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Utility of Per Vessel Coronary Artery Calcium (CAC) Score in Symptomatic Patients Undergoing Coronary Computed Tomography in Predicting Major Adverse Cardiovascular Events: Single Center Experience and Literature Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author AMS designed the study, assisted in data collection, and was senior editor of the manuscript. Author RLP performed data collection, statistical analysis, and wrote the first draft. Authors MLB and DMT performed data collection and manuscript revisions/rewrites. Authors RLJ, HRA, CKL and RJM performed data collection, data interpretation/analysis, and manuscript editing. Author BJR assisted with statistical analysis and provided valuable input on the final manuscript.

Original Research Article

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ABSTRACT

Background: Atherosclerotic vascular disease remains a significant etiology of morbidity and mortality in the United States. Coronary artery calcium (CAC) is associated with increased stroke incidence and coronary atherosclerotic burden. Uncertainty remains regarding how best to interpret non-zero CAC scores, particularly in symptomatic patients.
Methods: A review of the first 1122 patients who underwent coronary CT angiography

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(CCTA) with CAC scoring from January 2005 until July 2012 was performed. Patients were dichotomized into 2 groups, zero CAC score and non-zero CAC score. Non-zero CAC patients were further subdivided based on the specific coronary artery containing calcium. Rates of major adverse cardiovascular events (MACE) defined as all-cause mortality, non-fatal myocardial infarction (MI), ischemic stroke, and late revascularization (>90 days following CCTA) were evaluated in each group.
Results: 505 patients (63% male, mean age 60 ± 11) with non-zero CAC scores were analyzed over a six year period with resultant median follow up period of 22 months (IQR25,75 13-34 months). Major adverse cardiovascular events were observed in 11 patients. Receiver-operator curve (ROC) analysis on each coronary segment showed significance with the presence of left main (LM) CAC (AUC 0.752, p=0.004).
Conclusions: The presence of CAC at any value in the LM in this case series appears to predispose patients to increased rates of MACE.

Keywords: CAC; left main coronary; symptomatic; outcomes; CCTA.

ABBREVIATIONS

CAC: Coronary Artery Calcium; CCTA: Coronary Computed Tomography Angiography; SCCT: Society of Cardiovascular Computed Tomography; MI: Myocardial Infarction; CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention; AUC: Area Under the Curve; IQR: Interquartile Range.

1. BACKGROUND

The addition of coronary artery calcium (CAC) scoring to traditional risk calculators such as the Framingham Risk Score serves as a powerful adjunct in the reclassification of asymptomatic, intermediate risk patients [1]. The presence of CAC is associated with overall atherosclerotic burden and higher calcium scores in asymptomatic patients have been shown to be associated with increased risk of cardiovascular events [2]. The role of CAC scoring in the symptomatic patient remains unclear. The objective of this review was to evaluate the prognostic significance of CAC per vessel in our cohort of symptomatic patients and to determine if the location of calcium within the coronary tree provides additional prognostic data.

2. METHODS

2.1 Cardiac Computed Tomography Angiography

We reviewed the rate of major adverse cardiovascular events (MACE) and stroke based upon the severity of coronary artery disease (CAD) based upon coronary CT angiography (CCTA) and CAC scoring in a total 1757 patients at a high volume, single center tertiary referral hospital from January 2008 to July 2012. Patients referred for CT imaging in the emergency department, inpatient, or outpatient setting for the indications of chest pain, dyspnea, or syncope. Patients with known CAD, a history of ischemic stroke, renal dysfunction with a glomerular filtration rate (GFR) <60mL/kg/min, detectable HCG, un interpretable CT images for any reason, or absent CAC scoring broken down by individual vessel were excluded. One thousand twenty-two met both inclusion criteria and thus underwent analysis.

CCTA images were analyzed by a Cardiologist with level III SCCT experience performed in accordance with SCCT guidelines [3]. From January 2005 to December 2007, images were obtained using a 16-slice CT scanner (Brilliance-16R, Phillips, Amsterdam, Netherlands). From January 2008 to March 2011, images were obtained using a retrospective helical protocol with a 64 slice CT scanner (Somatom Definition CTR, Siemens, Erlagen, Germany). From March 2011 to March 2012, images were obtained utilizing a prospective sequential protocol with 60-80% image acquisition window. In March of 2012 to July 2012, images were obtained using a 128-slice dual head scanner with a single heart beat image acquisition of the complete coronary when a heart rate of less than 60 was achieved(Somatom Definition Flash CTR, Siemens, Erlagen, Germany). CAC scores were determined using the Agatston Method at the time of the initial CCTA read [4]. Total CAC scores were reported in addition to CAC scores for the left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary (RCA). A total CAC score cutoff of 100 was chosen to further analyze the group based on previously published data [5].

2.2 Study Endpoints

The primary endpoint was composite MACE, defined as all-cause mortality, stroke, non-fatal MI, and late revascularization, defined as revascularization performed within 90 days of CCTA with CAC imaging. ICD-9 codes for all-cause mortality (798.1, 798.2, 798.9, and V12.53), stroke (434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 997.02, and V12.54), non-fatal MI (410.0-410.9), and late revascularization with PCI (92980, 92981, 92982, 92995, and 92996)or CABG (33510-33514, 33516, and 33533-33536) were used for initial data extraction followed by Department of Defense (DOD) outpatient and inpatient electronic medical records (EMR) verification of events. We determined mortality using the social security death index (SSDI) followed by re-verification using EMR for last visit date as well as Tricare healthcare informatics division verification. All events identified by ICD-9 code were adjudicated.

2.3 Statistical Analysis

Statistical analysis was performed using IBM SPSS version 19.0 (IBM, Arnock, New York). Continuous variables are presented as means ± standard deviation and medians with inter quartile range, as appropriate. Categorical variables are presented as frequencies with percentages. Comparison of means between low and high CAC groups was performed using one-way ANOVA with p-values <0.05 considered statistically significant. Per vessel CAC score cutoff values were determined by receiver operating characteristics (ROC) curves, area under the curve, sensitivity/specificity, and negative/positive predictive values.

3. RESULTS

A total of 1122 patients met the study criteria and were analyzed with a mean follow up of 24 months (median 22 months and IQR of 13 to 34 months). Non-zero CAC scores were reported in 505 patients (45%). Of this group, 296 patients had a CAC score <100 (58.6%) and 209 patients had a CAC score >100 (41.4%). Baseline demographic data is outlined in (Table1). Non-zero CAC patients with CAC<100 were younger (59±14 years vs. 62±11 years, $p<0.001$) than patients with CAC >100, while the higher CAC cohort were more likely to be male (70% vs. 58%, $p=0.005$) and carry a diagnosis of hyperlipidemia (51% vs. 41%, $p=0.022$). (Table 2) outlines the total CAC burden in each group. The mean total CAC in the low CAC group was 28.63 (median 20.0, IQR of 5.0-49.0) compared with a mean total CAC

in the high CAC group of 491.43 (median 269, IQR of 151.50-497.0). MACE was reported in 11 patients (2.2%) within the non-zero CAC population. Events were reported in 5 patients (1.7%) in the low CAC (<100) cohort compared with 6 patients (2.9%) in the high CAC (>100) cohort (p=0.371). Mean total CAC amongst the 5 patients who had events in the low CAC group was 45.8±35.03 (IQR 15.0-79.5) compared with a mean CAC of 616±681.04(IQR 205.25-893) in the 6 high CAC patients with events (p=0.43). The total number of patients with LM CAC in the low CAC group was 32 (10.8%) with total LM Agatston score ranging 1-57. LM CAC was present in 96 patients (45.9%) in the high CAC group with LM Agatston score ranging 3-206. LM CAC was present in 4 of the 5 patients with MACE in the low CAC group and 5 out of 6 patients with MACE in the high CAC group.

Table 1. Baseline demographic data

Variable	Overall (n=505)	Total CAC <100(n=296)	Total CAC >100(n=209)	p-value
Age	60.2±11	59 ±11	62 ±11	<0.001
Male	63%	58%	70%	0.005
HTN	51%	48%	56%	0.60
HLP	45%	41%	51%	0.022
DM	7%	7%	8%	0.700

Table 2. Total CAC score characteristics between low and high CAC groups

Total CAC score	N	Mean	Standard deviation	Minimum	Maximum	Median (IQR)
CAC<100	296	28.63	27.75	1	98	20.0 (5.0-49.0)
CAC>100	209	491.43	779.95	101.00	6570.00	269.0 (151.50-497.0)

A receiver operating characteristics (ROC) curve was used in the per vessel CAC analysis (Fig. 1) ROC analysis of the LM yielded statistical significance with an AUC of 0.752 (CI 0.630-0.884, p=0.004).The LCX was found to also be significant with an AUC of 0.674 (CI 0.505-0.843, p=0.048), however analytic interpretation shows the 95% confidence interval approaching the reference line at its lower limits, thus making it a poor screening test. More data points and/or events are needed to determine whether the LCX data represents true significance, especially at lower CAC levels. The LAD and RCA were not statistically significant. CAC score of 0.50 (positive score defined as >1) in the LM was associated with increased risk of MACE to include ischemic stroke with a sensitivity of 81.8%, specificity of 72.5%, negative predictive value of 99% (CI=98-100), and positive predictive value of 6 (CI=3-11) (Table 3).

Table 3. Test characteristics using threshold of 0.50 for both LM and CFX as determined by ROC analysis

Vessel	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Positive predictive value (%)
LM	81.8	72.5	99 (CI=98-100)	6 (CI=3-11)
CFX	72.7	56.3	99 (CI=97-100)	4 (CI=2-7)

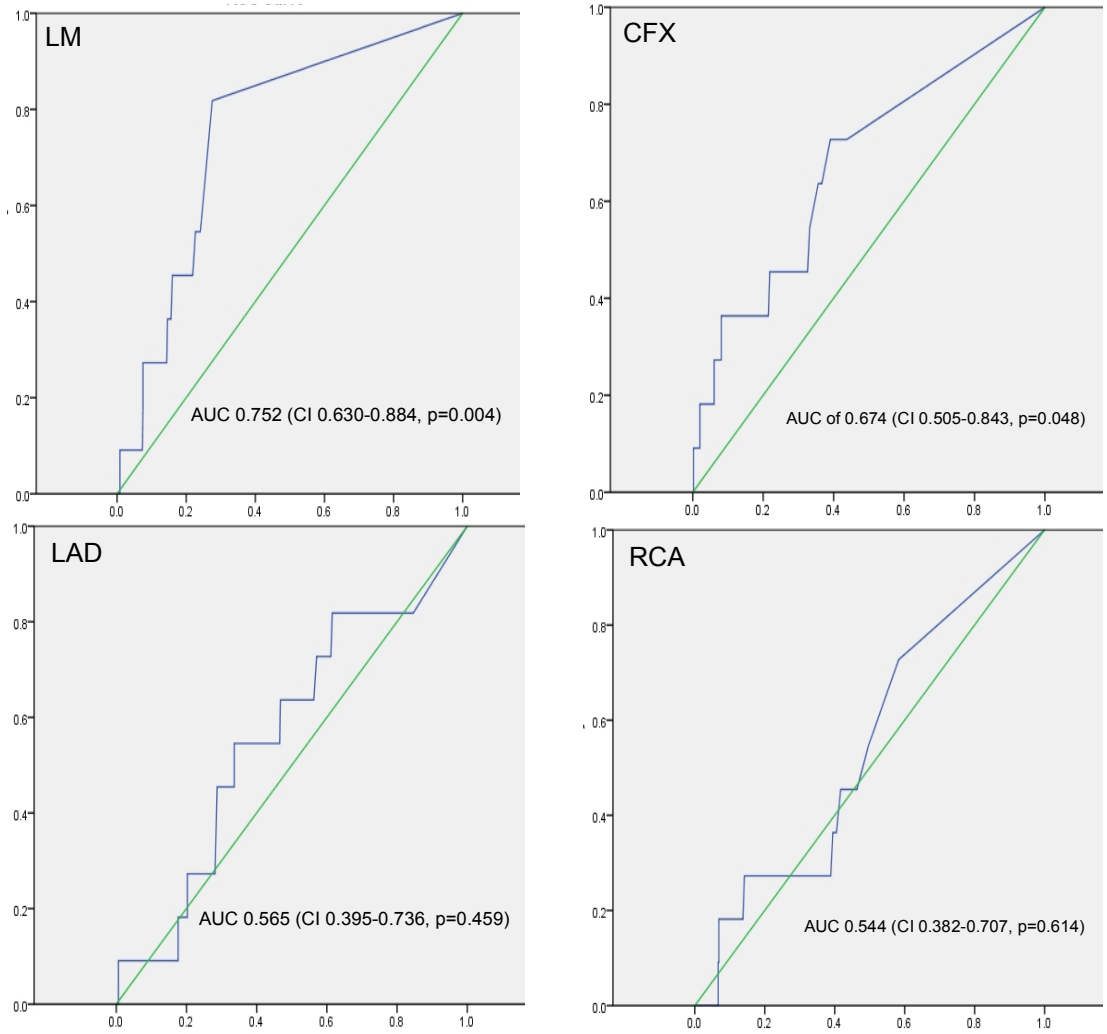

Fig. 1. ROC graph separated by specific coronary artery

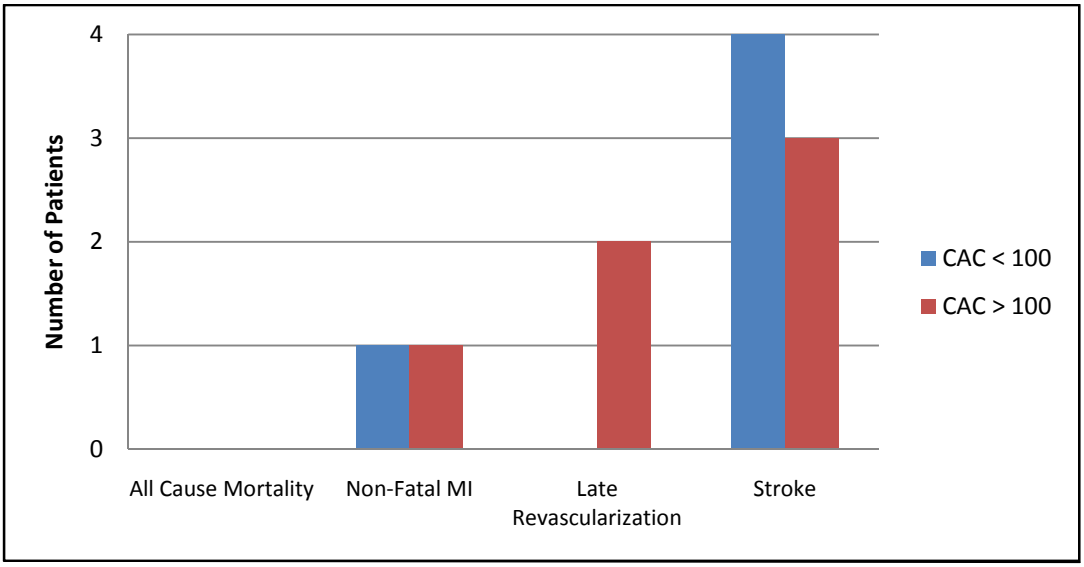

Fig. 2. MACE Breakdown of 11 patients

4. DISCUSSION

The application of CAC scoring in symptomatic patients is not novel; however its utility is still uncertain. Laudon et al. published a prospective study in 2010 in which 263 low to intermediate risk patients presenting with chest pain underwent CAC scoring [6]. Determination of cardiac chest pain was made using confirmatory testing such as exercise treadmill testing, myocardial perfusion imaging, stress echocardiography, and coronary angiography. ROC analysis performed on total CAC score revealed a threshold of 36 as predictive of cardiac chest pain. Becker et al. reported a sensitivity of 89% and specificity of 80% in predicting CAD in symptomatic patients using a total CAC cut off of 100 [5].

Our data found LM calcium to be present in 82% of patients with adverse events (9 of the 11 total). Of these 9 individuals, 4 of them had a total CAC score less than 100 (Fig. 2). This cutoff of 100 has been called into question by other authors given the sensitivity of CAC scoring in detecting the presence of CAD, and have instead advocated for a CAC threshold of zero in symptomatic patients to exclude angina [7]. Data from several authors suggests that the presence of CAC only indicates the presence of coronary atherosclerosis and does not gauge the degree of intraluminal stenosis [2]. In fact, obstructive CAD with luminal stenosis by CCTA of at least 70% has been reported in up to 1.4% of patients with CAC scores of zero [8]. Williams et al, demonstrated that the CAC per vessel is associated with increased mortality in the LM in a population of 14,759 asymptomatic patients with significantly high rates of mortality with left main CAC scores of 0 to 10, 11 to 100, 101 to 399, and 400 to 999 with annual risk-adjusted mortality was 0.33%, 0.81%, 1.73%, and 7.71%, respectively ($p<0.0001$). Though these were asymptomatic patients as compared to our symptomatic case series, the large sample size undeniably solidify our observation [9].

Given these mixed results, the use of CAC in symptomatic patients has yet to be fully endorsed in current ACC/AHA guidelines, and only a class II recommendation is given in asymptomatic patients [10]. National Institute of Health and Care Excellence (NICE) in the

United Kingdom advocates for the use of CAC scoring as a reasonable test in symptomatic patients with stable chest pain and a pre-test likelihood of CAD of 10-29% [11]. Our findings suggest that LM CAC, particularly in patients with total CAC<100, may provide additional prognostic value as it pertains to MACE prediction above that which would be predicted by total CAC score alone in symptomatic patients.

There are several limitations to this retrospective study. The primary imaging modality in the majority of this cohort was CCTA resulting in an unknown number of patients being excluded secondary to renal insufficiency. Furthermore, this cohort included active duty military and while many presented with atypical complaints, it must be acknowledged that this population's level of physical fitness may not mirror that of the general population. Cardiovascular adverse events were likely underestimated in this study due to short term follow up given the expected event rates in this population. It should be noted that none of the 15 patients lacking per vessel CAC score breakdown had MACE, thus no additional events were excluded based on this criteria.

5. CONCLUSION

This is the first study to demonstrate that the presence of detectable CAC in the LM correlates with increased MACE in a symptomatic cohort independent of total CAC score. Our findings suggest that MACE rates in patients with non-zero CAC scores <100 may be underestimated by total CAC score if LM calcification is present.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. This project has been cleared for publication by the department of clinical investigation, Brooke Army Medical Center.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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