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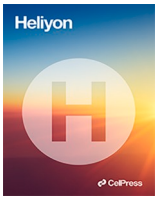

# Coronary artery calcium (CAC) score for cardiovascular risk stratification in a Thai clinical cohort: A comparison of absolute scores and age-sex-specific percentiles

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A B S T R A C T

*Purposes:* Coronary artery calcium (CAC) score provides a quantification of atherosclerotic plaque within the coronary arteries. This study aimed to examine the prevalence and CAC score distribution and to evaluate the association of each CAC score classifications with major adverse cardiovascular events (MACE) in a Thai clinical cohort.

*Methods:* This study was a retrospective observational cohort. We included patients aged above 35 years who underwent CAC score testing. The absolute and age-sex specific percentile classifications were categorized as 0, 1 to 10, 11 to 100, 101 to 400, and >400 and 0, $<75^{th}$, $75^{th}$ – $90^{th}$, and $>90^{th}$, respectively. The endpoint was MACE, including cardiovascular death, myocardial infarction, heart failure hospitalization, coronary artery revascularization procedure, and stroke. Multivariable Cox regression was used to estimate the hazard ratios. The discriminative performance between classifications were compared using Harrell's C-statistics. The agreement was assessed via Cohen's Kappa.

*Results:* This study included 440 patients, with approximately 70% of Thai patients exhibiting a CAC score. CAC score distributed higher in male than female and increased with age. Both CAC score classification demonstrated the acceptable predictive performance. However, fair agreement was observed between classifications (Cohen's kappa 0.51, 95%CI 0.42–0.59). Within the absolute classification, a higher CAC score was associated with increased hazard ratios for MACE across stratified age-sex-specific percentile levels. In contrast, the hazard ratios for MACE did not consistently rise with higher age-sex-specific percentile CAC score when stratified by absolute CAC score levels.

*Conclusions:* Both absolute and age-sex-specific percentile CAC score demonstrated acceptable performance in predicting MACE. However, the absolute CAC score classification may be more suitable for risk stratification within the Thai clinical cohort. Our findings offer supportive information that could inform future recommendations for CAC score testing criteria within national clinical practice guidelines.

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## 1. Introduction

Coronary artery calcium (CAC) score was introduced in the late 1990s to assess coronary artery calcification with non-invasive imaging techniques [1]. The score provides a precise quantification of calcified atherosclerotic plaque within the coronary arteries and has demonstrated a strong association with major adverse cardiovascular events (MACE) [2]. The presence of a CAC score is indicative of a significant risk of developing atherosclerotic cardiovascular disease (ASCVD) and coronary heart disease (CHD) [3–6]. In contrast, a CAC score of zero or a low CAC score suggests a low risk of cardiovascular events [7]. An ample body of research and guidelines supporting the potential of CAC score as a cardiovascular risk stratification tool has accumulated over the years [8]. Moreover, studies have affirmed that the CAC score not only surpasses conventional methods as a standalone predictor but also enhances the discriminative ability of other traditional scores in predicting cardiovascular risk [8,9].

Although CAC score has a high prognostic ability, its interpretation can be challenging due to different ways of expressing and stratifying patients' risk [10,11]. CAC score can be commonly expressed using two classifications: absolute scores, based on the exact amount of CAC score measured in Agatston units, and percentile-based rank scores, based on the percentile rank of CAC score stratified by the patient's sex, age, and/or race [12–14]. Owing to the distinctive rationale of score expression, disagreement between risk groups defined by different score types, even within the same population, is commonly reported [14]. However, different score types may have varied predictive performance based on population mix and prediction time frame, and one may be more beneficial in different contexts [15]. Standard guidelines recommend using both absolute and percentile-based scores for risk stratification. For example, the American Heart Association/American College of Cardiology (AHA/ACC) cholesterol guideline suggests initiating statins for intermediate risk adults with a CAC score greater than 100 or the 75$^{th}$ percentile [16–18].

In Thailand, there are currently no official guidelines regarding the use of CAC score for cardiovascular risk assessment and CAC score cut-points for statin initiation, and there is insufficient evidence to support the appropriateness of the CAC score cut-points suggested by standard western guidelines in the Thai population. Most CAC score studies have been conducted in Western nations, with only a small number of Asian patients included. Additionally, there is evidence that CAC score distribution may vary across ethnic groups, and the results may not be applicable to other populations using the same cut-point system [[19,20],. This study has three main objectives. First, to examine the prevalence and CAC score distribution in a Thai clinical cohort. Second, to determine the association of each CAC score classification with MACE and to validate the discriminative performance of CAC score for risk stratification of MACE. Third, to examine the agreement between the two CAC scoring classification and compare their performance in risk stratification.

## 2. Methods

### 2.1. Study design and population

We conducted a retrospective observational cohort study that included Thai patients who met the following inclusion criteria: (1) were aged above 35 years, and (2) underwent CAC score testing at Maharaj Nakorn Chiang Mai Hospital between January 1, 2012 and March 31, 2020. The exclusion criteria were patients with pre-existing cardiovascular diagnoses (e.g., myocardial infarction, heart failure hospitalization, and ischemic stroke or transient ischemic attack), coronary artery revascularization procedure, incomplete data for traditional cardiovascular risk calculation, missing official report of CAC score or loss of follow-up after CAC score measurement. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Faculty of Medicine, Chiang Mai University (MED-2563-07435). Informed consent was waived owing to retrospective data collection.

### 2.2. Data collection

The data regarding age, sex, smoking status, diabetes mellitus (DM), systolic blood pressure, total cholesterol, low-density cholesterol (LDL-C), high-density cholesterol (HDL-C), creatinine, and Estimated Glomerular Filtration Rate (eGFR) were collected by reviewing individual electronic medical records on the date of CAC score measurement.

### 2.3. Calcium coronary calcium (CAC) score

CAC score was determined through the use of a non-contrast prospective electrocardiogram (ECG) gating scan of the heart, conducted with a cutting-edge 192-slice Dual Source CT scanner (Somatom Force, Siemens). If the patient's heart rate exceeded 75 beats per minute, we employed the ECG-triggered sequential scan technique. This involved performing a systolic ECG-Triggered Sequential Shuttle mode scan with a delay of 280–320 ms. In cases where the patient's heart rate was below 75 beats per minute, the high-pitch scan technique was utilized. We conducted data acquisition of CAC in a craniocaudal direction during mid-inspiratory breath-hold, employing the high-pitch mode gated with the patient's ECG in a prospective manner. To ensure comprehensive coverage of the heart within a single middiastolic phase, the start for the acceleration of the table and initiation of data collection were determined based on the analysis of multiple heartbeats before data collection. The most cranial section was set at 65 % of the R–R interval in all patients. A 3 mm slice thickness was used in conjunction with a tube voltage of 120 kV. Certified radiologists applied the Agatston scoring method to measure the extent of CAC [21].

The absolute CAC score was categorized into five groups using cut-points from previous studies [12,22]: 0 (zero or absent), >0 to 10 (minimal), 11 to 100 (moderate), 101 to 400 (high), and >400 (extensive). As no studies have reported the distribution and percentiles

of CAC score across different age and sex groups in any Thai clinical cohort, we calculated the CAC percentile for each individual based on this cohort. We stratified all patients within thecohort into six groups (males aged <55, males aged 55–64, males aged >64, females aged <55, females aged 55–64, and females aged >64) [23] and assigned patients to one of four percentile ranges based on their strata-specific CAC score percentile: CAC = 0 (zero or absent), <75$^{th}$ (intermediate), 75$^{th}$ – 90$^{th}$ (high), and >90$^{th}$ (very high) [13,14].

## 3. Outcome and follow-up

The main outcome of the study was the occurrence of MACE, which was defined as a composite of cardiovascular death, myocardial infarction (MI), hospitalization due to heart failure, coronary artery revascularization procedure, and ischemic stroke or transient ischemic attack [24]. Cardiovascular deaths were defined as those with documented coronary artery disease and no other known causes of death. The term coronary artery revascularization referred to any procedures performed to enhance the heart's blood supply. In our institution, only two revascularization procedures were available: percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). We excluded hospitalization for unstable angina (UA) from the MACE criteria in our study, as the definition of UA in retrospective medical records can be subjective, may not be thoroughly verified, and has the potential to introduce bias in a retrospective design.

We followed all included patients from the time of their CAC score measurements and continued until the event date or death, whichever came first. Each patient received a phone call from a trained interviewer who inquired about their myocardial infarction event, hospitalization for heart failure, revascularization, and stroke. All patients' electronic medical records were reviewed and verified by investigators. Patients who did not have events and did not lose follow-up at the time the study was closed were marked as censored.

### *3.1. Statistical analysis*

All analyses were performed using Stata 17.0 (StataCorp, College Station, Texas, USA). The results were considered statistically significant at a p-value <0.05. Demographics and baseline characteristics were presented as a number (%), mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate. The prevalence of each CAC score was estimated and reported with its corresponding 95% confidence interval (CI). To compare baseline characteristics across five absolute CAC score categories, we used an extended Wilcoxon rank-sum test by Cuzick [25] for trending numerical and categorical variables.

To identify the association with MACE, a time-to-event analysis was employed. MACE incident rates were annualized and reported per 1000 person-years. Kaplan–Meier methods were used to estimate the probabilities of MACE in both CAC score classificaion systems. Since the CAC score was highly skewed, it was transformed using the natural logarithm function. Log-transformed continuous CAC scores and categorized CAC scores (both absolute and age-sex-specific percentile) were fitted using a multivariable Cox model adjusted for confounders [26,27] including age, sex, DM, total cholesterol, HDL-C, LDL-C, smoking status, and creatinine to estimate the adjusted hazard ratio (HR) for MACE. Patients with CAC scores of zero (CAC score 0) were the reference group. A subgroup analysis was performed for each sex. Proportional hazards assumption was assessed via Schoenfeld residuals test.

The predictive performance of the categorized CAC scores were validated in terms of discriminative performance using Harrell's C-statistics [28]. Harrell's C-statistics were estimated from a univariable Cox proportional hazards model that includes only the variables

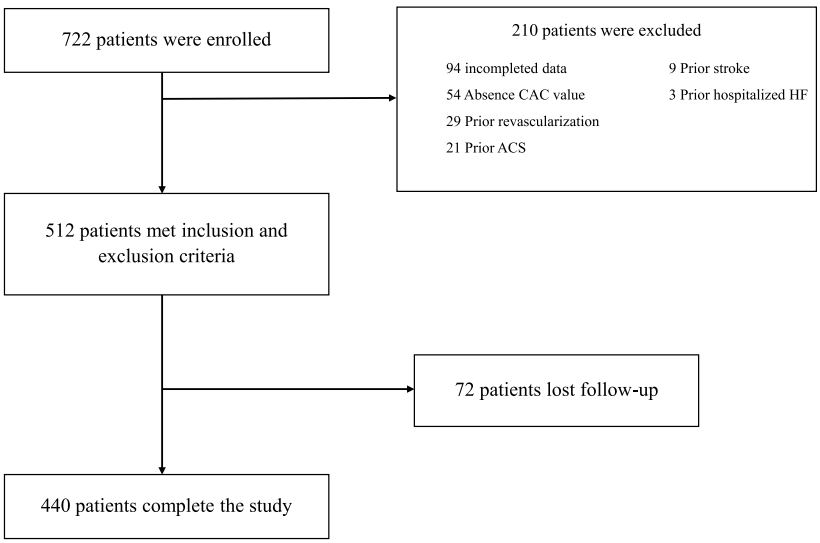


**Fig. 1.** Patient flow diagram
Caption: Abbreviation: CAC; coronary artery calcium, HF; heart failure, ACS; acute coronary syndrome.

for the categorized CAC scores as we aimed to assess the isolated performance of the CAC score. A value of C-statistics = 0.5 corresponds to a non-informative prediction whereas C-statistics = 1 corresponds to a perfect prediction[28].

A higher Harrell's C-statistics indicated a greater overall discriminative ability of the categorized CAC scores. To examine the agreement between the absolute CAC score and the age-sex-specific percentile score, we excluded patients with CAC scores of zero from this part of the analysis. We hypothesized that patients with age-sex-specific percentile-based CAC scores <75$^{th}$, 75$^{th}$ – 90$^{th}$, and >90$^{th}$ might have a similar prognosis to patients with absolute CAC scores of 1–100, 101–400, and >400, respectively [14–17]. We calculated the overall agreement percentage and linear-weighted Cohen's Kappa. Cohen's Kappa values of <0.4, 0.40–0.59, 0.60–0.74, and 0.75–1.00 would be clinically interpreted as poor, fair, good, and excellent, respectively [29].

In case the two classification types did not agree well, we performed an additional analysis to identify a more robust one for risk stratification by assessing the predictive performance and the association with MACE of absolute CAC score classification within each level of age-sex-specific CAC score classification, and vice versa. We defined a more robust classification as the one that showed higher discriminative ability and preserved HR trend for MACE in every level of another classification.

## 4. Results

### 4.1. Prevalence of CAC score and characteristics across CAC score categories

During the study period, a total of 722 patients received a CT coronary angiogram at our institution. Among them, 282 patients were excluded, 94 due to incomplete data, 54 without CAC score data, 62 with previous MACE history, and 72 lost to follow-up after undergoing CAC score testing. The final number of patients included in our analysis was 440 (Fig. 1). The prevalence of each CAC score category in this cohort was as follows: 31.1% (95%CI 26.8–35.7%) for CAC 0, 14.1% (95%CI 11–17.7%) for CAC >0–10, 17.5% (95% CI 14.1–21.4%) for CAC 11–100, 20.2% (95%CI 16.6–24.3%) for CAC 101–400, and 17.1% (95%CI 13.6–20.9%) for CAC >400).

Table 1 compares the baseline characteristics across the CAC score categories. The mean age of all patients was 62.5 ± 10.4 years. Nearly half of the patients were men (47.3 %). Age, sex, total cholesterol, LDL-C, creatinine, and eGFR showed a statistically significant trend across CAC score categories. We observed an increase in the proportion of patients with DM across higher CAC score categories.

### 4.2. CAC score distribution

Fig. 2 shows age-sex-specific percentiles of CAC score, with significantly higher percentiles observed in males and older age groups compared to females and younger age groups. A similar trend was observed in the subgroup analysis among patients with DM(Supplementary Fig. S1). Among patients without DM, females under 64 years old had CAC scores below 100 at the 75$^{th}$ percentile, while males in all age groups had scores above 100. A similar trend was observed in patients with DM. Females under 64 consistently had CAC scores below the 75$^{th}$ percentile, while males in all age groups had significantly higher scores. The exact CAC scores are presented in Supplementary Table S1.

**Table 1**
Baseline characteristic in each coronary artery calcium score category.

| | Missing n (%) (n = 440) | Overall (n = 440) | CAC score 0 (n = 137) | CAC score 1-10 (n = 62) | CAC score 11-100 (n = 77) | CAC score 101-40 (tn = 89) | CAC score >400 (n = 75) | P-value |
|---|---|---|---|---|---|---|---|---|
| Age (years) | 0 (0%) | 62.5 ± 10.4 | 57.5 ± 9.7 | 60.5 ± 9.09 | 63.1 ± 9.36 | 67.1 ± 9.64 | 67.5 ± 9.86 | <0.001 |
| Sex | 0 (0%) | | | | | | | |
| Male | | 208 (47.3%) | 41 (29.9%) | 30 (48.4%) | 40 (52.0%) | 48 (53.9%) | 49 (65.3%) | <0.001 |
| Female | | 232 (52.7%) | 96 (70.1%) | 32 (51.6%) | 37 (48.0%) | 41 (46.1%) | 26 (34.7%) | |
| Smoking status | 11 (2.3%) | | | | | | | |
| Current smoking | | 6 (1.4%) | 1 (0.7%) | 2 (3.3%) | 1 (1.3%) | 1 (1.2%) | 1 (1.3%) | 0.719 |
| Non-current smoking | | 424 (96.4%) | 134 (97.8%) | 59 (95.2%) | 74 (96.1%) | 83 (93.3%) | 74 (98.7%) | |
| DM status | 12 (2.7%) | | | | | | | |
| DM | | 96 (21.8%) | 24 (17.5%) | 10 (16.1%) | 15 (19.5%) | 21 (24.7%) | 26 (34.7%) | 0.056 |
| No DM | | 332 (75.5%) | 110 (80.3%) | 51 (82.3%) | 58 (75.3%) | 64 (71.9%) | 49 (65.3%) | |
| SBP (mmHg) | 19 (4.3%) | 130.8 ± 14.4 | 129.7 ± 13.3 | 131.3 ± 15.6 | 129.5 ± 15.5 | 132 ± 14.3 | 131.9 ± 14.3 | 0.313 |
| Total Cholesterol (mg/dl) | 0 (0 %) | 178.4 ± 46.5 | 185.2 ± 42.7 | 178.2 ± 41.0 | 180.6 ± 45.2 | 175.8 ± 53.8 | 165.6 ± 49.0 | 0.003 |
| LDL-C (mg/dl) | 56 (12.7%) | 114.7 ± 41.5 | 119.7 ± 38.4 | 115.4 ± 36.7 | 117.2 ± 43.0 | 114.2 ± 46.0 | 103.5 ± 42.7 | 0.006 |
| HDL-C (mg/dl) | 61 (13.8%) | 54.1 ± 14.1 | 56.2 ± 16.0 | 51.3 ± 10.5 | 53.7 ± 11.9 | 54.6 ± 14.4 | 52.9 ± 14.8 | 0.406 |
| Creatinine (mg/dl) | 32 (7.3%) | 0.98 ± 0.7 | 0.83 ± 0.2 | 0.92 ± 0.24 | 1.01 ± 0.77 | 0.95 ± 0.27 | 1.30 ± 1.3 | <0.001 |
| eGFR (mL/min/1.73m$^{2)}$ | 32 (7.3%) | 80.2 ± 19.5 | 87.2 ± 18.2 | 80.2 ± 16.8 | 77.7 ± 18.1 | 77.3 ± 15.8 | 73.8 ± 24.8 | <0.001 |

**Abbreviations:** DM, diabetes mellitus; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

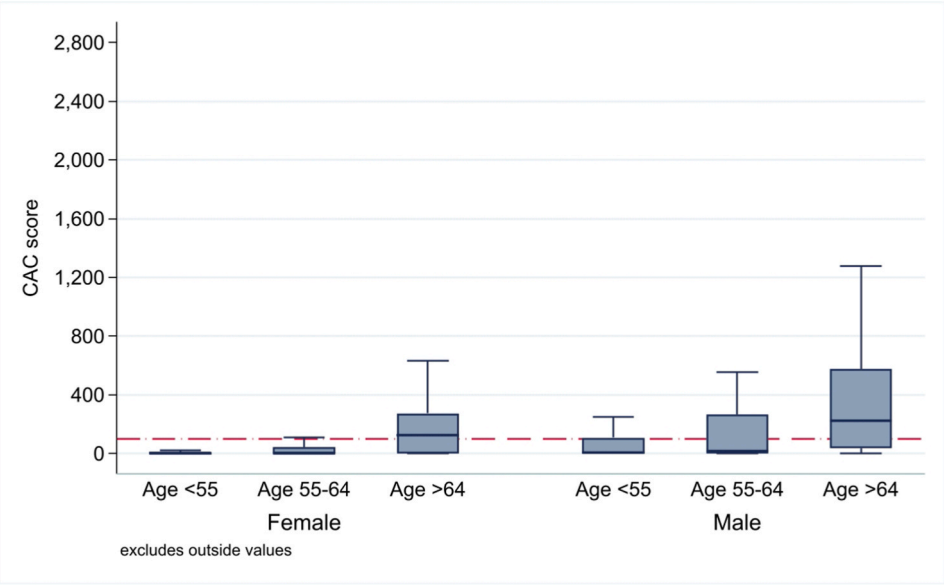


**Fig. 2.** The distribution of CAC score stratified by sex and age groups
Caption: Patients distribution in each subgroup were presented in percentile using box plot. Red solid line is CAC scores at 100. Abbreviation: CAC; coronary artery calcium.

### *4.3. The association between CAC score classifications and MACE*

A total of 82 MACEs (18.6%) occurred during follow-up (Supplementary Table S2). The median duration of follow-up was 41 months (range 18–109). The probability of MACE progressively increased with higher CAC score categories in both classifications (Fig. 3A and B). The probability remained above 25% in those with a CAC scores >100 during follow-up. Compared to CAC score of zero, patients with CAC scores >10 showed a significantly higher HR for MACE: CAC scores 11–100 (HR 5.93, 95%CI 1.63–21.55, p =

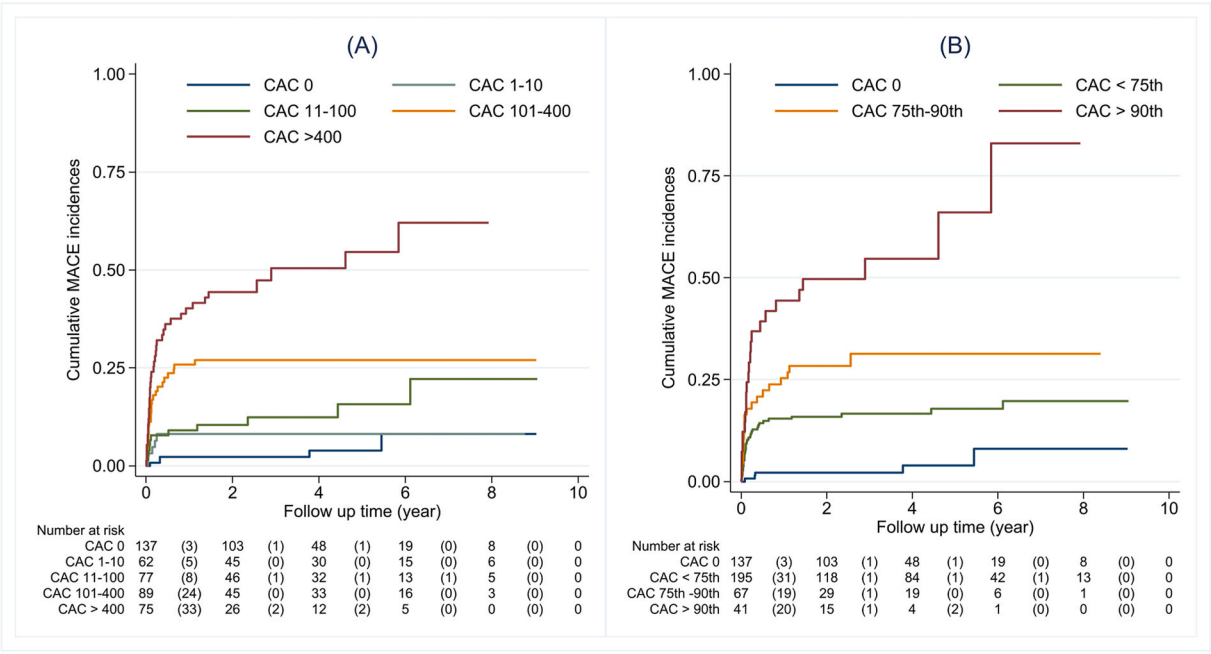


**Fig. 3.** Kaplan-Meier estimates for MACE probability for each CAC category
Caption: Fig. 3A, the estimated MACE probability in Absolute CAC score classification; Fig. 3B, the estimated MACE probability in Age-sex-specific percentile CAC score classification **Abbreviation**: CAC; coronary artery calcium.

0.007), CAC scores 101–400 (HR 10.18, 95 % CI 2.91–35.49, p ≤ 0.001), and CAC scores >400 (HR 18.40, 95%CI 5.38–62.87, p ≤ 0.001) (Table 2). Patients with CAC scores <75$^{th}$ also had a significantly increased HR for MACE (HR 4.5, 95%CI 1.34–15.09, p = 0.015) compared to patients with CAC scores of zero. The results of the subgroup analysis regarding the association with MACE are presented in Table 2.

### 4.4. Predictive performance of CAC score classifications

Both the absolute and age-sex-specific percentile CAC score classifications demonstrated similar acceptable discriminative performance based on Harrell's C statistics, with values of 0.76 (95%CI 0.72, 0.81) and 0.75 (95%CI 0.70, 0.79), respectively. The absolute CAC score classification consistently showed a Harrell's C statistics values of 0.76 (95%CI 0.72, 0.81) for both sexes. In contrast, the age-sex-specific percentile CAC score classification exhibited a slightly lower value of 0.73 (95%CI 0.68, 0.77) (Table 2).

### 4.5. Agreement between the absolute and age-sex-specific percentile CAC score classifications

In patients with the presence of CAC scores, approximately 90.7% of those with CAC scores between 1 and 100 fell below the 75$^{th}$ age-sex-specific percentile stratum, while 65% of patients below the 75$^{th}$ percentile had CAC scores less than 100. Among patients with CAC scores between 101 and 400, 71.9% were categorized below the 75$^{th}$ percentile with only 23.6% within the 75$^{th}$ and 90$^{th}$ percentiles. Additionally, only 6.7% of patients with CAC scores greater than 400 were categorized below the 75$^{th}$ percentile (Table 3). The linear-weighted Cohen's Kappa indicated fair agreement between the two classifications, at 0.51 (95% CI 0.42–0.59).

**Table 2**
Incident rate and Hazard ratio for absolute and age-sex-specific cut-points with subgroup analysis for sex.

| | n | MACE events | Incidence rate (1000 person-years) | aHR (95% CI) | P-value | Harrell's C-statistics* (95% CI) |
|---|---|---|---|---|---|---|
| CAC score (Agatston) | | | | | | |
| **Overall event (%)** | | | 82 (18.6) | | | |
| **(log transform)** | | | – | 1.57 (1.37–1.79) | <0.001 | |
| **Absolute score** | | | | | | 0.76 (0.72–0.81) |
| 0 | 137 | 5 | 9.9 (4.1–23.9) | 1.00 (Reference) | | |
| 1-10 | 62 | 5 | 20.3 (5.9–70.3) | 1.61 (0.32–8.12) | 0.563 | |
| 11-100 | 77 | 11 | 40.6 (14.1–116.8) | 5.93 (1.63–21.55) | 0.007 | |
| 101-400 | 89 | 24 | 87.9 (33.6–230.5) | 10.18 (2.91–35.49) | <0.001 | |
| >400 | 75 | 37 | 258.2 (101.5–656.8) | 18.40 (5.38–62.87) | <0.001 | |
| **age-sex-specific percentile** | | | | | | 0.75 (0.70–0.79) |
| 0 | 137 | 5 | 9.9 (4.1–23.9) | 1.00 (Reference) | | |
| < 75$^{th}$ | 195 | 34 | 49.1 (19.2–125.5) | 4.5 (1.34–15.09) | 0.015 | |
| 75$^{th}$-90$^{th}$ | 67 | 20 | 115.7 (43.4–308.3) | 10.30 (2.97–35.70) | <0.001 | |
| >90$^{th}$ | 41 | 23 | 339.0 (128.7–890.4) | 18.75 (5.43–64.75) | <0.001 | |
| **Subgroup analysis in men** | | | | | | |
| **Absolute score** | | | | | | 0.76 (0.72–0.81) |
| 0 | 41 | 3 | 20.8 (6.7–64.6) | 1.00 (Reference) | | |
| 1-10 | 30 | 3 | 26.0 (5.2–128.8) | 2.05 (0.18–23.83) | 0.566 | |
| 11-100 | 40 | 8 | 52. (13.9–198.6) | 8.46 (1.03–69.04) | 0.046 | |
| 101-400 | 48 | 12 | 80.1 (22.7–283.7) | 10.34 (1.26–84.84) | 0.030 | |
| >400 | 49 | 26 | 278.3 (84.2–919.4) | 18.40 (2.37–143.06) | 0.005 | |
| **age-sex-specific percentile** | | | | | | 0.73 (0.68–0.77) |
| 0 | 41 | 3 | 20.8 (6.7–64.6) | 1.00 (Reference) | | |
| <75$^{th}$ | 116 | 24 | 59.3 (17.7–197.0) | 6.97 (0.91–53.22) | 0.061 | |
| 75$^{th}$–90$^{th}$ | 31 | 13 | 178.9 (51.0–627.5) | 14.25 (1.76–115.09) | 0.013 | |
| >90$^{th}$ | 20 | 12 | 360.7 (101.7–1278.2) | 19.20 (2.28–161.60) | 0.007 | |
| **Subgroup analysis in women** | | | | | | |
| **Absolute score** | | | | | | 0.76 (0.72–0.81) |
| 0 | 96 | 2 | 5.6 (1.3–22.2) | 1.00 (Reference) | | |
| 1-10 | 32 | 2 | 15.4 (2.2–109.5) | 1.18 (0.10–13.54) | 0.894 | |
| 11-100 | 37 | 3 | 25.2 (4.2–151.0) | 3.39 (0.56-2-.61) | 0.186 | |
| 101-400 | 41 | 12 | 97.7 (21.9–436.7) | 11.65 (2.41–56.38) | 0.002 | |
| >400 | 26 | 11 | 220.6 (48.9–995.1) | 21.80 (4.59–103.56) | 0.000 | |
| **age-sex-specific percentile** | | | | | | 0.73 (0.68–0.77) |
| 0 | 96 | 2 | 5.6 (1.3–22.2) | 1.00 (Reference) | | |
| <75$^{th}$ | 79 | 10 | 34.8 (7.6–158.9) | 3.52 (0.71–17.49) | 0.124 | |
| 75$^{th}$–90$^{th}$ | 36 | 7 | 70.2 (14.6–337.9) | 7.63 (1.56–37.46) | 0.012 | |
| >90$^{th}$ | 21 | 11 | 318.4 (70.5–1436.2) | 23.91 (5.09–112.33) | <0.001 | |

P values were estimated from Cox regression. *, Harrell's C-statistics was estimated from from a univariable Cox proportional hazards model **Abbreviations:** CI, confidence interval; aHR, adjusted hazard ratio.

**Table 3**
Degree of disagreement between the absolute and age-sex-specific cut-point represented by the inconsistency of CAC proportion and weighted Cohen's Kappa.

| | $< 75^{th}$ | $75^{th}$-$90^{th}$ | $> 90^{th}$ | Total |
|---|---|---|---|---|
| **CAC 1–100** | 126 (64.6%) (90.7%) | 13 (19.4%) (9.4%) | 0 (0%) 0 (0%) | 139 (100%) |
| **CAC 101–400** | 64 (32.8%) (71.9 %) | 21 (31.3%) (23.6%) | 4 (9.8%) (4.4%) | 89 (100%) |
| **CAC > 400** | 5 (0.03%) (6.7%) | 33 (49.3%) (44%) | 37 (90.2%) (49.3%) | 75 (100%) |
| **Total** | 195 (100%) | 67 (100%) | 41 (100%) | 303 |
| **Linear-weighted agreement** | 79.5% | | | |
| **Linear-weighted Cohen's Kappa (95% CI)** | 0.51 (0.42–0.59) | | | |

**Abbreviations:** CI, confidence interval.

### *4.6. Comparison between the absolute and age-sex-specific percentile CAC score classifications*

Classification based on the absolute CAC score exhibited acceptable discrimination, with Harrell's C statistics surpassing 0.70 for every age-sex specific percentile categories, comparable to the C-statistics value for the entire cohort. Conversely, the C-statistics for the age-sex specific percentile classification showed inadequate discriminative performance in each subgroup of the absolute CAC score category (Table 4).

Consistency in the association between MACE and the absolute CAC score classification was observed across all levels of age-sex-specific percentile classification, showing higher HRs in higher absolute CAC score categories (Table 4). However, the association between MACE and age-sex-specific percentile classification was not consistent across all levels of absolute CAC score classification (Table 4).

## 5. Discussion

In this study, we described the prevalence of CAC scores and their distribution of CAC score using both absolute CAC score and age-sex-specific percentile-based classifications within the Thai clinical cohort. Our findings suggest that both CAC score classifications demonstrate significant associations with MACE occurrence, with higher magnitude at higher levels of classification. However, the agreement between the two classifications was only fair, rendering it inappropriate to use them interchangeably. Our analysis indicates that the absolute CAC score classification is superior to the age-sex-specific percentile classification in providing a more robust

**Table 4**
Trending of adjusted hazard ratio by each absolute score in subgroup analysis across age-sex-specific and vice versa.

| | n (%) | aHR (95% CI) | P-value | Harrell's C-statistic (95% CI) |
|---|---|---|---|---|
| Across age-sex-specific percentile | | | | |
| CAC $<75^{th}$ | | | | 0.76 (0.72–0.81) |
| 1-100 | 126 (64.6%) | 1.00 (Reference) | | |
| 101-400 | 64 (32.8%) | 2.29 (0.92–5.71) | 0.076 | |
| >400 | 5 (0.03%) | 6.19 (1.07–35.88) | 0.042 | |
| **CAC $75^{th}$ – $90^{th}$** | | | | 0.74 (0.69–0.79) |
| 1-100 | 13 (19.4%) | 1.00 (Reference) | | |
| 101-400 | 21 (31.3%) | 5.12 (0.50–52.45) | 0.169 | |
| >400 | 33 (49.3%) | 5.63 (0.18–175.43) | 0.325 | |
| **CAC >$90^{th}$** | | | | NA |
| 1-100 | 0 (0%) | NA | NA | |
| 101-400 | 4 (9.8%) | NA | NA | |
| >400 | 37 (90.2%) | NA | NA | |
| **Across Absolute score** | | | | |
| **CAC 1–100** | | | | 0.44 (0.39–0.49) |
| Age -sex-specific $<75^{th}$ | 126 (90.7%) | 1.00 (Reference) | | |
| Age -sex-specific $75^{th}$ –$90^{th}$ | 13 (9.4%) | 1.82 (0.16–20.65) | 0.629 | |
| Age -sex-specific $>90^{th}$ | 0 (0%) | NA | NA | |
| **CAC 101–400** | | | | 0.47 (0.40–0.54) |
| Age -sex-specific $<75^{th}$ | 64 (71.9%) | 1.00 (Reference) | | |
| Age -sex-specific $75^{th}$ –$90^{th}$ | 21 (23.6%) | 0.39 (0.64–2.36) | 0.304 | |
| Age -sex-specific $>90^{th}$ | 4 (4.5%) | 0.35 (0.02–6.59) | 0.486 | |
| **CAC > 400** | | | | 0.53 (0.46–0.60) |
| Age -sex-specific $<75^{th}$ | 5 (6.7%) | 1.00 (Reference) | | |
| Age -sex-specific $75^{th}$ –$90^{th}$ | 33 (44%) | 0.50 (0.12–2.08) | 0.342 | |
| Age -sex-specific $>90^{th}$ | 37 (49.3%) | 1.40 (0.31–6.21) | 0.662 | |

**Abbreviations:** CI, confidence interval; aHR, adjusted hazard ratio; NA, not applicable.

predictive performance for risk stratification.

About 70% of patients in our cohort had CAC score, and their average CAC score was higher than in previous studies conducted in Japan, Korea, and Saudi Arabia [22,30,31]. These studies reported a higher percentage of people with CAC scores of zero, ranging from 57% to 73% [22,30,31]. The higher baseline cardiovascular risk in our cohort could be attributed to the different ways of recruiting source populations. In Korean and Japanese studies, the study population was recruited from a health check-up program, which included people in good health and low cardiovascular risk [22,30]. In contrast, our study included patients aged over 35 who were sent for CAC score testing due to the decisions made by their attending physicians. Compared to previous studies, the prevalence of the CAC scores and the average CAC scores in our cohort were similar to that of the white population in the Framingham Heart study [14]. The distribution of the CAC score was higher among males, older individuals, and patients with DM, which is consistent with previous studies [22,30–32]. The CAC score is likely to progress faster in male regardless of DM status [33]. The factors found to be associated with a higher CAC score level among our cohort included age, sex, total cholesterol, LDL-C, creatinine, and eGFR. Surprisingly, total cholesterol and LDL-C demonstrated a reverse trend across the CAC score levels. The lower cross-sectional levels of serum LDL-C and total cholesterol might be confounded by a higher frequency of lipid-lowering drug intake at higher CAC score levels.

Our results indicate that both the absolute and age-sex-specific percentile classifications of CAC scores demonstrated acceptable discriminative performance in stratifying the risk for MACE. The overall performance based on Harrell's C-statistics was comparable to previous studies [34,35]. However, the disagreement between the two classifications of CAC scores become more apparent when examining the predictive performance of one classification across different levels of another. Our study results showed that within the absolute classification, higher HRs were consistently observed in higher absolute CAC score categories, contrasting with the age-sex-specific percentile classification. This result aligns with the findings from the MESA cohort [15]. It should be noted that neither classification should be preferred over the other. According to a recent review [36], both the absolute and percentile-based classifications of CAC scores provide important information regarding MACE events. While the absolute score classification is considered the best predictor for an individual's risk in the next 5–10 years, providing short-term predictive value, the percentile-based classification offers insights into long-term prognosis and is a better predictor of lifetime risk.

This disagreement in our findings highlights the importance of considering different classification methods and their implications when assessing CAC scores in clinical practice. Based on our results, it appears that the absolute CAC score classification may be appropriate for risk stratification in this Thai clinical cohort. According to standard guidelines [16–18], statin initiation may be implied for Thai patients with an absolute CAC scores $\geq$100 or $\geq 75^{th}$ percentile due to the strong association with MACE. However, our findings suggest that the high MACE incidence rates in patients with an absolute CAC scores between 11 and 100 or those with an age-sex-specific percentile score below $75^{th}$ may not be adequately captured by current guideline recommendations for statin initiation. Considering the retrospective nature of our data, which encompassed patients who had used statins, we cannot conclude whether the current suggestion would lead to undertreatment. Therefore, large prospective studies with longer and standardized follow-up in statin-naïve patients are needed to confirm whether the current CAC score cut points are appropriate for the Thai population or whether new cut points should be identified.

This study is the first to report on the prevalence and distribution of CAC score in a clinical population in Thailand that underwent CAC score testing. Our study provides a comprehensive evaluation of the predictive performance of both absolute and age-sex-specific CAC score classifications for MACE outcomes, investigates the agreement between the two classifications, and proposes a superior classification for cardiovascular risk stratification. The findings of this study have significant implications for the development of guidelines for CAC score testing in the Thai patient population. However, there were some limitations to our study. First, this was a retrospective observational study, which may have been affected by biases during data collection and follow-up. In addition, it is possible that some patients who were lost to follow-up might represent informative censoring. However, the data were obtained from routine standardized forms with only a small proportion of missing values, nearly all variables were objective, and the MACE outcomes could be accessed via the hospital network system. Second, our institution had a higher rate of revascularization, accounting for 73% of all MACE, compared to other centers where it ranged from 6% to 42% [37–39]. This indicates that a high CAC score level may have served as a guide for a significant number of revascularizations in our study, potentially inflating the incidence of MACE. Thus, the impact of revascularization on MACE should be carefully considered as theirs might be selection bias. Third, the indication for CAC score testing in our cohort was not clearly defined and documented, and the sampling scheme was consecutive and non-probability. This means that not all patients visiting our institution had an equal chance of being offered CAC score testing, potentially affecting the generalizability of our results. Finally, our study was conducted at a single tertiary care center in Northern Thailand, so the results may only be applicable to similar clinical contexts. Further research is recommended to investigate CAC score prevalence and distribution in a health check-up or screening population in Thailand.

## 6. Conclusions

About 70% of Thai patients who underwent CAC score testing had CAC scores. The CAC score was increasingly distributed among male, elderly, and DM patients. A higher CAC score level was found to be significantly associated with a higher incidence of MACE. Both absolute and age-sex-specific percentile CAC score showed acceptable performance in predicting MACE. However, it is likely that the classification of absolute CAC score may be more robust and appropriate for risk stratification.

## Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee

of the Faculty of Medicine, Chiang Mai University (MED-2563-07435).

## Consent to participate

Informed consent was waived owing to the retrospective data collection.

## Consent to publish

This study does not contain any individual person's data in any form.

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## CRediT authorship contribution statement

**Supitcha Kitjanukit:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Srun Kuanprasert:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Pannipa Suwannasom:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Arintaya Phrommintikul:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Pakpoom Wongyikul:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Phichayut Phinyo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

## Declaration of AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT 3.5 in order to check and correct grammatical errors during the manuscript writing process. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23901.

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