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CLINICAL STUDY

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Development and external validation of a machine learning model for cardiac valve calcification early screening in dialysis patients: a multicenter study

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ABSTRACT

Background: Cardiac valve calcification (CVC) is common in dialysis patients and associated with increased cardiovascular risk. However, early screening has been limited by cost concerns. This study aimed to develop and validate a machine learning model to enhance early detection of CVC.

Methods: Data were collected at four centers between 2020 and 2023, including 852 dialysis patients in the development dataset and 661 in the external validation dataset. Predictive factors were selected using LASSO regression combined with univariate and multivariate analyses. Machine learning models including CatBoost, XGBoost, decision tree, support vector machine, random forest, and logistic regression were used to develop the CVC risk model. Model performance was evaluated in both validation sets. Risk thresholds were defined using the Youden index and validated in the external dataset.

Results: In the development dataset, 32.9% of patients were diagnosed with CVC. Age, dialysis duration, alkaline phosphatase, apolipoprotein A1, and intact parathyroid hormone were selected to construct the CVC risk prediction model. CatBoost exhibited the best performance in the training dataset. The logistic regression model demonstrated the best predictive performance in both internal and external validation sets, with AUROCs of 0.806 (95% CI 0.750–0.863) and 0.757 (95% CI 0.720–0.793), respectively. Calibration curves and decision curves confirmed its predictive accuracy and clinical applicability. The logistic regression model was selected as the optimal model and achieved excellent risk stratification in CVC risk prediction.

Conclusion: The predictive model effectively identifies CVC risk in dialysis patients and offers a robust tool for early detection and improved management.

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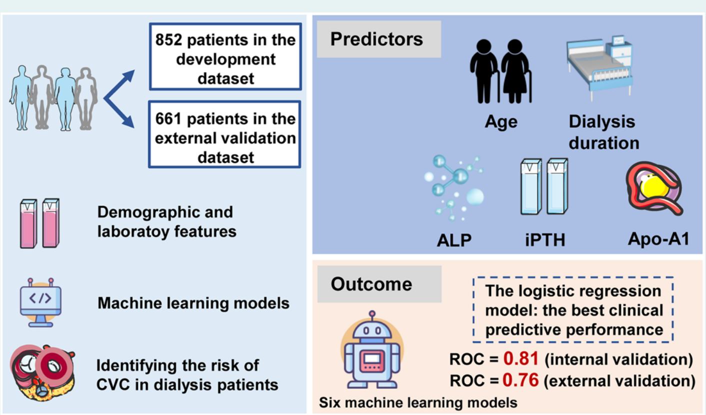
GRAPHICAL ABSTRACT



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Introduction

Cardiac valve calcification (CVC) is a common complication in dialysis patients, with a prevalence eight times higher than that of the general population [1]. CVC can cause valve stenosis or insufficiency and impact cardiac structure and function, increasing the risk of arrhythmia and sudden death [2]. Moreover, CVC is independently linked with myocardial ischemia, which further contributes to coronary heart disease (CHD) risk [3]. Therefore, early identification of CVC in dialysis patients is clinically important and may help in developing more effective treatment strategies to prevent cardiovascular risk.

Conventional methods, such as echocardiography, have been widely used to assess CVC. Nonetheless, these methods are limited by operator dependency and lack sensitivity in detecting early lesions. In addition, diagnosing CVC typically relies on clinical examinations following symptom onset, which often results in delayed detection and intervention. Routine screening procedures are time-consuming and costly, making screening for CVC in dialysis patients not yet widespread. Recently, the emergence of machine learning algorithms offers a new perspective and methodology for developing models that can detect CVC by using extensive clinical data, offering significant potential for early identification and management of CVC. However, there are currently no studies utilizing machine learning models to predict CVC risk in dialysis patients.

This study aims to use data from large clinical centers to develop and externally validate methods for identifying CVC in dialysis patients, and to determine the prevalence of CVC and associated independent risk factors. Using a combination of clinical parameters and laboratory indices, we will validate the model's ability to identify CVC, providing a reliable tool for better patient identification in daily practice. This will help optimize the management pathway of dialysis patients and reduce the incidence of cardiovascular complications.

Material and methods

Study population and design

A total of 2,681 end-stage renal disease patients aged 18 to 80 were enrolled from four clinical centers in China between January 2020 and June 2023. These patients were undergoing regular hemodialysis (HD) or peritoneal dialysis (PD) in the nephrology departments and blood purification centers. All patients underwent echocardiographic evaluation during their hospitalization. This study excluded participants (1) previously diagnosed with valvular heart disease, rheumatic heart disease, or arrhythmia; (2) those with a history of cardiac surgery (Figure 1). This study obtained ethical approval from the Medical Research Ethics Committee at Zhongda Hospital (Approval No. 2023ZDSYLL172-P01). The requirement for signed informed consent was waived due to the retrospective nature of the study.

Echocardiography

Two-dimensional echocardiograms were conducted on non-dialysis days using Vivid 7 (GE Medical Systems, Milwaukee, WI, USA). All echocardiographic measurements followed the guidelines established by the American Society of Echocardiography and were performed by two sonographers blinded to other clinical data [4]. The assessment of the aortic and mitral valves was carried out in two dimensions using parasternal long-axis and short-axis views, along with continuous wave Doppler ultrasonography. CVC was characterized by the presence of bright echoes > 1 mm on one or more cusps of aortic valve, mitral valve, or mitral annulus. Patients were categorized into three distinct groups based on the extent of valve calcification: (1) no calcification; (2) calcification in a single valve (either aortic or mitral); and (3) calcification in both valves (aortic and mitral) [5]. Echocardiography parameters, including the interventricular septum thickness (IVST), left ventricular end-diastole diameter (LVEDD), left posterior wall thickness (PWT), and left ventricular ejection fraction (LVEF), were assessed. The left ventricular mass (LVM) was obtained by converting the volume of myocardium to mass, multiplying it by the myocardial density (1.04 g/mL): $\text{LVM} = 0.8 \times 1.04 \times [(\text{LVEDD} + \text{IVST} + \text{PWT})^3 - \text{LVEDD}^3] + 0.6\,\text{g}$ [6]. The left ventricular mass index (LVMI) was calculated by normalizing the left ventricular mass to body surface area (g/m^2). Pulse-wave Doppler measurements of transmitral inflow velocity were recorded from the apical five-chamber view to evaluate diastolic function.

Clinical baseline data

Data were collected by trained researchers, ensuring that all procedures and equipment used across the four study sites were standardized. Patient information was obtained from medical records, including variables such as age, sex, weight, height, smoking history, dialysis modalities (HD or PD), dialysis duration, medical history, and medication usage history. Definitions of diabetes, hypertension, CHD, hyperlipidemia, and stroke are detailed in the Supplementary Method S1.

Standard laboratory procedures were employed for blood tests, which included assessments of white blood cell counts (WBC), hemoglobin (Hb), albumin (ALB), fasting plasma glucose (FPG), uric acid (UA), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) (Lp(a)), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), bicarbonate, serum calcium, serum phosphate, calcium-phosphorus product ($Ca \times P$), and intact parathyroid hormone (iPTH). $Ca \times P$ (mg^2/dL^2) was calculated as serum calcium (mmol/L) $\times$ serum phosphate (mmol/L) $\times$ 12.4.

Statistical analyses

In this analysis, numerical variables were presented as mean (SD) or median (IQR), depending on the normality of their distribution. Categorical variables were reported as frequencies (percentages). Group comparisons for continuous data were conducted using the independent samples t-test or the

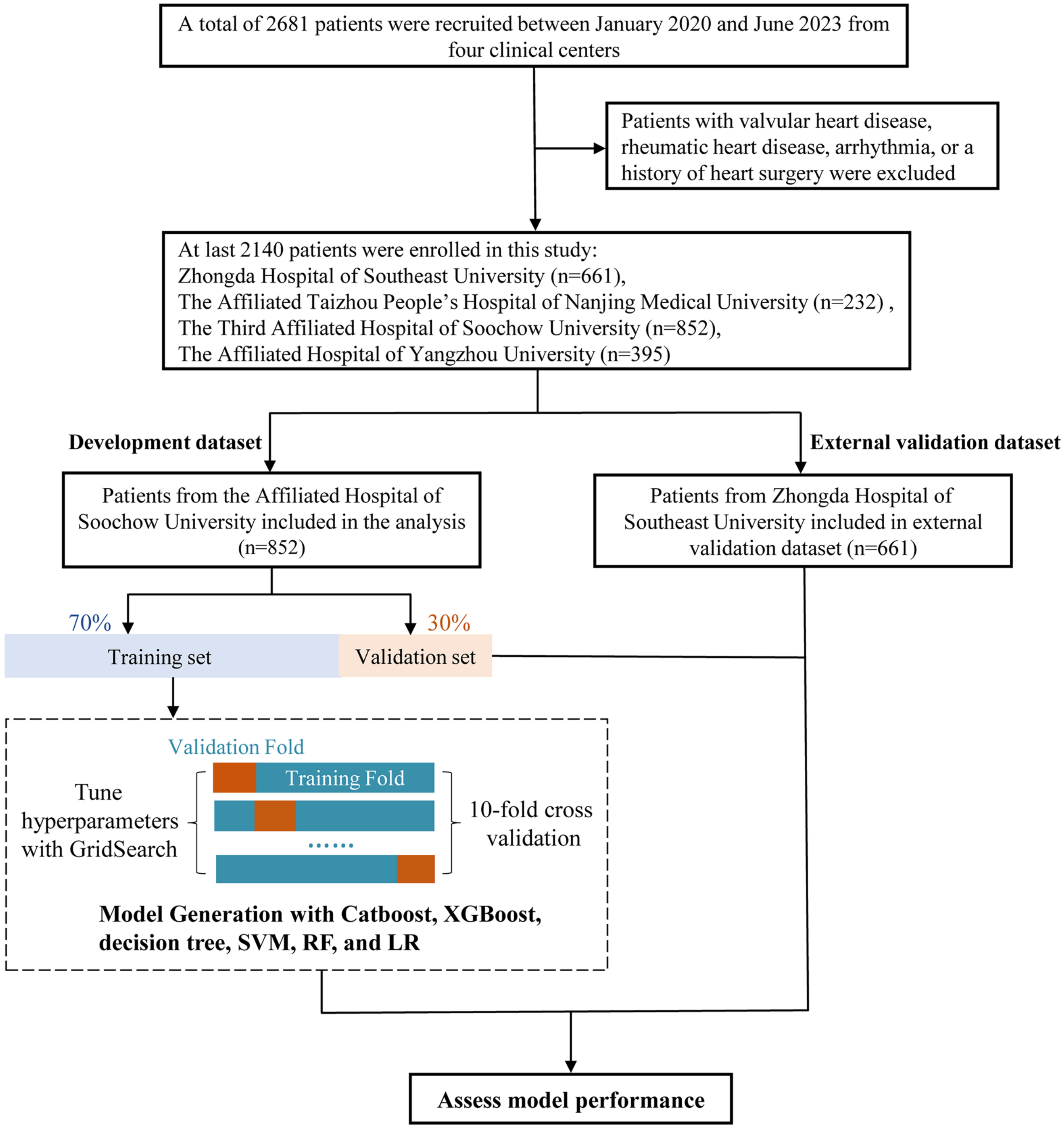

Figure 1. Flowchart of the study participants. CatBoost: category boosting; XGBoost: extreme gradient boosting; SVM: support vector machine; RF: random forest; LR: logistic regression.

Mann-Whitney U test, based on distribution normality. The chi-square test was employed for categorical data comparison. Given the limitations of *p*-values in detecting differences between groups in large sample sizes, we utilized the standardized mean difference (SMD) as an alternative approach. SMD provides a standardized measure for comparing group differences, regardless of sample size, measurement scales, or variance [7]. An SMD with an absolute value of less than 0.20 indicates a small difference, and an absolute value below 0.10 suggests a negligible difference. Data from the four centers were analyzed using multivariate logistic regression to determine independent risk factors associated with CVC. Statistical analyses were conducted using R 4.3.1 and STATA 16.0. All tests were two-tailed, with $p < 0.05$ deemed statistically significant.

We utilized the Least Absolute Shrinkage and Selection Operator (LASSO) regression approach to reduce the dimensionality of the data and select initial predictors [8,9]. This method effectively handles multicollinearity and increases model parsimony by imposing penalties on the regression coefficients, which results in the exclusion of variables that are either less significant or exhibit high collinearity. The variables selected through LASSO regression were subsequently analyzed using univariate and multivariate logistic regression to determine the final predictive variables. Due to variations in patient numbers across the four centers, the patients from The Third Affliated Hospital of Soochow University were selected as the development dataset (Figure 1), which was then randomly split into a training set and an internal validation set in a 7:3 ratio [9,10]. The patients from Zhongda Hospital of Southeast University were used as the external validation dataset to evaluate the model's generalizability. In developing the prediction models, we employed six machine learning algorithms, including category boosting (CatBoost), extreme gradient boosting (XGBoost), decision tree, support vector machine (SVM), random forest, and logistic regression, based on the results of feature selection to construct risk models. During model training, we used 10-fold cross-validation to evaluate predictive performance. In both internal and external validation datasets, model performance was evaluated through the area under the receiver operating characteristic curve (AUROC) and the precision-recall curve (AUPRC). We also calculated metrics such as accuracy, sensitivity, specificity, precision, and *F*-1 score. Calibration was assessed using calibration curves and the Brier score, and decision curve analysis was used to evaluate clinical applicability.

If logistic regression outperforms the other methods, we will construct a nomogram based on its results for practical application. The nomogram translates each regression coefficient proportionally into a 0 to 100-point scale, where 100 points corresponds to the maximum β coefficient. The overall score is obtained by adding up the individual points assigned to each variable, which is subsequently transformed into a predicted probability [11].

The risk thresholds were established using the Youden index and the distribution of predicted risk probabilities in the internal validation dataset to categorize participants into high-, intermediate-, and low-risk groups. Specifically, the high-risk group was identified using the Youden index, and the median of the predicted probabilities from our model was used as a cutoff to divide the remaining individuals into intermediate- and low-risk groups. These thresholds were then validated in the external validation dataset.

Results

Characteristics of study participants

A total of 2,140 dialysis patients were included in the study (Figure 1). The median age was 56 years, with 1,259 males (58.8%). Among these patients, 782 (36.5%) were diagnosed with CVC. Echocardiography showed that patients with CVC had lower IVST ($p < 0.001$) and LVEF ($p = 0.010$), higher left ventricular posterior wall thickness (LVPW) ($p < 0.001$), and increased LVM ($p < 0.001$), LVMI ($p < 0.001$), and prevalence of left ventricular diastolic dysfunction (LVDD) ($p = 0.001$), as detailed in Table 1.

Among the 852 participants in the development dataset, 32.9% (280/852) were diagnosed with CVC, and the median age was 60 years. Participants with CVC were generally older, had longer dialysis duration, and showed higher systolic blood pressure (SBP), AST, ALP, GGT, and FPG but lower diastolic blood pressure (DBP) and ALB levels compared to those without CVC. Moreover, the prevalence of diabetes, CHD, and hyperlipidemia, as well as the usage rates of antidiabetic and lipid-lowering medications, were higher in the CVC group (Table 2).

In the external validation dataset of 661 patients, 49.3% (326/661) were identified with CVC, with a median age of 63 years. Detailed characteristics are provided in Supplementary Table S1. Differences between the development and external validation datasets are summarized in Supplementary Table S2. Some variables were observed to have significant differences ($p < 0.05$) between the two datasets, such as age, BMI, SBP, smoking history, dialysis duration, diabetes, CHD, stroke, Hb, Ca × P, ALP, GGT, FPG, UA, TC, HDL-C, LDL-C, Apo-B, and iPTH.

Independent risk factors

Based on data from four centers, we investigated the factors independently contributing to CVC. Through univariate regression analysis, 20 potential risk factors of CVC were identified. Variables with $p < 0.05$ included age, DBP, dialysis modality (hemodialysis), dialysis duration, as well as histories of diabetes, hypertension, CHD, hyperlipidemia, and stroke. Additionally, the use of antidiabetic medications and lipid-lowering agents was significant ($p < 0.05$), along with factors including Ca × P, ALP, GGT, FPG, UA, TC, LDL-C, Apo-A1, and iPTH (Table 3). Finally, multivariate logistic regression analysis identified 7 (70.83%) independent risk factors for CVC, as shown in Table 3. These included age (OR = 1.058, 95% CI 1.049–1.068, $p < 0.001$), dialysis duration (OR = 1.008, 95% CI 1.006–1.010, $p < 0.001$), ALP (OR = 1.0013, 95% CI 1.0002–1.0025, $p = 0.020$), TC (OR = 1.225, 95% CI 1.004–1.496, $p = 0.046$), LDL-C (OR = 0.752, 95% CI 0.579–0.978, $p = 0.033$),

Table 1. Echocardiographic characteristics in dialysis patients with and without CVC.

Echocardiography variables	Without CVC ($n = 1{,}358$)	With CVC ($n = 782$)	Total ($n = 2{,}140$)	p-value
IVST, mm	10.8 (2.1)	11.5 (2.0)	11.1 (2.1)	<0.001
LVEDD, mm	51.1 (7.0)	51.2 (6.9)	51.1 (7.0)	0.782
LVPW, mm	10.3 (1.9)	10.7 (1.7)	10.5 (1.8)	<0.001
LVM, g	194.3 (156.9 – 249.3)	213.9 (174.7 – 263.6)	205.0 (158.8 – 255.5)	<0.001
LVMI, g/m^2	118.0 (97.2 – 145.3)	128.6 (106.6 – 156.1)	121.7 (99.9 – 149.6)	<0.001
LVEF, %	64.0 (59.0 – 68.0)	63.0 (57.0 – 69.0)	63.0 (58.0 – 69.0)	0.010
LVDD, n (%)	1005 (74.0%)	630 (80.6%)	1635 (76.4%)	0.001

CVC, cardiac valve calcification; IVST, inter ventricular septum thickness; LVEDD, left ventricular end-diastole diameter; LVPW, left ventricular posterior wall thickness; LVM, left ventricular mass; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LVDD, left ventricle diastolic dysfunction.

Table 2. Characteristics of participants in the development dataset.

Characteristic	Total (n = 852)	CVC (n = 279)	Non-CVC (n = 573)	p-value	SMD
Age, years	52.0 (41.0 – 63.0)	60.0 (51.0 – 69.0)	48.5 (39.0 – 58.0)	<0.001	−0.800
Sex, n (%)				0.977	0.001
Male	487 (57.2%)	160 (57.3%)	328 (57.2%)		
Female	365 (42.8%)	119 (42.7%)	245 (42.8%)		
BMI, kg/m^2	22.7 (3.7)	22.9 (3.6)	22.6 (3.8)	0.203	−0.093
Systolic BP, mm Hg	149.7 (25.9)	152.2 (26.7)	148.4 (25.4)	0.045	−0.147
Diastolic BP, mm Hg	90.6 (15.6)	88.2 (14.6)	91.7 (15.9)	0.002	0.230
Heart rate, times/minute	81.2 (12.9)	82.1 (13.9)	80.8 (12.3)	0.172	−0.100
Smoking history, n (%)	104 (12.2%)	35 (12.5%)	69 (12.0%)	0.833	−0.013
Dialysis modality, n (%)				0.063	−0.131
Hemodialysis	605 (71.0%)	210 (75.3%)	396 (69.1%)		
Peritoneal dialysis	247 (29.0%)	69 (24.7%)	177 (30.9%)		
Dialysis duration, months	40.2 (49.9)	50.8 (56.5)	35.0 (45.5)	<0.001	−0.321
Diabetes, n (%)	205 (24.1%)	106 (38.0%)	99 (17.3%)	<0.001	−0.493
Hypertension, n (%)	732 (85.9%)	248 (88.9%)	484 (84.5%)	0.082	−0.129
Coronary heart disease, n (%)	33 (3.9%)	17 (6.1%)	16 (3.0%)	0.029	−0.170
Hyperlipidemia, n (%)	85 (10.0%)	42 (15.1%)	43 (7.5%)	<0.001	−0.251
Stroke, n (%)	78 (9.1%)	32 (11.5%)	46 (8.0%)	0.102	−0.117
Medication history, n (%)					
Activated vitamin D and its analogues	421 (49.4%)	129 (46.2%)	291 (50.8%)	0.213	0.089
Calcium supplements	158 (18.5%)	50 (17.9%)	107 (18.7%)	0.790	0.013
Non-calcium-containing phosphate binders	341 (40.0%)	99 (35.5%)	242 (42.2%)	0.059	0.131
Antidiabetics	134 (15.7%)	73 (26.2%)	60 (10.5%)	<0.001	−0.447
Lipid-lowering drugs	89 (10.4%)	43 (15.4%)	46 (8.0%)	<0.001	−0.240
Laboratory results					
WBC, *10^9/L	6.1 (4.9 – 7.5)	6.1 (5.2 – 7.6)	6.1 (4.8 – 7.4)	0.549	0.021
Hemoglobin, g/L	97.1 (21.2)	97.1 (21.2)	97.1 (21.2)	0.986	−0.001
Ca × P, mg^2/dL^2	52.1 (17.8)	51.5 (16.4)	52.5 (18.4)	0.437	0.057
Bicarbonate, mmol/L	23.4 (4.2)	23.3 (3.5)	23.5 (4.4)	0.437	0.057
Albumin, g/L	33.7 (5.2)	32.9 (4.9)	34.1 (5.4)	0.001	0.236
ALT, U/L	11.3 (7.3 – 17.3)	11.6 (7.4 – 16.6)	11.2 (7.2 – 17.8)	0.925	−0.044
AST, U/L	16.1 (12.1 – 21.2)	16.6 (12.7 – 22.1)	15.9 (11.6 – 20.7)	0.036	−0.139
ALP, U/L	85.0 (67.0 – 113.0)	93.0 (73.0 – 124.0)	82.0 (65.0 – 107.0)	<0.001	−0.272
GGT, U/L	20.4 (13.9 – 34.5)	23.1 (14.8 – 39.5)	19.1 (13.7 – 31.5)	<0.001	−0.219
FPG, mmol/L	5.4 (4.4 – 7.2)	5.7 (4.6 – 8.3)	5.3 (4.3 – 6.8)	<0.001	−0.415
Uric acid, μmol/L	403.5 (133.2)	392.8 (127.3)	408.7 (135.8)	0.103	0.119
Triglycerides, mmol/L	1.4 (1.0 – 1.9)	1.4 (1.0 – 1.9)	1.3 (1.0 – 2.0)	0.695	0.071
Total cholesterol, mmol/L	4.1 (1.3)	4.0 (1.2)	4.1 (1.3)	0.312	0.074
HDL cholesterol, mmol/L	1.0 (0.3)	1.0 (0.3)	1.0 (0.3)	0.977	0.002
LDL cholesterol, mmol/L	2.4 (0.9)	2.4 (0.9)	2.4 (1.0)	0.643	0.034
Lp(a), mg/L	199.7 (101.0 – 386.0)	221.2 (104.2 – 461.5)	192.4 (96.6 – 360.4)	0.053	1.139
Apo-A1, g/L	1.0 (0.3)	1.0 (0.3)	1.0 (0.3)	0.312	0.074
Apo-B, g/L	0.8 (0.6 – 1.0)	0.8 (0.6 – 1.0)	0.8 (0.6 – 1.0)	0.940	−0.005
iPTH, pg/mL	258.1 (137.3 – 468.3)	266.5 (127.2 – 539.7)	245.9 (141.1 – 437.0)	0.131	−0.323

BMI, body mass index; BP, blood pressure; WBC, white blood cell count; Ca × P, calcium-phosphorus product; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; iPTH, intact parathyroid hormone.

Apo-A1 (OR = 0.484, 95% CI 0.314–0.747, p = 0.001), and iPTH (OR = 1.0004, 95% CI 1.0002–1.0007, p = 0.002).

Development and validation of predictive models

LASSO regression analysis identified 12 predictive variables associated with the risk of CVC in dialysis patients, as depicted in Figure 2a and b. These variables include age, dialysis duration, diabetes, CHD, hyperlipidemia, stroke, non − calcium − containing phosphate binders, antidiabetics, ALP, FPG, Apo-A1, and iPTH. The 12 predictive variables identified through LASSO regression were further analyzed using univariate and multivariate logistic regression. Ultimately, five key features were determined: age, dialysis duration, ALP, Apo-A1, and iPTH (Table 4). These variables were then used as predictors to construct a risk prediction model for the presence of CVC.

To ensure optimal performance for each machine model, further adjustments were made to its hyperparameters. The values of hyperparameters for each algorithm are listed in Supplementary Table S3. In the training dataset, models' predictive accuracy was evaluated using 10-fold cross-validation. As illustrated in Figure 3, CatBoost provided the top clinical predictive accuracy, achieving an AUROC of 0.719 (95% CI: 0.667–0.765), and the logistic regression model followed with an AUROC of 0.710 (95% CI 0.619–0.755).

Based on this, the stability and generalizability of the six predictive models were systematically validated on both internal and external validation datasets. The logistic regression model demonstrated the highest performance, with an AUROC of 0.806 (95% CI 0.750–0.863) in the internal validation dataset and 0.757 (95% CI 0.720–0.793) in the external validation dataset, outperforming all other models (Figure 4). The model performance in terms of AUPRC was in line with

Table 3. Univariate and multivariate logistic regression analyses of risk factors for cardiac valve calcification.

	Univariate logistic regression analyses		Multivariate logistic regression analyses	
Variables	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.059 (1.051 – 1.067)	<0.001	1.058 (1.049 – 1.068)	<0.001
Sex (Female)	0.959 (0.802 – 1.146)	0.644		
BMI	1.019 (0.996 – 1.042)	0.105		
Systolic BP	1.000 (0.997 – 1.004)	0.900		
Diastolic BP	0.979 (0.973 – 0.985)	<0.001	1.004 (0.997 – 1.012)	0.275
Heart rate	0.996 (0.989 – 1.003)	0.280		
Smoking history	1.004 (0.775 – 1.301)	0.977		
Dialysis modality (Hemodialysis)	1.819 (1.432 – 2.309)	<0.001	1.026 (0.780 – 1.348)	0.856
Dialysis duration	1.007 (1.006 – 1.009)	<0.001	1.008 (1.006 – 1.010)	<0.001
Diabetes	2.040 (1.692 – 2.460)	<0.001	1.287 (0.922 – 1.799)	0.139
Hypertension	1.507 (1.143 – 1.985)	0.004		
Coronary heart disease	2.542 (1.971 – 3.279)	<0.001		
Hyperlipidemia	1.830 (1.468 – 2.282)	<0.001		
Stroke	1.998 (1.571 – 2.541)	<0.001		
Activated vitamin D and its analogues	0.942 (0.790 – 1.124)	0.507		
Calcium supplements	0.877 (0.719 – 1.069)	0.193		
Non-calcium-containing phosphate binders	1.069 (0.896 – 1.276)	0.458		
Antidiabetics	2.099 (1.716 – 2.568)	<0.001	1.271 (0.903 – 1.789)	0.169
Lipid-lowering drugs	1.930 (1.557 – 2.393)	<0.001	2.167 (0.926 – 5.072)	0.075
WBC	1.032 (0.999 – 1.067)	0.056		
Hemoglobin	1.002 (0.998 – 1.006)	0.228		
Ca×P	0.994 (0.989 – 0.998)	0.009	1.001 (0.995 – 1.007)	0.650
Bicarbonate	0.989 (0.969 – 1.009)	0.287		
Albumin	0.991 (0.975 – 1.006)	0.243		
ALT	1.000 (0.996 – 1.004)	0.972		
AST	1.002 (0.999 – 1.005)	0.290		
ALP	1.002 (1.001 – 1.003)	<0.001	1.0013 (1.0002 – 1.0025)[a]	0.020
GGT	1.003 (1.001 – 1.005)	0.003	1.000 (0.997 – 1.002)	0.774
FPG	1.101 (1.068 – 1.135)	<0.001	1.016 (0.978 – 1.055)	0.423
Uric acid	0.999 (0.998 – 0.999)	<0.001	1.000 (0.999 – 1.001)	0.563
Triglycerides	0.995 (0.935 – 1.059)	0.875		
Total cholesterol	0.868 (0.802 – 0.938)	<0.001	1.225 (1.004 – 1.496)	0.046
HDL cholesterol	0.784 (0.591 – 1.040)	0.092		
LDL cholesterol	0.794 (0.713 – 0.884)	<0.001	0.752 (0.579 – 0.978)	0.033
Lp(a)	0.794 (0.713 – 0.885)	0.190		
Apo-A1	0.426 (0.301 – 0.605)	<0.001	0.484 (0.314 – 0.747)	0.001
Apo-B	0.729 (0.524 – 1.013)	0.060		
iPTH	1.0004 (1.0002 – 1.0006)[a]	<0.001	1.0004 (1.0002 – 1.0007)[a]	0.002

[a]Values are presented to four decimal places to accurately reflect differences in *p*-values that remain undetectable when rounded to three decimal places.

BMI, body mass index; BP, blood pressure; WBC, white blood cell count; Ca×P, calcium-phosphorus product; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; iPTH, intact parathyroid hormone.

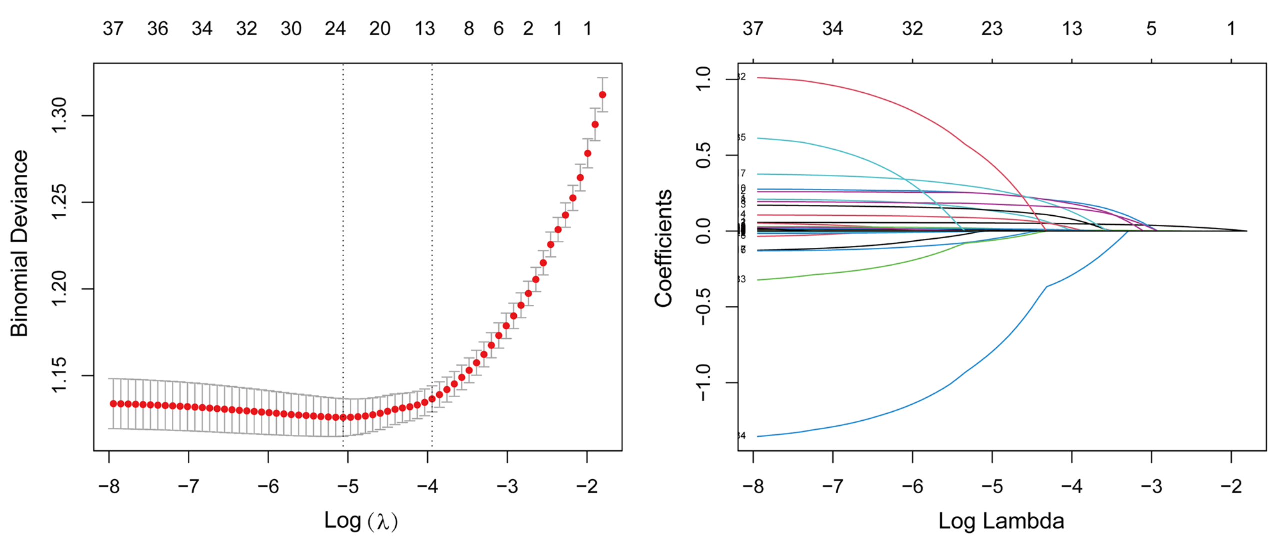

Figure 2. Screening of characteristic predictors using the LASSO regression analysis. (a) The optimal lambda parameter in the LASSO model was selected using 10-fold cross-validation, depicted as a curve showing the relationship between binomial deviance and log(λ). Vertical dotted lines, clearly marked on the plot, represent the lambda values chosen based on the minimum deviance criteria and the 1 SE rule. This approach helps in minimizing overfitting while maintaining model accuracy. (b) This plot illustrates the coefficient profiles of the variables, each represented by a uniquely colored line, against the log(λ) sequence. As lambda increases, coefficients of less relevant predictors shrink toward zero, indicating a process of feature selection where only the most significant variables are retained in the final model. LASSO: least absolute shrinkage and selection operator; SE: standard error.

Table 4. Cardiac valve calcification prediction model in dialysis patients based on logistic regression.

Variable	OR	95% CI	*p*-value
Age	1.056	1.047–1.065	<0.001
Dialysis duration	1.008	1.006–1.010	<0.001
ALP	1.001	1.0002–1.0023[a]	0.019
Apo-A1	0.560	0.383–0.820	0.003
iPTH	1.0004[a]	1.0002–1.0007[a]	0.001

[a]Values are presented to four decimal places to accurately reflect differences in *p*-values that remain undetectable when rounded to three decimal places.
OR, odds ratio; CI, confidence interval; ALP, alkaline phosphatase; Apo-A1, apolipoprotein A1; iPTH, intact parathyroid hormone.

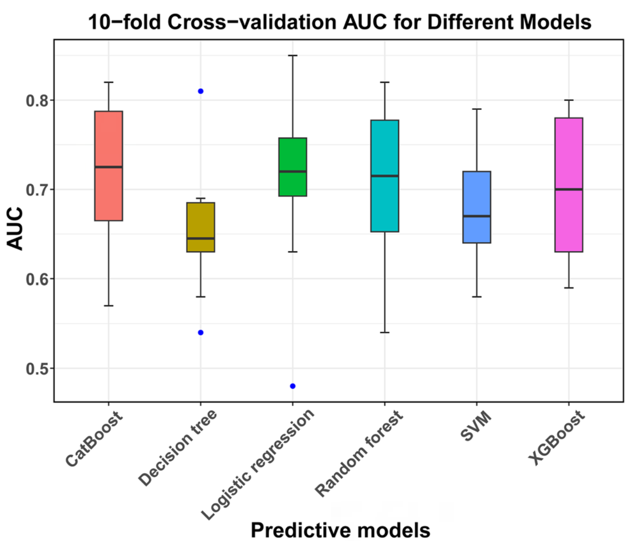

Figure 3. Clinical prediction accuracy of six machine learning models using 10-fold cross-validation in the training dataset. CatBoost: category boosting; SVM: support vector machine; XGBoost: extreme gradient boosting.

the AUROC (Supplementary Figure S1). In addition, separate ROC analyses for PD and HD patients confirmed the logistic regression model's robustness across patient subgroups (Supplementary Figures S2 and S3). Specifically, for PD patients, the AUROC in internal validation was 0.750 (95% CI 0.630–0.870), and 0.816 (95% CI 0.731–0.900) in external validation (Supplementary Figure S2). For HD patients, the AUROC for the logistic regression model was 0.723 (95% CI 0.645–0.801) in internal validation and 0.712 (95% CI 0.669–0.755) in external validation (Supplementary Figure S3). These results demonstrate consistent predictive performance across dialysis modalities, whether peritoneal or hemodialysis.

As indicated in Table 5, the logistic regression model showed consistent and robust results in terms of accuracy, sensitivity, specificity, precision, and *F*-1 score across both internal and external validation datasets. The model calibration results for both validation sets showed that the calibration curve of the logistic regression model was closer to the ideal line, with a Brier score of 0.170 in the internal validation dataset and 0.221 in the external validation dataset, indicating superior calibration compared to other models (Figure 5). Additionally, decision curve analysis indicates that, based on the combined predictive performance of the internal and external validation sets, clinical predictions derived from logistic regression achieve the highest overall net benefit, and offer benefits for patients across most risk threshold levels (Figure 6).

Considering that the logistic regression model showed superior clinical predictive value across both internal and external validation datasets, it was chosen as the optimal model and depicted using a dynamic nomogram (Figure 7). For example, when a dialysis patient is aged 61 years, with a

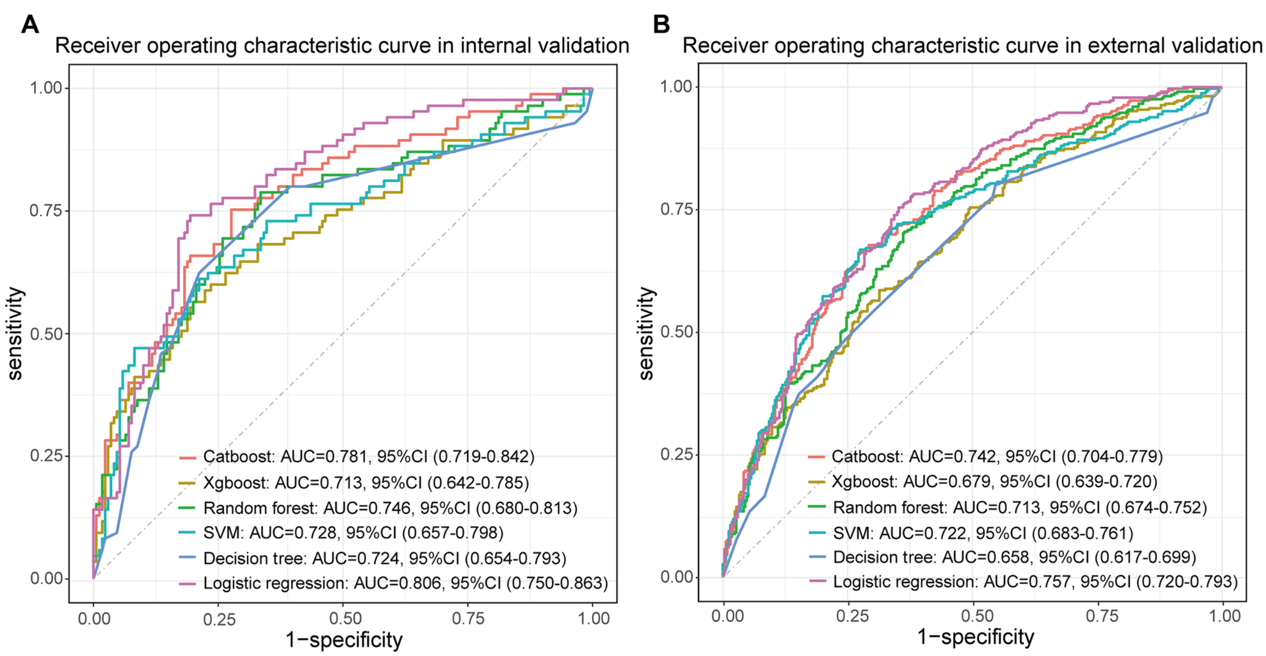

Figure 4. Receiver operating characteristic curve analysis for predicting the risk of CVC in dialysis patients in (A) internal validation dataset and (B) external validation dataset. CAC, cardiac valve calcification; CatBoost, category boosting; XGboost, extreme gradient boosting; SVM, support vector machine; AUC, area under the curve.

Table 5. Comparison of performance parameters for 6 machine learning prediction models in internal and external validation datasets.

Predictive models	Accuracy	Sensitivity	Specificity	Precision	F_{-1} score
Internal validation					
CatBoost	0.757	0.659	0.806	0.629	0.643
XGBoost	0.675	0.682	0.671	0.509	0.583
SVM	0.729	0.612	0.788	0.591	0.601
Random forest	0.718	0.765	0.694	0.556	0.644
Decision tree	0.733	0.624	0.788	0.596	0.609
Logistic regression	0.784	0.741	0.806	0.656	0.696
External validation					
CatBoost	0.688	0.644	0.731	0.700	0.671
XGBoost	0.616	0.718	0.516	0.591	0.648
SVM	0.690	0.629	0.749	0.709	0.667
Random forest	0.664	0.752	0.579	0.635	0.688
Decision tree	0.622	0.546	0.696	0.636	0.587
Logistic regression	0.682	0.647	0.716	0.690	0.668

CatBoost, category boosting; XGBoost, extreme gradient boosting; SVM, support vector machine.

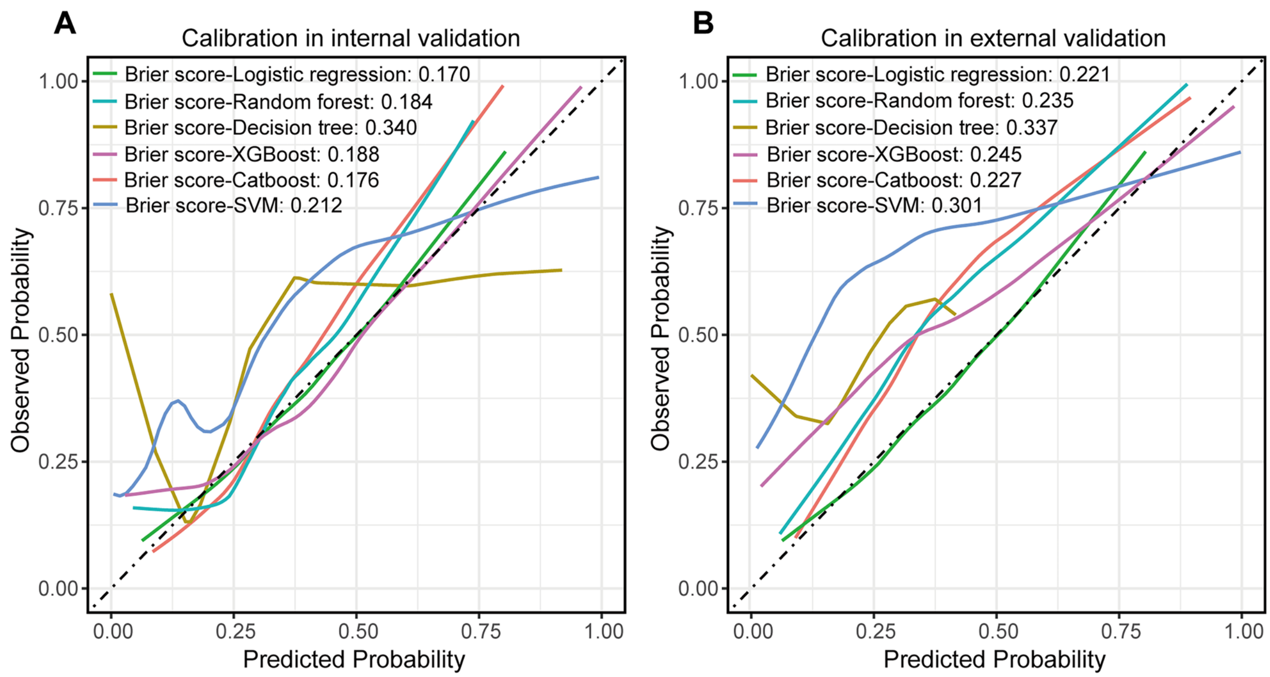

Figure 5. Calibration curve analysis for predicting the risk of CVC in dialysis patients in (a) internal validation dataset and (b) external validation dataset. The x-axis represents the predicted probability of CVC, and the y-axis shows the observed probability based on actual diagnoses. The diagonal dotted line indicates perfect prediction, where predicted probabilities match observed outcomes. The solid lines reflect each model's performance, with a closer fit to the dotted line indicating better calibration. Lower brier scores reflect better calibration for each model. CAC, cardiac valve calcification; CatBoost, category boosting; XGBoost, extreme gradient boosting; SVM, support vector machine.

dialysis duration of 128 months, ALP of 497 U/L, Apo-A1 of 1 g/L, and iPTH of 2161 pg/mL, we can estimate their risk of having CVC to be 78.5% (Figure 7). Furthermore, we developed an online tool to simplify the application of CVC risk prediction models [12].

The predicted risk probabilities for participants with CVC were computed in the two validation datasets, with the histograms shown in Figure 8. Using the Youden index to distinguish between high-risk and non-high-risk patients, we divided patients into these two groups based on a proportion of 62%. According to the distribution of predicted probabilities, patients with values below 31% were classified as low risk. Our results showed that the prevalence of CVC in the high-, intermediate-, and low-risk groups was 65.6%, 20.2%, and 7.5%, respectively. When these defined cutoffs were applied to the external validation dataset, the prevalence of CVC in the high-, intermediate-, and low-risk groups was 68.9%, 43.2%, and 14.2%, respectively. Risk stratification exhibited excellent differentiation in both the internal and external validation groups (all p-values < 0.001). These findings indicate that the selected risk cutoffs successfully differentiate dialysis patients into varying levels of severity based on their risk of CVC.

Sensitivity analysis

Apo-A1 is the primary protein component of HDL, and the two are strongly correlated (Pearson's correlation coefficient,

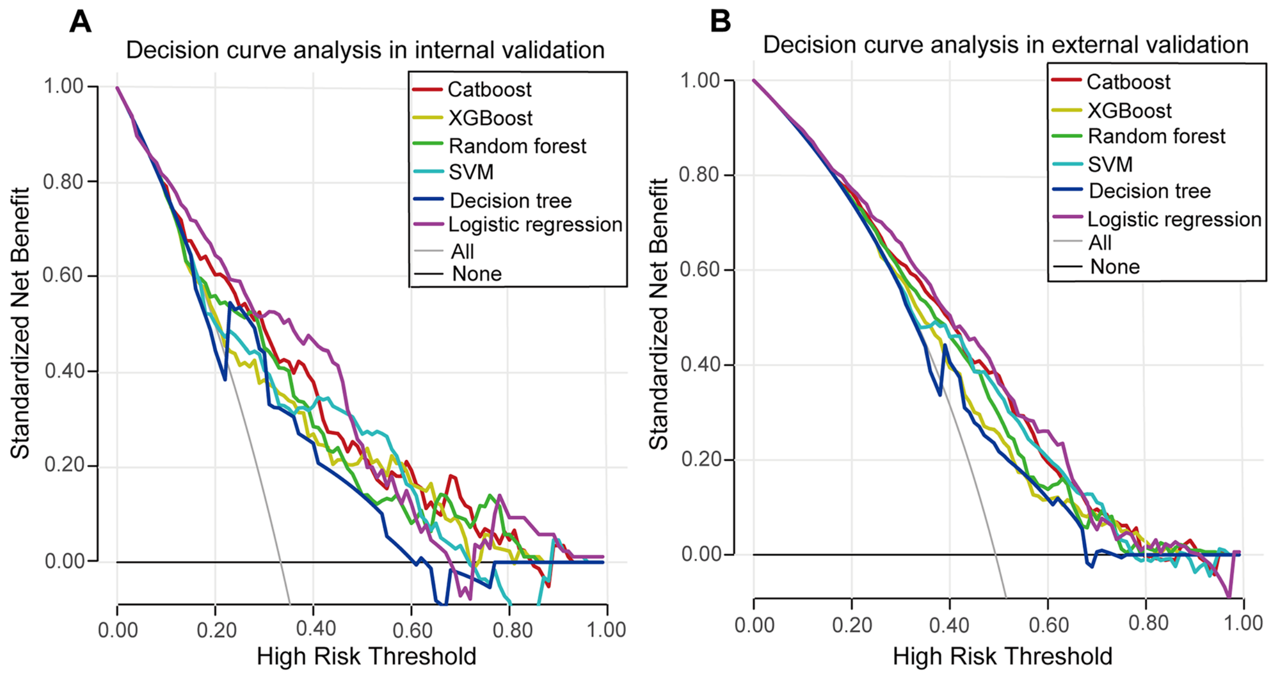

Figure 6. Decision curve analysis for predicting the risk of CVC in dialysis patients in (a) internal validation dataset and (b) external validation dataset. The black straight line indicates the net benefit when no participants are considered at risk for CVC, and the light gray curve shows the net benefit when all participants are assumed to be at risk for CVC. The area between the model's colored curves and the light gray curve indicates the clinical utility of the model. Higher net benefit areas represent better clinical usefulness of the model. CAC, cardiac valve calcification; CatBoost, category boosting; XGBoost, extreme gradient boosting; SVM, support vector machine.

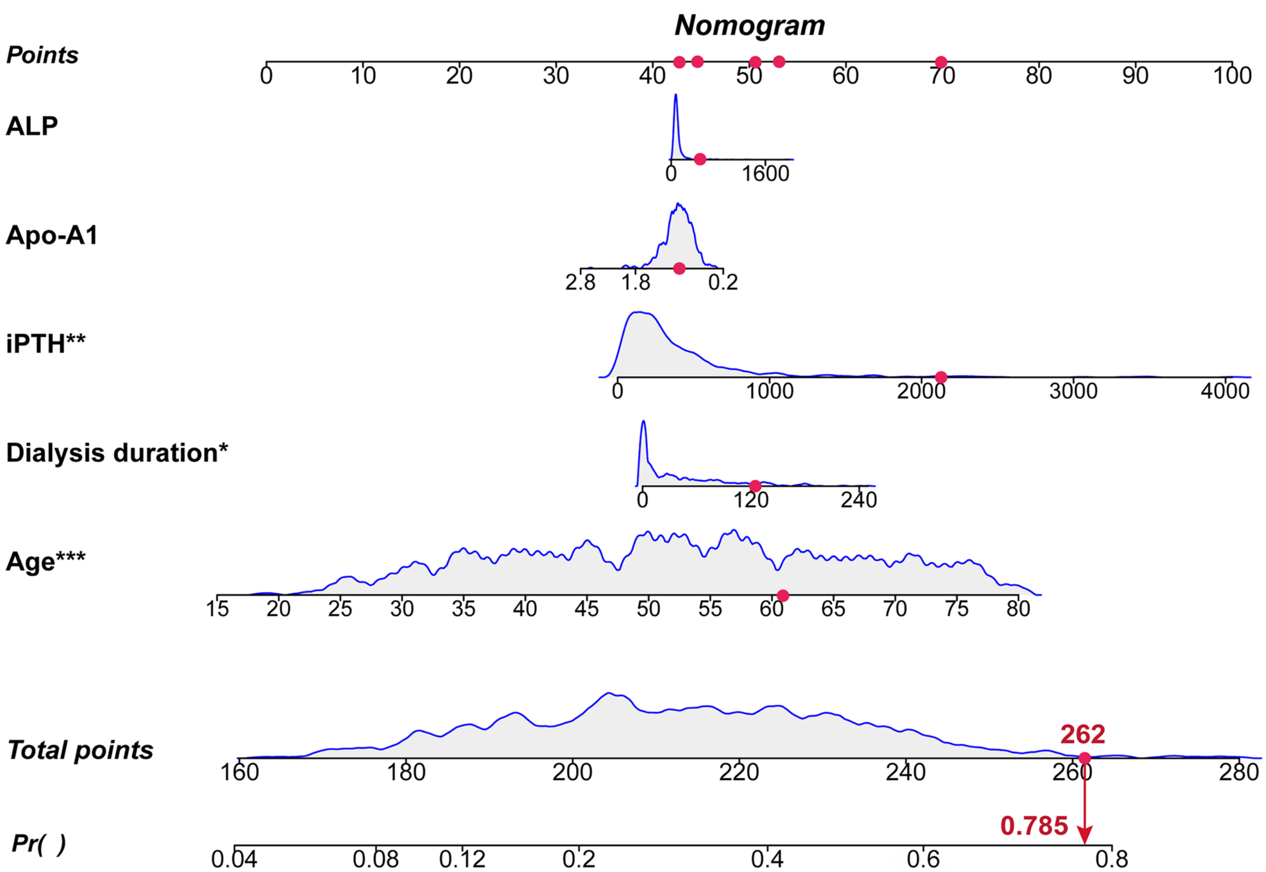

Figure 7. Nomogram for predicting the risk of CVC in dialysis patients. The nomogram generates a score for each variable based on its corresponding scale. The scores for each variable are summed to obtain the total score, which is then used to determine the predicted probability of CVC. The vertical line drawn from the total points row to the probability scale shows the estimated risk of CVC for an individual patient. Higher total scores correspond to a higher risk of CVC. CAC, cardiac valve calcification; ALP, alkaline phosphatase; Apo-A1, apolipoprotein A1; iPTH, intact parathyroid hormone.

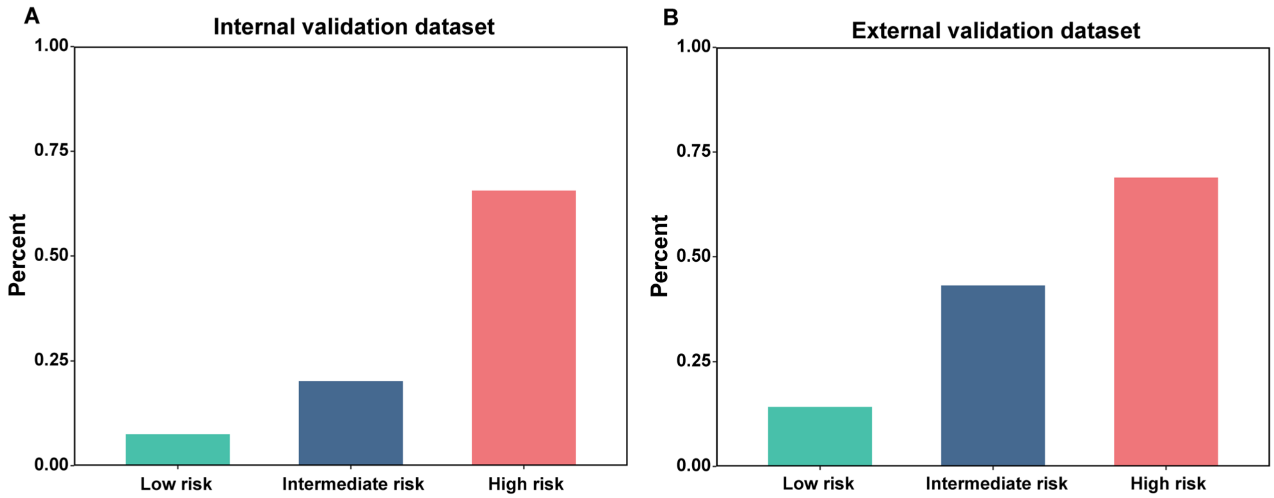

Figure 8. Risk stratification plot generated by the cardiac valve calcification prediction model in dialysis patients in (a) internal validation dataset and (b) external validation dataset. The risk categories are divided into low risk, intermediate risk, and high risk based on predicted probabilities. Different levels of risk are represented by colored bars, with the height of each bar corresponding to the risk proportion, which is calculated by the prevalence rate in each risk level.

$r = 0.708$, $p < 0.001$ in our dataset). Since HDL is more widely used in clinical practice, we evaluated whether substituting HDL-C for Apo-A1 would achieve similar predictive performance. In both internal and external validation datasets, the modified model showed performance comparable to the original (Supplementary Figure S4 and Figure 4). In the external dataset, the best-performing model had an AUC of 0.757 with Apo-A1 and 0.755 with HDL-C. This minimal change supports HDL-C as a practical alternative where routine apolipoprotein measurements are unavailable, further reinforcing the robustness and clinical applicability of our predictive model. Apo-A1 was identified as a predictor in the LASSO model, likely due to its significant impact on enhancing the predictive dimension of the dependent variable. Apo-A1 may offer stronger predictive value in settings where apolipoprotein measurement is available.

Discussion

In this study, we identified age, dialysis duration, ALP, TC, LDL-C, Apo-A1, and iPTH as independent risk factors for CVC in dialysis patients. We developed six machine learning models, with the logistic regression model demonstrating the highest clinical predictive value. Utilizing only five variables (age, dialysis duration, ALP, Apo-A1, and iPTH), this model achieved AUROCs of 0.806 (95% CI 0.750–0.863) in the internal validation dataset and 0.757 (95% CI 0.720–0.793) in the external validation dataset. Consequently, we created a user-friendly model for predicting CVC in dialysis patients, along with a web-based calculator to enhance clinical applicability.

Cardiovascular disease is the primary cause of death among dialysis patients, accounting for more than half of all deaths in this population [13,14]. In dialysis patients, CVC predominantly occurs in the mitral and aortic valves, leading to structural heart changes and playing a pivotal role in the progression of cardiovascular disease. The incidence of CVC is higher in dialysis patients, and its progression rate is 10 times faster than in the general population [15]. A meta-analysis involving 3,376 dialysis patients revealed a CVC prevalence ranging from 23.5% to 57.6%, averaging 51.5% in HD patients and 26.9% in PD patients [16]. In our study, the incidence of CVC was 36.5%, aligning with these findings [16,17]. A recent meta-analysis found that CVC in dialysis patients leads to a 1.6-fold increase in all-cause mortality and a 2.4-fold increase in cardiovascular mortality [16]. Furthermore, CVC can directly precipitate severe cardiovascular events, including valve stenosis or insufficiency, arrhythmias, myocardial ischemia or infarction, and congestive heart failure [2]. Despite its significance, CVC remains underappreciated, highlighting the necessity for early detection and intervention to improve cardiovascular outcomes in dialysis patients.

Traditional CVC risk factors encompass advanced age, smoking history, obesity, diabetes, hypertension, and dyslipidemia [18,19]. Consistent with previous studies, our findings confirmed that age is an independent risk factor for CVC among dialysis patients. Research involving 144 American hemodialysis patients and 434 Chinese hemodialysis patients showed that individuals with CVC were significantly older than those without [20,21]. Aging is considered a strong predictor of CVC in dialysis patients [22]. Furthermore, lipid-related parameters, including TC, LDL-C, and Apo-A1, were independently associated with CVC risk in our study. A 27-year follow-up of the Framingham Offspring Study (FOS) demonstrated a 1.74-fold increase in aortic valve calcification risk for each standard deviation rise in TC levels and a 23% reduction in risk per standard deviation increase in HDL-C [23]. The role of elevated LDL-C as a risk factor for calcific aortic valve disease (CAVD) remains debated [24]. While substantial evidence links high LDL-C levels to CAVD [25,26], randomized clinical trials, including the SALTIRE, SEAS, and ASTRONOMER studies, have shown that aggressive LDL-C-lowering therapies do not attenuate CAVD progression [27–30]. In our study, we found an inverse association between LDL-C and CVC. This finding could be explained by the malnutrition-inflammation complex syndrome (MICS) common in dialysis patients, which alters lipid metabolism. Specifically, low LDL-C levels might reflect a state of malnutrition or chronic inflammation, both of which are known to exacerbate cardiovascular outcomes in dialysis patients [31]. Wu et al. analyzed 3,565 peritoneal dialysis patients and found that malnutrition (serum albumin <36.0 g/L) and low LDL-C levels were significantly associated with increased cardiovascular mortality risk [32]. The average serum albumin level in our study was 34.8 g/L, suggesting that the inverse relationship between LDL-C and CVC risk in this study may be related to malnutrition. Additionally, dialysis patients are often in a state of chronic inflammation. Yan et al. found that patients with a substantial inflammatory burden show an association between low lipid levels and increased cardiac mortality risk [33]. Apo-A1, the principal apolipoprotein of HDL, possesses various protective functions, including anti-inflammatory and antioxidant effects, as well as facilitating cholesterol efflux [34]. Numerous research findings have demonstrated a negative correlation between Apo-A1 and the risk of fatal myocardial infarction, major adverse cardiovascular events, cardiac mortality, and cancer-related deaths [33,35–37]. However, recent analyses encompassing 23 studies with 152,854 participants found that the associations between Apo-A1 and all-cause mortality were not obvious [38]. Our study is the first to reveal an independent inverse correlation of Apo-A1 with CVC risk in dialysis patients, suggesting a protective role of Apo-A1 against CVC in this population. Furthermore, our study confirmed that ALP served as an independent predictor for CVC, aligning with findings from earlier research. ALP is believed to be crucial in the processes of atherosclerotic lesion calcification or demineralization, as well as in the calcification of cardiac valves [39,40]. In addition to traditional risk factors, studies have found that a series of consequences resulting from the progressive decline in kidney function, particularly elevated PTH levels, increased Ca $\times$ P, and excessive 1,25-dihydroxyvitamin D, play a significant role in the progression of CVC [41]. Our study also demonstrated that high iPTH levels and longer dialysis duration were independent risk factors for CVC in dialysis patients.

Early detection and prevention of CVC are essential for improving cardiovascular outcomes in dialysis patients. Echocardiography is recommended for detecting the presence of CVC [42]. However, due to limited medical resources, comprehensive screening of dialysis patients *via* echocardiography is often impractical. Establishing a risk prediction model offers an effective alternative for screening CVC. Such a model allows physicians to identify high-risk patients for further diagnostics and interventions, optimize resource allocation, and enhance patient outcomes. While numerous studies have investigated the risk factors for CVC in dialysis patients [43], there are currently no published studies on risk prediction models for CVC. As medical technology advances, the volume of clinical data continues to increase [44]. Although translating this data into effective clinical decision support tools poses challenges, machine learning algorithms present new opportunities due to their capacity to analyze large and complex datasets, performing tasks that are challenging for human analysis [45]. Machine learning can enhance risk stratification by effectively processing and analyzing extensive clinical data. Nomograms are visual tools that compute personalized probabilities of clinical events by combining various outcome and predictor factors. They integrate biological data with clinical prediction models, allowing for personalized risk assessment and decision-making in clinical practice [46,47]. In this study, we selected clinical indicators including age, dialysis duration, ALP, Apo-A1, and iPTH through LASSO and logistic regression analyses. Using these indicators, we constructed a risk prediction model for CVC employing machine learning algorithms. The logistic regression model, which demonstrated superior predictive performance, was selected as the final model and represented with a dynamic nomogram. The decision curve analysis showed that the clinical predictions from the logistic regression model provided the highest net benefit across most risk thresholds, maximizing clinical benefit for patients. Therefore, we calculated the predicted risk probabilities using logistic regression and subsequently applied the Youden index to construct thresholds that distinguish high-risk from non-high-risk patients, ultimately developing a risk stratification approach. This approach effectively categorizes patients into different risk groups, assisting clinicians in early identification of high-risk patients for CVC and thus optimizing resource allocation. A web-based dynamic calculator was also developed to facilitate the practical application of this prediction model, enhancing clinical decision-making and patient management.

This study holds significant clinical implications. To our knowledge, this is the first model utilizing machine learning to predict the risk of CVC in dialysis patients. Cardiovascular mortality is the leading cause of death in dialysis patients, and CVC is closely linked to cardiovascular outcomes. Early identification of high-risk CVC patients through this model would enable physicians to implement timely interventions, potentially improving cardiovascular outcomes in dialysis patients. The indicators required for this model are commonly available in clinical settings and can be easily obtained across various levels of healthcare institutions, making the model highly feasible and broadly applicable for screening CVC. The model not only exhibits high predictive value but has also undergone internal and external validation using multicenter data to ensure its generalizability. Additionally, to enhance clinical applicability, we developed a web-based calculator with an intuitive interface and clear instructions, making it user-friendly. The calculator automatically generates results upon entering the required variables, requiring no additional training for clinicians, thus significantly improving workflow efficiency. By providing a clear risk stratification method, clinicians can easily categorize patients into low-, intermediate-, and high-risk groups, aiding in more accurate risk assessment and treatment decision-making in different clinical settings.

Several limitations should be noted. First, this study is retrospective, and the clinical data collection is not comprehensive, which may overlook potential predictive factors. For example, there was insufficient information on factors such as residual renal function, dialysis prescription, and Kt/V, which could impact the prediction of CVC in dialysis patients. Second, as the study exclusively included Chinese dialysis patients, the applicability of the findings to other ethnic groups requires further validation. Third, since no data on the intraobserver and interobserver variability of echocardiographic parameters were available, their consistency could not be assessed. Finally, lifestyle factors, such as diet and exercise, which may significantly influence the occurrence of CVC, were not considered in this study.

Conclusion

In summary, this study identified seven independent risk factors associated with CVC in the Chinese dialysis population, including age, dialysis duration, ALP, TC, LDL-C, Apo-A1, and iPTH. Furthermore, we developed a risk prediction model utilizing five characteristic variables to identify individuals at high risk for CVC. This model demonstrated high predictive accuracy, underscoring its significance for preventing and improving cardiovascular outcomes in dialysis patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data supporting this article will be available upon reasonable request to the corresponding author.

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