Original Article

New look at the power of zero coronary artery calcium (CAC) in Asian population: a systemic review and meta-analysis

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Background: Numerous studies have validated a 5-year warranty period for heart health in Western populations with a coronary artery calcium (CAC) score of zero. While the calcium score is a crucial cardiovascular risk indicator, its interpretation in Asian populations remains unclear. This meta-analysis aimed to clarify the uncertainty surrounding the prevalence, warranty period, and prognostic implications of zero CAC scores in Asian populations. It also examined the impact of sex on subclinical CAC progression. While the calcium score is a crucial cardiovascular risk indicator, its interpretation in Asian populations remains unclear. The study aimed to shed light on these issues by exploring the specificities of subclinical CAC progression in the Asian context.

Methods: Our systematic literature search, from the study's inception to October 2023, targeted studies on subclinical CAC progression in the Asian population with a zero CAC score. We searched the Cochrane Library, and PubMed. The search terms included "zero score", "coronary calcification", "zero CAC score", and "CAC scan".

Results: We evaluated seven published studies through a meta-analysis and assessed the risk of bias using the Newcastle-Ottawa Scale (NOS). In this meta-analysis of three observational studies addressing zero CAC prevalence (n=7,661), the pooled prevalence of zero CAC scores in the Asian population was 18.2% [95% confidence interval (CI): 12.5–25.9%]. A significant difference in follow-up warranty period was observed between the CAC zero group and subclinical CAC progression group (mean difference, 1.26 years; 95% CI: 0.94–1.58; P<0.001). Furthermore, the conversion rate of subclinical CAC progression differed significantly between males and females (risk ratio, 2.37; 95% CI: 1.98–2.84; P<0.001). Analysis of four studies revealed a notable discrepancy in the major adverse cardiovascular event (MACE) rate between the CAC (–) and CAC (+) groups (risk ratio, 4.78; 95% CI: 2.21–10.36; P<0.001).

Conclusions: The meta-analysis of zero CAC scores in Asian populations suggested an 18.2% prevalence. A 5-year warranty period was noted, with heightened subclinical CAC progression likelihood after this duration. Additionally, sex-based differences were observed in subclinical CAC progression rates. These findings will provide clinical cardiovascular risk stratification for guiding gender-specific clinical decision-making in asymptomatic in Asian individuals.

Keywords: Zero coronary artery calcium (zero CAC); Asian population; meta-analysis; subclinical CAC progression

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Introduction

Cardiovascular disease is a leading cause of mortality globally, impacting individuals' health significantly. The coronary artery calcium (CAC) score is a powerful biomarker for cardiovascular risk stratification, independent of traditional cardiovascular risk factors (1,2). Numerous recent studies have demonstrated that people with zero CAC scores have a protective effect against subclinical CAC progression with 5 years of warranty period in Western countries (3-7). In addition, recent evidence has shown that people with zero CAC scores have a high negative predictive value for ruling out obstructive coronary artery disease (CAD) (8,9). Several studies have demonstrated that a calcium score of zero would be a powerful negative marker with cardiovascular events within 5 years of the warranty period, suggestive of "the power of zero" in Western population (10-12). However, few studies have attempted to address the effect of the warranty period and prognostic outcome of a zero CAC score in the Asian population (13-19). Additionally, the effect of sex on subclinical CAC progression is still not well understood in Asian populations. Therefore, our aim was to systematically review the literature on zero CAC scores in Asian populations and assess the quality of selected studies using the current evaluation criteria for the meta-analysis of relevant topics. Thus, this study aimed to investigate the utility of CAC scan assessment in evaluating the prevalence of subclinical coronary atherosclerosis and the natural course of subclinical CAC in an Asian population with a CAC score of zero. We also sought to investigate the warranty period and prognostic outcome of zero CAC score in the Asian population and the sex differential impacts in Asian asymptomatic populations with zero CAC scores among subjects with and without detectable CAC. We present this article in accordance with the PRISMA reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-474/rc).

Highlight box

Key findings

- This research underscores the significance of zero coronary artery calcium (CAC) scores in Asians, aligning with Western data, serving as a pivotal risk assessment tool revealing sex-based differences in CAC progression.

What is known and what is new?

- In Western countries, individuals with zero CAC scores are safeguarded from subclinical CAC progression for a 5-year warranty period.
- This study solidifies the importance of zero CAC scores with a 5-year warranty in Asians, mirroring Western findings, and highlighting sex-based disparities in CAC progression.

What is the implication, and what should change now?

- The identification of a 5-year warranty period, along with heightened subclinical CAC progression likelihood and sex-related disparities, informs clinical decisions in asymptomatic individuals for cardiovascular risk stratification and prevention.

Methods

Literature search

This meta-analysis followed the guidelines of the PRISMA statement issued in 2009. First, we performed a literature search to identify studies published in English or other languages (British English, French, and Latin) in the PubMed, and Cochrane Library. Duplicate results were removed and the remaining articles as well as all references cited in them were evaluated. Literature search strategies were independently performed by two authors (F.Z.W. and Y.J.W.) using the following search terms: "zero score", "coronary calcification", "zero CAC score", and "CAC scan" (Appendix 1). The study conducted an extensive review of relevant literature from its commencement up to October 15, 2023. The prespecified inclusion criteria were as follows: (I) Observational studies investigating the prevalence of subclinical CAC progression in an Asian population with a CAC score of zero; (II) research must be conducted in an Asian country and the study group must be of Asian ethnicity; (III) for each study, the mean difference, standard deviation (SD), and sample size of subjects in the zero CAC group (–) and CAC progression (+) groups were reported in the relevant articles; and (IV) For each study, relevant study interest related to the differential effect between sex and prognostic outcome related to

major adverse cardiovascular events (MACEs). Studies were excluded if they didn't meet inclusion criteria, lacked sufficient data, or contained duplicate information.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (20). Each study was assigned a score between 0 and 9 based on the specific criteria outlined in the scale. In this assessment, studies that achieved a score of 7 or higher were considered high quality. The overall study quality was classified as moderate [6–7] or low (<5) based on the total scores of all subscale items.

Data collection

The following information were collected from the included studies: primary 1st author, year of publication, region/area, sample size, follow-up period, and mean patient age. In line with the study's focus, we conducted a systematic literature review to identify relevant papers for each predefined research question (1-4). Subclinical CAC progression was defined as progressive developing CAC formation in participants with a baseline zero CAC score during the follow-up period. Cardiac events were defined as MACE, revascularization, or acute coronary syndrome (ACS).

The following four specific questions were asked: The prespecified study Question 1 aimed to determine the prevalence of subclinical CAC progression in the Asian population. The prespecified study Question 2 was used to determine the follow-up periods between the two groups to determine warranty periods (CAC zero group versus subclinical CAC progression group). CAC zero group is defined as a baseline examination with a calcium score of zero, and subsequent follow-up examinations with a cardiac calcium score of 0 during the follow-up time. The subclinical CAC progression group refers to individuals with no initial cardiac calcification but exhibiting new coronary calcification during the follow-up period. The warranty period encompasses the transition from zero CAC to developing CAC calcification in the follow-up CAC scan. The prespecified study Question 3 aimed to determine the impact of sex differences on the subclinical CAC progression rate in Asian populations. The prespecified study Question 4 aimed to determine the prognostic cardiac event rate in the Asian population according to the CAC (+) group and CAC (–) group. The CAC (+) group is defined as the group with presence of calcium score on CAC scan. On the contrary, the CAC (–) group is defined as the group with zero score on CAC scan. Finally, all seven published research studies that met the prespecified inclusion criteria were included in the qualitative and quantitative systematic reviews and meta-analyses. The selection process for the studies is illustrated in a flow diagram, and *Figure 1* illustrates the retrieval process. *Table 1* lists the characteristics of the seven eligible studies selected for the meta-analysis.

Statistical analysis

The statistical method of meta-analysis was used to analyze the pooling outcomes for each pre-specific question. The meta-analysis was performed using the computer program Review Manager (RevMan; version 5.4, The Cochrane Collaboration, 2020). For the for-pooled prevalence analysis, we used Onlinemeta v1.0, to determine the overall pooled prevalence of CAC progression. Heterogeneity was evaluated with Cochran's *Q*-test and I^2 value. An I^2 value close to 0% indicates homogeneity, while <25%, 25–75%, and >75% indicate low, moderate, and high heterogeneity, respectively. In cases of an I^2 value higher than 50%, a random effect model was used; two-sided P values <0.05 were considered significant. Additionally, all reports with their corresponding 95% confidence intervals (CIs) were calculated in term of generalized linear mixed model (GLMM), risk ratio, and mean difference.

Results

Study selection and characteristics

A total of 2,345 articles were identified after searching the databases. After omitting duplicated or ineligible studies, 931 articles were further screened for title and abstract. Of these, 10 articles were selected for full-text review. Finally, seven articles were included in the data quality assessment and data analysis. The study selection process is shown in *Figure 1*. A total of 11,513 patients were studied in all included papers. The mean age of the included patients ranged from 48.00 to 58.84 years. The study characteristics of the included studies are summarized in *Table 1*.

The prevalence of CAC progression in Asian population with zero CAC score

All seven published studies that met the inclusion criteria were considered eligible for further meta-analysis. Of the seven articles evaluated, five obtained NOS scores of 7 or higher, indicating that they were classified as high-quality. On the other hand, the remaining two papers received a

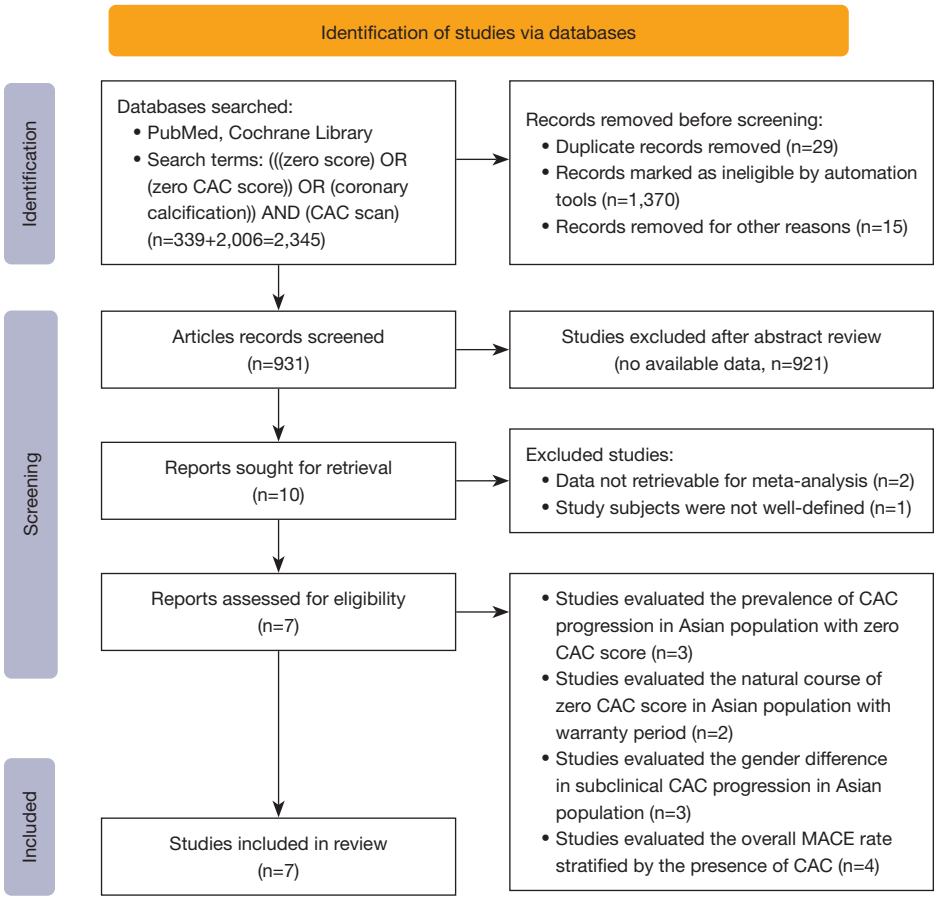

Figure 1 Flowchart for identifying eligible relevant studies on subclinical CAC progression in Asian population with zero CAC score. CAC, coronary artery calcium; MACE, major adverse cardiovascular event.

Table 1 Characteristics of seven included studies in each meta-analysis

No.	First author	Time	No. of patients	Age (years)	Region/area	Follow-up period (years)
1	Shen *et al.* (15)	2020	459	51.42±8.44	Taiwan	4.67±2.46
2	Lee *et al.* (14)	2019	6,268	48.00±7.10	Korea	9.08
3	Yang *et al.* (19)	2023	934	Female: 52.22±7.92	Taiwan	4.35±2.37
				Male: 50.67±8.35		
4	Kim *et al.* (13)	2012	2,088	58.6±9.8	Korea	2.83
5	Ueda *et al.* (18)	2012	753	64.7±10.7	Japan	2.17
6	Tay *et al.* (17)	2017	509	Female: 58.84±10.00	Taiwan	3.00
				Male: 57.79±10.60		
7	Shiga *et al.* (16)	2020	502	CAC =0 (n=202): 62±12	Japan	3.5±0.6
				CAC >0 (n=300): 69±9		

Data are expressed as mean ± SD or mean. CAC, coronary artery calcium; SD, standard deviation.

Table 2 Quality of seven included studies in meta-analysis assessed using NOS for non-randomized studies

No.	First author	Representatives of exposed cohort	Selection of control group	Exposure ascertainment	Outcome of interest	Comparability	Outcome assessment	Adequacy of follow-up duration	Adequacy of follow-up cohorts	Total
1	Shen *et al.* (15)	1	1	1	1	1	1	1	1	8
2	Lee *et al.* (14)	1	1	1	1	1	1	1	1	8
3	Yang *et al.* (19)	1	1	1	1	1	1	1	1	8
4	Kim *et al.* (13)	1	1	1	1	1	1	1	1	8
5	Ueda *et al.* (18)	1	1	1	0	1	0	1	0	5
6	Tay *et al.* (17)	1	1	1	0	1	0	1	0	5
7	Shiga *et al.* (16)	1	1	1	1	1	1	1	0	7

NOS, Newcastle-Ottawa Scale.

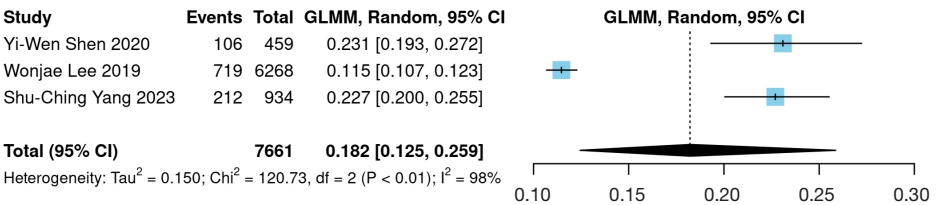

Figure 2 Forest plot demonstrating pooled prevalence of subclinical CAC progression in Asian population with baseline zero CAC score. GLMM, generalized linear mixed model; CI, confidence interval; CAC, coronary artery calcium.

Table 3 Demographics of included studies in investigation of the prevalence of subclinical CAC progression

References	Year	No. of patients (baseline zero CAC)	Subclinical CAC progression (event)†	Region/area	Follow-up period (years)
Shen *et al.* (15)	2020	459	106	Taiwan	4.67±2.46
Lee *et al.* (14)	2019	6,268	719	Korea	9.08
Yang *et al.* (19)	2023	934	212	Taiwan	4.35±2.37

Data are expressed as mean ± SD or mean. †, the subclinical CAC progression is defined as individuals with zero calcium scores at baseline but subsequent developing CAC calcification in the follow-up CAC scan. CAC, coronary artery calcium; SD, standard deviation.

score of five points, which suggests they are of medium quality according to the NOS (summarized in *Table 2*). The results of the meta-analysis are presented in *Figure 2* and include three studies (summarized in *Table 3*). The overall pooled prevalence of subclinical CAC progression in Asian population with the baseline zero CAC score was 18.2% (95% CI: 12.5–25.9%) in a random-effect pooled analysis of these studies. Cochran's Q was significant (Q =120.73; df =2; P<0.01), suggesting heterogeneity across the prevalence estimates; the I^2 statistic was 98%, indicating very high heterogeneity.

Natural course of zero CAC score in Asian population with warranty period

Based on the natural course of CAC formation in the Asian population with a baseline CAC score of zero, patients were divided into CAC zero group and subclinical CAC progression group to analyze the average follow-up period between the two groups. The results of the meta-analysis are presented in *Figure 3*, including those of two studies (summarized in *Table 4*). With regard to the follow-up period in Asian people with baseline zero CAC score, there was a significant difference in the mean follow-up period

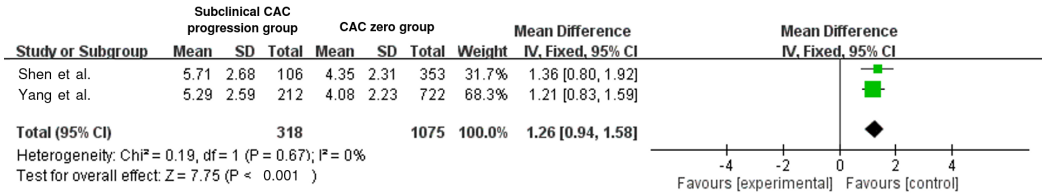

Figure 3 Forest plot with warranty period in subjects with CAC zero group and subclinical CAC progression group according to subclinical CAC progression status. CAC, coronary artery calcium; SD, standard deviation; IV, interval variable; CI, confidence interval.

Table 4 Demographics of included studies in investigation of warranty follow-up period according to CAC zero group and subclinical CAC progression group

References	Year	No. of patients	CAC zero group†			Subclinical CAC progression group‡		
			Mean years	SD	Total	Mean years	SD	Total
Shen *et al.* (15)	2020	459	4.35	2.31	353	5.71	2.68	106
Yang *et al.* (19)	2023	934	4.08	2.23	722	5.29	2.59	212

†, the CAC zero group is defined as individuals with zero calcium scores on both baseline and follow-up cardiac calcium scans; ‡, the subclinical CAC progression group is defined as individuals with zero calcium scores at baseline but subsequent developing CAC calcification in the follow-up CAC scan. CAC, coronary-artery calcium; SD, standard deviation.

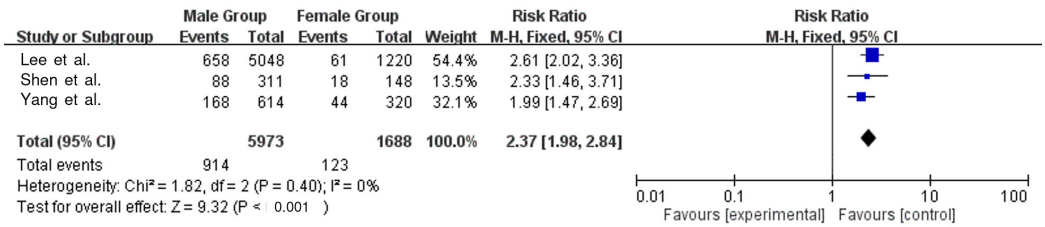

Figure 4 Forest plot demonstrating the impact of gender effect on subclinical CAC progression in Asian population with baseline zero CAC score. M-H, Mantel-Haenszel; CI, confidence interval; CAC, coronary artery calcium.

between CAC zero group and subclinical CAC progression group (mean difference, 1.26 years; 95% CI: 0.94–1.58; P<0.001) in a fix-effect pooled analysis of these studies. No statistically significant heterogeneity was observed in the results (P=0.67; I^2=0%).

Gender difference in subclinical CAC progression in Asian population

With regard to the effect of sex difference on the natural course of subclinical CAC progression in Asian people with a baseline CAC score of zero, the participants were divided into male and female groups to analyze the conversion rate of subclinical CAC progression between the two groups. The results of the meta-analysis are presented in *Figure 4* and include three studies (summarized in *Table 5*). There was a significant difference in the conversion rate of subclinical CAC progression between male and female groups (risk ratio, 2.37; 95% CI: 1.98–2.84; P<0.001) in a fixed-effect pooled analysis of these studies. No evidence of statistically significant heterogeneity was observed in the study results (P=0.40; I^2=0%).

Overall MACE rate stratified by the presence of CAC

With regard to the status of the presence of CAC or not in Asian population, it was divided into CAC (–) group and CAC (+) group to analyze the MACE rate among the two groups. The results of the meta-analysis, including four eligible studies with a total of 3,852 participants

Table 5 Demographics of included studies in investigation of subclinical CAC progression according to gender difference

References	Year	No. of patients	Male group		Female group		Region/area	Follow-up period (years)
			Total	Event	Total	Event		
Shen *et al.* (15)	2020	459	311	88	148	18	Taiwan	4.67±2.46
Lee *et al.* (14)	2019	6,268	5,048	658	1,220	61	Korea	9.08
Yang *et al.* (19)	2023	934	614	168	320	44	Taiwan	4.35±2.37

Data are expressed as mean ± SD or mean. CAC, coronary artery calcium; SD, standard deviation.

Table 6 Demographics of included studies in investigation of overall MACE rate according to CAC (+) and CAC (–) group

References	Year	No. of patients	CAC (–)†		CAC (+)‡		Region/area	Follow-up period (years)
			Total	Event	Total	Event		
Kim *et al.* (13)	2012	2,088	1,114	14	974	46	Korea	2.83
Ueda *et al.* (18)	2011	753	260	4	493	83	Japan	2.17
Tay *et al.* (17)	2017	509	227	0	282	13	Taiwan	3.00
Shiga *et al.* (16)	2020	502	202	10	300	36	Japan	3.5±0.6

Data are expressed as mean ± SD or mean. †, the CAC (–) group is defined as the group with zero score on CAC scan; ‡, the CAC (+) group is defined as the group with presence of calcium score on CAC scan. MACE, major adverse cardiac events; CAC, coronary artery calcium; SD, standard deviation.

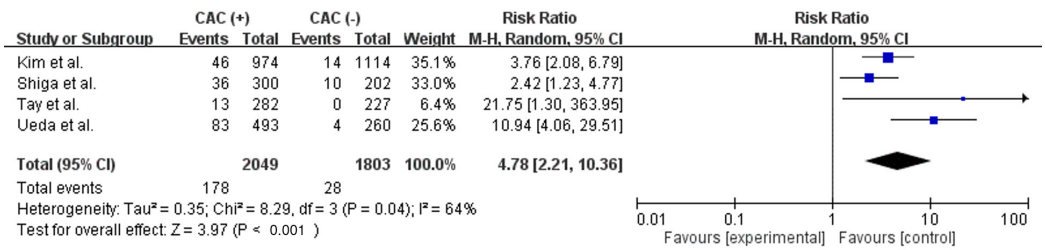

Figure 5 Forest plot with MACEs in subjects with CAC (–) group and CAC (+) group. The CAC (–) group is defined as the group with zero score on CAC scan; the CAC (+) group is defined as the group with presence of calcium score on CAC scan. CAC, coronary artery calcium; M-H, Mantel-Haenszel; CI, confidence interval; MACE, major adverse cardiovascular event.

(summarized in *Table 6*), are presented in *Figure 5*. There was a significant difference in the MACE rate between CAC (–) and CAC (+) groups (risk ratio, 4.78; 95% CI: 2.21–10.36; P<0.001) in a random-effect pooled analysis of these studies. A moderate degree of heterogeneity was observed among the studies (P=0.04; I^2=64%).

Discussion

The present systematic review and meta-analysis illustrated four important points in the Asian population with a baseline CAC score of zero. First, the pooled prevalence of CAC progression in Asian population with zero CAC score is about 18.2% (range, 12.5–25.9%). Second, to explore the natural history of CAC development between the two groups, there were significant differences between the two groups (CAC zero group versus subclinical CAC progression group: +1.26 years in mean difference according to pooled meta-analysis; reference group: CAC zero group). Third, compared with female group, male group have 2.37 times the risk of CAC development according to pooled meta-analysis. Fourth, those who had CAC have 4.78 times higher risk of MACE than those with a zero CAC score in the pooled meta-analysis. This systematic

review meta-analysis was the first to address the natural course in Asian populations with a zero score in terms of the prevalence of subclinical CAC conversion, warranty period of CAC conversion, sex difference effect, and MACE rate. These findings offer valuable insights for the Asian population, particularly in the field of cardiovascular preventive medicine.

Recent studies have demonstrated that CAC scoring and classification assessed by CAC scans have been used as biological gatekeepers for noninvasive cardiovascular risk stratification (21-23). Recently, CAC scanning has been endorsed by the 2019 American College of Cardiology/American Heart Association (ACC/AHA) guidelines as a class IIa recommendation for the Primary Prevention of Cardiovascular Disease for the use of CAC quantification in intermediate-risk populations to improve cardiovascular risk assessment (24). Many recent studies have confirmed that people with a calcium score of zero have a relatively low risk of MACE with a warranty period of 5-year a zero CAC score in Western populations with an intermediate risk for atherosclerotic cardiovascular disease (ASCVD) (25,26). However, few studies have attempted to address this issue in Asian population (13,16-18). In this systematic review and meta-analysis, we attempted to address the warranty period in an Asian population with zero CAC score and the prevalence of subclinical CAC progression from a baseline zero CAC score. With regard to the prevalence of subclinical CAC progression, the pooled average prevalence of subclinical CAC progression in Asian population was 18.2% (95% CI: 12.5–25.9%; I^2=98%). However, the heterogeneity among the studies may be due to differences in the cardiovascular risk percentiles and follow-up periods of the subjects. Lee *et al.* investigated a study cohort of 6,268 subjects with low cardiovascular risk during follow-up period of 9 years (14). Finally, approximately 11.4% of patients developed subclinical CAC progression. For the low-to-intermediate Framingham risk score percentile in the Asian population with a baseline CAC score of zero, Shen *et al.* confirmed that the CAC progression rate was approximately 23.09% during a follow-up period of 5 years (15). In addition, regarding the warranty period of zero CAC scores in Asian populations, people with zero CAC have a warranty period of 4.08 to 4.35 years. In people with CAC progression from zero CAC group, the average follow-up duration was within the range of 5.29 to 5.71 years. The study findings also support the warranty period to perform a subsequent CAC scan with a follow-up period of 3–5 year after the baseline CAC score of zero in patients at intermediate ASCVD risk (11). In the future, there is a need for large, multicenter studies involving diverse populations to further validate the endorsement of a warranty period for subsequent coronary artery calcium (CAC) scans. This would involve establishing follow-up intervals of 3–5 years after an initial CAC score of zero, especially for individuals at intermediate ASCVD risk. The relevance of this approach to the Asian population underscores the necessity for such studies to address the existing knowledge gap specific to this demographic. These efforts would contribute to the refinement of risk assessment and management strategies tailored to the unique characteristics and susceptibilities of individuals within the Asian population.

Regarding sex differences in CAC progression, the MESA study in Western countries demonstrated that men have a higher rate of CAC progression than women (27). In addition, CAC scores were generally higher in men than in women within the same age percentile (28). However, studies regarding the differences in CAC progression by sex in Asian populations are sparse. When comparing subclinical CAC progression between male and female groups, three studies, including a total of 7,662 participants, were enrolled. Meta-analysis showed a significant difference in the event rate of subclinical CAC progression in Asian population with zero CAC score (risk ratio, 2.37; 95% CI: 1.98–2.84; P<0.001) with no heterogeneity observed across studies. Evidence from this systematic review and meta-analysis suggests a possible role of sex differences in the development of subclinical CAC progression in the middle-aged Asian population. Compared to women, men with low to intermediate cardiovascular risk have an estimated two-fold increased risk of subclinical CAC formation. In addition, previous studies have demonstrated that the magnitude of the difference in subclinical CAC progression between men and women diminishes with increasing age or cardiovascular risk percentile (28). Therefore, according to a meta-analysis of empirical evidence, disparities observed between men and women in subclinical coronary atherosclerosis can serve as a basis for developing sex-specific cardiovascular risk prevention strategies. These strategies can inform gender-specific approaches to clinical decision-making.

In this systematic review and meta-analysis, we compared MACE in subjects in the zero CAC group versus the non-zero CAC group in an Asian population, and the

results showed that a zero CAC score was an independent predictor of subsequent MACE during a follow-up period of 3 years. According to the pooled analysis from the meta-analysis, the CAC (+) group showed a 4.78-fold increased risk of MACE compared to the CAC (–) group in the Asian population with stable chest pain. Previous studies have demonstrated that subjects with zero CAC scores have a very low annualized MACE event rate of 0.5% in Western countries during a follow-up period of approximately 2 years (8). We also observed a very low MACE rate (0% to 0.7%) in the Asian population with a zero CAC score. These findings also support that a zero CAC score is a value-based protective gatekeeper for the Western population with suspicion of CAD, as well as for the Asian population. Overall, the current systematic review and meta-analysis supports the use of zero CAC as a strong negative risk marker for MACE in both Western and Asian populations to guide downstream cardiovascular risk stratification. The study identified obstacles and guiding directions for future research. However, the current studies included have an observation period of approximately 2.17 to 3.5 years. Therefore, future research will still require multi-center prospective studies to investigate the impact of coronary calcification for over 10 years on cardiac events.

Limitation

Finally, this systematic review and meta-analysis had three major limitations. First, this meta-analysis included only three studies investigating sex effects. Therefore, larger studies are needed to clarify the subgroup effects on the effect of a zero CAC score. Second, our pooled analysis could not differentiate outcomes based on different ASCVD risk percentiles because of the insufficient accessibility of the available data. Further studies based on different ASCVD risk percentiles and subgroup MACE rates are warranted. Third, there were uncharted territories with a CAC score with the development of non-calcified soft plaques in the coronary arteries. According to previous literature reviews, young subjects tend to have more soft plaque formation in the coronary trees than older ones (27). Therefore, it is important to identify subjects with zero CAC scores who are at high risk of developing obstructive CAD in the future. Few studies have addressed prediction models to identify subjects with double-zero scores for obstructive CAD (15,29). The unknown areas related to a zero CAC score still need to be further investigated in the field of preventive medicine using cardiovascular imaging.

Conclusions

In summary, this systematic review and meta-analysis reaffirms the value of power of zero with a warranty period of 5 years in the Asian population. Accumulating evidence in Asian region/area is consistent with results in Western countries.

This suggests that an important role of zero CAC role as a biological gatekeeper in cardiovascular risk stratification and prognostic outcome prediction in Asian populations. In the future, additional research is needed to address the sex difference effect based on a large cohort with different percentile rankings and the development of double-zero scores with obstructive CAD to identify high-risk subjects with zero CAC scores in a preventive cardiology healthcare setting.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-474/rc

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-474/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-474/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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