



Predictive Value of a Zero Coronary Artery Calcium Score in Major Adverse Cardiac Events in Old Age

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ABSTRACT

Background: By estimating the total coronary plaque burden, the Coronary Artery Calcium (CAC) score determines the risk of Coronary Artery Disease (CAD). The presence of a zero CAC score may be highly predictive of very low risk patients for Major Cardiac Adverse Events (MACEs) due to its close relation with the severity of CAD.

Objective: The present study aimed to evaluate the value of a zero CAC score for predicting MACEs in patients older than 60 years suspected of CAD.

Methods: Between April 2011 and March 2012, 128 patients aged > 60 years with a zero CAC score on admission without a previous history of CAD were consecutively included in this study with a mean follow-up period of 45.7 months. The continuous variables were compared using t-test or Mann-Whitney U test and the categorical ones were compared using chi-square test. The statistical analyses were done using the SPSS statistical software, version 23.0.

Results: This study was conducted on 128 patients (35 males and 93 females). The incidence of MACEs was 2.3% in a mean follow-up period of 45.7 months and 0.6 per 100 patient-years. Additionally, the MACE-free survival rates were 99.1%, 99.1%, and 87.7% in one, three, and five years, respectively. The negative predictive value of a zero CAC score for predicting long-term MACEs was 100% in the patients older than 70 years and 96.8% in those aged between 60 and 70 years. No cardiac-related death was recorded within the follow-up period.

Conclusion: A zero CAC score had a high negative predictive value for predicting long-term MACEs in elderly patients with mild to moderate pretest probability of CAD, which reached 100% among the patients older than 70 years.

1. Background

The value of Coronary Artery Calcium (CAC) as assessed by non-contrast Electrocardiographic (ECG)-gated cardiac Multi-Detector Computed Tomography (MDCT) in determining the presence and extension of coronary atherosclerosis has already been well identified (1, 2). By estimating the total coronary plaque burden, the CAC score determines the risk of Coronary Artery Disease (CAD). Recent investigations have revealed an association between CAC and the severity of symptoms as well as adverse events

in patients with CAD insofar as those with mild symptoms and no CAC tended to develop lower rates of adverse cardiac events (3, 4). Recently, the American College of Cardiology/American Heart Association consensus recommended this scoring system as a valuable tool in the emergency room for distinguishing between high-risk patients who need admission in coronary care units and low-risk ones (5). In other words, patients without CAC may not be candidate for further evaluation for atherosclerotic coronary involvement. Thus, the CAC score may be a powerful scoring system to stratify CAD patients at risk of Major Cardiac Adverse Events (MACEs) (6-8). Nonetheless, the clinical use of a zero CAC score for determining the prognosis of CAD and predicting early and long-term MACEs in elder patients has

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not been well elucidated.

2. Objectives

The present study aims to explore the value of a zero CAC score in predicting MACEs in patients older than 60 years with a mild to moderate risk for CAD. Because CAC score analysis can be done without using iodine contrast, it can be done in elder patients with nephropathy.

3. Patients and Methods

3.1. Study Selection and Data Extraction

The present study was prospectively conducted in Rajaie Cardiovascular Medical and Research Center, which is a main referral heart center for cardiovascular diseases in Tehran, Iran. Between April 2011 and March 2012, 128 patients with mild to moderate pretest probability of CAD, according to the Duke Clinical Score (9), who were referred from outpatient clinics for coronary CT angiography without a previous history of CAD were consecutively included in this study. Pretest probability was defined in accordance with the guidelines of the European Society of Cardiology (10). All patients aged 60 years or higher and had a zero CAC score. Patients with known CAD or CAC scores higher than 0 were excluded. The information of 27 patients was incomplete; therefore, the data of the remaining 128 patients were included in the final analysis.

CAC scoring was achieved on unenhanced axial images obtained before coronary CT angiography. The scans were performed using a 128-slice multi-detector CT system, and CAC was quantified via the Agatston scoring method (11). The scan was done when the patient had a heart rate fewer than 70 beats per minute. All scans were evaluated by one cardiologist and one radiologist who were both experienced in cardiovascular CT interpretation. The total calcium score was determined using the sum of the individual scores from the four major coronary arteries, namely left main, left anterior descending, circumflex, and right coronary arteries, and was stratified as G0 (no CAC, score = 0), G1 (moderate CAC, score = 1 – 100), and G2 (high CAC, score \geq 101). Only the first group was finally assessed. The baseline characteristics and the clinical data of the participants were collected via face-to-face interviewing or by reviewing the hospital recorded files, if required. MACEs were assessed by following up all participants through phone calls for a minimum follow-up period of three years. In this study, MACE was defined as the presence of at least one of the following events: cardiac death, fatal or non-fatal myocardial infarction, occurrence of acute coronary syndrome, or hospitalization for cardiac revascularization within the follow-up period. The study protocol was approved by the institutional review board.

3.2. Statistical Analysis

The results were presented as mean \pm Standard Deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical ones. The continuous variables were compared using t-test or Mann–Whitney U test whenever the data did not appear to have normal distribution or when the assumption of

equal variances was violated across the study groups. The categorical variables were, on the other hand, compared using chi-square test. Moreover, the number of true negatives divided by the number of negative calls was used to estimate the negative predictive value. A P-value of equal to or less than 0.05 was considered to be statistically significant. All statistical analyses were done using the SPSS statistical software, version 23.0 for Windows (IBM, Armonk, New York).

4. Result

This study was conducted on 128 patients (35 males and 93 females). The baseline characteristics of the study population have been presented in Table 1. In terms of age, 26.5% of the participants were older than 70 years. Clinically, 40.2% of the participants had cardiac-related symptoms. Regarding coronary CT angiography results, 100 patients (78.1%) had normal epicardial coronary arteries, while minimal CAD and single-, two-, and three-vessel involvements were revealed in 18 (14.1%), three (2.3%), one (0.8%), and two (1.6%) patients, respectively. Additionally, coronary ectasia and left main lesion were seen in three (2.3%) and one (0.8%) patients, respectively. With regard to MACEs rate, 2.3% of the patients suffered from at least one episode of long-term MACEs within a mean follow-up time of 45.7 months. Indeed, non-fatal myocardial infarction occurred in two patients and one patient developed unstable angina. The incidence rate of MACEs per 100 patient years was 0.60. Moreover, the total mortality rate was 2.3%. No cardiac-related death was recorded within the follow-up period.

Table 1. Baseline Characteristics of the Study Population

Male gender	35 (27.3%)
Diabetes mellitus	21 (16.4%)
Hypertension	54 (42.2%)
Dyslipidemia	65 (50.8%)
Current smoking	18 (14.1%)
Family history of CAD	12 (9.4%)
Laboratory parameters	
Serum fasting blood sugar, mg/dL	101.13 \pm 21.17
Serum triglyceride, mg/dL	132.93 \pm 59.25
Serum total cholesterol, mg/dL	174.82 \pm 41.04
Serum HDL, mg/dL	47.30 \pm 9.30
Serum LDL, mg/dL	104.02 \pm 30.60

Abbreviations: CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein

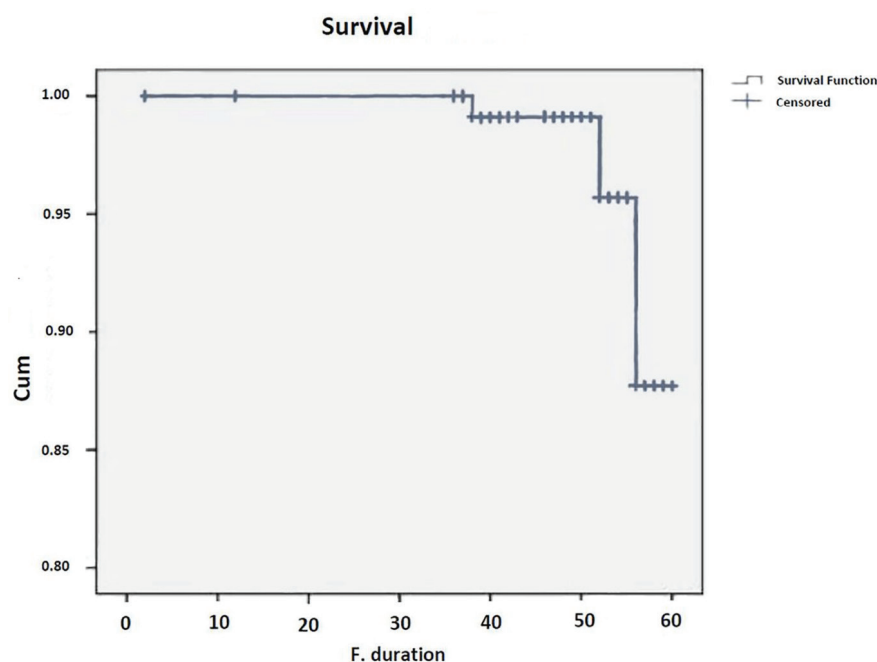
The results of univariate analysis (Table 2) showed no significant associations between long-term MACEs and baseline parameters, including CAD severity according to the number of involved coronary arteries, gender, age, diabetes mellitus, hypertension, dyslipidemia, current smoking, family history of CAD, and presence of cardiac symptoms.

The 1-, 3-, and 5-year MACE-free survival rates were 99.1%, 99.1%, and 87.7%, respectively (Figure 1). Furthermore, the negative predictive value of zero CAC score for predicting long-term MACEs was estimated to be 100% for patients older than 70 years and 96.8% for those aged 60 - 70 years.

Table 2. The Association between Major Adverse Cardiac Events and Baseline Variables

Parameter	Group without MACEs (125)	Group with MACEs (3)	P value
Male gender	34 (27.2%)	1 (33.3%)	0.999
Age > 70 years	27 (21.6%)	0 (0.0)	0.999
Diabetes mellitus	21 (16.8%)	0 (0.0)	0.999
Hypertension	52 (41.6%)	2 (66.7%)	0.573
Dyslipidemia	63 (50.4%)	2 (66.7%)	0.999
Current smoking	17 (13.6%)	1 (33.3%)	0.368
Family history of CAD	11 (8.8%)	1 (33.3%)	0.258
Minimal disease	17 (13.6%)	0 (0.0)	0.368
Single-vessel disease	2 (1.6%)	1 (33.3%)	0.069
Two-vessel disease	1 (0.8%)	0 (0.0)	0.999
Three-vessel disease	1 (0.8%)	1 (33.3%)	0.999
Left main lesion	0 (0.0)	1 (33.3%)	0.999
Non-significant LM lesion	1 (0.8%)	1 (33.3%)	0.999
Coronary ectasia	3 (2.4%)	0 (0.0)	0.999

Abbreviations: CAD, coronary artery disease; LM, left main

**Figure 1.** Kaplan-Mayer Survival Curve for Determining Long-Term MACE-Free Survival Rate

5. Discussion

The results indicated that a zero CAC score had a very high negative predictive value for predicting long-term MACEs in old patients with a low to intermediate pretest probability of CAD. The MACE-free survival rates were 99.1%, 99.1%, and 87.7% in one, three, and five years, respectively. The value of zero CAC increased in the patients older than 70 years as no MACEs occurred in patients > 70 years with zero CAC score. More interestingly, no cardiac-related deaths occurred in the three-year follow-up period.

Because CAD is a major cause of mortality and morbidity in both developing and developed countries, identifying valid factors for predicting cardiovascular events and stratifying patients as low to high risk is necessary for patient management and reduction of morbidity and mortality. In this regard, employing novel scoring systems, such as CAC score, has been recently described as a valuable factor to predict long-term MACEs. Recent articles have emphasized that non-calcified plaques in the setting of zero CAC could

cause cardiovascular events. These non-calcified plaques are found in early stages of CAD with the calcification of plaque occurring later (12). On the other hand, zero CAC in low risk patients was associated with a low possibility of atherosclerotic plaque development and these patients had a very low risk of cardiovascular events in the next two to five years (13). As the occurrence of coronary calcification is not always predictable by coronary risk factors, it can be an effective independent predictor of CAD (14). Indeed, the predictive power of the traditional risk factors in predicting cardiovascular MACEs decreases in elderly patients (15). Because aging is an important factor in predicting cardiovascular events in absolute risk-based algorithms, patients older than 60 years have a high possibility of being stratified in the high-risk group and as such need preventive medications, such as statin therapy (16).

In contrast to the previous studies having shown that cardiovascular events increased in advanced ages, Totamaharaj et al. demonstrated in a recent study that zero-

CAC patients aged at least 75 years had a cardiovascular mortality rate similar to that in younger patients (five-year survival rate = 98%) (17). Consistently, the findings of the present study on patients with a mild to moderate risk of CAD who underwent coronary CT angiography showed that the overall prevalence of long-term MACEs was 2.3% in those with a zero CAC score, including a case with non-fatal myocardial infarction and two cases requiring coronary revascularization. Another study was conducted on 5007 patients with chest pain who underwent coronary CT angiography in China (18) and revealed CAC score as a predictive factor for MACEs and reported a significant relationship between the CAC score and the patients' prognosis. The current study results indicated a high negative predictive value for the CAC scoring system to predict long-term MACEs, with the negative predictive value of 100% in the patients aged over 70 years and 96.8% in those aged between 60 and 70 years. More interestingly, no MACEs occurred in the patients with zero CAC score who were older than 70 years. What is also deserving of note is that most of the study patients were female. Because male gender has been a main traditional risk factor for CAD, considering and performing coronary CT angiography instead of coronary angiography for the participants could be predictable. Likewise, Raggi et al. disclosed that although their older patients (> 70 years old) had higher CAD risk factors (1.6 risk factors in the patients older than 40 years and 0.9 in those aged below 40 years), the mortality rate was very low in the older patients with zero CAC (19). Abbott et al. also followed up 224 patients for 2.5 years and reported no deaths in the patients aged between 84 and 96 years with CAC scores of less than ten (20). In another study in Turkey in 2013 (21), only 10% of the patients with a zero CAC score had atherosclerotic plaques, and 2.5% of these patients had coronary stenosis. In other words, the presence of a CAC score of zero could not rule out coronary atherosclerotic lesions. Hultén et al. reported that a zero CAC score was associated with a minimum 2% obstructive CAD. Nevertheless, even this low rate of obstructive CAD did not affect future adverse events in these patients (22, 23). Hence, it seems that CAC score can be used for risk stratification of older patients admitted in out-patient clinics due to cardiac symptoms.

5.1. Conclusion

In summary, given the high negative predictive value of a zero CAC score for predicting long-term MACEs in old individuals with a mild to moderate pretest probability of CAD, it can be considered as a noninvasive and relatively low-cost method to predict MACEs. Zero CAC score in ages > 70 years had a very high negative predictive value (about 100%) for predicting MACEs in one and three years.

5.2. Informed Consent

All patients agreed to participate in this study.

5.3. Ethical Approval

This study was approved by the Ethics Committee of the University (registry No. 93.1817).

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Authors' Contribution

All authors: data collection; M A and H P: statistical analysis; A S: study design; M K, A A, R H, and H N H: quality assessment; all authors: final revision and grammar editing.

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The authors have no financial interests related to the material in the manuscript.

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