INTRODUCTION

Cardiovascular disease (CVD) is the most significant cause of death globally according to the World Health Organization, and accounted for 17% of deaths in 2016 in Singapore [1]. A screening tool to evaluate risk of coronary heart disease (CHD) and identify individuals who have subclinical CVD aids in early prevention and treatment [2]. Currently, the Framingham risk score (FRS) is the widely used model for predicting 10-year risk of CHD in individuals without previous CVD. However, studies have consistently shown that FRS overestimates this risk [3,4].

Coronary artery calcium (CAC) is associated with the presence of coronary atherosclerotic plaque and is a prognostic factor of cardiovascular events. CAC varies among ethnic groups in patients of the same age and gender. Studies on the prognostic value of CAC in a multi-ethnic Asian population have yet to be performed. We aim to study the association of CAC and ethnicity, all-cause mortality, and acute myocardial infarction (AMI).

OBJECTIVE: Coronary artery calcium (CAC) is associated with the presence of coronary atherosclerotic plaque and is a prognostic factor of cardiovascular events. CAC varies among ethnic groups in patients of the same age and gender. Studies on the prognostic value of CAC in a multi-ethnic Asian population have yet to be performed. We aim to study the association of CAC and ethnicity, all-cause mortality, and acute myocardial infarction (AMI).

MATERIALS AND METHODS: This is a retrospective study with a multi-ethnic cohort aged 35–84 years from a single tertiary institution between 2007–2017. The individuals were all clinically referred for cardiac CT calcium scanning. CAC was determined by Toshiba Aquilion One 320 Multi-detector Row CT (Toshiba Medical System).

RESULTS: This study had 65% males at an average age of 55 years. In our multivariable analysis of 16561 individuals, CAC is generally higher in the Malay than Chinese ethnic group [odds ratio (OR)=1.30, 95% confidence interval (CI)=1.10–1.55] and did not differ among Indians and Chinese (p=0.400). Increasing CAC was associated with higher all-cause mortality (OR=1.27, 95% CI=1.17–1.36) and AMI (OR=1.50, 95% CI=1.35–1.66) after adjusting for known cardiovascular risk factors. Incorporation of CAC into a model with known cardiovascular risk variables enhanced prediction of all-cause mortality [area under the curve (AUC)=0.78] and AMI (AUC=0.85).

CONCLUSION: This study is the largest performed in a multi-ethnic Asian cohort. Malay ethnicity seems to confer a higher likelihood of coronary calcification compared to the Chinese and Indians. CAC was associated with higher all-cause mortality and AMI and complemented traditional cardiovascular risk factors in risk prediction, confirming its applicability in a multi-ethnic Asian population.

Key words Coronary artery · Calcium · Prognosis · Ethnic · Asian.
is the largest multi-ethnic study of subclinical CVD in the United States for analysis of the spectrum and prognostic value of CAC [9]. There were 6814 individuals of White, African-American, Hispanic, or Chinese ethnicity who were free of clinical CVD at baseline. The Asian population consists of 11% of the study cohort and was represented by the Chinese ethnic group [10]. Studies conducted by Bild et al. [11] and McClelland et al. [10] have shown that the prevalence, quantity, and prognostic value of coronary calcification vary among ethnic groups. However, to date, no studies have investigated the prevalence and prognostic value of CAC in a multi-ethnic Asian population.

In our study of three major ethnic groups within a local population, we aim to investigate the relationship between coronary calcification and ethnicity amongst Malay, Indian, and Chinese groups.

We further aim to study the associations between coronary calcification and incidence of all-cause mortality and acute myocardial infarction (AMI) to determine whether a greater amount of coronary calcification would be associated with a higher incidence of these outcomes. We also aim to assess whether the use of CAC when combined with traditional cardiovascular risk factors would have an incremental effect in predicting outcomes of all-cause mortality and AMI.

**MATERIALS AND METHODS**

**Study design and participants**

This is a retrospective study of a multi-ethnic cohort, comprising individuals aged 35–84 years from a single tertiary institution between February 2007 and June 2017, who had a clinical referral for cardiac CT calcium scanning. The initial sample size was 18871, and all participants were free of clinically important CVD symptoms (i.e., typical angina) and had no history of ischemic heart disease at the time of CAC scan. This study excluded 1264 individuals with missing calcium score or who had undergone coronary artery bypass graft or percutaneous coronary intervention as their calcium score could not be assessed accurately. A total of 614 repeated CAC measurements that occurred subsequently after the first CAC measurement was excluded. The final study included 16561 patients. Data on baseline clinical characteristics of the study population were obtained from the CT coronary calcium database and electronic medical records and include age, gender, race/ethnicity, presence or absence of diabetes mellitus, hypertension, hyperlipidemia, smoking status, systolic blood pressure (SBP), serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, statin use, and antihypertensive medication. Data on all-cause mortality and AMI were collected from the National Registry of Diseases Office between February 2007 and 31 October 2017. The study was approved by the ethics committee of SingHealth Institutional Review Board (CIRB 2017/2852).

**Multidetector CT**

CAC scans were conducted with Toshiba Aquilion One Scanner 320 Detector Row Multidetector CT (Toshiba Aquilion 64-slice before year 2009, Toshiba Medical System, Japan) at National Heart Center Singapore. This is a non-contrast and non-invasive test used with a slice thickness of 3 mm. Images were acquired with prospective electrocardiogram triggering at 75% or 40% of the cardiac cycle depending on heart rate during a single breath-hold. We quantified coronary calcifications in the epicardial coronary system with semiautomatic software (Vitrea; Vital Images Inc., Minnesota, MN, USA). All pixels with a density greater than 130 Hounsfield units according to the Agatston scoring method were detected for determination of CAC from CT scans [12]. The Agatston score is the product of within-slice CAC plaque area and a plaque-specific density factor of 1, 2, 3, or 4, summed for all cardiac CT slices. The density factor reflects increasing categories of Hounsfield units.

**Statistical analysis**

Statistical analysis was performed using SAS version 9.4 for Windows (SAS Inc., Cary, NC, USA). Baseline demographics and clinical features were reported as mean and standard deviation for continuous variables and as number (percent) for categorical variables. FRS was calculated based on age, gender, SBP, total cholesterol, HDL-cholesterol, diabetes mellitus, smoking status, and antihypertensive medication. FRS of low risk is defined as FRS<10%, intermediate risk as FRS between 10–20%, and high risk as FRS>20%. The associations between the presence of CAC and demographic and clinical variables were tested using univariate and multivariable logistic regression analyses. Analysis of variance or chi-square tests were conducted to investigate the distribution of CVD risk factors, all-cause mortality, and AMI outcomes among the CAC categories. Univariate and multivariable logistic analyses were performed to assess the association between all-cause mortality and AMI with baseline demographics, clinical features, and CAC score. Statistical significance was set at p≤0.05.

**Sample size justification**

Regression of CAC score on ethnicity as a binary factor with a sample size of 16561 individuals (of which ~50% are Chinese) achieved >80% power. The sample size calculation was based on a multivariable regression method after adjustment for the other demographic variables in the logistic regression obtained an R-square of 0.3. The significance level was set to 5%, and sample size calculation was performed using PASS v.14 (NCSS Statistical Software; LCC, Kaysville, UT, USA).
Outcomes

The primary outcome of this study was the presence of coronary calcification and its association with ethnicity after adjusting for known cardiovascular risk factors, which include the presence of hypertension, hyperlipidemia, diabetes mellitus, and smoking. Hypertension was clinically diagnosed and defined as diastolic blood pressure ≥90 mm Hg, SBP ≥140 mm Hg, or use of antihypertensive medications; if no information was found, absence of hypertension was assumed. Hyperlipidemia was clinically diagnosed; lack of information was assumed as the absence of hyperlipidemia. Diabetes mellitus was clinically diagnosed and defined as random blood glucose ≥11.1 mmol/L, fasting blood glucose ≥7.0 mmol/L, or 2-hour post-challenge glucose ≥11.1 mmol/L for 2 separate measurements in asymptomatic individuals or single measurement in symptomatic individuals; if no information was found, absence of diabetes mellitus was assumed [13].

Secondary outcomes were the incidence of all-cause mortality and AMI, defined as the occurrence of the first outcome since CAC measurement. This study included Type 1 myocardial infarction and its definition according to the 2012 Third Universal Definition of Myocardial Infarction consensus document [14]. The covariates chosen were age, gender, race/ethnicity, SBP, LDL-cholesterol, HDL-cholesterol, total cholesterol, the presence of diabetes mellitus, smoking status, antihypertensive medication, and statin use are based on the Framingham risk variables and published data [6,15]. We classified CAC according to the 4 standardized categories [16]. A CAC of 0 is associated with the absence of calcified coronary atherosclerotic plaque, 1–99 is mild coronary atherosclerotic plaque, 100–399 is moderate coronary atherosclerotic plaque, and ≥400 is severe coronary atherosclerotic plaque.

Log(CAC+1) transformation has been widely used for analysis [6,7]. This method allows for normal distribution of CAC for interpretation as a continuous variable to retain as much information as possible [15].

RESULTS

Study population

Table 1 presents the baseline characteristics of the 16561 participants of the study. The sample was comprised of 65.1% males and had an average age of 54.5±10.2 years. The race/ethnicity distribution was 73.4% Chinese, 4.4% Malay, 9.7% Indian, and 12.5% other nationalities. In these participants, 24.6% had hypertension, 29.2% had hyperlipidemia, and 17.8% had diabetes mellitus. Majority of the cohort had never smoked, and 4.7% were current smokers; 33.4% were on antihypertensives, and 29.2% used statins. The mean FRS was 16.7% (12.9%), with 37.5% FRS in the low-risk group, 33.7% FRS in the intermedi-

Table 1. Characteristics of the study population (n=16561)

| Variable               | Values     |
|------------------------|------------|
| Age, year              | 54.5±10.2  |
| Male                   | 10786 (65.1)|
| Ethnicity              |            |
| Chinese                | 12151 (73.4)|
| Malay                  | 729 (4.4)  |
| Indian                 | 1614 (9.7) |
| Others                 | 2067 (12.5)|
| Hypertension           | 4082 (24.6)|
| Hyperlipidemia         | 4839 (29.2)|
| Diabetes mellitus      | 2943 (17.8)|
| Smoking status         |            |
| Current smoker         | 785 (4.7)  |
| Former smoker          | 531 (3.2)  |
| Non smoker             | 15245 (92.1)|
| Systolic blood pressure, mm Hg | 131±17 |
| Total cholesterol, mg/dL | 210±45 |
| Low-density lipoprotein-cholesterol, mg/dL | 132±39 |
| High-density lipoprotein-cholesterol, mg/dL | 51±15 |
| FRS, 10-year risk of cardiovascular disease (%) | 16.7 (12.9) |
| Low (FRS<10%)          | 3515 (37.5) |
| Intermediate (FRS=10–20%) | 3160 (33.7)|
| High (FRS≥20%)         | 2701 (28.8) |
| CAC score              | 171±540    |
| 0                      | 7511 (45.4) |
| 1–99                   | 4933 (29.8) |
| 100–399                | 2327 (14.1) |
| ≥400                   | 1790 (10.8) |
| Antihypertensive medicine | 5530 (33.4)|
| Statin use             | 4837 (29.2) |
| Log(CAC+1)             | 2.33±2.55  |

Data are presented as mean±standard deviation or n (%). FRS: Framingham risk score, CAC: coronary artery calcium

Coronary calcification and ethnicity

Table 2 shows logistic regression analysis of the association of various demographics and risk factors with the presence of coronary calcification. Multivariable analysis showed that CAC generally increases with age [odds ratio (OR)=1.13, 95% confidence interval (CI)=1.12–1.13; p<0.001], is higher in men than women across all ages (OR=3.70, 95% CI=3.40–4.01; p<0.001), is higher in the Malay than Chinese ethnic group (OR=1.30, 95% CI=1.10–1.55; p=0.003), and did not differ among Indians and Chinese (p=0.400). CAC is generally higher in individuals with hyperlipidemia (OR=1.21, 95% CI=1.11–1.31; p<0.001), diabetes mellitus (OR=1.45, 95% CI=1.32–1.60; p<0.001), or
Table 2. Association analysis of demographics and clinical variables with the presence of coronary calcification using logistic regression analysis

| Variable | Univariate analysis | Multivariate analysis |
|----------|---------------------|-----------------------|
|          | Crude OR (95% CI)   | p-value               | Adjusted OR* (95% CI) | p-value |
| Age, year| 1.10 (1.10, 1.11)  | <0.001               | 1.13 (1.12, 1.13)     | <0.001 |
| Male     | 1.56 (1.46, 1.66)  | <0.001               | 3.70 (3.40, 4.01)     | <0.001 |
| Race     | 0.002               |                       | 0.003                 |         |
| Chinese  | Reference           |                       | Reference             |         |
| Malay    | 1.00 (0.86, 1.16)  | 0.970                | 1.30 (1.10, 1.55)     | 0.003  |
| Indian   | 0.99 (0.89, 1.10)  | 0.873                | 1.05 (0.94, 1.18)     | 0.400  |
| Others   | 1.20 (1.09, 1.31)  | <0.001               | 1.14 (1.03, 1.28)     | 0.015  |
| Smoking  | 1.22 (1.06, 1.42)  | 0.007                | 1.30 (1.10, 1.54)     | 0.003  |
| Diabetes mellitus | 1.70 (1.56, 1.84) | <0.001 | 1.45 (1.32, 1.60) | <0.001 |
| Hypertension | 2.12 (1.96, 2.28) | <0.001 | 1.37 (1.25, 1.50) | <0.001 |
| Hyperlipidemia | 1.72 (1.60, 1.84) | <0.001 | 1.21 (1.11, 1.31) | <0.001 |

*adjusted for age, male, race, smoking, diabetes mellitus, hypertension, hyperlipidemia. CI: confidence interval, OR: odds ratio

Table 3. Distribution of demographics, clinical characteristics, and outcomes by CAC category

| Variable               | 0 (n=7511) | 1–99 (n=4933) | 100–399 (n=2327) | ≥400 (n=1790) | p-value* |
|------------------------|------------|---------------|------------------|---------------|----------|
| Age, year              | 49.9±8.6   | 55.5±9.3      | 59.9±9.1         | 64.2±9.3      | <0.001   |
| Male                   | 4480 (59.7)| 3373 (68.4)   | 1638 (70.4)      | 1295 (72.4)   | <0.001   |
| Ethnicity              |            |               |                  |               |          |
| Chinese                | 5576 (74.2)| 3570 (72.4)   | 1684 (72.4)      | 1321 (73.8)   | 0.006    |
| Malay                  | 335 (4.46) | 218 (4.42)    | 87 (3.74)        | 89 (4.97)     |          |
| Indian                 | 743 (9.9)  | 489 (9.9)     | 232 (10.0)       | 150 (8.4)     |          |
| Others                 | 857 (11.4) | 656 (13.3)    | 324 (13.9)       | 230 (12.9)    |          |
| Clinical characteristics|            |               |                  |               |          |
| Hypertension           | 1301 (17.3)| 1227 (24.9)   | 797 (34.3)       | 757 (42.3)    | <0.001   |
| Hyperlipidemia         | 1742 (23.2)| 1448 (29.4)   | 853 (36.7)       | 796 (44.5)    | <0.001   |
| Diabetes mellitus      | 1026 (13.7)| 867 (17.6)    | 501 (21.5)       | 549 (30.7)    | <0.001   |
| Current smoking        | 319 (4.25) | 235 (4.76)    | 137 (5.89)       | 94 (5.25)     | 0.008    |
| Systolic blood pressure, mm Hg | 128.2±16.7| 131.7±17.0 | 133.4±17.6 | 134.7±19.2 | <0.001 |
| Total cholesterol, mg/dL| 211.6±41.6| 211.7±45.1 | 210.0±48.8 | 204±47.9 | <0.001 |
| Low-density lipoprotein-cholesterol, mg/dL | 133.3±36.3| 132.9±38.6 | 131.5±41.6 | 124.3±42.1 | <0.001 |
| High-density lipoprotein-cholesterol, mg/dL | 53.0±15.2| 50.3±13.8 | 49.6±14.2 | 48.9±13.9 | <0.001 |
| Antihypertensive treatment | 1646 (21.9)| 1683 (34.1) | 1115 (47.9) | 1086 (60.7) | <0.001 |
| Statin use             | 1742 (23.2)| 1448 (29.4) | 851 (36.6)      | 796 (44.5)    | <0.001   |
| FRS, 10-year risk of cardiovascular disease (%) | 10.8±8.5| 16.4±11.4 | 21.2±13.6 | 26.5±15.8 | <0.001 |
| Low (FRS<10%)          | 2025 (59.2)| 1012 (34.6) | 317 (19.6)      | 161 (11.5)    | <0.001   |
| Intermediate (FRS=10–20%) | 1011 (29.5)| 1112 (38.0) | 611 (37.7) | 426 (30.3) | <0.001 |
| High (FRS≥20%)         | 386 (11.3) | 805 (27.5)   | 692 (42.7)      | 818 (58.2)    | <0.001   |
| Clinical outcomes      |            |               |                  |               |          |
| All-cause mortality    | 48 (0.64)  | 58 (1.18)     | 46 (1.98)        | 111 (6.20)    | <0.001   |
| Acute myocardial infarction | 11 (0.15) | 23 (0.47) | 37 (1.59) | 62 (3.46) | <0.001 |

Continuous variables reported as mean±standard deviation, categorical variables reported as n (percentage). *analysis of variance for continuous variables; chi-square test for categorical variables. CAC: coronary artery calcium, FRS: Framingham risk score
hypertension (OR=1.37, 95% CI=1.25–1.50; p<0.001) and is higher in smokers than non-smokers (OR=1.30, 95% CI=1.10–1.54; p=0.003) after adjusting for confounding variables.

**Coronary calcification and outcomes**

Table 3 presents the CVD risk factors, all-cause mortality, and AMI outcomes according to category of CAC. Maximum follow up was 10.2 and 9.2 years for mortality and AMI cases, respectively. All-cause mortality increased with CAC category from 0.64% at the CAC 0 category to 6.20% at CAC ≥ 400. AMI also progressively increased by CAC category from 0.15% at the CAC 0 category to 3.46% at CAC ≥ 400. For outcomes of all-cause mortality, the OR for all-cause mortality was 1.85 for those with CAC 1–99 and 10.2 for CAC ≥ 400 (p<0.001) compared to individuals with CAC 0. For outcomes of AMI, the OR was 3.12 for those with CAC 1–99 (p=0.003), 10.7 for CAC 100–399, and 23.6 for CAC ≥ 400 (p<0.001) compared with individuals with CAC 0.

Table 4 presents the logistic regression analysis according to all-cause mortality and AMI outcomes. All-cause mortality increases with increasing CAC (OR=1.27, 95% CI=1.17–1.36; p<0.001), is generally higher with increasing age (OR=1.08, 95% CI=1.06–1.10; p<0.001), in individuals with diabetes mellitus (OR=1.59, 95% CI=1.15–2.20; p=0.005), and those on antihypertensive medication (OR=3.26, 95% CI=2.54–4.19; p<0.001).

Table 4. Association analysis of all-cause mortality and acute myocardial infarction outcomes with demographics and clinical variables using logistic regression analysis regression

| Variables           | Univariate analysis | Multivariate analysis |
|---------------------|---------------------|-----------------------|
|                     | Crude OR (95% CI)   | p-value               | Adjusted OR* (95% CI) | p-value          |
| All-cause mortality |                     |                       |                       |
| Age, year           | 1.10 (0.85, 1.41)   | <0.001                | 1.08 (1.06, 1.10)     | <0.001           |
| Male                | 1.09 (1.07, 1.10)   | 0.479                 | 1.22 (0.86, 1.73)     | 0.262            |
| Race                |                     |                       |                       |
| Chinese             | Reference           |                       |                       |
| Malay               | 1.84 (1.17, 2.89)   | <0.001                | 1.59 (0.79, 3.21)     | 0.194            |
| Indian              | 1.20 (0.82, 1.76)   | 0.215                 | 0.93 (0.57, 1.51)     | 0.762            |
| Others              | 0.43 (0.25, 0.73)   | <0.001                | 0.56 (0.24, 1.31)     | 0.180            |
| Diabetes mellitus   | 2.29 (1.77, 2.97)   | <0.001                | 1.59 (1.15, 2.20)     | 0.005            |
| Smoking             | 1.35 (0.81, 2.23)   | 0.247                 | 1.26 (0.66, 2.41)     | 0.485            |
| SBP, mm Hg          | 1.01 (1.00, 1.02)   | 0.004                 | 1.00 (0.99, 1.01)     | 0.805            |
| Total cholesterol, mg/dL | 1.00 (1.00, 1.00) | 0.634                 | 1.00 (1.00, 1.00)     | 0.544            |
| HDL-C, mg/dL        | 1.00 (0.99, 1.00)   | 0.312                 | 1.00 (0.99, 1.01)     | 0.839            |
| Antihypertensive medication | 3.26 (2.54, 4.19) | <0.001                | 1.76 (1.26, 2.48)     | 0.001            |
| Statin use          | 1.29 (1.00, 1.67)   | 0.050                 | 0.63 (0.45, 0.87)     | 0.005            |
| Log(CAC+1)          | 1.42 (1.35, 1.50)   | <0.001                | 1.27 (1.17, 1.36)     | <0.001           |

**Acute myocardial infarction**

| Variables           | Univariate analysis | Multivariate analysis |
|---------------------|---------------------|-----------------------|
|                     | Crude OR (95% CI)   | p-value               | Adjusted OR* (95% CI) | p-value          |
| Age, year           | 1.06 (1.04, 1.07)   | <0.001                | 1.00 (0.98, 1.02)     | 0.801            |
| Male                | 0.62 (0.42, 0.92)   | 0.017                 | 1.08 (0.68, 1.72)     | 0.729            |
| Race                |                     |                       |                       |
| Chinese             | Reference           |                       |                       |
| Malay               | 2.04 (1.07, 3.88)   | 0.126                 | 1.59 (0.79, 3.21)     | 0.194            |
| Indian              | 2.33 (1.50, 3.61)   | 0.005                 | 2.04 (1.25, 3.33)     | 0.004            |
| Others              | 0.78 (0.42, 1.45)   | 0.020                 | 0.56 (0.24, 1.31)     | 0.180            |
| Diabetes mellitus   | 2.02 (1.39, 2.92)   | <0.001                | 0.88 (0.58, 1.34)     | 0.540            |
| Smoking             | 3.48 (2.14, 5.66)   | <0.001                | 3.29 (1.94, 5.60)     | <0.001           |
| SBP, mm Hg          | 1.03 (1.02, 1.03)   | <0.001                | 1.02 (1.01, 1.03)     | 0.001            |
| Total cholesterol, mg/dL | 1.00 (1.00, 1.01) | 0.491                 | 1.00 (1.00, 1.01)     | 0.047            |
| HDL-C, mg/dL        | 0.97 (0.96, 0.98)   | <0.001                | 0.98 (0.96, 1.00)     | 0.016            |
| Antihypertensive medication | 5.41 (3.69, 7.92) | <0.001                | 2.74 (1.74, 4.32)     | <0.001           |
| Statin use          | 1.42 (1.00, 2.03)   | 0.049                 | 0.64 (0.43, 0.95)     | 0.026            |
| Log(CAC+1)          | 1.64 (1.51, 1.78)   | <0.001                | 1.50 (1.35, 1.66)     | <0.001           |

*adjusted for Framingham risk variables (age, gender, diabetes mellitus, smoking, SBP, total cholesterol, HDL-C, antihypertensive medication), race, statin use, and log(CAC+1). CAC: coronary artery calcium, SBP: systolic blood pressure, HDL-C: high-density lipoprotein-cholesterol, OR: odds ratio, CI: confidence interval
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pertensives (OR=1.76, 95% CI=1.26–2.48; p=0.001) and did not reveal an association with ethnicity (p=0.127). Statin use was associated with a lower all-cause mortality (OR=0.63, 95% CI=0.45–0.87; p=0.005) after adjusting for confounding variables.

AMI increases with increasing CAC (OR=1.50, 95% CI=1.35–1.66; p<0.001) and is higher in the Indian than the Chinese ethnic group (OR=2.04, 95% CI=1.25–3.33; p=0.004), smokers than non-smokers (OR=3.29, 95% CI=1.94–5.60; p<0.001), individuals with a higher SBP (OR=1.02, 95% CI=1.01–1.03; p=0.001), or those on antihypertensives (OR=2.74, 95% CI=1.74–4.32; p<0.001). Statin use was associated with a lower AMI (OR=0.64, 95% CI=0.43–0.95; p=0.026) after adjusting for confounding variables.

Incorporation of CAC with these known cardiovascular risk variables enhanced prediction of all-cause mortality [area under the curve (AUC)=0.78] and AMI (AUC=0.85) as shown in Fig. 1.

DISCUSSION

Coronary calcification and ethnicity

To the best of our knowledge, the current study is the largest performed in a multi-ethnic Asian cohort and showed Malay ethnicity to confer a higher chance of coronary calcification compared to individuals of Indian or Chinese ethnicity. The findings that CAC differs among the ethnic groups corroborate those of MESA [10,11]. However, the study conducted on the prevalence of CAC in Singapore did not reveal any association between ethnicity and CAC, though that could be due to their smaller study population that reduced the power of the study [17].

This study did not demonstrate any difference in the prevalence and quantity of coronary calcification among the Indians and Chinese, even though individuals of Indian ethnicity are known to be at a higher risk of coronary events [18-20]. The higher incidence of coronary events in the Indian ethnic group could be due to their higher propensity for non-calcified atherosclerotic plaque or for plaque rupture [11,20,21]. The amount of radiographically detectable coronary calcification does not increase proportionately to reflect the extent of coronary atherosclerotic plaque in the Indians compared to the Chinese ethnic group. These ethnic differences need to be adjusted for when evaluating CAC in predicting the risk of CVD in a multi-ethnic Asia cohort [11].

Coronary calcification and association with demographics and clinical variables

This study found that CAC had a positive correlation with age, male gender, smoker, hypertension, hyperlipidemia, and diabetes mellitus. The study performed in Korea found that individuals of older age, male gender, smokers, and with hypertension, hyperlipidemia, or diabetes mellitus had a higher propensity for CAC [22]. The study performed in Singapore showed age, smoker, and hypertension as independent predictors of CAC [17].

Coronary calcification and outcomes

This study assessed the association of CAC with outcomes of all-cause mortality and AMI. Higher coronary calcification is positively associated with all-cause mortality and AMI, indicating poorer clinical outcomes. This was consistent with the American College of Cardiology/American Heart Association Expert Consensus Document and MESA [5,6].

![Fig. 1. Receiver operating characteristic curves for the models with incorporation of CAC. Adjusted for Framingham risk variables (age, gender, diabetes mellitus, smoking, systolic blood pressure, total cholesterol, high-density lipoprotein-cholesterol-C, antihypertensive medication), race, statin use, and log(CAC+1). AUC: area under the curve, CAC: coronary artery calcium.](image-url)
The results of this study showed that higher coronary calcification, older age, antihypertensive medication, and the presence of diabetes mellitus appear to confer a higher chance of all-cause mortality, while statin use decreases this risk. There was no difference between ethnic groups in the associations of CAC or other traditional cardiovascular risk factors with all-cause mortality.

For outcomes of AMI, association was shown with higher coronary calcification, Indian ethnicity, smoker, use of antihypertensive medication, and high SBP, while statin use decreases this risk. This study did not reveal any significant age and gender differences with AMI.

This study showed that individuals on antihypertensive medications were at an increased risk of all-cause mortality and AMI, which is consistent with MESA by McClelland et al. [15]. However, this does not imply that treatment with antihypertensives is not effective, only that they do not lower the risk to that of those who do not have hypertension. Statin therapy had a beneficial effect, resulting in a lower incidence of all-cause mortality and AMI.

CAC categories and outcomes
In our study, the incidence of all-cause mortality and AMI were 6.20% and 3.46%, respectively, for CAC greater than or equal to 400. This is consistent with published data as the results fall within the range of 4–9% for incidence due to cardiac cause and of AMI in individuals with CAC scores greater than 300 or 400 who were followed for 5 years [23].

Shaw et al. [24] demonstrated that the mortality rates for all patients were 1.0%, 2.6%, 3.8%, and 6.3–12.3% for calcium scores of 10 or less, 11–100, 101–400, and greater than 400, respectively (p=0.001). This is in agreement with the incidence of all-cause mortality in our study (CAC 0, 0.64%; CAC 1–99, 1.18%; CAC 100–399, 1.98%; CAC≥400, 6.2%).

Absence of coronary calcification was associated with a low incidence rate of 0.64%, 0.15% for all-cause mortality and AMI, respectively. These data corroborate with previous findings of low risk for coronary events in individuals without coronary calcification [23,25,26].

While absence of coronary calcification is associated with low incidence rates, studies have shown that these individuals could still have obstructive CHD since atherosclerosis can occur without calcification [27,28]. In particular, a study reported that Asians experiencing acute chest pain despite having zero coronary calcification can have significant CHD [29].

CAC in the prediction of outcomes
CAC complements traditional cardiovascular risk factors in predicting coronary events and all-cause mortality. The AUC predicting the association with all-cause mortality and AMI was 0.78 and 0.85, respectively, which were within the range of 0.69 to 0.86 from a systematic review [30]. The good agreement with findings in the MESA, Heinz Nixdorf Recall, and Rotterdam studies included in the systemic review confirms CAC applicability in a multi-ethnic Asian population.

Study strengths
The strengths of this study include its large study cohort and its novelty in being the first study performed in a multi-ethnic Asian population. The results of this study corroborate those of several large cohort studies including MESA. The results of multivariable analysis could be utilized to devise a MESA-equivalent risk calculator to aid in clinical management in Asia.

According to Lee et al. [31], the FRS underestimates cardiac risk of AMI in young adults in Singapore in whom many traditional cardiovascular risk factors are undiagnosed. As such, we included individuals 35 years and older in our study, including those 10 years younger than in MESA.

Study limitations
Limitations of this retrospective study are that a temporal relationship is frequently difficult to assess, and the follow-up period could not be strictly controlled, unlike in a prospective study. Not all patients underwent blood tests to determine total cholesterol, LDL-cholesterol, and HDL-cholesterol at baseline screening of CAC, limiting the data for a proportion of the study population. Knowledge of the baseline clinical characteristics was gathered from the National Heart Center Singapore database and electronic medical records.

Conclusions
This study is the largest performed in a multi-ethnic Asian cohort and showed that Malay ethnicity is at a higher risk for coronary calcification compared to Chinese and Indians. Interestingly, the Indian ethnic group does not have higher coronary calcification although they are at higher risk for coronary events. These ethnic differences need to be accounted for using a predictive model incorporating CAC. Coronary calcification is associated with a higher incidence of all-cause mortality and AMI. Addition of CAC to a model with traditional cardiovascular risk factors enhances risk prediction. Further studies should be performed prospectively to develop an improved model that is adjusted for a multi-ethnic population to predict the 10-year risk for CHD.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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None.
Author Contributions

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