



# Absolute coronary artery calcium score is the best predictor of non-calcified plaque involvement in patients with low calcium scores (1–100)



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## ABSTRACT

**Objective:** We sought to identify the predictors of non-calcified plaque (NCP) burden in patients with low coronary artery calcium (CAC) scores of 1–100.

**Methods:** We studied 920 consecutive patients clinically referred for coronary CT angiography (CCTA) with concomitant CAC scoring. The 276 patients with CAC 1–100 were divided into four groups based on the CAC score: CAC = 0, 1–10, 11–50, and 51–100. Univariate and multivariate linear regression analyses were performed for the demographic, risk factor, and CAC score predictors of number of coronary segments with NCP.

**Results:** Mean age was  $55 \pm 11$  years and 56% were women. Demographics and risk factors failed to identify NCP involvement in univariate models. The lone predictor of NCP burden was the absolute CAC score, which was persistently associated with NCP in multivariable models (CAC 51–100 vs. CAC 1–10,  $\beta$ -coefficient 0.35,  $p = 0.03$ ).

**Conclusions:** Absolute CAC score is the lone robust predictor of NCP burden when CAC is 1–100. Risk within this mild coronary calcification group is likely heterogeneous, driven by the absolute CAC score.

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## 1. Introduction

CAC scoring using non-contrast cardiac CT is an excellent method for detecting subclinical calcified coronary plaque, and its selective use is supported by a wealth of prognostic data. For example, a CAC score of zero is associated with an excellent prognosis and a low risk of significant coronary artery disease [1]. In contrast, minimal levels of CAC (1–10) are associated with a 2-fold increased risk for cardiovascular events and mortality [2]. In many prognostic studies, patients with low CAC scores of 1–100 are routinely grouped into a single group with intermediate or moderate cardiovascular risk.

A weakness of CAC is the inability to quantify non-calcified plaque (NCP), which has a higher propensity to rupture than

calcified plaque [3]. NCP occurs earlier in the natural history of atherosclerosis, and may be more likely to cause acute coronary syndromes and predict future cardiac events [4,5]. While there have been many studies on the existence of NCP in patients with CAC = 0 [6] – where prognosis is usually favorable [7] – there has been little emphasis on patients with low calcium scores (1–100). In this study, we aim to identify the predictors of NCP burden in patients with low CAC scores of 1–100.

## 2. Methods

### 2.1. Study population

We considered a registry of 920 consecutive patients referred for coronary CT angiography (CCTA) with concomitant CAC scoring at Henry Ford Health Systems, Detroit, MI between January 2006 and December 2009. After exclusion of patients with CAC > 100 and known CAD, 688 patients were available for our study. Of these, 276

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had CAC scores of 1–100. The patients were followed for a mean of  $3.2 \pm 2.1$  years for all-cause mortality. All-cause mortality was ascertained via an automated search of the United States Social Security Administration Death Master File (DMF), which includes over 90–95% of all deaths amongst registered persons in the United States.

## 2.2. CT data acquisition

All patients underwent CAC scoring and CCTA on a 64-slice computed tomography scanner (Lightspeed VCT, GE Healthcare, Milwaukee, WI, USA). CAC was calculated from non-enhanced images using the Agatston score [8]. Patients with a pre-scan heart rate  $>65$  received intravenous beta-blockers (metoprolol 5–10 mg). Nitroglycerin was given in most patients as appropriate based on blood pressure and heart rate after beta blocker administration. For the CT scan, 60–80 cc of iodinated contrast was used per scan (5 ml/s). Retrospective ECG-gating was used in all patients scanned prior to 2008. Prospective ECG-gating was used in nearly 70% of the patients after June 2008. Retrospective ECG-gated CCTA resulted in a mean radiation dose per scan of 14 mSv and prospective ECG-gated CCTA resulted in a mean radiation dose per scan of 5 mSv. CCTA was performed with  $64 \times 0.625$  mm collimation, 350 ms gantry rotation time, 500–600 mA tube current, and 100–120 kV voltage.

## 2.3. Image analysis

Images were read by two experienced readers who provided a consensus interpretation. At least 3 contiguous pixels with a density of  $>130$  HU were identified as calcium. Lesions greater than  $1 \text{ mm}^2$  within or adjacent to the vessel lumen but distinct from the epicardial fat and vessel lumen were defined as plaques. The established AHA 15-segment coronary model was used for image analysis. One plaque type was assigned to each coronary segment. NCP (HU  $< 130$ ) was defined as no calcified portions. Plaque stenosis was evaluated on a per segment basis by visual estimation.

## 2.4. Statistical analysis

The subjects were divided into four groups based on the CAC score: CAC = 0, 1–10, 11–50, and 51–100. The burden of NCP was defined as both: 1) the total number of coronary segments with NCP (continuous); and 2) presence of any exclusively NCP (binary). We performed univariable and multivariable linear and logistic regression to assess the association of demographic variables, risk factor data, and the CAC score with total NCP involvement among

the CAC 1–100 group. In addition, we used Cox proportional hazards models to model time-to-all-cause mortality with CAC = 0 as the reference group.

## 3. Results

### 3.1. Patient characteristics

The mean age of the study population was  $55 \pm 11$  years and 55% were women. The ethnic distribution of the patients was: 56% Caucasian, 36% African-American, 4% Asian and 2% Hispanic. Approximately 93% of patients were referred for symptoms, which predominantly included atypical chest pain. In our sample, 11% of patients had typical chest pain, 62% had atypical chest pain, and 8% had suspected non-cardiac chest pain (Table 1). A total of 35% of the population noted exertional shortness of breath at the time of scanning (Table 1). Nearly 50% of the study population had a stress test in the preceding 3 months, of which 68% were clinically interpreted as abnormal or equivocal. A total of 30% were on statins at baseline.

Of the 276 patients with CAC scores of 1–100, 81 (29%) had CAC 1–10, 117 (42%) had CAC 11–50, and 78 (28%) had CAC 51–100. Patients with CAC = 0 were younger than patients with CAC 1–100, although there was no age difference between the CAC 1–100 subgroups ( $59 \pm 10$  years for CAC 1–10 vs.  $60 \pm 9$  years for CAC 11–50 vs.  $58 \pm 10$  for CAC 51–100 [ $p = 0.51$ ]). Women comprised 63% of the CAC = 0 group and 44% of the CAC 1–100 group, although there was no statistical difference between the CAC 1–100 subgroups ( $p = 0.52$ ). There were no significant differences in any of the remaining measured baseline characteristics shown in Table 1 among the CAC 1–100 subgroups.

### 3.2. Prevalence and composition of coronary artery disease

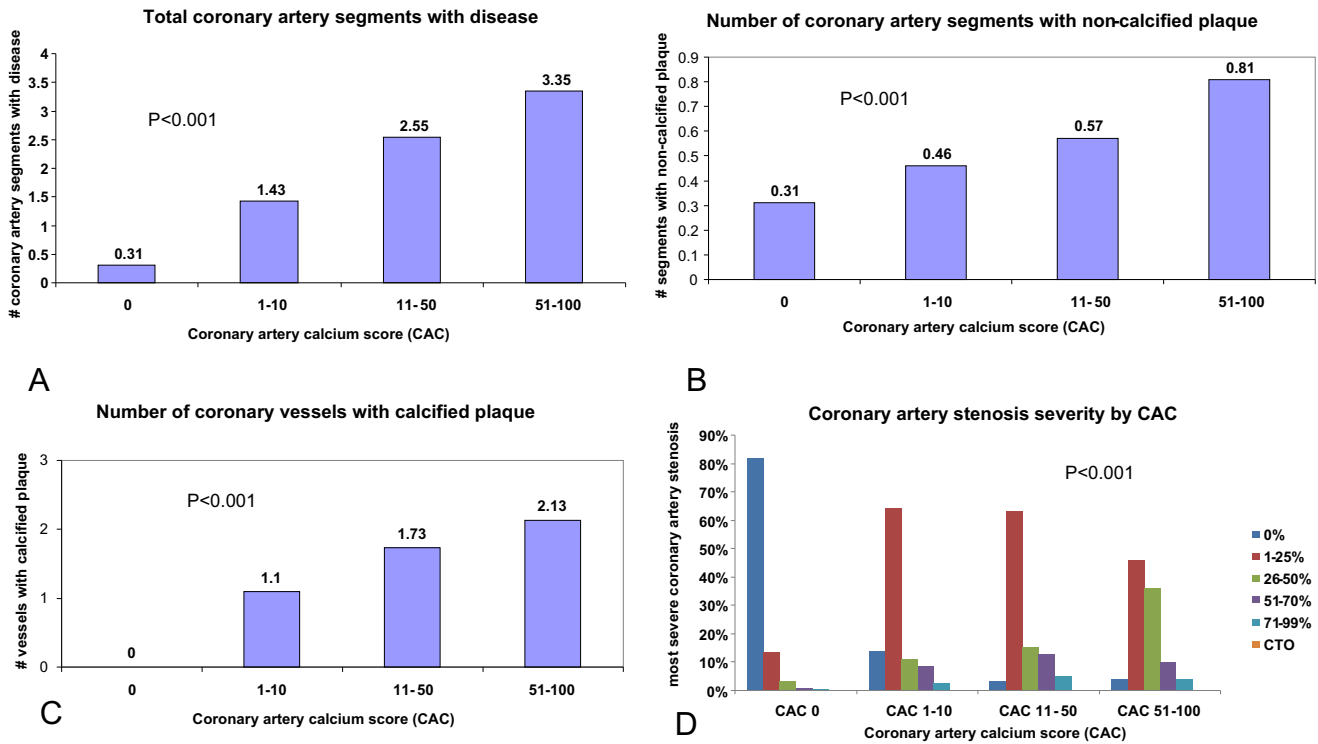
The number of coronary artery segments with atherosclerotic disease increased with higher CAC score (Fig. 1A). Moreover, there was a graded increase in the prevalence of NCP with rising CAC score (Fig. 1B). The number of vessels with calcified plaque was higher in patients with higher CAC scores (Fig. 1C). A higher CAC score was also associated with an increased prevalence of obstructive coronary artery disease ( $>50\%$  lumen stenosis) (Fig. 1D).

### 3.3. Predictors of non-calcified plaque in the CAC 1–100 group

The univariate predictors of NCP burden in the CAC 1–100 group are shown in Table 2. Demographic variables and traditional risk

**Table 1**  
Baseline characteristics stratified by CAC score.

	CAC = 0 (N = 412)	CAC 1–10 (N = 81)	CAC 11–50 (N = 117)	CAC 51–100 (N = 78)	p-value	p-value for CAC 1–100 groups
Age, years	$51.9 \pm 11$	$58.5 \pm 10$	$59.8 \pm 9$	$58.4 \pm 10$	$<0.001$	0.51
Gender, women	63%	41%	48%	41%	$<0.001$	0.51
Race, white	53%	63%	56%	62%	0.64	0.45
BMI, kg/m <sup>2</sup>	$31.0 \pm 8$	$30.2 \pm 6$	$30.7 \pm 6$	$30.3 \pm 7$	0.80	0.19
Smoking, active	14%	21%	10%	14%	0.001	0.39
Family history of CHD	35%	28%	36%	35%	0.71	0.52
Diabetes	15%	16%	25%	22%	0.05	0.36
Hypertension	65%	75%	77%	74%	0.03	0.92
Hyperlipidemia	58%	69%	74%	65%	0.004	0.39
Statin use	24%	38%	38%	42%	$<0.001$	0.84
Renal disease	4%	5%	3%	4%	0.61	0.41
Creatinine (mg/dL)	$1.1 \pm 1.5$	$1.1 \pm 1.2$	$1.2 \pm 1.4$	$1.6 \pm 2.9$	0.19	0.23
Referred for symptoms?	94%	90%	92%	90%	0.36	0.79
Atypical chest pain?	63%	62%	59%	62%	0.86	0.91



**Fig. 1.** Among patients with CAC 1–100, increasing absolute CAC score is associated with: A) A greater number of total coronary artery segments with atherosclerosis; B) A greater number of segments with non-calcified plaque; C) A greater number of segments with calcified plaque; and D) A greater prevalence of obstructive coronary artery disease.

factors were not predictive of non-calcified plaque in our study population except for BMI. The association of BMI with NCP lost statistical significance after adjustment for age, gender, and race. In contrast, a CAC score of 51–100 was highly associated with a higher burden of non-calcified plaque. In multivariable models, a CAC score of 51–100 continued to be associated with a greater burden after adjustment for age, gender, and race (B-coefficient 0.35,  $p = 0.03$ ). The absolute calcium score and NCP burden were moderately correlated in the CAC 1–100 group ( $\rho = 0.26$ ,  $p < 0.001$ ).

**Table 2**  
Predictors of non-calcified plaque burden and presence.

Risk factor	Burden of NCAP (# of segments)		Presence of NCAP	
	B-coefficient	95% CI	Odds ratio	95% CI
Age (per 10 years)	−0.04	−0.02 to 0.01	0.92	0.70–1.20
Gender (women)	−0.03	−0.27 to 0.22	0.89	0.54–1.47
Race caucasian	0.02	−0.23 to 0.27	1.13	0.68–1.88
BMI	<b>0.02</b>	<b>0.00 to 0.04</b>	1.04	0.99–1.08
Smoker	0.07	−0.05 to 0.19	1.13	0.89–1.43
Family history of coronary artery disease	−0.01	−0.27 to 0.25	0.91	0.53–1.54
Diabetes	0.13	−0.17 to 0.43	0.98	0.54–1.81
Hypertension	0.09	−0.20 to 0.38	1.07	0.60–1.93
Hyperlipidemia	0.11	−0.15 to 0.38	0.99	0.58–1.71
Total cholesterol (per mg/dL)	0.001	−0.002 to 0.004	1.002	0.99–1.01
LDL-C (per mg/dL)	0.001	−0.002 to 0.005	1.002	0.99–1.01
HDL-C (per mg/dL)	−0.002	−0.01 to 0.01	0.99	0.98–1.01
Triglycerides (log-transformed)	0.09	−0.13 to 0.33	1.48	0.92–2.40
Absolute CAC score <sup>a</sup>				
1–10	Ref	Ref	Ref	Ref
11–50	0.12	−0.18 to 0.41	1.73	0.90–3.32
51–100	<b>0.35</b>	<b>0.03 to 0.67</b>	<b>1.81</b>	<b>1.0–3.30</b>

**BOLD** indicates statistical significance at  $p < 0.05$ .

<sup>a</sup> Only variable that predicts NCP after multivariable adjustment.

#### 3.4. All-cause mortality

There was a higher all-cause mortality rate (14.1 vs. 5.5 per 1000 patient-years) in patients with CAC scores 1–100 (14 deaths in 276 patients) compared to those with CAC = 0 (9 deaths in 411 patients). The age, gender, and race-adjusted hazard ratio for the CAC 1–100 group was 2.6 (95% confidence interval 1.0–6.8). The hazard ratio was similar among the CAC 1–100 subgroups (2.7 for CAC 1–10 vs. 2.4 for CAC 11–50 vs. 2.8 for CAC 51–100), although the total number of events was low when considering these small subgroups. Further adjustment for NCP burden in the above models did not attenuate the mortality risk associated with increasing CAC score.

#### 3.5. Myocardial infarction and cardiovascular mortality

The total number of cardiovascular-specific events was low, and not sufficient to perform adjusted statistical analysis. In brief, there was 1 acute myocardial infarction and 2 cardiovascular deaths amongst 411 patients with CAC = 0. In the case of the 1 acute myocardial infarction when CAC = 0, the CTA also showed no coronary atherosclerosis. There were 3 myocardial infarctions and 5 cardiovascular deaths amongst the 276 people with CAC 1–100. Regarding the 3 myocardial infarctions in patients with CAC 1–100, 1 had a maximal 26–50% stenosis, 1 had a maximal 51–70% stenosis, and 1 had a maximal 71–99% stenosis on concomitant CCTA imaging.

## 4. Discussion

The present study demonstrates a graded relationship between the absolute CAC score and NCP burden in patients with low CAC scores (1–100) after adjustment for other variables. Multiple efforts have been devoted to find the best predictor of non-calcified plaque

including epicardial adipose tissue volume [9], hypercholesterolemia [10], adiponectin level [11], diabetes [10] and smoking [12]. Our results suggest that the absolute calcium score is the best predictor of NCP burden in patients with low CAC scores.

Our findings are in agreement with the findings of Nasir et al. who found that an increasing CAC score is associated with a higher prevalence of heterogeneous coronary plaque, consisting of both calcified and non-calcified plaque, as well as mixed plaque [13]. In that study, the prevalence of having at least two coronary segments with mixed plaques was 4% among individuals with CAC scores of 1–10, increasing to 18% in individuals with CAC scores of 11–100. In contrast to our results, Yoo et al. showed that BMI, hypertension, diabetes, total cholesterol, HDL cholesterol, and serum creatinine are predictors of NCP in patients with low CAC scores (defined as CAC score of 1–50 in men and 1–10 in women) [14]. However, this study did not control for the absolute CAC score in the model, instead considering low CAC score as a single homogenous group.

Our study also implies that the continued search for clinical predictors of NCP in patients undergoing CAC scoring for prognostic purposes is likely to be fruitless. Once the CAC score is known to be non-zero, it will be difficult to add to the absolute CAC score for predicting the NCP and total plaque burden using routinely measured clinical factors. An important message from our study is that the CAC score is a graded risk factor for NCP and total plaque burden even within established CAC score groups, such as the CAC 1–100 group. Clinicians and researchers should refrain from artificially grouping patients into CAC score groups, knowing that the absolute CAC score predicts the burden of NCP even within the low CAC score groups (1–100).

Our study has limitations. The study population included mostly symptomatic patients who were referred for further evaluation by CCTA. As a result, selection bias cannot be excluded, as our study population may not represent the subjects who are asymptomatic but have low CAC scores. However, the robust association between CAC score and NCP burden persisted after adjustment for all pertinent clinical variables.

In conclusion, we found that absolute CAC score is the lone robust predictor of NCP burden when the CAC score is 1–100. Patients with low CAC scores likely represent a heterogeneous risk group, and further prognostic research is warranted to explore the details of the relationship between absolute CAC scores and future

adverse events when the CAC score is 1–100 and prognosis is indeterminate.

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