Appendix 1 CTA interpretation and ICA analysis

Considering that the interval between CTA and ICA was too short to demonstrate predictive value, we excluded patients with an interval of less than 3 months. All scanned datasets were subjected to curved projection reformation and volume reformation through a dedicated postprocessing workstation (Vitrea, version 7.6; Vital Images). The CTA dataset was evaluated by two local observers with extensive experience in cardiac imaging who were unaware of the patient's clinical information, and lesions with DS ≥30% were included in subsequent studies. ICA was performed by two experienced interventional cardiologists according to local criteria and identified culprit and nonculprit lesions. If there were culprit lesions on one vessel, the most severe stenosis was selected as the measurement lesion of the blood vessel. Thus, the culprit lesion also represented the culprit vessel.

Coronary plaque analysis

The MLA was the narrowest luminal area of the plaque. The distance from the ostium was defined as the distance from the narrowest point of the plaque to the opening of the vessel. Spotty calcification was defined as calcifications <3 mm in diameter on multiple reconstructed images.

Regarding the definition of plaque components, plaques with CT attenuation <30 Hounsfield units (HU) were defined as LAP. CT values between 30 and 149 HU were defined as FP, and CT values ≥150 HU were defined as CP. TP was calculated using the following formula: TP = CP + noncalcified plaque (NCP); where NCP = LAP + FP volume. Wall-to-lumen volume ratio was calculated using the following formula: wall-to-lumen volume ratio = wall volume/lumen volume; where the wall is the space between the inner and outer contours, the wall volume is the vessel volume minus the lumen volume and the vessel volume is the volume within the outer wall contour of the affected segment of the lesion. The remodeling index (RI) was the ratio of the vessel area of the lesion (the area within the outer contour) divided by the vessel area of the proximal reference point, with positive remodeling when RI≥1.1. Plaque burden was calculated using the following formula: plaque burden=plaque volume×100%/vessel volume.

Analysis of hemodynamic parameters based on CFD

For the hemodynamic analysis, a software model based on the principles of computational fluid dynamics (CFD) (Shukun Technology) was used as described previously, and the calculation of fractional flow reserve was performed by an independent blinded analyst on a conventional CTA dataset. The software calculated the ratio of coronary pressure drop (Pd) across a stenosis to intra-aortic pressure (Pa) as a surrogate measure of ischemia and allowed physicians to create a patient-specific coronary vascular tree model. FFRCT and VFFRCT ≤0.8 were considered abnormal. Vessels were excluded from the analysis when the vessel diameter was less than 1.5 mm for which FFRCT could not be calculated.

Machine learning

With the rapid development of artificial intelligence in the field of medical imaging, machine learning (ML) has been introduced into cardiovascular imaging as a field of computer science, helping clinicians diagnose diseases more quickly and accurately as well as helping clinicians to perform risk assessment and outcome prediction with high efficiency. In the present study, noninvasive parameters from CTA were used in combination with ML to improve the ability of outcome prediction.

The predictive model of ACS was constructed based on the following ten risk factors: DS, lesion length, MLA, low attenuation plaque, fibrous plaque, positive remodeling, VFFRCT, ΔFFRCT, proximal FAI and lesion-specific FAI. The odds ratio of each parameter in the model is shown in *Figure 1*.

Logistic regression (LR), random forest (RF), Bayesian and K-nearest neighbor (KNN) algorithms were applied to build models. These algorithms can learn from the training set data to achieve the purpose of performing a given task and use the test set with no time overlap with the training set to validate the accuracy of the trained machine learning model.

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Predictive value of machine learning for ACS

As an algorithmic tool, ML has been frequently used in medical research in recent years. We used ML to predict ACS in coronary artery disease and obtained good prediction results. During this process, we built the model using four ML algorithms to make the model predictions the best. In the present results, the ROC curve and DCA curve of the RF model in the training set were significantly higher than those in the test set (AUC: 0.990 [95% CI: 0.976-1] *vs.* 0.754 [95% CI: 0.739-0.878]). Because the difference was large, the RF model was rejected. If the branch of the decision tree model grows to far in the RF model, it may find irregularities in the training dataset, resulting in overfitting.

The final results showed that compared to the other candidate models in machine learning, the LR model provided better predictive performance in terms of discrimination and decision-making ability. Therefore, the ML model was a combined model based on the LR algorithm. At the same time, the prediction results of the ML combined model (Model 5) were better than those of the traditional classification prediction models (Models 1-4), but Model 1 had better prediction results than Model 2 and Model 3 in the single-classification model comparison, which may be due to the inclusion of too many parameters in the classification of plaque characteristics.

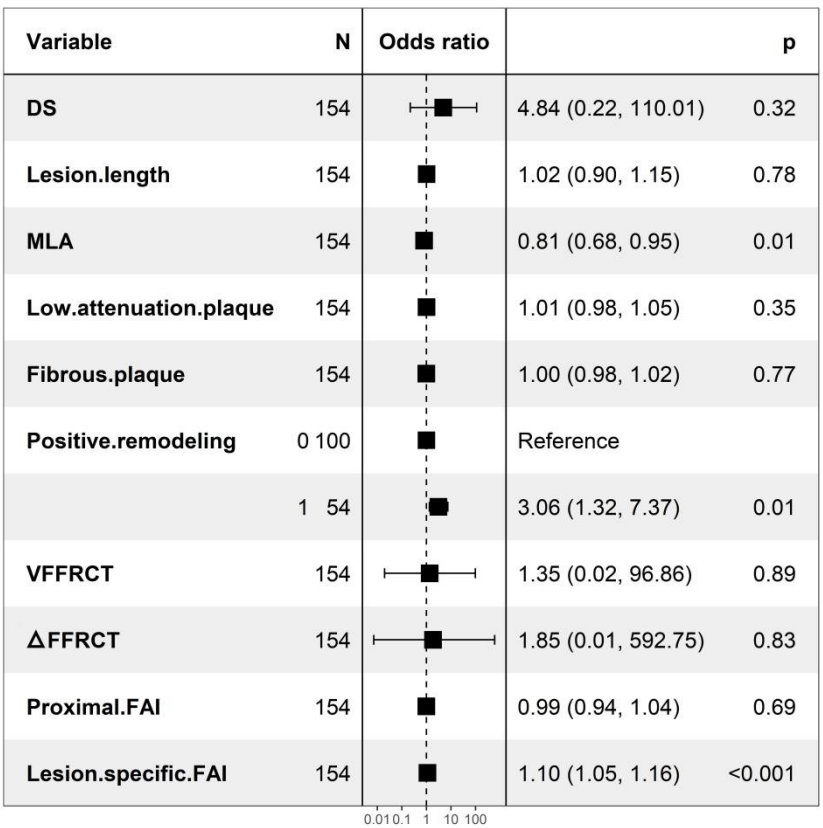

Figure S1 The risk of each parameter in the model built by machine learning. In positive remodeling, 0 represents RI <1.1, and 1 represents RI ≥1.1. DS: diameter stenosis, MLA: minimal lumen area, FFRCT: computed tomography-derived fractional flow reserve, VFFRCT: vessel FFRCT, ΔFFRCT: Delta FFRCT, FAI: fat attenuation index, RI: remodeling index.

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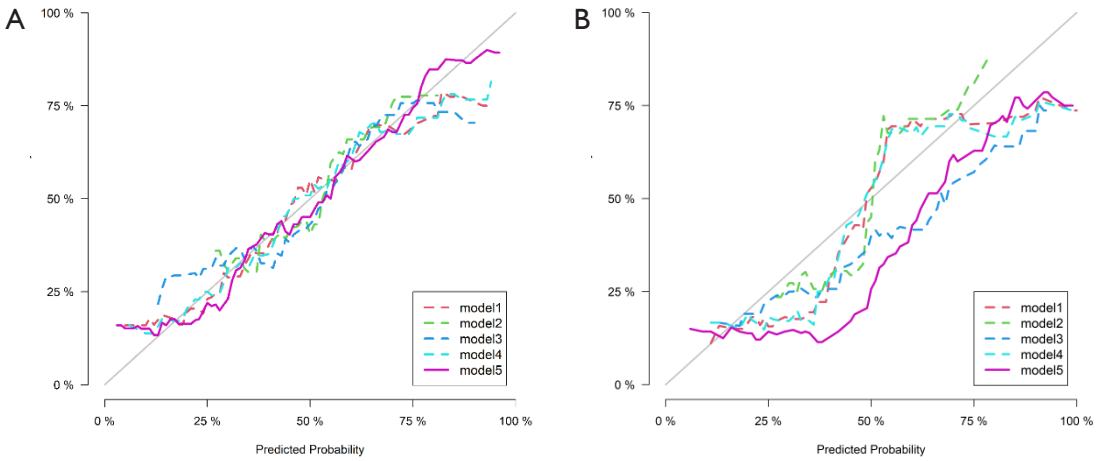

Figure S2 Calibration curves of different combination models in the training set (A) and test set (B). Model 1 includes plaque characteristics. Model 2 includes hemodynamic parameters. Model 3 includes PCAT attenuation. Model 4 includes plaque characteristics, hemodynamic parameters. Model 5 includes plaque characteristics, hemodynamic parameters and PCAT attenuation. Among the models, Model 5 was best calibrated in the training set and better calibrated in the test set. PCAT: pericoronary adipose tissue.

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