The Egyptian Journal of Hospital Medicine (January 2022) Vol. 86, Page 742-747

Predictors of high Calcium Score in Patients with Negative Myocardial Perfusion Imaging

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ABSTRACT

Background: Coronary artery disease (CAD) is one of the major cardiovascular diseases. Myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) plays an important role in the diagnosis and prognosis of CAD.

Objective: The aim of the present study was to reduce the generalization of doing calcium score for all coronary cardiac patients with negative myocardial perfusion imaging.

Patients and methods: A retrospective cohort study analysis using data from Alfa Scan Center, a major outpatient radiology center in Cairo, Egypt, and conducted in Cardiology Department, Faculty of Medicine, Zagazig University that included a total sample of 1168 participants with negative myocardial perfusion imaging not known to have history of CAD, and age ranged between 20 to 80 years from both sexes. All patients were subjected for SPECT-MPI after the intravenous injection of 99mTc-sestamibi.

Results: There was statistically significant difference between the two groups regarding age, gender, weight, chest pain, hypertension, dyslipidemia, diabetes, family history of CAD, beta blockers, aspirin, resting diastolic blood pressure (DBP), rest ECG abnormalities and exercise duration. Age, gender, diabetes mellitus and dyslipidemia were the predictors of any coronary artery calcification (CAC > 0) in patients with negative myocardial perfusion imaging. Age, gender and Duke Treadmill Score were the predictors of significant coronary artery calcification (CAC > 100) in patients with negative myocardial perfusion imaging.

Conclusion: Calcium score for all not known coronary cardiac patients with negative MPI is a mandatory, particularly if they are old, male gender and have multiple risk factors.

Keywords: Calcium Score, Coronary Arteriography, Myocardial Perfusion.

INTRODUCTION

Coronary artery disease (CAD) is one of the major cardiovascular diseases affecting the global human population. This disease has been proved to be the major cause of death in both the developed and developing countries. Lifestyle, environmental factors, and genetic factors pose as risk factors for the development of cardiovascular disease. The prevalence of risk factors among healthy individuals elucidates the probable occurrence of CAD in near future [(1)].

The diagnosis of CAD takes into account the presence of symptoms, risk factors and complementary diagnostic methods that generally use stress mechanisms, with the goal of diagnosing the presence of myocardial ischemia. Among these, myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) plays an important role in the diagnosis and prognosis of CAD [(2)].

SPECT studies with non-significant perfusion defects for myocardial ischemia may represent a challenge, sometimes leading to unnecessary indication for cardiac catheterization. A multicenter study demonstrated that, based on the available algorithms used for the evaluation of patients with suspected CAD, about 40% of patients undergoing coronary arteriography showed no coronary obstruction [(3)].

Coronary computed tomography angiography (CCTA) is also an important method in the evaluation of the coronary arteries with high accuracy in the diagnosis and prognosis of coronary heart disease. In addition, coronary artery calcium (CAC) scoring has an established role in risk-stratifying asymptomatic patients at intermediate risk of CAD [(4)].

Evidence shows that CAC scoring is a strong independent predictor of CHD events and improves classification of intermediate risk individuals, causing a large shift in the distribution of CVD risk. Currently, European, and American guidelines recommend considering additional CAC scoring to guide preventive therapy decisions in intermediate-risk adults [(5,6)].

Therefore, this study aimed to reduce the generalization of doing calcium score for all coronary cardiac patients with negative myocardial perfusion imaging.

PATIENTS AND METHODS

The study was carried out as retrospective study in Alfa Scan Center, a major outpatient radiology center in Cairo, Egypt. Data were collected from the records of patients from 1st of January 2014 to 31st of December 2019 .

Received: 13/9/2021
Accepted: 10/11/2021

Ethical approval:

The study was approved by by institutional research board (IRB) of Zagazig Faculty of Medicine, Zagazig University and an informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Population subjects: Coronary cardiac patients with negative myocardial perfusion imaging.

Inclusion criteria: Patients of both sexes with negative SPECT myocardial perfusion imaging. Patients not known to have history of CAD.

Exclusion criteria: Patients with positive SPECT myocardial perfusion imaging, patients known to have history of CAD, and patients who refuse to do calcium score test or unavailability of CT.

Methods:

All the patients were subjected for a medical history taking and a physical examination performing by a physician then documentation of the data of presenting complaint: especially chest pain, persons who smoked regularly during the previous 12 months were classified as smokers, height and weight were measured, and body mass index (kg/m^2) was calculated.

Two blood pressure determinations after the participant was sitting at least 5 minutes, and the average was used for the analyses. Positive family history of coronary artery disease: especially when involving premature CAD in a first-degree relative before the age of 45 years.

Hypertension was categorized according to blood pressure readings by the fifth Joint National Committee report on the detection, evaluation, and treatment of high blood pressure (JNC-V) definitions: optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal blood pressure (systolic 120 to 129 mm Hg or diastolic 80 to 84 mm Hg), high normal blood pressure (systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg), hypertension stage I (systolic 140 to 159 mm Hg or diastolic 90 to 99 mm Hg), and hypertension stage II–IV (systolic ≥160 or diastolic ≥100 mm Hg). When systolic and diastolic pressures fell into different categories, the higher category was selected for the purposes of classification. The medication history of using any antihypertensive medication was also considered[(7)].

In diabetic patients without obstructive coronary disease, myocardial perfusion study can be predictor of cardiac events. A negative study can be an indicator of a better cardiovascular prognosis [(8)].

Dyslipidemia was diagnosed by elevation of plasma cholesterol, triglycerides (TGs), or both, or a low HDL cholesterol level. The medication history of using any drugs for treatment of dyslipidemias such as: statins, cholesterol absorption inhibitors, bile acid sequestrants, lomitapide, mipomersen, fibrates, n-3 fatty acids and nicotinic acid was also documented.

Laboratory investigations:

Including lipid profile (total cholesterol, LDL-C, HDL-C and triglycerides); kidney profile (serum creatinine and urea); glycosylated hemoglobin (HBA1c); fasting and 2 hours postprandial blood glucose level.

Collection of samples:

Blood sampling: 5 ml of peripheral venous blood were taken from each subject under complete aseptic conditions and were divided into 3 portions. 1. 1 ml was collected on fluoride oxalate (2:1) 2 mg/ml for estimation of plasma glucose (fasting and 2 hours postprandial). 2. 1 was ml collected with potassium EDTA 1 mg/ml for measurement for glycohemoglobin (HbA1c). 3. 3 ml were left for 30-60 minutes for spontaneous clotting then centrifuged at 3000 rpm for 10 minutes; serum samples were separated into another set of tubes and kept frozen at -80º C till use.

Fresh, mid-stream urine was collected from all patients and refrigerated at -20˚C. Using Bayer CLINITEK Microalbumin Reagent Strips, a semi quantitative method for microalbuminuria. analysis was done using the CLINITEK Analyzer. According to the manufacturer, the Bayer Microalbustix test has a sensitivity of 90% and a specificity of 88% for the urinary albumin/creatinine ratio.

HbA1C determination:

The HbA1c determination is based on the turbid metric inhibition immunoassay (TINIA) for hemolyzed whole blood. O Test principle: This method uses TTAB (Tetra decyl trimethyl ammonium bromide) as the detergent in the hemolyzing reagent to eliminate interference from leukocytes (TTAB does not lyses leukocytes).

Sample pretreatment to remove labile HbA1c is not necessary. All hemoglobin variants which are glycated at the β chain N terminus and, which have antibody recognizable regions identical to that of HbA1c are measured by this assay. Consequently, the metabolic state of patients having uremia or the most frequent hemoglobinopathies (Hb AS, Hb AC, Hb AE) can be determined using this assay.

Technique: Allow blood specimen and hemolyzing reagent for Tina quant HbA1c to3. Sample was diluted with hemolyzing reagent for Tina quant HbA1c (Cat. No. 11488457 122) in the ratio 1:101 (1+100) [(9)].

Echocardiography:

To detect wall motion abnormalities and assessment of LV systolic function. Using standard

echocardiographic views, EDD, ESD, PWD, IVSD, FS, LVEF, LA dimension and RV function by TAPSE were estimated using [Philips Epic 7 machine (California, USA) in National heart institute and Vivid 9, General Electric Healthcare (GE Vingmed, Norway) in Zagazig university] and all measures were taken by blindly by two independent echo experts for all subjects according to ASE recommendations [(10)].

Electrocardiogram:

Standard 12-lead ECG recordings were obtained from all patients both resting and stress ECG to document sinus rhythm.

All patients were subjected for single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) after the intravenous injection of Tc-99m-sestamibi (99mTc-sestamibi) and documentation of the data.

Coronary artery calcium (CAC) scans:

For estimating overall coronary plaque burden using noncontrast-enhanced calcium scoring CT (CSCT) (following the [negative] SPECT-MPI) and documentation of the data. CAC was quantified using the Agatston scoring method and was confirmed when needed in OsiriX, Version 3.9 (Pixmeo, Switzerland) 64-bit image processing software. CT scanning was performed on a Philips ICT 256 (Alfa scan, Cairo, Egypt).

Ethical Consideration:

The study was approved by the Ethical Committee of Zagazig Faculty of Medicine. An informed consent was obtained from all patients to use their data in researches. All given data were used for the current medical research only.

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for the Social Sciences) version 17. Qualitative data were represented as frequencies and relative percentages.

Chi square test ($\chi 2$) was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean± SD and range. Student t test was used to calculate difference between quantitative variables. Logistic regression model was done to assess the predictors of CAC. All statistical comparisons were significant when level of P-value ≤ 0.05 and $p < 0.001$ indicated highly significant difference.

RESULTS

Table 1 shows the demographic data of a total sample of 1168 participants**.**

Table (1): Demographic data of the participants

Variables	n= 1168
Age Mean± SD	48 ± 9 years
Male n (%)	770 (66)
Weight Mean± SD	90 ± 15 kg
Height Mean± SD	169 ± 9 cm
Chest pain n (%)	775 (66.4)
Hypertension n (%)	543 (47)
Dyslipidemia n (%)	684 (59)
Diabetes Mellitus n (%)	299 (26)
Smoking n (%)	449 (38)
Family history of CAD n (%)	52 (5)
Obesity n (%)	820 (70)
Beta blockers n (%)	446 (38)
Nitrates n (%)	137 (11.7)
Statin n (%)	459 (39)
Aspirin n (%)	506 (43)

51.2% of the participants had resting ECG abnormalities and 18.5% had exercise chest pain **(Table 2).**

Table (2): Exercise stress test results among the participants

Variables	n= 1168 Mean± SD
Resting HR (bpm)	86 ± 15
Resting SBP (mmHg)	134 ± 68
Resting DBP (mmHg)	81 ± 6
Resting ECG Abnormalities Yes n (%)	610 (51%)
Exercise duration (sec)	480 ± 119
Exercise chest pain Yes n (%)	216 (19%)
Peak HR (bpm)	162 ± 13
Peak SBP (mmHg)	186± 13
Peak DBP (mmHg)	91± 8
No of leads	2± 3
METS	10± 2

METS: metabolic equivalents of task, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

On comparing between CAC=zero and CAC >0 regarding other variables, there was statistically significant difference between the two groups regarding age, gender, weight, chest pain, hypertension, dyslipidemia, diabetes, family history of CAD, beta blockers, aspirin, resting DBP, rest ECG abnormalities and exercise duration **(Table 3).**

Table 3. Comparison between the participants regarding CAC score

Variables	CAC=0 n=744	CAC>0 n= 422	P value
Age Mean± SD	46.1 ± 8.2	52.3± 7.9	**<0.001***
Male n (%)	390 (52)	380 (90)	**0.032***
Weight Mean± SD	88.5 ± 15.3	91.4± 15.4	**0.002***
Height Mean± SD	168.7 ± 8.6	169.7± 8.7	0.070
Chest pain n (%)	385 (52)	390 (92)	**0.031***
Hypertension n (%)	257 (35)	286 (68)	**<0.001***
Dyslipidemia n (%)	367 (49)	317 (75)	**<0.001***
Diabetes mellitus n (%)	109 (15)	190 (45)	**<0.001***
Smoking n (%)	269 (36)	180 (42)	0.095
Family history of CAD n (%)	20 (3)	32 (8)	**0.009***
Beta Blockers n (%)	166 (22)	280 (66)	**<0.001***
Nitrates n (%)	85 (11)	52 (12)	0.202
Statin n (%)	304 (41)	155 (37)	0.330
Aspirin n (%)	236 (32)	270 (64)	**<0.001***
Rest HR Mean± SD	85.9 ± 14.1	85.4± 15.2	0.602
Rest SBP Mean± SD	133.9 ± 73.1	134.8± 57.8	0.816
Rest DBP Mean± SD	80.6 ± 5.8	82.3± 6.3	**<0.001***
Rest ECG abnormalities n (%)	340 (46)	270 (64)	**0.039***
Exercise duration mean± SD	488 ± 117	457± 118	**<0.001***

*p value is significant

According to **Table (4)**: age, gender, diabetes mellitus and dyslipidemia were the predictors of any coronary artery calcification (CAC > 0) in patients with negative myocardial perfusion imaging.

Table (4): Regression model for any coronary artery calcification (CAC > 0)

Variable	Wald test	p value	95% C.I. for EXP (B)	
			Lower	Upper
Age	99.449	**<0.001***	1.081	1.123
Gender	11.111	**0.001***	1.271	2.520
Hypertension	2.138	0.144	0.932	1.623
Diabetes mellitus	5.408	**0.020***	1.057	1.926
Dyslipidemia	4.414	**0.036***	1.020	1.785
Smoking	2.558	0.110	0.962	1.459
DTS	0.181	0.671	0.965	1.023
Exercise EF	0.066	0.797	0.980	1.015

DTS: Duke treadmill score, EF: Ejection fraction

In **Table (5)**: age, gender and Duke Treadmill Score are the predictors of significant coronary artery calcification (CAC > 100) in patients with negative myocardial perfusion imaging.

Table (5): Regression model for significant coronary artery calcification (CAC > 100)

Variable	Wald test	p value	95% C.I. for EXP(B)	
			Lower	Upper
Age	64.245	**<0.001***	1.098	1.166
Gender	13.275	**<0.001***	1.586	4.641
Hypertension	2.003	0.157	0.884	2.144
Diabetes mellitus	0.120	0.729	0.586	1.453
Dyslipidemia	2.513	0.113	0.916	2.304
Smoking	1.280	0.258	0.605	1.144
DTS	4.002	**0.045***	0.916	0.999
Exercise EF	1.477	0.224	0.956	1.011

DISCUSSION

Computed tomography coronary artery calcium (CAC) is a highly specific feature of coronary artery atherosclerosis and is an effective imaging modality increasingly accepted as a first-line test to diagnose (CAD), also it has prognostic implications for patient management providing valuable information for risk stratification and clinical decision-making in subjects with known or suspected CAD [(11)]. CAC is considered an appropriate test for asymptomatic patients at intermediate to high cardiovascular risk [(12)].

Patients with normal myocardial perfusion imaging (MPI) have a good prognosis. However, pre-clinical coronary and extracoronary atherosclerosis may exist in the absence of myocardial ischemia [(13)]. An imaging strategy to detect coronary atherosclerosis could lead to greater understanding of the natural history of atherosclerosis in its long pre-clinical phase and possibly to earlier preventive strategies [(14)].

Allam *et al.* [(13)] reported that the quantitative assessment of calcification in different vascular beds demonstrates that many patients without known CAD and normal myocardial perfusion, even those with CAC = 0, often have significant atherosclerosis in extracoronary vascular bed.

Importantly, the role of measuring coronary calcium score (CCS) was studied in the context of improving predictive accuracy and risk stratification during MPI studies. This is mainly because, MPI provides no insight into non-flow limiting plaques. On the other hand, the coronary artery calcium score (CACS) is an excellent anatomic measure of atherosclerotic plaque burden and is a well-established risk predictor [(15)].

The presence of ischemia could be used to classify the patients as having CAD and candidates for receiving aggressive medical therapy and management. However, a normal MPI does not necessarily exclude significant coronary stenosis, while high CAC scores sometimes do not result in abnormal perfusion on MPI [(16)]. Currently, European, and American guidelines recommend considering additional CAC scoring to guide preventive therapy decisions in intermediate-risk adults [(6)].

This study conducted in Cardiology Department, Faculty of Medicine, Zagazig University. It included a total sample of 1168 participants with negative myocardial perfusion imaging not known to have history of CAD, and age ranged between 20 to 80 years from both sexes. Our study aimed to reduce the generalization of doing calcium score for all coronary cardiac patients with negative myocardial perfusion imaging, and also to determine the factors that may predict high calcium score in these patients. According to the demographic data of all participants the mean age was 48 ± 9 years, which was slightly higher compared to other similar studies. Majority of the patients were within the age group of (40-60) years which have 899 patients, followed by patients within the age group of (20-40) years which have 192 patients. The patients within the age group of 60–80 years were minimum with 76 patients, which is in line with that observed by **Pereira *et al.*** [(17)] in their studies.

Moreover, the study also included assessment of the traditional risk factors that predisposes patients to CAD. Statistics from the data we collated showed that dyslipidemia was the most prevalent risk factor among the study population, 58.6% had dyslipidemia, followed by 46.5% had hypertension. There were 25.6% having diabetes mellitus. Among the participants there were 38.4% smokers. A similar trend was observed by **Schuhbaeck *et al.*** [(18)] in their study on patients with suspected CAD, where hypertension and diabetes accounted for 56% and 10%, respectively.

Stress testing detects the functional consequences of atherosclerosis but does not diagnose atherosclerosis because myocardial ischemia can be caused by other conditions such as microvascular disease or left ventricular hypertrophy. Exercise ECG remains the recommended initial diagnostic test modality by the American College of Cardiology and American Heart Association (ACC/AHA) guidelines on exercise testing, diagnosis, and management of stable ischemic heart disease in patients with intermediate pre-test probability who are able to exercise and have an interpretable rest electrocardiogram (ECG) [(19)]. Exercise stress test results among the participants showed that 51.2% had resting ECG abnormalities, the mean exercise duration was 480.4 ± 118.6 seconds and 18.5% complained of chest pain during exercise.As a culmination of the various studies that show a strong relationship between coronary artery calcium scores and risk of coronary artery disease, the National Institutes for Health and Care Excellence, deemed calcium scores to be an important determinant in deciding the management of patients presenting with acute onset chest pain [(20)]. The Multi-Ethnic Study of Atherosclerosis (MESA) trial data found that in a prediction model based on the traditional risk factors for coronary artery disease, the addition of Calcium scoring (CS), significantly improved risk stratification and placed more individuals in the higher risk categories [(21)].

We demonstrated a non-negligible prevalence of CAC in young adults, which was associated with a clear graded increase in the incidence and hazards of CVD events with increasing CAC scores. While these findings suggest that the clinical utility of CAC testing may extend to select younger adults, particularly those with risk factors. Future development of age-sex percentile scores for young adults could be useful for guiding interpretation of CAC scores and subsequent intensity of preventive interventions, as they have been for middle and older aged adults. Therefore, this age group calcium score test should be a mandatory for prevention of the vascular ageing

Among all participants, only 422 patients (36.19%) had CAC score > zero, while 744 of patients (63.8%) had CAC = 0. We compared between CAC=zero and CAC >0 regarding other variables. The mean age was 46.1± 8.2 among CAC=0 and 52.3± 7.9 among CAC>0. However, the CAC score has a low

specificity for predicting major adverse cardiovascular events, especially if the CAC value of >0 is used (35%). Specificity increased with higher cut off values (>100, 67%; >400, 85%) but at the expense of sensitivity (61% and 31%, respectively) [(12)]. Our study shows that even among those with low risk/negative MPI; CAC was shown to strongly correlate to age and male gender. Regardless of all other risk factors, age, and male gender were associated with a higher incidence of CAC > 0. Statistical analysis showed that all the traditional risk factors (chest pain, hypertension, dyslipidemia, diabetes, family history of CAD) were also linked to higher CAC even in the setting of a normal MPI study.

CACS of zero is a powerful negative risk marker with a long-term warranty period in asymptomatic patients. Although non-calcified plaque is observed in 1%-2% of symptomatic patients with CACS of 0, their prognosis remains excellent [(15)]. Our results were in agreement with **Fernandez-Friera *et al.*** [(22)] who reported that the CAC score has been shown to be predictive of obstructive CAD independent of cardiovascular risk factors, and despite that, it is far more practical to interpret the CAC score in association with the presence of known cardiovascular risk factors.

CONCLUSION

We concluded that doing calcium score for all not known coronary cardiac patients with negative MPI is a mandatory, particularly if they are old, male gender, have multiple risk factors, and do not perform well on the treadmill.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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