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# Natural course of coronary artery calcium progression in Asian population with an initial score of zero

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## Abstract

**Background:** We aimed to investigate the natural course of coronary artery calcium progression in an Asian population with a baseline coronary artery calcium (CAC) score of zero, and to determine subclinical coronary atherosclerosis.

**Methods:** Four hundred fifty-nine subjects with at least two CAC scans with an initial score of zero were included. CAC progression (+) was defined by the development of any CAC (i.e., CAC > 0) during subsequent CT scans. Clinical characteristics and Framingham risk profiles were also recorded.

**Results:** Among 459 subjects, 106 (23.09%) experienced CAC progression during the average follow-up period of  $5.71 \pm 2.68$  years. Older age, male gender, HDL-C, total cholesterol and higher Framingham risk score were independently associated with CAC progression. Framingham risk score had the better discriminative ability (AUC = 0.660) to predict CAC progression compared to the other parameters with a sensitivity of 75.24% and specificity of 53.95%. For the double zero score with coronary artery atherosclerosis prediction, older age, triglycerides, hypertension, and Framingham risk score were significantly associated with these events. Among these parameters, Framingham risk score may be a relatively acceptable parameter with high negative predictive (NPV = 96.4%) value to rule out double zero score with obstructive coronary artery atherosclerosis scenario with an optimum cut-off value of <16.9 (AUC = 0.652, sensitivity of 57.69%; specificity of 68.82%).

**Conclusions:** A baseline zero CAC score in asymptomatic Chinese population with low to intermediate risk have a low incidence for CAC progression within the 5-years period. For CAC progression prediction, Framingham risk score with the cutoff < 11.1 may help confirm subjects at low risk to improve cardiovascular risk stratification and reclassification in the field of preventive cardiology.

**Keywords:** Coronary artery calcium, Zero score, vulnerable plaque

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## Background

Coronary artery calcification is considered being characteristic of subclinical atherosclerosis burden. In recent years, coronary artery calcium (CAC) scoring assessed by computed tomography has been proposed as a gatekeeper for non-invasive coronary artery diseases stratification and reclassification [1–7]. Many studies have investigated that CAC progression may be more predictive of future cardiac events than traditional cardiovascular risks [8–10]. Therefore CAC scanning has now been given a class IIa recommendation by the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease for the use of CAC quantification in intermediate risk population to improve cardiovascular risk assessment [11–13].

Recent studies have demonstrated that individuals with calcium score of zero have a very low risk of coronary artery disease (CAD) with a warranty period of 5 years in Western population [9, 14–16]. There is limited evidence that absence of CAC has a protective effect against CAD in non-Western populations [8, 17]. The natural course of CAC progression in Asian population remains to be established according to different Framingham risk scores. In addition, recent studies have showed that absence of coronary artery calcification does not completely exclude obstructive coronary artery disease, but the prevalence is variable between 1 to 20% [18–23]. It is important to determine clinical parameters for predict obstructive CAD in this clinical scenario. Therefore, using an Asian cohort of low to intermediate risk stratification by Framingham Risk Score, we aimed to investigate the natural course of coronary artery calcium progression in an Asian population with a baseline CAC score of zero, and to determine CAC progression according to different risk stratification algorithm. In addition, we identified independent clinical parameters in prediction of CAC progression and obstructive coronary artery atherosclerosis in the clinical scenario of double-zero score.

## Methods

### Study population

Between April 2005 and March 2017, we identified 459 subjects with the baseline CAC score of zero who underwent 2 consecutive scans (CAC scan and coronary CT angiography) over a period of average  $4.67 \pm 2.46$  years. Clinical characteristics and Framingham risk profiles were collected retrospectively by means of detail questionnaires such as age, sex, body mass index (BMI), hypertension, diabetes, current smoking, pack-year, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, hemoglobin A1c (HbA1c) and Framingham risk score at the baseline health checkup. The institutional

review board committees of our hospital approved this retrospective study and waived the need for informed consent.

### CAC scan

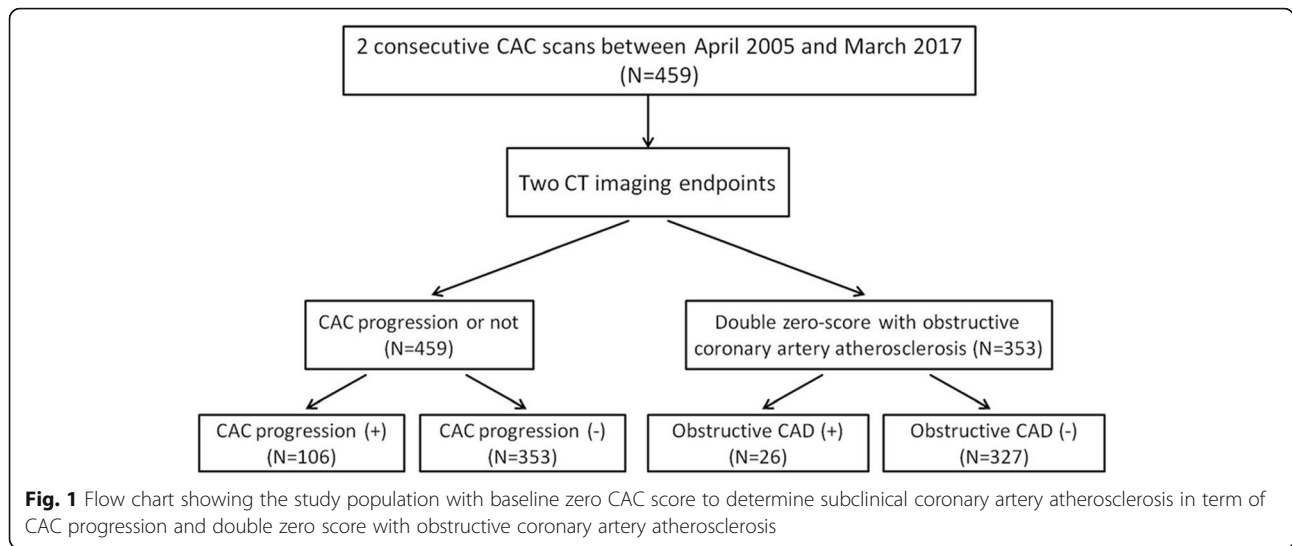
All CAC scans were performed with a 64-slice computed tomography (CT) (Aquilion 64; Toshiba Medical Systems), and 256-slice CT (Revolution CT, GE Healthcare, Milwaukee, USA). Coronary artery calcification was defined based on the Agatston method, for the quantification of the CAC score. In the Agatston method, calcification is defined as a hyper-attenuating lesion with a density  $> 130$  Hounsfield units (HU) and area  $> 3$  adjacent pixels ( $\geq 1 \text{ mm}^3$ ) [24].

### Coronary CT angiography image acquisition and analysis

We performed ECG-gated CT angiography of the coronary arteries according to the guidelines of the society of cardiovascular computed tomography (SCCT) [25]. All patients were scanned with a 64-slice CT (Aquilion 64; Toshiba Medical Systems), and 256-slice CT (Revolution CT, GE Healthcare, Milwaukee, USA). We administered oral beta-blockers (metoprolol) if heart rate exceeded 65 beats per minute 1 h before the coronary CT angiography examination. All patients received 0.8 mg of sublingual nitroglycerin shortly prior to the contrast-enhanced scan. All coronary CT angiography images were acquired using prospective electrocardiogram (ECG) triggering. Images were acquired and reconstructed at diastole (75–81% of the R-R interval) or at systole (37–43% of the R-R interval) if heart rate was still above 70 bpm despite premedication. Two primary CT imaging endpoints were investigated using Cox regression analysis. Among the 459 participants with the baseline CAC score of zero, CAC progression (+) was defined by the development of any CAC (i.e., CAC  $> 0$ ) during subsequent CT scans. In addition, we also evaluate the clinical scenario of double zero score with obstructive coronary artery atherosclerosis (defined as CAD-RADS $\geq 3$  or vulnerable plaques formation in the final round of the CT exam). Vulnerable plaques were defined as the presence of at least 2 features of spotty calcification, low attenuation plaque, or positive remodeling in final CT scans according to the SCCT guideline [26]. The study cohort was summarized according to the status of CAC progression and double zero score with obstructive coronary artery atherosclerosis shown in Fig. 1.

### Statistical analysis

All statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL). Continuous variables are presented as mean  $\pm$  standard deviation (SD), and categorical variables as counts with proportions.



Continuous variables were compared between groups using the Student’s t-test for normally distributed data and the Wilcoxon rank-sum test for non-normally distributed data. Categorical variables were compared between groups using the  $\chi^2$  test or Fisher’s exact test, as appropriate.

The Kaplan-Meier curves were also used to estimate the distribution of the time to CAC progression according to the cardiovascular risk parameters, and differences among groups were evaluated with the log-rank test. Cox regression model was used to explore the impact of

cardiovascular risk parameters on two CT imaging endpoints (CAC progression and double zero score with obstructive coronary artery atherosclerosis). A stepwise multivariate analysis was used to estimate the hazard ratios (HRs) based on the Cox regression model. The all Cox regression models retained a significant model (Omnibus test of model coefficients:  $p < 0.05$ ). Collinearity among the included variables was tested using variance inflation factors (VIFs), and values less than 4.0 were considered to indicating non-collinearity. For CAC progression prediction, ROC curve analysis was used to

**Table 1** Baseline characteristics of 459 subjects with a baseline CAC score of zero and stratified according to CAC progression

	Total population (n = 459)	CAC progression (+) (n = 106)	CAC progression (-) (n = 353)	P-value
Age	51.42 ± 8.44	53.07 ± 8.06	50.92 ± 8.49	0.021
Gender (% male)	311 (67.8%)	88 (83.0%)	223 (63.2%)	0.0001
BMI (kg/m <sup>2</sup> )	24.94 ± 3.46	25.73 ± 2.94	24.70 ± 3.57	0.007
Hypertension (%)	163 (35.7%)	51 (48.6%)	112 (31.9%)	0.002
Diabetes (%)	70 (15.3%)	20 (18.9%)	50 (14.2%)	0.281
Current smoking (%)	149 (34.0%)	44 (43.1%)	105 (31.3%)	0.032
Pack-year	9.89 ± 17.24	13.73 ± 20.06	8.72 ± 16.14	0.010
Total cholesterol (mg/dL)	207.56 ± 36.55	211.29 ± 38.64	206.44 ± 35.89	0.231
HDL-C (mg/dL)	46.46.43	42.93 ± 10.17	47.52 ± 14.11	0.002
LDL-C (mg/dL)	114.13 ± 28.63	117.20 ± 31.45	113.20 ± 27.71	0.208
Triglyceride (mg/dL)	157.03 ± 106.19	168.50 ± 96.38	153.58 ± 108.85	0.205
HbA1c (%)	5.87 ± 0.86	5.96 ± 0.81	5.85 ± 0.87	0.255
Framingham risk score (%)				0.0001
<6	119 (25.9%)	8 (7.5%)	111 (31.4%)	
≥6	340 (74.1%)	98 (92.5%)	242 (68.6%)	
Follow-up period (years)	4.67 ± 2.46	5.71 ± 2.68	4.35 ± 2.31	0.0001
CAC score in the final round (median, range)	6.24 (0,0–431)	27.29 (13,1–431)	0 (0,0)	0.0001

BMI body mass index, CAC coronary artery calcification, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, HbA1c Glycosylated hemoglobin A1c

determine the optimal cutoff value of cardiovascular risk parameters. For double zero score with obstructive coronary artery atherosclerosis, ROC curve analysis was used to determine the optimal cutoff value of cardiovascular risk parameters. Sensitivity, specificity, positive likelihood ratio (positive LR), negative likelihood ratio (negative LR), positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were determined from the optimal threshold by the Youden index.

## Result

The clinical characteristics of the study cohort with baseline zero CAC score are summarized in Table 1. The study cohort was comprised of 459 participants (mean age  $51.42 \pm 8.44$ ), who had undergone 2 CT scans with an average of  $4.67 \pm 2.46$  year. Of the 459 included participants with a baseline CAC score of zero, CAC progression was observed in 106 participants during the follow up, and the average time to CAC progression was  $5.71 \pm 2.68$  years. There were no significant differences in diabetes, total cholesterol, LDL-C, triglyceride, and HbA1c among these two groups. Compared with the CAC progression (-) group, there was significantly higher age, male sex, BMI, hypertension, current smoking, pack-year, follow-up period, CAC scan in the final round, and Framingham risk score in the CAC progression (+) group. CAC progression (-) group had a higher proportion of HDL-C level than CAC progression (+) group.

## Frequency and temporal change of CAC progression from zero to > 0

Of the 459 included participants with a baseline CAC score of zero, CAC progression was observed in 106 (23.09%) participants during the follow-up period of  $5.71 \pm 2.68$  years. Male gender, higher Framingham risk score rank according to 10, 20 and 30%, higher age rank (age cutoff of 40, 50 and 65 years) at the baseline were significantly associated with the risk of CAC progression to > 0. The cumulative proportion of CAC progression in this study cohort stratified by gender, Framingham risk score rank and age rank is summarized in Table 2. The 5-year progression rate of male group subjects was 28.29%, which was significantly higher than female group subjects (12.16%). For CAC progression, the mean progression time for male was  $7.93 \pm 0.27$  years and the median progression was  $7.86 \pm 0.47$  years; The female group had a mean progression time of  $9.70 \pm 0.40$  years and a median of  $10.56 \pm 0.45$  years. There was a significant difference in progression periods between the two groups (log-rank test  $p < 0.0001$ ). In term of Framingham risk score rank, the higher Framingham risk score group had shorter conversion time of CAC progression than the lower Framingham risk score group (Framingham risk score cut-off values of 10, 20, and 30%, log-rank test  $p = 0.0001, 0.0001, 0.007$ ). In term of age rank, the higher age rank group had shorter conversion time of CAC progression than the lower age rank group (age rank cutoff values of 40, 50, and 65 yrs. log-rank test  $p = 0.044, 0.025, 0.006$ ).

**Table 2** CAC conversion rates for subjects with a baseline CAC score of zero stratified according to traditional cardiovascular risk factors

Risk Factor	Converted	P value	Time to Conversion, yrs. (mean)	Time to Conversion, yrs. (median)	P value
Female	18/148 (12.16%)	0.0001	$9.70 \pm 0.40$	$10.56 \pm 0.45$	0.0001
Male	88/311 (28.29%)		$7.93 \pm 0.27$	$7.86 \pm 0.47$	
Framingham risk score (%)					
<10	23/194 (11.85%)	0.001	$9.98 \pm 0.36$	$10.96 \pm 0.50$	0.0001
$\geq 10$	83/265 (31.32%)		$7.48 \pm 0.26$	$7.49 \pm 0.62$	
<20	68/349 (19.48%)	0.002	$9.00 \pm 0.27$	$10.29 \pm 0.73$	0.0001
$\geq 20$	38/110 (34.54%)		$6.85 \pm 0.34$	$6.92 \pm 0.65$	
<30	85/400 (21.25%)	0.02	$8.68 \pm 0.25$	$9.72 \pm 0.94$	0.007
$\geq 30$	21/59 (35.59%)		$7.11 \pm 0.47$	$7.46 \pm 1.05$	
Age, yrs					
<40	4/35 (11.42%)	0.098	$10.24 \pm 0.90$	-	0.044
$\geq 40$	102/424 (24.05%)		$8.27 \pm 0.23$	$8.52 \pm 0.62$	
<50	35/194 (18.04%)	0.033	$9.07 \pm 0.39$	$9.72 \pm 1.02$	0.025
$\geq 50$	71/265 (26.79%)		$80.2 \pm 0.27$	$8.48 \pm 0.62$	
<65	93/425 (21.88%)	0.035	$8.55 \pm 0.24$	$9.03 \pm 0.75$	0.006
$\geq 65$	13/34 (38.23%)		$6.84 \pm 0.81$	$5.94 \pm 0.97$	

CAC coronary artery calcification

**Table 3** Multivariate Cox regression for CAC progression in the study cohort with a baseline CAC score of zero

Variable	Model 1			Variable	Model 2		
	HR	95% CI	P		HR	95% CI	P
Age	1.057	1.030–1.085	< 0.0001	Framingham risk score (%)	1.056	1.035–1.078	< 0.0001
Gender (male)	2.284	1.273–4.099	0.006				
LDL-C (mg/dL)	0.990	0.977–1.003	0.147				
HDL-C (mg/dL)	0.976	0.953–0.999	0.043				
Total cholesterol (mg/dL)	1.016	1.004–1.028	0.008				
Triglyceride (mg/dL)	0.998	0.995–1.002	0.362				
Diabetes	1.092	0.621–1.922	0.759				
Hypertension	1.211	0.793–1.847	0.376				
Current smoking	1.258	0.791–2.000	0.332				

CAC coronary artery calcification, CI confidence interval, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, HR Hazard Ratio

### Cox regression for predictors of CAC progression

Among subjects with a zero CAC score at baseline, model 1 showed that age, male gender, HDL-C, and total cholesterol were significantly associated with CAC progression. For Framingham risk score stratification, model 2 showed that Framingham risk score were significantly associated with CAC progression shown in Table 3. Among these parameters, Framingham risk score had the better discriminative ability to predict CAC progression with a sensitivity of 75.24% and specificity of 53.95% (PPV = 32.60%; NPV = 88.00%) shown in Supplement Table 1. Framingham risk score had the better discriminative ability to predict CAC progression compared to the other biochemical markers. We further used the Youden index test and found an optimum cut-off value for Framingham risk score of  $\geq 11.1$  with the highest discriminant ability than other values (AUC = 0.660) shown in Fig. 2. Among these potential predictive parameters, age and male gender were the two most sensitive signs. However, the HDL-C and total cholesterol were the two most specific signs.

### Cox regression for predictors of double zero score with obstructive coronary artery atherosclerosis

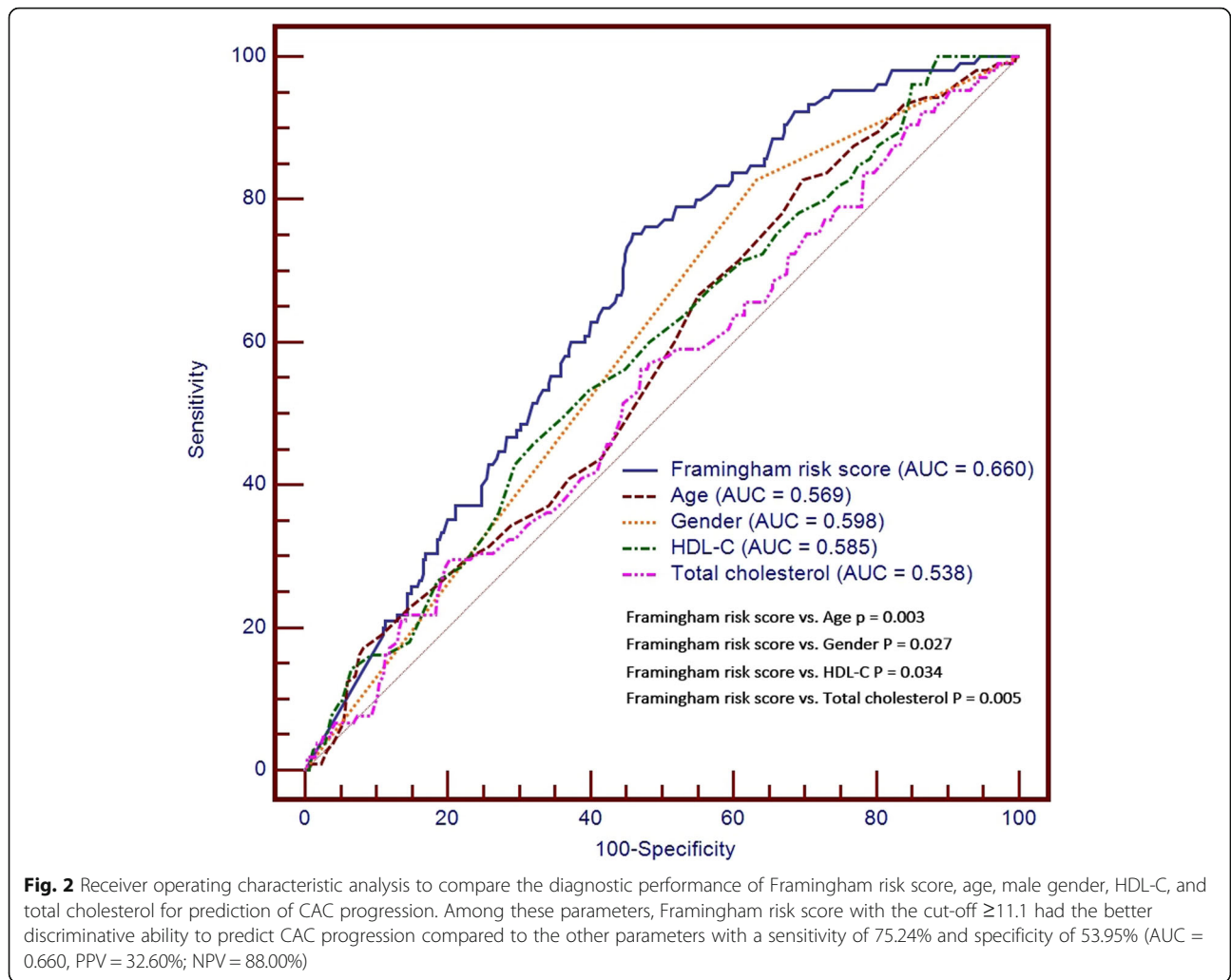
Of the 353 subjects with the double zero CAC score in this cohort, there were 26 subjects with obstructive coronary artery atherosclerosis events diagnosed by coronary CT angiography in the final round of the CT exam. Model 1 showed that older age, triglyceride, and hypertension were significantly associated with these events of double zero score with obstructive coronary artery atherosclerosis. For Framingham risk score stratification, model 2 showed that Framingham risk score were significantly associated with these events (double zero score with obstructive coronary artery atherosclerosis) shown in Table 4. We further used the Youden index test and found an optimum cut-off value for Framingham risk score  $< 16.9$  with the high negative predictive value

(NPV = 96.4%) shown in Supplement Table 2 and Fig. 3 (AUC = 0.652; sensitivity = 57.69%; specificity = 68.82%).

### Discussion

This is a retrospective study for the first time investigating the natural course of coronary atherosclerosis burden in asymptomatic Asian population with an initial CAC score of zero in term of CAC progression and double zero score with obstructive coronary artery atherosclerosis. In this study, we demonstrated five major findings. The first one is that CAC progression rate was about 23.09% in low to intermediate risk Asian population with baseline zero score during the follow-up period of  $5.71 \pm 2.68$  years. Second, older age, male gender, HDL-C, total cholesterol and higher Framingham risk score were independently associated with CAC progression and shorter acceleration time of CAC progression. Third, for CAC progression, Framingham risk score had the better diagnostic ability performance with an AUC of 0.660 (sensitivity of 75.24%; specificity of 53.95%) than other parameters. Forth, for double zero score with obstructive coronary artery atherosclerosis event, older age, triglyceride, hypertension and Framingham risk score were independent important risk factors for event prediction. Finally, for rule out double zero score with obstructive coronary artery atherosclerosis event, Framingham risk score with an optimum cut-off value of less than 16.9 may be a relatively acceptable parameter with high negative predictive (NPV = 96.4%) value for rule out obstructive coronary artery atherosclerosis scenario (sensitivity of 57.69%; specificity of 68.82%).

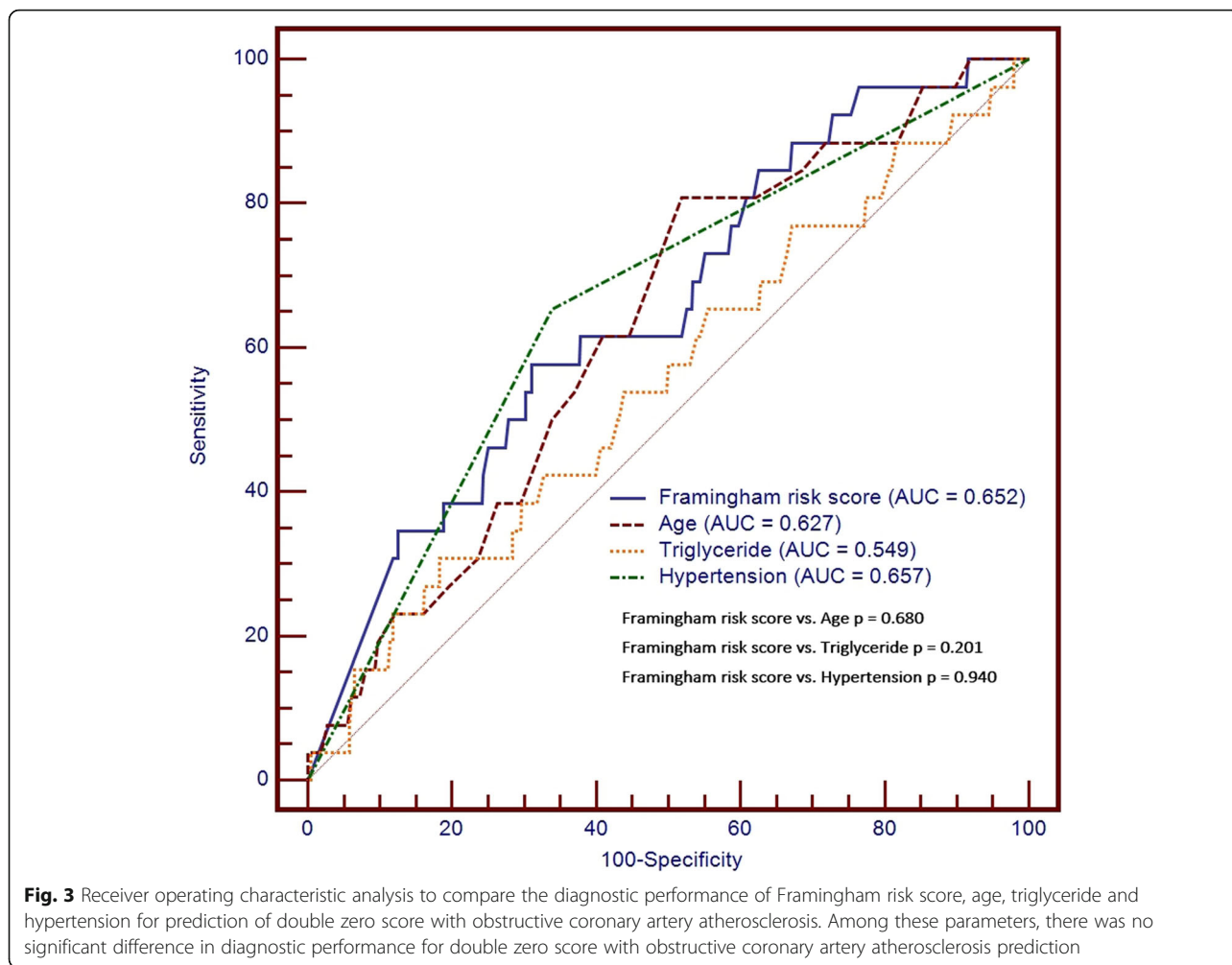
The accumulating evidences from previous studies regarding CAC progression in the general population suggest that zero CAC score at the baseline scan provides the 5-year warranty period for asymptomatic subjects, especially in the Western population [9, 14–16]. However, there is limited research regarding the CAC progression in the Asian population with a baseline zero



**Table 4** Multivariate Cox regression for obstructive coronary artery atherosclerosis in the study cohort with double zero score

Variable	Model 1			Variable	Model 2		
	HR	95% CI	P		HR	95% CI	P
Age	1.065	1.013–1.119	0.014	Framingham risk score (%)	1.055	1.014–1.098	0.008
Gender (male)	1.150	0.398–3.323	0.796				
LDL-C (mg/dL)	1.025	0.984–1.067	0.240				
HDL-C (mg/dL)	1.026	0.979–1.075	0.283				
Total cholesterol (mg/dL)	0.982	0.947–1.017	0.303				
Triglyceride (mg/dL)	1.005	1.001–1.009	0.025				
Diabetes	1.746	0.699–4.363	0.233				
Hypertension	2.482	1.047–5.884	0.039				
Current smoking	0.97	0.374–2.520	0.951				

CAC coronary artery calcification, CI confidence interval, LDL-C low density lipoprotein cholesterol, HDL-C high density lipoprotein cholesterol, HR Hazard Ratio



CAC score [8, 17]. A previous study demonstrated that a baseline CAC score of zero is associated with the low probability of CAC progression in Korean population with a nonlinear increasing trend over time [17]. Our results are in line with previous studies. Thus, the beneficial prognosis of zero CAC score for the warranty period of 5 years to prevent CAC progression is also further supported in the Asian population in our study result. In addition, our study demonstrated that age, male gender, HDL-C, total cholesterol and Framingham risk score are important predictors of CAC progression. However, Lee et al. previously reported that age, male sex, waist circumference, diabetes, and low-density lipoprotein cholesterol level independently associated with an increased risk of annualized CAC progression in Korean population [17]. In addition, age > 40 years, diabetes, and smoking are independently associated with the risk of conversion to a CAC score > 0 in Western population with a baseline CAC score of zero in the previous study by Min et al. [16]. Therefore, the difference between these studies could be partly explained by ethnic

differences and study endpoints. However, the present study, which focuses exclusively on the Chinese population with a baseline zero CAC score, provides important information regarding Framingham risk score  $\geq 11.1$  associated with a high risk of CAC progression in the Chinese population in the warranty period. Cardiovascular risk assessment by Framingham risk score stratification could help guide the management and prevent subclinical coronary atherosclerosis.

Lehmann et al. previously reported that double-zero CAC scans in a 5-year period mean an excellent prognosis for cardiovascular events [9]. However, recent studies have showed that absence of coronary artery calcification does not completely exclude obstructive coronary artery disease, but the prevalence is variable between 1 to 20% [18–23]. Our study results demonstrated that older age, triglyceride, hypertension and Framingham risk score were the independent most important risk factors for prediction of double-zero CAC with obstructive coronary artery atherosclerosis. For prediction of double-zero CAC with coronary artery atherosclerosis, the

Framingham risk score may be a relatively acceptable parameter at an optimum cut-off value of less than 16.9 for rule out double-zero CAC with obstructive coronary artery atherosclerosis. However, Framingham risk score was a just relatively acceptable parameter among these parameters for events prediction because of high NPV of 96.4% in the clinical setting of low to intermediate cardiovascular risk. In this study we have demonstrated that Framingham risk score significantly associated with CAC progression or double zero score with obstructive coronary artery atherosclerosis. But the poor discrimination ability may be revealed by the AUC range of 0.6 to 0.7 in the prediction of CAC progression or double zero score with obstructive coronary artery atherosclerosis. These questions raised by this study warrant further investigation of a better risk score model.

Currently, there is controversy about the prognosis of obstructive CAD in subjects with a zero CAC score [18–20]. Previous studies demonstrated that zero CAC score can't be used to totally exclude obstructive CAD or adverse cardiac events in symptomatic Korean subjects [20]. However Mittal et al. previously showed that the presence of non-calcified atheroma/plaques on coronary CT angiography in subjects with zero CAC score did not affect the prognostic outcome [19]. Therefore, our proposed "Framingham risk score threshold less than 16.9" may help confirm subjects at low risk of double zero score with obstructive coronary artery atherosclerosis to improve cardiovascular risk stratification and reclassification. Previous studies also demonstrated that 1.9 ~ 4.3% subjects found to have obstructive CAD  $\geq 50\%$  among symptomatic subjects with zero CAC score [20, 27, 28]. This study supported previous findings and could further help to reclassify high-risk group with high Framingham risk score. Therefore, this high-risk group with zero CAC score could benefit prognostically from optimal medical treatment as demonstrated in the Scottish Computed Tomography of the HEART Trial (SCOTHEART) [29, 30].

There are some limitations in this study. First, this is a retrospective study based in a single-center with self-referral healthy population of low to intermediate cardiovascular risk. Therefore, the risk of selection bias should be considered.

Second, we did not specifically investigate the clinical outcomes or mortality for the primary outcome analysis. Therefore, future studies are warranted to investigate these issues based on multicenter prospective studies to determine the prognostic outcome of CAC progression and double zero score with obstructive coronary artery atherosclerosis in Asian population. Third, a potential problem of overfitting the model should be concerned because of a small number of events for double zero score with obstructive coronary artery atherosclerosis.

Therefore, large prospective cohort studies are needed to validate this study outcome.

## Conclusion

The present study results demonstrate that the Asian population in Taiwan with low to intermediate risk has a low conversion rate of CAC progression within the 5-year warranty period. Framingham risk score  $\geq 11.1$  associated with a high risk of CAC progression in the warranty period. In addition, a zero CAC score may serve as a gatekeeper for cardiovascular event prevention. For CAC progression prediction, Framingham risk score with the cutoff  $< 11.1$  may help confirm subjects at low risk to improve cardiovascular risk stratification and reclassification in the field of preventive cardiology.

## Supplementary information

**Supplementary information** accompanies this paper at <https://doi.org/10.1186/s12872-020-01498-x>.

**Additional file 1: Supplement Table 1.** The diagnostic performance among CAD risk parameters used for predicting CAC progression in the study cohort with a baseline CAC score of zero. **Supplement Table 2.** The diagnostic performance among CAD risk parameters used for predicting in the study cohort with double zero score with obstructive coronary artery atherosclerosis.

## Abbreviations

CAC: Coronary artery calcium; CAD: Coronary artery disease; BMI: Body mass index; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; HbA1c: Hemoglobin A1c; SCCT: Society of cardiovascular computed tomography; HU: Hounsfield units; VIFs: Variance inflation factors; ECG: Electrocardiogram; positive LR: Positive likelihood ratio; negative LR: Negative likelihood ratio; PPV: Positive predictive value; NPV: Negative predictive value; SD: Standard deviation

## Acknowledgements

None.

## Authors' contributions

FZW conducted the experiments. YWS, YJW, CCH, SHC, YCH and GYM were responsible for data analysis. FZW and YWS were responsible for clinical sample collection and experiment design. FZW supervised this work. FZW, CCH, MTW and YWS wrote the manuscript first. All eight authors (YWS, YJW, CCH, SHC, YCH, MTW, FZW and GYM) worked together with interpretations of the data. All eight authors (YWS, YJW, CCH, SHC, YCH, MTW, FZW and GYM) reviewed and edited the manuscript. The all authors read and approved this manuscript.

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## Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because the information and data of the study population were extracted from Hospital Information System and were recorded manually in EXCEL to form our private database. But the data are available from the corresponding author on reasonable request.



**Ethics approval and consent to participate**

This study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the Clinic Institutional Review Board of Kaohsiung Veterans General Hospital, and informed consent was waived (Reference number: VGHS19-CT6-02).

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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