Original Article

Prevalence of Calcified Coronary Plaque burden in Thais

Gumpanart Veerakul[1] ; Lertlak Chaothawee[2] ; Warut Chaiwong[3] ; Sergio Fazio[4]



Gumpanart Veerakul

[1] Preventive Cardiology Clinic, Bangkok Heart hospital, Bangkok, Thailand.
[2] Cardiac Imaging Unit, Bangkok Heart hospital, Bangkok, Thailand.
[3] BDMS Health Research Center, Bangkok Dusit Medical Services PCL., Bangkok, Thailand
[4] Stanford University, Stanford, CA.

*Address Correspondence to author:
Gumpanart Veerakul
Preventive Cardiology Clinic,
Bangkok Heart hospital,
2 soi Soonvijai 7, New petchaburi Rd.,
Bangkok 10310, Thailand.
email: gumprevention@gmail.com

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Abstract

OBJECTIVES: Although quantification of calcified coronary artery plaque burden by computerized tomography scan (coronary artery calcium score, CACS or CAC) has been validated in Western populations as a tool to predict future cardiovascular events, its role in cardiovascular disease (CVD) risk assessment remains to be established in Thais. A 10-yr prospective study in asymptomatic Thais with zero CACS has shown a rate of four times higher in CVD events compared with a report on Western subjects. In addition, the mean CACS in patients with acute coronary syndrome (ACS) or stroke was quite low, less than 50 AU. This suggests that plaque calcification may have unique drivers and predictive value in Thais. To explore this, we studied the distribution of calcified coronary plaque among male and female Thais of different ages, and with or without history of CVD.

MATERIALS AND METHODS: We retrospectively retrieved CACS (Agaston-130 method) results of a total of 4,104 Thai patients (men 62%, median age 61 years, range 30-96 years) who underwent CACS screening between 2012 and 2021, from eight Bangkok Dusit Medical Service (BDMS) chain hospitals. Median and percentile of CACS were calculated in each age range of both genders. Patients were divided in two groups, those with and those without CVD, by use of diagnostic ICD code (I20-25 for coronary artery disease and I63-69 for cerebrovascular disease). Additionally, CACS results in subjects without prior CVD were compared with those published for asymptomatic Western and Asian populations.

RESULTS: Overall, CACS scores were significantly higher in Thai men than Thai women in the same age range, with significant CAC detected ten years earlier, beginning at age of 40 years. There were 1,764 cases among those who had prior diagnosis of CVD (CAD 85.5%, stroke 15.5%), and these subjects were significantly older, with more males, and had higher CACS severity in comparison with those without CVD (CAC = 0: 14.8% vs 40.0%, CAC > 0: 85.2% vs 60.0%, respectively; $p < 0.001$). In unmatched comparisons between asymptomatic populations, absolute CACS severity (>100 AU) was highest among US subjects (23.7%), followed by Thais (14.9%) and then Koreans (11.6%). On the other hand, zero CACS was highest in Koreans (47.5%), followed by Thais (40%), and lowest in US cases (13.8%). In unmatched comparisons with results from a pooled analysis of CAC studies involving 134,336 Western subjects and 33,488 Asians, Thai men had higher CACS percentiles of 50 and 75 than those of Asians but lower than those of Western men. For Thai women, the *p*-50 and *p*-75were higher than those of Asians but close to that of Western subjects and even higher after age of 65. However, the 90th percentile in Thai men and women was closer to that of the Western group and highest among Thai women older than 65 years.

CONCLUSION: Our cross-sectional data support CVD prediction by CACS in Thais, with the higher CACS detected, the higher the likelihood of having CVD. However, the lesser severity of CACS and higher proportion of zero CACS in Thais in comparison with asymptomatic US subjects suggest the existence of differences between ethnic groups and the need for local CVD screening and prevention guidelines.

Keywords: calcified coronary plaque burden,CACS, coronary artery calcium scoring

The burden of atherosclerotic cardiovascular disease (CVD) has been rising in Asian populations over the past decade. In 2015, nearly half of the global CVD prevalence was observed among East, South and SE Asian countries.[1] In Thailand, the incidence of coronary artery disease (CAD) and stroke has consistently risen from 2007 to 2014, by 24% and 41%, respectively.[2,3] Similarly, CVD mortality has increased from 21.3 to 35.1 per 100,000 for CAD (2008-2022) and 20.8 to 58.0 per 100,000 for stroke (2008-2022).[2-4] Thus, primary CVD prevention and identification of high-risk individuals with a reliable screening tool have become an area of critical interest for the health of the Thai population.

In Western populations, quantifying calcified coronary plaque burden by computerized axial tomography (coronary artery calcium scoring, CACS), has been extensively studied, validated as an independent predictor of future CVD events, and a guide for preventive interventions.[5-8] In asymptomatic individuals, higher CACS increases the likelihood of cardiovascular events and all-cause mortality.[5,6] On the other hand, asymptomatic individuals with zero CAC have much lower rates of CVD events in the next 10-15 years (<1%) in comparison with those positive for CACS.[9,10] However, racial differences in CACS have been observed in several multi-ethnic studies,[6,11-13] and thus CVD prediction in non-Western populations may be less effective.[13] In one MESA study[11] statistically significant higher CACS were observed among Whites, in comparison to Black, Hispanic, and Chinese subjects. In addition, the prognostic implications of CACS have also differed by race and ethnicity, with Blacks and Hispanics having greater risk for all-cause and cardiovascular mortality compared with Whites and Asians with similar CACS.[13] In the KOICA study, Hans et al reported a statistically significant lower CACS among asymptomatic Koreans in comparison to matched US subjects.[14] A recent pooled-analysis of CACS percentiles confirmed that CAC percentiles are higher in Western subjects compared with Asians (mostly Koreans).[15]

In Thailand, the utility and predictive role of CACS remained to be established. Chaothawee and colleagues prospectively studied the CVD prediction by CACS in 239 healthy volunteers for a consecutive ten years and found that the total events (ACS, stroke and death) were not statistically significantly different between cases with or without calcified plaque (CAC = 0 vs CAC > 0: 8.1% vs 11.2%, $p = 0.43$). The total rate of CVD in the zero CACS cases was 5.8%, and the mean CACS in ACS and stroke cases were rather low, 32.8 (0-53) and 23.7 (0-181) respectively.[16] Since the prevalence of calcified coronary plaque in Thais was not known, we studied CACS in both CVD and non-CVD Thais and compared results of non-CVD Thais CACS with those of asymptomatic subjects of other nationalities or ethnicities.

Material and Methods

After approval from the Bangkok Hospital Institutional Review Board, we retrieved CACS results of all patients who had CAC screening check-up during 2/2012 to 3/2021, in eight BDMS chain hospitals **(Appendix 1)**, from electronic medical records. Of the total of 7,285 retrieved cases, 3,181 cases (43.6%) were excluded because of non-Thai race, Figure 1. The personal and hospital ID of 4,104 Thai cases were electronically assigned to a blinded investigator team. All of the CACS studies were performed with multi-slice CT scanner without contrast agent and measured by Agaston-130 method, AU.[17]

The diagnosis of CVD was attributed by ICD-10 codes, I20-25 for CAD and I63-67.9 for carotid and cerebrovascular disease were applied, see **Appendix 2**. These ICD codes have been used in the 10-yr prospective UK study for CVD risk prediction by machine learning.[18] Median and CACS percentile were calculated in each age range of both genders in each group.

The absolute CACS of non-CVD Thais was used to compare with those of two other unmatched populations from a cross-sectional study by Hans et al.,[14] consisting of 7,533 asymptomatic US cases (no known CAD and CAC scans between 1996 and 1999) and 15,128 asymptomatic Koreans, who underwent a health check-up in Korea between 2002 and 2014.

The percentile distribution of CACS in Thais without CVD was compared with that of other asymptomatic individuals without CVD from the pooled CAC analysis study, including 134,336 Western cases (US 89%, Brazil 2%, Europe 9%, German 5%, Iceland 4%) and 33,488 Asian cases (Koreans 92%, Japanese 5% and the US Asians 3%), available at https://www.calciumscorecalculator.com.[15]

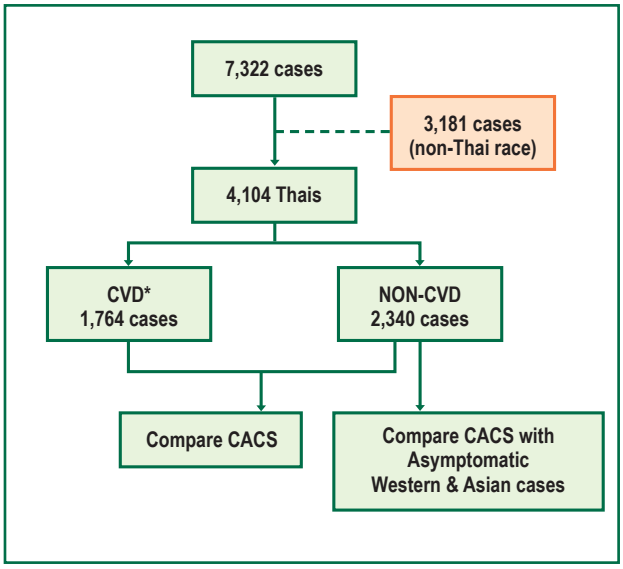


Figure 1: Study population (CVD* was defined by ICD I20-25, I63-67.9)

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Statistical Analyses

Continuous variables were displayed by mean (with SD), median and analyzed by the Student-T test and Mann-Whitney U test. Categorical data were presented as percentages and compared by the Pearson's Chi-square test. The CACS percentile was calculated in age ranging of < 40, 40-44, 45-49, 50-54, 55-59, 60-64,65-69,70-74, and above 74 years of each gender. Data preparation and analysis were performed using STATA vision 15, under the licensing of BDMS. A p-value below 0.05 was considered statistically significant.

Results

A total of 4,104 Thais who underwent CAC screening had equal mean and median age of 61 (30-96) years, and 62% of them were men. The absolute and percentile CACS of both genders are displayed in Figure 2 and Table 1.

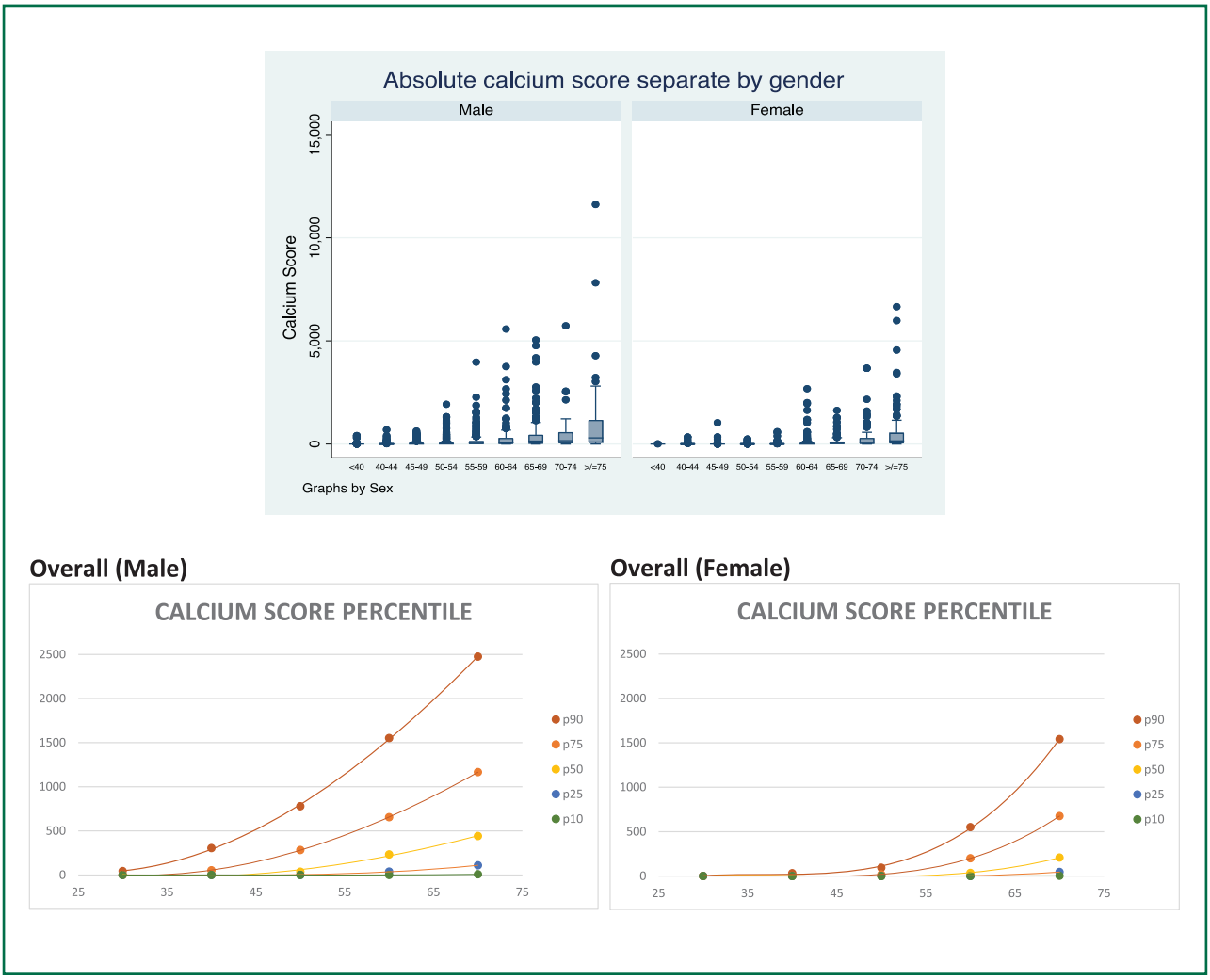


Figure 2: Overall absolute and CAC percentile distribution between gender of all 4,104 cases.

Table 1: CACS percentiles of all cases were displayed in each age range and both genders. A significantly higher percentile was noted in men than women in every age group.

	30 - 39		40 - 49		50 - 59		60 - 69		70 - 89		≥ 90		*p*- value
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	
P25	0	0	0	0	0	0	31	0	96	36	1,426	123	< 0.001
P50	0	0	1	0	29	0	212	29	390	191	1,799	641	< 0.001
P75	0	0	47	0	257	11	620	169	1,072	634	2,202	956	< 0.001
P90	36	0	255	47	718	81	1,552	490	2,320	1,492	3,027	2,327	< 0.001

A total of 1,764 cases (42.6%), had a prior diagnosis of CVD, including CAD (85.5%) and cerebrovascular diseases (14.5%), whereas 2,340 cases (57.4%) were free of prior CVD. The mean age, gender, absolute CAC severity of both groups are presented in Figure 3 and Table 2.

The absolute CACS of the non-CVD Thai group (2,340 cases), were compared with those of asymptomatic US (7,533 cases) and Korean population (15,128 cases),[14] as shown in Table 3.

The 50th,75th,90th percentile CACS for the non-CVD group were displayed in Table 4 and compared, in similar age range, with those of the pooled analysis CAC study including 134,336 Western (US 89%, Brazil 2%, Europe 9%, German 5%, Iceland 4%) and 33,488 Asian cases (Koreans 92%, Japanese 5% and the US Asians 3%); available at https://www.calciumscorecalculator.com. The results for Thais without CVD are shown in Table 4, and the comparison with others were illustrated in Figure 4-6 below.

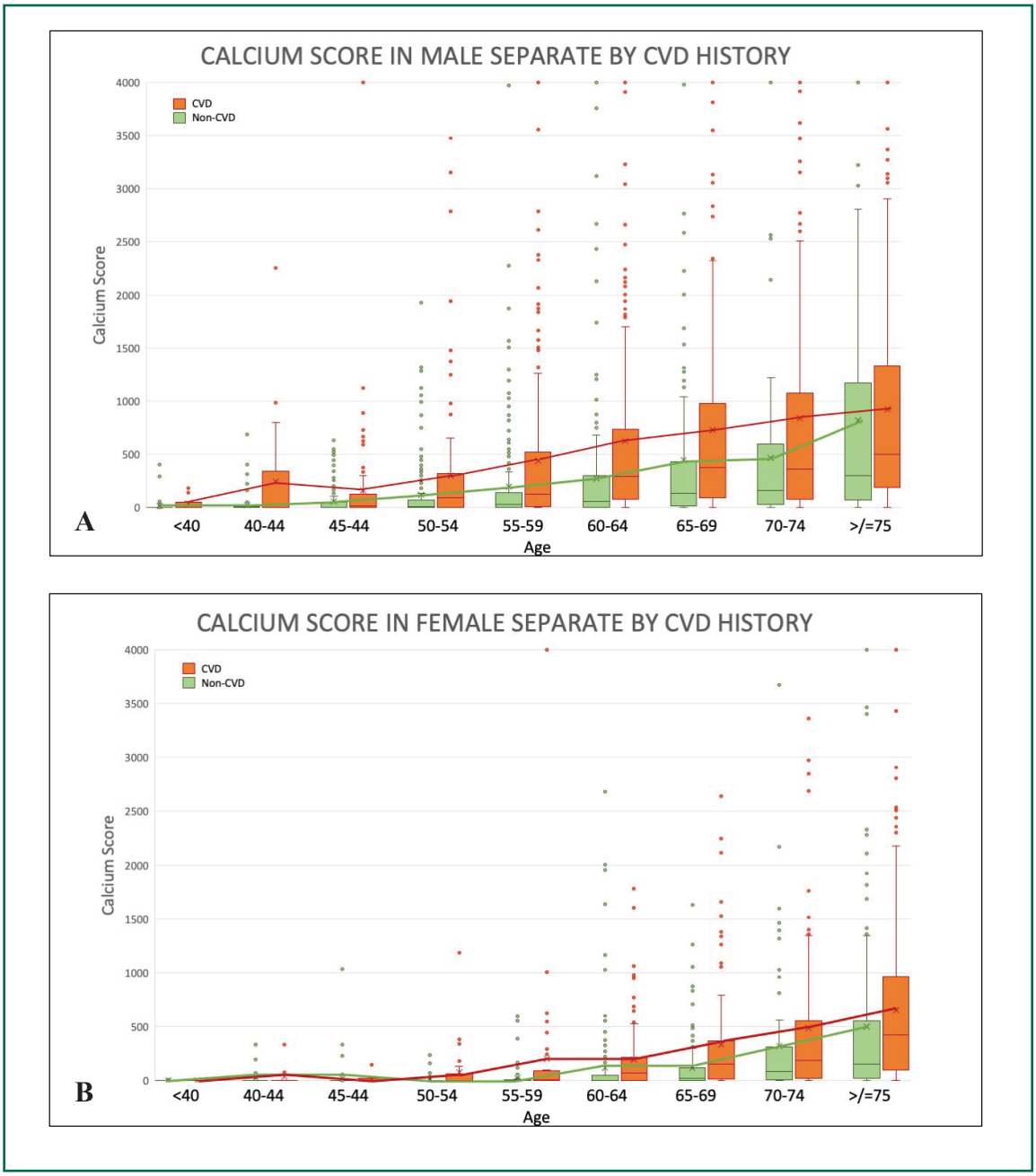


Figure 3: Absolute CACS distribution between CVD (orange) and non-CVD (green) men (A) and women (B). CACS values rose with age and were higher in the CVD group for both men and women.

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Table 2: Age, gender prevalence and severity of CACS between two groups were displayed. The age, male gender and CACS severity (CACS > 100) were significantly higher in the CVD group. In addition, a high proportion of zero CACS (14.9%) in the CVD Thais was noted.

Data	CVD	Non-CVD	*p*
	n (%)	n (%)	
n	1,764	2,340	
Age (years)			
Mean ± SD	65.1 ± 11.4	58.1 ± 12.1	< 0.001[a]
Median age (range)	65 (31-96)	58 (30 - 95)	< 0.001[b]
Age 31 - 40	29 (1.6)	29 (7.1)	< 0.001[c]
Age 41 - 50	161 (9.1)	467 (20.0)	
Age 51 - 60	420 (23.8)	720 (30.7)	
Age 61 - 70	615 (34.9)	629 (26.9)	
Age > 70	539 (30.6)	357 (15.3)	
Gender			
Men	1180 (66.9)	1369 (58.5)	< 0.001[c]
Women	584 (33.1)	974 (41.5)	
Coronary artery calcium score (CACS)			
0	262 (14.9)	936 (40.0)	< 0.001[c]
> 0 - 100	430 (24.4)	751 (32.1)	
> 100 - 400	448 (25.4)	349 (14.9)	
> 400	627 (35.3)	304 (13.0)	

a: student t-test, b: Mann-Whitney U test, c: Pearson's chi square test

Table 3: Absolute CACS severity in asymptomatic US adults, Korean and Thais (non-CVD). Significantly higher absolute CACS (CACS > 100) was observed in US, followed by Thais and Koreans while a finding of zero CACS was highest in Koreans, followed by Thais and US adults. It should be noted the non-CVD Thais had statistically significant higher mean age than others and this probably explained the highest prevalence of CAC > 400.

Variables	US adults n (%)	Korean adults n (%)	Thai adults n (%)	*p*
n	7,533	15,128	2,340	
Mean age ± SD	56.2 ± 7.7	56.2 ± 6.9	58.2±12.1	< 0.001[a]
Male (%)	4,298 (57.1)	10,398 (68.7)	1,369 (58.5)	< 0.001[b]
Coronary artery calcium score (CACS)				
0	1,040 (13.8)	7,175 (47.4)	936 (40.0)	< 0.001[b]
> 0 - 100	3,998 (53.1)	5,688 (37.6)	751 (32.1)	
> 100 - 400	1,784 (23.7)	1,748 (11.6)	349 (14.9)	
> 400	711 (9.4)	517 (3.4)	304 (13.0)	

a: Student t-test, b: Parson's chi square test

Table 4: CACS percentiles of the non-CVD Thais in different age range of both genders. Detection of CACS (>0) at 50th percentile was present, at least ten years, earlier in men than in women.

Thai-men (non-CVD) 1,369 cases										
	Age	<40	40-44	45-49	50-54	55-59	60-64	65-69	70-74	>74
	n	105	122	190	238	206	197	152	69	90
Percentile	10th	0	0	0	0	0	0	0	0	19
	25th	0	0	0	0	0	3	20	33	71
	50th	0	0	0	7	32	56	141	160	297
	75th	0	6	50	69	140	296	447	581	1,170
	90th	12	19	191	412	608	622	1,274	1,205	2,174
	95th	44	160	359	755	1,033	1,218	2,023	2,144	3,027

Thai-women (non-CVD) 971 cases										
	Age	<40	40-44	45-49	50-54	55-59	60-64	65-69	70-74	>74
	n	33	44	85	133	137	149	147	102	141
Percentile	10th	0	0	0	0	0	0	0	0	5
	25th	0	0	0	0	0	0	0	8	26
	50th	0	0	0	0	0	1	27	86	153
	75th	0	1	0	1	6	53	122	297	541
	90th	0	71	5	41	61	273	302	1,026	1,376
	95th	0	198	58	76	123	602	516	1,398	2,110

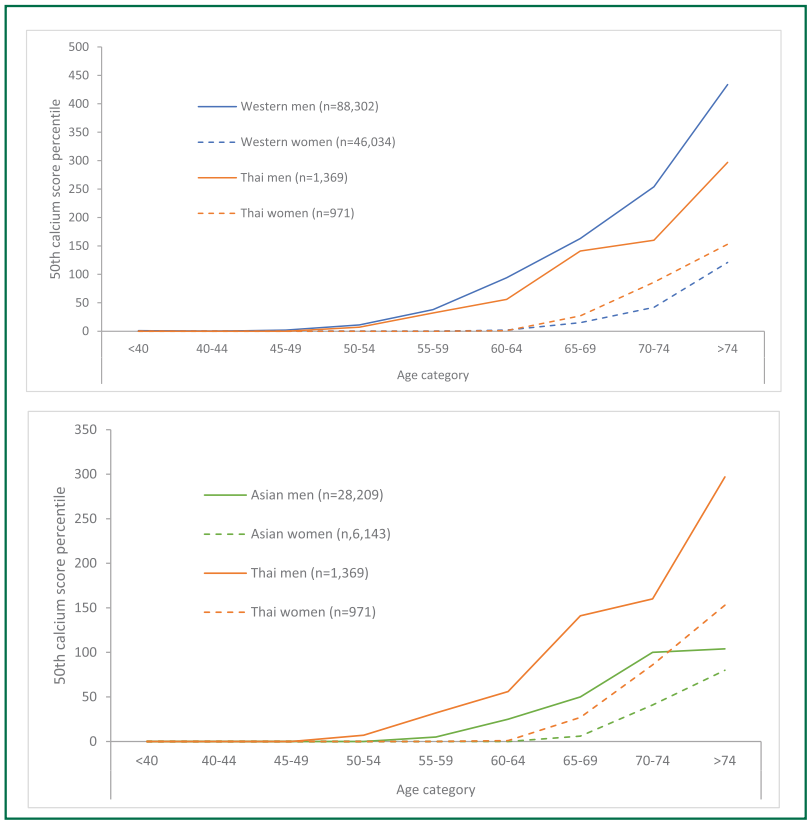


Figure 4: Comparison of the median (50th percentile) CACS between non-CVD Thais and Western (upper figure) and Asian (lower figure) populations of each gender.

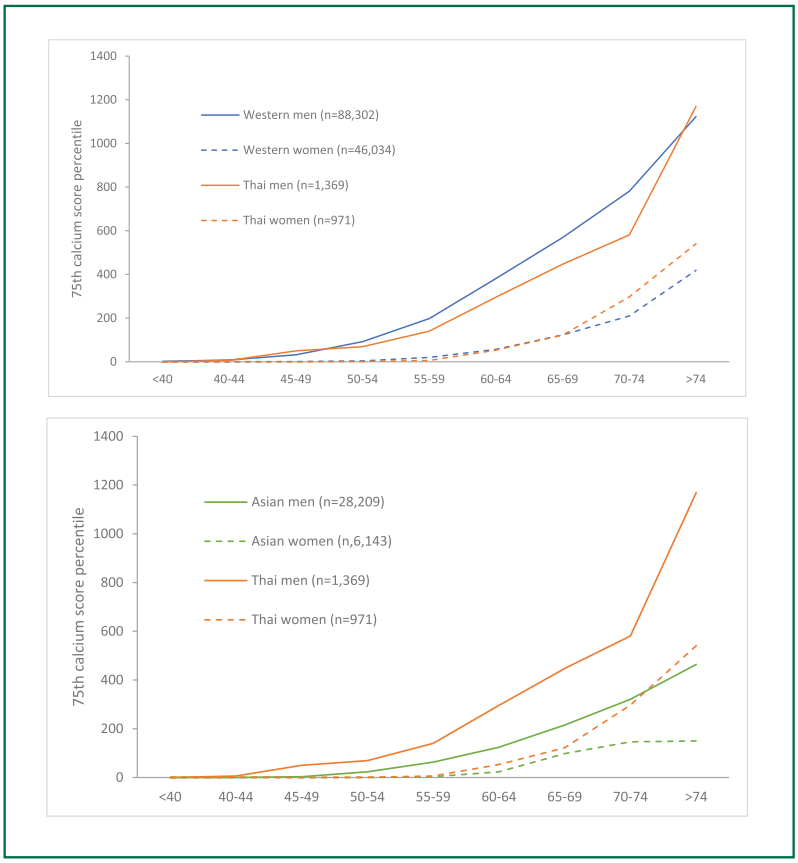


Figure 5: Comparison of the 75th CACS percentile between the non-CVD Thais and Western (upper figure) and Asian (lower figure) populations of each gender.

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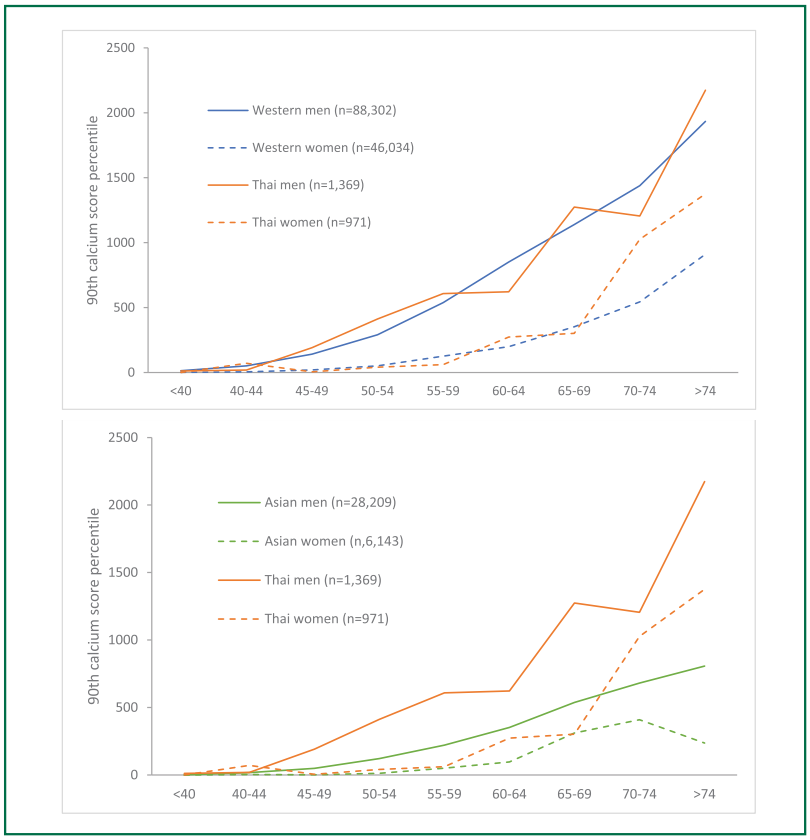


Figure 6: Comparison of the 90th CACS percentile between non-CVD Thais vs Western (upper figure) and Asian (lower figure) populations of each gender.

Discussion

Racial difference of CACS affects CVD prediction

Racial variation in coronary calcification has been documented in multi-ethnic studies[6,11-13] and could compromise the accuracy of CVD risk prediction in non-Western populations.[13] For example, a 47 years-old, non-smoker, hypercholesterolemic Thai man had CACS of 53.5 in 2006. By using data for the Chinese population instead of Thai, the calculated 10-yr MESA CHD risk[29] was only 6.7% indicating a low risk of future CVD. However, despite having normal exercise stress test and Ankle Brachial index (ABI), he developed acute anterior wall myocardial infarction in 2009 and received an uneventful stent implantation. This is a reminder that the role of CACS in CVD prediction needs to be established in Thais. From our prospective study, the mean CACS of asymptomatic Thai subjects who developed CVD events within 10 years was quite low, <50 AU.[16] These results suggested the CACS prevalence of Thais might be lower than others, so the study of calcified coronary plaque prevalence in an unselected Thai population, both with and without CVD, is of critical importance for our national screening, prevention guidelines and for the health of our citizens.

Gender difference of CACS, Thai men had higher CACS for all age ranges than women did and detected calcified coronary plaque at least ten years earlier.

Of the total 4,104 cases, Thai men had statistically significant higher CACS than women, for all age ranges **(Figure 2, Table 1).** For example, the 50th percentile of CACS in Thai women was above 0 after age of 60, while median CACS in men was higher than zero among 40-49 years old **(Table 1).** These findings might suggest the proper age of CAC screening in asymptomatic Thais, i.e. at age of 40 for men and 50 for women. This male predominance pattern was observed in other racial studies.[13,14,22,23] Generally male gender is a strong unmodifiable risk factor for CAD[24,25] since men have higher calcified coronary plaque burden,[14] presumably from differences in the balance of sex hormones,[25] and develop CVD events 7-10 years earlier than women do.[2] In asymptomatic Koreans, male gender was the strongest predictor of CACS severity.[14]

The higher the CACS, the higher the likelihood of having CVD

Calcification is a natural part of the vascular healing that occurs as part of the chronic inflammatory process in atherosclerosis. By histology, the degree of coronary calcification correlates well with atheroma stage and duration,[20] and thus CACS does reflect arterial degenerative changes.[21] These facts were endorsed by our findings **(Table 2),** where the subjects in the Thai CVD group (85.5% had CAD) were not only statistically significantly older but also had a higher proportion of male gender and higher CACS severity, than those of the non-CVD group. For example, the prevalence of CACS ≥100

of those with vs those without CVD was 61% and 28%, respectively ($p < 0.001$). Thus, it is quite reasonable to assess the feasibility of CACS for CVD prediction in Thais, as shown in one study that used absolute CACS numbers (but where 30% of cases were not Thais).[19]

High prevalence of zero CACS in CVD Thais precluded promising safety for future CVD events

It should be noted that the prevalence of zero CACS of Thai CVD group was quite high, 14.9%, three-times higher than that reported in Western studies of subjects with acute coronary syndrome (ACS), which was below 5%.[27-29] This observation supports our previous finding that zero CACS might not warrant protection against future CVD. In our 10-year prospective study, 5.8% of asymptomatic Thais candidates with zero CACS later developed either ACS or stroke.[16] It has been shown that micro-calcification not detected by conventional CT, played a major role in plaque capsule instability, leading to plaque ruptured and ACS.[30] In the MESA study, former or current smokers and diabetics with zero CACS had a much lower prevalence of future CVD than Thais, only 0.8%.[31] Since it does not seem that the protective power of zero CACS applies universally, and it is especially not true for Thais, more proper risk positioning and careful risk factors control is still mandatory for the asymptomatic Thais with absent calcified coronary plaque.

Asymptomatic (non-CVD) Thais had higher absolute CACS than Koreans but lower than US cases

In comparison with a published report from Hans et al.,[14] asymptomatic Thais generally had higher absolute CACS >100 AU (14.9%) than asymptomatic Koreans (13.7%), but lower than asymptomatic US subjects (23.7%), $p < 0.001$, see **Table 3.** In contrast, the prevalence of CACS >400 AU in Thais (13%) was higher than that of US (9.4%) and Korean subjects (3.4%), $p < 0.001$. This was possibly due to the higher mean age of Thais vs the other populations **(Table 3).** Owing to incomplete data recorded, we could not make adjustments for age, gender, and risk factors for a more rigorous comparison. On the other hand, the prevalence of zero CACS was highest in Koreans (47.5%), followed by that in Thais (40%) and lowest in US subjects (13.8%), $p < 0.001$. Reasons for these differences, likely including environmental, genetic, and behavioral contributors, remain to be determined.

Racial, gender and age difference indicated proper assessment of CACS severity by percentile rank

Regarding the influence of age and gender, it seems more reasonable to use CACS percentile in each race rather than an absolute CACS for CVD prediction. Someone with CACS above the 75th percentile (p-75) has increased risk of future coronary events, and CACS values beyond the 90th percentile (p-90) predict accelerated atherosclerosis disease.[26] Thus, we compared CACS percentiles for Thais without CVD with those of a pooled analysis study (15) involving 134,336 Western (US 89%, Brazil 2%, Europe 9%, German 5%, Iceland 4%) and 33,488 Asian subjects (Koreans 92%, Japanese 5% and the US Asians 3%). Thai men had higher *p*-50 and *p*-75 than those of Asians but lower than those of Western group. For Thai women, the *p*-50 and *p*-75 were higher than those of Asians but close to that of Western subjects and even higher after age of 65. It should be noted that the numbers of the Thai women (non-CVD) recruited beyond age of 70, >74 years were much higher than those of Thai men in that age ranges, Table 4, which might contribute to these observations. For *p*- 90, both Thai men and women were close to that of the Western group but remained higher than those of Asians, Figure 4-6. However, the lack of individual-level data of these studies precluded us from performing proper matching analyses, and thus these observations require further study.

For asymptomatic Thai subjects with no prior CVD, it is reasonable to use CACS percentile for CVD prediction

Back to our sample case, the MESA CHD Risk Score[29] underestimated a 47-years old, non-smoker, hypercholesterolemic, asymptomatic Thai man, who had a heart attack six years later, by predicting low future CVD risk (only 6.7%). However, as seen in Table 4, his CACS, 53.5 (2006), placed him above the 75th percentile for Thai men, in his age range (45-50 years), indicating a much higher future CVD risk. This case highlights the harmful effect of applying a score from an unrelated population instead of using local CACS data for CVD risk stratification.

Study limitations

Several limitations reduce the rigor and applicability of our study. First, age, gender distribution, selection criteria for screening and social status could be influenced by hospital-based referral cases. Second, information on risk exposure was limited due to incomplete records in the clinical database, and this precluded matching comparison with other populations. In addition, some risk factors, i.e. serum cholesterol and blood pressure were likely better controlled in subjects with prior diagnoses of CVD than in subjects without CVD. Third, ICD codes I20-25 and I63-67.9, included coronary, carotid and cerebral atherosclerotic disease but did not cover other vascular groups, such as peripheral and aortic diseases. Fourth, we could not exclude the presence of subclinical CVD in our population without prior CVD diagnoses, which could be as high as 4.7%.[16] Lastly, this was a cross-sectional and observational study, and thus it needs to be properly designed and longer-term studies are necessary to fully determine the role of CACS in CVD risk prediction and management.

Conclusions

Despite these limitations, our cross-sectional study provides the largest Thai CACS dataset and support a reasonable role for CACS in CVD prediction for Thai people. We confirm that, the higher CACS detected, the higher the likelihood of having CVD. The reduced CACS severity and higher proportion of zero CACS in Thais (and Koreans), in

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comparison to asymptomatic US, strongly suggest the existence of racial differences, and that proper CVD prediction and intervention should be based on local population data rather than the global standards. Finally, unlike reports from Western studies, the relative high prevalence of zero CAC in the CVD in Thais is not associated with protection and does not support the so-called "power of zero" warranty of good coronary health.

Acknowledgements

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Ethical approval

Approval was granted by the Ethics Committee of the BDMS head quarter (IRB COA.2019-060).

Informed Consent to participate was waived owing to the retrospective data collection with blinded ID.

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Disclosures

All Authors declare that there is no conflict of interest.

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Appendix 1

Eight Hospitals in Bangkok Dusit Medical Service Contributed:

1. Bangkok Hospital Headquarter
2. Bangkok Hospital Pattaya
3. Bangkok Hospital Hua Hin
4. Bangkok Hospital Chiang Mai
5. Bangkok Hospital Chiang Rai
6. Samitivej Sukhumvit Hospital
7. Samittivej Srinakarin Hospital
8. Samitivej Chinatown Hospital

Appendix 2
ICD-10 code for CVD

I20.9 Angina Pectoris,

I21 – Acute myocardial infarction

- I21.0 – ST elevation (STEMI) myocardial infarction of anterior wall
- I21.1 – ST elevation (STEMI) myocardial infarction of inferior wall
- I21.2 – ST elevation (STEMI) myocardial infarction of other sites
- I21.3 – ST elevation (STEMI) myocardial infarction of unspecified site
- I21.4 – Non-ST elevation (NSTEMI) myocardial infarction
- I21.9 – Acute myocardial infarction, unspecified

I25 – Chronic ischemic heart disease

- I25.1 – Atherosclerotic heart disease of native coronary artery
- I25.10 – Atherosclerotic heart disease of native coronary artery, without angina pectoris
- I25.11 – Atherosclerotic heart disease of native coronary artery with angina pectoris
- I25.110 – Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
- I25.111 – Atherosclerotic heart disease of native coronary artery with unstable angina pectoris, with documented spasm
- I25.118 – Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris
- I25.119 – Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris

I63.9 CVA

I63.9 Stroke

I65.23 Carotid Artery Occlusion, Bilateral

I65.23 Carotid Artery Stenosis, Bilateral

I65.29 Carotid Artery Occlusion

I65.29 Carotid Artery Stenosis

I67.2 Cerebral Atherosclerosis

I67.9 Ischemic Cerebrovascular Diseases

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