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Title page

Title

# Development and Validation of a Nomogram for Predicting Recurrence in Patients with AF Who Underwent Ablation within one year

Short title: Nomogram for predicting recurrence of AF radiofrequency ablation.

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# Abstract

**Background：** With the improvement of radiofrequency catheter ablation technology, an increasing number of patients with atrial fibrillation (AF) choose it as the treatment option. However, the individual recurrence rate after ablation is difficult to accurately predict.

**Objective：** This study aimed to develop and validate an effective prognostic nomogram for predicting long-term recurrence of patients with AF who underwent ablation.

**Methods:** We conducted a retrospective single-center cohort study of 493 patients with AF from five wards in The First Affiliated Hospital of Soochow University from January 1, 2015 to December 31, 2019. Three quarters of patients(n=371) were randomly assigned to the training cohort, and the rest (n=122) were assigned to the validation cohort. Univariate and multivariate cox regression analysis was performed using R software version 3.6.2 to prognostic variables for recurrence and develop a nomogram. The C index, ROC, calibration curve, Greenwood-D'Agostino-Nam, and DCA were used for verification in the modeling cohort and the verification cohort respectively for validation.

**Results:** Multivariate cox regression analysis shown that 6 independent predictors were identified: age, female, AF duration, AF type, coronary artery disease, left atrial diameter. And these predictors were entered into the nomogram, which shown

favorable discrimination and calibration both in the training cohort and validation cohort.

**Conclusion:** The proposed nomogram can accurately predict recurrence of patients after AF ablation. Compared to the CHA2DS2-VASc score, clinicians can promote individual-oriented therapy and disease management by using this tool.

**Keyword：** Atrial fibrillation; Radiofrequency Catheter Ablation; Recurrence rates; Nomogram.

# Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia. A global epidemiological survey shown that the current estimated prevalence of AF is about between 1% and 4% in Australia, Europe and the USA, with lower prevalence evident in Asia (0.49%-1.9%).[1] Radiofrequency Catheter Ablation (RFCA) is the most effective treatment of AF, but the efficacy is uncertain and postoperative recurrence rate is about 30%-50%.[2] At present, there is no accurate prediction model to predict the recurrence rate of patients with AF who underwent RFCA. Although the clinician use CHA2DS2-VASc or CHA2DS2 scores to roughly predict the recurrence rate, and some studies have shown that the higher the two scores, the higher the probability of recurrence,[3, 4] multiple clinical studies have confirmed that the prediction results of these two scores are inaccurate. [5, 6]Therefore, this study aims to build and verify a reasonable and effective prediction model of AF recurrence. This study synthesizes global research on risk variables for AF recurrence and includes the following variables：age, gender, AF type, coronary artery disease(CAD), left atrial

diameter(LAD), AF duration, number of antiarrhythmic drugs failed before ablation, estimate glomerular filtration rate(eGFR), CHA2DS2-VASc score, CHA2DS2 score, hypertension, diabetes, body mass index(BMI), total cholesterol(TC), triglyceride(TG), serum globulin(S-GLB), ejection fraction(EF), neutrophil lymphocyte ratio(NLR). Finally, 6 independent predictors were identified and entered into the nomogram, which shown favorable discrimination and calibration both in the training cohort and validation cohort.

# Methods

**Patient population.** We conducted a retrospective single-center cohort study of 493 patients with AF from five wards in The First Affiliated Hospital of Soochow University from January 1, 2015 to December 31, 2019. The inclusion criteria were: Electrocardiogram confirmed atrial fibrillation; No serious complications occurred during the operation and sinus rhythm restored after the operation; Following the doctor's instructions and was followed up regularly; During the hospitalization, all enrolled patients or their guardians signed an informed consent form.

**Ablation protocol.** The 3D image acquired through electroanatomic mapping was integrated into the 3D image of the MDCT scan using the navigation system CARTO or ENSINT. After the electroanatomic reconstruction of the atrium, the ablation of left and right pulmonary veins was conducted.

The main ablation strategy for patients with paroxysmal AF was circumferential pulmonary vein isolation, and patients with atrial flutter underwent tricuspid isthmus ablation at the same time. In addition to the above ablation, linear ablation was

performed on the LA roof, bottom and tricuspid valve in patients with persistent AF, and performed on the superior vena cava if necessary.

**Data collection.** Collecting baseline data of patients from hospital documents retrospectively, which including age, gender, AF type, LA, CAD, AF duration, number of antiarrhythmic drugs failed before ablation, eGFR, CHA2DS2-VASc score, CHA2DS2 score, hypertension, diabetes, BMI, TC, TG, S-GLB, EF, NLR.

AF type was categorized as paroxysmal: lasting <1 week; persistent: lasting >1 week and <1 year or requiring pharmacological or electrical cardioversion to convert to sinus rhythm in <1 week; long-standing persistent: lasting >1 year or cannot be converted to sinus rhythm or relapse within 24 hours after conversion.

**Follow up.** All patients were treated with antiarrhythmic drugs during the first 3 months after ablation and were followed up for one year. During the follow-up, patients without any discomfort were asked to recorded their heart rhythm daily, provided ECG data weekly, and examined HOLTER every 3 months. Patients with discomfort such as palpitations and chest tightness immediately went to the hospital for ECG to capture the recurrence of AF.

Recurrence conditions were defined as the occurrence of AF, flutter, or tachycardia lasting more than 30 seconds off antiarrhythmic drugs after a 3-month blanking period. [7]

**Statistical analysis.** The statistical analyses were performed using R software version 3.6.2. Continuous data are presented as mean±SD and categorical data as

counts and percentages. The significant level was set at 0.05 and all tests were two sided.

For nomogram construction and validation, we randomly assigned three quarters of the patients (n=371) to the training cohort and one quarters (n=122) to the validation cohort. The t test and $\chi 2$ test were used to compare clinical characteristics and variables between the two cohorts. Univariate and Multivariate COX regression analysis was performed on 18 variables of training cohort to determine independent prognostic variables. The COX proportional hazards assumption was examined using Schoenfeld residual plots and multicollinearity was examined using variance inflation factor (VIF). Based on the independent prognostic variables, a nomogram predicting 1-year recurrence free probabilities was constructed. Nomogram validation consisted of three parts. Discrimination was evaluated using a concordance index (C-index) and receiver operating characteristic (ROC) curve. ROC curve was performed to calculate the optimal cutoff values that were determined by maximizing the Youden index (i.e. sensitivity + specificity-1). Calibration was evaluated using calibration curve and Greenwood-D'Agostino-Nam. And clinical validity was evaluated using DCA. In addition, to further examine the discrimination of the proposed nomogram, we categorized the patients of the training cohort into four cohorts by the quartiles of nomogram total points and then calculated each cohort's MST and plot each cohort's Kaplan-Meier curve. These curves were compared using log-rank test.

# Results

**Cohort characteristics：** A total of 493 patients were followed-up, including 228 patients with recurrence of AF. 371 patients were randomly assigned to the training cohort, including 172(46.36%) patients with recurrence. And 122 patients were assigned to the validation cohort, which included 56(45.90%) patients with recurrence. The patient characteristics were listed in Table 1. There were no significant differences among the following variables between two cohorts.

**Independent prognostic variables：** The results of Univariate cox regression were listed in Table 2. Female, old age, AF duration, Non-paroxysmal AF, CAD, HD, DM, and high CHA2DS2-VASc score/CHA2DS2 score were associated with AF recurrence.

When performing multivariate COX regression analysis, we excluded CHA2DS2-VASc and CHA2DS2 score because their VIF＞5 and cannot provide independent clinical information. The multivariate analysis shown that 6 variables were independent predictors of long-term freedom from AF ablation: age, LAD, gender(female), non-persistent AF, CAD, duration(≥5years). Repeat multivariate analysis using these 6 variables alone, which shown in the Table 3, indicated that all remained statistically significant independent predictors of recurrence of AF.

**Prognostic nomogram：** The prognostic nomogram that integrated all the variables selected by multivariate cox regression was shown in Fig. 1. The nomogram illustrated LAD as sharing the largest contribution to prognosis, followed by age, AF type, duration, gender, CAD. Each subtype within these variables was assigned a score on the point scale. By adding up the total score and locating it on the total point

scale, we can easily draw a straight line down to determine 1-year recurrence free probability.

**Validation of the nomogram.** Nomogram validation consisted of three parts including discrimination, calibration, and clinical validity.

Discrimination was evaluated using a concordance index (C-index) and receiver operating characteristic (ROC) curve. In the training cohort, the C-index was 0.750 (95% CI: 0.709 to 0.785), P<0.001, which was significantly higher than that of the CHA2DS2-VASc score system (C-index = 0.620, 95% CI:0.576 to 0.664, P<0.001). In the validation cohort, the C-index was 0.762 (95% CI: 0.699 to 0.826), P<0.001, which was also significantly higher than that of the CHA2DS2-VASc score system (C-index = 0.592, 95% CI: 0.508 to 0.677, P=0.01).

The area under ROC curve (AUC) of the training cohort and validation cohort were shown in Fig 2. In the training cohort, the AUC of nomogram and CHA2DS2-VASc score were 0.722(Cutoff point=167.5, Sensitivity=70.7%, Specificity=67%) and 0.647 (Cutoff point=2.5, Sensitivity=54.7%, Specificity=32.7%) respectively. In the validation cohort, the AUC of nomogram and CHA2DS2-VASc score were 0.809(Cutoff point=166.5, Sensitivity=79.6%, Specificity=77.2%) and 0.597 (Cutoff point=2.5, Sensitivity=53.6%, Specificity=36.4%) respectively.

Both C-index and ROC curve illustrated that Nomogram has an excellent discrimination and is superior to the traditional CHA2DS2-VASc score.

Calibration was evaluated using calibration curve and Greenwood-D'Agostino-Nam.

The calibration curve of the training cohort and validation cohort were shown in Fig 3 and Fig 4. Both of the curves shown good agreement between the nomogram prediction and actual observation for 1-year recurrence probability.

The Greenwood-D'Agostino-Nam test of training cohort and validation cohort is $X^2$=1.43(p=0.997>0.05）and $X^2$=5.10(p= 0.648>0.05）respectively, indicated that the model was well-calibrated.

We examined the performance of nomogram of training cohort with Decision Curve Analysis (DCA）, and compared it to the CHA2DS2-VASc score. As shown in Fig 5, nomogram lead to higher values of net benefit in a wide range of threshold levels than CHA2DS2-VASc score. And the same conclusion was obtained in the validation cohort. It shown that it is beneficial to use nomogram in respect of net benefit regardless of the current threshold probability. These results shown that nomogram can be used in clinical practice.

In addition, to determine the performance of the proposed nomogram in stratifying risk of patients, we categorized the patients of the training cohort into four subgroups based on the quartiles of nomogram total points (i.e. lowest to 158, 159 to 167, 168 to 176, 177 to highest). Fig 6. illustrated the Kaplan–Meier curves according to the nomogram-based groupings. The survival times were significantly differentiated between the subgroups ($P < 0.001$).

# Discussion

Individual recurrence rate varies after radiofrequency catheter ablation of AF, and it is very inaccurate to estimate the recurrence rate only based on the CHA2DS2-VASC

score. Although a number of predictive models of AF recurrence have been reported previously, no nomograms have been developed. Therefore, we try to develop and validate a nomogram to predict the late recurrence of patients with AF Ablation. We collected baseline data of 493 patients retrospectively, all of which were characterized by easy to obtain and high repeatability. Most of these variables are classical predictors of long-term recurrence of AF, such as age, gender, type of AF, LAD, CAD, AF duration, hypertension, diabetes, CHA2DS2- VASc scores, which have been confirmed by multiple studies.[8] And some variables are newly discovered in recent years, which have not been widely proved, such as S-GLB,[9] NLR,[10] BMI, [11]number of antiarrhythmic drugs failed before ablation,[12] and eGFR.[5] The main purpose of the inclusion of TC, TG and EF is mainly to study whether hyperlipidemia and decreased left ventricular systolic function are predictors of recurrence of AF. In the end, we found 6 independent predictors of AF recurrence (i.e. age, gender, AF type, LAD, CAD, AF duration), all of which are classical predictors. Based on multivariate COX analysis of these 6 variables, the nomograph constructed has good discrimination, calibration and clinical validity, which is significantly superior to CHA2DS2-VASC score. In addition, it is helpful to individually predict the postoperative recurrence rate of patients with AF and guide the work of clinicians. Reviewing the nomogram, we can find that LAD is absolutely dominant in the forecasting indicators. This result is similar to the conclusions of other prediction models. Among the CAAP-AF scores developed by Winkle RA et, LAD is also the factor with the highest score. [12]This is mainly related to the mechanism of AF. It is

generally believed that ectopic activity and re-entry are major arrhythmogenic mechanisms in AF. [13]The enlarged atrium (myocardial remodeling) may promote the formation of multiple reentrant activities, and increase the risk of atrial fibrosis,[14, 15] which may lead to incomplete ablation during the operation and the re-formation of the reentry after the operation, and eventually leads to recurrence of AF. Furthermore, there is a complementary relationship between AF and the increase of LAD.

Long-term left atrial fibrillation causes the increase of LAD and atrial cardiomyocyte fibrosis. In turn, changes of atrial structure affect ion channels of cardiomyocytes, and thus lead to abnormality of cardiac electrical conduction and increase of myocardial automaticity, which further promotes the occurrence of AF. [16]That also explains why the AF duration，non-paroxysmal AF, age and CAD are also independent predictors of AF recurrence, because these factors can promote myocardial remodeling in varying degrees.

The reason why female is an independent predictor may be that women are more likely to trigger non-pulmonary vein ectopic beats than men. Lee et al. reported that female hormones and women with higher parasympathetic activity might have a higher incidence of superior vena cava ectopic beats initiating AF.[17]

Among the verification indicators of the nomogram, the calibration curves of the training cohort and the validation cohort both suggest that the nomogram is well calibrated. However, both sets of data indicated that the calibration of high recurrence risk group (recurrence free probability<60%) is lower. This mainly due to the small sample size and short follow-up time currently included, and many patients with high

risk do not have recurrence within one year. The result suggests that it is necessary to prolong the follow-up time for patients with high risk of recurrence in clinical and research work.

In addition, although the verification index of the nomogram in this study is good, and the prediction of individual recurrence rate of atrial fibrillation is high, it is only a probability provided to ordinary patients based on a few simple clinical data, and cannot determine clinical decision-makings. We encourage patients with low recurrence rates to choose radiofrequency catheter ablation as a treatment method as soon as possible to restore sinus rhythm and improve myocardial remodeling, so as to avoid the increased difficulty of surgery and recurrence probability caused by prolonged duration of disease and enlarged LAD. For patients with high predicted recurrence rate and complicated conditions, a decision needs to be made after further communication with the doctors.

## Study limitations

This study is a retrospective study of single-center. Although the operation is independent among the five wards, the patient population is limited to nearby cities, it remains for other centers with slightly different ablation techniques or experience to verify or improve upon the nomogram in their populations. And even we asked patients to record their heart rhythm daily and provide ECG data weekly during the follow-up, there was no guarantee that all recurrences were included in the study. But any missed AF recurrence should have been distributed across all nomogram and should not influence the overall conclusions of our study. In addition, due to the small

sample size and the lack of prospective data, many predictors of AF recurrence, such as obstructive sleep apnea syndrome and left atrial volume index, cannot be included in the nomogram. Finally, the follow-up time of this study is short, and a better predictive model still need long-term follow-up.

## Conclusion

In conclusion, the proposed nomogram can provide accurate individual recurrence rate for patients with AF who underwent RFCA. Compared to the CHA2DS2-VASc score, clinicians can promote individual-oriented therapy and disease management by using this tool.

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## Tables

**Table 1. Characteristics of the training cohort and validation cohort.**

| Variables | Training (N=371) | Validation (N=122) | Total (N=493) | P value |
|---|---|---|---|---|
| Gender n (%) | | | | 0.571 |
| Male | 214 (57.68%) | 77 (63.11%) | 291 (59.03%) | |
| Female | 157 (42.32%) | 45 (36.89%) | 202 (40.97%) | |
| AF Type n (%) | | | | 0.722 |
| Paroxysmal | 307 (82.75%) | 97 (79.51%) | 404 (81.95%) | |
| Non-paroxysmal | 64 (17.25%) | 25 (20.49%) | 89 (18.05%) | |
| Age (years) | 61.68±9.50 | 61.22±10.07 | 61.57±9.64 | 0.649 |
| AF duration（year) , n(%) | | | | 0.776 |
| < 1 | 144 (38.81%) | 40 (32.79%) | 184 (37.32%) | |
| 1-5 | 133 (35.85%) | 45 (36.89%) | 178 (36.11%) | |
| > 5 | 94 (25.34%) | 37 (30.33%) | 131 (26.57%) | |
| Number of antiarrhythmic drugs failed n (%) | 1.16±0.82 | 1.07±0.75 | 1.14±0.81 | 0.312 |
| CHA2DS2-VASc score | 2.42±1.44 | 2.44±1.46 | 2.42±1.44 | 0.869 |
| CHA2DS2 score | 1.40±0.97 | 1.38±1.74 | 1.39±1.12 | 0.730 |
| BMI(kg/㎡) | 24.99±3.19 | 24.77±3.27 | 24.93±3.21 | 0.509 |
| eGFR(ml/min) | 92.37±26.39 | 93.89±31.77 | 92.75±27.79 | 0.636 |
| LAD (mm) | 41.82±5.72 | 41.89±5.67 | 41.83±5.70 | 0.896 |
| Hypertension n (%) | | | | 0.907 |
| NO | 139 (37.47%) | 43 (35.25%) | 182 (36.92%) | |
| YES | 232 (62.53%) | 79 (64.75%) | 311 (63.08%) | |
| Diabetes n (%) | | | | 0.979 |
| NO | 322 (86.79%) | 105 (86.07%) | 427 (86.61%) | |
| YES | 49 (13.21%) | 17 (13.93%) | 66 (13.39%) | |
| CAD n (%) | | | | 0.805 |
| NO | 302 (81.40%) | 96 (78.69%) | 398 (80.73%) | |
| YES | 69 (18.60%) | 26 (21.31%) | 95 (19.27%) | |
| TC (mmol/L) | 4.35±1.13 | 4.29±0.86 | 4.33±1.07 | 0.586 |

| Variables | Training (N=371) | Validation (N=122) | Total (N=493) | P value |
|---|---|---|---|---|
| TG (mmol/L) | 1.72±1.25 | 1.59±0.81 | 1.69±1.16 | 0.302 |
| S-GLB(g/L) | 26.45±7.29 | 25.53±3.35 | 26.22±6.55 | 0.177 |
| NLR | 2.13±1.35 | 2.20±1.71 | 2.14±1.44 | 0.653 |
| EF (%) | 63.24±7.13 | 63.21±7.82 | 63.23±7.30 | 0.971 |

Abbreviations: AF=Atrial fibrillation; CAD=coronary artery disease; LAD=left atrial diameter. BMI=body mass index, TC=total cholesterol, TG=triglyceride, S-GLB=serum globulin, EF=ejection fraction, NLR=neutrophil lymphocyte ratio.

**Table 2. Univariate cox regression of the training cohort**

| Variables | β | HR | HR 95% CI | Z value | P value |
|---|---|---|---|---|---|
| Gender | 0.477 | 1.612 | 1.195-2.175 | 3.12 | **0.002** |
| AF type | 0.743 | 2.103 | 1.499-2.952 | 4.29 | **<0.001** |
| Age | 0.043 | 1.044 | 1.025-1.064 | 4.78 | **<0.001** |
| AF duration | 0.558 | 1.748 | 1.275-2.396 | 3.47 | **<0.001** |
| Number of antiarrhythmic drugs failed | 0.151 | 1.162 | 0.968-1.395 | 1.62 | 0.106 |
| CHA2DS2 score | 0.185 | 1.203 | 1.039-1.394 | 2.47 | **0.014** |
| CHA2DS2-VASc score | 0.226 | 1.253 | 1.14-1.378 | 4.71 | **<0.001** |
| BMI | 0.045 | 1.046 | 0.998-1.096 | 1.88 | 0.059 |
| eGFR | -0.004 | 0.996 | 0.989-1.002 | -1.33 | 0.155 |
| LAD | 0.078 | 1.081 | 1.052-1.111 | 5.57 | **<0.001** |
| Hypertension | 0.447 | 1.563 | 1.125-2.173 | 2.66 | **0.008** |
| Diabetes | 0.48 | 1.616 | 1.1-2.373 | 2.45 | **0.014** |
| CAD | 0.576 | 1.779 | 1.265-2.502 | 3.31 | **<0.001** |
| TC | -0.147 | 0.863 | 0.741-1.006 | -1.88 | 0.059 |
| TG | -0.008 | 0.992 | 0.874-1.125 | -0.12 | 0.899 |
| S-GLB | -0.008 | 0.992 | 0.966-1.019 | -0.57 | 0.552 |
| NLR | 0.087 | 1.091 | 0.984-1.21 | 1.64 | 0.099 |
| EF | -0.006 | 0.994 | 0.973-1.016 | -0.55 | 0.61 |

HR = Hazard Ratio; CI = Confidence Interval; Values in bold signify P<0.05.

**Table 3. Multivariate cox regression of the training cohort**

| Variables | β | HR | HR 95% CI | Z value | P value |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | | Ref | | | |
| Female | 0.524 | 1.688 | 1.238-2.303 | 3.31 | <0.001 |
| AF type | | | | | |
| Paroxysmal | | Ref | | | |
| Persistent/long-standing | 0.731 | 2.077 | 1.454-2.969 | 4.01 | <0.001 |
| Age | 0.035 | 1.036 | 1.015-1.057 | 3.44 | <0.001 |
| AF duration （years） | | | | | |
| <5 | | Ref | | | |
| ≥5 | 0.570 | 1.769 | 1.230-2.543 | 3.08 | 0.002 |
| LAD | 0.064 | 1.066 | 1.034-1.098 | 4.15 | <0.001 |
| CAD | | | | | |
| No | | Ref | | | |
| Yes | 0.437 | 1.548 | 1.091-2.198 | 2.45 | 0.014 |

Ref = Reference group; HR = Hazard Ratio; CI = Confidence Interval.

## Figures

**Fig 1:** Nomogram for predicting long-term recurrence within 1 year in patients with AF Ablation. Abbreviations: AF=Atrial fibrillation; CAD=coronary artery disease; LAD=left atrial diameter. To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the recurrence free axes to determine the recurrence free probability.

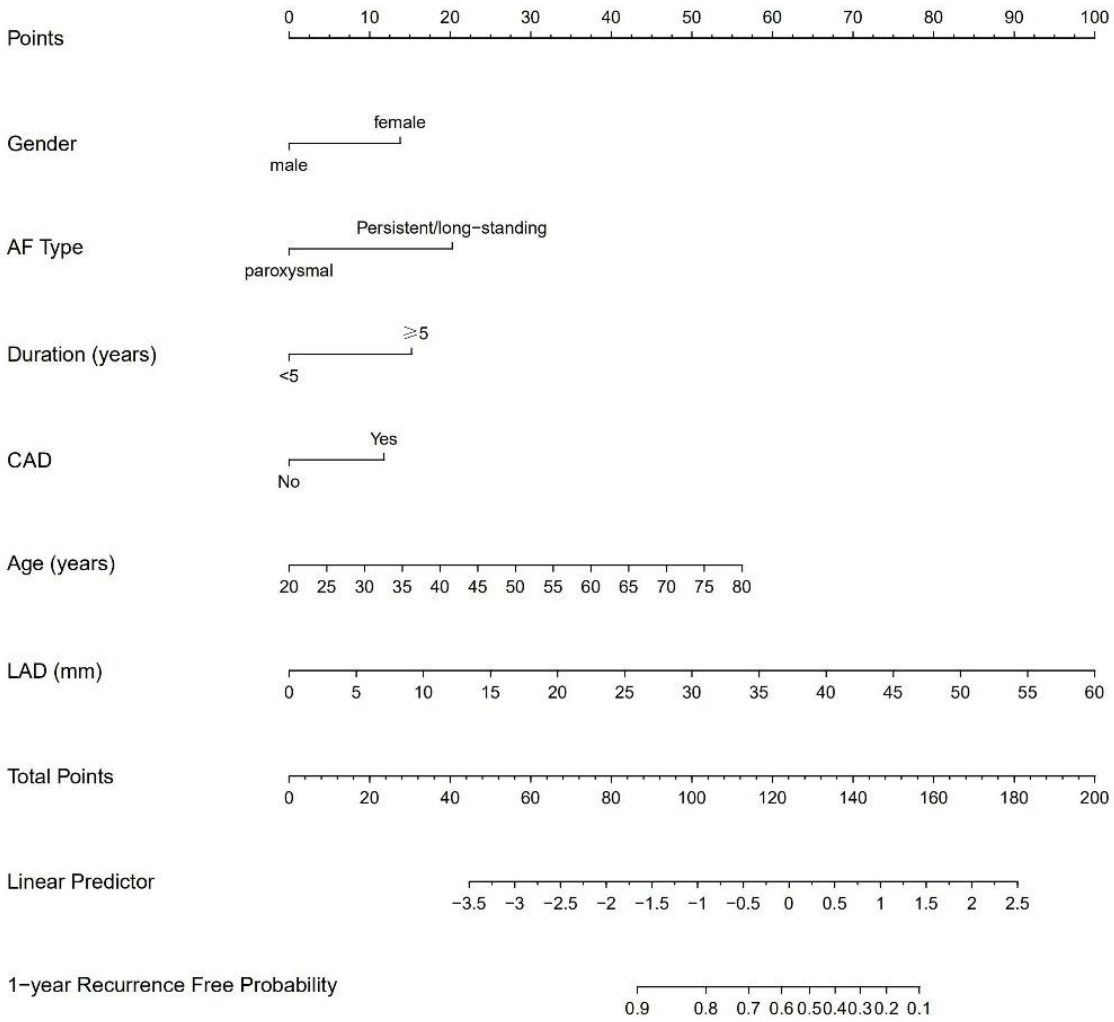
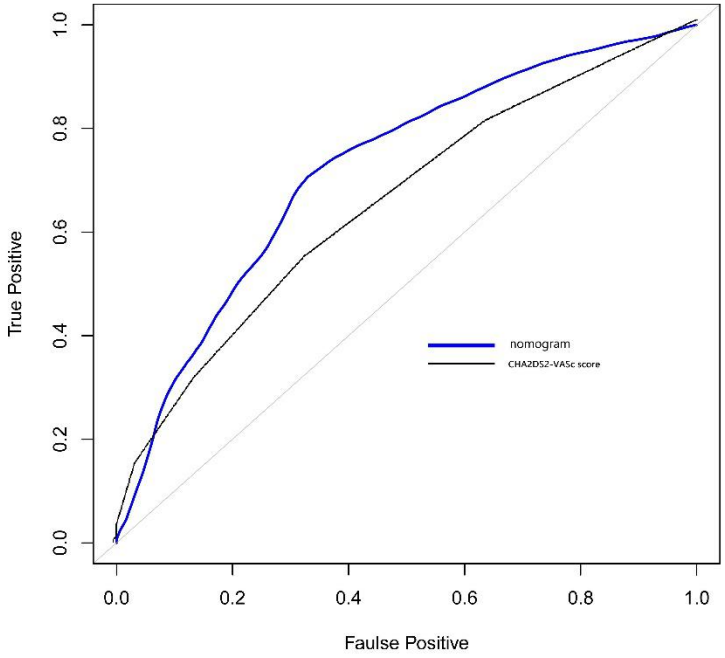
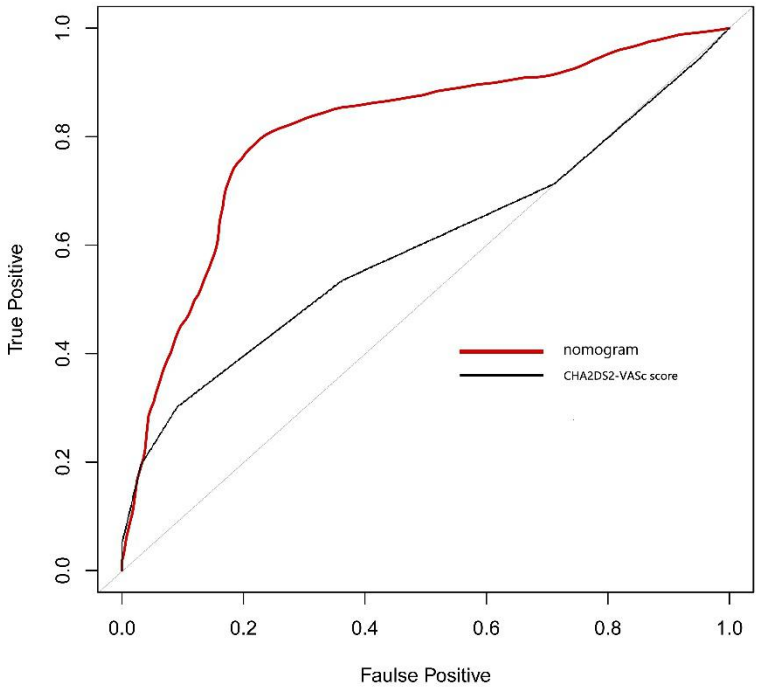


Fig 2：ROC of nomogram and CHA2DS2-VASc score in the training cohort and validation cohort.




A：ROC of training cohort




B：ROC of validation cohort

Fig 3：calibration curve of training cohort.

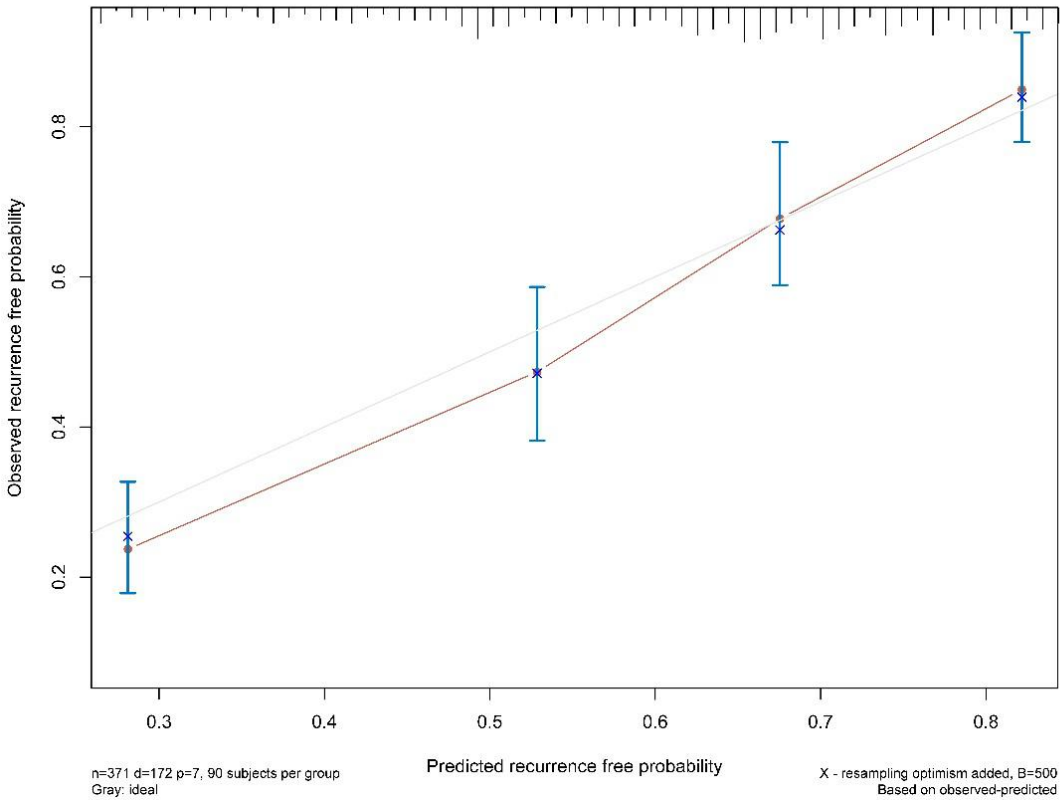


Fig 4：calibration curve of validation cohort.

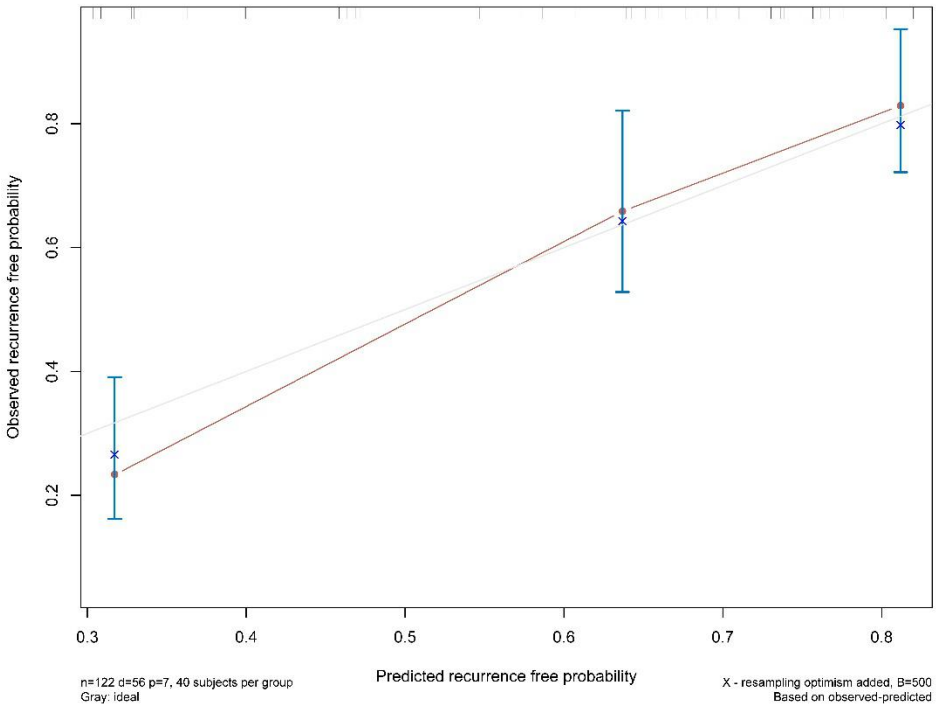


Fig 5：DCA of training cohort. The vertical axis represents the value of net benefit, and the horizontal axis represents the threshold level (possible probability cut-points). Plotting net benefit in function of threshold level yields the decision curve.

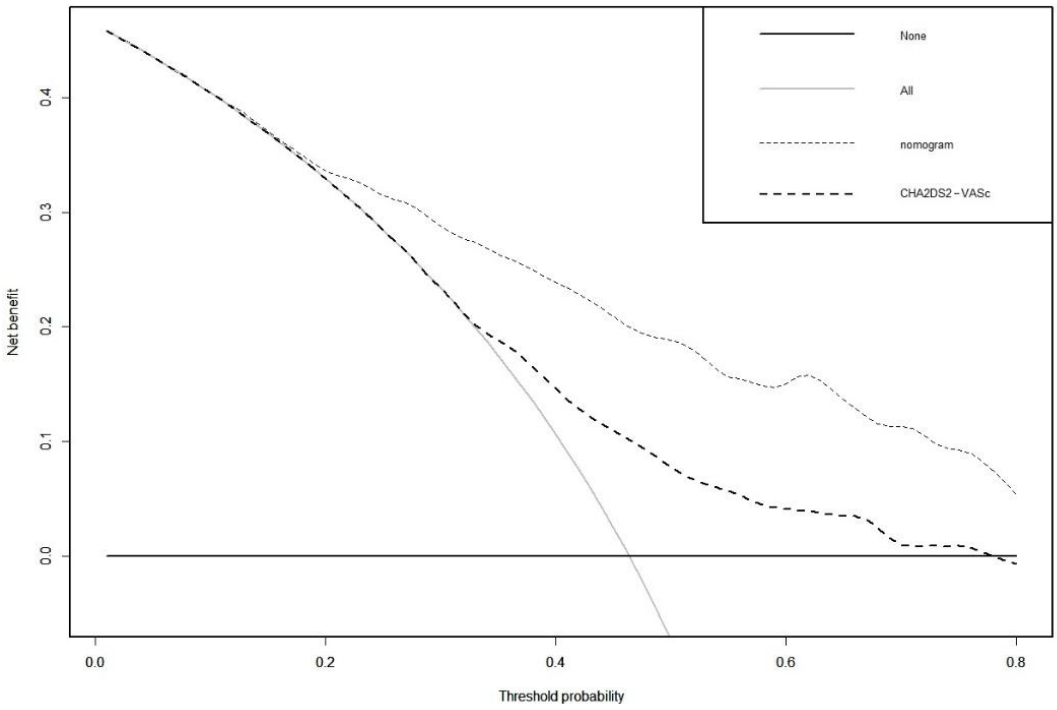


Fig 7. Kaplan-Meier curves of training cohort categorized by the quartiles of proposed nomogram total points.