Simplified Approach to Predicting Obstructive Coronary Disease With Integration of Coronary Calcium: Development and External Validation

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Abstract: BACKGROUND The Diamond-Forrester model was used extensively to predict obstructive coronary artery disease (CAD) but overestimates probability in current populations. Coronary artery calcium (CAC) is a useful marker of CAD, which is not routinely integrated with other features. We derived simple likelihood tables, integrating CAC with age, sex, and cardiac chest pain to predict obstructive CAD. METHODS AND RESULTS The training population included patients from 3 multinational sites (n=2055), with 2 sites for external testing (n=3321). We determined associations between age, sex, cardiac chest pain, and CAC with the presence of obstructive CAD, defined as any stenosis ≥50% on coronary computed tomography angiography. Prediction performance was assessed using area under the receiver-operating characteristic curves (AUCs) and compared with the CAD Consortium models with and without CAC, which require detailed calculations, and the updated Diamond-Forrester model. In external testing, the proposed likelihood tables had higher AUC (0.875 [95% CI, 0.862-0.889]) than the CAD Consortium clinical+CAC score (AUC, 0.868 [95% CI, 0.855-0.881]; P=0.030) and the updated Diamond-Forrester model (AUC, 0.679 [95% CI, 0.658-0.699]; P<0.001). The calibration for the likelihood tables was better than the CAD Consortium model (Brier score, 0.116 versus 0.121; P=0.005). CONCLUSIONS We have developed and externally validated simple likelihood tables to integrate CAC with age, sex, and cardiac chest pain, demonstrating improved prediction performance compared with other risk models. Our tool affords physicians with the opportunity to rapidly and easily integrate a small number of important features to estimate a patient's likelihood of obstructive CAD as an aid to clinical management.

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ORIGINAL RESEARCH

Simplified Approach to Predicting Obstructive Coronary Disease With Integration of Coronary Calcium: Development and External Validation

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Key Words: cardiovascular computed tomography ■ coronary artery disease ■ epidemiology ■ risk estimation

When evaluating patients with suspected coronary artery disease (CAD), physician decisions on appropriate testing and patient management rely heavily on estimations of patients' likelihood of obstructive CAD.[1,2] The original Diamond-Forrester model has been used extensively for this purpose because of its simplicity.[3] However, the prevalence of obstructive CAD has decreased over time.[4] As a result, the original Diamond-Forrester model tends to overestimate prevalence of obstructive CAD.[5,6]

Genders et al recently updated the Diamond-Forrester model to better reflect contemporary patients

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CLINICAL PERSPECTIVE

What Is New?

- We developed and validated simple likelihood tables to integrate coronary artery calcium with age, sex, and cardiac chest pain, with improved prediction performance for obstructive coronary artery disease compared with other models.
- Integrating coronary artery calcium was primarily responsible for the improved performance compared with existing risk scores.

What Are the Clinical Implications?

- The likelihood tables offer a simple way for clinicians to rapidly integrate a small number of clinical features to more accurately predict the presence of obstructive coronary artery disease.
- Physicians may be able to use this information to improve test selection or target medical therapies.

Nonstandard Abbreviations and Acronyms

Cons-CAC	coronary artery disease consortium clinical and coronary artery calcium model
Cons-Clin	coronary artery disease consortium clinical model

using a cohort of 2260 patients for retraining and 454 patients for testing.[5] The model could potentially be further informed by using coronary artery calcium (CAC) scoring. CAC is a robust marker of atherosclerosis,[7] which is highly predictive of obstructive CAD,[8] making it an ideal component for models aimed at predicting obstructive CAD. The CAD Consortium developed a basic model (age, sex, and symptoms) and a clinical model (Cons-Clin; age, sex, symptoms, and medical history), which were significantly improved upon by considering CAC (Cons-CAC; clinical model and CAC) when predicting obstructive CAD.[9,10] However, these models require detailed calculations that physicians would need to access online calculators to complete. In comparison, 1 of the major advantages of the original Diamond-Forrester model was that predicted probabilities could be referenced quickly using likelihood tables posted in clinical areas for easy access.

In this study, we aimed to address this clinical need by replicating the simplicity of the original Diamond-Forrester model by generating likelihood tables that incorporate CAC with the most pertinent patient features (age, sex, and cardiac chest pain). We derived the likelihood tables using 3 large, international populations undergoing coronary computed tomography angiography (CCTA). We then tested the prediction performance and calibration of the likelihood tables in a separate external population with comparisons to existing risk models.

METHODS

Patient Populations

The training population included patients from 3 separate sites (Henry Ford Hospital [n=853], Ottawa Heart Institute [n=808], and University Hospital Zurich [n=394]). The testing population included patients undergoing CCTA from Cedars-Sinai Medical Center (n=1632) or Academic Hospital Parma Italy (n=1689). The populations used for external testing were selected randomly to include both European and North American populations. However, this selection also led to a similar proportion of obstructive CAD between populations (23.0% versus 23.3%; P=0.795). All CCTA was performed during routine clinical practice, with interpretation performed at the time. Studies deemed nondiagnostic at the time of clinical reporting were not included. We excluded patients with known CAD, defined as previous myocardial infarction or revascularization.[11] The study protocol was approved by the institutional review boards of all centers, and, when required, all patients provided written informed consent. Data will be made available to the extent allowed by data sharing agreements, on receipt of written request.

Data Elements

Clinical demographics and medical history were collected at the time of CCTA. Chest pain was collected as typical chest pain, atypical chest pain, or nonanginal chest pain using standardized criteria.[12] However, patients with typical chest pain were classified as having cardiac chest pain and all other patients were classified as having noncardiac chest pain to be consistent with current guidelines.[2]

CCTA Acquisition and Interpretation

All testing, data acquisition, and image postprocessing were performed in accordance with the Society of Cardiovascular Computed Tomography guidelines.[13] All studies were uniformly acquired by multidetector row computed tomography scanners of ≥64 rows with radiation dose reduction strategies. CAC score was measured using established methods.[14] CAC score was categorized as follows: 0, 1 to 100, 101 to 400, 401 to 1000, and >1000.

Each site interpreted CCTA in accordance with Society of Cardiovascular Computed Tomography guidelines.[13] A 16-segment coronary artery tree model

was used at all sites. In each coronary segment, coronary atherosclerosis was defined as any tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. Each identified lesion was examined with the use of maximum intensity projection and multiplanar reconstruction techniques along multiple longitudinal axes and in the transverse plane. To be concordant with the previous approaches to prediction of CAD, obstructive disease was defined as stenosis >50%.[15] We also evaluated prediction performance using the criteria of 50% left main stenosis or ≥70% stenosis in the 3 other vessels.

Likelihood Table Development

A mixed-effect logistic regression model was used to identify features associated with the presence of obstructive coronary artery disease. In the primary model, we evaluated associations with age, sex, CAC, and the presence of cardiac chest pain. We evaluated several definitions of chest pain, including typical only, typical or atypical, and any chest pain (typical, atypical, or nonanginal).[10,15] The increase in likelihood-ratio χ^2 was highest with the use of typical angina alone (15.3 for typical angina, 5.9 for typical or atypical angina, and 1.08 for any chest pain; $P<0.01$ for all), and therefore, this was used in the model. We evaluated the potential first-order interactions between variables in the model, with age and CAC modeled as continuous variables. Interactions that were considered of potential importance ($P<0.100$) were included in the analysis to ensure that the model reflected differential effects across categories. Site was treated as a random effect to account for variability between sites.[16] Age and CAC were modeled as categorical variables. We also evaluated a model considering medical history. However, there was minimal improvement in prediction performance with the addition of medical history, and this would increase complexity for likelihood tables. Last, we evaluated a model without cardiac chest pain to evaluate its importance in the prediction. The models were developed in the training population and used to predict likelihood of obstructive CAD for each potential group.

Comparison Models

We compared the new model with the updated Diamond-Forrester model, as previously described.[5] We also evaluated the performance of the European Society of Cardiology pretest probability tables.[1] In addition, we compared our likelihood tables to the Cons-Clin and Cons-CAC models.[9,10] The Cons-Clin model incorporates age, sex, cardiac chest pain, hypertension, diabetes, dyslipidemia, and smoking. The Cons-CAC model incorporates the components of the clinical model plus CAC. Both scores are calculated by multiplying each variable by the associated β coefficient and then summing the subsequent values and converting this to an expected probability of CAD.

Positron Emission Tomography Cohort

To better evaluate the performance of the model when applied in a population with higher baseline risk, we also evaluated a cohort of 3074 consecutive patients without known CAD undergoing positron emission tomography (PET) myocardial perfusion imaging with CAC scanning at Cedars-Sinai Medical Center. Patients without known CAD routinely had CAC scores acquired. PET interpretation was performed by expert visual interpretation of perfusion using the standard 17-segment, 5-point scoring with the summed stress score >3[17] being considered abnormal. Prediction performance for abnormal perfusion was used as the outcome, because not all patients were referred for subsequent invasive coronary angiography. However, none of the evaluated risk scores were developed for this outcome.

Statistical Analysis

Categorical variables were summarized as number (proportion) and compared with a χ^2 or Fisher exact test as appropriate. Continuous variables were summarized as mean (SD) if normally distributed and median (interquartile range) otherwise. Receiver operating characteristic curves for identifying patients with obstructive CAD were generated, and area under the receiver operating characteristic curve (AUC) was used to compare prediction performance of models using the method described by Delong et al.[18] Model calibration was assessed with calibration graphs and Brier scores, including assessment across important subgroups.[19,20] These analyses were performed in both the training population and the external testing populations. Prediction performance for abnormal myocardial perfusion and revascularization was assessed in the PET population. No missing data were present, and all analyses were performed using Stata, version 14.2.

RESULTS

Patient Populations

There were 2055 patients in the training population and 3321 in the external testing population, as shown in Table 1. Patients in the training population were younger (median age, 58 versus 62 years; $P<0.001$) and less likely to have cardiac chest pain (11.3% versus 19.6%; $P<0.001$) compared with patients in the external testing population. Prevalence of obstructive CAD was similar in the training and external testing

populations (23.0% versus 23.3%; *P*=0.795). Details of patients with and without obstructive CAD in both cohorts are shown in Table S1. The distribution of CAC scores across age categories in the training population is shown in Table S2.

Predictors of Obstructive CAD

The multivariable logistic regression model used to derive predicted probabilities is shown in Table 2. Increasing CAC category was the strongest predictor of the presence of obstructive CAD. Compared with patients with CAC 0, the adjusted odds ratio (OR) ranged from 10.0 (95% CI, 4.6–22.1; *P*<0.001) for patients with CAC 1 to 99, to 146 (95% CI, 40.8–520; *P*<0.001) for patients with CAC ≥1000. The final multivariable model included an interaction between male sex and cardiac chest pain (interaction OR 1.34; *P*=0.035) and an interaction between male sex and CAC (interaction OR 0.85; *P*=0.007).

The likelihood tables derived from the logistic regression model in the training population according to age, sex, and the presence of cardiac chest pain are shown in Figure 1. The relationship between CAC scores, age, sex, and presence or absence of cardiac chest pain is also expressed as a series of likelihood curves, as shown in Figure 2. Patients with CAC 0 had a low (<5%) likelihood of obstructive CAD regardless of age, sex, and chest pain history. With increasing CAC, there was an increasing prevalence of obstructive CAD, with almost all patients with CAC ≥400 having >50% likelihood of obstructive CAD. Among patients with cardiac chest pain, almost all patients with CAC ≥100 had a high likelihood (>50%) of obstructive CAD. Among female patients without cardiac chest pain, almost all patients with CAC <100 had a low (<15%) likelihood of obstructive CAD, except for patients aged 50 to 59 years (15.2% likelihood of obstructive CAD). Probability of obstructive CAD as a function of CAC alone is shown in Table S3.

Table 1. Baseline Population Characteristics

Variables	Training population (n=2055)	External testing population (n=3321)	*P* value
Age, median (IQR), y	58 (49–65)	62 (52–71)	<0.001
<40 y, n (%)	140 (6.8)	198 (6.0)	
40–49 y, n (%)	383 (18.6)	438 (13.2)	
50–59 y, n (%)	632 (30.8)	775 (23.3)	
60–69 y, n (%)	588 (28.6)	968 (29.2)	
≥70 y, n (%)	312 (15.2)	942 (28.4)	<0.001
Male sex, n (%)	1093 (53.2)	1934 (58.2)	<0.001
Cardiac chest pain, n (%)	232 (11.3)	651 (19.6)	<0.001
Noncardiac chest pain, n (%)	675 (32.9)	929 (28.0)	<0.001
CAD risk factors, n (%)			
Hypertension	1264 (61.5)	1874 (56.4)	<0.001
Dyslipidemia	1159 (56.4)	1889 (56.9)	0.729
Diabetes	336 (16.4)	416 (12.5)	<0.001
Smoking	370 (18.0)	743 (22.4)	<0.001
CAC score, median (IQR)	13 (0–164)	16 (0–213)	0.237
CAC score group, n (%)			
0	813 (39.6)	1352 (40.7)	
1–99	611 (29.7)	824 (24.8)	
100–399	331 (16.1)	594 (17.9)	
400–999	196 (9.5)	316 (9.5)	
≥1000	104 (5.1)	235 (7.1)	<0.001
Obstructive CAD (stenosis ≥50%), n (%)	472 (23.0)	773 (23.3)	0.795
Obstructive CAD (stenosis ≥70%*), n (%)	255 (12.4)	513 (15.5)	0.002
Proximal LAD ≥70%, n (%)	75 (3.7)	138 (4.2)	0.356
Proximal circumflex ≥70%, n (%)	30 (1.5)	61 (1.8)	0.298
Proximal RCA ≥70%, n (%)	59 (2.9)	93 (2.8)	0.879
Left main ≥50%, n (%)	26 (1.3)	43 (1.3)	0.925

Population characteristics are given for the derivation and external testing populations. CAC indicates coronary artery calcification; CAD, coronary artery disease; IQR, interquartile range; LAD, left anterior descending; and RCA, right coronary artery.

*Also includes patients with left main stenosis ≥50%.

Table 2. Multivariable Logistic Regression Model With Mixed Effects in Training Data

Variable	Odds ratio (95% CI)	*P* value
Age categories, y		
<40	Reference	…
40–49	1.32 (0.46–3.84)	0.607
50–59	1.72 (0.61–4.83)	0.304
60–69	1.36 (0.48–3.86)	0.559
≥70	1.31 (0.45–3.78)	0.617
Male sex	1.65 (0.6–4.52)	0.330
Cardiac chest pain	2.15 (1.23–3.76)	0.007
CAC score group		
0	Reference	…
1–99	10.0 (4.6–22.1)	<0.001
100–399	37.3 (16.7–83.1)	<0.001
400–999	91.3 (37.3–223)	<0.001
≥1000	146 (40.8–520)	<0.001

The multivariable model also included interactions between sex and cardiac chest pain, as well as an interaction between sex and CAC category. CAC indicates coronary artery calcium.

Prediction for Obstructive CAD: Training Population

Prediction performance for obstructive CAD, defined as stenosis ≥50% in any vessel, in the training population using receiver operating characteristic curves is shown in Figure 3. The proposed likelihood tables had higher AUC (AUC, 0.866 [95% CI, 0.848–0.883]) compared with Cons-CAC (AUC, 0.852 [95% CI, 0.834–0.871]), Cons-Clin (AUC, 0.720 [95% CI, 0.695–0.746]), European Society of Cardiology pretest probability (AUC, 0.685 [95% CI, 0.659–0.712]), and the updated Diamond-Forrester models (AUC, 0.698 [95% CI, 0.671–0.624]; *P*<0.01 for all). Both models with CAC significantly outperformed models without CAC (*P*<0.001 for all). The prediction performance for CAC category alone (AUC, 0.852 [95% CI, 0.834–0.870]) was similar to the Cons-CAC model (*P*=0.929) but was lower compared with the likelihood tables (*P*<0.01). The likelihood table prediction performance was not significantly lower without inclusion of cardiac chest pain (AUC, 0.860 [95% CI, 0.842–0.878]; *P*=0.088). The calibration for the likelihood tables was better compared with the Cons-CAC model (Brier score, 0.118 versus 0.128), with calibration graph shown in Figure S1.

Prediction for Obstructive CAD: External Testing Population

Prediction performance for obstructive CAD, defined as stenosis ≥50% in any vessel, in the external population is shown in Figure 4. The proposed likelihood tables had higher AUC (AUC, 0.875 [95% CI, 0.862–0.889]) compared with Cons-CAC (AUC, 0.868 [95% CI, 0.855–0.881]; *P*=0.030), Cons-Clin (AUC, 0.738 [95% CI, 0.719–0.757]; *P*<0.001), European Society of Cardiology pretest probability (AUC, 0.665 [95% CI, 0.644–0.685]; *P*<0.001), and the updated

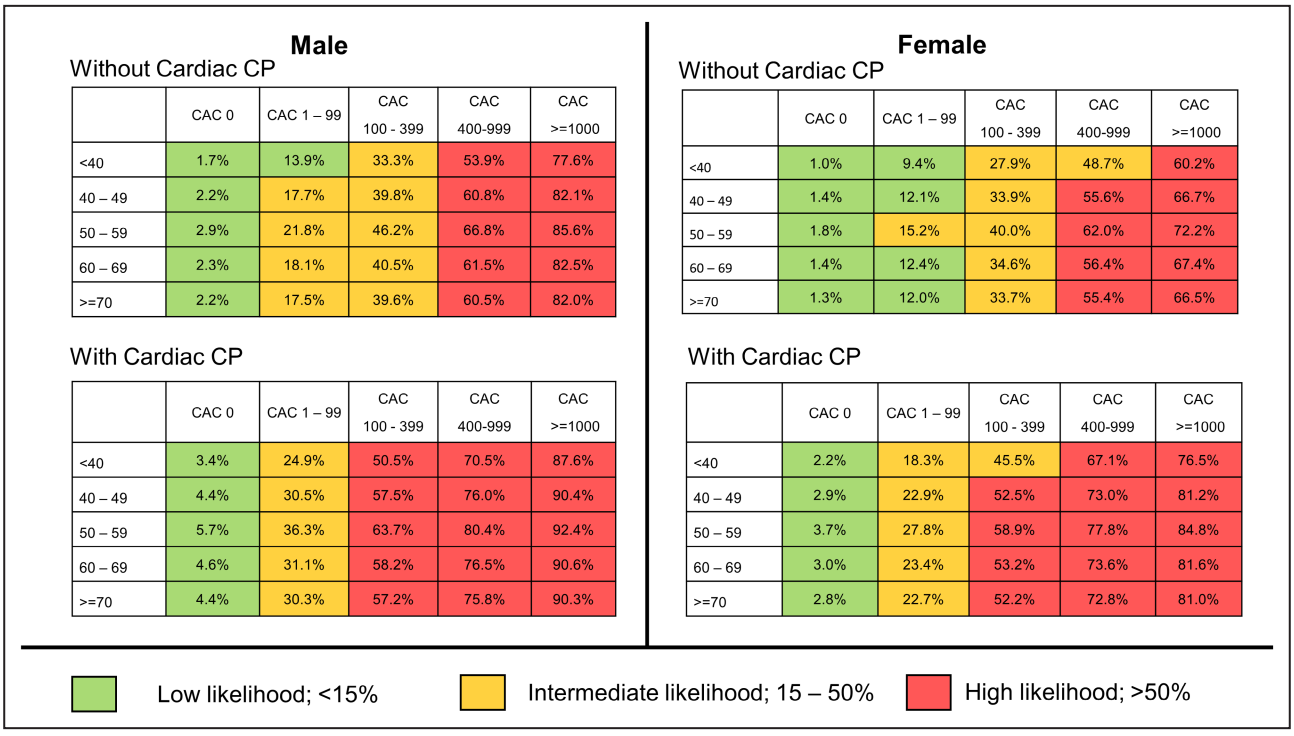

Figure 1. Predicted probability of coronary artery disease, defined as stenosis ≥50% in any vessel, according to age, sex, cardiac chest pain (CP), and coronary artery calcium (CAC) score.

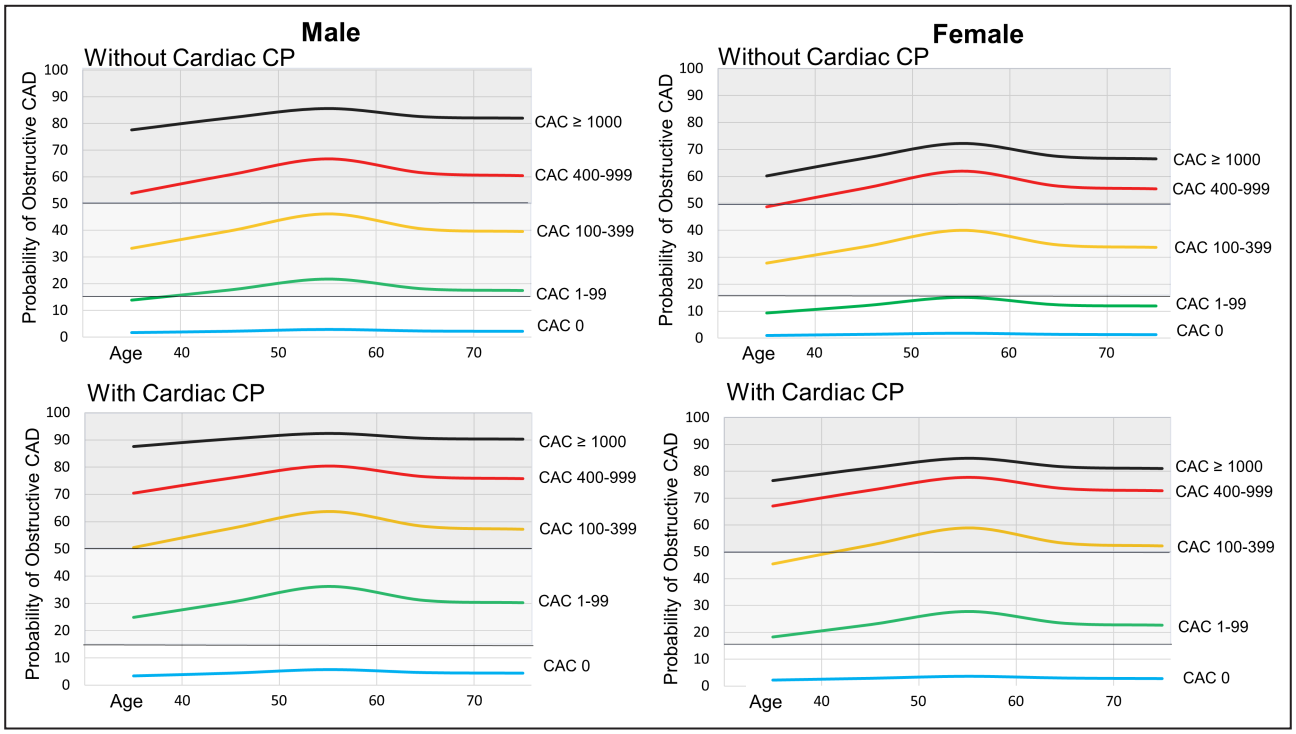

Figure 2. Predicted probability of obstructive coronary artery disease (CAD), defined as stenosis ≥50% in any vessel, according to sex, cardiac chest pain (CP), and coronary artery calcium (CAC) score.

Diamond-Forrester models (AUC, 0.679 [95% CI, 0.658–0.699]; *P*<0.001). Both models with CAC significantly outperformed models without CAC (*P*<0.001 for all). The prediction performance for CAC category alone (AUC, 0.865 [95% CI, 0.851–0.878]) was lower compared with the likelihood tables (*P*<0.01) but similar to the Cons-CAC model (*P*=0.453).

The calibration for the likelihood tables was improved compared with the Cons-CAC model (Brier score, 0.116 versus 0.121; *P*=0.005), with calibration graph shown in Figure S2. Calibration was better in women compared with men (Brier score, 0.093 versus 0.131; *P*<0.001), and in patients with CAC <400 compared with CAC ≥400 (Brier score, 0.098 versus 0.205; *P*<0.001).

Prediction for ≥50% Left Main or ≥70% Stenosis

Likelihood tables for ≥50% left main stenosis or ≥70% stenosis in other vessels are shown in Figure S3. Prediction performance for ≥50% left main stenosis or ≥70% stenosis in other vessels in the training population is shown in Figure S4. In the external testing population, prediction performance was not significantly different for the proposed likelihood tables (AUC, 0.859 [95% CI, 0.843–0.874]) compared with the Cons-CAC model (AUC, 0.857 [95% CI, 0.841–0.873]; *P*=0.283) (Figure S5). However, both models with CAC had significantly higher prediction performance compared with models without CAC (*P*<0.001).

Prediction Performance in PET Population

We included a PET population to evaluate model performance in a higher-risk population. Details of the PET population are shown in Table S4. The AUC for predicting abnormal myocardial perfusion was similar for the likelihood tables (AUC, 0.672 [95% CI, 0.645–0.700]) and the Cons-CAC model (AUC, 0.672 [95% CI, 0.646–0.700]), with full results in Figure S6. The prediction performance for the likelihood tables and Cons-CAC model was significantly higher than that of models without CAC (*P*<0.01 for all).

DISCUSSION

Accurately estimating a patient's likelihood of obstructive CAD is central to informing diagnostic strategies and management plans. To this end, guidelines suggest that physicians use contemporary risk scores[4,21] in conjunction with clinical factors, such as age and CAC information, when available.[1,2] Although various likelihood algorithms have been proposed, there is a need to make their use as simple as possible to foster widespread clinical use. To address this need, we

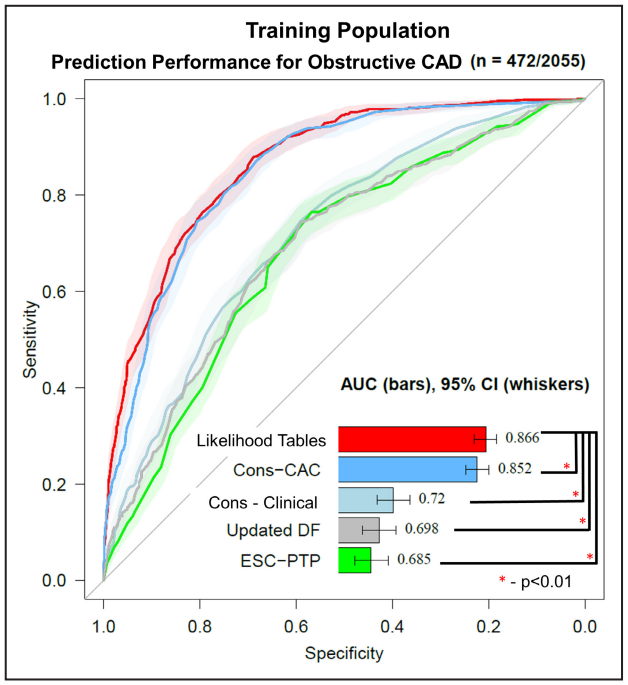

Figure 3. Prediction performance for obstructive coronary artery disease (CAD), defined as any stenosis ≥50%, in the training population.
AUC indicates area under the receiver-operating characteristic curve; Cons-CAC, CAD Consortium clinical and coronary artery calcium model; Cons-Clinical, CAD Consortium clinical model; DF, Diamond-Forrester; and ESC-PTP, European Society of Cardiology pretest probability.

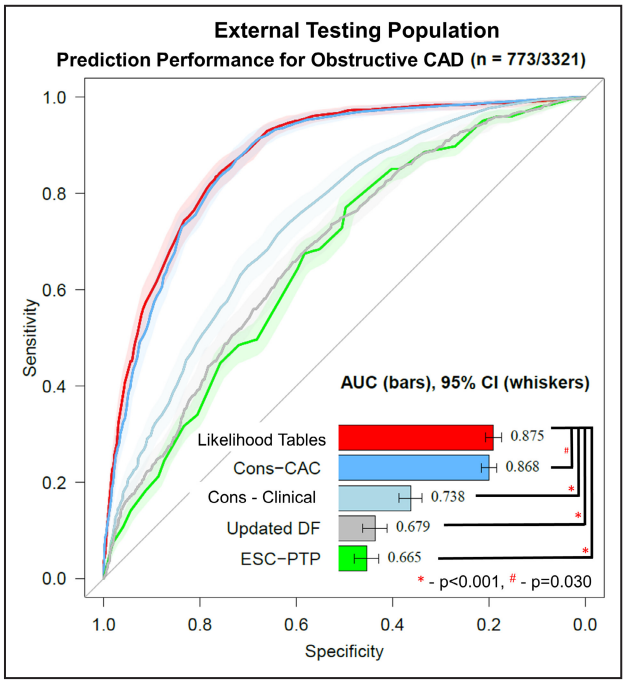

Figure 4. Prediction performance for obstructive coronary artery disease (CAD), defined as any stenosis ≥50%, in the external testing population.
AUC indicates area under the receiver-operating characteristic curve; Cons-CAC, CAD Consortium clinical and coronary artery calcium model; Cons-Clinical, CAD Consortium clinical model; DF, Diamond-Forrester; and ESC-PTP, European Society of Cardiology pretest probability.

developed simplified likelihood tables to predict a patient's likelihood of having obstructive CAD from age, sex, chest pain history, and CAC. Simplification is useful only if it does not result in a significant loss of diagnostic accuracy. We found that our simplified likelihood tables had high predictive performance for obstructive CAD, including higher prediction performance in external testing compared with the CAD Consortium models. More important, although prediction performance was higher, the likelihood tables should be substantially easier to use as no calculations are required. In addition, the likelihood tables have improved calibration compared with the CAD Consortium models, suggesting good correlation between predicted and actual likelihood of obstructive CAD. Last, prediction performance for the likelihood tables was similar to more complicated models when applied in a higher-risk population undergoing PET. This information could potentially be used by physicians to make decisions on testing or treatment strategies for patients with suspected obstructive CAD.

For many years, the original Diamond-Forrester model was used extensively for estimating a patient's pretest probability of obstructive CAD. An important characteristic of its appeal was its ease of use. The relationship between symptoms, sex, and likelihood of obstructive CAD could be determined with a quick glance. However, the original Diamond-Forrester model was developed when the prevalence of obstructive CAD was significantly higher than today.[3] Since then, advances in therapeutics and prevention have resulted in a marked decline in the incidence of severity of myocardial infarction[22] and frequency of inducible myocardial ischemia.[23] Correspondingly, the original Diamond-Forrester algorithm overestimates the likelihood of obstructive CAD in contemporary populations.[4] Since this realization, there has been a concerted effort to develop an updated algorithm for predicting obstructive CAD, which would perform well in contemporary populations and be broadly accepted into clinical practice.

Our novel likelihood tables address this need by ensuring high prediction performance while maintaining the simplicity provided by the original Diamond-Forrester model. The updated Diamond-Forrester model may have higher prediction performance when applied in populations with a higher prevalence of cardiac chest pain and male patients (AUC, 0.767), as demonstrated previously by Baskaran et al.[10] However, the prediction performance in the same population

was significantly lower in women (AUC, 0.686). The likelihood tables had high predictive performance in both internal and external testing. In addition, our likelihood tables were well calibrated, suggesting good agreement between predicted and actual prevalence of obstructive CAD, which can impact downstream management.[24] Last, we evaluated performance in a PET population, demonstrating better prediction performance for the likelihood tables compared with risk models without CAC in terms of predicting abnormal perfusion. In combination, these results suggest that the proposed likelihood tables should be broadly generalizable to current populations.

In our likelihood tables, patients with a CAC of 0 had a low likelihood of obstructive CAD regardless of age and sex. In addition, even in the presence of cardiac chest pain, a 0 CAC score was associated with a <10% likelihood of obstructive CAD in men and a <5% likelihood in women, across the span of age groups. Calcium scores of 100 to 399 were generally associated with an intermediate likelihood of CAD, except in patients with cardiac chest pain, in whom the likelihood of obstructive CAD was higher. The presence of CAC >400 was associated with a >50% likelihood of obstructive CAD in almost all patients. In fact, CAC was the dominant feature in our model, with only modest improvements in prediction performance by integrating chest pain, age, and sex. Interestingly, the probability of obstructive CAD plateaued for most CAC groups after the age of 50 years. We identified that older patients were more likely to be in higher CAC categories. As a corollary, patients with higher CAC scores at a younger age have more accelerated disease compared with older patients with similar CAC scores, at least partially accounting for the influence of age. For example, a 50-year-old male patient with calcium score of 100 would be in the 89th percentile for age and sex, but only the 24th percentile with the same calcium score at the age of 80 years.[25] In addition, we excluded patients with known CAD, which likely leads to some selection bias. This may be particularly relevant to older patients, because they had survived to that age without experiencing cardiovascular events. However, these probability tables were designed for use in patients without known CAD and, therefore, the populations are reflective of the patients where they would be applied.

To further assess the utility of our model, we compared it with other recent algorithms. One of the most comparable approaches to our current study is the updated Diamond-Forrester model, which integrates age, sex, and chest pain to derive pretest probabilities, but with updated predictions to perform better in contemporary populations.[5] Our model, which incorporates CAC, showed substantially higher prediction performance in training and external testing populations. In our study, model performance was not meaningfully improved by considering risk factors, making it possible to determine probability of obstructive CAD without the interim step of calculating clinical pretest probability.[21] Increasingly complex models have also been proposed by the CAD Consortium.[9] The models can incorporate age, sex, medical history, and CAC information, with calculation of pretest probability using dedicated online calculators to combine the contributions from each feature. Although incorporating more information into prediction models tends to improve the accuracy of predictions, each additional variable adds to the complexity and time required for calculations. More important, even if these calculations were automated, the inclusion of more features increases the probability that some data will be missing. Our previous work showed that removing variables is one of the most effective ways for dealing with missing values,[26] further supporting a role for simplified prediction tools. It may be possible to fully integrate multiple prediction models (to account for missing values), but the data infrastructure to support these types of tools is not routinely available in most electronic medical records. This is particularly true for community practices, where many of the initial decisions about testing take place. Last, we have previously demonstrated that with machine learning models for major adverse cardiovascular event prediction, it is possible to maintain prediction performance while reducing the number of variables by >75%,[27] by focusing on inclusion of the most important predictors. In this case, CAC is the most important predictor in both the proposed likelihood tables and the CAD Consortium model. The practical difference between our model and the CAD Consortium model is the relative simplicity of the likelihood tables and their easy implementation, requiring simply the 4 variables of age, sex, cardiac chest pain, and CAC score.

An important predictor of CAD in our model was the extent of CAC. In fact, both the current and the Consortium-CAC models that incorporated CAC had significantly higher prediction performance compared with models without this information. In addition, there was only a small improvement by incorporating CAC into a model compared with CAC alone. These findings highlight the role for CAC to estimate probability of CAD, a marker of atherosclerosis, by providing a measure of the cumulative, lifetime effects of all atherogenic factors in an individual patient. CAC overcomes the limitations of global risk factor scores, which fail to account for the chronicity or magnitude of the risk factors, and numerous known risk factors, which are not included in the scores and unknown factors.[28] Physicians reporting the results of CAC scans could potentially include the likelihood of obstructive CAD, derived from the proposed likelihood tables in the CAC scan report. This could guide referring physicians on the need for additional testing and facilitate earlier targeted medical

therapy in appropriate individuals.[29] For example, a 65-year-old woman with noncardiac chest pain would have a pretest probability of 28% for obstructive CAD with the updated Diamond-Forrester model. If her CAC was 10, she would be low risk using the likelihood tables proposed here, and her physician may decide that additional testing is not needed but may still consider intensifying medical therapy. If her CAC was 0, the physician may decide that no additional testing or change in medical therapy was needed. Among higher-risk patients, this information would give physicians the opportunity to assess the impact of medical therapy on chest pain symptoms while awaiting additional testing, because this information would help guide future revascularization decisions.

Limitations

Our study has several limitations. The score was derived and tested in patients undergoing CCTA with available CAC scores, which is typically a lower-risk population compared with patients undergoing myocardial perfusion imaging. However, prediction performance was also good in a PET referral population for the outcomes of abnormal perfusion and revascularization. In addition, there were significant differences between the training and external testing populations, suggesting the proposed risk tables may be broadly generalizable. The model incorporates CAC, which is currently not available for most patients presenting with suspected CAD. However, CAC can also be estimated from standard nongated, noncontrast chest computed tomography[30,31] or quantified automatically from nongated computed tomography attenuation scans using artificial intelligence[32–34]; therefore, CAC assessment could potentially be available in a much larger proportion of patients. For example, Peng et al recently demonstrated that CAC could be derived automatically from chest computed tomography scans performed for a variety of reasons to help predict cardiovascular events.[35] The use of CCTA as the standard for assessment of percentage coronary stenosis assumes equivalence of this assessment by CCTA and invasive angiography. Particularly in heavily calcified lesions, interpreters may overestimate the degree of stenosis on CCTA,[36] potentially inflating the prevalence of obstructive CAD in the high CAC groups. This could be contributing to the high prediction performance of CAC.[37] Future studies should evaluate the prediction performance and calibration when applied to cohorts of patients undergoing invasive angiography. We used cohorts of patients who underwent CCTA, and it is possible that this may overestimate population prevalence of obstructive CAD, because many low-risk patients may not be referred for testing.[1,2] However, previous models have been developed using invasive coronary angiography populations,[5] which would be expected to be higher risk, leading to greater overestimation. Last, we do not have information on racial or ethnic characteristics of our populations and, therefore, are not able to incorporate these into the likelihood tables.

CONCLUSIONS

We have developed and externally validated simple likelihood tables incorporating CAC, age, sex, and cardiac chest pain in symptomatic patients, which had higher prediction performance for obstructive CAD compared with the updated Diamond-Forrester and CAD Consortium clinical and CAC models. Our tool affords physicians with the opportunity to rapidly and easily integrate age, sex, symptoms, and CAC to estimate a patient's likelihood of obstructive CAD as an aid to clinical management.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S6

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