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Research paper

Maximization of the usage of coronary CTA derived plaque information using a machine learning based algorithm to improve risk stratification; insights from the CONFIRM registry

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ABSTRACT

Introduction: Machine learning (ML) is a field in computer science that demonstrated to effectively integrate clinical and imaging data for the creation of prognostic scores. The current study investigated whether a ML score, incorporating only the 16 segment coronary tree information derived from coronary computed tomography angiography (CCTA), provides enhanced risk stratification compared with current CCTA based risk scores.

Methods: From the multi-center CONFIRM registry, patients were included with complete CCTA risk score information and ≥3 year follow-up for myocardial infarction and death (primary endpoint). Patients with prior coronary artery disease were excluded. Conventional CCTA risk scores (conventional CCTA approach, segment involvement score, duke prognostic index, segment stenosis score, and the Leaman risk score) and a score created using ML were compared with the C-statistic. Only 16 segment based coronary stenosis (0%, 1–24%, 25–49%, 50–69%, 70–99% and 100%) and composition (calcified, mixed and non-calcified plaque) were provided to the ML model. A boosted ensemble algorithm (extreme gradient boosting; XGBoost) was used and the entire data was randomly split into a training set (80%) on which 5-fold internal cross validation was done to tune the model. The performance of this model was independently tested using the test set (20%).

Results: In total, 8844 patients (mean age 58.0 ± 11.5 years, 57.7% male) were included. During a mean follow-up time of 4.6 ± 1.5 years, 609 events occurred (6.9%). No CAD was observed in 48.7% (3.5% event), non-obstructive CAD in 31.8% (6.8% event), and obstructive CAD in 19.5% (15.6% event). Discrimination of events as expressed by C-statistic was significantly better for the ML based approach (0.771) vs the other scores (ranging from 0.685 to 0.701), $P < 0.001$. Net reclassification improvement analysis showed that the improved risk stratification was the result of down-classification of risk among patients that did not experience events (non-events).

Conclusion: A risk score created by a ML based algorithm, that utilizes standard 16 coronary segment stenosis and composition information derived from detailed CCTA reading, has greater prognostic accuracy than current CCTA integrated risk scores. These findings indicate that a ML based algorithm can improve the integration of CCTA derived plaque information to improve risk stratification.

1. Introduction

Coronary computed tomography angiography (CCTA) is a non-invasive technique that provides direct visualization of the coronary arteries. Due to its high negative predictive value, CCTA is especially suited to rule out hemodynamically significant coronary artery disease (CAD).[1] Among symptomatic patients with suspected CAD, the presence or absence of CAD helps to classify chest pain into angina or chest pain not related to CAD.[2] Besides the diagnostic role, CCTA can risk stratify patients with suspected CAD for future major cardiovascular events.[3,4] Patient without evidence of CAD have an excellent prognosis and increasing severity of CAD relates to worsening outcome.[5] The great ability of CCTA to classify patients at low and high risk has translated into alterations of subsequent medical treatment (e.g. initiation of statin or aspirin therapy) according to abnormalities observed on CCTA.[6] Recently, these changes in preventive medical therapy prescription have resulted in significant reductions in fatal and non-fatal myocardial infarctions (MI).[7]

Current CCTA risk scores classify the severity of CAD mainly using the presence, extent and severity of CAD.[3,8,9] Plaque information derived during CCTA acquisition and subsequently classified according to the 16-segment coronary tree model is typically integrated into a single score, assuming linear relationships between CAD extent and risk.[10] Machine learning (ML) is a field in computer science that uses algorithms to combine a big data in order to optimize prediction. Previous studies have demonstrated that ML can increase predictive value for death and myocardial ischemia compared to conventional scores.[11,12] ML can integrate an unlimited number of input variables, does not have prior assumptions about causative factors, and does not overlook interactions between prognostically weaker variables. Therefore, ML has the potential to maximize the information that can be extracted from CCTA. The current study investigated whether a ML score, using only plaque stenosis and composition information from the 16 coronary segments, has better predictive accuracy compared to the traditional CCTA based risk scores.

2. Methods

The CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry is a dynamic, international, multicenter, observational cohort that prospectively collects clinical, procedural and follow-up data from patients who underwent ≥64 slice CCTA for clinically suspected coronary artery disease (CAD), as previously described.[13] The current study included 8844 patients without known CAD (defined as previous MI, percutaneous coronary intervention or coronary artery bypass grafting), at least 3-year follow-up duration for myocardial infarction (MI) and death and complete information for all CCTA risk scores (described below). Institutional review board approval was obtained at each site and patients provided informed consent.

2.1. Image acquisition and analysis

CCTA images were acquired using ≥64 detector row scanners from multiple vendors and acquisition protocols at each site were in adherence with the Society of Cardiovascular Computed Tomography guidelines.[14] Level III-trained experts in CCTA reading interpreted the images uniformly using the 16-segment coronary artery tree model. In each coronary artery segment, the presence of plaque was reported with corresponding stenosis severity. Plaque was defined as a tissue structure $> 1\ mm^2$ within or adjacent to the coronary artery lumen that could be distinguished from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself.[3] Coronary plaques were classified as non-calcified, mixed and calcified plaques. Subsequently, the corresponding stenosis severity of the plaques was classified as 0%, 1–24%, 25–49%, 50–69%, 70–99% and 100%, as previously described.[3]

2.2. Outcome

The primary outcome was a composite endpoint of all-cause death

Abbreviations

CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
MI	Myocardial infarction
ML	Machine learning
SIS	Segment involvement score
SSS	Segment stenosis score

and non-fatal MI. Detailed follow-up methodology has been previously described.[13] The Social Security Index was reviewed for assessment of mortality within the United States or determined through mail or telephone contact with the patients, family or physician or review of medical records for the other countries. MI events were collected through a combination of direct interviewing of patients using scripted interview with confirmation of event by reviewing the patient's medical files.[13]

2.3. Conventional CCTA scores

Conventional CCTA scores included only information on coronary plaque severity and plaque composition from the 16-segment coronary tree: (1) the modified Duke prognostic index, (2) CCTA Leaman score, (3) segment stenosis score (SSS), (4) segment involvement score (SIS) and (5) traditional CAD classification. The modified Duke prognostic index[3] was defined as follows: (0) = normal CCTA; (1) = 1–24% stenosis or at most lesion with 25–49% stenosis; (2) = ≥2 lesions with 25–49% stenosis; (3) = 1 vessel with 50–69% stenosis; (4) = 2 lesions with 50–69% stenosis or 1 lesion with ≥70% stenosis; (5) = 3 lesions with 50–69% stenosis or 2 vessels with ≥70% stenosis or a lesion with ≥70% stenosis in the proximal LAD; (6) = 3 vessels with ≥70% stenosis or 2 vessels with ≥70% stenosis including the proximal LAD; (7) = left main stenosis ≥50% stenosis. The CCTA Leaman score provides different weights for plaque composition, stenosis severity and location and combines them into a continuous score (0–33).[8] The SSS scores coronary segments based on stenosis severity (0–3) and sums the scores for the values for the individual segments into a total score (0–48).[3] The SIS is equal to the number of coronary segments exhibiting plaque (0–16).[3] The traditional CAD classification is defined as (0) = normal CCTA; (1) = ≤50% stenosis; (2) = 1 vessel with ≥50% stenosis, (3) = 2 vessels with ≥50% stenosis; (4) = 3 vessels or left main with ≥50% stenosis.

2.4. Machine learning score

In total, 35 CCTA variables (stenosis severity and plaque composition considering the 16 coronary segments, 2 variables for posterolateral branch when dominance was unknown and coronary artery dominance) were incorporated in the machine learning score. Machine learning involved both model building and feature selection using XGBoost algorithm[15] (Extreme Gradient Boosting), an implementation of gradient-boosted decision trees (GBDT), which is an open source scalable machine learning system for tree boosting. Feature importance score was evaluated using a functionality from XGBoost library by summing up how many times each feature is split on; analogous to the Frequency Metric in R[16]. All machine learning analysis was done using scikit-learn[17] python library in Python 3.5.0. The data was randomly split such that 80% was used for both training and internal validation, and the true model performance was tested on the remaining 20% of data. The XGBoost hyperparameters namely-maximum depth of trees, minimum child weight, gamma, subsample size and number of estimators were optimized (using area under the receiver operating characteristics curve [AUC] as a metric) based on grid search technique and performing 5-fold stratified cross validation on the training set. The 5-fold stratified cross validation involved splitting the training dataset into 5 equal folds in which 4 folds were used for training the model and the remaining fold is used for internal validation. The optimized model whose hyperparameter-permutation yielded the highest mean AUC was used as the trained model. This trained model was then used to generate the prediction probabilities (ML score) on the independent validation test set (20% of data). While comparing with the conventional CCTA scores, the performance of the ML model is derived from this independent test set.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as counts (%). The performance of the ML score to predict the primary outcome (MI and death) was compared to conventional CCTA scores using C-statistic analysis. For comparisons with the ML score, predicted probabilities were created for the comparator CCTA scores using logistic regression analysis. Calibration of the ML model was assessed with the Brier score method (ranging from 0 to 1), which calculates the difference between the estimated risk and the observed risk for occurrence of the primary outcome; and smaller values mean better calibration.[18] Additionally, isotonic regression[19,20] was used to recalibrate the prediction probabilities from the XGBoost model (test set). Continuous (category-free) net reclassification improvement (NRI) analysis was used to evaluate whether both patients that will and not will experience future events received more appropriate risk stratification by the new ML score. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patients

Table 1 describes the baseline characteristics of the study population (N = 8844). Mean age was 58.0 ± 11.5 years and 57.7% were male. No CAD was observed in 48.7% of the CCTA examinations and 19.5% of the patients had obstructive CAD (≥50% stenosis). During a mean follow-up of 4.6 ± 1.5 years, 609 events (350 death and 259 non-fatal MI) occurred.

Table 1
Baseline patient characteristics.

Characteristic	Value (N = 8844)
Age, years	58.0 ± 11.5
Sex, male	5106 (57.7)
BMI	26.7 ± 4.62
Symptoms	
No chest pain	3108 (41.5)
Non-anginal	789 (10.5)
Atypical	2803 (37.4)
Typical	795 (10.6)
CAD risk factors	
Diabetes	1282 (14.6)
Hypertension	4534 (51.7)
Dyslipidemia	4874 (55.4)
Familial history for CAD	2197 (25.0)
Currently smoking	1680 (19.0)
CCTA findings	
No CAD	4306 (48.7)
Non-obstructive CAD	2816 (31.8)
1 vessel with ≥50%stenosis	992 (11.2)
2 vessels with ≥50%stenosis	421 (4.8)
3 vessels/left main with ≥50%stenosis	309 (3.5)

Values are mean ± SD or counts (%).
BMI, body mass index; CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

3.2. Comparator CCTA and the ML score

As shown in Fig. 1, the C-statistic for prediction of the primary outcome was 0.694 for the Duke prognostic index, 0.690 for the CCTA Leaman score, 0.701 for the SSS, 0.694 for the SIS and 0.685 for the traditional CAD classification. The curve for the ML score as shown in Fig. 1 represents the performance in the validation cohort (20% of the total cohort not used for model building). The C-statistic of the ML score was 0.771; significantly higher than each of the conventional CCTA scores ($P < 0.001$ compared with all). As shown in Fig. 2, the three variables strongest correlated with the primary outcome were stenosis severity in the proximal left ascending coronary artery, left main and the proximal right coronary artery. The continuous NRI of the ML model compared to the SSS (conventional CCTA score with highest C-statistic) was 0.72 (95% CI 0.54–0.90, $P < 0.001$). The improved NRI was driven by reclassification of patients that did not experience events (NRI 0.82, 95% CI 0.79–0.84, $P < 0.001$) compared with reclassification for patients that experienced events (NRI -0.10, 95% CI -0.28 – 0.078, P = 0.275).

3.3. Machine learning score calibration

The Brier score for the ML model to predict the primary outcome was 0.216 before calibration and 0.059 after calibrating, indicating a good fit of the model[21] and low difference between the predicted risk and the actual observed risk for events.

4. Discussion

The main findings of the current analysis are that a ML score that incorporates 16-segment coronary plaque stenosis and composition information provides increased risk stratification compared with conventional CCTA based risk scores. Reclassification analysis showed that the improved prognostic value of the ML score is the result of more correctly down classification of risk for patients that will not experience events compared with the best performing CCTA score.

4.1. Risk stratification with CCTA

Risk stratification for future cardiovascular events is commonly performed using demographical, clinical and laboratory patient indices as for instance in the Atherosclerotic Cardiovascular Disease (ASCVD) risk score.[22] However, risk scores perform well on population level but may be sub-optimal for individual patients. Moreover, it was recently shown that ASCVD significantly overestimates the amount of risk among multiple ethnic subpopulations.[23] CCTA provides direct visualization of the presence, extent, location and composition of CAD and multiple studies have demonstrated that CCTA detected CAD improves risk stratification above patient's clinical risk profile.[24,25] Even in absence of modifiable cardiovascular risk factors, Cheruvu showed that the severity of CAD is related to major cardiovascular events; 5.6% for no CAD, 13.2% for non-obstructive CAD and 36.3% among 5.6 ± 1.3 years of follow-up.[26] Besides maximal severity per patient, the number of segments with plaque, location and composition improve risk assessment.[27] However, the prognosis of coronary atherosclerosis is determined by a complex interplay between coronary anatomy, physiology and plaque morphology.[28] Furthermore, specific interactions between CAD and clinical patient profile exist. For instance, Xie et al. showed worse outcome of non-obstructive left main CAD in women versus men.[29] Conventional CCTA scores may not fully incorporate this interplay between CAD presence, composition, severity, location and outcome.

4.2. Machine learning to improve integration of coronary plaque and stenosis

ML, a subset of artificial intelligence, does not have prior assumptions about which factors will be significant predictors while building statistical models, is able to integrate a large number of input variables, and explores all available data for non-linear relationships with outcome.[10] The feasibility of ML has been demonstrated previously in the CAD risk stratification field. Motwani et al. showed that ML, using 25 clinical and 44 CCTA variables, significantly improved prediction of death compared with the Framingham Risk Score, SSS, SIS and Duke prognostic index.[11] Moreover, Dey et al. demonstrated that a ML model incorporating semi-automatically quantified measures of coronary plaque (plaque volumes, stenosis severity, lesion length and contrast density difference) identified vessels with hemodynamically significant CAD (fractional flow reserve ≤ 0.80) with very high accuracy (AUC 0.84). Specifically, the ML model showed higher diagnostic accuracy than a conventional statistical model that utilized the exact same data.[12] These findings indicate that a complex ML algorithm improves integration of the available data for prediction of a certain outcome. Detailed reading of CCTA includes assessment of coronary stenosis and plaque composition of the 16 coronary segments. The current study showed that ML maximizes the utilization of this readily available information compared with prior CCTA scores (AUC 0.771 vs 0.684–0.701, $P < 0.001$ for all comparisons) for the prediction of MI and death during approximately 5 years of follow-up. Recently, the strong prognostic value of CCTA was shown to translate into changes in medical therapy and improved patient outcome. Williams et al. showed that CCTA findings significantly down- or upscaled preventive therapy compared with standard care.[7] Moreover, these alterations were associated with reductions in occurrence of non-fatal MI's. Potentially, ML can aid by translation of detailed 16-segent CCTA reads into an individualized risk report that help physicians to tailor preventive medical therapy initiation (fitting the concept of precision medicine).

Although the ML model portended greater overall prediction of outcome, reclassification analysis demonstrated that only patients that will not develop events received more appropriate risk estimation. Potentially, the inclusion of high risk plaque features as napkin ring sign or low attenuation plaque may improve a ML model even further.[30]

Although the CONFIRM registry is the largest currently existing CCTA registry with prospective long term follow up, the current study is an observational analysis with all its inherent limitations including selection bias. The ML model consisted of 16 segment CCTA data only and demonstrated to increase integration of these data compared with current CCTA scores. However, the current study did not investigate the

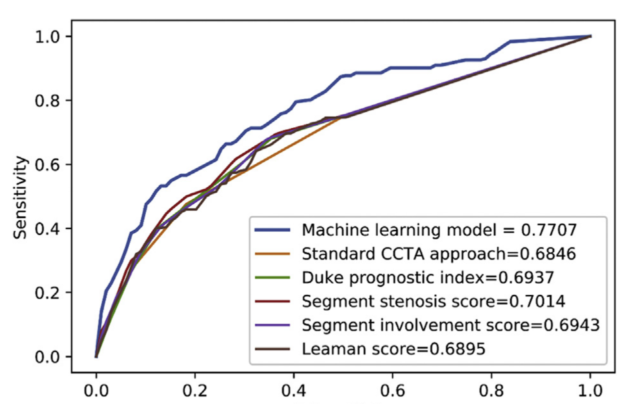

Fig. 1. Performance of ML and CCTA scores.
Area under receiver operating characteristics cure for prediction of a composite endpoint of myocardial infarction and death. The Machine learning score shows the highest predictive performance compared with the other coronary computed tomography angiography scores.

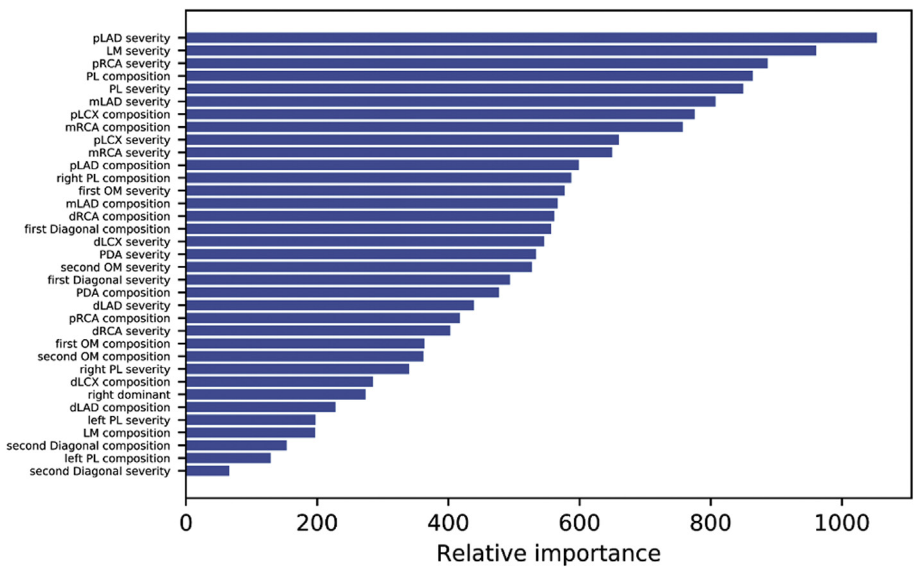

Fig. 2. Relative importance of the specific coronary plaque features in the ML score.
The relative prognostic importance of the 35 coronary computed tomography angiography features as included in the ML score. The features considering the maximal stenosis per coronary segment had each 6 categories (0%, 1–24%, 25–49%, 50–69%, 70–99% and 100%). The plaque composition features had 3 categories (non-calcified, mixed and calcified). Coronary dominance was categorized as right or left.

incremental prognostic value over risk scores including demographical and clinical patient characteristic, which should be studied further. Finally, although attempts to prevent over-fitting of the ML model were applied by using the 5-fold cross validation (4 folds for training and the remaining for validation) on 80% of the dataset and final validation in the independent 20% of the dataset, ideally, the prognostic accuracy will be tested in an external cohort.

5. Conclusion

The current analysis demonstrated that a ML model, that utilizes coronary stenosis and plaque composition derived from detailed 16-segment CCTA reading only, improves risk stratification for major cardiovascular events compared with current CCTA risk scores. ML may maximize utilization of plaque information from CCTA to further improve risk assessment of patients with suspected CAD.

Disclosures

Dr. James K. Min serves on the scientific advisory board of Arineta, has ownership in MDDX, and has a research agreement with GE healthcare. No other authors have conflicts of interest to report.

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