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Prognostic Value of Coronary Artery Calcium in the Intermediate-Risk Population of Developing Coronary Artery Disease

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Abstract

Background: The present study was designed to estimate the coronary artery calcium score (CACS) and its association with the incidence of major adverse cardiovascular events (MACE) in asymptomatic patients who are at risk of coronary artery disease (CAD).

Objective: To estimate the CACS and its association with the incidence of MACE in asymptomatic patients.

Methods: In this prospective cross-sectional observational study, 108 consecutive patients were enrolled. Demographic details and clinical data including lipid profile, systolic blood pressure, electrocardiography, 2D echocardiography, and routine blood investigations were reported. CACS was derived from computed tomography using a 256-slice scanner with a rotation time of 270 milliseconds. MACE was recorded at a one-year follow-up.

Results: The mean age was 54.55 ± 7.7 years with male predominance (62%). CACS categories 0, 1-99, 10-399, 400-999, and more than 1000 constituted 43.5%, 28.7%, 18.52%, 8.33%, and 0.93% respectively. The correlation between the groups of positive and negative CACS and the presence or absence of standard risk factors was found to be statistically significant in diabetes mellitus (P=<0.001), hypertension (P=<0.001), and history of CAD in the family (P = 0.036). Although the association between smokers and calcium was statistically insignificant, it had clinical significance (P= 0.294). Out of 108 patients, MACE was observed in 16 (14.81%) patients with positive CACS at the 1-year follow-up.

Conclusion: CACS measurement is often regarded as the primary non-invasive approach for risk stratification, MACE estimation, and promptly identifying high-risk asymptomatic individuals.

Introduction

One of the leading causes of death worldwide is atherosclerotic heart disease. In recent years, non-fatal acute myocardial infarction (MI) or sudden death has been experienced by at least 25% of patients without prior symptoms [1]. Thus, the identification of asymptomatic individuals at intermediate risk who may experience future cardiovascular events is fundamental for primary preventive strategies for atherosclerotic cardiovascular disease.

Traditionally, a medical risk model, for instance, the Framingham risk score, has been used to stratify (low, intermediate, or high) risk of coronary events in individuals without prior symptoms of coronary artery disease (CAD) and thus determine the aggressiveness of management [2]. However, there are some limitations. For instance, potential overestimation in a low-risk population or underestimation in a high-risk one [3]. The assessment of coronary artery calcium score (CACS) by computed tomography (CT) in asymptomatic patients is an alternate strategy to improve risk prediction over the Framingham risk score [4].

Coronary calcifications are usually expressed as "Agatston score" and in numerous studies, CACS has been demonstrated to be an excellent prognosticator of cardiac incidents [4-6]. Cardiac calcification and atherosclerotic disease clinical manifestation is associated with an Agatston score. >400 and is undoubtedly a strong indicator of increased risk for future cardiovascular problems [7,8]. However, the widespread use of CACS has not occurred due to cost and radiation exposure [9]. Moreover, there is a lack of literature on risk stratification using CACS among asymptomatic individuals from India. Thus, the present study aimed to estimate CACS and its association with the incidence of major adverse cardiovascular events (MACE) in asymptomatic individuals at intermediate risk of CAD.

Methods

A cross-sectional prospective observational study was carried out at a tertiary care center in India between 1st April 2017 and 31st March 2018. A total of 180 asymptomatic patients (aged ≥40 years) with a family history of premature cardiovascular disease, atypical chest pain, and an intermediate risk level (absolute 10-year cardiovascular risk score between 10 and 20) were included. The study excluded patients with poor technical quality CT images, chronic renal disease, and uncontrolled tachycardia.

Demographic details and clinical characteristics were recorded. Data on type 2 diabetes mellitus, systemic arterial hypertension, dyslipidemia, smoking, and family history of premature CAD were collected using a standardized questionnaire. Patients at intermediate risk were estimated using the Framingham risk score. After clinical assessment, patients underwent electrocardiography, 2D echocardiography, routine blood investigations, and CACS measurements for diagnostic evaluation. CT scan was performed on a 256-slice scanner with a rotation time of 270 milliseconds per rotation. The effective radiation dosage in this investigation was between 1 and 1.2 mSv using the 256-slice Philips Brilliance CT system with Essence Technology by Philips. A CT scan without contrast was performed to score calcium, encompassing the region between the diaphragm and the tracheal bifurcation. The following specifications

were used: 120 KVp, 300 mA, 0.270 s rotation time, 3 mm slice thickness with 3 mm intervals, and 80 mm coverage per gantry rotation. Each area and vessel's calcium scores were computed offline using dedicated software on a commercially available workstation. Calcium scores were divided into the following categories [10]:
CACS of 0; CACS between 1 and 99; CACS between 10 and 399; CACS between 400 and 999; CACS of 1000 or higher.

The patients were regularly monitored for a period of one year, and the occurrence of MACE, which includes coronary revascularization, cardiac mortality, and nonfatal MI, was recorded, and analyzed.

Statistical method

The descriptive analysis involved calculating the mean and standard deviation for normally distributed quantitative variables, determining the median and interquartile range for non-normally distributed quantitative variables, and examining the frequency and proportion of categorical variables. For statistical analysis, IBM SPSS (Chicago, IL, USA; version 22) was used. A P-value less than 0.05 was statistically significant when examining the association between categorical variables and non-normally distributed variables using the Mann-Whitney U test/Kruskal-Wallis test. The correlation between two quantitative variables was evaluated using Pearson/Spearman rank correlation coefficient. Cross tabulation was used to analyze the association between two categorical variables, and the chi-square test/Fisher's exact test was used to assess the statistical significance of the difference between the proportions.

Ethical statement

This research was authorized by the Institutional Human Ethics Committee of Ramesh Hospitals, Vijayawada, Andhra Pradesh India on 3 May 2019 (number: ECR/81/INST/AP/2013/RR/2016). All participants were provided with comprehensive information regarding the study objectives, the possibility of risks and benefits, and the fact that participation is voluntary. Informed written consent was then obtained from each participant. Throughout the study, strict confidentiality measures were implemented to safeguard the privacy and confidentiality of the participants.

Results

The study included 108 patients. The average age of the study population was 54.55 ± 7.7 years, and males (62.0%) were predominant over females (38.0%). Demographic details with descriptive analysis of risk factors and CACS groups are portrayed in Table 1.

Positive CACS existed in 50.8% of diabetic patients, 31.1% of hypertensive, 23% of smokers, 68.9% of individuals who had a family history of CAD, 72.1% of males, and 27.9% of females.

Table 1: Demographic data, risk factors, and CACS groups (n=108)

Parameters	n (%)
Age groups (years)	
40-50	34 (31.5%)
51-60	52 (48.1%)
>61	22 (20.4%)
Gender	
Males	67 (62.0%)
Females	41 (38.0%)
Risk factors	
Hypertensive	59 (54.6%)
Non-hypertensive	49 (45.4%)
Diabetic	40 (37.0%)
Non-diabetic	68 (63.0%)
Positive F/H/O pre-matured CAD	65 (60.2%)
Negative F/H/O pre-matured CAD	43 (39.8%)
Smokers	21 (19.4%)
Non-smokers	87 (80.6%)
CACS groups	
0	47 (43.5%)
36161	31 (28.7%)
10-399	20 (18.52%)
400-999	9 (8.33%)
>1000	1 (0.93%)
F/H/O: Family history of, CAD: Coronary Artery Disease, CACS: Coronary Artery Calcium Score	

Table 2: Descriptive evaluation of risk factors with positive calcium score (n=108)

Risk factor	CACS category n (%)		Chi-squre	P-value
	Positive CACS	Negative CACS		
Diabetes mellitus				
Diabetic	31 (50.8%)	9 (19.1%)	11.418	<0.001
Non diabetic	30 (49.2%)	38 (80.9%)		
Hypertension				
Hypertensive	19 (31.1%)	40 (85.1%)	31.184	<0.001
Non-hypertensive	42 (68.9%)	7 (14.9%)		
Smoking				
Smokers	14 (23.0%›)	7(19%)	1.1	0.294
Non-smokers	47 (77.0%)	40 (85.1%)		
F/H/O CAD				
Positive	42 (68.9%)	23 (48.9%)	4.394	0.036
Negative	19 (31.1%)	24 (51.1%)		
Gender				
Males	44 (72.1 %)	23 (48.9%)	6.064	0.014
Females	17 (27.9%)	24 (51.1%)		

Table 2 represents the descriptive analysis of risk factors associated with a positive calcium score. The mean age of patients with positive and negative calcium scores was found to be 57.11 ± 7.86 years and 51.21 ± 6.33 years, respectively. Table 3 displays the descriptive analysis of the mean age for individuals with positive and negative calcium scores in the study population.

Table 3: Descriptive evaluation of mean age of positive and negative calcium scores in the study population (n=108)

Parameter	CASC GROUP (Mean± SD)			P value
	Positive CACS (N=61)	Negative CACS (N=47)	T calculated	
AGE (YRS)	57.11 ± 7.86	51.21 ± 6.33		<0.001
Min	40	40	t = 4.20 (df=106)	
Max	73	68		

Table 4: Major cardiovascular events occurring among the study population

Parameters	n (%)			
Overall MACE	16 (14.81)			
Cardiac death	0			
Non-fatal myocardial infarction	0			
Coronary revascularization	16 (14.81)			
PCI	12 (11.11)			
CABG	4 (3.70)			
Timing for development of MACE				
Within 1 month	0			
Between 1 and 3 months	3 (2.78)			
Between 3 and 6 months	7 (6.48)			
Between 6 and 12 months	6 (5.55)			
Telephonic follow-up after enrollment into study	**Stable angina**	**Unstable angina**	**Non-fatal MI**	**Death**
0-1 months	0	0	0	0
1-3 months	0	3	0	0
3-6 months	0	7	0	0
6-12 months	1	4	1	0

The occurrence of MACE among the study population is illustrated in Table 4. Among the 108 patients, 4 (3.70%) underwent CABG and 12 (11.11%) underwent PCI. Table 5 illustrates the descriptive analysis of the event occurrence among different CACS groups among the study participants. There were no reported events in the group with a calcium score of zero. In the CACS group with 1-99 Agatston units (AU), the event rate was 9.68%. For the group with 10-399 AU, the event rate was 26.31%. In the group with 400-999 AU, the event rate was 70%, while in the group with over 1000 AU, the event rate was 100%. Calcium score and the risk of events were found to be directly proportional.

Discussion

In the present study, CACS, and its association with MACE among non-symptomatic patients at transitional risk of CAD were assessed, where in total 108 consecutive patients were included. Analysis of the calcium score based on

gender revealed a higher prevalence of calcification in coronary arteries among males compared with females. Similar findings were observed in previous studies. [11,12] In total, 61 patients (56.5%) had positive CACS. Additionally, this study evaluated the common risk factors that put patients at risk for CAD, where hypertension (54.6%) was most prevalent, followed by diabetes mellitus type- 2 (37%), smoking (19.40%), and a family history of premature CAD (60.2%).

Table 5: Descriptive evaluation of event occurrence in different CACS groups among the study population (n=108)

Positive CACS (N=61)	Frequency	Percentages of Event occurrence
1-99 (n=31)	3	9.68%
10-399 (n=20)	5	25%
400-399 (n=9)	7	77.78%
>1000 (n=1)	1	100%

Among patients with diabetes, 50.8% had a positive CACS, while 19.1% had a negative CACS. The association between these two groups was statistically significant (Chi-square=11.418, P=<0.001). The existence of any degree of coronary artery calcification in individuals with type 2 diabetes was found to indicate a greater risk of all-cause mortality compared with non-diabetic individuals. This result was followed by Raggi et al., [13] who observed that the survival rate of diabetes patients without any signs of coronary calcification is the same as that of non-diabetic people with a calcium score of zero throughout the five-year follow-up period. Based on these findings, it could be inferred that the evaluation of coronary calcium levels could be valuable in enhancing the stratification of short-term risk among patients with diabetes. Previously, in a meta-analysis, it was reported that people with a CACS <10 were 6.8 times less likely to experience cardiovascular events and a CACS of more than 10 has been allied to elevated mortality and cardiovascular events, demonstrating high sensitivity but low specificity [14]. Hypertensive patients with positive and negative CACS constituted 31.1% and 85.1%, respectively, and statistical analysis revealed a significant association between the groups (Chi-square=31.184, P=<0.001). Sung et al. [15] and colleagues found comparable outcomes in which hypertension was positively correlated with calcification of the coronary arteries. Smokers who had positive or negative CACS were present in percentages of 23% and 19%, respectively, and there was no statistically significant relationship between the groups (Chi-square = 1.100, P = 0.294) but clinically there was a significant relationship between smokers and coronary calcium. In contrast, a study conducted by McEvoy et al. [16] reported that higher CACS was associated with an increased hazard of all-cause mortality among both smokers as well as non-smokers, compared to CACS=0. Among the patients with a family history of CAD, 68.9% had a positive CACS, whereas 48.9% had a negative CACS. The statistical analysis indicated a significant association between these two groups (chi-square= 4.394, P = 0.029). Otaki et al. [17] reported that a positive family history of CAD was associated with the presence of obstructive CAD. The mean age of individuals in the group with a positive calcium

score was 57.1 ± 7.86 years, while among the negative calcium score group, the mean age was 51.51 ± 6.33 years (t = 4.2700, P < 0.001), reinforcing the observation that coronary artery calcification increases with age [18].

No MACE was reported in patients under the CACS=0 category whereas only 9.68% of patients with a CACS of 1 AU or higher but less than 100 AU suffered MACE, even though a CACS of 1 AU or higher was linked to an increased risk of MACE. In cases where the CACS was below 10 AU, the need for CABG or PCI was infrequent. A CACS of 100 AU or greater significantly enhanced the need for PCI. CABG was necessary when the CACS exceeded 565 AU. In this research, the identification of a particularly vulnerable group was made possible by the addition of a new stratum for people whose CACS was greater than 1000 AU; this group had a 100% MACE rate. Although further research is required to validate this statement, as in our study only one patient had CACS >1000 AU. Our results were consistent with those of Al-Mallah et al. [19] who found that a CACS of 400 AU or above improved cardiac event prediction beyond the information provided by clinical data.

Study limitations

There are some drawbacks in this research. Primarily, since this study was conducted at a tertiary care center with multidisciplinary care, the generalizability of the findings to the wider population may be limited. Subsequently, this study had a smaller sample size and a short follow-up duration to evaluate the MACE. There was variation in the effective radiation dose for this procedure. Moreover, elevated calcium levels could occasionally be accompanied by subsequent diagnostic tests for cardiac disorders, which might or might not yield clinically valuable results and may be accompanied by adverse outcomes. Further evidence is required for using CACS as the primary non- invasive test in risk stratification.

Conclusion

The present study concluded that in non-symptomatic individuals with a moderate risk of developing CAD, the CACS assessment might be thought of as the non-invasive approach of first choice for risk stratification, early identification of high-risk asymptomatic people, and estimating the risk of MACE.

Ethical Approval: Ethics Committee Approval: This research was authorized by the Institutional Human Ethics Committee of Ramesh Hospitals, Vijayawada, Andhra Pradesh India on 3 May 2019 (number: ECR/ 81/INST/AP/2013/RR/2016).

Conflict of Interest: Nil

Financial Disclosure: None

References

1. Neves PO, Andrade J, Monção H. Coronary artery calcium score: current status. *Radiol Bras.* 2017;50:182-9.
2. Kirsch J, Buitrago I, Mohammed TL, Gao T, Asher CR, Novaro GM. Detection of coronary calcium during standard chest computed tomography correlates with multi-detector computed tomography coronary artery calcium score. *Int J Cardiovasc Imaging.* 2012;28:1249-56.
3. Lee DH, Youn HJ, Jung HO, Chang K, Choi YS, Jung JI. Coronary artery calcium score plays an important role for cardiovascular risk stratification in the statin benefit groups of asymptomatic individuals. Lipids Health Dis. 2017;16:172.
4. Johnson KM, Dowe DA. The detection of any coronary calcium outperforms Framingham risk score as a first step in screening for coronary atherosclerosis. *AJR Am J Roentgenol*. 2010;194:1235-43.
5. Gaikwad A, Khan Y, Singh AK. Assessment of Impact of Coronary Artery Calcium On Cardiovascular Risk Stratification in an Indian Cohort. *Cardiol Cardiovasc Med*. 2019;3:373-85.
6. Kaur M, Rahimi R, Razali F, Mohd Noor N, Omar E, Abdul Manaf Z, et al. Association of coronary artery calcium score with calcification and degree of stenosis: An autopsy study. *Malays J Pathol*. 2019;41:177-83.
7. Budoff MJ, Gul KM. Expert review on coronary calcium. *Vasc Health Risk Manag*. 2008;4:315-24.
8. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA*. 2010;303:1610-6.
9. Kim KP, Einstein AJ, Berrington de González A. Coronary artery calcification screening: estimated radiation dose and cancer risk. *Arch Intern Med*. 2009;169:1188-94.
10. Lee J. Coronary artery calcium scoring and its impact on the clinical practice in the era of multidetector CT. *Int J Cardiovasc Imaging.* 2011;27(1):9-25.
11. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi- Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2006;113:30-7.
12. Tabbalat RA, Khader YS, Hammoudeh AJ, Alhaddad IA. Age and Gender- Based Coronary Artery Calcium Scores in a Middle Eastern Population. *Cardiovascular Imaging Asia*. 2021;5:37-43.
13. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol*. 2004;43:1663-9.
14. Kramer CK, Zinman B, Gross JL, Canani LH, Rodrigues TC, Azevedo MJ, et al. Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. *BMJ.* 2013;346:f1654.
15. Sung KC, Lee MY, Kim JY, Park JB, Cho EJ, Avolio A. Prediction of incident hypertension with the coronary artery calcium score based on the 2017 ACC/ AHA high blood pressure guidelines. *Hypertens Res*. 2020;43:1293-300.
16. McEvoyJW,BlahaMJ,RiveraJJ,BudoffMJ,KhanAN,ShawLJ,etal.Mortality rates in smokers and nonsmokers in the presence or absence of coronary artery calcification. *JACC Cardiovasc Imaging*. 2012;5:1037-45.
17. Otaki Y, Gransar H, Berman DS, Cheng VY, Dey D, Lin FY, et al. Impact of family history of coronary artery disease in young individuals (from the CONFIRM registry). *Am J Cardiol.* 2013;111:1081-6.
18. Pereira AC, Gomez LM, Bittencourt MS, Staniak HL, Sharovsky R, Foppa M, et al. Age, gender, and race-based coronary artery calcium score percentiles in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Clin Cardiol.* 2016;39:352-9.

19. Al-Mallah MH, Qureshi W, Lin FY, Achenbach S, Berman DS, Budoff MJ, et al. Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international CONFIRM registry. *Eur Heart J Cardiovasc Imaging*. 2014;15:267-74.