Efficacy of SPECT Myocardial Perfusion Imaging (MPI) in Combination with Coronary Artery Calcium (CAC) Score for the Diagnosis of Coronary Artery Disease (CAD)

[1]Dilruba Amin, [2] Shamim Momtaz Ferdousi Begum, [2] Pupree Mutsuddy, [2] Tapati Mandal, [2] Sanhita Majumder, [2] Khokon Kumar Nath and [2] Md. Saiful Islam

[1]Medical Officer, Department of Anesthesiology, Kurmitola General Hospital, Dhaka
[2]National Institute of Nuclear Medicine and Allied Sciences, BSMMU Campus, Dhaka

Correspondence Address: Dr. Dilruba Amin, Medical Officer, Department of Anesthesiology, Kurmitola General Hospital, Dhaka, Email: dilrubaamin55099@gmail.com

ABSTRACT

Background: Cardiovascular disease (CVD) is an important cause of morbidity and mortality in Bangladesh. The coronary artery calcium (CAC) score is a readily and widely available tool for noninvasive diagnosis of atherosclerotic coronary artery disease (CAD).

Aims: To evaluate the diagnostic efficacy of combined CAC score with Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging (MPI) for the diagnosis of CAD.

Methods: This cross sectional study was carried out in the National Institute of Nuclear Medicine & Allied Sciences (NINMAS) during July 2017 to June 2018. A total of 33 participants with known or suspected cases of CAD were included in this study who underwent SPECT MPI and CAC imaging. Statistical analyses of the results were obtained by using Statistical Packages for Social Sciences (SPSS-22).

Results: Nearly half (48.5 %) of the participants belonged to age 51-60 years. Was male predominant in this study, 93.9% and 6.1% ware female. Regarding MPI 69.7% participants had severely abnormal perfusion and 21.2% had normal perfusion. According to CAC score 33.3% participants had moderate calcification in coronary artery. Significant CAD was found in 81.82% participants in Coronary Angiogram (CAG) study. Combined SPECT MPI and CAC score diagnosed significant CAD in 90.9% patents. The performance test of CAC score showed 96.3% sensitivity, 33.3% specificity, 84.8%accuracy, 86.7% positive predictive value (PPV) and 66.7% negative predictive value (NPV) for diagnosis of significant CAD. The performance test of SPECT MPI has sensitivity of 85.2%, specificity 50%, accuracy 78.8% and PPV 88.5% and NPV 42.8%. The performance test of combined SPECT MPI and CAC score, has 96.3% sensitivity, 50% specificity, 87.8% accuracy, 89.6% PPV and NPV 75%. CAC score with a cut off value of 12.5 had best combination of sensitivity 93.9% and specificity 50% for identifying the CAD missed by SPECT MPI.

Conclusion: The CAC score may offer incremental diagnostic information over SPECT MPI for identifying patients with significant CAD and negative MPI results.

Key words: **coronary artery disease; coronary artery calcium score; gated SPECT MPI; coronary angiography**

Bangladesh J. Nucl. Med. Vol. 23 No. 1 & 2 year 2020
Doi: https://doi.org/10.3329/bjnm.v23i1-2.57704

INTRODUCTION

Coronary artery disease (CAD) also called coronary heart disease (CHD) or coronary atherosclerosis, is the most common type of heart disease and the prime cause of death globally. CAD results from impedance or blockage of one or more arteries that supply blood to the heart usually due to atherosclerosis. Centers for Disease Control and Prevention, Global Health- Bangladesh state that ischemic heart disease (IHD) is fourth among top ten causes of death in Bangladesh and the last estimated prevalence of CAD in Bangladesh is 5.1% which was responsible for 17% of national deaths (1,2). Different test werw used for diagnosis of CAD, e.g. exercise ECG, echocardiography, coronary angiography (CAG), gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), coronary artery calcium (CAC) score etc. MPI with gated SPECT is a well-established and widely accepted non-invasive test for the diagnostic and prognostic evaluation of patients with known or suspected CAD. There is a growing interest in the use of CAC imaging to diagnose early subclinical atherosclerosis and to improve risk stratification in asymptomatic individuals (3).

Now a days MPI has become one of the most utilized non-invasive methods in cardiology for diagnosis of CAD due to its fairly high sensitivity (4). MPI is carried

out as one or two days stress-rest protocol. Stress study is performed with any one of the methods a) exercise stress by treadmill using Bruce/Modified Bruce protocol or b) pharmacological stress using pharmacological agents (Adenosine, Dipyridamole, Regadenoson, Dobutamine and Arbutamine). SPECT MPI is a method based on image formation through the acquisition of photons emitted by radioisotope ^{99m}-Technetium (^{99m}Tc) and captured by gamma-camera located in the detectors. Status of myocardial perfusion are reconstructed into multi-planar images through specific software which corresponds to cardiac tissue perfusion at the moment of radioisotope administration (5). A semi quantitative visual interpretation of the attenuation-corrected stress and rest images are performed. Segments are scored depending on the radiotracer uptake with a 5-point score; 0 = normal, 1 = equivocal, 2 = moderately reduced, 3 = severely reduced and 4 = absent. Fixed perfusion defect represent infarction and reversible defect represent ischemia (3).

The presence of Coronary Artery Calcium (CAC) is an important marker of atherosclerosis burden and the evaluation of the extent of CAC may be used in clinical management of asymptomatic patients with intermediate risk of CAD. High CAC score is associated with higher probability of significant CAD and a strong predictor for risk assessment of cardiovascular events (6). CAC score is obtained from the acquisition of axial chest images, synchronized to the electrocardiogram at 3 mm slices without use of iodinated contrast (7).

Coronary angiogram (CAG) is an invasive and the most expensive clinical test for CAD with a highest effective radiation dose (8). CAG is a procedure that uses X-ray imaging to see the coronary blood vessels. It is generally done to see the condition of blood flow to the heart. For this procedure a dye is injected into the blood vessels of the heart which is visible by an X-ray machine. The X-ray machine rapidly takes a series of images of coronary vessels called angiograms (9). On the basis of CAG findings significant CAD is considered when ≥ 50% occlusion is evident in any major coronary artery e.g. LAD, LCX and RCA (3).

PATIENTS AND METHODS

Total 33 individuals, who were referred to NINMAS at Bangabandhu Sheikh Mujib Medical University (BSMMU) campus, Dhaka for SPECT MPI during July 2017 to June 2018, were included in this study. After proper counseling and informed consents, all the patients were interviewed and complete clinical profile were recorded. Caffeine containing beverages were stopped 24 hours prior to the test and fasting for 4 hours before the stress study were ensured. SPECT MPI with ^{99m}Tc Sestamibi (MIBI) was done as one day stress-rest protocol which is practiced in NINMAS. Stress study was performed with any one of the methods a) Exercise stress by treadmill using Modified Bruce protocol or b) Pharmacological stress using Adenosine or Dobutamine. The stress images were acquired on the Dual headed SPECT gamma camera after 30 min of intravenous injection of radiotracer. On the same day, after a 90 minutes rest period radiotracer was injected with three times higher dose. Rest images were obtained one hour after the injection. Summed Stress Score (SSS) is used for global scoring of myocardial perfusion measurement. When the SSS is less than 4, the perfusion is considered as normal or no significant perfusion defect. SSS categorized as 4-8 = mildly abnormal perfusion, 9-13 = moderately abnormal perfusion and >13 = severely abnormal perfusion (10).

CAC imaging with ECG-gated scan was done within a week of MPI study. CAC imaging was acquired by using 3 mm each 128 slice CT scanner (GE Discovery CT 710) without iodinated contrast. Then the images were reconstructed, image analysis and score calculation was done. Smart Score software was used for CAC score. Amount of calcium deposition in the coronary arteries is obtained with cardiac CT. CAC scores are described as, 0 = absence of disease, 1-10 = minimal calcification, 11-100 = mild calcification, 101-400 = moderate calcification, 401-1000 = severe calcification, >1000 = extensive calcification (11).

CAG findings were collected and recorded within the 60 days of CAC imaging. On the basis of CAG findings, significant CAD is considered when ≥50% occlusion is evident in any major coronary artery e.g. LAD, LCX and RCA (3). Receiver-operating characteristic (ROC) curve

was constructed using CAC score value of the patients with a best combination of 93.9% sensitivity and 50% specificity, which gave CAC score cut off value of 12.5 for this study to identify CAD which were missed by SPECT MPI.

RESULTS

Among the 33 patients, male (n = 31) 93.9%, female (n = 2) 6.1% with mean age 54.15±7.71 years were found. The most common risk factor was MI, found in 69.7%. The other risk factors were smoking 60.6%, hypertension 57.6%, diabetes 51.5%, dyslipidemia 51.5% and IHD 39.4%. Out of 33 participants, MPI revealed severely reduced perfusion in 69.7% (n=23) and no perfusion defect in 21.2% (n=7) (Table 1).

Table 1: Distribution of the study subjects by SSS (n=33)

SSS	Number of participants	Percentage (%)
<4	7	21.2
Mild (4-8)	2	6.1
Moderate (9-13)	1	3.0
Severe (>13)	23	69.7
Mean± SD	18.70±11.6	
Range (min-max)	0-35	

CAC score shows maximum 33.3% (n=11) had moderate calcification and 9.1% (n=3) absence of calcification in coronary arteries (Table 2).

Table 2: Distribution of the study subjects by CAC score (total) (n=33)

CAC score (total)	Number of participants	Percentage (%)
Absent (0)	3	9.1
Insignificant (1-10)	1	3.0
Mild (11-100)	5	15.2
Moderate (101-400)	11	33.3
Severe (401-1000)	9	27.2
Extensive (>1000)	4	12.1
Mean± SD	424.82±463.14	
Range (min-max)	0-1701	

According to CAG, significant CAD was found in 81.8% (n=27) participants and 18.2% (n=6) participants had no significant disease (Table 3).

Table 3: Distribution of the participants by Significant CAD diagnosed by CAG (n=33)

Significant CAD in CAG	Number of participants	Percentage (%)
Present (≥ 50% occlusion in any one artery)	27	81.8
Absent (<50% occlusion in any one artery)	6	18.2

When combined CAC score and SPECT MPI was used 87.9% (n=29) has CAD, To diagnose CAD by SPECT MPI in comparison to CAG was 23 true positive, three false positive, four false negative and three true negative. According to the case finding the performance test of SPECT MPI show 85.8% sensitivity, 50% specificity, 78.8% accuracy, 88.6% positive predictive value (PPV) and 42.5% negative predictive value (NPV) (Table 4).

Table 4: Performance test of SPECT MPI (n=33)

SPECT MPI	CAG		
	CAD Positive	CAD Negative	Total
CAD Positive	23	3	26
CAD Negative	4	3	7
Total	27	6	33

Validity test	Percentage
Sensitivity	85.8
Specificity	50.0
Accuracy	78.8
Positive predictive value	88.6
Negative predictive value	42.5

To diagnose CAD by CAC score in comparison to CAG true positive was 26, false positive four cases, false negative one case and true negative two cases. The performance test of CAC score for diagnosis of CAD has sensitivity 96.3%, specificity 33.3%, accuracy 84.5%, PPV 86.7% and NPV 66.7% (Table 5).

Table 5: Performance test of CAC score (n=33)

CAC score	CAG		
	CAD Positive	CAD Negative	Total
CAD Positive	26	4	30
CAD Negative	1	2	3
Total	27	6	33

Validity test	Percentage
Sensitivity	96.3
Specificity	33.3
Accuracy	84.8
Positive predictive value	86.7
Negative predictive value	66.7

Table 6: Performance test of Combined SPECT MPI with CAC score (n=33)

Combined SPECT MPI with CAC score	CAG		
	CAD Positive	CAD Negative	Total
CAD Positive	26	3	29
CAD Negative	1	3	4
	27	6	33

Validity test	Percentage (%)
Sensitivity	96.3
Specificity	50.0
Accuracy	87.9
Positive predictive value	89.6
Negative predictive value	75.0

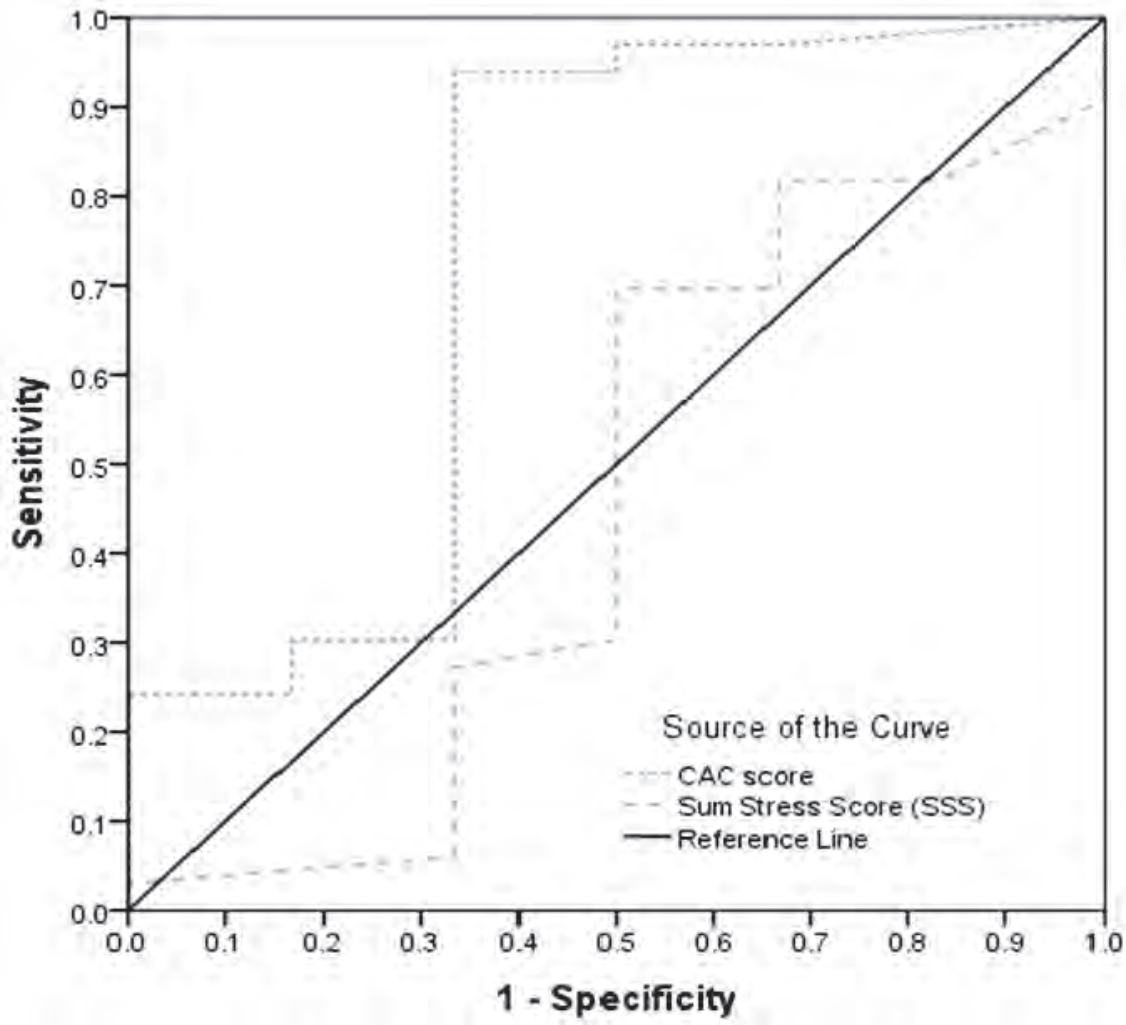
To diagnose CAD by combined SPECT MPI and CAC score in comparison to CAG in current study 26 were found true positive, three false positive, one false negative and three true negative cases.

The performance test of combined SPECT MPI and CAC score in diagnosis of CAD has sensitivity 96.3%, specificity 50%, accuracy 87.9%, PPV 89.6% and NPV 75% (Table 6).

Receiver-operating characteristic (ROC) curve was constructed using CAC score and SSS value of the participants. ROC curve has given CAC score cut off value of 12.5 for this study with a best combination of 93.9% sensitivity and 50% specificity to identify CAD. This cut off value of CAC score for the present study was used to diagnose significant CAD which were missed by SPECT MPI (Table 7 and figure 1).

Table 7: Receiver-operating characteristic (ROC) curve of CAC score and SSS for prediction of CAD

	Cutoff value	Sensitivity	Specificity	Area under the ROC curve	P value	95% Confidence interval (CI)	
						Lower bound	Upper bound
CAC score	12.50	93.9	50.0	0.737	0.027	0.465	1.000
Sum Stress Score (SSS)	4.00	81.8	33.3	0.460	0.055	0.168	0.751



Diagonal segments are produced by ties.

Figure 1: Receiver-operating characteristic (ROC) curve of CAC score and SSS for prediction of CAD.

DISCUSSION

CAC is a reliable non-invasive diagnostic tool for the prediction of subsequent cardiovascular events in populations with elevated conventional risk factors (12). In an observational report by Budoff et al. 10 years survival of asymptomatic patients with CAD was found in 99.4% patients with a CAC score of 0 (zero). Nearly 87.8% patients having CAC score of greater than 1000 had 10 years survival (13).

About 33.3% patients of this study belonged to moderate (101-400) CAC score and 6% had insignificant (1-10) CAC score. CAC score was zero in three (9.1%) participants. The mean ± SD of CAC score was found 424.82±463.14, ranged from 0-1701. Yuoness et al. reported that 26 patients with a CAC score >1,000 and among them 58% patients had severe coronary disease (14). Schepis et al. observed that 77 subjects had a CAC score with mean of 560±682 ranged from 023 - 968. Twelve patients (16%) had minimal or insignificant CAC score (≤10), 13% had mild CAC score (11– 100), 26% had moderate CAC score (101–400), 26% patients had severe CAC score (401–1,000) and 19% patients had extensive CAC score (>1,000). These findings correspond with the current study (3).

The SSS of all segments found that 69.7% had severe perfusion defect indicating high risk. Seven (21.2%)

participants had normal perfusion or no risk. The mean±SD of SSS was found 18.70±11.6 with a range of 0 to 35.

Present study revealed significant CAD (≥50% occlusion in any single artery)in CAG was found in 81.82% patients. Schepis et al. showed that 42 (55%) of the 77 patients had significant CAD in their study (3).

CAC score is a non-invasive modality which detects coronary calcifications being a surrogate marker for cardiac atherosclerosis (15). According to current literature the amount of calcified tissue correlates with the risk of developing adverse cardiac events in the future, such as MI or sudden cardiac death. In addition, it seems that CAC score is a better risk predictor for prospective cardiac events than currently available risk stratification score systems, such as Framingham or ATP-III risk score (16). CAC score reflected individual atherosclerotic

disease burden. The exclusion of coronary calcifications has been shown to exclude significant CAD in symptomatic patients (12). According to current guidelines in symptomatic patients CAC score might additionally serve as a useful filter prior to invasive coronary angiography or stress nuclear imaging due to its high sensitivity for flow-limiting CAD (17).

It is to be noted that significant CAD in CAG in comparison to CAC score correlated with the finding of Ziegler et al. who calculated a sensitivity of 99.2%, specificity 30.3%, PPV 46.5% and NPV 98.5%. The diagnostic accuracy was 56.4% for calcium scoring alone with respect to significant CAD detection (15). A high sensitivity and a high NPV from the above findings suggested CAC score being a useful tool for ruling out CAD by exclusion of calcified plaque tissue. In these patients an additional SPECT MPI did not further increase diagnostic accuracy as the negative predictive value of SPECT MPI is limited to 92.1% reported by the authors. Increasing CAC score thresholds would lead to an increase in specificity and PPV. Thus CAC score would no longer be suitable as a filter for invasive angiography and still not sufficient for the detection of relevant stenosis with a PPV of 84.4%. Still, diagnostic accuracy of CAC score at a threshold of 100 is comparable to the diagnostic performance of SPECT MPI. Due to low specificities of positive CAC scores, a functional test like SPECT MPI following initial CAC score in case of calcified tissue detection is reasonable (15).

This study was aimed to evaluate the performance of SPECT MPI test using SPECT imaging as stand-alone modality for significant CAD detection. Schepis et al. found a sensitivity of 76%, specificity 91%, PPV 91%, NPV 76% using SPECT imaging as stand alone modality (3). In another study, Klocke et al. found MPI to have an average sensitivity of 89% and an average specificity of 75% in vasodilator stress studies (18). The findings correlate with the present study.

Schepis et al.observed that the vast majority of patients for whom true-negative findings were obtained by the combination of SPECT and the CAC score had substantial calcifications, although the CAC score was below the cutoff. Atherosclerosis does not necessarily show perfusion abnormalities on perfusion imaging. On the other hand, normal MPI does not exclude subclinical or obstructive CAD (3).

Schepis et al. studied observed 77 patients with detectable coronary calcifications and found SPECT MPI with CAC score had sensitivity = 86%, specificity = 86%, PPV= 88% and NPV= 83% where a CAC score of greater than or equal to 709 was the optimal cutoff for detecting patients with CAD despite normal MPI results. The authors also mentioned that the combination of the CAC score and SPECT improved sensitivity and NPV in detecting patients with coronary stenosis over SPECT alone without a significant decrease in specificity. This technique may improve the identification of patients requiring further investigation with conventional coronary angiography (3).

In this study, ROC was constructed using CAC score value of the patient's CAD with a best combination of sensitivity and specificity for CAD which gave CAC score cut off value of 12.50 with 93.9% sensitivity and 50.0% specificity as the value and for identifying the CAD. SSS cut of value 4 showed sensitivity 81.8% and specificity 33.3% as the value and for identifying the CAD.

Schepis et al. observed that the optimal CAC score threshold was determined the best sensitivity for the

detection of significant CAD with an associated specificity of greater than 90%(3). CAC score greater than or equal to 709 was the optimal cut-off for detecting patients with CAD missed by SPECT. In this threshold, combined MPI and the CAC score had a sensitivity of 86% and a specificity of 86% for the detection of patients with CAD. Thus, the combined CAC and SPECT have improved the sensitivity of SPECT from 76% to 86% without a significant decrease in specificity from 91% to 86%. Accordingly, the PPV decreased from 91% to 88% and the NPV increased from 76% to 83% when the combined approach was used (3). Sensitivity of combined SPECT MPI and CAC score also increased from 80.7% to 96.3% than that of SPECT MPI alone.

The study results revealed that the CAC score may improve the diagnostic performance of SPECT MPI in identification of significant CAD in a risk population.

Combining morphological and anatomical information by CAC score with functional information obtained from SPECT MPI provides complementary information by reflecting different pathophysiologic aspects of CAD

CONCLUSION

CAC score in adjunct to SPECT MPI increases the diagnostic efficacy for the diagnosis of CAD. CAC score is a diagnostic, sensitive and specific modality for identifying patients with significant CAD. In patients with a positive CAC score with combination SPECT MPI increased sensitivity, specificity, PPV and NPV for the detection of CAD significantly then SPECT MPI alone. SPECT MPI and CAC also gave additional information on patients' coronary atherosclerosis and cardiovascular risk.

REFERENCES

1. CDC Global Health-Bangladesh (2014). Top 10 causes of death. Available at https://www.cdc.gov/globalhealth/countries/bangladesh/default.htm.
2. Islam M. Cardiovascular Disease in Bangladesh: A Review. Bangladesh Heart Journal 2016;31(02):80-99.
3. Schepis T, Gaemperli O, Koepfli P, Namdar M, ValentaI, Scheffel H, Leschka S, Husmann L, Eberli FR&Luscher TF. Added value of coronary artery calcium score as an adjunct to gated SPECT for the evaluation of coronary artery disease in an intermediate-risk population. J Nucl Med 2007;48:1424-1430.
4. Notghi A and Low CS. Myocardial perfusion scintigraphy: past, present and future. Br J Radiol 2011;84:S229-S236.
5. Hung GU. Diagnosing CAD: additional markers from myocardial perfusion SPECT. J Biomed Res 2013;27:467.
6. Assante R, Klain M and Acampa W. Use of coronary artery calcium scanning as a triage for invasive coronary angiography. J Nucl Cardiol 2019 Apr;26(2):613-615
7. Siqueira FPR, Mesquita CT, Santos AASMD and Nacif MS. Relationship between calcium score and myocardial scintigraphy in the diagnosis of coronary disease. Arquivos brasileiros de cardiologia 2016;107:365-374.
8. Brindis RG, Douglas PS, Hendel RC et al. ACCF/ASNC appropriateness criteria for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI): a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group and the American Society of Nuclear Cardiology endorsed by the American Heart Association, J Am Coll Cardiol 2005;46:1587-1605.
9. Ryan TJ. The coronary angiogram and its seminal contributions to cardiovascular medicine over five decades. Trans Am Clin Climatol Assoc 2002;113:261-71
10. Monika C, Zbigniew W, Agata D, Dominik S, Jan G, Moriusz G and Jaroslaw PW. Interpreting myocardial perfusion scintigraphy using single-photon emission computed tomography. Polish Journal of Thoracic and Cardiovascular surgery 2017;14(3):192-199.
11. Detrano R, Guerci AD, Carr J J, Bild D E, Burke G, Folsom AR, Liu K, Shea S, Szklo M and BluemkeDA . Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358,1336-1345.
12. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffman U, Cury RC, Abbar S, Brady TJ, Budoff MJ, Blumenthal RS and Nasir K. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging 2009;2(6),675-688.
13. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS and Mosler TP. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am CollCardiol 2007;49(18),1860-1870.
14. Yuoness SA, Goha AM, Romsa JG, Akincioglu C, Warrington JC, Datta S, Massel DR, Martell R, Gambhir S, Urbain JLC. andVezina WC. Very high coronary artery calcium score with normal myocardial perfusion SPECT imaging is associated with a moderate incidence of severe coronary artery disease. Eur J Nucl Med Mol Imaging 2015;42(10),1542-1550.
15. Von Ziegler F, Brendel M, Uebleis C, Helbig S, Greif M, Ruemmler J, Becker C, Hacker M, Steinbeck G and Becker A. SPECT myocardial perfusion imaging as an adjunct to coronary calcium score for the detection of hemodynamically significant coronary artery stenosis. BMC Cardiovasc Disor 2012;12(1):116.
16. Knez A, Becker A, Leber A, White C, Becker CR, Reiser MF, Steinbeck G and Boekstegers P. Relation of coronary calcium scores

by electron beam tomography to obstructive disease in 2,115 symptomatic patients. Am J Cardiol 2004;93(9):1150-1152.

17. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, Lauer MS, Post WS, Raggi P, Redberg RF and Rodgers GP. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). Circulation 2007Jan 23;115(3):402-26.

18. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, T O'Gara P, Carabello BA, Russell RO, CerqueiraMD and Sutton MGSJ. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am CollCardiol 2003;42(7):1318-1333.