

Transient Ischemic Dilation is Associated with Severity of Coronary Artery Disease: a Systematic Review and Meta-analysis

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Abstract

Background: Transient ischemic dilation (TID) indicates left ventricle (LV) volume changes which can be associated with both myocardial and endocardial ischemia. The purpose of this study was to evaluate any association between TID ratio and severity of coronary artery disease (CAD) involvement in a systematic review and meta-analysis.

Methods: We conducted a systematic search on electronic databases (PubMed, Scopus, Embase and Web of Science) up to 1 January 2017. The reference lists of all included studies were searched for a higher accuracy. The search strategy was according to a defined PICO as P: susceptible patients for CAD, I: Transient ischemic dilation, C: Angiographies, O: Severity of CAD. Statistical analysis was done by Comprehensive meta-analysis software version 2 (CMA-2).

Results: After study selection process, 7 studies were selected for data extraction. TID was studied since 1987. A total number of 1700 patients were enrolled in our quantitative analysis. Ranges of TID in different groups were extracted as mean \pm SD and were compared based on severity of CAD. We found a significant difference in TID between 1) normal or no significant group and mild to moderate group (0.034 with 95% CI of 0.007, 0.061), 2) mild to moderate group and severe or extensive group (0.085 with 95% CI of 0.017, 0.152) and 3) normal or no significant group and severe or extensive group (0.113 with 95% CI of 0.049, 0.177).

Conclusion: Our findings show that there is a significant association between TID ratio and severity of coronary artery disease. Although in this study meta-analysis was done, but some technical differences such as the software differences were ignored. Thus performing more studies in this field can help future researchers to update this meta-analysis with subgroup analysis based on different techniques.

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Keywords: Transient ischemic dilation; systematic review; single photon emission computerized tomography; meta-analysis; coronary artery disease; cardiovascular disease

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Introduction

Transient ischemic dilation (TID) is defined as post-stress left ventricular (LV) cavity dilation visualized in single photon emission computed tomography (SPECT) imaging.¹ TID is explained as stress LV volume to rest LV volume ratio. TID is a reliable indicator of LV volume changes which is repeatedly reported to be associated with both myocardial and endocardial ischemia.²

TID is a sensitive and highly specific marker of increased risk for a severe coronary artery disease (CAD).³ TID as a clinical parameter that can be used for detecting balanced ischemia or globally reduced myocardial flow reserve. TID is known as a prognostic and diagnostic indicator for CAD.⁴ TID, is also reported as an independent predictor of CAD by software packages.⁵

Different studies are performed on importance of TID ratio to predict severe coronary artery disease.⁶ Some more detailed studies even evaluated the association between TID ratio and severity of CAD in diabetic patients.⁷ Considering high number and variety of primary researches and even some review articles in this field, we believe that now this is the time to perform a systematic review and meta-analysis to achieve a final conclusion about importance of TID in cardiac nuclear imaging.⁸

Based on all mentioned above, purpose of this study was to evaluate association between TID ratio and severity of CAD in a systematic review and meta-analysis manner.

Methods

Data Sources

We conducted a systematic search on electronic databases including PubMed, Scopus, Embase and Web of Science up to 1 January 2017. Bibliography of all included studies were also checked to obtain a higher accuracy. The whole study was designed and performed based on PRISMA guidelines.

Search strategy

Search keywords were elected based on our PICO

as P: susceptible patients for CAD, I: Transient ischemic dilation, C: Angiographies, O: Severity of CAD. For a better search result, we adjusted keywords and their combinations based on requirements of each database. Only English studies were chosen for further evaluation.

Eligible Studies

We included diagnostic studies if they reported TID and severity of CAD reported by gold standard modality, Angiography. Case reports, letter and review articles were excluded. We also excluded patients with history of prior coronary revascularization, valvular heart disease, or non-ischemic cardiomyopathy.

All included studies defined patients with TID according to the standard definition (TID as stress volume/rest volume ratio) and patients underwent coronary angiography within limited period of 6 months.

Severity of CAD was defined as: 1) normal or no significant disease, 2) mild to moderate disease and 3) severer or extensive disease. Different studies categorized patients with different classifications but in all of them a principal triple division was seen and small differences were truly ignorable.

Quality Assessment and Data Extraction

Two of co-authors conducted data extraction independently using pre-specified inclusion and exclusion criteria. Discrepancies were resolved by consensus and if required, a third co-author qualified the studies. STARD 2015 checklist was used for this purpose. All studies were checked in accordance with STARD 2015 standards and all included studies meet minimal requirements. Extracted data included: first author name, date of publication, sample size, study design and SPECT variables (Type of scan, Type of stress), Angiographic findings, software and TID ratio as mean±SD.

Statistical Analysis and Data Synthesis

All Statistical analyses were performed by Comprehensive meta-analysis software version 2 (CMA-2). For all analyses random effects model was applied. Heterogeneity tests were used including I², Cochrane Q test statistic and associated P-values. Publication bias was also checked using funnel plots and

begg's and egger's tests were used for this mean. "One study Removed" sensitivity analysis was also performed. Results are presented in form of forest and funnel plots.

Result

Search results

423 papers were obtained with primary search. While going through bibliography of these included studies 2 more papers were also included to our primary search results. After removing 54 duplicate records, 371 studies were selected for title and abstract screening in which 309 studies were excluded because of irrelevant title or abstract. Remaining 61 papers underwent full texts screening. During full text evaluation, 1 article could not pass critical appraisal step, 7 papers were reporting same research material, 10 papers did not contain PET comparisons and 36 of them did not report angiography related results. Finally, only 7 articles were eligible to enter analysis and data synthesis process. Figure no.1 shows the flowchart of study selection.

Studies and patient's characteristics

Table no.1 shows the characteristics of the seven included studies. Sample size of included studies ranged

between 86 and 547. All studies were diagnostic and coronary angiography was done maximum within 6 months. Table no.2 shows the baseline characteristics of the patients in all enrolled studies for systematic review.

Meta-analysis for normal or no significant CAD vs. mild to moderate CAD

In this part we performed a meta-analysis to see if there is any significant difference between TID ratio between "normal or no significant" group and "mild to moderate" group. As seen in figure No.2a, all seven studies were eligible to enter this analysis. The results show that patients with "mild to moderate CAD" have a higher TID ratio in comparison to patients with "normal or no significant CAD". With a mean difference of 0.034 (95% CI 0.007, 0.061) and a P-value=0.013, this difference was seen to be statistically significant.

Based on our funnel plot which is seen with imputed mode in figure No.2b and egger's test with a P-value=0.15, there was no publication bias in this analysis.

Considering high heterogeneity of this analysis ($I^2=60.34$, Cochrane Q statistic=15.13, P-value=0.019) we performed some subgroup analyses based on radionuclide agent, stress type or SPECT technique but we could not solve the heterogeneity and it seems it is because of study nature and is inevitable. Meta

Table 1 Characteristics of all included studies.

First Author	Publication Year	Sample Size	Scan Protocol	Scan Type	Stress Type	software
Weiss, AT(1)	1987	89	Thallium-201	single	Treadmill	Visual assessment
Mazzanti, M(12)	1996	97	Thallium-201/ Tc-99m Sestamibi	Dual (201Tl rest/99mTc Sestamibi stress)	Treadmill	Automatic measurement
Abidov, A(13)	1999	179	Thallium-201/ Tc-99m Sestamibi	Dual (201Tl rest/99mTc Sestamibi stress)	adenosine	QPS
Fallahi, B(16)	2010	86	Thallium-201/ Tc-99m Sestamibi	Dual (201Tl rest/99mTc Sestamibi stress)	dipyridamole	Pegasys (ADAC)
Katz, JS(10)	2012	155	Thallium-201/ Tc-99m Sestamibi	Dual (201Tl rest/99mTc Sestamibi stress)	Regadenosine	The Emory Cardiac Toolbox
Xu, Y(3)	2012	547	Tc-99m Sestamibi	Single	Treadmill	QPS
Golzar, Y(6)	2015	547	Tc-99m Sestamibi	single	Regadenosine	4DM-SPECT version 5.1

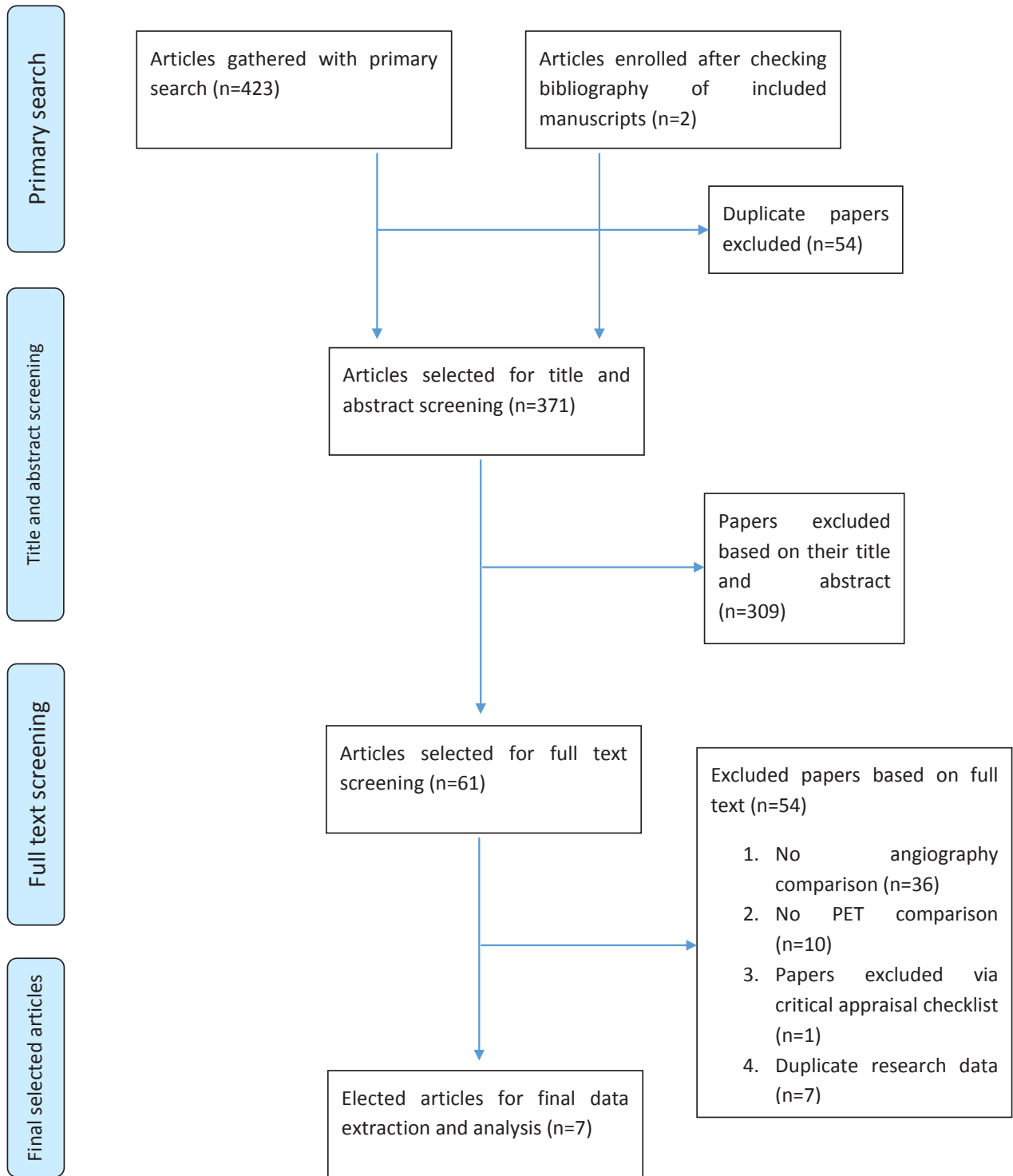


Figure 1 Diagram indicating our search strategy.

Table 2 Baseline characteristics of studied patients.

Study population	Weiss, AT(1)	Mazzanti, M(12)	Abidov, A(13)	Fallahi, B(16)	Katz, JS(10)	Xu, Y(3)	Golzar, Y(6)	
	89	97	179	86	155	547	547	
Age	58 (ranged between 37 to 77)	65±12	69±11.4	56.14±10.96	67.1±11.8	56.9±10.57	62±13	
Women percentage	19 (21.34%)	N/A	82 (45.8%)	66 (76.7%)	80 (52%)	284 (51.9%)	275 (50%)	
Smoking	N/A	N/A	N/A	15 (17.4%)	56 (36%)	112 (20%)	N/A	
Hypertension	N/A	N/A	123 (69.7%)	47 (54.7%)	120 (77%)	253 (46%)	471 (86%)	
Hyperlipidemia	N/A	N/A	N/A	31 (36%)	97 (63%)	237 (43%)	347 (63%)	
Diabetes mellitus	N/A	N/A	54 (30.5%)	23 (26.7%)	69 (45%)	39 (7%)	N/A	
	Normal or no significant CAD	1.02±0.05	1.06±0.05	1.21±0.16	1.15±0.09	1.09±0.16	0.99±0.11	1.04±0.18
TID	Mild to moderate CAD	1.05±0.05	1.07±0.11	1.20±0.16	1.18±0.10	1.15±0.19	1.07±0.13	1.06±0.16
	Severe or extensive CAD	1.09±0.08	1.23±0.13	1.45±0.21	1.16±0.09	1.19±0.26	1.18±0.18	1.06±0.17

regression models were not also helpful to detect any kind of clue for this case. We also went through all included studies but we could not find any kind of clue for cause of this heterogeneity. We think that this can be due to genetic differences of studies population because almost all of them chose TID ratio cut off based on their own study population. Other inevitable etiologies for heterogeneity such as angiography report and etc. can also be responsible.

A sensitivity analysis was also performed using “one study removed” method and final results were not different when any of the studies were removed and it means that our meta-analysis results is not significantly relied on any of primary studies.

Meta-analysis for normal or no significant CAD vs. severe or extensive CAD

Results associated with difference in TID ratio between “normal or no significant CAD” and “severe or extensive CAD” obtained from all 7 studies showed that with a P-value=0.001, there is a significant difference in mean TID ratio between mentioned groups. As seen in forest plot in figure No.3a, with a mean difference of 0.113 (95% CI 0.049, 0.177), it can be concluded that patients with “severe or extensive CAD” have a higher TID ratio in comparison to patients with “normal or no significant CAD”.

As seen in funnel plot in figure No.3b, with a P-value=0.90 for egger’s test, there is no publication bias detected for this analysis.

Again there is a very high heterogeneity in included studies with an I²=91.062, Cochrane Q statistic=67.129 and a P-value=0.0001. We tried different subgroup analysis and meta regression models and we think that this heterogeneity is rooted in natural design of TID related studies. Almost each of them had their own cut off based on their own study population.

We performed a “one study removed” sensitivity analysis and the results indicated that our results are not significantly affected by any of included primary studies.

Meta-analysis for mild to moderate CAD vs. severe or extensive CAD

All seven studies were eligible for this meta-analysis too. As seen in figure No.4a, there is also a statistically significant difference (P-value=0.015) in TID ratios between “mild to moderate CAD” and “severe or extensive CAD” groups (0.085, 95% CI (0.017, 0.152)) which means patients with “severe or extensive CAD” have a significantly higher TID ratio when compared to patients with “mild to moderate CAD”.

As seen in associated funnel plot figure No.4b, with an egger’s P-value=0.88, there is no publication bias in included studies.

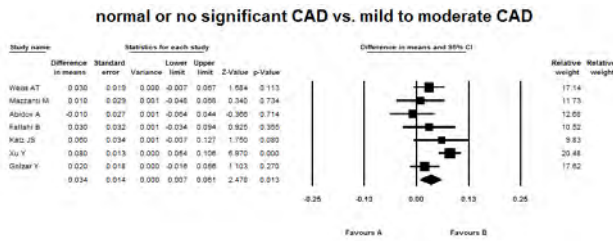


Figure 2a Raw mean difference between normal or no significant CAD group vs. mild to moderate CAD group. Patients with mild to moderate CAD have 0.034 higher mean TID in comparison to patients with normal or no significant CAD. (P-value=0.013)

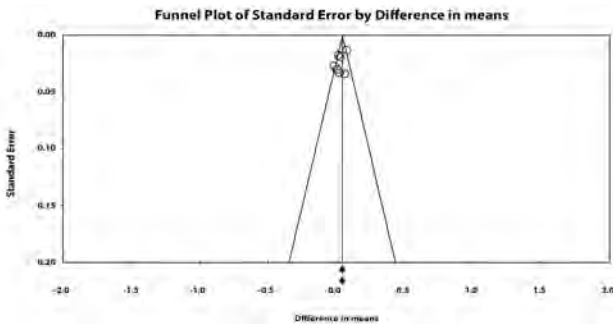


Figure 2b No study is imputed and the red plot is exactly the same as the primary underlying plot which shows lack of publication bias. (P-value=0.15 with 95% CI -6.81, 1.44)

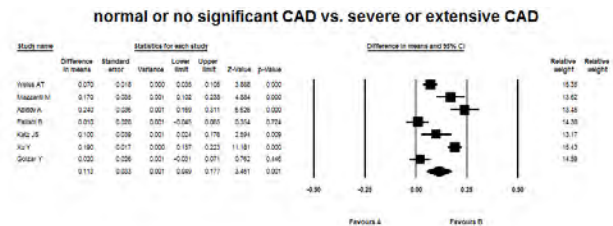


Figure 3a Unstandardized mean difference between TID in normal or no significant CAD vs. severe or extensive CAD groups indicate that patients with severe or extensive CAD have a TID averagely 0.113 higher than patients with normal or no significant CAD. (P-value=0.001)

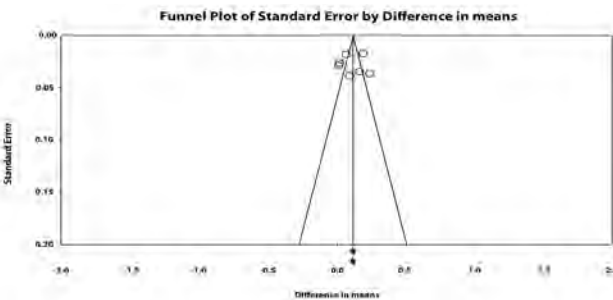


Figure 3b As seen in this figure, no new study is imputed by the software and the red plot is exactly the same as primary plot which means no publication bias was detected in enrolled studies in forest plot 3a. (P-value=0.90 with 95% CI -12.11, 11.02)

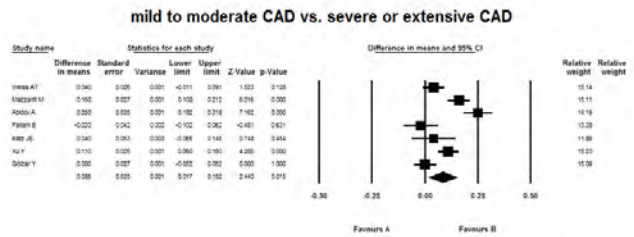


Figure 4a Raw mean difference of TID compared between mild to moderate CAD group vs. severe to extensive CAD group. Results indicate that patients with severe or extensive CAD have averagely a TID 0.085 higher than patients with mild to moderate CAD. (P-value=0.015)

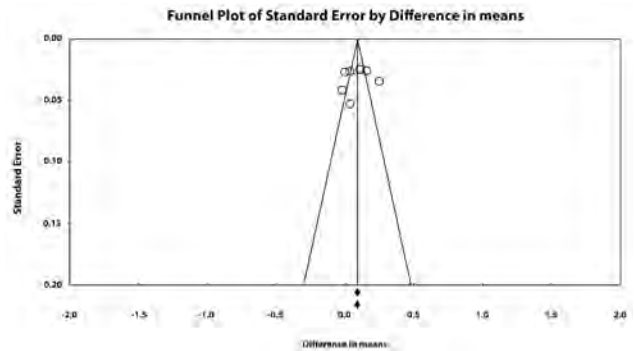


Figure 4b Considering lack of any imputed study and exact match of the red plot and primary plot, no publication bias was detected in included studies for comparing mild to moderate CAD group vs. severe to extensive CAD group based on TID ratio. (P-value=0.93 with 95% CI -9.55, 10.26)

We again observed a high inevitable heterogeneity in included studies ($I^2=86.17$, Cochrane Q statistic=43.391, P-value=0.0001) which could not be solved by any kind of subgroup analysis and points out to natural heterogeneity in included studies.

Our “one study removed” sensitivity analysis did not show any significant reliance of our results on any of included studies.

Discussion

Our findings show a significant association between severity of CAD and TID ratio. On basis of extensive literature reports, TID of LV is an accurate marker for detecting severity of CAD.⁷ TID is an important diagnostic and prognostic marker in MPI. TID value can be reported differently based of different stress methods (Exercise treadmill test or pharmacologic

stress), radiopharmaceuticals (TC agents, thallium, dual isotope) imaging protocols and software tools. Agreement between common softwares (cedar, 4DM SPECT and Emory toolbox) for TID evaluation is controversial in available literature.⁹⁻¹¹

There is no certain cut off value for abnormal TID and arbitrary thresholds are used for diagnostic utility of TID in detecting CAD. In many studies TID range is reported as mean TID \pm 2 standard deviations. While using TID as a binary index, a major question appears in mind if upper normal limits of TID has similar diagnostic accuracy to lower normal limits or not.^{12, 13}

Certainly use of TID as a continuous variable can improve diagnostic accuracy especially when perfusion scan reveals no appreciable perfusion abnormality and LM or three vessel disease is considered as a differential diagnosis.¹⁴

There is no specific pathognomonic perfusion abnormality pattern for detecting LM or three vessel disease and rarely no appreciable perfusion abnormality is detected. In all included studies in this review, the method for determining a cut off was similar and researchers used patients with normal angiography to obtain a cut off for their study.

For example, Weiss et al.¹ study suggested 1-1.12 TID ratio for non-critical CAD in patients underwent exercise and single radiotracer while in Xu et al.³ study 0.96-1.20 was advocated. Wide confidence interval is a diagnostic problem that could result to an uncertain or false diagnosis. On the other hand in Xu study 0.88 to 1.10 is considered as non-significant CAD and 0.94 to 1.20 as significant CAD and this question is unanswerable that patients with 1.10 to 1.20 TID had significant CAD or Not⁽³⁾. Also in pharmacologic stress test and single radiotracer, TID ratio more than 1.22 and 1.37 suggests significant CAD. Overall TID ratio in exercise stress test is less than the pharmacologic stress test. In the extensive angiographic CAD, TID ratio was increased dramatically compared to non-extensive or significant CAD. TID ratio in dual isotope scan is mostly reported to be higher than single isotope.^{12, 13, 15}

In this study we aimed to evaluate importance of an abnormal TID ratio regardless of how it is obtained to see if this index can be routinely used as a continuous marker for estimating severity of coronary artery disease or not.

All mentioned above items are somehow questioning

quality of our meta-analysis but considering the fact that nuclear medicine is not yet a well-developed field and number of researches are limited, we can defend what we did in this meta-analysis.

There was a very similar systematic review and meta-analysis performed in this field by Alama, M et al.⁸ in which researchers evaluated diagnostic and prognostic importance of TID in MPI. In that excellent research, they were focused on importance of TID in predicting only severe and critical CAD.

We believe that our paper is novel in its kind because we separated patients based on severity of CAD and performed separate analyses to achieve a continuous result about TID ratio and different levels of coronary artery involvement which can solve cut off issue in many ways.

In mentioned meta-analysis the researchers reported different patients' population, techniques and diagnostic cut offs as reasons for clinical heterogeneity. We think in our paper we could somehow solve cut off differences issue. We know that this issue is not even completely solved and this is why we think more primary researches are needed in field of cardiac nuclear imaging and TID ratio.

We wanted to assess a logical association between severity of CAD and TID ratio and we had no other solution except unifying studies based on severity of CAD and ignore small differences between TID cut offs. Our results show a very high heterogeneity and the reason is not that hard to understand and is not way different from previous meta-analysis⁽⁸⁾ except TID cut off.

We still think this study is applicable and can be helpful but indeed more primary studies are needed before we can update this meta-analysis with a strong subgroup analysis based on different factors.

Conclusion

By this meta-analysis, importance of TID in predicting severity of CAD was revealed in a population of 1700 patients but the blind side of TID ratio in clinical work was also noticed. Even considering high heterogeneity in all included studies, we believe that this paper can warn clinicians to keep a closer eye on TID ratio when reading a nuclear imaging report specially when is normal.

Our review documented, that there were some few well designed studies on TID and to assess a better association between severity of CAD and TID ratio with less heterogeneity, more new studies are needed.

Conflict of interests

Authors declare that they have no conflict of interests to disclose.

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