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ORIGINAL RESEARCH

A Machine Learning Model Integrating Tongue Image Features and Myocardial Injury Markers Predicts Major Adverse Cardiovascular Events in Patients with Coronary Heart Disease

Mi Zhou[1], Jieyun Li[1], Jiekee Lim[1], Xinang Xiao[1], Yumo Xia[2], Qingsheng Wang[3], Zhaoxia Xu[1,4,5]

[1]School of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, People's Republic of China; [2]Shanghai Anji Outpatient Department, Shanghai, 201203, People's Republic of China; [3]Shigatse People's Hospital, Department of Integrated Traditional and Western Medicine, Xizang, 857012, People's Republic of China; [4]Shanghai Key Laboratory of Health Identification and Assessment, Shanghai, 201203, People's Republic of China; [5]Shanghai Guangde Traditional Chinese Medicine Outpatient Department, Shanghai, 201203, People's Republic of China

Correspondence: Zhaoxia Xu, Shanghai University of Traditional Chinese Medicine, 1200 Cailun Road, Pudong New Area, Shanghai, 201203, People's Republic of China, Email zhaoxia7001@shutcm.edu.cn

Objective: The aim of this retrospective cohort study was to analyse the relationship between markers of myocardial injury, tongue parameters and major adverse cardiovascular events (MACE) in 1293 patients diagnosed with coronary heart disease(CHD).

Methods: This was a retrospective cohort study in which data were collected from patients diagnosed with CHD at the Department of Cardiology of Yueyang Hospital of Integrative Medicine and Shuguang Hospital in Shanghai, China, between 1 January 2023 and 31 December 2024, etc. All the patients were classified into two different groups according to follow-up results showed whether there was MACE, and the tongue image of each patient was performed using SMX System 2.0 to normalised acquisition was performed using SMX System 2.0, and tongue body (TC_) and tongue coating (CC_) data were converted to RGB and HSV model parameters. Five supervised machine learning classifiers, including XGBoost, logistic regression, KNN, LightGBM, AdaBoost, were used in building the MACE prediction model.

Results: 1293 patients were finally included in this study, with MACE occurred in 279 (21.6%) participants. After sample balancing using the SMOTE method, non-parametric tests revealed significant differences in imaging indicators, some myocardial injury markers, and tongue image parameters between the 2 groups of patients:LDH,MYO,TC_ROOT_R,TC_ROOT_G (P<0.05); the XGBoost, LightGBM models had the highest predictive power (The AUC values of the verification set > 0.97); the combination of SHAP values revealed the importance of the features and provided a quantitative metric to assess the contribution of each feature to the prediction results, Finally, subgroup analysis was conducted based on specific events of MACE.

Conclusion: This study provides insight into the potential application of myocardial injury markers, tongue colour parameters, in the prediction of MACE, and future studies could extend the optimisation of the prediction model and explore its application in other cardiovascular diseases.

Keywords: machine learning, coronary heart disease, major adverse cardiovascular events, markers of myocardial injury, tongue image, prediction models

Introduction

Coronary atherosclerotic heart disease refers to the accumulation of fatty plaques in the epicardial arteries, coronary atherosclerosis leads to stenosis or occlusion of the lumen and leads to myocardial ischemia, hypoxia or necrosis, abbreviated as coronary heart disease(CHD),which is the most common type of organ lesions caused by atherosclerosis. It is a disease with high morbidity and mortality worldwide, with a high incidence of recurrent events in patients and insufficient prediction tools available.[1,2] Therefore, enhancing the prediction and prevention of MACE in CHD is essential to improve clinical prognosis and patient quality of life.

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Studies have shown[3–5] that myocardial injury markers: creatine kinase isoenzyme (CK-MB), creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), troponin I (cTnI), troponin T (cTnT), ultrasensitive troponin (hs-cTnI), myoglobin (MYO), cardiac-type fatty acid binding protein (H -FABP), brain natriuretic peptide (BNP), and N-terminal B-type natriuretic peptide precursor (NT-proBNP) can be used as the core indexes for the diagnosis and prognosis of cardiovascular diseases, which need to be further studied in depth. Currently, some studies have shown that the prediction accuracy of hs-cTnI in predicting short-term MACE in patients with non-ST-segment elevation myocardial infarction reached 92.3% by logistic regression analysis;[6] the use of randomised survival forest model for predicting cardiovascular outcomes has revealed that cTnT is an important predictor of the occurrence of heart failure (HF), and the model has a better prediction accuracy.[7]

The 4 core diagnostic methods of traditional Chinese medicine(TCM) - inspection, auscultation and olfaction, inquiry and palpation - are collectively known as the "Four Diagnostic Methods", which form the basis of syndrome differentiation and treatment in TCM. Each method collects patient information from different perspectives and ultimately makes a comprehensive judgment on the nature of the disease. Among the four diagnostic methods in TCM, inspection is the most important. It is an important means for doctors to understand a patient's physical condition and disease changes by observing their complexion, tongue body, tongue coating, eyes and other external manifestations. Inspection not only enables a preliminary diagnosis of the disease but also provides an important basis for the other three diagnostic methods. At present, the research on inspection mainly focuses on tongue diagnosis and facial diagnosis. Auscultation and olfaction is a diagnostic method that acquires patient information by smelling odors and listening to sounds. It is of great significance for judging internal organ diseases, the severity of the condition, and the prognosis of the disease. The position of inquiry in the four diagnostic methods has always been highly valued by all medical practitioners. The process of inquiry not only enables a judgment on the patient's condition, reducing the interference of subjective consciousness in the other three diagnostic methods, but also allows for an understanding of the patient's mental state, emotions, etc. It serves as a "bridge" between doctors and patients. However, unlike the other three diagnostic methods, inquiry does not have specific images, sounds, tastes, and pulses that can be referred to and transformed. The content of the medical consultation is not easy to quantify, and it also varies according to each doctor's academic thoughts and clinical experience. At the same time, it is an important basis for the final determination of the disease. Palpation is a process where doctors use their fingers or palms to perform various forms of palpation on certain parts of the patient's body to assess the condition and understand the illness. At present, palpation in TCM mainly refers to pulse diagnosis, which has been highly valued by medical practitioners throughout history. Different schools of thought have different interpretations of pulse diagnosis, which depends on the clinical experience and theoretical knowledge of medical practitioners, making it difficult to standardize pulse diagnosis in TCM.[8]

Tongue diagnosis is an important method of diagnosis in TCM, reflecting the state of systemic diseases through tongue images. However, traditional tongue diagnosis relies on the subjective experience of doctors, and the diagnostic results lack consistency and repeatability.[9] With the application of artificial intelligence and image processing technology in the study of objectivation of the four diagnostic methods of TCM, the research of modern diagnostic techniques based on objectivated tongue diagnostic parameters has been initially developed in recent years. For example, the non-invasive diagnosis and identification model of CHD established by feature fusion algorithm, both of which have an accuracy rate of more than 80%, provide a new idea for large-scale screening and convenient diagnosis of CHD, and at the same time indicate that the tongue information may become an effective marker for the diagnosis of CHD;[10,11] in the preliminary stage of this project, we analysed the relationship between the tongue colour of the patients with coronary arteriography and the severity of the stenosis in coronary arteries through the retrospective cohort study, and the results showed that tongue colour parameters could provide a reference for predicting the degree of coronary artery stenosis, and it was also suggested that future studies could extend the tongue features, optimise the prediction model, and explore the application in other cardiovascular diseases.[12]

In recent years, the rapid development of artificial intelligence has provided new ideas for exploring non-invasive prognostic methods for CHD. Machine learning (ML) has advantages over traditional statistical methods when clinical data exhibit complexity and multidimensionality, eg, ML involves the selection and integration of multiple models, and also automatically learns to deal with non-linear relationships and select useful predictive features. Therefore ML can reveal hidden relationships in data more effectively and is increasingly used for diagnosis and risk prediction of clinical diseases.[7] A study has developed an ML model that predicts mortality in patients with HF caused by CHD and evaluated the performance of the ML model to provide an explicit interpretation of individualised risk prediction through the combination of ML and SHAP, and to intuitively understand the impact of the key features in the model, leading to a better treatment plan and optimal allocation of resources for patients. In addition, the interpretable framework increases the transparency of the model and facilitates physicians to understand the reliability of the predictive model.[13,14]

The innovativeness of this study lies in exploring the joint analysis of multimodal data (myocardial injury markers and tongue images) with the help of modern technologies such as ML, providing important theoretical support and methodological basis for the construction of the MACE prediction model for patients with CHD with the combination of TCM and Western medicines, promoting the individualised secondary prevention, and providing a certain research basis for the future development of a more efficient and accurate prognostic prediction tool for MACE in patients with CHD. The flow chart of this study is shown in Figure 1.

Material

Research Subjects

All patients with CHD originated from the cardiology outpatient clinics and wards of Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Yueyang Combined Hospital of Traditional Chinese Medicine and Western Medicine, Jiading Central Hospital, AnTu Division of Shanghai YangPu Central Hospital and Shanghai YangPu Hospital of Traditional Chinese Medicine in the year 2023–2024. A total of 1,398 patients were collected, follow-up observation was performed at 6 months, 9 months and 12 months after the first collection, and clinical information and MACE were recorded, and the final total valid sample was 1,293 patients according to the inclusion criteria and exclusion criteria nadir, among which the number of cases without MACE was 1014; the number of MACE cases was 279. Retrospective analyses were performed based on the participants' original clinical data and follow-up data.

Diagnostic Criteria for CHD

Coronary angiography (CAG) examination reveals that the diameter of the subepicardial coronary artery is narrowed by more than 50%, and the patient has typical angina pectoris symptoms, evidence of ischemic changes is shown through electrocardiogram (such as ST-segment elevation or reduction, T-wave inversion, etc)., which can be diagnosed as CHD.[15]

Inclusion Criteria

① Meet the western medical diagnostic criteria of CHD; ② Men and women are not limited, age 35–85 years old; ③ Patients' informed consent; ④ Clinical literature and information are complete and accurate.

Exclusion Criteria

① Acute and chronic nephritis, urinary tract infections, hypertrophic cardiomyopathy, trauma, surgery, acute infectious diseases and severe hepatic and renal insufficiency; ② pregnancy, lactating women, mental disorders; ③Subjects who voluntarily propose to withdraw; ④ Serious complications or deterioration of the condition during the study, requiring emergency measures; ⑤Incomplete clinical information or failure to comply with the follow-up and data collection process.

Clinical Information

General Clinical Data

Basic information such as participants' age, gender, BMI, blood pressure, heart rate, disease duration, smoking history, alcohol consumption history, and past medical history; laboratory test results (LVEF,Gensini and myocardial injury marker indicators) and follow-up results (whether recurrence of MACE), and tongue parameters were recorded.

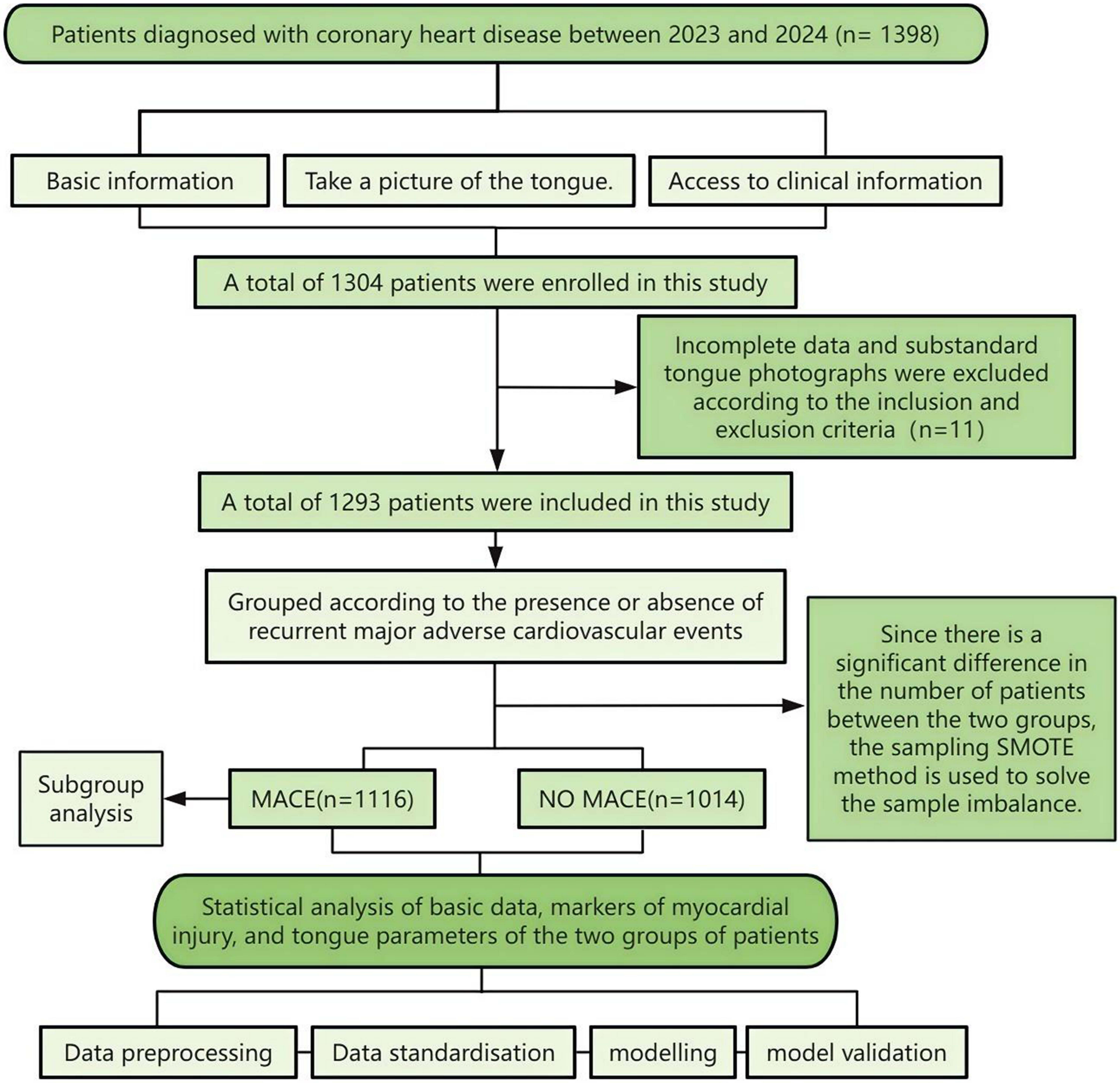

Figure 1 Flowchart.

MACEs in Patients with CHD

MACE is a composite indicator event of clinical events,[16,17] and is usually measured in clinical trials for cardiovascular patients. It may include multiple endpoint indicators, such as ① recurrent unstable angina pectoris: Patients report that the sudden onset lasts for a short period of time, with pain centered on the posterior part of the sternum, or spreading to the upper arm, left chest, and neck; ② Revascularization of the target vessels again: It refers to the revascularization surgery (PCI or coronary artery bypass grafting) performed on the infarct-related vessels treated by the previous PCI, including target vessel revascularization (TVR) and target lesion revascularization (TLR). The former refers to the revascularization of any part of the target vessel, including Target Lesion (TLR) and Non-Target Lesion (non-TLR); The latter specifically refers to the repeated intervention of the stent implantation site or within a 5mm range of its proximal/ distal end; ③ Non-fatal recurrent myocardial infarction: The results of echocardiography, myocardial enzymes, etc. indicate myocardial ischemia and myocardial injury, myocardial cell death, myocardial necrosis, and local circulatory disorders and other pathological conditions; ④ Heart failure: According to the guidelines of the European Society of Cardiology, the diagnosis of heart failure refers to ventricular filling and/or ejection dysfunction caused by various structural or functional diseases of the heart, where the cardiac output cannot meet the metabolic needs of body tissues, resulting in clinical manifestations such as breathing difficulties, limited physical activity, and fluid retention. ⑤ Cardiac death. The fundamental and direct cause of death lies in the structural or functional abnormalities of the heart itself, mainly caused by sudden cardiac death, acute congestive heart failure, acute myocardial infarction, severe arrhythmia and other structural/functional heart diseases. ⑥ Stroke. The definition of stroke is based on imaging findings or typical symptoms.

Tongue Image Collection and Parameter Extraction

① Tongue image acquisition: Canon PowerShot SX720 HS digital camera and Aisle X-rite ColorChecker Classic mini professional 24-colour card were used to acquire tongue images of the CHD patients and extract the tongue parameters; the subjects avoided drinking water for half an hour, avoided eating for one hour, rested quietly for more than 5 minutes, took the orthopedic sitting position or the supine position, opened their mouths and stretched their tongues, relax the facial muscles, hold the position for 3 seconds, and take the tongue picture; the collection of tongue diagnostic parameters was carried out by 2 experienced TCM practitioners (M-Z, JY-L).

② Tongue parameters extraction: tongue body and tongue coat were separated and segmented using "SMX System 2.0 tongue image analysis software" (registration number: 2008SR12316). The tongue image parameters used in this study mainly take the RGB model and HSV model as measurement indicators to describe the color parameters of tongue tissue (TC_) and tongue coating (CC_), including the tongue colour parameters RGB, HSV, and the indices of tongue fatness and thinness, pitting, dentition, petechiae, etc.; and the coat colour parameters RGB, HSV, and the indices of coat thickthin, curdygeasy and peeledcoating.

As shown in Figure 2[12] the RGB model is an additive colour model that represents various colours through different combinations of intensities of the primary colours red, green and blue. The intensity of each colour is usually represented by an integer between 0 and 255, where 0 means no colour and 255 means maximum intensity. On the other hand, the HSV model is a colour model based on human visual perception. In this particular model, the H-value (hue) denotes the basic attributes such as red, green, and blue; the S-value (saturation) denotes purity or brightness; and the V–value denotes lightness.

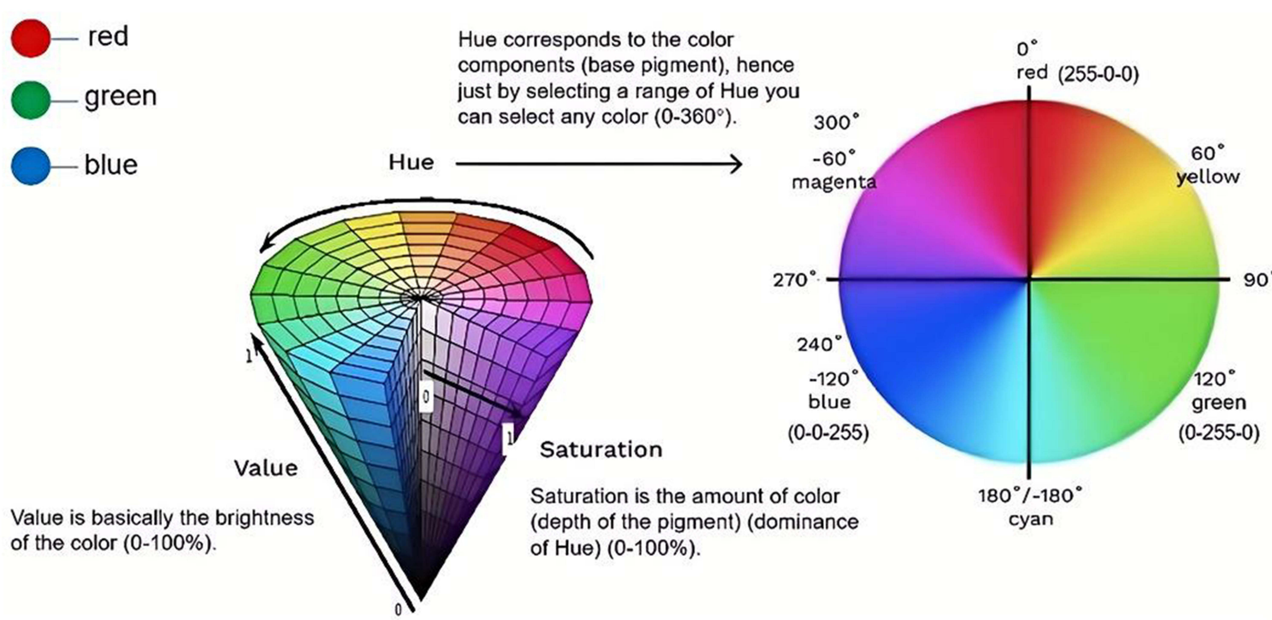

Figure 2 RGB and HSV colour models.

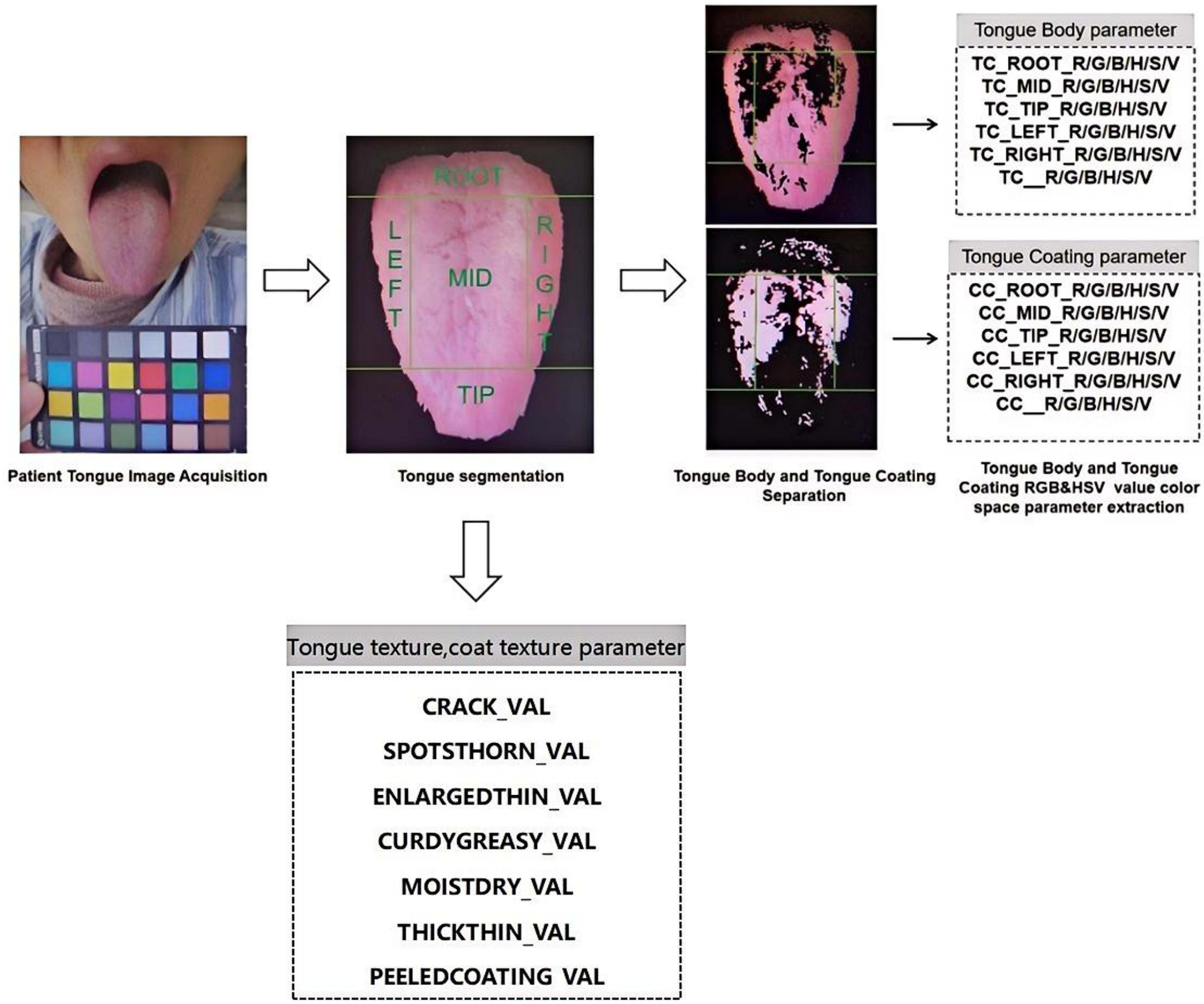

Figure 3 Methods for collecting and extracting parameters from tongue images.

In addition, since the tongue is a complex organ whose surface is covered with papillae and taste buds, different regions of the tongue may exhibit specific tongue features under the influence of different diseases or pathological processes. As shown in Figure 3, in order to observe and analyse these features in a more systematic way, the system parameters divide the tongue into root(ROOT), middle(MID), tip(TIP), left (LEFT)and right(RIGHT).

Data Collection and Quality Control

In this study, all data were obtained from the original clinical literature and clinical data collection was carried out by postgraduate students. It was checked by the researchers and imported into the EpiData database. To ensure the accuracy of the data, each case was checked for consistency and revised by at least two data managers for any inconsistencies until the information was accurate. Two experienced postgraduate students were designated as quality control supervisors to oversee the data collection process, data checking and data quality control. All patient-related information in this study was kept intact for patient privacy considerations.

Statistical Analysis

Statistical Methods

All statistical tests were conducted using two-sided hypothesis tests at a level of P= 0.05 ($P\leq$ value 0.05 indicates statistical significance). The specific principles were as follows: (1) Quantitative data were described by means and standard deviations, and hypothesis tests were performed using the *t*-test (normal distribution) or Wilcoxon rank sum test. (2) Qualitative data were described by frequencies and percentages, and hypothesis testing was done using chi-square test or Fisher's test. Rank-level data were analysed using Wilcoxon rank sum test. After statistical analysis, radar charts were used to visualise the changes in the characteristic parameters of tongue body and tongue coat colour in different MACE groups.

Analysing Risk Factors for MACE Using Non-Parametric Tests

Non-parametric test was performed with MACE as the primary endpoint and myocardial injury markers and tongue parameters as covariates. Non-parametric test analysis was used to screen out significant variables (P= 0.05), which were estimated using maximum likelihood algorithm, and odd ratios (OR) and 95% CIs were calculated. Software SPSS 27 was used for data analysis. Feature selection is crucial in the process of building clinical prediction models, as some features may have no effect on the prediction results or even interfere with the validity of the prediction model. Although ML-based feature selection methods have the ability to automatically select features, their results are convoluted and difficult to interpret.By comparing the differences in myocardial injury markers and tongue parameters between different groups, we can directly understand which features are associated with MACE.

Feature Screening Is Carried Out After LASSO Dimension Reduction

Lasso regression compresses the variable coefficients in the regression model by generating a penalty function to prevent overfitting and solve the problem of severe collinearity. Lasso regression was first proposed by the British Robert Tibshirani and is currently widely used in prediction models. In the New Gran literature, it is recommended that for model fitting with too many variables and a small sample size, Lasso regression should be considered first for variable screening. Default cross-validation is 10% off.

ML Methods to Build Prediction Models and Verification

ML algorithms can extract useful information from massive data and make objective and accurate predictions through algorithmic models. We hope to analyse myocardial injury markers and tongue parameters through ML to more comprehensively assess the application value of myocardial injury markers and tongue parameters in predicting MACE. In this study, we explored and validated the hypothesis that the analysis of myocardial injury markers and tongue colour parameters can be used as a clinical auxiliary diagnostic method by building a MACE prediction model based on myocardial injury markers and tongue colour parameters. To compare the predictive ability of 5 different models (XGBoost, logistic regression, KNN, LightGBM, AdaBoost), a cross-validation approach was used with a number of times of 2, a random seed of 44, automated grid-seeking of parameters, calculation of accuracy, sensitivity, and specificity, and plotting of decision curve analysis (DCA). These are the classical ML models used to build predictive models that have been shown to be effective in previous heart disease studies.[18–20] In each modelling process, the dataset was randomly divided into a training set and a test set in a ratio of 8:2.The training set is used for model training and the test set is used to validate the model performance. All feature values are normalised by a standard scaler, which works by subtracting the mean and dividing by the variance so that all values are centred on zero with a variance of 1. During model training, parameters are optimised using hierarchical 2-fold cross-validation and grid search. The categorical metrics used to assess the performance of model training and validation are accuracy, sensitivity, specificity, and F1 score: ①Accuracy is the most commonly used categorical metric. It indicates the proportion of samples correctly predicted by the model to the total number of samples; ② Sensitivity indicates the proportion of all samples predicted as positive by the model that are actually positive. This helps us to understand how accurately the model predicts the positive class; ③ Specificity is the proportion of the number of samples correctly predicted as negative by the model to the number of actual negative samples; ④Recall indicates the proportion of samples correctly predicted by the model to be positive out of all samples that were actually positive;⑤The F1 score is the reconciled mean of precision and recall, which takes into account the performance of precision and recall; the higher the F1 score, the better the model performs in terms of precision and recall.The ROC curve is a graphical tool used to evaluate the performance of a classification model, which shows the relationship between the True Positive Rate (TPR) and the False Positive Rate (FPR) at different classification thresholds. The AUC value (area under the curve) represents the area under the ROC curve and reflects the overall performance of the model at different classification thresholds. The AUC values range from 0.5 to 1, where 0.5 indicates that the model performance is comparable to random guessing and 1 indicates perfect model performance. By comparing the AUC values of the five models, it is possible to see the performance ability of myocardial injury markers and tongue feature parameters in predicting MACE.

In order to improve the credibility of the model and facilitate its use by clinicians, it is important not only to report the prediction results but also to interpret the model. Traditional feature importance can only indicate the importance of the feature values, but cannot clearly describe their impact on the prediction results. Therefore, in our study, we used the SHapley Additive Explanatory Values (SHAP) for visualisation and analysis.The SHAP values not only reveal the importance of the features, but also provide a quantitative metric for assessing the contribution of each feature to the predicted outcome. This allows us to accurately compare the impact of different markers of myocardial injury, and different tongue features, on model output results. In addition, the SHAP values reveal the interactions between features, allowing us to gain a deeper understanding of the interactions between these features and a comprehensive understanding of the relationship between myocardial injury markers and MACE. In this study, the best ML algorithm for MACE will be used to plot the SHAP values for each sample using the Extreme Intelligence Analytics platform.

Results

Baseline Information

A total of 1398 patients with CHD from 1st January 2023 to 31st December 2024, finally 1293 participants were included in the final study according to the inclusion criteria and exclusion criteria, with a mean age of 70 years (the youngest was 34 years and the oldest was 85 years), 688 males (53.2%) and 605 females (46.8%);913 had hypertension (70.61%), 427 had diabetes mellitus (30.30%), 115 had hyperlipidaemia (8.90%), 475 had a history of smoking (36.73%),416 had a history of alcohol consumption (32.17%). According to the follow-up results, of the 1293 patients included in the study, MACE occurred in 279 (21.6%) participants.Since the sample sizes of the MACE group and the non-MACE group differ significantly, the SMOTE method was used to balance the samples of 279 MACE patients according to the characteristics of specific MACE events. Eventually, there were 1116 cases in the MACE group and 1014 cases in the non-MACE group.There was no statistically significant difference between the MACE group and the non-MACE group in terms of age, gender, systolic blood pressure, diastolic blood pressure, heart rate, BMI, history of smoking, history of alcohol consumption, duration of the disease, and previous history (history of hypertension, diabetes mellitus, and history of hyperlipidaemia) (P>0.05), and in terms of whether or not the group had PCI (P< 0.05) was statistically significant (Table 1).

Non-Parametric Test of Risk Factors for MACE in Patients with CHD

Non-parametric test was used to screen the risk factors for the occurrence of MACE in patients with coronary heart disease. Myocardial injury markers, tongue parameters and other indicators were included in the data. The results showed that:Gensini, LVEF,LDH,MYO,CKMB,cTnT,BNP,NTproBNP,TC_ROOT_R,TC_ROOT_G,TC_ROOT_B,TC_ROOT_S,TC_ROOT_V, TC_MID_S,TC_TIP_B,TC_TIP_S,TC_RIGHT_R,TC_RIGHT_V,TC_R,TC_S,TC_V,CC_ROOT_H,CC_ROOT_S, CC_MID_G,CC_MID_B,CC_MID_H,CC_MID_S,CC_TIP_R,CC_TIP_G,CC_TIP_B,CC_TIP_H,CC_TIP_V,CC_LEFT_R, CC_LEFT_G,CC_LEFT_B,CC_LEFT_V,CC_RIGHT_G,CC_RIGHT_S,CC_G,CC_B,CC_H,CC_S, CURDYGREASY_VAL,THICKTHIN_VAL,PEELEDCOATING_VAL (p <0.05) by Mann–Whitney-U test showed a statistically significant difference between the groups, indicating that these indicators led to the occurrence of MACE in this

Table 1 Comparison of Baseline Data Between the Non-MACE Group and the MACE Group [n(%) or M(Q1, Q3)]

General Information	Classifications	NO MACE =1014	MACE=1116	*r*	*P*
Age		70.000 [63.000;75.000]	70.000 [62.000;76.000]	−0.991	0.321
Sex, N (%):				0.094	0.792
	Female	473 (46.647%)	528 (47.312%)		
	Male	541 (53.353%)	588 (52.688%)		
SBP		130.000 [120.000;141.000]	129.000 [120.000;141.000]	0.029	0.029
DBP		78.000 [70.000;83.000]	77.000 [70.000;83.000]	0.314	0.314
Heart rate		76.000 [68.000;80.000]	76.000 [68.000;80.000]	0.668	0.668
BMI		24.035 [21.774;26.667]	24.490 [22.093;26.814]	0.009	0.009
Smoking,N(%):				0.108	0.777
	No	643 (63.412%)	700 (62.724%)		
	Yes	371 (36.588%)	416 (37.276%)		
Drinking, N (%):				0.391	0.563
	No	685 (67.554%)	768 (68.817%)		
	Yes	329 (32.446%)	348 (31.183%)		
Hypertension, N (%):				2.670	0.113
	No	305 (30.079%)	300 (26.882%)		
	Yes	709 (69.921%)	816 (73.118%)		
DM, N (%):				0.743	0.415
	No	683 (67.357%)	732 (65.591%)		
	Yes	331 (32.643%)	384 (34.409%)		
Hyperlipidemia, N (%):				0.634	0.471
	No	926 (91.321%)	1008 (90.323%)		
	Yes	88 (8.679%)	108 (9.677%)		
Disease course, N (%):				8.794	0.118
	0-1 year	516 (50.888%)	564 (50.538%)		
	1-5 year	275 (27.120%)	260 (23.297%)		
	5-10 year	97 (9.566%)	124 (11.111%)		
	10-15 year	35 (3.452%)	48 (4.301%)		
	More than 15 year	37 (3.649%)	60 (5.376%)		
	Unclear	54 (5.325%)	60 (5.376%)		
PCI N (%):				5.155	0.026
	No	352 (34.714%)	336 (30.108%)		
	Yes	662 (65.286%)	780 (69.892%)		

study (p=0.05) (Table 2, note: Table 2 only includes statistically significant results; see Table 1S for full table). Radar charts visualised the changes in tongue colour,coat colour and tongue shape characteristic parameters in different MACE groups (Figures 4–5).

Multivariate Logistic Regression Analysis of Risk Factors for MACE in Patients with CHD

Multivariate logistic regression analysis was conducted on imaging indicators and myocardial injury markers in patients with CHD based on whether MACE occurred. Multivariate regression analysis was carried out when the single-factor P value was <0.1, and two-way stepwise regression analysis was also conducted. The results showed that the differences in Gensini, AST, LDH and NT-proBNP in the multivariate regression analysis were statistically significant (P<0.05). Due to the large collinearity of tongue image parameters, it was not involved in the multivariate regression analysis. See Table 3 for details.

Table 2 Non-Parametric Tests for the Presence or Absence of Risk Factors for the Development of MACE in Patients with CHD

	NO MACE (n=1014)	MACE (n=1116)	*r*	*p*
Gensini	37.500[0.000,160.000]	55.000[0.000,215.000]	−3.074	0.002
LVEF	63.700[61.000,66.000]	64.000[61.000,68.000]	−2.728	0.006
LDH	196.710[170.000,229.000]	188.000[161.000,222.000]	3.228	0.001
MYO	31.000[23.103,46.720]	32.633[25.389,46.498]	−2.395	0.017
CKMB	2.620[1.380,6.000]	3.000[1.700,7.000]	−3.870	<0.001
cTnT	0.013[0.006,0.023]	0.020[0.007,0.050]	−5.443	<0.001
BNP	142.424[80.351,267.221]	68.000[33.000,156.000]	13.938	<0.001
NTproBNP	257.760[107.783,648.900]	387.626[139.000,918.000]	−4.677	<0.001
TC_ROOT_R	127.973[112.771,147.509]	123.286[105.803,139.862]	5.321	<0.001
TC_ROOT_G	88.739[74.259,106.934]	85.922[70.049,99.965]	3.856	<0.001
TC_ROOT_B	87.854[72.695,105.851]	85.546[70.402,100.774]	3.805	<0.001
TC_ROOT_S	0.320[0.264,0.375]	0.305[0.251,0.371]	3.142	0.002
TC_ROOT_V	0.553[0.473,0.687]	0.534[0.436,27.482]	2.910	0.004
TC_MID_S	0.311[0.261,0.358]	0.297[0.247,0.343]	4.795	<0.001
TC_TIP_B	104.362[90.081,117.468]	106.207[92.421,118.522]	−2.401	0.016
TC_TIP_S	0.403[0.359,0.449]	0.399[0.346,0.438]	3.154	0.002
TC_RIGHT_R	169.118[149.975,185.093]	165.354[148.879,184.433]	2.086	0.037
TC_RIGHT_V	169.118[149.975,185.093]	165.354[148.879,184.433]	2.086	0.037
TC_R	163.544[150.709,176.718]	162.010[148.774,174.925]	2.571	0.010
TC_S	0.335[0.293,0.375]	0.332[0.288,0.365]	2.512	0.012
TC_V	163.544[150.709,176.718]	162.010[148.774,174.925]	2.571	0.010
CC_ROOT_H	22.838[11.803,346.013]	31.024[13.949,347.580]	−2.825	0.005
CC_ROOT_S	0.283[0.209,0.353]	0.272[0.201,0.337]	2.443	0.015
CC_MID_G	130.435[114.670,144.610]	133.857[117.962,148.049]	−3.042	0.002
CC_MID_B	133.364[116.793,149.911]	135.681[120.307,154.964]	−2.891	0.004
CC_MID_H	341.472[14.585,348.907]	342.443[18.325,350.161]	−2.298	0.022
CC_MID_S	0.286[0.233,0.341]	0.268[0.221,0.332]	4.001	<0.001
CC_TIP_R	165.243[136.529,186.965]	169.556[146.560,188.496]	−3.275	0.001
CC_TIP_G	104.049[80.702,124.091]	111.719[88.602,131.048]	−4.426	<0.001
CC_TIP_B	110.498[84.444,134.217]	120.760[96.587,137.550]	−4.018	<0.001
CC_TIP_H	345.118[8.769,349.558]	345.723[15.038,351.205]	−3.471	<0.001
CC_TIP_V	165.243[136.529,186.965]	169.556[146.560,188.496]	−3.275	0.001
CC_LEFT_R	161.103[131.833,185.689]	168.205[140.486,188.073]	−2.797	0.005
CC_LEFT_G	111.094[86.461,135.695]	120.012[90.050,138.164]	−3.026	0.002
CC_LEFT_B	114.700[87.509,141.105]	119.967[94.919,145.861]	−3.172	0.002
CC_LEFT_V	161.103[131.833,185.689]	168.205[140.486,188.073]	−2.792	0.005
CC_RIGHT_G	123.330[98.917,141.977]	124.983[105.184,145.095]	−2.080	0.037
CC_RIGHT_S	0.281[0.220,0.349]	0.272[0.215,0.340]	2.105	0.035
CC_G	121.880[105.815,137.452]	123.155[108.843,140.309]	−2.826	0.005
CC_B	124.219[106.326,141.689]	127.057[109.311,145.560]	−2.658	0.008
CC_H	340.900[13.849,349.683]	342.250[17.515,351.187]	−2.282	0.023
CC_S	0.291[0.239,0.345]	0.280[0.233,0.339]	3.057	0.002
CURDYGREASY_VAL	0.797[0.720,0.886]	0.806[0.728,0.894]	−2.212	0.027
THICKTHIN_VAL	0.076[0.039,0.122]	0.073[0.034,0.121]	2.016	0.044
PEELEDCOATING_VAL	33.459[23.786,47.624]	36.070[26.113,49.231]	−3.949	<0.001

Note: This Table Only Includes Statistically Significant Results; See Supplementary Material Table 1S for Full Table.

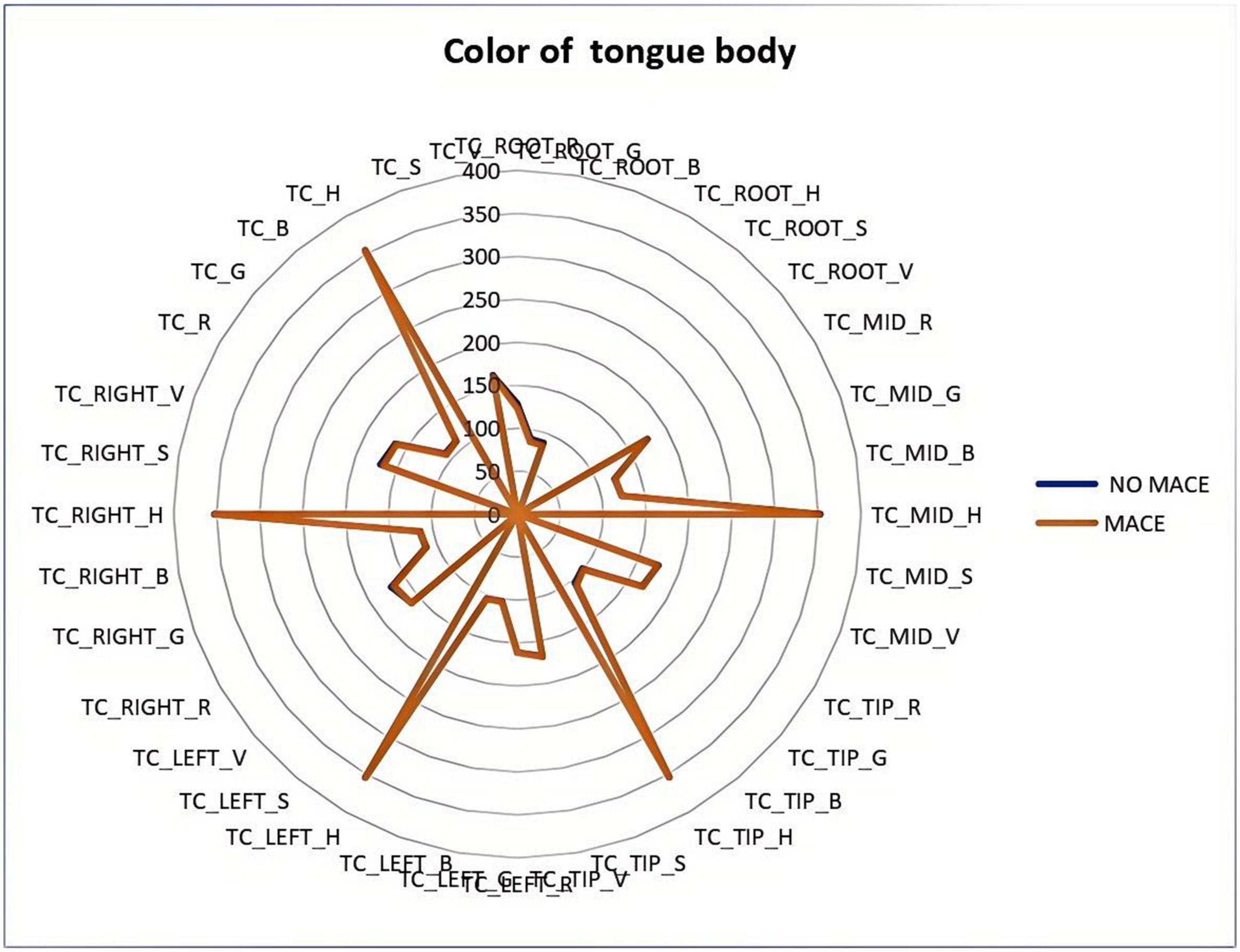

Figure 4 Radar map of tongue colour distribution.

Feature Dimension Reduction

Feature dimension reduction was performed using LASSO, and the obtained feature factors were: Gensini score, AST, LDH, NT-proBNP, TC_ROOT_R, TC_MID_S, TC_TIP_B, CC_MID_B, CC_TIP_G, and PEELEDCOATING_VAL. Figure 6 is the cross-validation curve of LASSO regression, and Figure 7 is the cross-sectional view of LASSO coefficients. The LASSO coefficient Table can be found in Table 2S.

ML Modelling to Compare the Joint Predictive Ability of Different Indicators

The XGBoost, logistic, KNN, LightGBM and AdaBoost models were used to predict MACE in order to train and verify the myocardial injury markers and tongue color parameters of the two groups of patients. The inclusion factor is the feature screening factor after LASSO dimension reduction. As shown in Table 4, except for the logistic model, the other 4 algorithms all exhibit relatively high verification results. In terms of the training set, XGBoost, KNN, and LightGBM have superior prediction performance, with accuracy, precision, sensitivity, specificity, and F1 scores all exceeding 70%. As shown in Table 5, in terms of the test set, XGBoost and LightGBM have the highest prediction performance. We integrated the training process of each model and 2x cross-validation using the training dataset. Based on the evaluation results of the two datasets (training and validation), XGBoost has been proven to be a highly stable model based on tongue image parameters and also the best predictive model for determining MACE. Figure 8 shows the ROC curves of different models using myocardial injury markers and tongue image parameter data. In this ROC curve graph, lines of different colors represent whether MACE occurs. The results of the validation set show that the predictive abilities of

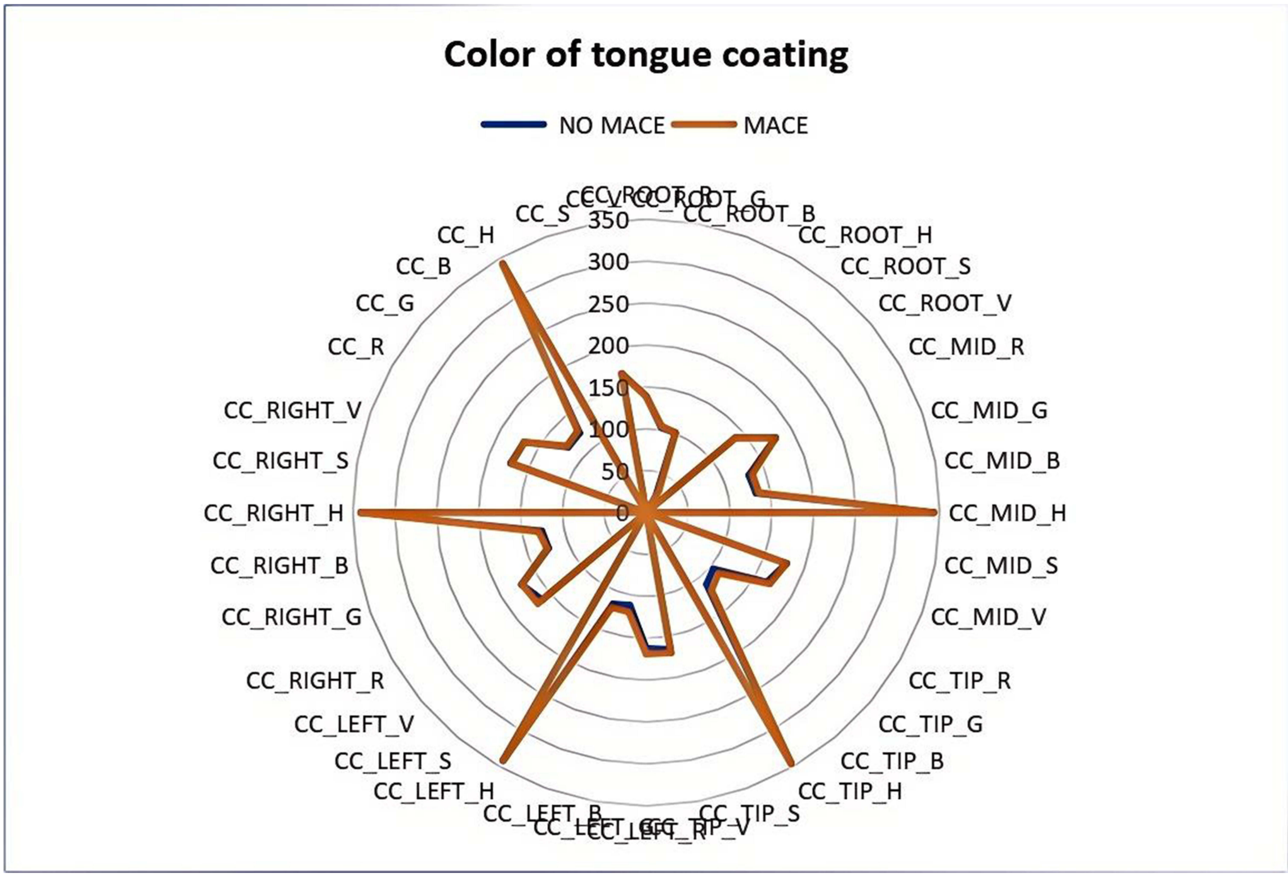

Figure 5 Radar map of coat colour distribution.

XGBoost and LightGBM for the occurrence of MACE are greater than 0.9 (AUC > 0.97). The ROC curve of the validation set is shown in Figure 4S, the calibration curve is shown in Figure 1S, the decision curve validation is shown in Figure 2S, the forest plot is shown in Figure 3S, and the PR curve of the training set is shown in Figure 4S.

Table 3 Multivariate Logistic Regression Analysis of Risk Factors for MACE in Patients with CHD

Variables	Single Factor					Multifactorial				
	β	S.E	Z	*P*	OR (95% CI)	β	S.E	Z	*P*	OR (95% CI)
Gensini	0.01	0.00	3.11	0.002	1.01 (1.01 ~ 1.01)	0.01	0.00	2.75	0.006	1.01 (1.01 ~ 1.01)
LVEF	−0.00	0.00	−0.37	0.714	1.00 (0.99 ~ 1.01)					
AST	−0.01	0.00	−2.95	0.003	0.99 (0.98 ~ 0.99)	−0.01	0.00	−2.71	0.007	0.99 (0.98 ~ 0.99)
LDH	−0.01	0.00	−3.54	<0.001	0.99 (0.99 ~ 0.99)	−0.01	0.00	−3.09	0.002	0.99 (0.99 ~ 0.99)
MYO	0.00	0.00	1.09	0.277	1.00 (1.00 ~ 1.00)					
CK-MB	0.00	0.00	0.95	0.341	1.00 (1.00 ~ 1.00)					
cTnT	0.00	0.00	1.07	0.286	1.00 (1.00 ~ 1.01)					
BNP	−0.00	0.00	−0.66	0.512	1.00 (1.00 ~ 1.00)					
NT-proBNP	0.01	0.00	2.53	0.011	1.01 (1.01 ~ 1.01)	0.01	0.00	2.35	0.019	1.01 (1.01 ~ 1.01)

Abbreviation: OR, Odds Ratio; CI, Confidence Interval.

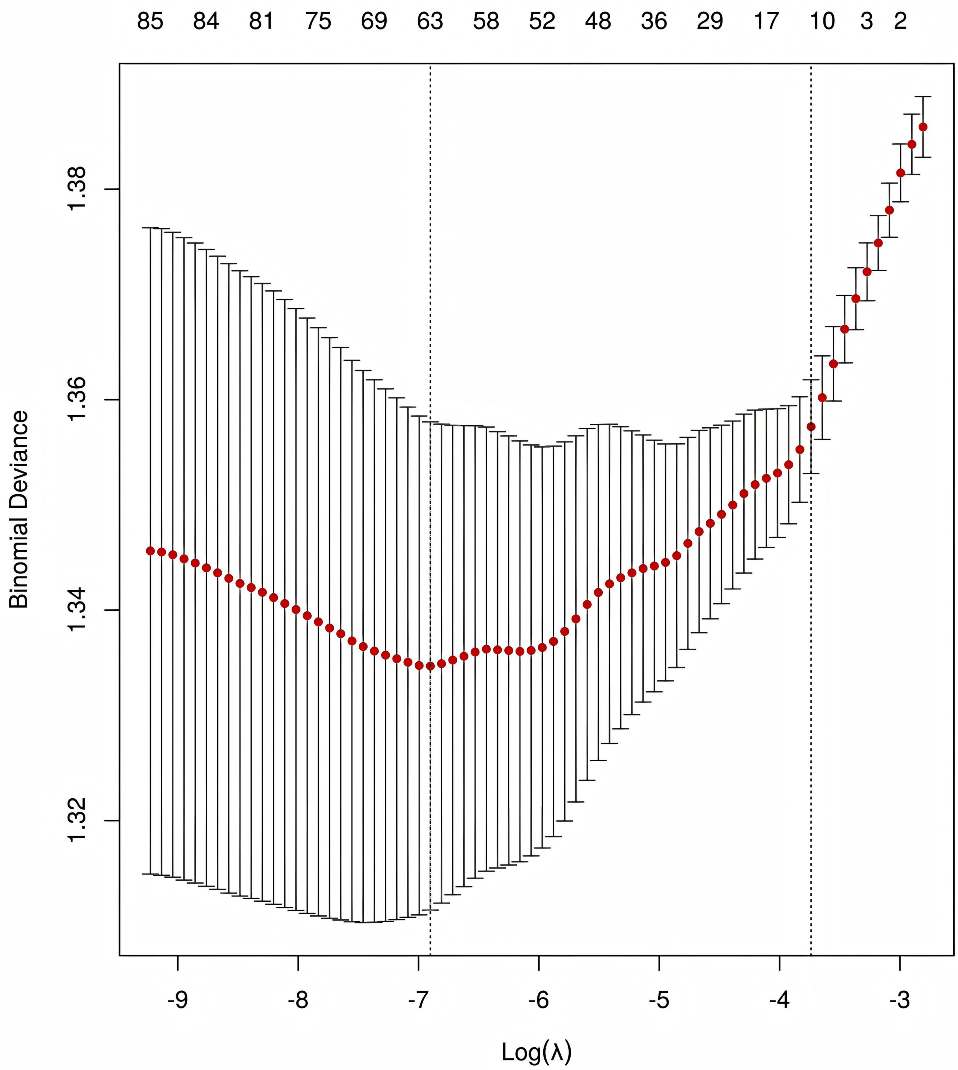

Figure 6 LASSO regression cross-validation curve.

SHAP Feature Values

According to the XGBoost model visualisation report, the magnitude of the output contribution of the 10 parametric features is shown in Figure 9, they are Gensini, AST, LDH, NT-proBNP, TC_ROOT_R, TC_MID_S, TC_TIP_B, CC_MID_B, CC_TIP_G, PEELEDCOATING_VAL,These features are associated with MACE.

In order to show more visually the output contribution of different groups of myocardial injury markers and tongue features, the SHAP value plot further shows the effect of myocardial injury markers and tongue colour parameter values on MACE. Each row represents a parameter and each dot represents a theme. The colour represents the size of the feature parameter, the larger the value, the redder the colour. The results are shown in Figure 10: High values of Gensini, CC_TIP_G, and low values of NT-proBNP, LDH, TC_ROOT_R, AST and TC_TIP_B positively predict MACE.

Conduct Subgroup Analysis on Specific MACE Events

A total of 1,116 MACE events were included in this study. According to the above classification and statistics, there were 636 cases of unstable angina pectoris, 308 cases of emergency revascularization, 52 cases of myocardial infarction, 60 cases of heart failure, 8 cases of cardiogenic death, and 52 cases of stroke.

In previous studies, MACE could be directly subdivided into different types of events, such as hospitalization and death.[21] Some studies also grouped MACE according to severity (no, mild, moderate, severe) to analyze the association

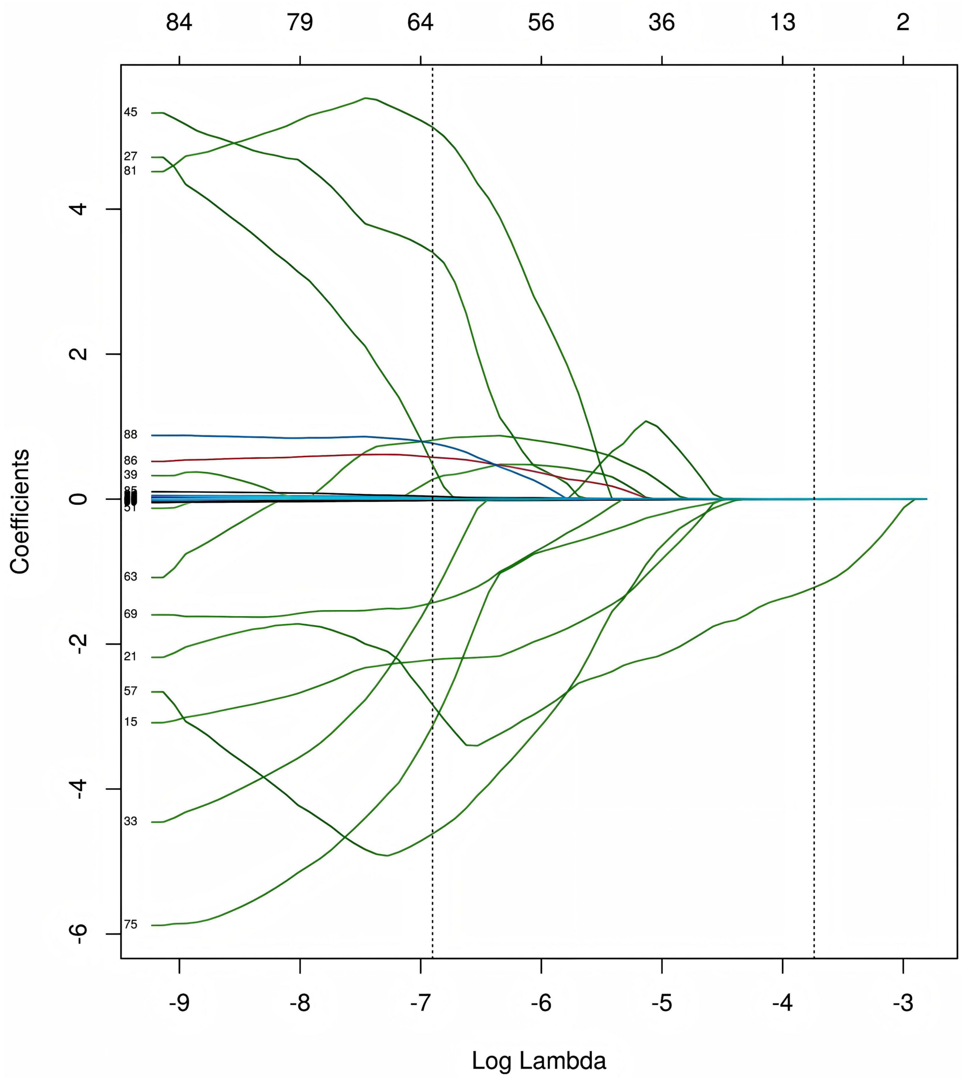

Figure 7 LASSO coefficient profile.

between different severity and clinical outcomes.[22] There are also studies that classify MACE into in-hospital MACE and non-in-hospital MACE based on whether MACE occurs in the hospital,[23] and some studies adopt stratified reporting (major MACE vs Extended MACE) has been widely accepted and applied in cardiovascular clinical research and is supported by a large number of authoritative literatures and guidelines. The core purpose of this stratified approach is to provide more comprehensive clinical event information while ensuring the comparability of core endpoints.[24–26] For example, in its numerous ACS and secondary prevention studies (such as PROVE IT-TIMI 22, TRITON-TIMI 38, PEGASUS-TIMI 54, etc)., the standard primary endpoint is usually a triple composite endpoint of cardiovascular death,

Table 4 Whether MACE Has Occurred Training Set

model	AUC(SD)	Accuracy(SD)	Sensitivity(SD)	Specificity(SD)	F1(SD)
XGBoost	1.000(0.000)	1.000(0.000)	1.000(0.000)	1.000(0.000)	1.000(0.000)
Logistic	0.624(0.005)	0.609(0.005)	0.599(0.049)	0.620(0.048)	0.615(0.021)
KNN	0.874(0.002)	0.783(0.006)	0.721(0.023)	0.852(0.014)	0.777(0.010)
LightGBM	1.000(0.000)	1.000(0.000)	1.000(0.000)	1.000(0.000)	1.000(0.000)
AdaBoost	0.786(0.004)	0.714(0.007)	0.732(0.036)	0.695(0.029)	0.728(0.014)

Table 5 Whether MACE Has Occurred Validation Set

model	AUC(SD)	Accuracy(SD)	Sensitivity(SD)	Specificity(SD)	F1(SD)
XGBoost	0.985(0.005)	0.969(0.008)	1.000(0.000)	0.934(0.016)	0.971(0.007)
Logistic	0.619(0.021)	0.592(0.017)	0.574(0.036)	0.612(0.062)	0.595(0.015)
KNN	0.671(0.027)	0.555(0.022)	0.419(0.047)	0.705(0.040)	0.496(0.037)
LightGBM	0.978(0.009)	0.929(0.020)	1.000(0.000)	0.851(0.042)	0.937(0.017)
AdaBoost	0.700(0.009)	0.645(0.016)	0.665(0.031)	0.623(0.034)	0.662(0.018)

myocardial infarction, and stroke. Secondary endpoints or exploratory endpoints usually include emergency revascularization, hospitalization due to unstable angina pectoris, hospitalization due to heart failure, etc. These events are often combined into extended composite endpoints.[27,28] Therefore, in this study, only 112 cases of the primary endpoint events were discussed (8 cases of cardiovascular death, 52 cases of myocardial infarction, and 52 cases of stroke).

Baseline Analysis of Patients with Different Primary Endpoint Events of MACE

As shown in Table 6: There were statistically significant differences among the groups of patients in terms of heart rate, BMI, disease duration, smoking history, history of hypertension, history of diabetes, and history of hyperlipidemia (P<0.05).

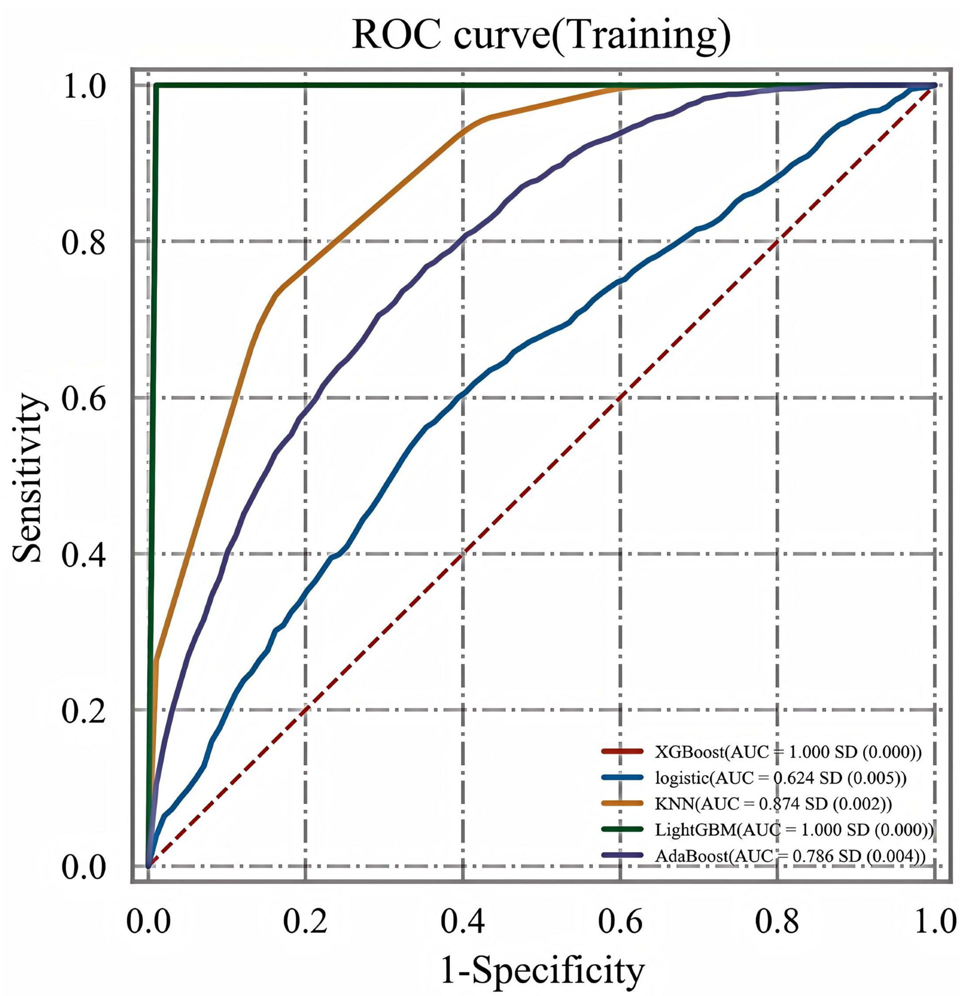

Figure 8 ROC curves for different models using myocardial injury markers, tongue parameter data.

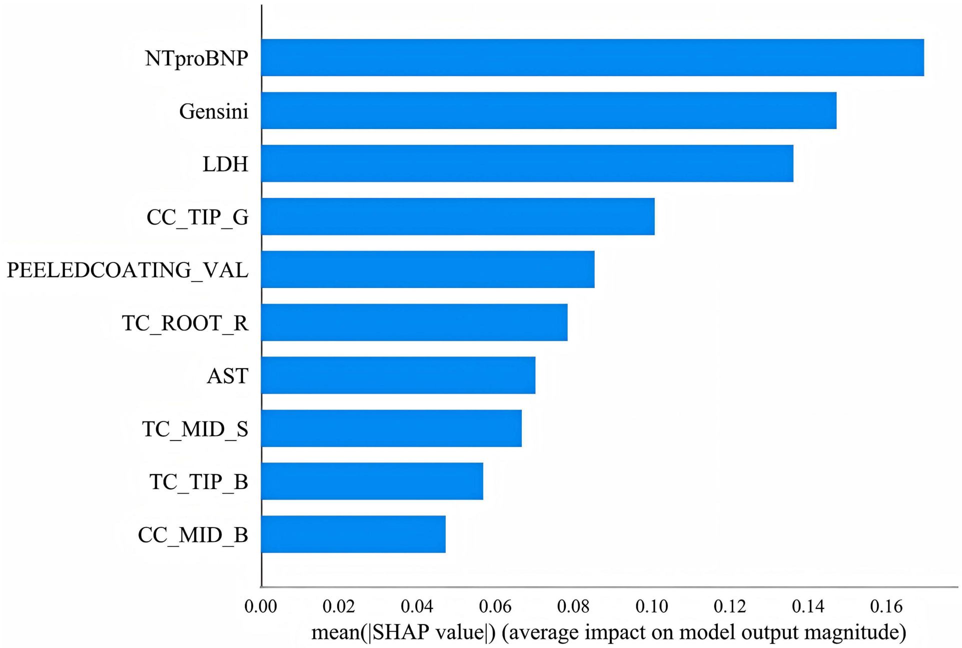

Figure 9 Summary of the characteristics of MACE-related impact parameters.

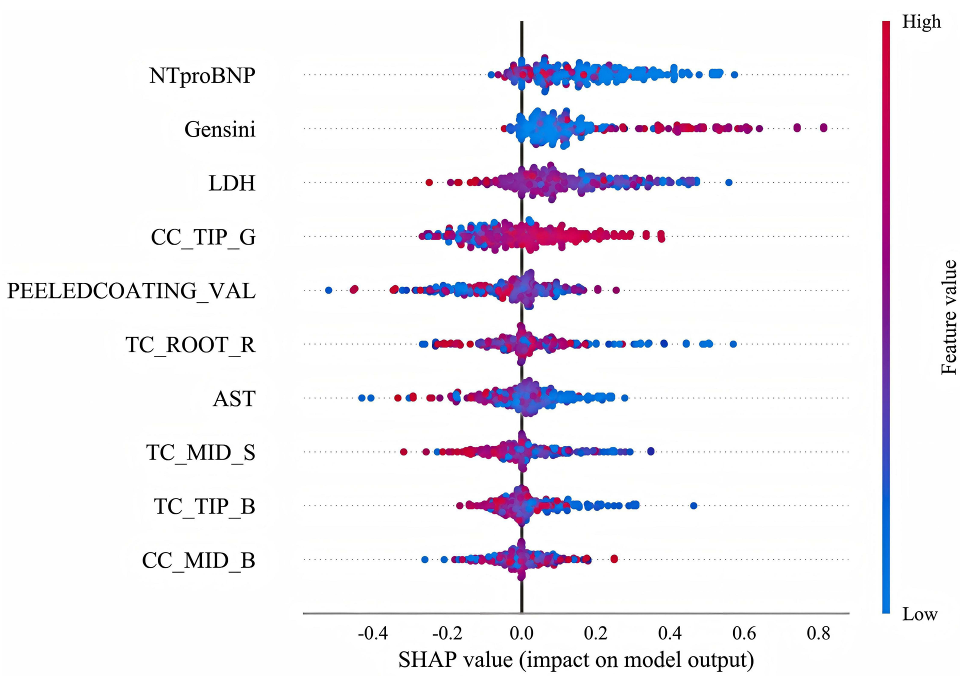

Figure 10 SHAP value plot of XGBoost for MACE features.

Comparison of Myocardial Injury Markers in Patients with Different Primary Endpoint Events of MACE

As shown in Table 7, AST,LDH,MYO and BNP of the three groups of patients were (P<0.05) statistically significant by Kruskal–Wallis test. The AST of patients with myocardial infarction was significantly higher than that of patients with stroke and death, the MYO was significantly lower than that of patients with stroke and death (P<0.01), the LDH of patients with stroke was significantly higher than that of patients with myocardial infarction and death (P<0.05), and the BNP of patients with death was significantly higher than that of patients with stroke and myocardial infarction (P<0.01).

Table 6 Baseline Analysis of Patients with Different Primary Endpoint Events of MACE

	Stroke N=52	Myocardial Infarction N=52	Death N=8	p
Age	72.000 [63.000;77.000]	73.000 [68.000;75.000]	72.500 [61.000;84.000]	0.748
SBP	135.000 [121.000;139.000]	125.000 [115.000;149.000]	123.000 [120.000;126.000]	0.398
DBP	75.000 [61.000;80.000]	76.000 [73.000;79.000]	70.000 [60.000;80.000]	0.434
Heart rate	70.000 [64.000;79.000]	77.000 [71.000;80.000]	71.500 [63.000;80.000]	0.005
BMI	25.720 [23.438;26.953]	23.460 [20.810;24.655]	22.680 [21.484;23.875]	0.007
Gensini	15.000 [0.000;265.000]	30.000 [0.000;175.000]	3.750 [0.000;7.500]	0.053
LVEF	66.000 [61.000;67.000]	65.000 [62.000;67.000]	65.500 [64.000;67.000]	0.810
Sex, N (%):				0.060
Female	24 (46.154%)	36 (69.231%)	4 (50.000%)	
Male	28 (53.846%)	16 (30.769%)	4 (50.000%)	
Disease course, N (%):				<0.001
0-1 year	32 (61.538%)	20 (38.462%)	4 (50.000%)	
1-5 year	8 (15.385%)	28 (53.846%)	0 (0.000%)	
5-10 year	4 (7.692%)	0 (0.000%)	0 (0.000%)	
10-15 year	4 (7.692%)	0 (0.000%)	0 (0.000%)	
More than 15 year	0 (0.000%)	4 (7.692%)	4 (50.000%)	
Unclear	4 (7.692%)	0 (0.000%)	0 (0.000%)	
Smoking,N(%):				0.001
No	36 (69.231%)	32 (61.538%)	0 (0.000%)	
Yes	16 (30.769%)	20 (38.462%)	8 (100.000%)	
Drinking, N (%):				0.132
No	40 (76.923%)	32 (61.538%)	4 (50.000%)	
Yes	12 (23.077%)	20 (38.462%)	4 (50.000%)	
Hypertension, N (%):				0.037
No	20 (38.462%)	24 (46.154%)	0 (0.000%)	
Yes	32 (61.538%)	28 (53.846%)	8 (100.000%)	
DM, N (%):				<0.001
No	20 (38.462%)	44 (84.615%)	8 (100.000%)	
Yes	32 (61.538%)	8 (15.385%)	0 (0.000%)	
Hyperlipidemia, N (%):				0.001
No	48 (92.308%)	36 (69.231%)	4 (50.000%)	
Yes	4 (7.692%)	16 (30.769%)	4 (50.000%)	

Table 7 Analysis of Myocardial Injury Markers in Patients with Different Primary Endpoint Events of MACE

	Stroke N=52	Myocardial Infarction N=52	Death N=8	r	p
AST	20.000[18.400,28.000]	29.000[17.000,30.000]	19.000[15.630,19.000]	8.527	0.014
LDH	189.000[151.000,215.000]	187.000[152.000,214.000]	159.000[134.000,159.000]	6.914	0.032
CK	78.306[62.000,97.000]	72.333[47.000,90.000]	76.152[21.900,76.152]	4.732	0.094
MYO	38.780[28.650,62.226]	25.901[21.000,37.333]	30.681[1.680,30.681]	14.515	<0.001
CKMB	2.630[1.260,3.930]	2.000[1.710,4.000]	2.700[1.950,2.700]	0.267	0.875
cTnT	0.018[0.013,0.020]	0.009[0.006,0.193]	0.117[0.006,0.117]	0.502	0.778
BNP	41.000[25.000,73.000]	59.320[27.000,135.000]	1384.000[53.000,1384.000]	11.103	0.004
NTproBNP	469.252[177.749,1036.419]	503.400[176.265,1377.000]	538.326[386.998,538.326]	0.320	0.852

Construction of Prediction Models for Different Primary Endpoint Events of MACE and Comparison of the Combined Predictive Capabilities of Different Indicators

Stroke Patients and Non-Stroke Patients

In this study, a total of 1,116 patients with MACE were mainly included, among whom 52 were stroke patients and 1,064 were non-stroke patients.When using LASSO for feature dimension reduction, the variable selection of the corresponding model is:Gensini+LVEF+LDH+MYO+CKMB+cTnT+BNP+NTproBNP+TC_ROOT_R+TC_ROOT_B+TC_ROOT_V +TC_MID_R+TC_MID_G+TC_MID_B+TC_MID_H+TC_MID_V+TC_TIP_R+TC_TIP_G+TC_TIP_B+TC_TIP_H +TC_TIP_S+TC_LEFT_R+TC_LEFT_B+TC_LEFT_H+TC_LEFT_V+TC_RIGHT_R+TC_RIGHT_B+TC_RIGHT_H +TC_RIGHT_V+TC_R+TC_G+TC_B+TC_H+TC_S+CC_ROOT_G+CC_ROOT_B+CC_ROOT_H+CC_ROOT_S +CC_MID_R+CC_MID_B+CC_MID_S+CC_MID_V+CC_TIP_B+CC_TIP_H+CC_TIP_S+CC_LEFT_R +CC_LEFT_G+CC_LEFT_B+CC_LEFT_S+CC_LEFT_V+CC_RIGHT_R+CC_RIGHT_B+CC_RIGHT_H +CC_RIGHT_S+CC_RIGHT_V+CC_R+CC_G+CC_B+CC_H+CC_S+CRACK_VAL+SPOTSTHORN_VAL +CURDYGREASY_VAL+MOISTDRY_VAL+THICKTHIN_VAL+PEELEDCOATING_VAL.

The XGBoost, logistic, KNN, LightGBM and AdaBoost models were used to predict the occurrence of stroke events. Five-fold cross-validation was employed to train and validate the myocardial injury markers and tongue color parameters of the two groups of patients. The inclusion factor is the feature screening factor after LASSO dimension reduction. Figure 11 shows the ROC curves of different models for verifying the occurrence of stroke.The results show that the three models of XGBoost, AdaBoost, and LightGBM in the training set and validation set have overfitting (AUC=1),

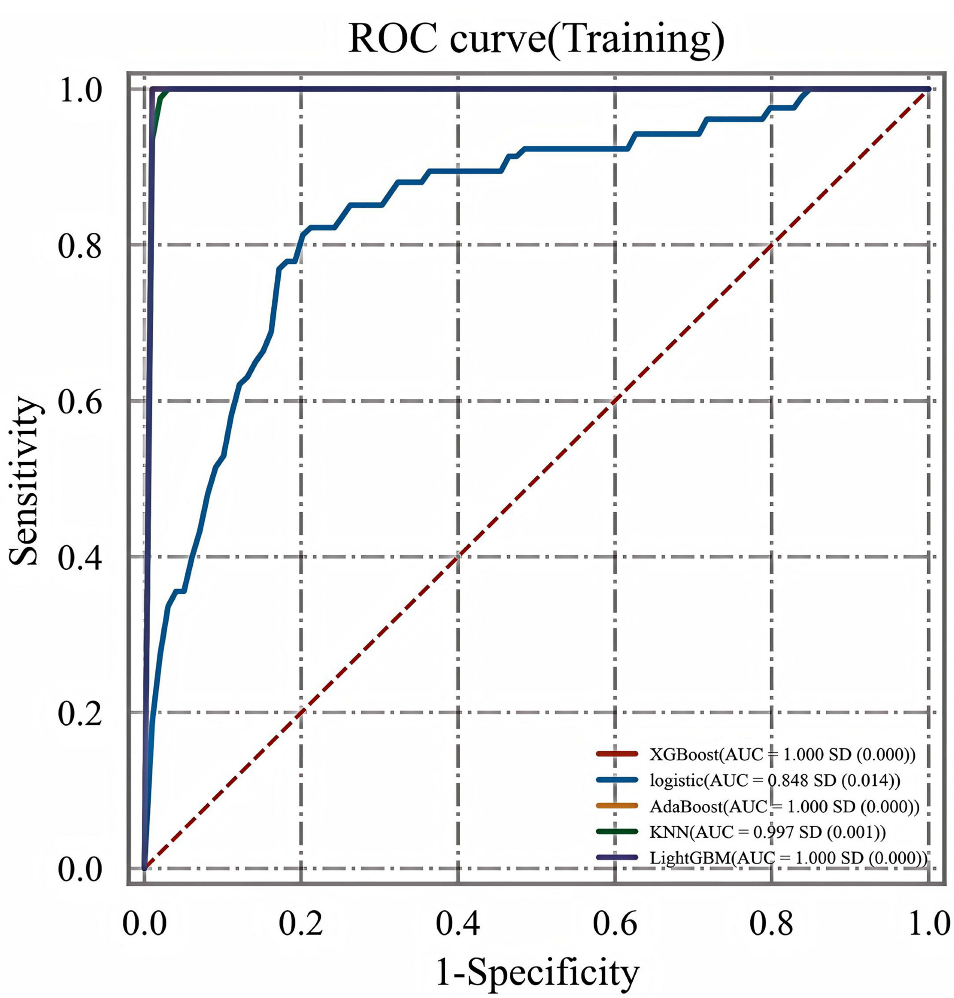

Figure 11 The ROC curves of stroke occurrence were verified by different models.

which may be caused by the excessive difference in sample size. It is recommended to expand the sample size in the future. Tables 3S and 4S show the specific results of the training set and feature set respectively.

Patients with Myocardial Infarction and Patients Without Myocardial Infarction

In this study, a total of 1,116 patients with MACE were mainly included, among whom 52 were patients with myocardial infarction and 1,064 were non- myocardial infarction patients.

When using LASSO for feature dimension reduction, the variable selection of the corresponding model is:Gensini +LVEF+AST+LDH+MYO+CKMB+cTnT+BNP+NTproBNP+TC_ROOT_R+TC_ROOT_H+TC_ROOT_S +TC_ROOT_V+TC_MID_R+TC_MID_H+TC_MID_S+TC_TIP_R+TC_TIP_G+TC_TIP_H+TC_TIP_V+TC_LEFT_R +TC_LEFT_G+TC_LEFT_H+TC_LEFT_S+TC_LEFT_V+TC_RIGHT_R+TC_RIGHT_G+TC_RIGHT_H +TC_RIGHT_S+TC_R+TC_G+TC_B+TC_H+TC_V+CC_ROOT_R+CC_ROOT_G+CC_ROOT_B+CC_ROOT_H +CC_ROOT_V+CC_MID_R+CC_MID_G+CC_MID_S+CC_TIP_H+CC_TIP_S+CC_LEFT_R+CC_LEFT_G +CC_LEFT_V+CC_RIGHT_R+CC_RIGHT_H+CC_RIGHT_S+CC_RIGHT_V+CC_R+CC_V+CRACK_VAL +SPOTSTHORN_VAL+ENLARGEDTHIN_VAL+MOISTDRY_VAL+PEELEDCOATING_VAL.

The XGBoost, logistic, KNN, LightGBM and AdaBoost models were used to predict the occurrence of myocardial infarction. Five-fold cross-validation was employed to train and validate the myocardial injury markers and tongue color parameters of the two groups of patients. The inclusion factor is the feature screening factor after LASSO dimension reduction. Figure 12 shows the ROC curves of different models for verifying the occurrence of myocardial infarction.

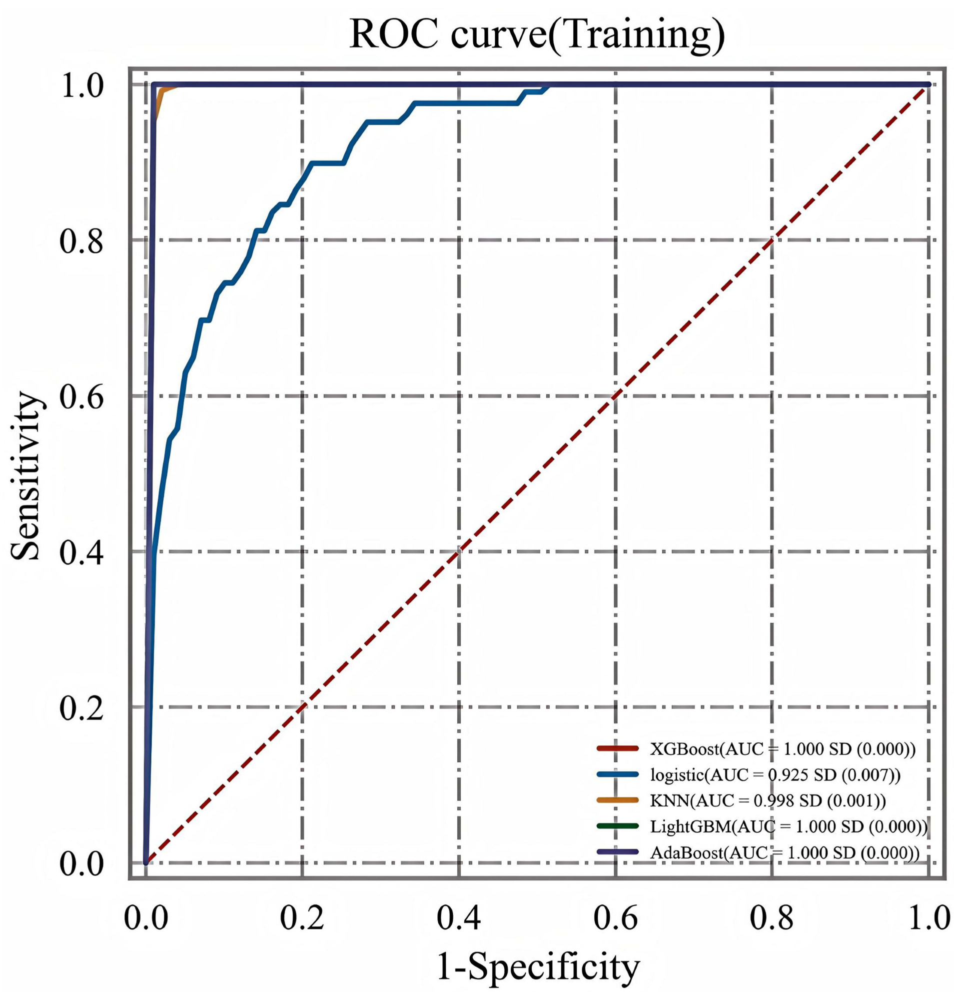

Figure 12 The ROC curves of different models for verifying the occurrence of myocardial infarction.

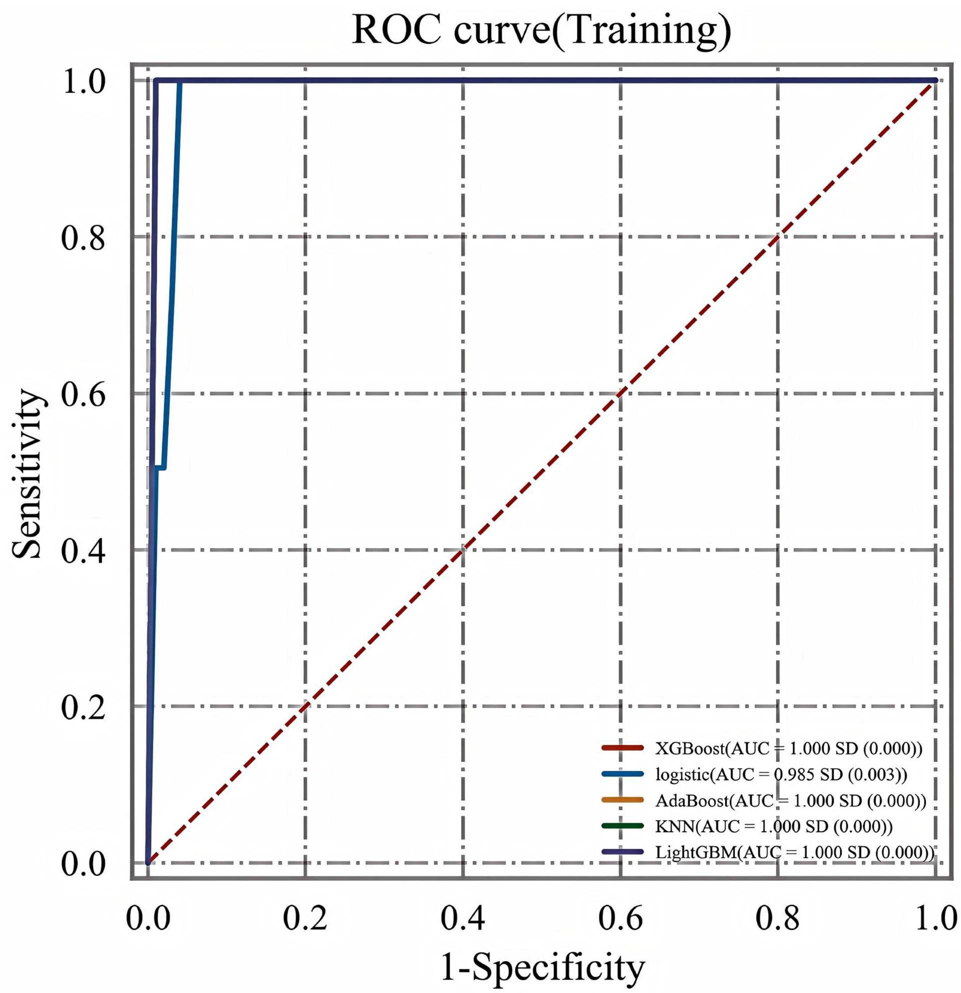

Figure 13 The ROC curves of death were verified by different models.

The results show that the three models of XGBoost, AdaBoost, and LightGBM in the training set and validation set have overfitting (AUC=1), which may be caused by the excessive difference in sample size. It is recommended to expand the sample size in the future. Tables 5S and 6S show the specific results of the training set and feature set.

Deceased Patients and Non-Deceased Patients

In this study, a total of 1,116 patients with MACE were mainly included, among whom 8 died and 1,108 were non-deceased.

When using LASSO for feature dimension reduction, the variable selection of the corresponding model is:Gensini +AST+BNP+TC_ROOT_B+TC_ROOT_H+TC_MID_S+TC_TIP_H+TC_TIP_S+TC_LEFT_H+TC_RIGHT_R +TC_RIGHT_V+CC_MID_R+CC_MID_V+CC_TIP_S+CC_LEFT_S+CC_RIGHT_S+CRACK_VAL +SPOTSTHORN_VAL+ENLARGEDTHIN_VAL+CURDYGREASY_VAL+PEELEDCOATING_VAL.

The XGBoost, logistic, KNN, LightGBM and AdaBoost models were used to predict the occurrence of myocardial infarction. Five-fold cross-validation was employed to train and validate the myocardial injury markers and tongue color parameters of the two groups of patients. The inclusion factor is the feature screening factor after LASSO dimension reduction. Figure 13 shows the ROC curves of different models for verifying the occurrence of death. Tables 7S and 8S show the specific results of the training set and the feature set.

Discussion

Relationship Between Tongue and MACE

The diagnostic and therapeutic method of inferring the heart's vitality by observing the tongue image is called "Si-wai-chuai-nei". The tongue image can objectively and accurately reflect the deficiency of the internal organs, the vitality of the qi and blood, the surplus and deficit of the fluid, the nature of the disease and the evil, the severity of the disease, its regression and the prognosis, etc., and it is a very important basis for the clinical diagnosis and treatment. "As the heart opens its orifices through the tongue", tongue image plays an important role in the diagnosis of CHD, and modern medicine also believes that nutritional status, microcirculation status, and hormone levels can affect the formation of tongue image.

In this study, the following tongue factors were found to be related to MACE:TC_ROOT_R, TC_MID_S, TC_TIP_B, CC_MID_B, CC_TIP_G, PEELEDCOATING_VAL.These tongue factors are broadly focused on the tongue colour at the root of the tongue, the tip of the tongue coat colour and peeling coat. According to the division of the tongue and the relationship between the organs, the root of the tongue corresponds to the kidneys, the tip of the tongue corresponds to the heart, lungs, CHD in the heart, but with the lungs, liver, spleen, kidneys, and other organs are related to the heart, the heart is the master of the blood, the lungs are the master of the joints, the two are coordinated with each other, the operation of qi and blood from the smooth. Heart disease yang qi insufficiency, can not promote the blood flow on the tongue, lung qi governance section failure, then blood stasis, tongue loss of moistening, so the tip of the tongue to see the light greenish purple; kidney is the foundation of the innate, kidney yang for the root of the body's yang qi, kidney yang insufficiency will lead to the heart yang is not vibrant, the heart veins lose warmth, which triggered thoracic paralysis cardiac pain, renal yin insufficiency is the deficiency of the heart yin, the heart fire is exuberant, burns the Jin for phlegm, phlegm stasis paralysis of the heart veins, resulting in thoracic paralysis cardiac pain. The findings are consistent with the pathogenesis of chest paralysis in TCM.[29] The Shanghanlunbenzhi - identify the tongue coat'said: 'tongue coat by the stomach in the anger of the appearance of the stomach qi from the heart and spleen, so no disease often have thin coat, is the stomach in the anger of the grass, such as the ground of the micro-herb also'. If the evil invasion of the body or the body of positive Qi weakness leads to the imbalance of yin and yang, qi and blood, fluid, tongue coating also occurs a variety of changes.

Previous studies have suggested that a sudden retreat of the tongue coating or the appearance of floral peeling of the coating suggests that the gastric qi is about to be extinguished and the disease is in danger, and the analysis of the present study also concludes that the peeling of the coating is correlated with MACE. All of the above risk factors reflect that "tongue is a candidate outside the heart", and thus tongue image can provide an important basis for predicting the judgement of MACE in CHD.

Currently, domestic studies on tongue and MACE still focus on small-sample, single-centre, correlation studies, and there are relatively few large-sample, multi-centre, prospective studies. The results of previous studies have shown[30–35] that old tongue, young tongue, tooth-marked tongue, green or blue-purple tongue, pale white tongue, peeling moss (excluding type of peeling moss), and purplish or reddish-purple sublingual veins are all relevant tongue factors for MACE in CHD; the scientific research team led by academician Chen KX has found that the indicators of purplish-purple sublingual veins, old tongue, and greenish-purple or greenish-purple tongue colour are closely correlated to MACE; a study has adopted the methodology of retrospective cohort study to establish and validate that stable CHD occurs in a single-centre, multi-centre, and prospective study. A study used a retrospective cohort study to establish and validate a combined Chinese and Western medicine prediction model for the occurrence of MACE in stable CHD, in which the dark red tongue and blood stasis were risk factors for the occurrence of cardiovascular events, with a validation set AUC value of 0.714; a study explored the correlation between the greenish purple tongue and the degree of risk of patients with acute myocardial infarction by observing the tongue of patients with acute myocardial infarction, and the results found that patients in the greenish purple tongue group had a higher degree of risk, more serious myocardial cell injury. The results found that the patients in the group with blue and purple tongue had a higher degree of danger, worse cardiomyocyte damage, worse cardiac function, and more serious inflammatory reaction, indicating that the appearance of blue and purple tongue in patients with acute myocardial infarction had a certain correlation with auxiliary examination indexes of the degree of danger of the disease, suggesting that tongue diagnosis of TCM, with blue and purple tongue has an important clinical value in the judgement of the degree of danger; it has been found that the level of BNP of patients with purple tongue is significantly higher than those with non-purple and purple tongue (P<0.05); the level of heart rate shock (HRT) is was significantly attenuated (P<0.05), suggesting that purple-darkened tongue may have some predictive value for the cardiovascular prognosis of patients with myocardial infarction; mirrored tongue is an independent risk factor for the occurrence of MACE in patients with acute heart failure (AHF) during the first year, and influences the occurrence of MACE in conjunction with age, length of hospitalisation, ejection fraction and NT-proBNP.

Relationship Between NT-proBNP and MACE

NT-proBNP is the most commonly used natriuretic peptide and plays a diagnostic role in the assessment of HF. It may be increased due to cardiac systolic or diastolic dysfunction, left ventricular hypertrophy, valvular heart disease, ischaemia or a combination of these factors. In addition to its use in the diagnosis of HF, NT-proBNP levels are very useful for risk stratification and management of patients with suspected HF: a trend towards decreasing levels of natriuretic peptide in the management of HF suggests an effective management strategy. In addition, several studies have demonstrated that NT-proBNP is also strongly associated with MACE in a variety of primary prevention and general populations;[36] in prospective cohort studies, it was found that patients undergoing multiple stenting were at increased risk of MACE with significantly elevated levels of NT-proBNP post-PCI, whilst other studies have reported a significant increase in the risk of MACE in patients who underwent multiple stents and had an increase in NT- proBNP levels increased more than threefold;[37] a review has shown that the predictive performance of the Revised Cardiac Risk Index (RCRI) in predicting MACE is improved with the addition of NT-proBNP, troponin, or their combination, and other studies have shown that NT-proBNP alone is more effective in predicting MACE. NT-proBNP may even have a higher discriminatory performance than RCRI when used alone;[38]

In a related study, NT-proBNP and hsTnT levels were found to be associated with the risk of future MACE in patients with primary and secondary prevention of T2DM, and these two cardiac biomarkers can help to identify patients at very high risk of atherosclerotic events;[39] and in a related cohort study, NYHA class III–IV, NT-proBNP, and β-blocker medication were found, five variables, including the presence of LGE and overall longitudinal strain (GLS) of the left ventricle, were significantly associated with MACE and were used to construct column line plots, which obtained good C-index differentiation in the development and validation cohorts, respectively;[40] and a study found that traditional cardiovascular risk factors (NT-proBNP) were associated with a higher risk of MACE.[41]

The Relationship Between LDH and MACE

LDH is widely present in various tissues of the human body (such as the heart, liver, skeletal muscle, red blood cells, kidneys, lungs, brain, etc). When these tissues are damaged due to ischemia (such as myocardial infarction), hypoxia, inflammation, necrosis, malignant tumors or mechanical injury (such as hemolysis), LDH within the cells will be released into the blood, leading to an increase in serum LDH levels. Elevated LDH levels may be associated with dyslipidemia, elevated low-density lipoprotein cholesterol (LDL-C), and the formation of atherosclerotic plaques, further promoting the occurrence of MACE.[42] The core events of MACE (such as myocardial infarction and heart failure) themselves can cause damage to myocardial cells and lead to an increase in LDH. Therefore, after acute myocardial infarction (AMI), LDH and its isoenzyme (LDH-1) were once regarded as important diagnostic and monitoring indicators (although troponin now has higher specificity and sensitivity). The fundamental causes of MACE often involve ischemia and hypoxia of the myocardium or brain tissue caused by atherosclerosis and thrombosis. Under hypoxic conditions, cell metabolism shifts from aerobic respiration to anaerobic glycolysis, generating a large amount of lactic acid. At the same time, the activity of LDH (which catalyzes the interconversion of pyruvate and lactic acid) increases. The continuous hypoxia eventually leads to cell damage and the release of LDH. The LDH level can be used as the basis for patient stratification. For example, in acute aortic dissection, 204 U/L is the optimal cutoff value of LDH, which is used to distinguish high-risk patients.[43] LDH combined with other biomarkers (such as AST, CK-MB, cTnI, α-HBDH) can significantly improve the accuracy of MACE prediction.[44]

The Relationship Between AST and MACE

AST is abundant in cardiomyocytes. When cardiomyocytes are damaged due to ischemia (such as coronary artery occlusion), hypoxia, inflammation or necrosis, the cell membrane ruptures, and the AST inside the cells is released into the blood, resulting in an increase in serum AST levels. In diagnosed AMI patients, the peak level of AST or the area under the curve is often used to roughly estimate the extent of myocardial infarction. The larger the infarction area, the more extensive the myocardial necrosis, the more AST is released, the higher the peak value, and the poorer the prognosis is usually (the risk of MACE such as heart failure, cardiogenic shock, and death is higher). Among AMI patients, the degree of elevated AST is independently associated with short-term and long-term poor prognosis (death, heart failure, reinfarction). A high peak or continuous increase often indicates a large infarction area and severe impairment of cardiac function. Studies have found that an elevated AST/ALT ratio is significantly associated with the risk of MACCE (Major adverse cardiovascular and cerebrovascular events) in patients with unstable angina pectoris, with an optimal threshold of 1.29. This suggests that the AST/ALT ratio can be used as an indicator to assess cardiovascular risk. However, AST itself is not a direct indicator for independently predicting MACE. The judgment needs to be made in combination with the clinical background (such as coronary artery lesions, metabolic syndrome) and comprehensive assessment tools (such as CT-FFR, F4I).[45] It was also found in this study that the AST of patients with myocardial infarction was significantly higher than that of patients with stroke and death (P<0.01).

The Relationship Between Gensini and MACE

The Gensini Score is an angiographic scoring system used to quantify the severity of coronary atherosclerotic lesions. It has a clear and close positive correlation with the risk of MACE (Major Adverse Cardiovascular Events). In short, the higher the Gensini score, the more severe the coronary artery lesion, and the higher the risk of developing MACE in the future. A high score indicates a more extensive and severe coronary artery stenosis, leading to a larger range and more severe degree of myocardial insufficiency (ischemia), which is the direct pathological basis for events such as myocardial infarction, angina pectoris, and ischemic heart failure. Although Gensini mainly assesses the degree of stenosis, extensive severe lesions are often accompanied by the presence of more vulnerable (unstable) plaques, and the rupture of these plaques is the main cause of acute coronary syndrome (ACS, such as STEMI/NSTEMI). Diffuse severe stenosis causes the myocardium to remain on the edge of ischemia for a long time, resulting in poor cardiac functional reserve and making it more prone to decompensation (heart failure) under stress (such as infection, surgery, arrhythmia). Patients with high scores often require more complex interventional therapy (PCI), and their risk of postoperative restenosis or stent thrombosis is relatively high. Even without intervention, severely stenotic areas are more prone to thrombosis and occlusion. Previous studies have mentioned that the Gensini score is an independent risk factor for predicting MACE in ACS patients after PCI. This indicates that the Gensini score has a certain role in predicting MACE. Although the sensitivity and specificity of the Gensini score in predicting MACE when used alone are limited, as a standardized assessment tool for the degree of coronary artery lesions, It can still serve as an important reference for comprehensive risk stratification, especially having significant advantages when combined with other biomarkers or clinical indicators.[46] In this study, the SHAP value graph also revealed that a high value of Gensini could positively predict MACE.

Application of ML in Predicting MACE

ML has a wide range of applications in predicting MACE; one study used cardiac magnetic resonance (CMR) parameters and clinical features for ML-empowered risk stratification, which was able to surpass the classical Risk-SCD model of sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM) and accurately predict MACE; in addition, the non-linear correlation between the CMR features (LGE and left ventricular pressure gradient) and MACE found in this study provides valuable insights into the clinical assessment and management of HCM;[47] a study evaluated the ability of different ML and traditional statistical methods in predicting MACE and found that ML methods improved the identification and prediction of patients at risk of MACE compared to traditional statistical methods even with a small sample size;[48] a study found that ML-based noninvasive fractional flow reserve (FFRCT) has prognostic value in predicting MACE after PCI in low and intermediate-risk patients;[49] and it was found that ML can accurately predict the risk of MACE in patients with suspected CHD who underwent SPECT MPI and CCTA, and that the ML feature ordering also shows which features are key to making such predictions, both at the sample and patient level.[50]

Potential Causes of Insufficient Model Performance

Data limitations: myocardial injury markers (such as troponin and CK-MB) have high specificity in predicting coronary heart disease events, but insufficient sample size or poor data quality (such as improper marker detection time window) may lead to model failure; (2) Feature fusion problem: The physiological correlation between tongue image parameters and myocardial markers should be clear (such as the pathological relationship between TCM tongue diagnosis and myocardial ischemia). If the feature selection does not reflect the synergistic effect, it may weaken the effect of the model; (3) Method suitability: Traditional models (such as Logistic regression) have limited ability to capture nonlinear relationships, while complex models (such as random forests) are easy to overfit in small samples.

Strengths and Limitations

Although this study adopted strict quality control measures throughout the process of data collection, processing and analysis to ensure the accuracy and reliability of the results, and systematically investigated the relationship between markers of myocardial injury, tongue parameters and MACE, there are still some limitations: firstly, the sample size is relatively small, which may not fully reflect the real situation, and future studies will expand the sample size and external validation to better verify the persuasiveness of this prediction model; secondly, the number of groups with and without MACE varied greatly. Although the SMOTE processing method was adopted, it still had a certain bias effect on the results; in addition, as a retrospective study, it may bring information bias and selection bias, and prospective design in future studies can mitigate the impact of these biases; finally, the current study lacked in-depth exploration of the pathogenesis of MACE and further studies are needed in the future to investigate the molecular association between tongue microvascular morphology and coronary microcirculatory disorders (eg, ET-1, VEGE expression), and combined with the dynamic changes of myocardial markers (such as the early increase of myoglobin and the long window period of troponin), the insufficiency of time series feature extraction was discussed.

Summary

In this study, through a retrospective cohort analysis, the characteristic changes of myocardial injury markers and tongue image parameters in patients with or without MACE were explored. LASSO was used for feature dimension reduction to verify the effectiveness of myocardial injury markers and tongue image parameters in predicting MACE. Finally, subgroup analyses were conducted for different MACE events. These findings not only provide a modern scientific basis for TCM tongue diagnosis, but also provide new ideas and methods for early diagnosis and condition assessment of MACE. Future studies can further expand the scope of combined Chinese and Western medicine research, optimise the prediction model and explore its application value in other cardiovascular diseases.

Data Sharing Statement

The authors will provide the raw data supporting the conclusions of this paper without reservation.

Ethical Review Statement

This research has been reviewed and approved by the Ethics Committee of Shanghai University of Traditional Chinese Medicine, with the approval number: 2023-3-10-08-07. At the same time, it is confirmed that informed consent has been obtained from the research participants and that the guidelines outlined in the Declaration of Helsinki have been adhered to and confirmed.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that this study was conducted without any business or financial relationship that could be considered a potential conflict of interest.

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