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ORIGINAL ARTICLE

Pre-screening for non-diagnostic coronary computed tomography angiography

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Abstract

Aims

Indiscriminate coronary computed tomography angiography (CCTA) referrals for suspected coronary artery disease could result in a higher rate of equivocal and non-diagnostic studies, leading to inappropriate downstream resource utilization or delayed time to diagnosis. We sought to develop a simple clinical tool for predicting the likelihood of a non-diagnostic CCTA to help identify patients who might be better served with a different test.

Methods and results

We developed a clinical scoring system from a cohort of 21 492 consecutive patients who underwent CCTA between February 2006 and May 2021. Coronary computed tomography angiography study results were categorized as normal, abnormal, or non-diagnostic. Multivariable logistic regression analysis was conducted to produce a model that predicted the likelihood of a non-diagnostic test. Machine learning (ML) models were utilized to validate the predictor selection and prediction performance. Both logistic regression and ML models achieved fair discriminate ability with an area under the curve of 0.630 [95% confidence interval (CI) 0.618–0.641] and 0.634 (95% CI 0.612–0.656), respectively. The presence of a cardiac implant and weight >100 kg were among the most influential predictors of a non-diagnostic study.

Conclusion

We developed a model that could be implemented at the 'point-of-scheduling' to identify patients who would be best served by another non-invasive diagnostic test.

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Graphical Abstract

Variable			
Age (y)			
<65 0 pts		≥65 8 pts	
Male 1 pt			
Weight (kg)			
<50 0 pts	50-75 1 pt	75-100 2 pts	>100 4 pts
Baseline Systolic BP (mmHg)			
<120 -1 pt	120-159 0	≥160 1 pt	
Chest pain -1 pt			
Hypertension 2 pts			
Hyperlipidemia 1 pt			
Smoking history			
Never 0 pts	Current 3 pts	Ex-smoker 2 pts	
Diabetes 4 pts			
Arrhythmia 2 pts			
Cardiac implant			
PPM 8 pts	ICD 9 pts	CRT 5 pts	
Serum creatinine >120 umol/L 1 pt			
ASA 1 pt			
P2Y12 Inhibitor 4 pts			
Anticoagulant 3 pts			
Bronchodilator 2 pts			
Metformin -4 pts			
Non-diagnostic CCTA likely if >23 pts			

Point scoring system for prediction of non-diagnostic coronary computed tomographic angiography (CCTA). Points are assigned for each variable in the table. The risk of obtaining a non-diagnostic CCTA study for the patient being considered is based on the total score. A patient with a score greater than 23 has a high likelihood of receiving a non-diagnostic CCTA study. ASA, acetylsalicylic acid; CCTA, coronary computed tomographic angiography; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; PPM, permanent pacemaker.

Keywords cardiac imaging techniques • coronary computed tomographic angiography • image interpretation • non-diagnostic tests • prediction model

Introduction

Coronary computed tomography angiography (CCTA) is endorsed as a Class I indication for investigating patients with suspected coronary artery disease (CAD).[1,2] Coronary computed tomography angiography appears to be best used in patients who have a low to intermediate pre-test likelihood of CAD.[3] The accuracy of CCTA is highly dependent on high-quality images, and image quality is dependent on both patient and technical factors. Patient factors such as body habitus, heart rate, severity of coronary calcification, cardiac motion, etc. can influence image quality and diagnostic accuracy.[3,4] With the wider adoption of CCTA, there is concern that indiscriminate referrals could result in a higher rate of equivocal and non-diagnostic studies, or false positive and false negative findings, leading to inappropriate downstream resource utilization and delays in diagnosis.[5] We sought to develop a simple clinical tool for predicting the likelihood of a non-diagnostic CCTA to help identify patients who might be better served with a different test. We validated the predictor selection and prediction performance using machine learning (ML).

Methods

Study design and patient eligibility

A retrospective analysis of a prospectively collected single-centre cardiac CT database was performed. Consecutive patients referred for CCTA between 2006 and 2021 were screened. Patients with a history of myocardial infarction, revascularization (i.e. coronary artery bypass grafting or percutaneous coronary intervention), atrial fibrillation, congenital heart disease, or a left ventricular assist device were excluded from the analysis. The study was approved by our institutional review board and reported according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement.

Coronary computed tomography angiography

The protocol for CCTA image acquisition adhered to guidelines for ≥64 slice cardiac CT.[6,7] Patients without contraindications received metoprolol, ivabradine, and/or diltiazem (oral and/or intravenous), targeting a heart rate of ≤65 beats/min, and sublingual nitroglycerine (0.8 mg).[6–8] After a timing bolus, a tri-phasic intravenous contrast administration protocol [100% contrast (40–170 cc), 40%/60% contrast/saline (50 cc), and saline (40 cc)] was used for CCTA image acquisition.[7] Coronary computed tomography angiography images were acquired using the GE single-source or the Siemens Flash dual-source ≥64 slice CT scanners,[9] with retrospective electrocardiogram (ECG)-gating or prospective ECG-triggering [GE Volume CT (GE, Milwaukee, WI, USA), 64 × 0.625 mm slice collimation, gantry rotation of 350 ms; Somatom Flash (Siemens, Erlangen, Germany) with 64 × 2 × 0.6 mm slice collimation, gantry rotation 280 ms]. For prospectively acquired images, images were acquired between 70 and 80% phases. Radiation dose saving techniques were adopted in accordance with the published guidelines (tube potential reductions, iterative reconstruction, and 4D X-ray tube modulation).[6]

Coronary artery disease was evaluated using a 17-segment model and a 4-point scale to grade the severity of stenosis [normal, mild (<50%), moderate (50–69%), severe (≥70%)].[7,10] Coronary computed tomography angiography findings were categorized according to CAD-RADS scoring.[11]

Outcomes

Coronary computed tomography angiography study results were categorized as normal, abnormal, or non-diagnostic. Patients with a 'non-diagnostic' CCTA study were identified. A normal CCTA was defined as any CCTA where all meaningful segments were evaluable, and there were no obstructive lesions. An obstructive lesion was defined as luminal stenosis ≥50% for the left main segment only and ≥70% for the remaining segments. An abnormal CCTA result was any test with at least one obstructive lesion (luminal stenosis ≥50% in left main, otherwise ≥70%) in a meaningful segment.

Meaningful coronary segments were those that supplied significant myocardium at risk of injury and were defined according to the Duke jeopardy score.[12] They included vessels ≥1.5 mm in diameter including the left main, left anterior descending (proximal or mid), first diagonal branch, left circumflex (proximal or mid), first obtuse marginal, ramus intermediate, dominant right coronary (proximal, mid, or distal), or posterior descending arteries. For left-dominant patients, segments in the right coronary artery (proximal, mid, or distal) were not considered meaningful segments. All remaining studies that could not be definitively categorized as normal or abnormal were classified as non-diagnostic.

Candidate predictors

Prior to time of CCTA, all patients referred for the test are interviewed by a trained nurse prior to the test to collect information regarding demographic data, past medical history and risk factors, symptoms, family history, social history and habits, medications, and prior coronary artery investigations. This interview is conducted as per a standardized registry form. After that, baseline blood pressure (BP), heart rate, body weight, and height are recorded, and an ECG is performed. The remainder of data points were recorded based on patient reporting and reviewing of medical charts.

From these, variables were selected based on the feasibility of collecting the same information at the time of booking for CCTA. Therefore, factors during image acquisition such as heart rate, severity of coronary calcification were not included.[4,13–15] In total, 54 candidate predictors met these criteria and were available for model development.

Missing data

Imputations were performed for the values with <10% missing.[9] Imputation was performed for patient height, weight, baseline heart rate, systolic and diastolic BP, and creatinine value. Menopausal status was missing in 4548 (21.2% of total) patients; however, a sub-group analysis was performed for female patients with available menopause data.

Statistical and ML analyses

Statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA), and statistical significance was defined by $P < 0.05$.

Continuous variables are presented as means and standard deviations, and categorical variables as frequencies and percentages. Comparisons were performed using Student's *t*-test for continuous variables, and the χ^2 test or Fisher exact test for categorical variables as appropriate.

To derive a clinical prediction model to predict the occurrence of non-diagnostic CCTA studies, multivariable logistic regression analyses were performed. Model development was based on a combination of univariable screening of the associations between candidate predictors and the outcome and subsequent stepwise selection of predictors that were significant ($P < 0.05$) in a multivariable model.[16] Continuous predictors were modelled as continuous variables without dichotomization or transformation.

We further developed a gradient boosting decision tree (GBDT) model to validate the predictor importance and prediction performance.[17] It was employed for a binary classification task based on the occurrence of non-diagnostic CCTA studies. Gradient boosting decision tree is a tree-based ML algorithm which has gained wide popularity for binary classification tasks. It is an ensemble algorithm, which learns a series of decision trees to predict the output.

The discriminative ability of the model was evaluated by generating receiver operating characteristic (ROC) curve for the multivariable model and examining the area under the curve (AUC) and the corresponding C statistics. We considered the performance difference as statistically significant if there was on overlap between 95% confidence intervals. Hosmer–Lemeshow statistics were used to assess model goodness of fit, where $P > 0.05$ indicates adequate fit.[16]

Bayesian optimization was applied with 10-fold cross-validation for GBDT model hyperparameter tuning on the number of leaves, maximum tree depth, and minimum number of training samples in each leaf. Predictor importance was calculated based on Shapley Additive Explanation (SHAP) values in the GBDT model.[18] The SHAP value is the average marginal contribution of a variable value across all the possible combinations of variables.

Table 1 Comparison of clinical characteristics for patients with and without a non-diagnostic CCTA study in the derivation cohort

Baseline characteristics	Derivation cohort ($n = 21492$)		
	Diagnostic ($n = 19192$)	Non-diagnostic ($n = 2300$)	*P*-value
Age (years)	57.8 (11.3)	61.3 (10.7)	<0.001
Men	10143	1301	<0.001
Height[a] (cm)	169.0 (10.4)	168.9 (10.3)	0.438
Weight[a] (kg)	83.6 (19.3)	85.8 (21.4)	<0.001
Baseline heartrate[a] (bpm)	66.3 (12.4)	66.5 (12.6)	0.579
Baseline systolic BP[a] (mmHg)	134.3 (19.3)	137.5 (19.9)	<0.001
Baseline diastolic BP[a] (mmHg)	78.6 (10.9)	78.7 (10.8)	0.739
Sinus ECG rhythm[a]	691 (3.6%)	108 (4.7%)	0.009
Reason for test			0.057
Chest pain, rule-out CAD, known CAD	17104 (89.1%)	2018 (87.7%)	
Dyspnoea, congestive heart failure	486 (2.5%)	53 (2.3%)	
Atrial fibrillation ablation, ventricular tachycardia	53 (0.3%)	11 (0.48%)	
Equivocal test	95 (0.5%)	16 (0.70%)	
Other	1454 (7.6%)	202 (8.8%)	
Chest pain	11 235 (58.5%)	1252 (54.4%)	<0.001
Dyspnoea	10 800 (56.3%)	1284 (55.8%)	0.683
Palpitations	8782 (45.8%)	1011 (44.0%)	0.101
Allergies	6173 (32.2%)	684 (29.7%)	0.018
Cardiac risk factors			
Family history	8510 (44.3%)	1035 (45.0%)	0.548
Hypertension	9267 (48.3%)	1364 (59.3%)	<0.001
Hyperlipidaemia	9987 (52.0%)	1396 (60.7)	<0.001
Smoking history			<0.001
Never	10677 (55.6%)	1142 (49.7%)	
Current	2859 (14.9%)	345 (15.0%)	
Ex-smoker (>1 year)	5656 (29.5%)	813 (35.4%)	
Diabetes	2755 (14.4%)	451 (19.6%)	<0.001
Other medical history			
Arrhythmia	1122 (5.9%)	175 (7.6%)	<0.001
Valvular heart disease	1595 (8.3%)	204 (8.9%)	0.36
Valvular repair or replacement	207 (1.1%)	33 (1.4%)	0.124
Congenital heart disease	0 (0.0%)	0 (0.0%)	—
Heart transplant	0 (0.0%)	0 (0.0%)	—
Congestive heart failure	545 (2.8%)	94 (4.1%)	<0.001
Cardiac implants			<0.001
None	18985 (98.9%)	2238 (97.3%)	
Permanent pacemaker	123 (0.64%)	39 (1.7%)	
Implantable cardioverter-defibrillator	77 (0.40%)	21 (0.91%)	
Cardiac resynchronization therapy	7 (0.04%)	2 (0.09%)	
Renal insufficiency	480 (2.5%)	77 (3.4%)	0.016
Creatinine (μmol/L)	79.8 (22.6)	83.148 (37.4)	<0.001
Prior tests			
Stress test	7601 (39.6%)	896 (39.0%)	0.548
Myocardial perfusion imaging	5800 (30.2%)	776 (33.7%)	<0.001
Stress echocardiogram	1268 (6.6%)	137 (6.0%)	0.233
Myocardial viability	20 (0.10%)	1 (0.04%)	0.378
Ribonucleic acid	182 (1.0%)	26 (1.1%)	0.399
Magnetic resonance imaging	187 (1.0%)	20 (0.87%)	0.207

Continued

Table 1 ***Continued***

Baseline characteristics	Derivation cohort ($n = 21492$)		
	Diagnostic ($n = 19192$)	Non-diagnostic ($n = 2300$)	*P*-value
Medications			
ASA	8467 (44.1%)	1143 (49.7%)	<0.001
P2Y12 inhibitor	546 (2.8%)	96 (4.2%)	<0.001
Antihypertensive	5792 (30.2%)	900 (39.1%)	<0.001
Mineralocorticoid	77 (0.40%)	19 (0.83%)	0.004
Beta-blocker	6685 (34.8%)	927 (40.3%)	<0.001
Calcium channel blocker	2693 (14.0%)	387 (16.8%)	<0.001
Ivabradine	27 (0.14%)	4 (0.17%)	0.692
Anticoagulant	774 (4.0%)	152 (6.6%)	<0.001
Antiarrhythmic	138 (0.72%)	24 (1.0%)	0.089
Digoxin	23 (0.12%)	3 (0.13%)	0.89
Nitrates	494 (2.6%)	84 (3.7%)	0.003
Vasodilator	71 (0.37%)	11 (0.48%)	0.426
Diuretic	3206 (16.7%)	517 (22.5%)	<0.001
Statin	8026 (41.8%)	1172 (51.0%)	<0.001
PCSK9 inhibitor	27 (0.14%)	4 (0.17%)	0.692
Other lipid-lowering agent	140 (0.73%)	23 (1.0%)	0.158
Bronchodilator	1879 (9.8%)	282 (12.3%)	<0.001
Metformin	1826 (9.5%)	270 (11.7%)	<0.001
Insulin	514 (2.7%)	100 (4.4%)	<0.001
Other hypoglycaemic	926 (4.8%)	159 (6.9%)	<0.001
PPI	1313 (6.8%)	177 (7.7%)	0.127

BP, blood pressure; CAD, coronary artery disease; ECG, electrocardiogram; PPI, proton pump inhibitor.
[a]Prior to the test, all patients referred for CCTA are interviewed by a trained nurse who performs a baseline examination to record blood pressure, heart rate, body weight, and height.

Development of a scoring system

A scoring system for clinical use was developed and its performance.[19,20] Classification performance of the score was assessed by applying the scoring system to patients in the derivation cohort and calculating the sensitivity and specificity.

We surveyed cardiologists and performed a Delphi analysis to determine the risk threshold for a non-diagnostic study whereby the clinician would choose an alternative test.

Results

A total of 21 492 patients who underwent CCTA between February 2006 and May 2021 remained in the model derivation cohort (*Table 1*). After applying our definitions for a non-diagnostic CCTA, we identified 2300 patients (10.7%) with a non-diagnostic study. With respect to scanners, 56.0% ($n = 12\,044$) of patients underwent CCTA with the GE single-source scanner and 44.0% ($n = 9448$) with the Siemens Flash dual-source scanner ($P < 0.001$). The majority ($n = 11\,109$; 51.6%) were prospective studies ($P < 0.001$).

Selection of predictors for multivariable analysis

We performed univariable screening on the 54 candidate predictors and those for which there were statistically significant differences in the mean or frequency between patients with and without a non-diagnostic CCTA study were used in the multivariable logistic regression analysis (*Table 2*). Stepwise selection of final predictors in the multivariable model revealed 17 variables that independently predicted a non-diagnostic CCTA.

The proposed model had an area under the ROC curve of 0.630 [95% confidence interval (CI) 0.618–0.641] (*Figure 1*). The GBDT achieved similar (no statistical difference) discriminative performance using the same predictors. The area under the ROC curve was 0.634 (95% CI 0.612–0.656). The area under the ROC curve and goodness-of-fit are described in *Table 3*. *Figure 2* lists the top-ranked important variables used in the GBDT for predicting a non-diagnostic study.

Score development

For the scoring system (range: −6 to 46 points), the estimated risk of a non-diagnostic study ranged from 2.9% to 67.9%. There were no patients in our sample that had less than −2 points (estimated risk: 4.0%) or greater than 34 points (estimated risk: 44.1%).

The area under the ROC curve and goodness-of-fit for applying the scoring system to the derivation cohort are described in *Table 3*, and the ROC curves are plotted in *Figure 1*.

Figure 3 shows the prevalence of non-diagnostic CCTA according to the number of points. The mean (standard deviation) of the scores was 9.89 (5.35).

Risk groups for non-diagnostic CCTA

Twelve practicing cardiologists responded to the survey. The median response was 25% as the risk threshold, whereby they would select another non-invasive diagnostic test over CCTA.

Table 2 Multivariable clinical model for non-diagnostic coronary CT angiography

Variable	Odds ratio (95% confidence interval)	*P*-value
Age (years)	1.025 (1.020–1.030)	<0.001
Men	1.095 (0.992–1.208)	0.073
Weight (kg)	1.005 (1.003–1.008)	<0.001
Baseline systolic BP (mmHg)	1.002 (1.000–1.005)	0.056
Chest pain	0.900 (0.823–0.985)	0.023
Hypertension	1.201 (1.088–1.326)	<0.001
Hyperlipidemia	1.124 (1.021–1.238)	0.017
Smoking history (reference category: never smoked)		<0.001
Current smoker	1.240 (1.087–1.414)	0.001
Ex-smoker (>1 yr)	1.183 (1.072–1.305)	<0.001
Diabetes	1.390 (1.170–1.651)	<0.001
Arrhythmia	1.157 (0.976–1.370)	0.092
Cardiac implants (reference category: none)		<0.001
Permanent pacemaker	1.937 (1.333–2.814)	<0.001
Implantable cardioverter-defibrillator	2.056 (1.250–3.381)	0.005
Cardiac resynchronization therapy	1.507 (0.308–7.365)	0.612
Serum creatinine (umol/L)	1.002 (1.000–1.003)	0.022
ASA	1.085 (0.990–1.190)	0.082
P2Y12 inhibitor	1.360 (1.085–1.705)	0.008
Anticoagulant	1.299 (1.075–1.570)	0.007
Bronchodilator	1.138 (0.992–1.305)	0.065
Metformin	0.747 (0.607–0.920)	0.006

ASA, acetylsalicylic acid; BP, blood pressure.

Based on the preferred risk thresholds, and the sensitivities and specificities of different score thresholds (see Supplementary data online, *Table S1*), low- and high-risk groups for non-diagnostic CCTA were defined. According to our definition of a non-diagnostic study, a patient with a score greater than 23 (estimated risk: 24.3%) had a high likelihood of a non-diagnostic CCTA study (specificity: 99.5%).

Table 3 Model performance for the prediction of non-diagnostic CCTA by multivariable logistic regression and gradient boosting decision trees

Model	Area under the ROC curve (95% CI)	Hosmer–Lemeshow goodness-of-fit test	
		χ^2	*P*-value
Multivariable model	0.630 (0.618–0.641)	27.452	<0.001
Simplified risk score	0.610 (0.599–0.622)	35.188	<0.001
Menopause sub-analysis multivariable model[a]	0.627 (0.609–0.645)	8.628	0.375
GBDT model	0.634 (0.612–0.656)	17.768	<0.001
GBDT model selected 17 variables	0.625 (0.603–0.647)	329.059	<0.001

[a]Sub-analysis was based on group of patients with complete data on menopausal status ($n = 5500$).
CI, confidence interval; ROC, receiver operating characteristic; GBDT, gradient boosting decision tree.

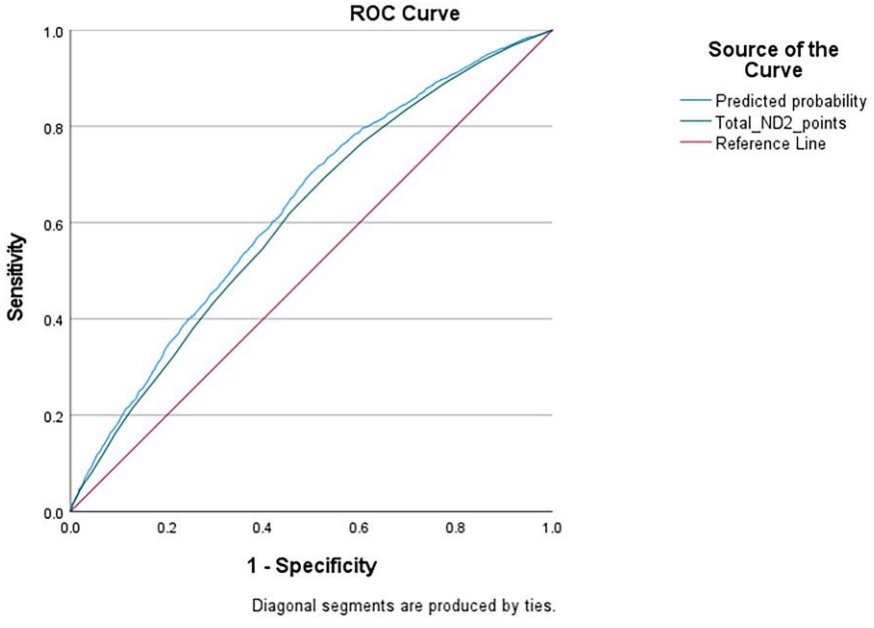

Figure 1 Receiver operating characteristic curve of the model to predict non-diagnostic CCTA in the model derivation cohort.

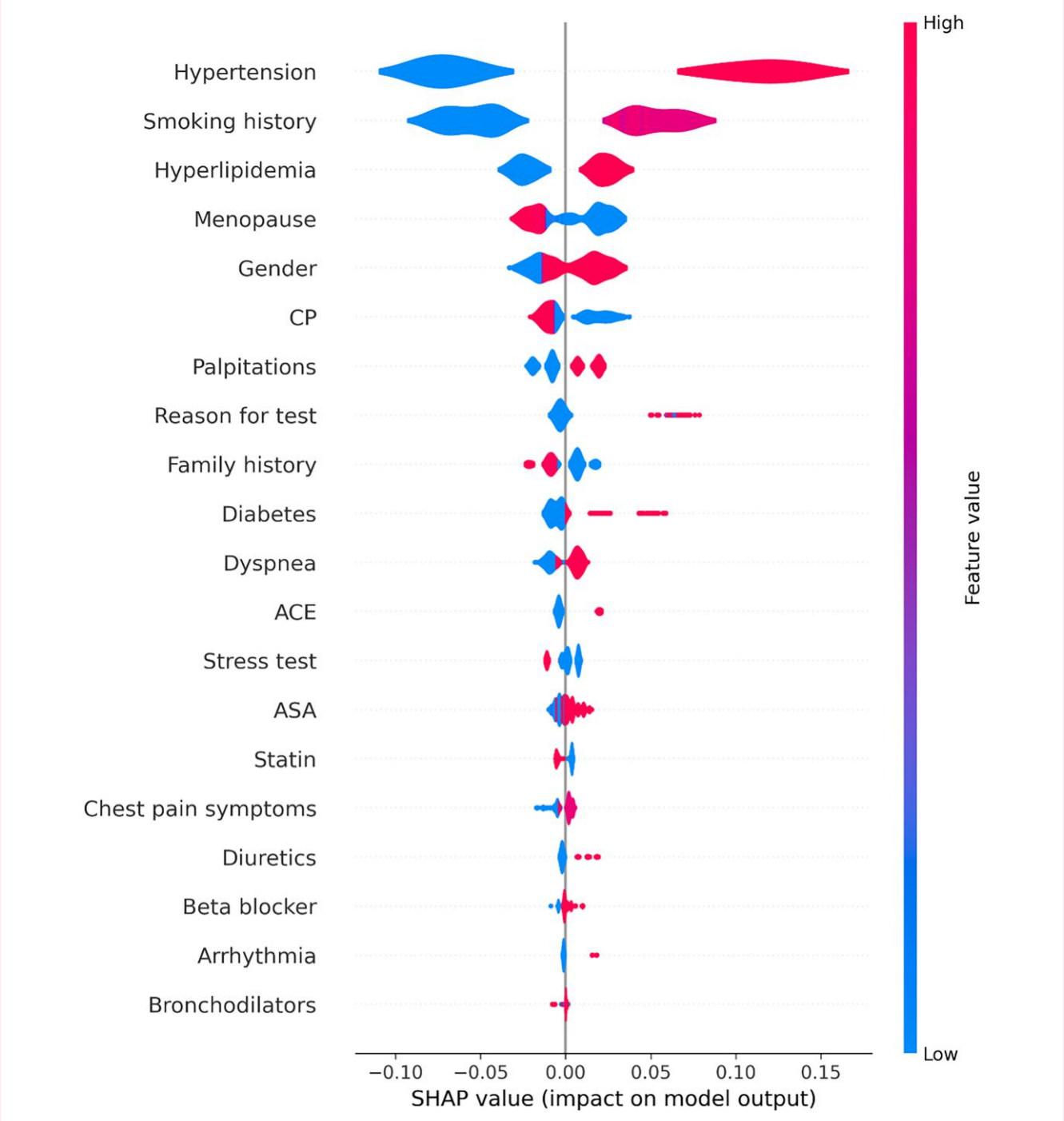

Figure 2 Variable (feature) importance plot for the GBDT model. The top 20 input variables are shown in this figure. The blue and red points in each row represent patients' low to high values of the specific variable, while the x-axis gives the SHAP values which measures the feature impact on the model. Positive SHAP values indicate the variable tend to drive the predictions towards events, and negative SHAP values indicate the variable tend to drive the prediction towards non-events. ACE, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; CP, chest pain; MRI, magnetic resonance imaging; PPI, proton pump inhibitors; SHAP , Shapley additive explanation.

Sensitivity analyses

Menopausal status was considered as a candidate predictor in a sub-group analysis. Only female patients with complete data on menopausal status were included ($n = 5500$). Univariable screening revealed a significant association between menopausal status and the outcome ($P < 0.001$). Thus, menopausal status was included in the model for multivariable analysis, but it was not retained as a final predictor after stepwise selection. Model performance for this sub-group analysis is described in *Table 3*.

In a *post hoc* analysis, given that both the scanner and acquisition protocol (prospective vs. retrospective) were significantly associated

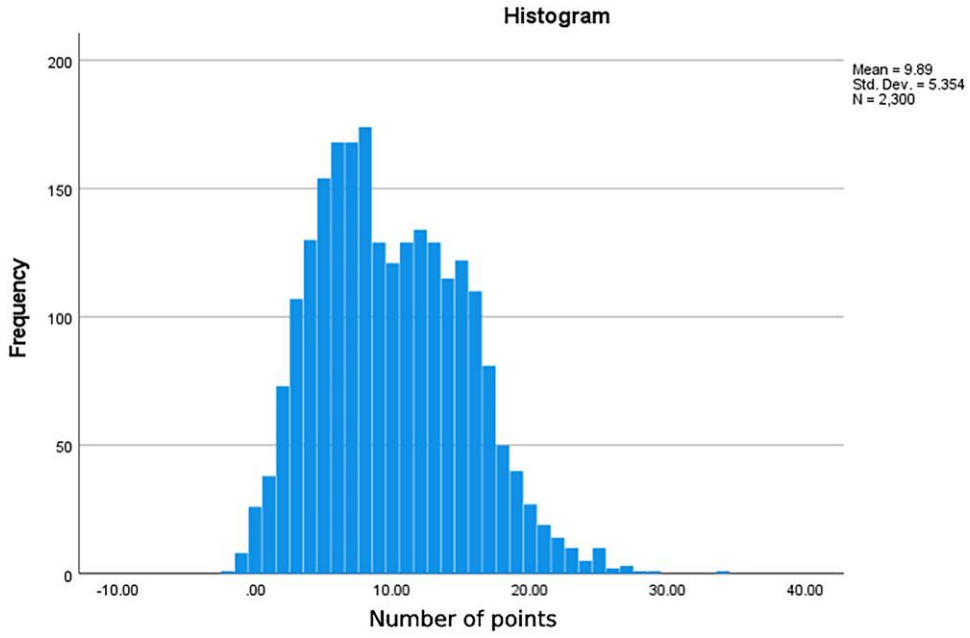

Figure 3 Prevalence of non-diagnostic CCTA at different scores. The distribution of the model derivation cohort according to the number of points assigned based on the scoring system to predict non-diagnostic CCTA. CCTA, coronary computed tomographic angiography.

with a non-diagnostic study on univariate screening, they were both entered into multivariable analyses in a sub-analysis and only the scanner type was significantly associated with the outcome ($P < 0.001$).

Discussion

With wider adoption of CCTA, clinicians may see indiscriminate CCTA referrals which could lead to higher rates of non-diagnostic CCTA results. When test results are of insufficient quality to provide meaningfully inform clinical decision-making, the non-diagnostic CCTA study may lead to misdiagnoses, inappropriate downstream resource utilization, delays in patient diagnosis, and increased healthcare costs.[5] We developed a prediction model that could be implemented at the 'point-of-scheduling' to identify patients who would be best served by another non-invasive diagnostic test.

The classification of a CCTA study as 'non-diagnostic' has been variably defined by different authors.[13,21,22] Bamberg *et al.*[22] considered an overall subjective assessment of image quality on a per-patient basis and the number of unevaluable coronary segments on a per-segment basis separately. Vanhecke *et al.*[13] considered a non-diagnostic study to be any CCTA study with ≥1 unevaluable coronary segments in segments posing substantial risk of myocardial injury. In contrast, Simon *et al.*[21] considered any CCTA with inadequate image quality in at least one segment, and which prompted the need for further testing, to be non-diagnostic. Our definition resembles the approach taken by previous authors with some notable differences. We defined non-diagnostic to mean any situation where the results of CCTA could not be used to definitively detect or exclude the presence of significant coronary stenosis in a meaningful segment. The presence of even a single unevaluable coronary segment can create uncertainty regarding underlying severe CAD, and we considered this to render the entire CCTA dataset non-diagnostic. Moreover, any CCTA with an obstructive lesion in a meaningful segment precluded the study from being categorized as non-diagnostic, as the presence of a significant stenosis was considered valuable diagnostic information. Using this definition, the prevalence of patients with a non-diagnostic CCTA in our study (10.7%) was lower than those observed by Bamberg *et al.* (16.1%) and Vanhecke *et al.* (16.3%),[13,22] and more closely aligned with the findings of Simon *et al.*[21] (6.7%). One potential explanation for this discrepancy is the advancements in CCTA technology which have occurred over time,[23] leading to better image quality and an overall reduction in the incidence of non-diagnostic studies.

The ability of CCTA to provide diagnostic information depends on adequate image quality, which is impacted by both technical and patient factors.[23] Patient factors are known to affect CCTA image quality;[24] however, there is limited guidance regarding how relevant factors should be used to inform appropriate patient selection for CCTA.[1] Our final model demonstrated that many pre-scan factors can be predictors of subsequent non-diagnostic test results. The presence of a cardiac implant (permanent pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy), a weight >100 kg, age, diabetes, and the administration of a P2Y12 inhibitor were also important (*Table 4*).

Gradient boosting decision tree, a popular ML technique,[17] was applied for model validation. Machine learning has the potential for several advantages over conventional regression techniques, such as a reduced requirement for *a priori* knowledge on predictors and better ability to manage large datasets.[25–27] Although the comparison of traditional statistical regression vs. ML methods for predictive modelling was not a primary objective in the present study, our findings support the feasibility of applying more advanced techniques, such as GBDT, in combination with traditional regression. The majority of predictors retained in the final model through multivariable logistic regression (*Table 2*) were also listed within the top-20 important variables ranked by the SHAP in GBDT model (*Figure 2*). The performance of GBDT was also similar to the model constructed by regression (*Table 3*). Preliminary data suggest that artificial intelligence may perform better than traditional statistical methods and identifies features that have not been previously considered or have been discounted by clinicians.[28] Findings in the present study suggest that ML is at least equivalent to traditional regression

Table 4 Point scoring system for prediction of non-diagnostic CCTA

Variable	Scoring point
Age (years)	
<65	0
≥65	8
Male	1
Weight (kg)	
<50	0
50–75	1
75–100	2
>100	4
Baseline systolic BP (mmHg)	
<120	−1
120–159	0
≥160	1
Chest pain	−1
Hypertension	2
Hyperlipidaemia	1
Smoking history	
Never	0
Current	3
Ex-smoker	2
Diabetes	4
Arrhythmia	2
Cardiac implant	
Permanent pacemaker	8
Implantable cardioverter-defibrillator	9
Cardiac resynchronization therapy	5
Serum creatinine >120 μmol/L	1
Acetylsalicylic acid	1
P2Y12 inhibitor	4
Anticoagulant	3
Bronchodilator	2
Metformin	−4
Min	−6
Max	46

and given the potential advantages of artificial intelligence as datasets continue to grow in size and complexity, further investigation directly comparing these two methods for prediction model development is warranted.

Several independent predictors of non-diagnostic CCTA revealed in our analysis may be significant, in part, due to their association with high coronary artery calcification (CAC), which is known to impair the diagnostic accuracy of CCTA.[15,29] For example, a higher CAC is more likely in patients who are older, diabetic, or hypertensive,[30–32] all of which were predictors retained in one or both of our final models. Because the results of coronary artery calcium score measurement are generally not available to the referring physician at the point of decision-making, we opted to exclude this variable from our analysis. Routine non-contrast-enhanced calcium scans prior to CCTA may improve patient selection, as the CAC score significantly increases the ability to identify patients in whom CCTA may not meaningfully inform decision-making for management.[21] However, the ability to defer patients with antecedent high calcium scores may not be feasible at all centres and would be an additional expense to the healthcare system. Findings from this study show that it is feasible to select appropriate candidates for CCTA based solely on pre-scan patient factors, and that several of these (e.g. age, diabetes, hypertension) may important due to their association with a higher CAC burden.

Our final model achieved fair discriminative ability but did not reach acceptable calibration (Hosmer–Lemeshow statistics: χ^2 statistic of 27.452, degree of freedom of 8, *P*-value of <0.001). Potential opportunity costs to deferring a patient from CCTA are substantial, therefore the specificity of a clinical tool for predicting non-diagnostic studies is important. Findings from our survey of practicing cardiologists reflected this: the median risk threshold of 25% favoured a low rate of false positives for the prediction of non-diagnostic results. For example, in the scoring system, cardiologists' preferred risk threshold corresponded with a cut-off score of 23 and a specificity of 99.5%. Further prospective validation is warranted to determine whether the use of this scoring system and the proposed risk threshold were useful for clinical decision-making and to assess its impact on downstream resource utilization.

This study has several limitations. This retrospective study is limited by an observational design at a single-centre and shares the inherent limitations of databases such as the presence of selection bias and confounding. We excluded patients from the CT registry with a history of myocardial infarction, revascularization, atrial fibrillation, congenital heart disease, or a left ventricular assist device; therefore, the results do not apply to these individuals. There was a high proportion of female patients with missing data on menopausal status ($n = 4548$, 21.2%), leading to its exclusion as a candidate predictor in the main analysis. However, in a sub-group analysis of 5500 female patients with complete data, menopausal status was not retained as a predictor in the final model and resultant model performance were similar (*Table 3*). External validation of our models and risk-scoring systems in other populations is needed to assess the generalizability of the findings and the transportability of the risk-scoring system in other settings. The results of this retrospective analysis are hypothesis generating and before clinical implementation, should be validated in a trial with a prospectively collected data. Our results pertain to 64 and 128 slice CT scanners and the results may not be translatable to newer CT scanners such as those with 320 detector rows, faster gantry rotations, and photon counting detectors. Moreover, the CT scanner was significantly associated with the primary outcome. However, there are many changes in software, hardware, and medical advancements (reconstruction algorithms, kernels, tube voltage, workstations, etc.) that were adopted over time. This highlights the importance of further validation and refinement of this model as technology advances. Despite these limitations, our large registry sample provides robust significance of the predictors of non-diagnostic CCTA in the proposed clinical risk scores.

Conclusion

A 'point-of-scheduling' prediction model may predict non-diagnostic CCTAs to identify patients who would be better served by a different diagnostic test. The use of this model may reduce the incidence of non-diagnostic CCTA results, thereby improving resource utilization and minimizing time to diagnosis in patients with suspected CAD.

Supplementary data

Supplementary data is available at *European Heart Journal - Imaging Methods and Practice* online.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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