**RESEARCH**

# Predicting angiographic coronary artery disease using machine learning and high-frequency QRS

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## Abstract

**Aim** Exercise stress ECG is a common diagnostic test for stable coronary artery disease, but its sensitivity and specificity need to be further improved. In this paper, we construct a machine learning model for the prediction of angiographic coronary artery disease by HFQRS analysis of cycling exercise ECG.

**Methods and results** This study prospectively included 140 inpatients and 59 healthy volunteers undergoing cycling exercise ECG. The CHD group ($N=104$) and non-CHD group ($N=95$) were determined by coronary angiography gold standard. Automated HF QRS analysis was performed by the blinded method. The coronary group was predominantly male, with a higher prevalence of age, BMI, hypertension, and diabetes than the non-coronary group ($P < 0.001$), higher lipid levels in the coronary group ($P < 0.005$), significantly longer QRS duration during exercise testing ($P < 0.005$), more positive leads ($P < 0.001$), and a greater proportion of significant changes in HFQRS ($P < 0.001$). Age, Gender, Hypertension, Diabetes, and HF QRS Conclusions were screened by correlation analysis and multifactorial retrospective analysis to construct the machine learning models of the XGBoost Classifier, Logistic Regression, LightGBM Classifier, RandomForest Classifier, Artificial Neural Network and Support Vector Machine, respectively.

**Conclusion** Male, elderly, with hypertension, diabetes mellitus, and positive exercise stress test HFQRS conclusions suggested a high risk of CHD. The best performance of the Logistic Regression model was compared, and a column line graph for assessing the risk of CHD was further developed and validated.

**Keywords** Machine learning, Coronary artery disease, High-frequency QRS

## Introduction

With economic development, the improvement of people's living standards, and the aging of society, the prevalence and mortality rate of coronary heart disease are on the rise, and currently cardiovascular disease is the number one cause of death among residents, seriously threatening their health [1]. The atherosclerotic process can be delayed or even reversed by improving lifestyle in the early stages of coronary artery disease (CHD). When acute myocardial infarction occurs, the occurrence of serious complications can be significantly reduced by early detection and diagnosis and early treatment to shorten the ischemia-re-perfusion time. The current auxiliary examinations for the diagnosis of CHD consist of electrocardiograms (ECG), coronary CT angiography (CTA), non-invasive examinations such as myocardial

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perfusion single photon emission computed tomography (MPI), and coronary angiography (CAG) [2].

ECG is a commonly used noninvasive diagnostic tool for cardiovascular diseases3, which is inexpensive, easy to perform, and free of radiographic burden, but the sensitivity and specificity of conventional 12-lead ECG are low [3]. The use of exercise electrocardiograms (Ex ECG), the continuous enrichment of new diagnostic variables, and the increase in the number of leads have improved the diagnostic efficacy of ECG for myocardial ischemia. Findings from the randomized controlled trials found that adding either exercise ECG or resting ECG to traditional cardiovascular disease risk factors (such as age, gender, current smoking, diabetes, total cholesterol levels, and HDL cholesterol levels) increased screening rates for asymptomatic cardiovascular disease in adults [4]. For Ex ECG, positive result is associated with an increased risk of adverse cardiac events, even if the stress echocardiogram is negative [5]. ECG-based machine learning models can potentially identify people with a high risk of undiagnosed and clinically significant structural heart disease while outperforming single disease models and improving practical utility through higher positive predictive values. This approach could facilitate targeted screening with echocardiography to improve the underdiagnosis of structural heart disease [6]. Heart rate variability (HRV), the change in the interval between consecutive heartbeats, is largely dependent on the external regulation of heart rate. HRV analysis is the ability to assess the overall health of the heart and the status of the autonomic nervous system (ANS), which is responsible for regulating cardiac activity. One study found that HRV analysis can monitor the risk of sudden cardiac death in post-infarction and diabetic patients [7], and the further improved HRnV analysis has good clinical application in predicting the risk of 30-day adverse major adverse cardiovascular events (MACEs) in patients with emergency chest pain [8].

There has been a great deal of enthusiasm for the study of ECG re-polarization parameters, and much deeper digging has been done on the basis of the ST criteria. One Ex ECG study performed on firefighters found that an ST/HR index ≤ 1.6 lV/bpm and an ST/HR slope ≤ 2.4 lV/bpm were related to an increased risk of ischemic heart disease (IHD) in three individual leads. Besides, the ST/HR loop area below the 5th percentile in non-IHD recipients suggests a risk of IHD in leads V4, V5, aVF, II, and aVR. In contrast, ST depression ≤ 0.1 mV was only associated with a risk of IHD in lead V4. Use of more complex variables in ST/HR analysis improves diagnosis and prognosis in some asymptomatic populations [9]. The diagnostic accuracy of ST segment/heart rate hysteresis in patients with CHD combined with hypertensive left ventricular hypertrophy is much better than that of ST segment depression criteria and heart rate recovery index [10]. The V index has been used as an ECG marker to quantify the spatial heterogeneity of ventricular repolarization. In addition to conventional ECG criteria, the use of V index increased the diagnostic accuracy of non-ST-segment elevation myocardial infarction (non-STEMI) diagnosis from 66% to 73% and the sensitivity of the ECG for acute myocardial infarction (AMI) from 41% to 86%, while the V index was also an independent predictor of MACEs during the 24-months follow-up of non-STEMI patients [11]. Sixty-seven leads high-resolution body surface potential mapping (HR-BSPM) has high spatial, temporal and amplitude resolution by recording and analyzing the complete distribution of action potentials on the thoracic surface, allowing the detection of ischemic changes in the ECG signal that are not observed at standard electrode positions. The sensitivity/specificity of the amplitude parameter $\delta$ST60 and the $\delta$T parameter, which show changes in wave form during exercise, in predicting ischemic cardiomyopathy were 70/69 and 59/62%, respectively. In contrast, the sensitivity/specificity of the standard 12-lead ECG system were 63/62 and 59/56%, respectively. It was also found that depolarization phase parameters describing only QRS morphological changes had diagnostic value and were much less accurate than the numerous repolarization amplitude-time parameters [12]. In the 1990s, people began to quantify exercise-induced changes in the depolarized phase QRS complex of the ECG, and Campen et al. [13] proposed the concept of the Athens QRS score, where the Q, R, and S wave amplitudes after exercise minus the pre-exercise level are noted as $\delta$Q, $\delta$R, and $\delta$S. The formula for the Athens QRS fraction (mm) is: $(\delta R - \delta Q - \delta S)AVF + (\delta R - \delta Q - \delta S)V5$. The Athens QRS score decreases as the number of obstructed coronary arteries increases, with negative (less than 0) scores consistently associated with CHD. The sensitivity and specificity of the Athens QRS score of 5 mm (the threshold value) for predicting CHD were (75%-86%, 73%-79%) higher than those of the Q wave (75%, 50%), R wave (65%, 55%), S wave (70%, 10%), and ST segment depression (62%, 70%). The high-frequency band of 150-250 Hz in the ventricular depolarizing QRS complex, known as the high-frequency QRS (HFQRS), is able to quantify the subtle changes in the propagation of depolarizing wave fronts as they pass through regions of the ischemic myocardium. Ringborn et al. [14] showed that the decrease in HFQRS amplitude assessed by root mean square RMS during coronary balloon dilation was more responsive to acute myocardial ischemia than ventricular repolarization ST elevation. Schaerli et al. [15] found that the sensitivity of myocardial ischemia assessed by MPI and CAG was increased from 43% to 63% and the

specificity was increased from 87% to 97% in the cycling exercise stress test using a combination of ST-segment deviation and HFQRS than in the analysis of myocardial ischemia by ST deviation alone. HFQRS was also an independent predictor of the occurrence of major adverse cardiac events (MACEs) during the 2-year follow-up. Balfour et al. compared the difference in diagnostic and prognostic accuracy and net reclassification between HFQRS analysis and standard ST-segment depression in identifying any and severe ($\geq$10% left ventricular) myocardial ischemia and found that HFQRS detected 84.6% of patients with MPI $\geq$ 10% left ventricular ischemia, whereas ST-segment depression was only detected in 61.5%. The combined strategy of ST depression and HFQRS analysis identified almost all patients with severe ischemia (92.3%) and greatly improved the sensitivity of exercise stress tests for myocardial ischemia [16].

Over the past two decades, researchers have developed numerous prediction models that mathematically combine multiple predictors to estimate the risk of developing cardiovascular disease (CVD). Health policymakers increasingly advocate for some prediction models and include them in clinical guidelines for therapeutic management. In the United Kingdom, electronic health records have been enhanced to incorporate the QRISK2 algorithm, which is used to calculate the risk of developing cardiovascular disease over a 10-year period [17–19]. Artificial intelligence (AI) has transformed key aspects of human life. Machine learning (ML), which is a subset of AI wherein machines autonomously acquire information by extracting patterns from large databases [20], has been increasingly used within the medical community [21, 22], specifically within the domain of cardiovascular diseases [23, 24]. It remains unclear whether AI can provide meaningful, generalizable improvements in predictive accuracy beyond the clinical risk factors for particular diseases. Whether contemporary machine learning methods can facilitate risk prediction by including a larger number of variables and identifying complex relationships between predictors and outcomes [25–27]. Cikes et al. [28] performed phenotypic grouping of heart failure (HF) cohorts using complex machine learning algorithms for echocardiographic data and clinical parameters, where two phenotypes included a higher proportion of known clinical features predicting CRT response and were associated with significantly better treatment outcomes with CRT-D. Furthermore, unsupervised machine learning may help optimize response rates to specific treatments.

The application of artificial intelligence had the potential to enhance the diagnostic capabilities of ECGs in the identification of arrhythmias. Recently, Karwath et al. [29] applied machine learning-based clustering analysis to pooled data from nine double-blind randomized controlled trials of beta-blockers to identify efficacy subgroups of patients with sinus rhythm and atrial fibrillation. In a study constructing a random forest model and comparing the predictive ability of machine learning models with standard cardiovascular risk scores for cardiovascular outcomes during 12-year follow-up in a multi-ethnic asymptomatic population, it was found that the random forest model outperformed established risk scores with higher predictive accuracy, potentially leading to greater insight into subclinical disease markers without the need for a priori causality assumptions [30, 31]. There was a study that enrolled 180,922 patients and 649,931 normal sinus rhythm ECGs to develop an artificial intelligence (AI)-enabled electrocardiograph (ECG) that could identify patients with atrial fibrillation during sinus rhythm [32]. D'Ascenzo's machine learning risk stratification model for predicting all-cause death, recurrent acute myocardial infarction, and major bleeding after acute coronary syndrome (ACS) by combining datasets showed accurate discriminatory ability, which was feasible and valid for identifying predictors of events after ACS and may help guide clinical decisions [33]. Explainable techniques can be trained using off-the-shelf 12-lead ECG data and applied to convolutional neural networks, which can perform on par with clinical cardiologists [34].

Lately, there have been continuous improvements and advancements in the algorithms used for machine learning diagnostic models. Jiang et al. [35] devised a diagnostic model using machine learning techniques to identify patients with gout who are at risk of developing coronary heart disease. The algorithm relies on straightforward clinical criteria for screening purposes. This strategy was developed to mitigate the possibility of both underdiagnosis and excessive testing. The learning classifier utilizes a combinatorial sampling strategy to tackle the issue of imbalance in the training dataset. A total of eight machine learning models were employed, namely logistic regression, decision trees, integrated learning models such as Random Forest, XGBoost, LightGBM, GBDT, Support Vector Machines (SVMs), and neural networks. The conclusive findings indicate that stepwise logistic regression and SVM outperformed other models in terms of AUC values, whereas Random Forest and XGBoost models exhibited superior performance in terms of recall and accuracy.

Nabrdalik et al. [36] created a machine learning model to forecast cardiovascular (CV) incidents in individuals with diabetes. The incidence of new cardiovascular events after discharge was recorded over the follow-up period, which extended for a duration of 5 years and 9 months. A novel machine learning approach was suggested, utilizing neighbourhood

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component analysis to develop discriminative predictors. This was followed by a hybrid sampling/ boosting classification algorithm, multiple logistic regression (MLR), or unsupervised hierarchical clustering. Among a cohort of 1735 individuals diagnosed with diabetes, 53% of whom were female, a total of 150 patients (8.65% of the cohort) experienced a new cardiovascular event during the follow-up period. The twelve patient parameters with the highest discriminatory power are coronary artery disease, heart failure, peripheral artery disease, stroke, diabetic foot disease, chronic kidney disease, eosinophil count, serum potassium level, and treatment with clopidogrel, heparin, proton pump inhibitor, and loop diuretic. The use of these variables led to an area under the receiver operating characteristic curve (AUC) ranging from 0.62 (95% confidence interval [CI] 0.56-0.68, $P < 0.01$) to 0.72 (95% CI 0.66-0.77, $P < 0.01$) across five nonoverlapping test folds. The MLR accurately identified 74.00% of high-risk patients and 62.40% of low-risk patients, resulting in an overall correct classification rate of 63.40% for all patients. The MLR algorithm has an AUC of 0.72 (95% CI 0.66-0.77), indicating its ability to identify patients at high risk of developing new cardiovascular events. This algorithm uses a small number of easily interpretable and obtainable parameters to identify these patients with diabetes.

A well-validated disease risk prediction model is important to carry out practical clinical applications. There is a lack of machine learning models for HFQRS analysis in exercise tests to predict angiographic coronary artery disease. 140 inpatients admitted with chest pain for non-emergency coronary angiography between October 2021 and April 2022 in the First Affiliated Hospital of Bengbu Medical University and 59 healthy volunteers recruited were included in this study. Six machine learning models for predicting CHD by HFQRS analysis in age, gender, hypertension, diabetes, and exercise tests were constructed, using coronary angiography as the gold standard. We constructed and validated column line tables for the risk of CHD and further interpreted the model using the SHAP force plot, while DCA curves suggested increased clinical decision benefit from HFQRS analysis. This study aims to improve the sensitivity and specificity of ECG detection of myocardial ischemia by HFQRS, reduce medical costs, and reduce the implementation of radioactive, invasive operations. More importantly, it can detect myocardial ischemia early, shorten the ischemia-reperfusion time in patients with acute myocardial infarction, and save the dying myocardium.

## Materials and methods
### Data collection
This was a prospective single-center experimental study that included 156 inpatients with chest pain admitted to the First Affiliated Hospital of Bengbu Medical University for non-emergency coronary angiography from October 2021 to April 2022, and HF QRS exercise testing was performed 1.5±1 day before coronary angiography, of which 16 patients were excluded without coronary angiography. The CHD group ($N = 104$) was confirmed by the gold standard of coronary angiography, and 36 inpatients with diameter stenosis (DS) %<50% and 59 healthy volunteers recruited formed the non-CHD group ($N = 95$). We collected basic information about the study participants, such as height, weight, hypertension, diabetes, history of cerebrovascular disease, and HF QRS exercise test parameters, including max heart rate percentage (MHRpercentage), QRS duration, max power, post-peak recovery heart rate (PPRHR), number of ischemic leads, and HFQRS conclusions. We also collected the clinical laboratory results of inpatients, which were white blood cell count (WBC), neutrophil percentage (N), red blood cell count (RBC), hemoglobin content (Hb), platelet count (P), aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid (UA), creatinine (Cr), potassium ion, C-reactive protein (CRP), creatine kinase (CK), creatine kinase myocardial band (CKMB), recombinant cardiac troponin I (cTnI), N-terminal brain natriuretic peptide pro (NT proBNP), DD dimers (DD), and cardiac ultrasound parameters including end-diastolic volume (EDV), end-systolic volume (ESV), left ventricular ejection fraction (LVEF), cardiac output (CO), and systolic volume (SV).

Exclusion criteria for researchers: acute myocardial infarction within 48 hours, myocardial infarction combined with ventricular wall tumor, severe heart valve disease, cardiomyopathy, congenital heart disease, uncontrolled unstable angina pectoris, symptomatic heart failure, uncontrolled arrhythmia, hemodynamic disorders, acute myocarditis, pericarditis, infective endocarditis, iodine or iodine contrast allergy, pulmonary embolism, non-carcinogenic disease that may be caused or aggravated by exercise, mental or physical impairment that prevents exercise testing, pregnancy or suspected pregnancy, concurrent or short-term presence of severe hepatic or renal insufficiency, tumors, hematologic disorders, immunologic disorders, acute infectious diseases, and individuals who refuse exercise testing.

### Coronary angiography
Coronary angiography (CAG) was performed by a qualified cardiologist using the Judkins method, and the

results were independently reviewed by two skilled cardiologists without knowledge of the patient's clinical information or HF exercise test results.The CHD is defined as a percentage of diameter stenosis (DS%)≥50% in the LAD, the circumflex, or the right coronary artery with a right-dominant, left-dominant, or co-dominant circulation. Left main disease, however, has also been defined as DS%≥50%.

### Cycling exercise ECG

All subjects underwent treadmill exercise stress ECG according to the Bruce or modified Bruce protocol, with resting heart rate, blood pressure, and 12-lead resting ECG recorded prior to exercise. A standardized, stepwise, and symptom-limited upright cycling exercise trial was performed. Beta-blockers and anti-anginal drugs were suspended for at least 48 hours and nitrates for at least 24 hours prior to the trial. Cycling exercise ECGs were reviewed by one of two experienced readers who were unaware of all other data, and some ambiguous studies were resolved by consensus. Immediate termination of the test if (a) other evidence of myocardial ischemia is present despite an increased exercise load; (b) a decrease in systolic blood pressure>10 mmHg from baseline despite an increased exercise load; (c) moderate to severe angina; (d) increased dyskinesia; (e) vertigo or near syncope; (f) poor perfusion, such as cyanosis or pallor (g) testing ECG or systolic blood pressure encounters technical difficulties; (h) the subject requests to stop the test; (i) persistent ventricular tachycardia; (j) or ST-segment elevation >1 mm in leads without diagnostic Q waves (except V1 or aVR). Exercise load was defined as the total metabolic equivalent achieved (METS).

### HF-QRS analysis

HFQRS analysis, performed using a designated software (HyperQ, BSP Ltd., Tel Aviv, Israel), has been previously described in detail [16]. In brief, a high-resolution 12-lead ECG was continuously recorded throughout the study. Beat averaging was applied to each of the leads until the level of noise was $\geq 1 \mu V$ to obtain a high signal-to-noise ratio. Noisy and ectopic beats were excluded, and a signal-averaged QRS was calculated.

HFQRS is a signal in the 150 to 250 Hz band obtained by digitally filtering the average QRS complex with a finite impulse response filter pair. The signal intensity of HFQRS is expressed as the root mean square (RMS). The RMS of the resultant HFQRS signal was derived in real-time, graphed over time in all 12 leads, and analyzed throughout the study. Ischemic HFQRS means a 50% relative reduction between the maximum and minimum values or $\geq 1 \mu V$ absolute reduction in individual leads

with adequate signal quality. Positive HFQRS is HFQRS ischemia in ≥ 3 leads; otherwise, it is negative HFQRS.

### Statistical analysis

Categorical variables are reported as percentage counts, and continuous variables are reported as the mean (SD). Categorical variables were compared using the Chi-square test for differences in baseline characteristics and HFQRS conclusions between the coronary and non-coronary groups, and t-tests were used for continuous variables if they passed the Chi-square; otherwise, MannWhitney-U tests were used. In univariate analysis, variables with a *p*-value < 0.05 were introduced as independent predictor variables in multivariate logistic regression. Age, Gender, Hypertension, Diabetes, and HF QRS Conclusions were screened to construct the machine learning (ML) models of XGBoost Classifier, Logistic Regression, LightGBM Classifier, RandomForest Classifier, Artificial Neural Network (ANN), and Support Vector Machine (SVM), respectively. 70% of the data is used to train the ML model, while the remaining 30% is used to test the ML model. We analyzed and compared the AUC (95% CI), accuracy, sensitivity, specificity, positive predictive value, and F1 score of the training and validation sets by 10-fold cross-validation and found that Logistics Regression performed the best. On this basis, we estimated the strength of the association between CHD risk and predictors by OR and 95% CI. Use the "Buckwald: Wald" method to select the significant variables and use them to construct a line chart. The total scores of the column line graphs were categorized by quartiles to verify the association of total scores with CHD risk. All statistical analyses were done using SPSS version 25.0, R version 3.6.3, and Python version 3.7.

## Results

### Clinical and HFQRS characteristics

The study enrolled 156 inpatients for non-emergency coronary angiography admitted to the First Affiliated Hospital of Bengbu Medical University from October 2021 to April 2022, of whom 16 were ruled out without coronary angiography. The CHD group (N = 104) was defined by coronary angiography criteria, and the non-CHD group (N = 95) consisted of 36 inpatients with DS <50% and 59 recruited healthy volunteers. The CHD group was predominantly male and older, with a higher BMI and a higher prevalence of hypertension and diabetes than the non-CHD group (*P*<0.001). Clinical laboratory examinations of the two populations, including white blood cell count, neutrophil percentage, platelet count, alanine aminotransferase, potassium ion, C-reactive protein, creatine kinase myocardial band, N-terminal brain natriuretic peptide pro, and DD dimers, showed

significant differences (*P*<0.005). And higher total cholesterol and LDL in the CHD group (*P*<0.005). Compared with non-CHD groups, patients with CHD had reduced end-systolic volume (ESV) and a lower ejection fraction (EF), while cardiac output (CO) increased instead, which may be related to the compensation of heart rate (*P*<0.005). Interestingly, the lower percentage of maximum heart rate (MHR) and lower post-peak recovery heart rate (PPRHR) in CHD groups suggested a possible relationship with the reduced heart rate reserve in CHD patients due to heart rate compensation, while the longer QRS duration in CHD patients showed prolonged ventricular depolarization time in CHD patients, which may be associated with myocardial ischemia, bundle branch conduction block, and electrolyte disturbances (*P*<0.005). In short, HF QRS sensitively detected more ischemic leads in patients with CHD, and HFQRS conclusions indicated significant differences between the two groups, which were highly consistent with coronary angiographic results (*P*<0.005) (Table 1).

### Univariate and multivariate regression analysis

We included factors that were significantly different between the CHD and non-CHD groups (*P*<0.005) in a univariate logistic regression analysis, after which (*P*<0.005) was further included in a multivariate regression analysis by stepwise backward method, as shown in Table 2. Gender, age, BMI, hypertension, diabetes, and conclusion (*P*<0.005) were independent predictors of coronary heart disease risk factors.

### Comparison of various machine learning models

We enrolled the mutually independent factors age, gender, diabetes, hypertension, and conclusions into the six machine learning models of XGBoost Classifier, Logistics Regression, LightGBM Classifier, RandomForest Classifier, Multilayer Perceptron Classifier/Artificial Neural Network (ANN), and Support Vector Machine (SVM) with non-CHD or CHD as binary results. 70% of the total data is used to train ML models, while the remaining 30% is used to test ML models. The model uses 10-fold cross-validation.

Based on the AUC ranking, among all the models, the RandomForest Classifier model is the best performer in the training set, and the Logistic Regression model is the best performer in the validation set (Fig. 1). The forest plot shows the ROC of each model into the prediction; the error line in the plot is the mean and SD of the ROC, which are cross-validated by 10 fold. Forest plots of AUC scores for each model demonstrate that the Logistic Regression model has the best performance (Fig. 2). The AUC, accuracy, sensitivity, specificity, positive predictive value, negative predictive value, F1 score, and Kappa of the training and validation sets of each model were analyzed comprehensively in Table 3, and the RandomForest classifier model is likely to have overfitting phenomena, while the Logistic Regression model is likely to have better stability (Fig. 3). The decision curve analysis (DCA) for the six model validation sets shows that the logistic regression model yields the maximal benefits (Fig. 4a).

We further investigated the DCA curve for the predictive value of HFQRS analysis for coronary heart disease. Logistic Regression model 1 included only the variables of sex, age, hypertension, and diabetes, while Logistic Regression model 2 added the HFQRS conclusion variables again on top of this, and the area under the curve (AUC) showed that model 2 was better than model 1 for prediction, indicating that HFQRS analysis is feasible for making useful clinical decisions (Fig. 4b).

### Development and validation of CHD predictive nomogram

The dichotomous logistic regression was constructed for Age, Gender, Hypertension, Diabetes, and Conclusions for the prediction of coronary heart disease risk. The AUC of the model was 0.88, and the model predicted well. Among the variables included in the model, the coefficient of the variable Age was 0.052 with a *p*-value of 0.002, which was significant. The coefficient of the variable Gender was 1.377 with a *p*-value of 0.001, which was significant. The coefficient of Hypertension was 1.879 with a *p*-value of 0, which was significant. The coefficient of the variable Diabetes was 2.099 with a *p*-value of 0.01, which was significant. The coefficient of the variable Conclusions was 1.763, *P*<0.01, which was significant. The results of the logistic regression analysis were used to construct a column line plot to more intuitively predict the risk of CHD (Fig. 5). By drawing a vertical line toward the vertex scale, the vertical line through the observed values of the variables can find the corresponding scores, and the sum of the scores of all observed variables is the predicted risk of developing coronary heart disease in that individual.

To further validate the columnar table, we divided the total score into four subgroups by quartiles. Figure 6 shows that the risk of CHD increased with increasing total score, with participants in quartile four (OR: 126.133, 95% CI: 28.376, 560.662) having a higher risk of CHD than those in the lower quartile (odds OR: 4.716, 95% CI: 1.572, 14.152) (*P*<0.01).

### SHAP

ML has emerged as a promising tool. However, one of the key factors in determining whether physicians will use ML model predictions for clinical decision-making is their ability to understand how ML models arrive at a given conclusion. Interpretability, or explainability,

**Table 1** Clinical and HFQRS characteristics

| Variables | Total (*n*=199) | Non-CHD (*n*=94) | CHD (*n*=105) | | *P*-value |
|---|---|---|---|---|---|
| Male, n (%) | 122 (61.6) | 46 (48.9) | 76 (73.1) | 12.166 | <0.001 |
| Age, median | 53.0 | 49.0 | 56.0 | -4.475 | <0.001 |
| BMI, median | 25.766 | 24.655 | 26.438 | -3.306 | <0.001 |
| **Clinical Disease** | | | | | |
| Hypertension, n (%) | 76 (38.4) | 15 (15.9) | 61 (58.7) | 38.057 | <0.001 |
| Diabetes, n (%) | 31 (15.7) | 2 (2.1) | 29 (27.9) | 24.805 | <0.001 |
| CerebrovascularDisease, n (%) | 15 (7.6) | 4 (4.3) | 11 (10.6) | 2.818 | 0.093 |
| **Laboratory Results** | | | | | |
| WBC, median | 5.110 | 5.110 | 5.870 | -2.359 | 0.017 |
| N, median | 2.925 | 2.820 | 3.540 | -2.381 | 0.016 |
| RBC, median | 4.460 | 4.460 | 4.460 | 0.693 | 0.482 |
| Hb, median | 135.000 | 135.000 | 134.500 | 0.951 | 0.334 |
| P, median | 196.000 | 194.000 | 223.000 | -3.36 | <0.001 |
| ALT, median | 17.000 | 16.000 | 21.000 | -3.809 | <0.001 |
| AST, median | 23.000 | 23.000 | 20.500 | 1.27 | 0.197 |
| UA, mean | 332.977 | 330.143 | 334.127 | -0.142 | 0.887 |
| Cr, median | 74.000 | 74.000 | 72.000 | -0.458 | 0.642 |
| K, median | 3.960 | 3.960 | 3.880 | 2.265 | 0.021 |
| CRP, median | 1.147 | 1.100 | 4.240 | -4.191 | <0.001 |
| CK, median | 70.000 | 70.000 | 67.000 | -0.597 | 0.545 |
| CKMB, median | 15.000 | 19.000 | 12.000 | 4.294 | <0.001 |
| cTnI, median | 0.340 | 0.340 | 0.250 | 1.537 | 0.119 |
| NTproBNP, median | 34.125 | 0.000 | 88.200 | -9.367 | <0.001 |
| TC, median | 4.010 | 4.010 | 3.600 | 2.953 | 0.003 |
| LDL, median | 2.850 | 2.930 | 2.180 | 3.913 | <0.001 |
| DD, median | 0.200 | 0.190 | 0.230 | -3.58 | <0.001 |
| **Echocardiography** | | | | | |
| EDV, median | 98.000 | 98.000 | 102.000 | -1.977 | 0.045 |
| ESV, median | 36.667 | 35.000 | 41.500 | -5.116 | <0.001 |
| EF, median | 0.614 | 0.643 | 0.584 | 6.554 | <0.001 |
| SV, median | 63.000 | 63.000 | 60.600 | 1.912 | 0.052 |
| CO, median | 4.200 | 4.200 | 4.300 | -3.134 | 0.001 |
| **Ex ECG** | | | | | |
| MHR percentage, mean | 0.779 | 0.801 | 0.759 | 2.595 | 0.01 |
| Max Power, mean | 10.612 | 10.468 | 10.745 | -0.572 | 0.568 |
| QRS Duration, mean | 97.586 | 95.382 | 99.510 | -2.426 | 0.016 |
| PPHR, mean | 131.938 | 140.111 | 124.725 | 4.43 | <0.001 |
| No. Ischemic leads, mean | 1.633 | 1.096 | 2.127 | -2.915 | 0.004 |
| Positive HFQRS Conclusions, n (%) | 67 (35.3) | 15 (16.0) | 52 (54.2) | 30.374 | <0.001 |

can be defined as the degree to which humans understand the reasons for ML model predictions. The more interpretable the model, the easier it is for physicians to understand why a given prediction was made and thus make the appropriate clinical decision in the best interest of the patient [37].

Shapley additive explanations (SHAP) analysis was based on the concept of coalitional game theory, where each feature variable in a dataset is considered a player, and the model is trained with that dataset to obtain predictions that can be seen as the benefits of many players cooperating on a project. SHAP analysis enabled the contribution of different features in risk prediction models to be investigated, and high-risk thresholds were identified by SHAP analysis, thus providing thresholds for the top predictive continuous clinical variables [38].

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**Table 2** Univariate and multivariate regression analysis

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | *P*-value | OR(95%CI) | *P*-value | OR(95%CI) |
| Gender | 0.001 | 0.353(0.195,0.639) | 0.002 | 0.258(0.105,0.599) |
| Age | 0 | 1.068(1.041,1.096) | 0.005 | 1.052(1.017,1.093) |
| BMI | 0.006 | 1.115(1.032,1.204) | | |
| Hypertension | 0 | 7.471(3.800,14.689) | 0 | 4.862(2.081,11.955) |
| Diabetes | 0 | 17.787(4.110,76.971) | 0.014 | 7.344(1.802,50.479) |
| WBC | 0.403 | 1.053(0.933,1.189) | | |
| N | 0.131 | 1.110(0.969,1.271) | | |
| P | 0.742 | 1.001(0.996,1.005) | | |
| ALT | 0.07 | 1.018(0.999,1.038) | | |
| K | 0.118 | 0.539(0.248,1.170) | | |
| CRP | 0.131 | 1.011(0.997,1.026) | | |
| CKMB | 0.52 | 1.001(0.997,1.006) | | |
| NTproBNP | 0.083 | 1.000(1.000,1.001) | | |
| TC | 0.153 | 0.801(0.591,1.086) | | |
| LDL | 0.005 | 0.563(0.377,0.840) | | |
| DD | 0.579 | 0.903(0.630,1.295) | | |
| EDV | 0.064 | 1.017(0.999,1.035) | | |
| ESV | 0 | 1.074(1.033,1.117) | 0.114 | 1.027(0.996,1.067) |
| EF | 0 | 0.000(0.000,0.005) | | |
| CO | 0.015 | 2.119(1.156,3.886) | 0.054 | 2.393(1.060,6.103) |
| MHRpercentage | 0.012 | 0.035(0.003,0.473) | | |
| PPRHR | 0 | 0.973(0.960,0.986) | | |
| QRS Duration | 0.024 | 1.032 | | |
| Number of positives | 0.007 | 1.188 | | |
| Conclusions | 0 | 6.224 | 0 | 5.728(2.497,14.019) |
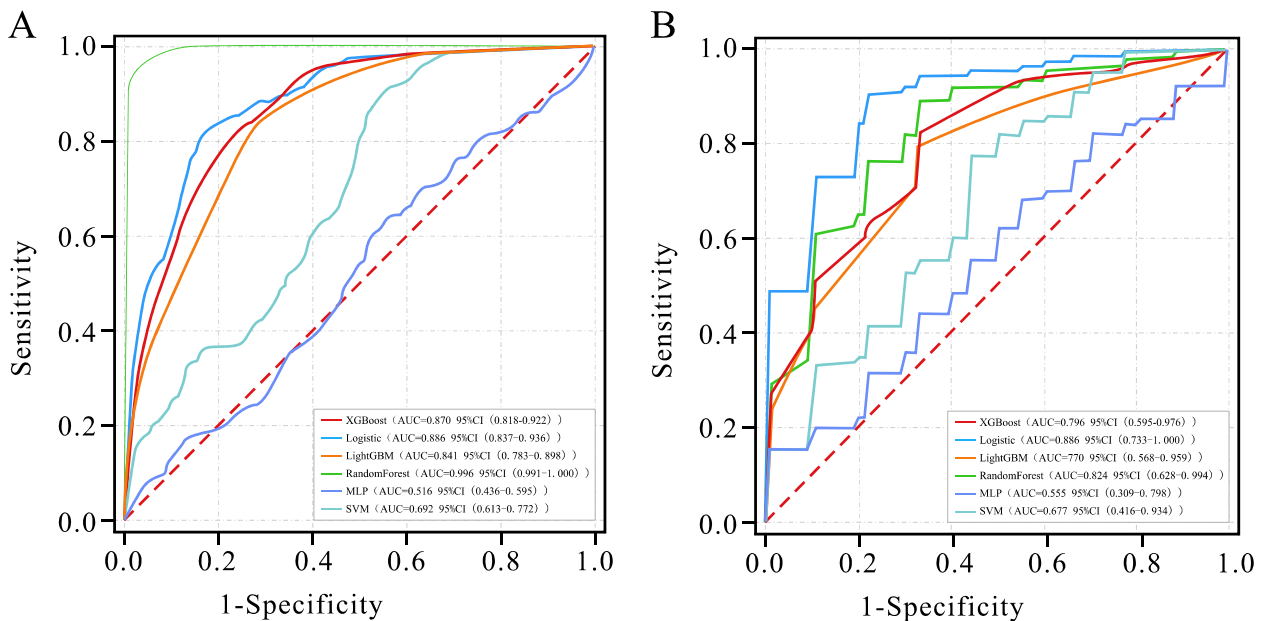


**Fig. 1** The ROC curves of multiple machine learning models: **A** On the training set, and **B** On the validation set
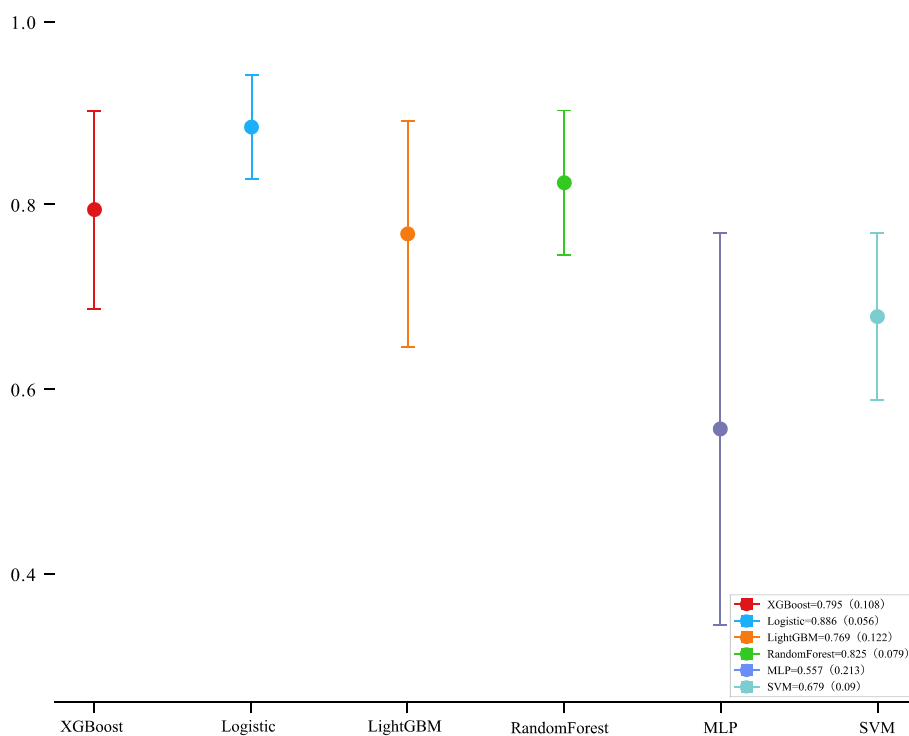
**Fig. 2** A forest plot of the AUC values of multiple machine learning models

Legend:
- XGBoost=0.795 (0.108)
- Logistic=0.886 (0.056)
- LightGBM=0.769 (0.122)
- RandomForest=0.825 (0.079)
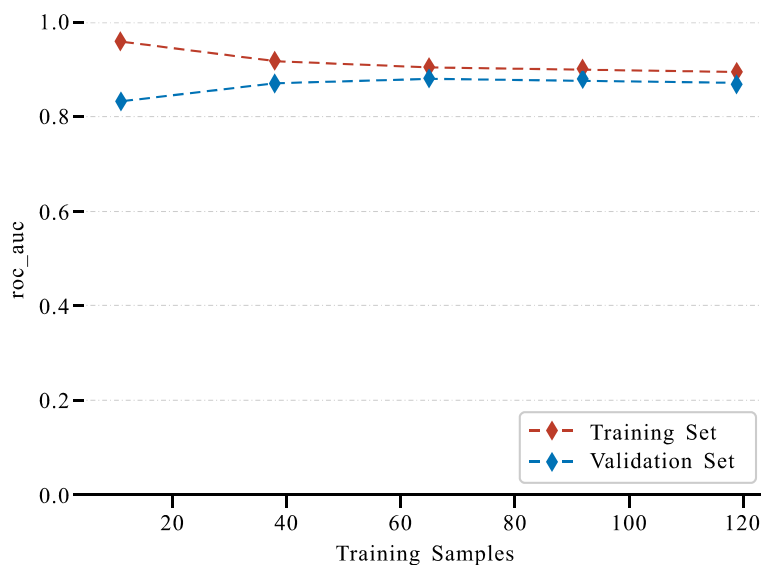- MLP=0.557 (0.213)
- SVM=0.679 (0.09)



**Fig. 3** The learning curve of the Logistic Regression model

SHAP value was the contribution made by each player to fairly distributing the benefits of cooperation. The summary plot presented all the sample points in the graph, as shown in Fig. 7. The color represented the size of the feature value, while the vertical coordinate was the size of the SHAP value. From the graph, we can see the feature of the HFQRS conclusion: the larger the value, the larger the SHAP value; in other words, the larger the HFQRS conclusion, the higher the risk.

We checked the SHAP of two samples; one was correctly predicted, and the other model prediction did not match the actual case. The positive case is a 71-year-old
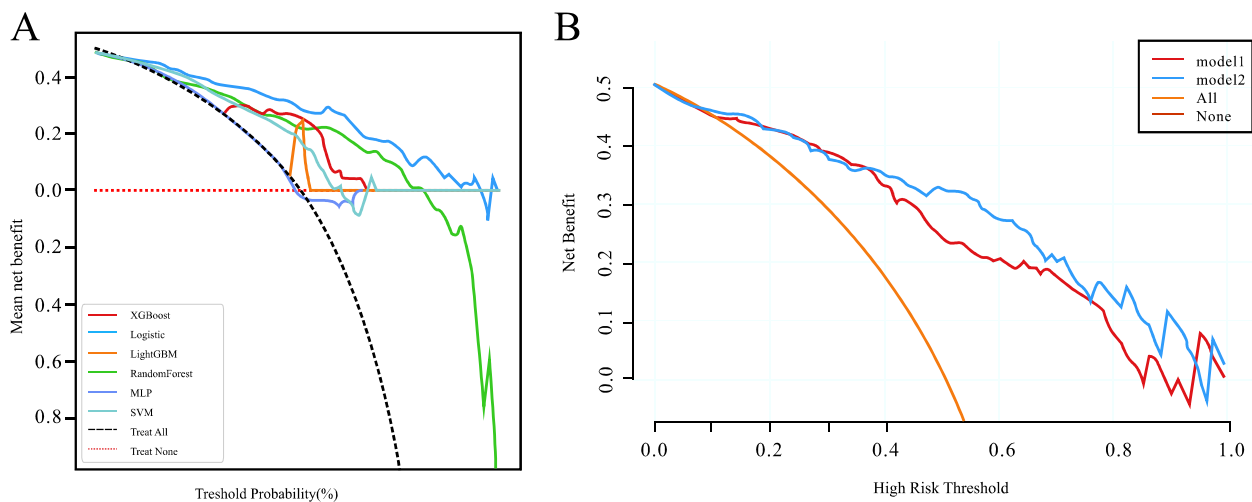
**Fig. 4** The DCA curves of **A** multiple machine learning models and **B** two Logistic Regression models

**Table 3** Performance of ML models

| Dataset | Model | Acc. | Sen. | Spe. | PPV | NPV | F1 | Kappa | AUC |
|---|---|---|---|---|---|---|---|---|---|
| Train | XGBoost | 0.767 | 0.832 | 0.769 | 0.803 | 0.749 | 0.816 | 0.685 | 0.870 |
| | Logistic | 0.825 | 0.823 | 0.839 | 0.838 | 0.814 | 0.830 | 0.645 | 0.886 |
| | LightGBM | 0.719 | 0.846 | 0.719 | 0.797 | 0.676 | 0.820 | 0.386 | 0.841 |
| | RandomForest | 0.955 | 0.939 | 0.983 | 0.983 | 0.930 | 0.960 | 0.947 | 0.996 |
| | MLP | 0.591 | 0.599 | 0.596 | * | 0.650 | * | 0.645 | 0.516 |
| | SVM | 0.678 | 0.902 | 0.462 | 0.628 | 0.803 | 0.740 | 0.353 | 0.692 |
| Validation | XGBoost | 0.695 | 0.801 | 0.766 | 0.752 | 0.674 | 0.763 | 0.685 | 0.796 |
| | Logistic | 0.789 | 0.858 | 0.874 | 0.811 | 0.800 | 0.830 | 0.645 | 0.886 |
| | LightGBM | 0.653 | 0.759 | 0.763 | 0.730 | 0.637 | 0.728 | 0.386 | 0.770 |
| | RandomForest | 0.737 | 0.856 | 0.779 | 0.783 | 0.746 | 0.812 | 0.947 | 0.824 |
| | MLP | 0.579 | 0.670 | 0.670 | * | 0.598 | * | 0.645 | 0.555 |
| | SVM | 0.668 | 0.874 | 0.594 | 0.623 | 0.790 | 0.724 | 0.366 | 0.677 |

female patient with hypertension and diabetes and a positive HFQRS conclusion from the cycling exercise test. The output value is higher than the base value, and the model predicts a high risk of coronary heart disease, which is actually diagnosed as coronary heart disease by coronary angiography (Fig. 7b). The negative example case is a 64-year-old female patient with hypertension and a positive HFQRS finding from cycling exercise testing, which the model predicts to be at high risk of coronary heart disease; however, the actual patient was excluded from coronary heart disease by coronary angiography (Fig. 7c).

## Discussion

In this study, our findings illustrate the significant contribution of age, gender, hypertension, diabetes, and exercise load test HF QRS conclusions to CHD prediction.

Using these variables, six machine learning models were developed and compared to yield the best performance of the Logistic Regression model, further establishing and validating a column line graph for assessing CHD risk, which we believe has potentially significant implications for CHD at the first level.

Previous studies have used deep learning algorithms to analyze routine 12-lead ECG in outpatients to predict the ability of CHD [39]. A recent study has developed a columnar table of the association of biological and psychological factors with the risk of coronary heart disease [40]. In contrast to earlier studies, our analysis of HFQRS in the exercise load ECG, combined with the admission routine findings, showed that five variables were significantly related to high CHD risk. Among them, there are two immutable factors (gender and age), which are very consistent with the previous studies [41].
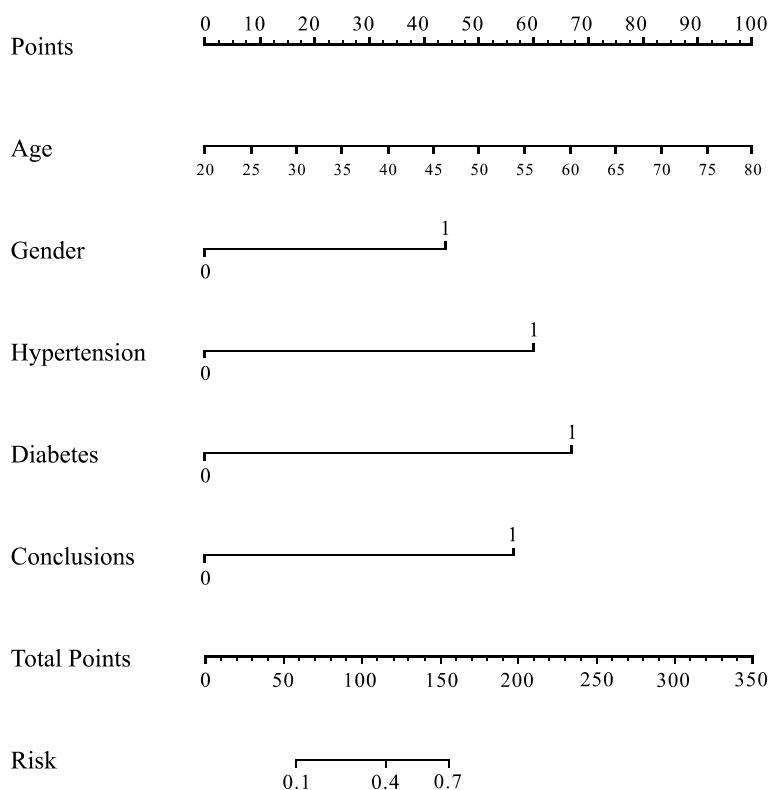
**Fig. 5** CHD predictive nomogram



**Fig. 6** Association between the total points of the nomogram and CHD. OR: odds ratio; CI: confidence interval

In general, hypertension and diabetes are also widely recognized risk factors for coronary heart disease [42]. We report an OR of 5.728 (95% CI: 2.497, 14.019) for the correlation between HF QRS findings and coronary heart disease prediction. False-positive rates for exercise ECG tests used to diagnose CHD are higher in women compared to men. Women are inherently a risk factor for false-positive exercise stress tests [43, 44] HFQRS response to myocardial ischemia was gender-independent, and Rosenmann et al. [45] found that the number of leads of ischemic HFQRS response correlated with the severity of CHD in 113 patients with non-urgent referral coronary angiography and that HFQRS analysis had a sensitivity of 70% and specificity of 80% for the detection of significant coronary artery obstruction (single vessel stenosis ≥70% or left main stem stenosis ≥50%) on the angiogram. In this paper, we innovatively constructed multiple machine learning models for HFQRS and clinical characteristics; the SHAP force plot increased the interpretability of the models; and we also developed
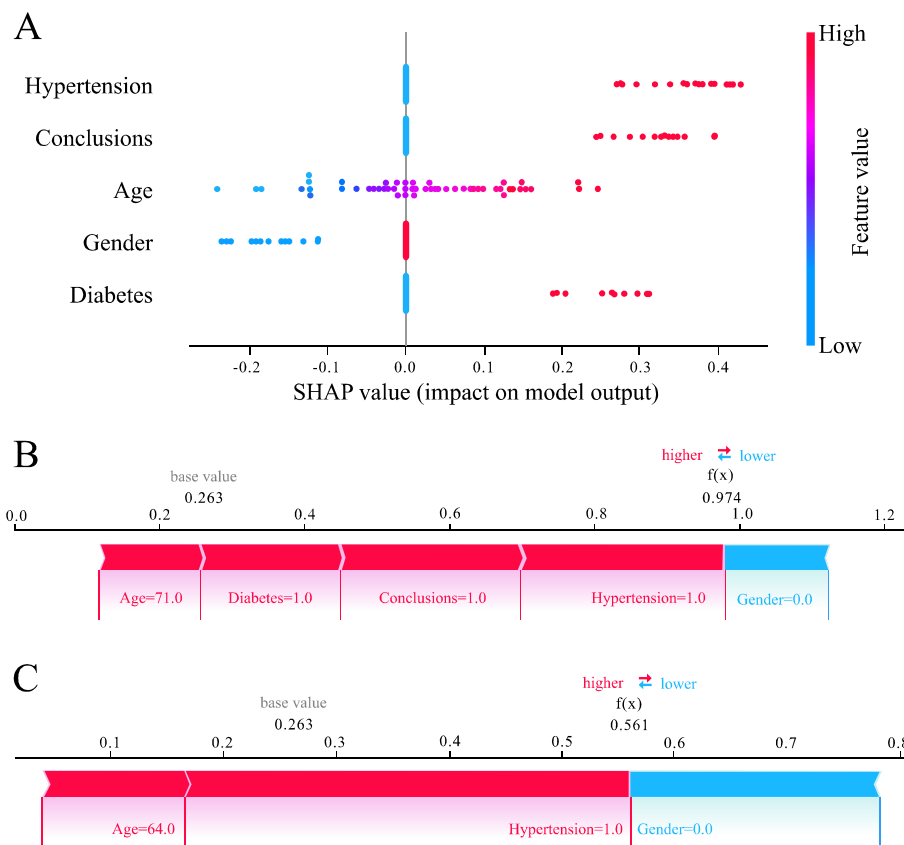
**Fig. 7** SHAP analysis. **A** SHAP summary plot of the top 5 features of the Logistic regression model; **B** A positive case; **C** A negative case

user-friendly column line tables with promising clinical applications. Although individual modifiable CHD risk factors contribute only modestly to prognostic performance, our models indicate that eliminating or controlling these individual factors would lead to substantial reductions in total population CHD events [46].

### Limitations and application prospects
Nevertheless, there are three important considerations that must be acknowledged. The exercise stress test is specifically restricted to pregnant women, those with motor limitations, and patients who have experienced acute myocardial infarction or other disorders within the past 48 hours. It is noteworthy that the analysis of high-frequency QRS (HFQRS) in resting electrocardiograms (ECGs) is currently being utilized. However, the analysis of HFQRS in patients with pacemakers is still in the clinical testing phase. Furthermore, there are multiple factors related to clinical characteristics. Despite our consideration of thirty-five variables, our analysis does not encompass all possible factors. Therefore, our findings and conclusions can only be applied to predicting the risk of CHD in the general population. To further

validate our findings, future studies should incorporate a broader range of variables. Ultimately, this study was conducted in a single medical facility and focused exclusively on Chinese patients from a specific geographic area, perhaps restricting its applicability to a broader population. Although we have performed a 10-fold cross-validation of our machine learning model, it is still necessary to conduct future prospective multi-center research to independently confirm our findings.

Omer et al. [47] conducted a study on the reaction of HFQRS signals from standard intracardiac electrodes (iHFQRS) to acute myocardial ischemia caused by coronary balloon dilation. They discovered that iHFQRS is a prompt indicator of myocardial ischemia, showing a significant decrease within seconds and responding to ischemic signals from various coronary arteries, including the LAD, LCX, RCA, and even distal vessels that supply less myocardium. These findings demonstrate that iHFQRS outperforms the conventional ST-segment deviation as a diagnostic tool for myocardial ischemia. The iHFQRS demonstrated excellent performance in animal tests, indicating good potential for future research of HFQRS in human implants. Research has demonstrated that monitoring

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energy levels in iHFQRS utilizing implantable devices, such as conventional intracardiac electrodes, situated in typical positions, can offer an early and dependable diagnosis of acute ischemia episodes.

## Conclusion

Our study demonstrated that men and older adults with hypertension, diabetes, and positive HFQRS conclusions on exercise stress tests suggested a higher risk of CHD. We developed a user-friendly column line graph that may be beneficial to the public and policymakers to establish effective CHD risk assessment and primary prevention strategies.

## Declarations

#### Ethics approval and consent to participate
This study was approved by the ethics committee of Bengbu Medical University (Ethics Section Approval [2021] No. 297). We certify that the study was performed in accordance with the 1964 declaration of HESINKI and later amendments. All participants provided written informed consent prior to enrolling in this study.

#### Consent for publication
Not applicable.

#### Competing interests
The authors declare no competing interests.

## References

1. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736–88. https://doi.org/10.1016/S0140-6736(18)32203-7.
2. Task Force Members, Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949–3003. https://doi.org/10.1093/eurheartj/eht296.
3. Chatterjee NA, Tikkanen JT, Panicker GK, Narula D, Lee DC, Kentta T, et al. Simple electrocardiographic measures improve sudden arrhythmic death prediction in coronary disease. Eur Heart J. 2020;41(21):1988–99. https://doi.org/10.1093/eurheartj/ehaa177.
4. Jonas DE, Reddy S, Middleton JC, Barclay C, Green J, Baker C, et al. Screening for cardiovascular disease risk with resting or exercise electrocardiography: evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2018;319(22):2315. https://doi.org/10.1001/jama.2018.6897.
5. Daubert MA, Sivak J, Dunning A, Douglas PS, Coyne B, Wang TY, et al. Implications of Abnormal Exercise Electrocardiography With Normal Stress Echocardiography. JAMA Intern Med. 2020;180(4):494. https://doi.org/10.1001/jamainternmed.2019.6958.
6. Ulloa-Cerna AE, Jing L, Pfeifer JM, Raghunath S, Ruhl JA, Rocha DB, et al. rECHOmmend: An ECG-Based Machine Learning Approach for Identifying Patients at Increased Risk of Undiagnosed Structural Heart Disease Detectable by Echocardiography. Circulation. 2022;146(1):36–47. https://doi.org/10.1161/CIRCULATIONAHA.121.057869.
7. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Biol Eng Comput. 2006;44(12):1031–51. https://doi.org/10.1007/s11517-006-0119-0.
8. Liu N, Guo D, Koh ZX, Ho AFW, Xie F, Tagami T, et al. Heart rate n-variability (HRnV) and its application to risk stratification of chest pain patients in the emergency department. BMC Cardiovasc Disord. 2020;20(1). https://doi.org/10.1186/s12872-020-01455-8.
9. Carlén A, Nylander E, Åström Aneq M, Gustafsson M. ST/HR variables in firefighter exercise ECG - relation to ischemic heart disease. Physiol Rep. 2019;7(2):e13968. https://doi.org/10.14814/phy2.13968.
10. Zimarino M, Montebello E, Radico F, Gallina S, Perfetti M, Iachini Bellisarii F, et al. ST segment/heart rate hysteresis improves the diagnostic accuracy of ECG stress test for coronary artery disease in patients with left ventricular hypertrophy. Eur J Prev Cardiol. 2016;23(15):1632–9. https://doi.org/10.1177/2047487316655259.
11. Abächerli R, Twerenbold R, Boeddinghaus J, Nestelberger T, Mächler P, Sassi R, et al. Diagnostic and prognostic values of the V-index, a novel ECG marker quantifying spatial heterogeneity of ventricular repolarization, in patients with symptoms suggestive of non-ST-elevation myocardial infarction. Int J Cardiol. 2017;236:23–9. https://doi.org/10.1016/j.ijcard.2017.01.151.
12. Kania M, Maniewski R, Zaczek R, Kobylecka M, Zbieć A, Królicki L, et al. High-Resolution Body Surface Potential Mapping in Exercise Assessment of Ischemic Heart Disease. Ann Biomed Eng. 2019;47(5):1300–13. https://doi.org/10.1007/s10439-019-02231-2.
13. Campen CMCV, Visser FC, Visser CA. Ischaemic heart disease: The QRS score: a promising new exercise score for detecting coronary artery disease based on exercise-induced changes of Q-, R- and S-waves: a relationship with myocardial ischaemia. Eur Heart J. 1996;17(5):699–708. https://doi.org/10.1093/oxfordjournals.eurheartj.a014936.
14. Ringborn M, Pettersson J, Persson E, Warren SG, Platonov P, Pahlm O, et al. Comparison of high-frequency QRS components and ST-segment elevation to detect and quantify acute myocardial ischemia. J Electrocardiol. 2010;43(2):113–20. https://doi.org/10.1016/j.jelectrocard.2009.11.009.
15. Schaerli N, Abächerli R, Walter J, Honegger U, Puelacher C, Rinderknecht T, et al. Incremental value of high-frequency QRS analysis for diagnosis and prognosis in suspected exercise-induced myocardial ischaemia. Eur Heart J Acute Cardiovasc Care. 2020;9(8):836–47. https://doi.org/10.1177/2048872619842988.
16. Thomas GS, Ghashghaei R. An opportunity to improve exercise test accuracy by incorporating high frequency QRS (HFQRS) waveform

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assessment. J Nucl Cardiol. 2020;27(6):2076–9. https://doi.org/10.1007/s12350-019-01600-7.

17. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. Circulation. 1998;97(18):1837–47. https://doi.org/10.1161/01.cir.97.18.1837.

18. Conroy R. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987–1003. https://doi.org/10.1016/s0195-668x(03)00114-3.

19. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ. 2010;341(dec09 1):c6624–c6624. https://doi.org/10.1136/bmj.c6624.

20. Liu H, Zhang S, Gamboa H, Xue T, Zhou C, Schultz T. Taxonomy and Real-Time Classification of Artifacts During Biosignal Acquisition: A Starter Study and Dataset of ECG. IEEE Sensors J. 2024;24(6):9162–71. https://doi.org/10.1109/JSEN.2024.3356651.

21. Yang C, Sheng D, Yang B, Zheng W, Liu C. A Dual-Domain Diffusion Model for Sparse-View CT Reconstruction. IEEE Signal Process Lett. 2024;31:1279–83. https://doi.org/10.1109/LSP.2024.3392690.

22. Zheng W, Lu S, Yang Y, Yin Z, Yin L. Lightweight transformer image feature extraction network. PeerJ Comput Sci. 2024;10:e1755. https://doi.org/10.7717/peerj-cs.1755.

23. Al'Aref SJ, Anchouche K, Singh G, Slomka PJ, Kolli KK, Kumar A, et al. Clinical applications of machine learning in cardiovascular disease and its relevance to cardiac imaging. Eur Heart J. 2018;40(24):1975–1986. https://doi.org/10.1093/eurheartj/ehy404.

24. Nguyen QH, Nguyen BP, Nguyen TB, Do TTT, Mbinta JF, Simpson CR. Stacking segment-based CNN with SVM for recognition of atrial fibrillation from single-lead ECG recordings. Biomed Signal Process Control. 2021;68:102672. https://doi.org/10.1016/j.bspc.2021.102672.

25. Khurshid S, Friedman S, Reeder C, Di Achille P, Diamant N, Singh P, et al. ECG-Based Deep Learning and Clinical Risk Factors to Predict Atrial Fibrillation. Circulation. 2022;145(2):122–33. https://doi.org/10.1161/CIRCULATIONAHA.121.057480.

26. Bing P, Liu Y, Liu W, Zhou J, Zhu L. Electrocardiogram classification using TSST-based spectrogram and ConViT. Front Cardiovasc Med. 2022;9. https://doi.org/10.3389/fcvm.2022.983543.

27. Khera R, Haimovich J, Hurley NC, McNamara R, Spertus JA, Desai N, et al. Use of Machine Learning Models to Predict Death After Acute Myocardial Infarction. JAMA Cardiol. 2021;6(6):633. https://doi.org/10.1001/jamacardio.2021.0122.

28. Cikes M, Sanchez-Martinez S, Claggett B, Duchateau N, Piella G, Butakoff C, et al. Machine learning-based phenogrouping in heart failure to identify responders to cardiac resynchronization therapy. Eur J Heart Fail. 2018;21(1):74–85. https://doi.org/10.1002/ejhf.1333.

29. Karwath A, Bunting KV, Gill SK, Tica O, Pendleton S, Aziz F, et al. Redefining β-blocker response in heart failure patients with sinus rhythm and atrial fibrillation: a machine learning cluster analysis. Lancet. 2021;398(10309):1427–35. https://doi.org/10.1016/S0140-6736(21)01638-X.

30. Ambale-Venkatesh B, Yang X, Wu CO, Liu K, Hundley WG, McClelland R, et al. Cardiovascular Event Prediction by Machine Learning: The Multi-Ethnic Study of Atherosclerosis. Circ Res. 2017;121(9):1092–101. https://doi.org/10.1161/CIRCRESAHA.117.311312.

31. Nakanishi R, Slomka PJ, Rios R, Betancur J, Blaha MJ, Nasir K, et al. Machine Learning Adds to Clinical and CAC Assessments in Predicting 10-Year CHD and CVD Deaths. JACC Cardiovasc Imaging. 2021;14(3):615–25. https://doi.org/10.1016/j.jcmg.2020.08.024.

32. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. Lancet. 2019;394(10201):861–7. https://doi.org/10.1016/S0140-6736(19)31721-0.

33. D'Ascenzo F, De Filippo O, Gallone G, Mittone G, Deriu MA, Iannaccone M, et al. Machine learning-based prediction of adverse events following an acute coronary syndrome (PRAISE): a modelling study of pooled datasets. Lancet. 2021;397(10270):199–207. https://doi.org/10.1016/S0140-6736(20)32519-8.

34. Hughes JW, Olgin JE, Avram R, Abreau SA, Sittler T, Radia K, et al. Performance of a Convolutional Neural Network and Explainability

Technique for 12-Lead Electrocardiogram Interpretation. JAMA Cardiol. 2021;6(11):1285. https://doi.org/10.1001/jamacardio.2021.2746.

35. Jiang L, Chen S, Wu Y, Zhou D, Duan L. Prediction of coronary heart disease in gout patients using machine learning models. Math Biosci Eng. 2022;20(3):4574–91. https://doi.org/10.3934/mbe.2023212.

36. Nabrdalik K, Kwiendacz H, Drożdż K, Irlik K, Hendel M, Wijata AM, et al. Machine Learning Predicts Cardiovascular Events in Patients With Diabetes: The Silesia Diabetes-Heart Project. Curr Probl Cardiol. 2023;48(7):101694. https://doi.org/10.1016/j.cpcardiol.2023.101694.

37. Deshmukh F, Merchant SS. Explainable Machine Learning Model for Predicting GI Bleed Mortality in the Intensive Care Unit. Am J Gastroenterol. 2020;115(10):1657–1668. https://doi.org/10.14309/ajg.0000000000000632.

38. Fahmy AS, Csecs I, Arafati A, Assana S, Yankama TT, Al-Otaibi T, et al. An Explainable Machine Learning Approach Reveals Prognostic Significance of Right Ventricular Dysfunction in Nonischemic Cardiomyopathy. JACC Cardiovasc Imaging. 2022;15(5):766–79. https://doi.org/10.1016/j.jcmg.2021.11.029.

39. Leasure M, Jain U, Butchy A, Otten J, Covalesky VA, McCormick D, et al. Deep Learning Algorithm Predicts Angiographic Coronary Artery Disease in Stable Patients Using Only a Standard 12-Lead Electrocardiogram. Can J Cardiol. 2021;37(11):1715–24. https://doi.org/10.1016/j.cjca.2021.08.005.

40. Huang S, Xie X, Sun Y, Zhang T, Cai Y, Xu X, et al. Development of a nomogram that predicts the risk for coronary atherosclerotic heart disease. Aging. 2020;12(10):9427–9439. https://doi.org/10.18632/aging.103216.

41. Hyvärinen M, Qiao Q, Tuomilehto J, Söderberg S, Eliasson M, Stehouwer CDA. The Difference between Acute Coronary Heart Disease and Ischaemic Stroke Risk with Regard to Gender and Age in Finnish and Swedish Populations. Int J Stroke. 2010;5(3):152–6. https://doi.org/10.1111/j.1747-4949.2010.00423.x.

42. Dugani SB, Moorthy MV, Li C, Demler OV, Alsheikh-Ali AA, Ridker PM, et al. Association of Lipid, Inflammatory, and Metabolic Biomarkers With Age at Onset for Incident Coronary Heart Disease in Women. JAMA Cardiol. 2021;6(4):437. https://doi.org/10.1001/jamacardio.2020.7073.

43. Fitzgerald BT, Scalia WM, Scalia GM. Female False Positive Exercise Stress ECG Testing – Fact Versus Fiction. Heart, Lung Circ. 2019;28(5):735–41. https://doi.org/10.1016/j.hlc.2018.02.010.

44. Denes P. Major and Minor ECG Abnormalities in Asymptomatic Women and Risk of Cardiovascular Events and Mortality. JAMA. 2007;297(9):978. https://doi.org/10.1001/jama.297.9.978.

45. Rosenmann D, Mogilevski Y, Amit G, Davrath LR, Tzivoni D. High-frequency QRS analysis improves the specificity of exercise ECG testing in women referred for angiography. J Electrocardiol. 2013;46(1):19–26. https://doi.org/10.1016/j.jelectrocard.2012.08.007.

46. Pencina MJ, Navar AM, Wojdyla D, Sanchez RJ, Khan I, Elassal J, et al. Quantifying Importance of Major Risk Factors for Coronary Heart Disease. Circulation. 2019;139(13):1603–11. https://doi.org/10.1161/CIRCULATIONAHA.117.031855.

47. Omer N, Bergman E, Ben-David T, Huri S, Beker A, Abboud S, et al. Changes in high-frequency intracardiac electrogram indicate cardiac ischemia. J Cardiovasc Transl Res. 2021;15(1):84–94. https://doi.org/10.1007/s12265-021-10146-4.

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