

Coronary Artery Calcification Across Ethnic Groups in Singapore

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Abstract

Introduction: In Singapore, the age-standardised event rates of myocardial infarction (MI) are 2- and 3-fold higher for Malays and Indians respectively compared to the Chinese. The objectives of this study were to determine the prevalence and quantity of coronary artery calcification (CAC) and non-calcified plaques across these 3 ethnic groups. **Materials and Methods:** This was a retrospective descriptive study. We identified 1041 patients (810 Chinese, 139 Malays, 92 Indians) without previous history of cardiovascular disease who underwent cardiac computed tomography for atypical chest pain evaluation. A cardiologist, who was blinded to the patients' clinical demographics, reviewed all scans. We retrospectively analysed all their case records. **Results:** Overall, Malays were most likely to be active smokers ($P = 0.02$), Indians had the highest prevalence of diabetes mellitus ($P = 0.01$) and Chinese had the highest mean age ($P < 0.0001$). The overall prevalence of patients with non-calcified plaques as the only manifestation of sub-clinical coronary artery disease was 2.1%. There was no significant difference in the prevalence of CAC, mean CAC score or prevalence of non-calcified plaques among the 3 ethnic groups. Active smoking, age and hypertension were independent predictors of CAC. Non-calcified plaques were positively associated with male gender, age, dyslipidaemia and diabetes mellitus. **Conclusion:** The higher MI rates in Malays and Indians in Singapore cannot be explained by any difference in CAC or non-calcified plaque. More research with prospective follow-up of larger patient populations is necessary to establish if ethnic-specific calibration of CAC measures is needed to adjust for differences among ethnic groups.

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Key words: Coronary artery disease, Myocardial infarction, Race

Introduction

Coronary artery calcification (CAC), as measured by computed tomography (CT), is a surrogate marker of coronary atherosclerosis and has been shown to be predictive of future coronary events.¹⁻⁴ Previous studies on race and CAC have yielded discordant results. The Coronary Artery Risk Development in Young Adults study reported an absence of racial differences in the prevalence and severity of CAC using coronary CT.⁵ Conversely, the Multi-Ethnic Study of Atherosclerosis has shown that CAC prevalence and amount are heavily influenced by ethnicity, in addition to age and gender.⁶

In Singapore, the age-standardised event rates of

myocardial infarction (MI) are 2- and 3-fold higher for Malays and Indians respectively compared to the Chinese.⁷ The multi-ethnic make-up of the Singapore population provides a unique opportunity to examine the distribution of CAC based on age, gender, and ethnicity in an Asian cohort without previous history of cardiovascular disease. The objectives of this study were to determine the prevalence and quantity of CAC across the 3 major ethnic groups and whether ethnic differences were significant after controlling for traditional cardiovascular risk factors. We also evaluated the prevalence and predictors of non-calcified plaques in the subgroup of patients who underwent both a non-contrast scan and a contrast-enhanced CT coronary angiography.

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Based on the local epidemiological data on MI event rates, we postulated that the Indians and Malays would have higher prevalence of CAC and/or non-calcified plaques than the Chinese.

Materials and Methods

Patients

Of all patients who underwent cardiac CT in our institution for atypical chest pain evaluation from 1 April 2007 to 30 April 2008, we identified consecutive ones with no history of clinically apparent cardiovascular disease (physician diagnosed heart attack, angina, stroke, transient ischaemic attack, or heart failure; current atrial fibrillation; taking nitroglycerin; or having undergone angioplasty, coronary artery bypass graft, valve replacement, pacemaker or defibrillator implantation, or any surgery on the heart or arteries). We retrospectively analysed all their case records. Baseline clinical characteristics were obtained from the coronary risk factors profile present on the patients' CT scan request forms and case records.

Multi-slice Cardiac CT

Scans were acquired with a 64-slice multi-slice CT scanner (SOMATOM Sensation Cardiac 64, Siemens, Germany). A non-contrast scan was performed to determine the total calcium burden of the coronary arteries (sequential scan with 64 x 0.6 mm collimation, tube current 60 mA at 120 kV). Contrast-enhanced CT coronary angiography data were acquired with the use of a spiral scan with 64 x 0.6 mm collimation, 330 ms gantry rotation, pitch of 0.2 and tube voltage at 120 kV. A total of 64 overlapping 0.6 mm slices per rotation were acquired with the use of a focal spot periodically moving in the longitudinal direction (z-flying focal spot). Tube current was modulated according to the electrocardiogram (ECG), with a maximum current of 850 to 950 mAs during a time period of approximately 330 ms centered at 375 ms before the next R-wave and reduction by 80% during the remaining cardiac cycle. Contrast agent (60 to 80 mL; Omnipaque™ GE Healthcare Inc) was injected intravenously (4.5 to 5.0 mL/s). Trans-axial images were reconstructed using an ECG-gated half-scan reconstruction algorithm (temporal resolution 164 ms) and kernel B30f.

Multi-slice CT Image Interpretation

A cardiologist, who was blinded to the patients' clinical demographics, reviewed the cardiac CT scans to ensure accurate validation and interpretation. The contrast-enhanced scans were evaluated on axial slices, multi-planar reformations and 3 thin-slab maximum intensity projections. Orientated along the heart axis, the thin-slab (5-mm thickness, 1-mm increment) maximum intensity projections

were reconstructed perpendicular to each other. The presence of non-calcified atherosclerotic plaque tissue was defined as any discernible structure in the coronary artery wall with a CT density less than the contrast enhanced coronary lumen but greater than the surrounding connective tissue. Vessel wall calcifications were quantified on a separate workstation (Wizard, Siemens Medical Solutions), based on the standard built-in algorithm using an Agatston score equivalent adapted for multi-slice CT. CAC was quantified using average Agatston score and presence of calcification was defined as an average Agatston score greater than 0. Calcified plaque components of mixed plaques (combined non-calcified and calcified plaque tissues) were excluded from the assessment of the non-calcified plaque density. Standard display settings were used for the evaluation of the contrast-enhanced multi-slice CT scans (window width 800 Hounsfield units [HU]; window center 250 HU).

Statistical Analysis

The mean age and CAC scores were compared across the 3 racial groups using the ANOVA test. The chi-square test was used to compare categorical variables across the 3 groups. The independent student t-test was used to compare age distribution between patients with and without non-calcified plaques, and the chi-square test used to compare proportions between the 2 groups. We used the logistic regression model to identify variables that were significantly and independently associated with non-calcified plaques. The backward likelihood test with probability of removal set at 5% was used for the multivariate model. We also analysed the actual calcium score, but transformed the data on the natural logarithmic scale as data were highly skewed. We used the linear regression model to examine factors that were associated with calcium score. Once again, the backward likelihood method with probability of removal set at 5% was used in the multivariate analysis. Data analysis was performed in Stata V11 (Stata Corp, College Station, Tx, USA) and level of significance set at 5%.

Results

There were 1041 eligible patients, of which 810 were Chinese, 139 Malays and 92 Indians. Table 1 displays the baseline clinical characteristics of the study population. Overall, Malays were most likely to be active smokers ($P = 0.02$), Indians had the highest prevalence of diabetes mellitus ($P = 0.01$) and Chinese had the highest mean age ($P < 0.0001$).

The overall prevalence of CAC in the 1041 patients was 49.5%. Among the Chinese, the prevalence of CAC was 50.4% with a mean CAC score of 173.9 ± 352.1 . In the Malay group, 46.8% had CAC, mean CAC score 190.2 ± 431.1 . Among the Indians, 45.7% had CAC and the mean

Table 1. Baseline Clinical Characteristics of Study Population

Characteristics	Chinese n = 810	Malays n = 139	Indians n = 92	P Value
Age	56.1 ± 11.1	51.9 ± 12.4	51.7 ± 11.5	<0.0001
Male (%)	484 (59.8)	81 (58.3)	59 (64.1)	0.21
Active smoking (%)	174 (21.5)	43 (30.9)	27 (29.4)	0.02
Hypertension (%)	233 (28.8)	30 (21.6)	31 (33.7)	0.11
Hyperlipidaemia (%)	419 (51.7)	63 (45.3)	50 (54.3)	0.31
Diabetes mellitus (%)	92 (11.4)	15 (10.8)	20 (21.7)	0.01
CAC score > 0 (%)	408 (50.4)	65 (46.8)	42 (45.7)	0.58
Mean CAC score	173.9 ± 352.1	190.2 ± 431.1	206.8 ± 356.1	0.83

CAC: Coronary artery calcification

CAC score was 206.8 ± 356 . There was no significant difference in the prevalence of CAC or mean CAC score among the 3 ethnic groups ($P = 0.48$). The linear regression model revealed active smoking, age and hypertension to be independent predictors of CAC.

A total of 718 patients had both non-contrast scan and contrast enhanced CT coronary angiography. No CAC was present in 349 of the 718 (48.6%) patients, whereas calcified plaques were determined in 369 of the 718 (51.4%) patients. Subsequent contrast enhanced CT coronary angiography revealed the presence of non-calcified plaques in 15 (4.3%) of the 349 patients who had no CAC. In these patients, non-calcified plaques were the only manifestation of sub-clinical coronary artery disease. The overall prevalence of patients with non-calcified plaques as the only manifestation of sub-clinical coronary artery disease was 2.1% (15 of 718 patients). In patients with coronary calcifications, additional non-calcified plaques were detected in 73 of 369 (19.8%) patients, whereas 296 of 369 (80.2%) patients were free of non-calcified plaques by CT angiography (Fig. 1).

Table 2 outlines the clinical characteristics of patients with and without non-calcified plaques. There was no significant difference in the prevalence of non-calcified plaques among the 3 ethnic groups: 11.9% among Chinese, 16.7% in the Malay group and 11.8% among the Indians ($P = 0.29$). Logistic regression showed non-calcified plaques to be positively associated with male gender, age, dyslipidaemia and diabetes mellitus.

Discussion

In this sample of patients without prior history of clinical cardiovascular disease, CAC and non-calcified plaque were associated with traditional coronary risk factors. Race was, however, not associated with the presence of CAC or non-calcified plaque, before or after adjustment for significant variables. The higher age-standardised event rates of MI in Malays and Indians in Singapore cannot be explained by any difference in CAC or non-calcified plaque. A similar CAC score therefore may not translate into the same MI

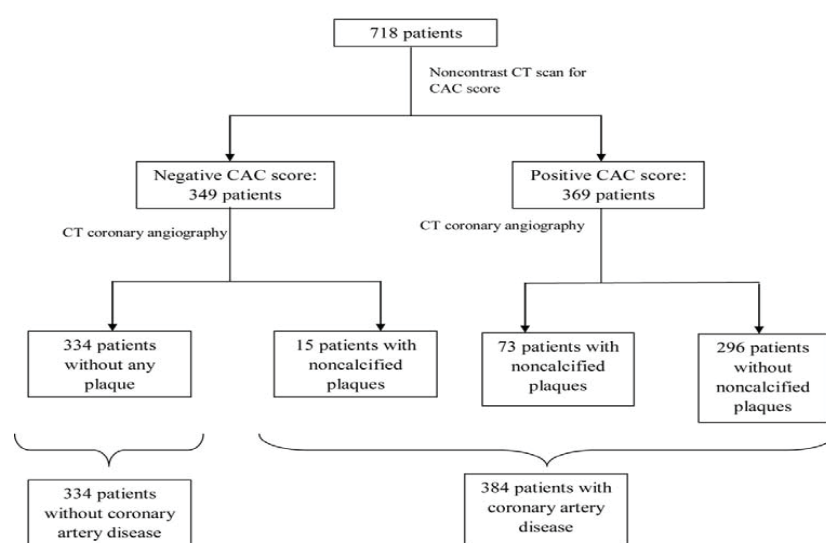


Fig. 1. Presence of calcified and non-calcified plaques in patients with both noncontrast scan and contrast enhanced CT coronary angiography.

Table 2. Clinical Characteristics of Patients with and Without Non-calcified Plaques

Characteristics	Patients with non-calcified plaques n = 88	Patients without non-calcified plaques n = 630	P Value
Age	58.3 ± 10.0	54.7 ± 11.7	0.007
Male (%)	64 (72.7)	369 (58.6)	0.01
Active smoking (%)	29 (32.9)	173 (27.5)	0.28
Hypertension (%)	53 (60.2)	201 (31.9)	<0.0001
Hyperlipidaemia (%)	65 (73.9)	312 (49.5)	<0.0001
Diabetes mellitus (%)	24 (27.3)	77 (12.2)	<0.0001

risk amongst individuals of the 3 major ethnic groups. The progression of coronary artery disease may also be variable across ethnic groups.

Published data revealed that the greater susceptibility of Indians to MI did not appear to be explained by higher prevalence of the traditional cardiovascular risk factors (cigarette smoking, hypertension or hypercholesterolemia)^{8,9} or hyperhomocysteinemia.¹⁰ However, when compared with the Malays and the Chinese, Indians were noted to have more abdominal obesity, insulin resistance, some components of Syndrome X (lower high density lipoprotein cholesterol, more glucose intolerance), higher levels of thrombogenic factors such as elevated plasminogen activator inhibitor type 1 and lipoprotein(a) (Lp(a)), which may partly explain their increased susceptibility.¹¹ Levels of Lp(a) are genetically determined. Genetic factors may therefore also contribute to inter-population differences, due to variable gene frequencies among ethnic groups.

Indians may experience more major adverse cardiovascular events for the same degree of atherosclerosis, suggesting greater proclivity to plaque rupture and thrombosis.¹² Lipid-rich coronary plaques have been associated with an increased vulnerability for sudden plaque rupture, leading to acute ischemic coronary syndromes.

In our study, 4.3% of patients with a zero CAC score had non-calcified plaques. These patients were more likely to be older males with hyperlipidemia and diabetes mellitus. The assessment of traditional coronary risk factors in combination with non-contrast CT scanning for CAC may fail to identify this patient population with a potentially higher cardiovascular risk. Hausleiter et al¹³ reported that the prevalence of non-calcified plaques as the only manifestation of CAD in patients at intermediate risk of coronary artery disease was 6.2%. In a substudy of CORE64 (Coronary Evaluation Using Multi-Detector Spiral Computed Tomography Angiography Using 64 Detectors) multicenter trial, 19% of patients with a zero CAC score had at least 1 ≥50% coronary artery stenosis and revascularisation was performed in 12.5% of patients

with a zero CAC score within 30 days of the scan.¹³ The overall sensitivity for a zero CAC score to predict the absence of ≥50% stenosis was 45%, specificity was 91%, negative predictive value was 68%, and positive predictive value was 81%.¹⁴ However, the risk for ischaemic events in patients with non-calcified plaques as well as the additive value of non-calcified plaque detection over traditional calcium scoring is currently not known.

Our study has several limitations. In the patient population, the number of Indians and Malays was much smaller than the Chinese. This difference may restrict the power of the study to fully address the relationship between race and CAC. This was a retrospective study with no prospective follow-up data on the patient management post CT scan and subsequent incidence of MI. The patients' baseline clinical characteristics were obtained from coronary risk factors profile available on the CT scan request forms and case records without full access to patients' blood investigations or medications, thereby restricting the comprehensiveness of risk profiling.

Conclusion

More research is necessary to establish if ethnic-specific calibration of CAC measures is needed to adjust for differences among ethnic groups. Long-term follow-up studies in larger populations are required to further investigate the impact of non-calcified plaque detection by multi-slice CT on cardiovascular events on top of the traditional assessments of cardiovascular risk factors and CAC. In addition, genotype-specific novel biomarkers for different ethnic groups, predisposed to higher risk of cardiovascular events, may be the key to understanding ethnic differences in the presentation of acute coronary syndromes.

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