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Original Article

Establishment and evaluation of a nomogram prediction model for recurrence risk of atrial fibrillation patients after radiofrequency ablation

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Abstract: Objective: To explore the risk factors for recurrence of atrial fibrillation (AF) in patients after radiofrequency ablation and construction of a targeted nomogram prediction model. Methods: A prospective cohort study design was used to select 312 patients who were separated into two groups; a recurrence group (n = 79) and a non-recurrence group (n = 233) with or without AF, who underwent radiofrequency ablation for the first time between January 2017 and December 2017, with a completed a 12-month follow-up after surgery. The recurrence of AF within 12 months after follow-up was recorded. The nomogram prediction model was established. The original data were resampled using the Bootstrap method. The recurrence risk after resampling was predicted using a nomogram model. The calibration curve and ROC curve of the nomogram model were established. The predicted calibration degree and discrimination degree of the nomogram model were evaluated with the Hosmer-Lemeshow deviation test and area under the curve. Results: The 12-month follow-up showed that a total of 79 patients (25.32%) had recurrence of AF. The type of AF, sex, gender, disease course, left atrial anteroposterior diameter, left atrial volume, and cardiac function classification were independent risk factors for the recurrence of AF ($P < 0.05$). After the nomogram prediction model passed the Bootstrap self-sampling 1000 times, Hosmer-Lemeshow deviation test: $\chi^2 = 8.070$, $P = 0.427$; the area under ROC curve was 0.852 (95% CI: 0.806-0.898), the sensitivity was 78.48%, and the specificity was 81.12%, suggesting that the nomogram model has better predictive calibration and discrimination. Conclusion: The recurrence rate in patients with AF after radiofrequency ablation is high. The nomogram model based on the risk factors of AF recurrence has high prediction accuracy and can be used to predict the recurrence risk of AF in patients after radiofrequency ablation.

Keywords: Atrial fibrillation, radiofrequency ablation, recurrence, risk factors, nomogram

Introduction

Atrial Fibrillation (AF) is the most common tachyarrhythmia observed in the clinical setting; it can lead to stroke and it has a high disability rate [1]. Radiofrequency Catheter Ablation (RFCA) for AF, is a newly emerging and rapidly developing treatment method, which has been widely used in the treatment of AF [2, 3]. Although radiofrequency ablation for AF has relieved pain in many patients with AF, several patients still have relapse after surgery. Preoperative assessment can reveal patients with a high risk of postoperative recurrence, and this seem to be an effective way to improve the success rate and avoid operation risks.

There are many reasons for postoperative recurrence of AF. Studies show that besides the operation methods and skills, the recurrence of AF is also influenced by factors, such as sex and LAD [4-8]. It is very difficult to judge the risk of recurrence for every patient with AF after surgery in the absence of tools for comprehensive evaluation of these risk factors. In this study, we aimed to establish a personalized nomogram prediction model by analyzing the current situation and risk factors of recurrence of AF

patients after radiofrequency ablation in our center to scientifically and effectively manage the risk of recurrence of AF patients after radiofrequency ablation.

Materials and methods

Research subjects

From January to December 2017, 312 consecutive patients with symptomatic AF who underwent radiofrequency ablation at our center and failed drug therapy were enrolled in this study.

All the patients met the diagnostic criteria of AF management guidelines issued by the American Heart Association (AHA) in 2014 [9]. Patients requiring cardioversion therapy with a duration of ≥ 7 days were diagnosed with persistent AF, and those with a disease duration of more than 12 months were diagnosed with long-term persistent AF [10].

Inclusion criteria: 1) A previous diagnosis of atrial fibrillation with at least one ECG confirming atrial fibrillation rhythm, or having started taking related drugs; 2) The first ECG or ECG examination during hospitalization showed atrial fibrillation and heart rhythm, and the diagnosis was confirmed.

Exclusion criteria: 1) We excluded those with rheumatic valvular disease, hypertensive heart disease, congenital heart disease, left ventricular systolic dysfunction; 2) We excluded those with thrombosis in the left atrium and left atrial appendage; 3) As well as thoes who could not successfully complete transthoracic and transesophageal examinations and the imaging data met the analysis requirement.

All the patients were examined before the operation to eliminate serious lung diseases; heart, liver and kidney insufficiency; coagulation dysfunction, etc. Left atrial appendage thrombi were excluded using transesophageal echocardiography, and left atrial anteroposterior diameter (LAD), left ventricular ejection fraction (LVEF), left atrial volume (LAVI), left ventricular end diastolic diameter (LVEDd) and other cardiac ultrasonic parameters were measured. According to the preoperative venous blood examination results of the patients, relevant laboratory parameters, such as plasma hs-CRP, serum creatinine, and N-terminal brain natriuretic peptide precursor (NT-proBNP) were measured. Moreover, data regarding the general characteristics, such as sex, age, educational level, AF type, disease course, complications, and cardiac function classification were collected and summarized. The BMI level and CHA2DS2-VASc scores of the patients were also calculated.

Pulmonary vein isolation surgery plan

Two catheters were placed through the left femoral vein; one decapolar catheter was placed into the coronary sinus, and a quadrupole catheter was placed into the right ventricular apex. The atrial septal puncture needle was inserted through the right femoral vein, and two catheters, one variable circular mapping catheter, were inserted after the atrial septal puncture was successful. An irrigated-tip ablation catheter was set. Radiofrequency ablation was performed at about 5 mm from the pulmonary vein opening with 4-mm point ablation isolation. Complete isolation of bilateral pulmonary veins was taken as the standard for a successful operation, and auxiliary ablation lines, such as left atrial apex, anterior wall, posterior wall, and even mitral isthmus are added when necessary for patients with persistent AF. Some patients also underwent electrical cardioversion when necessary. Oral warfarin was used for anticoagulation before surgery and within 6 months after the surgery. Thereafter, we decided to continue medication or stop medication according to CHA2D 2-VASC Criteria (CHADS 2 before 2009). The INR value of blood was regularly measured to serve as a reference for adjusting the warfarin dosage. Routine oral administration of class I and class III antiarrhythmic drugs was performed for 3 months after surgery for patients with persistent AF did not represent surgical failure.

Study end point and patient follow-up

All patients who underwent pulmonary vein isolation surgery were followed up on time to record the ECG changes of symptoms after surgery; the 24-h dynamic ECG was reexamined in March, June, September, and December. Patients with symptomatic AF or AF detected using electrocardiogram were diagnosed with recurrent AF, and AF occurring within 3 months was considered temporary [11, 12]. Recurrence

Table 1. Baseline patient characteristics

Variable	All patients (n = 312)
Age (years)	57.25 ± 11.60
Male sex-no. (%)	218 (69.87)
Educated-no. (%)	109 (34.94)
Course of AF (years)	4.12 ± 1.51
Persistent AF-no. (%)	125 (40.06)
HTN-no. (%)	97 (31.09)
DM-no. (%)	69 (22.12)
Heart Function class (NYHA, III or IV)	57 (18.27)
BMI (kg/m^2)	22.27 ± 2.93
CHA2DS2-VASc score	1.56 ± 0.51
LAD (mm)	44.23 ± 7.72
LVEF (%)	56.24 ± 5.92
LAV (mL)	101.28 ± 15.58
LVEDd (mm)	48.08 ± 3.38
hs-CRP (mg/L)	2.78 ± 1.09
Scr (μmol/L)	73.47 ± 12.96
NT-proBNP (ng/mL)	707.64 ± 75.78

Educated: educational level of senior middle school or above, HTN: complicated with hypertension, DM: complicated with diabetes, LAD: left atrial diameter, LAV: left atrial volume, Scr: serum creatinine concentration.

of AF was defined as AF or other atrial tachycardia that occurs after a 3-month blank period and lasts for more than 30 seconds [12]. The application of antiarrhythmic drugs within 3 months after operation does not represent the failure of the operation.

Statistical methods

The research design and statistical analyses of this study were performed in strict accordance with the TRIPOD statement of the prediction model [13]. All the data were analyzed using R software 3.6.1 (http://www.R-project.org, The R Foundation). Data were visualized using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA). Single factor analysis and logistic regression analysis were used to analyze various risk factors. On the basis of the above risk factors, the RMS package was used to establish the nomogram model of recurrence risk of AF patients after radiofrequency ablation. The original data were resampled using the Bootstrap method, and the recurrence after resampling was predicted using the nomogram model. Hosmer-Lemeshow deviation test and calibration curve were used to evaluate the calibration degree of the nomogram model. The area under the curve (AUC) was used to evaluate the discrimination degree of the nomogram, and the test level was $\alpha = 0.05$.

Ethical standards

The research process was approved by the appropriate medical ethics committee of the First Affiliated Hospital of University of Science and Technology of China. All the patients involved in the study signed the informed consent forms for surgery and the related data publication. The study conforms to the ethical standards set by the 1964 Declaration of Helsinki.

Results

Patient characteristics

The clinical baseline characteristics such as Age (years), Male sex-no. (%), Educated-no. (%), Course of AF (years), Persistent AF-no. (%), HTN-no. (%), DM-no. (%), Heart Function class (NYHA, III or IV), BMI (kg/m^2), CHA2DS2-VASc score, LAD (mm), LVEF (%), LAV (mL), LVEDd (mm), hs-CRP (mg/L), Scr (μmol/L), NT-proBNP (ng/mL) of the 312 patients in this study are summarized in **Table 1**.

Recurrence of AF patients after radiofrequency ablation and single factor analysis results

After 12 months of follow-up, 79 (25.32%) of the 312 patients with AF experienced recurrence and 233 (74.68%) did not experience recurrence. We compared the general data, ultrasonic examination results, and laboratory examination results of the two groups of patients. The variables with statistically significant differences in distribution were age, sex, course of disease, AF type, cardiac function classification, LAD, LAV, and hs-CRP (**Table 2**).

Logistic regression analysis results of recurrence risk factors of AF patients after radiofrequency ablation

According to the above results of single factor analysis on recurrence of AF, logistic regression analysis was performed with variables that were significantly different in the single factor analysis ($P < 0.05$) as independent variables

Table 2. Comparison of postoperative recurrence in atrial fibrillation patients

Projects	Recurrence group (n = 79)	No recurrence group (n = 233)	t/χ^2	P
Age (years)	59.97 ± 11.25	56.33 ± 11.59	2.432	0.016
Male sex-no. (%)	45 (56.96)	173 (74.25)	8.375	0.004
Educated-no. (%)	30 (37.97)	79 (33.91)	0.430	0.512
Course of AF (years)	4.78 ± 1.71	3.89 ± 1.36	4.705	< 0.001
Persistent AF-no. (%)	50 (63.29)	75 (32.19)	23.767	< 0.001
HTN-no. (%)	28 (35.44)	69 (29.61)	0.936	0.333
DM-no. (%)	16 (20.25)	53 (22.75)	0.213	0.644
NYHA III or IV	25 (31.65)	32 (13.73)	12.676	< 0.001
BMI (kg/m^2)	22.62 ± 2.48	22.15 ± 3.06	1.224	0.222
CHA2DS2-VASc score	1.58 ± 0.52	1.55 ± 0.51	0.495	0.621
LAD (mm)	47.97 ± 6.63	42.96 ± 7.66	5.193	< 0.001
LVEF (%)	56.73 ± 5.30	56.08 ± 6.12	0.851	0.395
LAV (mL)	109.03 ± 11.38	98.65 ± 15.95	5.337	< 0.001
LVEDd (mm)	47.92 ± 3.76	48.14 ± 3.25	0.484	0.629
hs-CRP (mg/L)	3.07 ± 0.91	2.69 ± 1.13	2.713	0.007
Scr (μmol/L)	73.23 ± 13.10	73.56 ± 12.94	0.197	0.844
NT-proBNP (ng/mL)	718.24 ± 62.89	704.05 ± 79.48	1.442	0.150

and recurrence after AF operation as dependent variables (assignment: recurrence = 1, no recurrence = 0). Regression method was used for variable selection (rejection standard: α = 0.05). Logistic regression analysis results for recurrence risk factors of AF patients after radiofrequency ablation are shown in **Table 3**.

Construction and evaluation of the recurrence nomogram system for AF patients after radiofrequency ablation

The nomogram prediction model of AF recurrence risk is established according to the regression analysis results, as shown in **Figure 1**. The Bootstrap method was used to resample 312 patients with AF for 1000 times to obtain the internal verification population. The established risk nomogram was used to predict the risk of the internal verification population to obtain the calibration curve and ROC curve of the nomogram model, as shown in **Figures 2** and **3**. The results reveal that Hosmer-Lemeshow deviation test: χ^2 = 8.070, P = 0.427, suggests that the nomogram model has good prediction consistency. The AUC was 0.852 (95% CI: 0.806~0.898), sensitivity was 78.48%, and specificity was 81.12%, suggesting that nomogram model has good discrimination.

Discussion

Currently, circumferential pulmonary vein isolation ablation is the most effective treatment method for AF. The recurrence of AF after surgery has great heterogeneity. Some patients relapse early, while others can be treated with Remen, Free of AF for Years [14]. In this study, we evaluated the risk factors related to patients who relapse after radiofrequency ablation for AF. The relatively high recurrence rate after ablation has affected its clinical application and therapeutic effect to some extent [15]; therefore, we may effectively identify the risk factors of recurrence after ablation of AF and intervene in time to ensure the therapeutic effect of surgery and improve patient prognosis.

Studies have demonstrated some discordance regarding the predictors of relapse of AF recurrence after PVI [16, 17]. Our analysis yielded the following six independent predictors of recurrence: LAD, sec, course of AF, NYHA III or IV, and Lavand type of AF (paroxysmal vs. non-paroxysmal). Multiple regression analysis showed that persistent AF is a risk factor for postoperative recurrence of AF, which is consistent with research from Mesquita et al [18]. Persistent AF and its recurrent attacks can lead to atrial electrical remodeling and tissue remodeling, resulting in arrhythmia cardiomyopathy, referred to as "AF leads to AF" [19, 20]. Moreover, this study showed that higher LAD and LAV levels, has a higher the risk of recurrence after surgery. LAD and LAV are both

Table 3. Logistic regression analysis results of recurrence risk factors of atrial fibrillation patients after radiofrequency ablation

Exposure	Category	N (%)	OR (95% CI)	P
Type of AF	Paroxysmal AF	187 (59.94)	1	
	Persistent AF	125 (40.06)	5.29 (2.11, 13.24)	< 0.001
Sex	Female	94 (30.13)	1	
	Male	218 (69.87)	4.59 (1.34, 15.68)	0.015
NYHA class	Increase by 1 level	312 (100.00)	2.14 (1.30, 3.54)	0.003
Course of AF	Increase by 1 year	312 (100.00)	1.53 (1.24, 1.89)	< 0.001
LAD	Increase by 1 mm	312 (100.00)	1.11 (1.06, 1.16)	< 0.001
LAV	Increase by 1 ml	312 (100.00)	1.05 (1.03, 1.08)	< 0.001

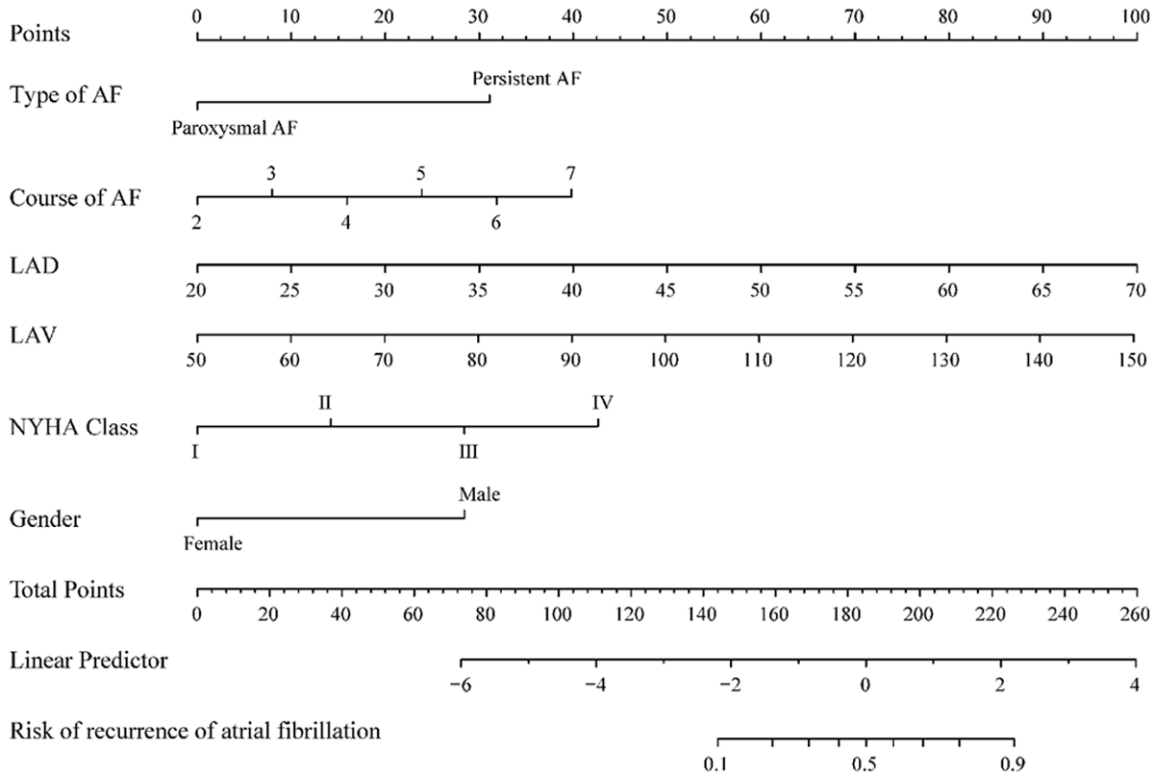

Figure 1. Nomogram model of recurrence risk after radiofrequency ablation for atrial fibrillation patients.

important indicators that reflect the size of the left atrium and the level of left ventricular function in patients. Enlargement of the left atrium can cause myocardial interstitial fibrosis, endocardium remodeling, and hypertrophy of myocardial cells, leading to electrophysiological changes of ion channels, with subsequent improvement in the myocardial excitability and self-discipline, inducing AF. Therefore, the larger the LAD, the larger the LAVI and the lower the maintenance rate of sinus rhythm after surgery [21, 22]. A meta-analysis on LAV and recurrence of AF after radiofrequency ablation shows that LAV can more accurately reflect asymmetric left atrial size than LAD [15]. At the same time, compared to patients without recurrence of AF, patients with recurrence of AF after radiofrequency ablation have a higher average LAV, and LAV measurements have an independent positive correlation with the recurrence rate of AF. Berruezo et al indicated that larger LAV resulted in a vicious circle of atrial remodeling and AF [23]. In this study, we observed that the recurrence rate of AF in male patients was high-

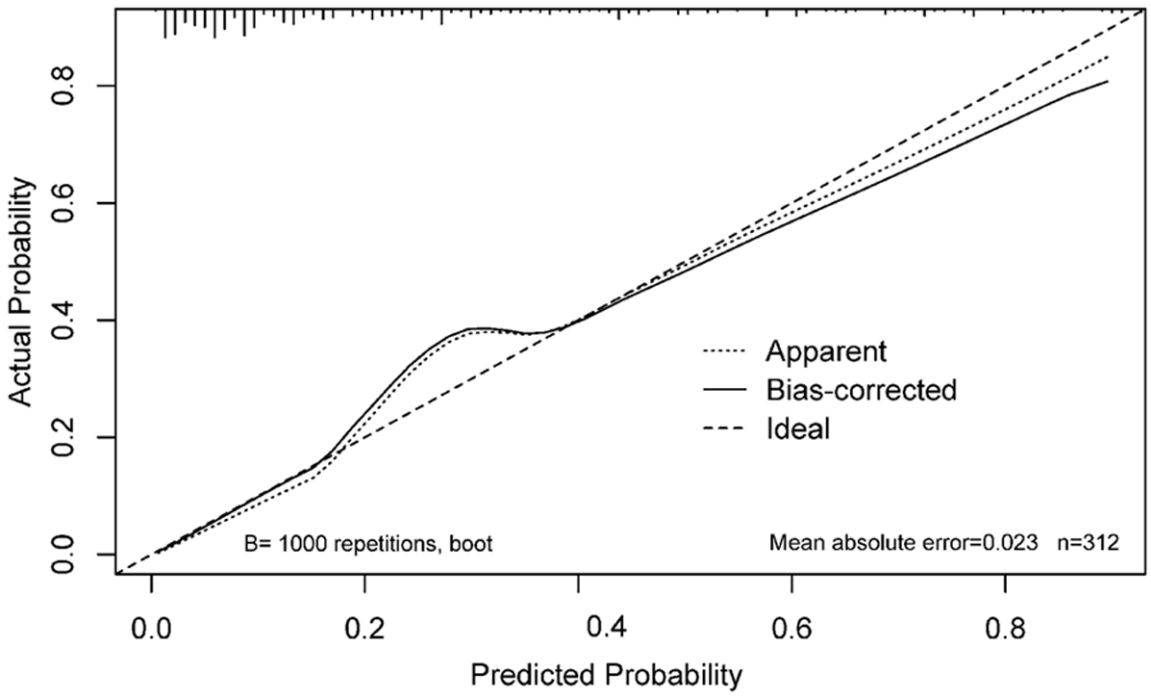

Figure 2. Calibration curve of nomogram model Bootstrap after self-sampling.

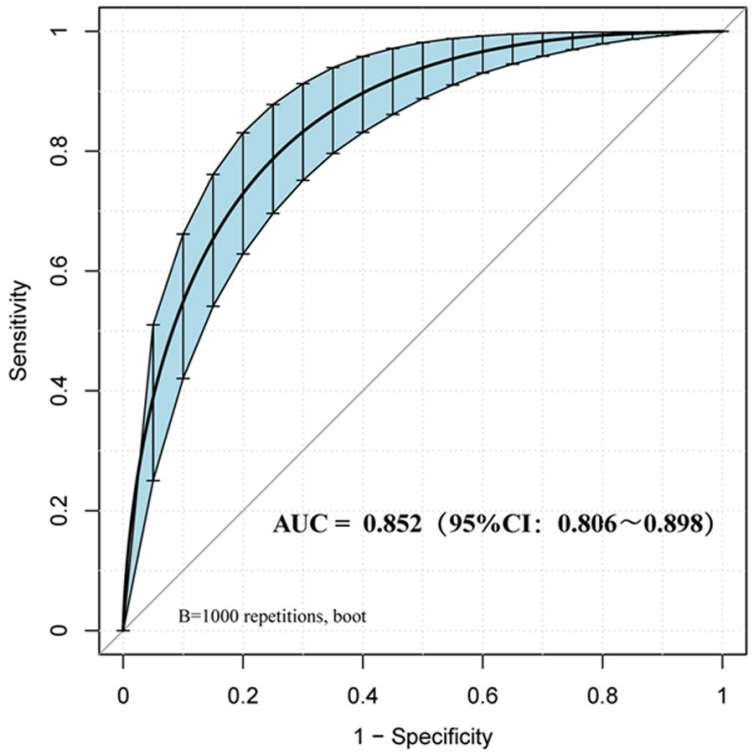

Figure 3. ROC curve of nomogram model Bootstrap after self-sampling.

er than that in female patients. The reason for this may be that male patients have high endogenous bioavailable testosterone levels, and the combination of endogenous bioavailable testosterone and other risk factors enables the recurrence of AF in male patients [24]. Orczykowski et al found that a long history of AF is an independent risk factor for the recurrence of AF [25], consistent with the results of this study. With prolongation of the disease course, the left atrium gradually expands; creating a larger left atrium, with more favorable formation of the AF matrix, thus making AF more likely to occur, and progress to persistent AF; furthering the chances of relapse after catheter ablation of AF also increases. Rostagno et al reported that the NYHA grading level is related to the maintenance of the sinus rhythm after radiofrequency ablation in patients with AF [26]. The results of this study show that patients with AF with higher NYHA classification have a higher risk of recur-

rence after surgery. The NYHA classification is closely related to LAD, left ventricular end diastolic diameter (LVEDD), LVEF, and other cardiac ultrasonic parameters in patients with AF; further, it is an important indicator that reflects the level of left ventricular function in patients. It is suggested that higher NYHA grades of patients with AF, the worse the left ventricular function and higher the recurrence risk of AF.

Construction and verification of recurrence nomogram system for AF after radiofrequency ablation

Evaluation of the nomogram model of AF recurrence risk shows that the Hosmer-Lemeshow deviation test: χ^2 = 8.070, P = 0.427, AUC = 0.852 (95% CI: 0.806-0.898), sensitivity 78.48%, specificity 81.12%; suggesting that the nomogram model of AF recurrence has good calibration and discrimination and can be used for screening the recurrence risk in AF patients after radiofrequency ablation. The medical staff can assess the risk of patients with AF according to the nomogram model and implement targeted intervention according to the recurrence risk of patients and specific risk factors to reduce the recurrence risk of AF.

Limitations of this study

The patients enrolled in this study were from an AF center, and the representativeness of the research sample is relatively insufficient, limiting the generalizability of the results. It is proposed that a larger, multi-center study should be conducted to further enhance the results.

Conclusion

Patients with AF have a high rate of recurrence after radiofrequency ablation. The nomogram models constructed by analyzing the risk factors of recurrence have good prediction ability and can provide reference for screening the recurrence risk of patients with AF after surgery.

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Disclosure of conflict of interest

None.

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