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ORIGINAL RESEARCH

Evaluating the Coronary Artery Disease Consortium Model and the Coronary Artery Calcium Score in Predicting Obstructive Coronary Artery Disease in a Symptomatic Mixed Asian Cohort

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BACKGROUND: The utility of a given pretest probability score in predicting obstructive coronary artery disease (CAD) is population dependent. Previous studies investigating the additive value of coronary artery calcium (CAC) on pretest probability scores were predominantly limited to Western populations. This retrospective study seeks to evaluate the CAD Consortium (CAD2) model in a mixed Asian cohort within Singapore with stable chest pain and to evaluate the incremental value of CAC in predicting obstructive CAD.

METHODS AND RESULTS: Patients who underwent cardiac computed tomography and had chest pain were included. The CAD2 clinical model comprised of age, sex, symptom typicality, diabetes, hypertension, hyperlipidemia, and smoking status and was compared with the CAD2 extended model that added CAC to assess the incremental value of CAC scoring, as well as to the corresponding locally calibrated local assessment of the heart models. A total of 522 patients were analyzed (mean age 54±11 years, 43.1% female). The CAD2 clinical model obtained an area under the curve of 0.718 (95% CI, 0.668–0.767). The inclusion of CAC score improved the area under the curve to 0.896 (95% CI, 0.867–0.925) in the CAD2 models and from 0.767 (95% CI, 0.721–0.814) to 0.926 (95% CI, 0.900–0.951) in the local assessment of the heart models. The locally calibrated local assessment of the heart models showed better discriminative performance than the corresponding CAD2 models ($P<0.05$ for all).

CONCLUSIONS: The CAD2 model was validated in a symptomatic mixed Asian cohort and local calibration further improved performance. CAC scoring provided significant incremental value in predicting obstructive CAD.

Key Words: Asia ■ coronary artery calcium ■ coronary artery disease ■ coronary computed tomography angiography ■ pretest probability ■ risk assessment

Coronary artery disease (CAD) is the most prevalent cardiovascular disease and the leading cause of morbidity and mortality, with significant corollary costs.[1–3] A frequent presenting symptom of stable CAD is chest pain.[4] Estimating pretest probability (PTP) of CAD is a guideline-recommended step in assessing stable chest pain, guiding downstream investigations.[5,6] A variety of PTP scores using

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CLINICAL PERSPECTIVE

What Is New?

- This was the first study to validate the ability of a contemporary pretest probability model, the Coronary Artery Disease consortium, to predict obstructive coronary artery disease in Singapore.
- The Coronary Artery Disease 2 model was locally calibrated to develop the local assessment of the heart model, that showed improved performance in predicting obstructive coronary artery disease in this symptomatic Asian cohort.
- Coronary artery calcium scoring provided incremental value, both to the Coronary Artery Disease 2 and the local assessment of the heart models in this cohort.

What Are the Clinical Implications?

- Our study reinforces that the performance of pretest probability scoring models is dependent on the population admixture; thus, local validation of these models is important.
- Coronary artery calcium scoring may be included as part of the risk assessment for coronary artery disease, serving as a potential gatekeeper to downstream investigations, such as coronary angiography, in symptomatic patients.

traditional cardiovascular risk factors to predict obstructive CAD have been developed and validated, including the CAD Consortium 2 (CAD2) model.[7–10] A version of the CAD2 incorporating updated pooled cohort data has been included in the latest European Society of Cardiology 2019 guidelines for chronic coronary syndromes.[6,11]

The performance of a PTP score depends on the prevalence of disease in the population studied.[6,12] Consequently, this performance can vary when applied to differing ethnic group compositions and geographical locations. Some scores derived and initially well validated in Western populations have performed less well in Asian cohorts.[13–17] Moreover, as assessing PTP has several limitations, the incorporation of the coronary artery calcium (CAC) score as a gatekeeper to further testing has been proposed.[5,6,18–20] This is based on robust literature that CAC is not only a predictor of cardiovascular events but of obstructive CAD.[21–25]

Despite being a small city-state, Singapore's immigratory history has resulted in a population comprising 3 major Asian ethnicities (Chinese [74.3%], Malay [13.5%], and Indian [9.0%]) that provide a unique snapshot of the genetic diversity across East Asia, Southeast Asia, and South Asia.[26,27]

As the utility of a given PTP score as well as CAC scoring should be tested in a variety of populations, we sought to externally validate the CAD2 model among a mixed Asian cohort with stable chest pain within Singapore. We compared its performance to a locally calibrated version of this model. We further evaluated the incremental value of CAC in predicting obstructive CAD in this cohort, as this not been previously studied.

METHODS

Study Population

The anonymized data that support the results of this study can be made available upon reasonable request with the appropriate ethical and legal clearance. This was a single-center, retrospective cohort study conducted on all patients who presented with chest pain and underwent cardiac computed tomography (CT; including CAC scoring and coronary angiography) at a tertiary cardiac institution in Singapore. The following patients were excluded: patients with a previous history of myocardial infarction, cardiac catheterization, percutaneous coronary intervention, or coronary artery bypass graft surgery. In total, 1035 symptomatic patients who underwent clinically indicated CT scans for suspected CAD from July 2015 to October 2017 were eligible. A total of 136 subjects with nondiagnostic CT scans were removed. A further 33 patients with prior history of CAD were excluded. As this study was intended to evaluate the risk scores in symptomatic subjects, 344 patients without 2-way confirmation of presence of risk factors or symptom typicality verified in both questionnaire and electronic health care records were excluded from the study. After these exclusions, 522 patients remained for analysis (Figure 1). This study was approved by Central Institutional Review Board (CIRB Ref. No.: 2020/2453), and a waiver of informed consent was granted.

Definition of Risk Factors

There was 2-way verification of risk factors and symptoms. First, based on a survey questionnaire filled in the CT laboratory. Second, with verification using electronic health care records comprising physician diagnosis in clinic and laboratory results. Both former and current smokers constituted a positive smoking history. Family history of premature CAD was considered positive if this was known in a first-degree male relative of age <55 years or a first-degree female relative of age <65 years. Hypercholesterolemia was defined as total serum cholesterol of >5.5 mmol/L or if the patient was on statin therapy. Patients were considered diabetic if they had any one of the following: (1) fasting plasma glucose ≥7 mmol/L (126 mg/dL), (2) glycated hemoglobin ≥6.5%, (3) an extant physician diagnosis, or (4)

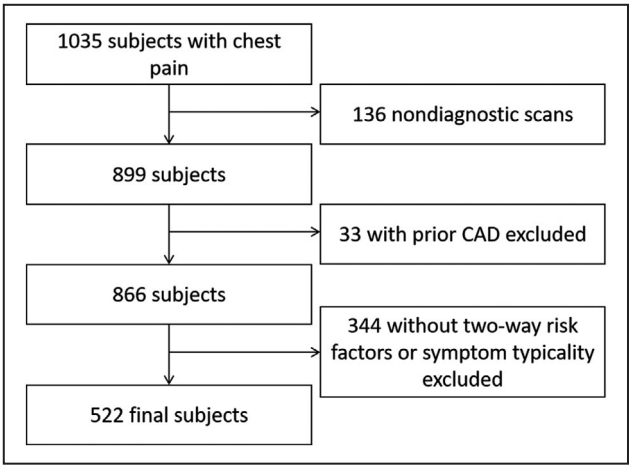

Figure 1. Of 1035 subjects referred for suspected CAD, participants were first selected for presence of symptoms and diagnostic scans, followed by absence of CAD history and finally complete risk factor profile.
Five hundred and twenty-two subjects were suitable for analysis. CAD indicates coronary artery disease.

were on diabetic medication. Patients were considered hypertensive if they had any one of the following: (1) systolic blood pressure ≥140 mm Hg, (2) diastolic blood pressure ≥90 mm Hg, (3) an extant physician diagnosis, or (4) were on antihypertensive medication. Chest pain symptoms were defined as typical, atypical, or nonanginal. Typical chest pain was defined as (1) substernal chest pain or discomfort; that was (2) provoked by exertion or emotional stress; and (3) relieved by rest or nitrate. Atypical chest pain was defined as 2 of the previously mentioned criteria. If 1 or none of the criteria was present, chest pain was categorized as nonanginal.[28,29] Dyspnea on exertion was considered as equivalent to typical chest pain.

CT Acquisition and Interpretation

Both coronary computed tomography angiography (CCTA) and CAC scans were performed using a 320 slice multidetector CT scanner (Toshiba Aquilion ONE) in accordance with the Society of Cardiovascular Computed Tomography guidelines.[30] CAC images were acquired using 120 kVp, 300–600 mAs, prospective ECG gating, and 3 mm reconstructions. CCTA was performed with prospective electrocardiographic gating using the following parameters: gantry rotation time of 350 to 400 ms, tube voltage of 100 to 120 kV, and a slice thickness of 0.5 mm. An oral or intravenous beta blocker was administered to moderate the heart rate. Sublingual glyceryl trinitrate was administered in the absence of any contraindications. Contrast enhancement was achieved with Omnipaque. Image acquisition was performed with an inspiratory breath-hold.

All scans were analyzed by level III or equivalent trained cardiologists or radiologists with extensive experience in cardiac CT analysis. The CCTAs were interpreted according to current guidelines.[31] Each coronary segment was analyzed for the presence of coronary atherosclerosis, and each lesion was quantified by visual estimation into 3 categories: no disease, nonobstructive disease (1%–49% stenosis), and obstructive disease (≥50% stenosis). Obstructive CAD was defined as at least 1 segment with a lesion with ≥50% stenosis. Obstructive CAD was further characterised as 1-, 2-, and 3-vessel disease. CAC was calculated using the Agatston quantification method.[32]

Risk Scoring for Prediction of Obstructive Coronary Artery Disease

The PTP of CAD was calculated for each patient using the CAD2 clinical model, based on published coefficients.[19] The CAD2 model was created to predict obstructive CAD from a pooled cohort and was itself an iterative update of the updated Diamond Forrester score.[18] It was selected for this study because has been evaluated against other contemporary scores with robust performance.[7,9,10] Further updating using pooled cohorts have resulted in it being included in the latest European Society of Cardiology 2019 guidelines.[6,11,33–35]

The CAD2 clinical model includes the following variables: age, sex, symptom typicality, diabetes, hypertension, hyperlipidemia, and smoking status. The CAD2 extended model adds the CAC score to these variables. Two locally calibrated models, termed the local assessment of the heart (LAH) clinical and extended models, were developed from the respective CAD2 models, using the same variables with updating of the regression coefficients to the study cohort. As these variables are known to be associated with CAD, they were entered concurrently in a multivariate, fixed effects, logistic regression model.

Statistical Analysis

Continuous data were expressed as mean± SD or median (interquartile range) and categorical data were reported as percentages where appropriate. Comparison between groups was performed using the unpaired *t* test for continuous data, and the χ^2 test for categorical data.

Receiver operating characteristic curves and the corresponding area under the curve (AUC) values were generated to compare the discriminatory power of CAC score for predicting obstructive CAD between sexes and age groups. To assess the calibration of the CAD2 clinical model to the population, observed and predicted risk was computed according to age and sex. The Hosmer-Lemeshow goodness-of-fit chi-square statistic across deciles of risk was calculated to measure the agreement between observed and predicted events. To evaluate the incremental value

of CAC score as a predictor of obstructive CAD, the AUC values of the CAD2 clinical model and the CAD2 extended model were compared. Moreover, the discriminatory performance of the LAH models was also compared with that of the equivalent CAD2 models using AUC. To estimate the impact of risk factor and symptom data quality on model performance, a sensitivity analysis was performed including patients without 2-way confirmation of presence of risk factors or symptom typicality. Risk factors or symptoms with single verification were assumed to be present, and dual blank fields were assumed to be absent for the corresponding risk factors or symptoms. Statistical significance was defined as a 2-tailed *P* value of <0.05. Statistical analyses were performed using SPSS version 27.0. Receiver operating characteristic curves and AUC values were generated using R version 4.0.0.

RESULTS

Clinical Characteristics

The mean age was 54±11 years and 43.1% were female (Table 1); 167 subjects (32.0%) were ≥60 years of age. The majority were of Asian descent (71.6% Chinese, 11.9% Indian, 5.6% Malay) and 0.8% other Asian ethnicities (including Eurasian, Indonesian, Bangladeshi, and Filipino). All patients were symptomatic and presented with chest pain. In total, 231 patients (44.3%) had no coronary stenosis on CCTA, whereas 165 patients (31.6%) and 126 patients (24.1%) had nonobstructive (1%–49% stenosis) and obstructive CAD (≥50% stenosis) respectively. Most patients with obstructive CAD had single-vessel disease (54.8%; 69/126).

Approximately half of the patients (49.2%; 257/522) had CAC=0. The median Agatston score in patients with CAC >0 was 81 (interquartile range, 20–296). Patients with CAC >0 were significantly more likely to be older, male, have hypertension, diabetes, or hyperlipidemia. Chest pain typicality was not significantly different between the CAC=0 group and the CAC >0 group. The mean PTP using the CAD2 clinical model was 12.8% (interquartile range: 4.9–28.5) and was significantly higher in the CAC >0 group (19.7% [interquartile range: 9.1–38.1]) than the CAC=0 group (7.5% [interquartile range: 3.2–17.3]) (*P*<0.001). For patients with CAC=0, 221 patients (86.0%) had no detectable stenosis and 36 (14.1%) had any CAD, of which 4 (1.6%) had obstructive CAD. For patients with CAC >0, 133 (50.2%) had nonobstructive CAD and of which 126 (46.0%) had obstructive CAD. Of those ≥60 years, 42 (25.1%) had CAC=0.

Calibration to Local Cohort and Development of Local Models

The calibration of the local cohort demonstrated a poor fit for the CAD2 clinical model across all deciles of risk (chi-square 49.72; *P*<0.001). Overall, the CAD2 clinical model overestimated the prevalence of obstructive CAD by 13% and 28% in women and men respectively (Figure 2). This overestimation was most marked in the age 60 to 69 years group in both women and men, by 24% and 46% respectively.

Two local logistic regression models were developed from the CAD2 models—the LAH clinical model, using the same variables as the CAD2 clinical model, and the LAH extended model, which included CAC score (Table 2). For the LAH clinical model, obstructive CAD was found to be significantly associated with age (odds ratio [OR], 1.07; 95% CI, 1.04–1.09) and male sex (OR, 4.56; 95% CI, 2.69–7.73). In the LAH extended model, obstructive CAD was only significantly associated with the CAC score (OR, 2.47; 95% CI, 2.06–2.96).

Comparison of Performance and Incorporation of Coronary Artery Calcium Score

The CAD2 clinical model obtained an AUC of 0.718 (95% CI, 0.668–0.767) (Figure 3). The locally-calibrated LAH clinical model (AUC, 0.767; 95% CI, 0.721–0.814) improved discrimination compared with its CAD2 counterpart (AUC, 0.767 versus 0.718; *P*=0.005). The CAD2 extended model obtained an AUC of 0.896 (95% CI, 0.867–0.925). In concordance, the LAH extended model (AUC, 0.926; 95% CI, 0.900–0.951) had improved discrimination compared with the CAD2 extended model (AUC, 0.926 versus 0.896; *P*=0.002).

Incorporation of the CAC score improved discrimination in predicting obstructive CAD in both the CAD2 and LAH models. The LAH extended model performed significantly better than the LAH clinical model for predicting obstructive CAD (AUC 0.926 versus 0.767). Likewise, the CAD2 extended model significantly outperformed the CAD2 clinical model in this cohort (AUC 0.896 versus 0.718; *P*<0.001 for all).

Overall, the incorporation of CAC improved both the CAD2 and LAH models when using a 15% PTP threshold (Figure 4). For the CAD2 model, positive predictive value improved from 38.1% (95% CI, 38.2–42.1) to 57.7% (95% CI, 52.4–62.9; *P*<0.001), negative predictive value from 87.6% (95% CI, 84.2–90.4) to 93.8% (95% CI, 91.1–95.7; *P*=0.007), specificity from 87.6% (95% CI, 84.2–90.4) to 93.8% (95% CI, 91.1–95.7; *P*<0.001) and sensitivity from 72.2% (95% CI, 63.5–79.8) to 83.3% (95% CI, 75.7–89.4; *P*=0.034). For the LAH model, positive predictive value improved from 34.2% (95% CI, 31.6–36.9) to 56.5% (95% CI, 51.9–61.1; *P*<0.001), negative predictive value from 91.3% (95% CI, 87.2–94.1) to 97.1% (95% CI, 94.8–98.5; *P*=0.003) and specificity from 91.3% (95% CI, 87.2–94.1) to 97.1% (95% CI, 94.8–98.5; *P*<0.001). Although sensitivity trended toward improvement from 85.7%

Table 1. Clinical Characteristics of Patients With a CAC Score of Zero and Patients With a CAC Score Greater Than Zero

Variable	All patients (n=522)	CAC=0 (n=257)	CAC >0 (n=265)	*P* value
Demographics				
Age, y	53.9±10.8	49.4±9.7	58.2±10.1	<0.001
Body mass index, kg/m^2	26.1±5.7	26.4±5.9	25.8±5.5	0.196
Female sex	225 (43.1)	131 (51.0)	94 (35.5)	<0.001
Ethnicity				0.436
Chinese	374 (71.6)	175 (68.1)	199 (75.1)	…
Malay	29 (5.6)	16 (6.2)	13 (4.9)	…
Indian	62 (11.9)	34 (13.2)	28 (10.6)	…
Others†	57 (11.0)	32 (12.5)	25 (9.5)	…
Medical history and risk factors				
Hypertension	212 (40.6)	74 (28.8)	138 (52.1)	<0.001
Diabetes	77 (14.8)	23 (8.9)	54 (20.4)	<0.001
Hyperlipidemia	305 (58.4)	115 (44.7)	190 (71.7)	<0.001
Smoking	123 (23.6)	60 (23.3)	63 (23.8)	0.908
Family history of CAD	234 (44.8)	108 (42.0)	126 (47.5)	0.205
Chest pain				0.694
Typical	190 (36.4)	89 (34.6)	101 (38.1)	…
Atypical	168 (32.2)	86 (33.5)	82 (30.9)	…
Non-anginal	164 (31.4)	82 (31.9)	82 (30.9)	…
Coronary artery stenosis				
Pretest probability*	12.8 [4.9, 28.5]	7.5 [3.2, 17.3]	19.7 [9.1, 38.1]	<0.001
No disease	231 (44.3)	221 (86.0)	10 (3.8)	…
Nonobstructive disease	165 (31.6)	32 (12.5)	133 (50.2)	…
Obstructive disease				…
1-vessel disease	69 (13.2)	3 (1.2)	66 (24.9)	…
2-vessel disease	37 (7.1)	1 (0.4)	36 (13.6)	…
3-vessel disease	20 (3.8)	0 (0)	20 (7.5)	…
Left main disease	4 (0.8)	0 (0)	4 (1.5)	…

CAC indicates coronary artery calcium; CAD, coronary artery disease; and CAD2, CAD consortium model.
*Pretest probability was calculated using the CAD2 clinical model.
†Others includes Eurasian, Indonesian, Bangladeshi, and Filipino.

(95% CI, 78.4–91.3) to 92.9% (95% CI, 86.9–96.7), this was not statistically significant (*P*=0.067). Sensitivity analysis upon inclusion of patients without 2-way confirmation of risk factors or symptom typicality did not affect diagnostic performance of any of the models (Table S1, Figure S1).

DISCUSSION

In this study, the CAD2 clinical model was validated among a mixed Asian cohort with stable chest pain in Singapore, with discriminative performance in predicting obstructive CAD that was further improved with local calibration. In both the CAD2 and LAH models, incorporation of the CAC score significantly improved discrimination of obstructive CAD.

This current study is the first examining both the clinical and extended CAD2 models in a symptomatic mixed cohort comprising East Asian, Southeast Asian, and South Asian ethnicities. In this study, the CAD2 clinical model overestimated the prevalence of obstructive CAD, especially in the 60 to 69 years age group. In a single-center Danish study by Reeh et al., the CAD2 model overestimated the prevalence of obstructive CAD, and model performance improved when tailored to the local population, congruent with the present study.[33] On the other hand, when validated using 1738 subjects from the SCOT-HEART (Scottish Computed Tomography of the HEART) trial, the CAD2 clinical score underestimated obstructive CAD risk.[7] This has also been demonstrated in other PTP scores. In an analysis of 2274 patients who underwent clinically indicated CCTA for suspected CAD in the North American Partners Registry by Bittencourt et al., the updated Diamond Forrester PTP score similarly overestimated obstructive CAD.[9]

The improved performance of the locally calibrated LAH compared with the CAD2 models does

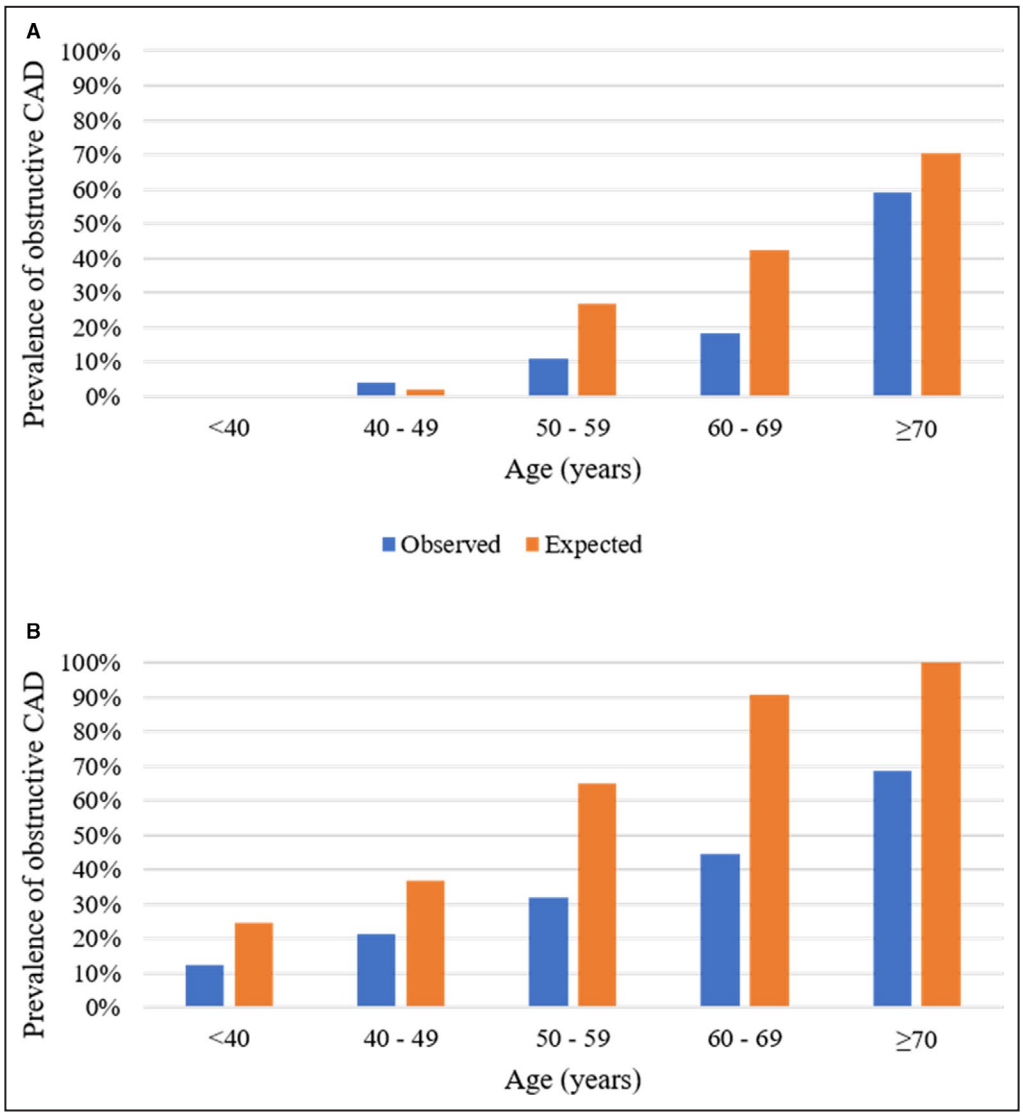

Figure 2. Observed (blue) vs expected (orange) prevalence of obstructive CAD according to age in (A) women and (B) men using the CAD2 clinical model.
CAD indicates coronary artery disease; and CAD2, CAD consortium model.

not prove the superiority of one over the other. Rather, it reinforces the importance of tailoring a specific PTP model to the population admixture.[12] The CAD2 model was developed using European and North American cohorts.[19] The poor fit and overestimation of the CAD2 model may be because of the lower prevalence of CAD in most East Asian cohorts, as reflected in the current study cohort, comprising a Chinese ethnic majority component. In the international multisite CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes) substudy, observed-to-expected ratios of obstructive CAD were up to 3 times lower only in the East Asian site, suggesting that the relationship between chest pain and obstructive CAD may be influenced by ethnicity or local interpretation of chest pain.[34] Furthermore, prevalence of CAD can be significantly different between different ethnicities even after matching for other risk factors.[14,36]

Nevertheless, the CAD2 model has displayed robust performance in multiple external validations. In the SCOT-HEART cohort, the CAD2 clinical score obtained an AUC of 0.79.[7] Comparable performance was obtained in the Partners Registry by Bittencourt et al.[9] In these studies, the slightly higher discriminative performance of CAD2 compared with the current study may be reflective of closer similarities between the respective validation cohorts and the original development cohort of the model. This discriminative performance is also modality agnostic. In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial using invasive coronary angiography (ICA) to

Table 2. Comparison of the CAD2 and the LAH Models That Did Not Incorporate CAC Scoring (Clinical Versions) and Those That Did (Extended Versions)

Variables	CAD2 clinical		CAD2 extended		LAH clinical		LAH extended	
	Coef.	OR	Coef.	OR	Coef.	OR (95% CI)	Coef.	OR (95% CI)
Intercept	−7.539	…	−5.975	…	−6.268	0.00 (0.00–0.01)	−4.241	0.01 (0.00–0.10)
Age	0.062	1.06	0.011	1.01	0.067	1.07 (1.04–1.09)*	0.000	1.00 (0.97–1.03)
Male sex	1.332	3.79	0.786	2.19	1.518	4.56 (2.69– 7.73)*	0.544	1.72 (0.85–3.48)
Chest pain								
Typical chest pain†	1.998	7.37	2.024	7.57	0.164	1.18 (0.69–2.02)	0.139	1.15 (0.57–2.33)
Atypical chest pain†	0.633	1.88	0.718	2.05	−0.090	0.91 (0.52–1.61)	−0.242	0.79 (0.38–1.64)
Hypertension	0.338	1.40	0.235	1.26	0.457	1.58 (0.99–2.51)	−0.143	0.87 (0.47–1.60)
Diabetes	0.828	2.29	0.658	1.93	0.417	1.52 (0.84–2.73)	−0.002	1.00 (0.47–2.11)
Hyperlipidemia	0.422	1.53	0.185	1.20	0.370	1.45 (0.88–2.39)	−0.157	0.86 (0.44–1.67)
Smoking	0.461	1.59	0.207	1.23	−0.364	0.69 (0.40–1.22)	−0.315	0.73 (0.36–1.50)
ln (CAC+1)	…	…	0.577	1.78	…	…	0.905	2.47 (2.06–2.96)*

CAC indicates coronary artery calcium; CAD2, CAD consortium model; Coef., beta-coefficient; LAH, local assessment of the heart model; and OR, odds ratio.

*For the LAH models, odds ratios in bold indicate (P<0.05).

†Compared with noncardiac chest pain.

define obstructive CAD, the CAD2 model obtained an AUC of 0.72, identical to the current study that uses CCTA instead.[10] In a larger study validated on a pooled cohort of 15 411 subjects from the Western Denmark Heart Registry, Danish study of Non-Invasive testing in Coronary Artery Disease and PROMISE studies by Winther et al., the CAD2 model obtained a comparable AUC of 0.75.[37] Other studies using ICA, fractional flow reserve (FFR), and stress testing end points produced similar results.[8,33] This robust performance has resulted in its inclusion in the European Society of Cardiology guidelines, with updated PTP recommendations.[6,28] Despite these multiple global validations, the current study is the first in a single mixed Asian ethnicity cohort.

The incorporation of the CAC score significantly improved diagnostic performance in both the CAD2 and LAH models. This is congruent with other studies, such as the validation of the CAD2 model in the PROMISE trial, where inclusion of CAC improved the AUC from

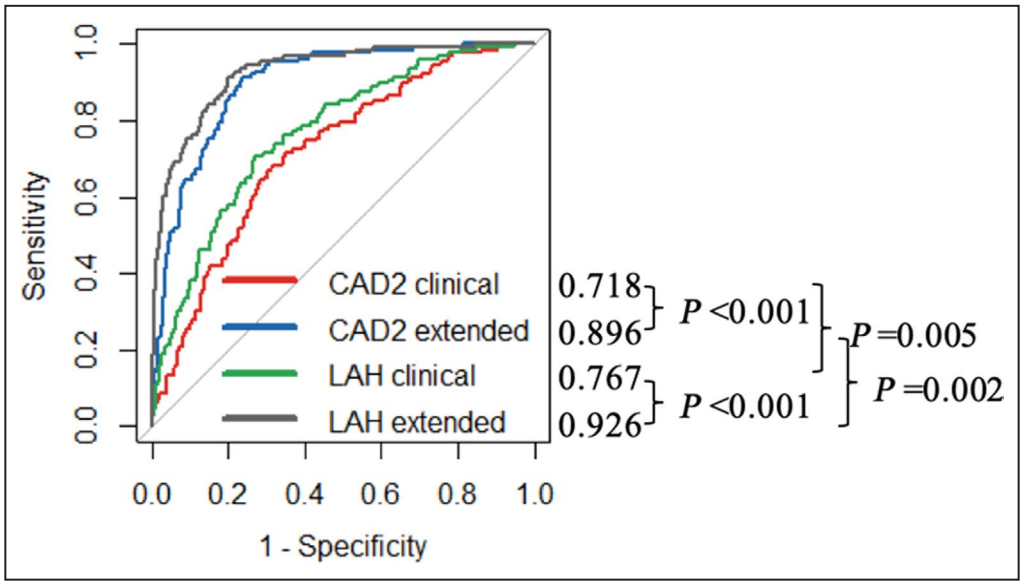

Figure 3. Comparison of ROC curves demonstrating discrimination of the CAD2 clinical (red), CAD2 extended (blue), LAH clinical (green), and LAH extended (grey) models in predicting obstructive CAD.

The respective AUC values are displayed in the legend. AUC indicates area under the curve; CAC, coronary artery calcium; CAD, coronary artery disease; CAD2, CAD consortium model; LAH, local assessment of the heart; and ROC, receiver operating characteristics.

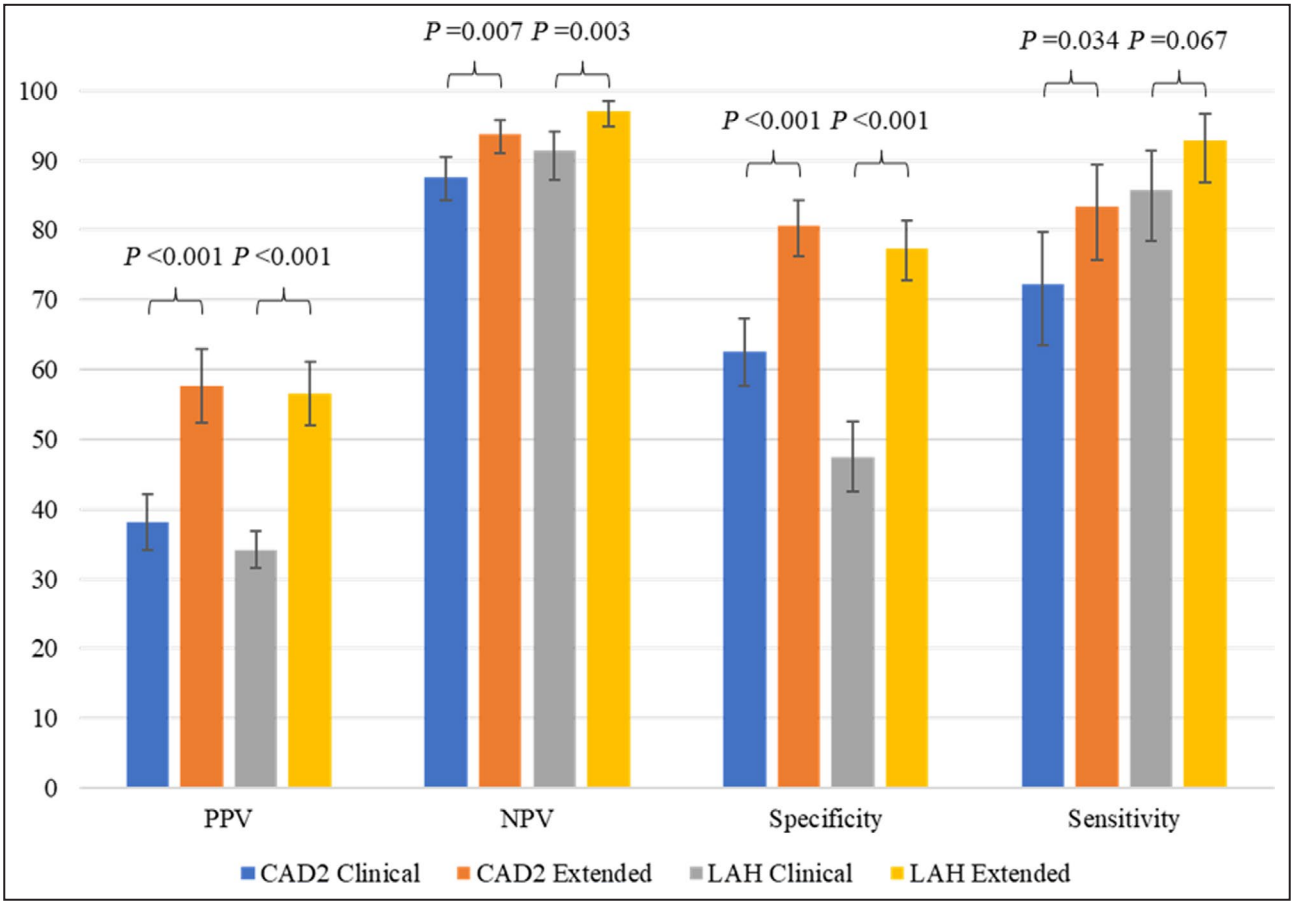

Figure 4. Comparison of the diagnostic performance of the CAD2 and LAH models in predicting obstructive CAD using a threshold PTP of 15% and including CAC.
CAC indicates coronary artery calcium; CAD, coronary artery disease; CAD2, CAD consortium model; LAH, local assessment of the heart; NPV, negative predictive value; PPV, positive predictive value; PTP, pretest probability.

0.72 to 0.86.[10] In the pooled cohort study by Winther et al., CAC improved the AUC from 0.75 to 0.85.[37] Overall, CAC improved the positive predictive value, negative predictive value, and specificity of both the CAD2 and LAH models. Compared with the CAD2 model, CAC incorporation did not significantly improve the sensitivity of the LAH clinical model, perhaps reflective of the better fit of this model to the cohort studied. Aside from the CAD2 model, other PTP models have also shown that CAC provided the strongest influence and improved performance significantly.[38–41] In a machine learning model developed using the CONFIRM cohort by Al'Aref et al., incorporation of the CAC score improved the AUC from 0.773 to 0.881, and feature ranking analysis showed that CAC scoring superseded all other clinical variables in determining obstructive CAD, including age and sex.[41]

With translatability across cohorts, the CAC score presents an uncomplicated, rapid, reproducible, and relatively low-cost method to function as a gatekeeper for further testing, including CCTA, CT perfusion, single-photon emission computed tomography–myocardial perfusion imaging, and ICA.[42,43] As CCTA has recently been endorsed in guidelines as an initial noninvasive test in assessing obstructive CAD, an increase in CCTA demand may be anticipated.[6,44,45] The incorporation of CAC assessment into PTP models may potentially reduce overburdening of CCTA provision in health care systems.

However, there may be pitfalls associated with CAC as a gatekeeper. In the present study, CAC=0 still had a prevalence of 14% for any CAD. This is comparable to a substudy of the PROMISE trial by Budoff et al., where this prevalence was 16%.[24] In a SCOT-HEART substudy, Williams et al. found the presence of CAD in 17% of the CAC=0 cohort, with a 1% event rate at 5 years.[46] This low event rate may be attributed to the use of preventative medication in 44% of the group. In the SCOT-HEART cohort 19.8% had a PTP of <15%, whereas the current study had a mean PTP of 13%.[47] A CONFIRM analysis by Villines et al. showed that CAC=0 had a negative predictive value of 96% for ≥50% stenosis. However, the presence of obstructive CAD in CAC=0 was associated with increased events

at 2 years.[25] In a study of 1753 symptomatic subjects, Wang et al. found a 10.3% prevalence of CAD in this group, with a 1.9 per 1000 person-years event rate over 2 years.[38] Therefore, CAC=0 may be associated with a nonnegligible risk of CAD and events, and its use as a gatekeeper should currently be limited to those with low-to-intermediate PTP until more substantial evidence suggests otherwise.

Limitations

The findings of this study must be read within the context of its design and accompanying limitations. First, this is a single-center study with a relatively small sample size within Singapore, and hence the findings may not be applicable to other geographic regions. However, it is one of the few studies evaluating the CAD2 model in a singular ethnically mixed Asian cohort. Furthermore, the LAH models were not externally validated. Future validation of the LAH model is required and planned within this working group. Evaluation of any PTP model should take into account local prevalence of disease.

Second, this study was retrospective with its inherent biases. As this registry was based on real clinical practice, a substantial proportion with stable chest pain may have been referred directly for other functional or anatomical testing based on individual clinician decision. However, this study is based on all-comers reflecting real-world clinical scenarios, including those with low likelihood of CAD, thus avoiding the selection bias inherent in some other studies, for example, those referred specifically for ICA. Contemporaneous inaccuracies from clinical history taking cannot completely be excluded. However, risk factor and symptom ascertainment used 2-way verification, and subjects failing this verification were excluded. Furthermore, sensitivity analysis including patients without 2-way verification of risk factor and symptom data did not affect the diagnostic performance of the respective models.

The current study was aimed at diagnostic rather than prognostic information and so may not be applicable with regard to guidance for preventative measures. This study used CCTA as a sole modality to define CAD, whereas a large body of studies examining the utility of the original Diamond Forrester, updated Diamond Forrester, and CAD2 scores used ICA.[8,19,29,33] When compared with ICA, CCTA has been shown to have false-positive findings in the detection of obstructive CAD.[48,49] Additionally, this study used obstructive CAD as an end point, rather than other physiological parameters such as FFR or FFR-CT. Although FFR-CT has been well validated and correlated to FFR, large definitive prognostic studies using FFR-CT have not been performed, whereas obstructive CAD was used in evaluating CCTA in the large-scale PROMISE and SCOT-HEART studies.[50–52] Furthermore, the wider usage of obstructive CAD as a definitive CT parameter in clinical practice, lower cost, and more global incorporation into clinical guidelines compared with FFR-CT may result in broader real-world applicability of the findings from this study.

Finally, although this study evaluated performance across sex and age, it did not evaluate performance between ethnicities, owing to inadequate power. The findings from this study cannot be generalized to the diverse Asian population as a whole, comprising 60% of humankind.[53] Furthermore, CAD burden can markedly vary between Asian ethnicities. Specifically, this study comprised a majority Chinese ethnicity component, known to have a lower CAD prevalence, while also consisting of a relatively small proportion of South Asian individuals, a diverse ethnic group that has been shown to have a higher prevalence of CAD and CVD risk.[54–57] However, it is representative of Singapore's ethnic composition, a unique singular cohort across 3 major Asian ethnicities.[26] In a separate study, whole genome sequencing uncovered 52 million novel variants with large genetic diversity within this population.[27] Larger studies are required to assess the value of guideline-recommended PTP models and CAC evaluation among various Asian geographies and ethnicities.

CONCLUSIONS

This study extended the global value of the CAD2 model in predicting obstructive CAD to a previously unrepresented mixed cohort of Asian subjects with stable chest pain within Singapore. Calibration to this population further improved performance. Incorporation of CAC in these models significantly improved the discrimination of obstructive CAD. These findings suggest a potential gatekeeping role for CAC scoring in guiding further downstream tests.

ARTICLE INFORMATION

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Supplemental Material

Table S1
Figure S1

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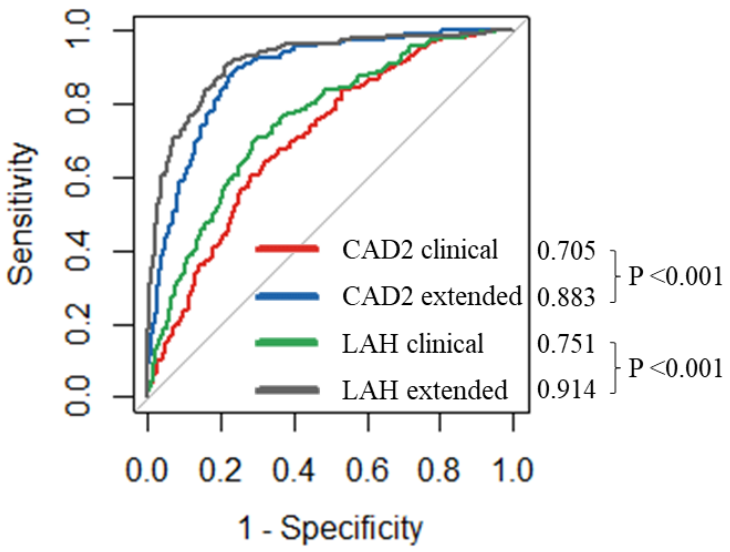
Supplemental Material

Table S1. Sensitivity analysis of diagnostic performance using 866 patients, including those without two-way confirmation of presence of risk factors or symptom typicality.

Model	TP	FP	TN	FN	PPV (95% CI)	NPV (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)
CAD2 Clinical	140	221	431	74	38.8 (35.4, 42.3)	85.3 (82.9, 87.5)	85.3 (82.9, 87.5)	65.4 (58.6, 71.8)
CAD2 Extended	176	129	523	38	57.7 (53.6, 61.7)	93.2 (91.1, 94.8)	93.2 (91.1, 94.8)	82.2 (76.5, 87.1)
P-value					**<0.001**	**<0.001**	**<0.001**	**<0.001**
LAH Clinical	183	364	288	31	33.5 (31.5, 35.4)	90.3 (87, 92.8)	90.3 (87, 92.8)	85.5 (80.1, 89.9)
LAH Extended	197	163	489	17	54.7 (51.3, 58.1)	96.6 (94.8, 97.9)	96.6 (94.8, 97.9)	92.1 (87.6, 95.3)
P-value					**<0.001**	**<0.001**	**<0.001**	**0.032**

CAC, coronary artery calcium; CAD, coronary artery disease; CAD2, CAD consortium model; FN, false negative; FP, false positive; LAH, local assessment of the heart; NPV, negative predictive value; PPV, positive predictive value; PTP, pre-test probability; TN, true negative; TP, true positive

Figure S1. Sensitivity analysis of discriminatory performance using 866 patients, including those without two-way confirmation of presence of risk factors or symptom typicality.



Comparison of ROC curves demonstrating discrimination of the CAD2 clinical (red), CAD2 extended (blue), LAH clinical (green), and LAH extended (grey) models in predicting obstructive CAD. The respective AUC values are displayed in the legend. AUC; area under the curve; CAC, coronary artery calcium; CAD, coronary artery disease; CAD2, CAD consortium model; LAH, local assessment of the heart; ROC; receiver operating characteristics