagreement between the two researchers was resolved by consensus.

**Quality assessment**

Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (scale 0-14, QUADAS) tool (21). In brief, the assessment was based on 14 items, including covered patient spectrum, reference standard, disease progression bias, verification bias, review bias, clinical review bias, incorporation bias, test execution, study withdrawals, and indeterminate results. A score of 7 of 14 is high-quality and scores below 7 is low-quality. It is used as an evidence based quality assessment tool to be used in systematic reviews of diagnostic accuracy studies.

**Statistical analysis**
All data from each eligible study were extracted and sorted out by Cochrane’s Review Manager (version 5.3). Categorical variables were expressed as percentages, and continuous variables were expressed as mean values. On the basis of the extracted $2 \times 2$ contingency tables, pooled measures for diagnostic performance, including sensitivity, specificity, diagnostic odds ratio (OR), summary receiver-operating-characteristic (ROC) curve and area under the curve (AUC) with 95% confidence intervals (CIs) were calculated. Between-study statistical heterogeneity was assessed using $I^2$ and the Cochrane Q test on the basis of the mixed-effects analysis (22). Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks and colleagues (23), with $P < 0.10$ for the slope coefficient indicating significant asymmetry. The data were analyzed at the patient level using a bivariate mixed-effects regression model (24-26) to express the diagnostic performance measures across studies and comparisons between different index tests (25,27).

The assumption of bivariate model is that the sensitivities from individual studies (after logit transformation) within a meta-analysis are approximately normally distributed around a mean value with a certain amount of variability around this mean. The same is true for the specificities of these studies. This leads to the bivariate normal distribution. These bivariate models can be analyzed using linear mixed model techniques. The parameters of the bivariate
model are estimated in a single model to incorporate the possible correlation between sensitivities and specificities (25). The summary ROC curves were also created using this model to estimate the AUC (28). Statistical analysis was performed using STATA (version 13, StataCorp LP, Texas, USA) and SAS (version 9.4, SAS Institute Inc., North Carolina, USA).

RESULTS

Study characteristics

A total of 441 articles were retrieved through the database from MEDLINE and EMBASE (Figure 1). After excluding conference articles, non-English articles, and those without abstracts, 201 articles remained. On the basis of title and abstract, an additional 158 articles were excluded. After full text review, 27 additional articles were excluded, and one study (17) was included after manual check from cited reference lists as shown in Figure 1, the flowchart of study selection.

Seventeen studies, with a total of 1,701 patients, were enrolled including five studies (with 522 patients) which used CTAC; 12 studies (with 1,179 patients) which used RAC; and 15 studies (with 1,543 patients) which reported NAC results. A review of each study’s characteristics revealed many differences between the included studies (Table 1) (7-10,17-20,29-37), which could potentially affect the diagnostic performance of MPI.
The methodological quality of the 17 studies was assessed using the QUADAS tool. Review of the QUADAS checklist for all studies showed that most studies (16/17) were scored above seven, which is considered good quality (21). Only one study showed poor quality with a QUADAS score of 3 (31). During QUADAS assessment, most studies were found to have problems with unclear blinding during interpretation of the reference test, blind reading of the index test, lack of reporting for uninterpretable results, and lack of explanation of withdrawals which may have resulted in bias.

The $I^2$ index showed substantial heterogeneity with regards to sensitivity and specificity for all index tests. The highest was 92.3% for CTAC and the lowest was 59.2% for RAC when measuring sensitivity. The funnel plot and regression tests showed a statistically non-significant $P$ value (0.51) for the slope coefficient, indicating symmetry in the data and a low likelihood of publication bias (23).

**Diagnostic performance**

The pooled sensitivities across studies were 0.80 (95%CI, 0.64-0.91), 0.85 (0.81-0.88), 0.84 (0.79-0.88) and 0.80 (0.75-0.85) for CTAC, RAC, all AC (CTAC plus RAC), and NAC,
respectively. The pooled specificities across studies were 0.83 (95%CI, 0.71-0.91), 0.81 (0.73-0.86), 0.80 (0.74-0.85), and 0.68 (0.61-0.74) for CTAC, RAC, all AC, and NAC, respectively. The pooled diagnostic OR were 20 (95%CI, 12-34), 24 (13-43), 22 (13-35) and 9 (7-11) for CTAC, RAC, all AC, and NAC, which were regarded minimally affected by verification bias. The pooled diagnostic accuracies across studies were 0.79 (95%CI, 0.71-0.87), 0.84 (0.80-0.87), 0.82 (0.78-0.86) and 0.75 (0.73-0.78) for CTAC, RAC, all AC, and NAC, respectively. The pooled results are shown in Table 2. The summary ROC curves are shown in Figure 2. For CTAC, RAC, all AC and NAC tests, the AUCs were 0.89 (95%CI, 0.86-0.91), 0.90 (0.87-0.92), 0.89 (0.86-0.92), and 0.81 (0.77-0.84), respectively.

There was no significant difference in sensitivity between one-by-one comparison among the four kinds of studies when comparing the diagnostic performance of CTAC, RAC, all AC, and NAC. There was no significant difference in specificity between CTAC vs. RAC ($P=0.60$). There was a significant difference in specificity in all AC vs. NAC ($P=0.008$), as well as in the subgroup analysis for CTAC vs. NAC ($P=0.028$) and RAC vs. NAC ($P=0.031$). There was also significant differences in diagnostic OR between all AC vs. NAC ($P=0.002$), CTAC vs. NAC ($P=0.048$) and RAC vs. NAC ($P=0.004$).
Eight (2 CTAC and 6 RAC studies, all reported NAC data (9,10,17-19,31,35,36) of the included studies provided information of normalcy. Considering these 8 studies, the pooled normalcies across studies were 0.95 (95%CI, 0.91-1.00), 0.95 (0.91-0.98), 0.95 (0.92-0.97), and 0.84 (0.78-0.90) for CTAC, RAC, all AC, and NAC, respectively.

DISCUSSION

This study showed no significant difference in sensitivity between CTAC, RAC, all AC, and NAC images but a significant difference in the specificity between all AC vs. NAC, as well as in the subgroup analysis for CTAC vs. NAC and RAC vs. NAC, without compromising the sensitivity. Regarding the diagnostic OR, a significant difference between AC (CTAC, RAC and all AC) vs. NAC was also noted.

Several meta-analyses had compared the diagnostic performance of SPECT-MPI and other modalities including echocardiography, cardiac CT, cardiac magnetic resonance, and positron emission tomography (13-16) in diagnosing CAD. These studies revealed a sensitivity of 0.88, 0.88, 0.83, and 0.74 and specificity of 0.73, 0.61, 0.77 and 0.79 only for MPI (13-16). Jaarsma et al. performed subgroup analyses comparing AC vs. NAC, but only five studies concerned the diagnostic performance of AC MPI, while 100 studies concerned the diagnostic performance of
NAC MPI, without overlapping studies. Their meta-analysis showed an increased specificity (0.60 vs. 0.78) but decreased sensitivity (0.89 vs. 0.80) of AC MPI vs. NAC MPI. The overall diagnostic performance was compared using diagnostic OR and showed no difference between NC vs. AC (NC vs. AC: 15 vs. 13, \( P=0.51 \)) (14). However, in the current study, AC showed increased specificity without decreasing the sensitivity. This discrepancy in results may be due to the type of studies selected. In our meta-analysis, studies which compared the two imaging techniques within the same participants (i.e., 15 studies had NAC and AC results from the same subjects) were primarily used, while the AC and NAC results evaluated in the study by Jaarsma et al. were from different studies.

de Jong et al. selected studies published after 2000 which were more homogeneous, with inclusion of prospective studies with CAG as a reference test (irrespective of index test result). The detailed imaging protocols (such as AC or NAC), however, were not mentioned in their data extraction. They showed similar results in sensitivity (0.83) but higher specificity (0.77) compared with the NAC results from this current meta-analysis. The discrepancy could be partly explained by verification bias in the current study, which may have inflated the sensitivity and deflated the specificity (15,38). On the other hand, Takx et al. included four AC and six NAC studies and showed lower sensitivity (0.74) but similar specificity (0.79) compared with the
current study’s AC result (16). However, Takx et al used a combination of luminal stenosis on CAG and fractional flow reserve as the diagnostic standard for CAD. In the current study, although the diagnostic sensitivity of CTAC and RAC (when compared with NAC) both failed to reach significance, CTAC and RAC both showed significant improvement in specificity when compared with NAC. No scatter correction was performed in all five CTAC studies while RAC studies did. In addition, the CT was used only for reconstructing attenuation map and attenuation correction in these CTAC studies. We propose that if scatter correction (39) and anatomic information such as coronary calcium or angiography from CT (40,41) could be applied, the diagnostic performance may show even greater improvement.

Considerable heterogeneity was noted among the enrolled studies, including variations in the study population, scanning and processing protocols, different radionuclide tracers used, different stress modes, and different angiographic criteria for CAD. Underwood et al. had also evaluated the diagnostic performance of MPI using different tracers and types of stress protocols and found a sensitivity ranging from 0.64 to 1.00 and a specificity ranging from 0.33-1.00. Although their ranges were wide, no statistical difference between these various protocols was noted (42).
Significantly higher specificity and diagnostic odds ratio were found in both CTAC and RAC subgroup analyses in our study. When considering radiation, dose from radionuclide transmission sources is lesser than SPECT-CT \((11)\). However, a lower radiation dose from SPECT-CT has been achieved by reducing X-ray tube current and incorporating new reconstruction methods and new protocols \((39, 43, 44)\). Also RAC is time consuming. SPECT-CT with faster scanning and reconstruction time makes CTAC more clinically practical.

**Strength**

The random-effects model of Der Simonian and Laird \((45, 46)\) was utilized to incorporate heterogeneity into the overall estimates. Because these conventional methods might introduce bias in meta-analyses of binary outcomes, such as sensitivity and specificity \((47, 48)\), and the normality assumption of estimates and its variance might not hold when dealing with few studies or sparse data \((47, 49)\), the current study used bivariate mixed-effects for more reliable estimates of parameters.

This is the first meta-analysis which focused on different imaging techniques (AC vs. NAC) in MPI. Fifteen studies with 1,543 patients evaluated both AC and NAC results in the same participants, as a precise comparison between different index tests requires the same original
individual patient-level data. This is also the first study to perform pooled sensitivity and specificity of AC MPI to support their clinical usefulness. No publication bias was identified among the selected studies, therefore, the results can be considered robust.

**Limitations**

This study had several limitations. Quantitative analyses of SPECT were not routinely used in the selected papers. Bias existed in the visual assessment, especially in those studies which used an unblinded method. In addition, gated SPECT or other non-perfusion parameters (such as lung uptake, right ventricular activity, or transient left ventricle dilatation after stress), were not routinely included for interpretation, which may have decreased the diagnostic accuracy of the study, especially in cases of multi-vessel disease. Verification bias may exist since results of MPI may have affected the clinical decision to use CAG. Only one study performed coronary angiography, irrespective of MPI results. The difference between the AUCs of AC and NAC could not be calculated due to limited information regarding relationships between AC and NAC in patients with CAD or not. Finally, using CAG as reference may have under-diagnosed the presence of microvascular CAD.
CONCLUSION

Our study results suggested attenuation correction should be applied to MPI because it affects diagnostic certainty in CAD with significant improvement of the specificity.

DISCLOSURE STATEMENT

The costs of the publication of this article were defrayed, in part, by the payment of page charges. Therefore, and solely to indicate this fact, the article is hereby marked "advertisement" in accordance with 18 USC section 1734.

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assessment of coronary artery disease: a meta-analysis of diagnostic performance. *Am Heart J.*

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and positron emission tomography imaging for the detection of obstructive coronary artery disease: a

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imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. *Circ
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Figure 1. Flowchart of study selection. Limited search of MEDLINE and EMBASE searches yielded 201 articles. After exclusion, a total of 17 studies (1,701 patients) were included in the final analysis.
Figure 2. Receiver-operating-characteristic curve for diagnosis of CAD using CTAC, RAC, or NAC. Each circle represents an individual included study. The diamond represents the summary operating point of pooled sensitivity and specificity. The dashed line represents 95% CIs and AUC represents area under the curve.
Table 1 Characteristics of selected studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>n</th>
<th>Age (SD)</th>
<th>% male</th>
<th>Type of AC</th>
<th>Tracer</th>
<th>Test interval</th>
<th>CAD definition</th>
<th>AC Sens</th>
<th>AC Spec</th>
<th>NAC Sens</th>
<th>NAC Spec</th>
</tr>
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<td>Yamauchi</td>
<td>2014</td>
<td>Japan</td>
<td>150</td>
<td>70 (7)</td>
<td>68</td>
<td>SSPAC</td>
<td>Tc-99m</td>
<td>3 mo</td>
<td>&gt;50%</td>
<td>0.91</td>
<td>0.90</td>
<td>0.77</td>
<td>0.76</td>
</tr>
<tr>
<td>Patil</td>
<td>2014</td>
<td>U.S.</td>
<td>54</td>
<td>66 (11)</td>
<td>74</td>
<td>Gd-153</td>
<td>Tc-99m</td>
<td>30 d</td>
<td>&gt;70% LM &gt;50%</td>
<td>0.89</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma</td>
<td>2012</td>
<td>India</td>
<td>171</td>
<td>55 (10)</td>
<td>82</td>
<td>CTAC</td>
<td>Tc-99m</td>
<td>3 mo</td>
<td>&gt;50%</td>
<td>0.57</td>
<td>0.89</td>
<td>0.65</td>
<td>0.83</td>
</tr>
<tr>
<td>Genovesi</td>
<td>2011</td>
<td>Italy</td>
<td>104</td>
<td>64 (10)</td>
<td>79</td>
<td>CTAC</td>
<td>Tc-99m</td>
<td>1 mo</td>
<td>&gt;70% LM &gt;50%</td>
<td>0.75</td>
<td>0.81</td>
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<td>China</td>
<td>99</td>
<td>62 (12)</td>
<td>56</td>
<td>CTAC</td>
<td>Tc-99m</td>
<td>60 d</td>
<td>&gt;70%</td>
<td>0.92</td>
<td>0.79</td>
<td>0.95</td>
<td>0.63</td>
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<td>Bateman</td>
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<td>U.S.</td>
<td>92</td>
<td>64 (12)</td>
<td>60</td>
<td>Gd-153</td>
<td>Tc-99m</td>
<td>181 d</td>
<td>&gt;70%</td>
<td>0.83</td>
<td>0.71</td>
<td>0.77</td>
<td>0.67</td>
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<td>Wolak</td>
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<td>0</td>
<td>Gd-153</td>
<td>Tc-99m</td>
<td>60 d</td>
<td>&gt;70%</td>
<td>0.81</td>
<td>0.73</td>
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<td>67 (-)</td>
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<td>&gt;70%</td>
<td>0.71</td>
<td>0.91</td>
<td>0.61</td>
<td>0.83</td>
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<td>67</td>
<td>CTAC</td>
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<td>0.59</td>
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<td>30</td>
<td>68 (-)</td>
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<td>CTAC</td>
<td>Tl-201</td>
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<td>Tc-99m</td>
<td>60 d</td>
<td>&gt;70%</td>
<td>0.86</td>
<td>0.79</td>
<td>0.89</td>
<td>0.50</td>
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<td>Spain</td>
<td>99</td>
<td>59 (-)</td>
<td>72</td>
<td>Gd-153</td>
<td>Tc-99m</td>
<td>3 mo</td>
<td>&gt;70%</td>
<td>0.76</td>
<td>0.71</td>
<td>0.92</td>
<td>0.46</td>
</tr>
<tr>
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<td>U.S.</td>
<td>66</td>
<td>- (-)</td>
<td>68</td>
<td>Gd-153</td>
<td>Tc-99m</td>
<td>trial period</td>
<td>&gt;50%</td>
<td>0.96</td>
<td>0.85</td>
<td>0.78</td>
<td>0.62</td>
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<tr>
<td>Lee</td>
<td>2000</td>
<td>Korea</td>
<td>68</td>
<td>59 (12)</td>
<td>43</td>
<td>Tc-99m</td>
<td>Tc-99m</td>
<td>2 mo</td>
<td>&gt;70%</td>
<td>0.74</td>
<td>0.75</td>
<td>0.67</td>
<td>0.59</td>
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<td>61 (12)</td>
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<td>Tc-99m</td>
<td>3 mo</td>
<td>&gt;50%</td>
<td>0.78</td>
<td>0.44</td>
<td>0.76</td>
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<td>64 (10)</td>
<td>65</td>
<td>Am-241</td>
<td>Tl-201</td>
<td>1-14 d</td>
<td>&gt;70%</td>
<td>0.94</td>
<td>0.91</td>
<td>0.79</td>
<td>0.80</td>
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<td>60</td>
<td>63 (12)</td>
<td>63</td>
<td>Am-241</td>
<td>Dual tracer</td>
<td>90 d</td>
<td>&gt;50%</td>
<td>0.88</td>
<td>0.82</td>
<td>0.84</td>
<td>0.46</td>
</tr>
</tbody>
</table>

SD standard deviation, mo month, d day, LM left main coronary artery, sens sensitivity, spec specificity

CTAC computed tomography attenuation correction

SSPAC attenuation correction using segmentation with scatter and photopeak window data,

Gd-153 Gadolinium-153, Tc-99m Technetium-99m, Am-241 Americium-241, Tl-201 Thallium-201,

# Thallium-201 for resting perfusion study and Technetium-99m for stress perfusion study

- no available information in the included study
Table 2 Diagnostic performance of MPI for the detection of CAD, pooled sensitivity, specificity and diagnostic OR of CTAC, RAC, all AC and NAC.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity [95% CI]</th>
<th>Specificity [95% CI]</th>
<th>Diagnostic OR [ 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTAC</td>
<td>0.80 [0.64, 0.91]</td>
<td>0.83 [0.71, 0.91] *</td>
<td>20 [12, 34] *</td>
</tr>
<tr>
<td>RAC</td>
<td>0.85 [0.81, 0.88]</td>
<td>0.81 [0.73, 0.86] *</td>
<td>24 [13, 43] *</td>
</tr>
<tr>
<td>All</td>
<td>0.84 [0.79, 0.88]</td>
<td>0.80 [0.74, 0.85] *</td>
<td>22 [13, 35] *</td>
</tr>
<tr>
<td>NAC</td>
<td>0.80 [0.75, 0.85]</td>
<td>0.68 [0.61, 0.74]</td>
<td>9 [7, 11]</td>
</tr>
</tbody>
</table>

* $P<0.05$, when comparing to NAC pooled estimates.
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Jei-Yie Huang, Chun-Kai Huang, Ruoh-Fang Yen, Hon-Yen Wu, Yu-Kang Tu, Mei-Fang Cheng, Ching-Chu Lu, Kai-Yuan Tzen, Kuo-Liong Chien and Yen-Wen Wu

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