A prediction model based on functional mitral regurgitation for the recurrence of paroxysmal atrial fibrillation(PAF) after post-circular pulmonary vein radiofrequency ablation (CPVA)

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Abstract

【**Abstract**】 **Aim** To construct a prediction model based on functional mitral regurgitation (FMR) in patients with paroxysmal atrial fibrillation (PAF) for predicting atrial fibrillation recurrence after the post-circular pulmonary vein radiofrequency ablation (CPVA). **Methods** We retrospectively analyzed 289 patients with PAF who underwent CPVA for the first time . The patients were randomly divided into modeling group and verification group at the ratio of 75:25. In the modeling group, the multivariate logistic regression was used to analyze and construct a prediction model for post-CPVA recurrence in PAF patients, which was then validated in the verification group. **Results** (1) After 3-6 months of follow-up, the patients were divided into sinus rhythm group (252 cases) and recurrence group (24 cases); (2) In the modeling group, the age, LAD(left atrial diameter) and degree of MR (mild, moderate, severe) were higher in recurrence group than that of the sinus rhythm group, and the left atrial appendage emptying velocity (LAAV) was lower in recurrence group (all $P<0.05$). (3) A model for predicting the recurrence of PAF after radiofrequency ablation was constructed in the modeling group. The equation was: Logit(P) = -3.253 + 0.092 × age + 1.263 × mild MR + 2.325 × moderate MR + 5.111 ×severe MR - 0.113 × LAAV. The area under the curve (AUC) of the model was 0.889 in modeling group and 0.866 in verification group, and the difference was not statistically significant ($P>0.05$). **Conclusion:** The prediction model of atrial fibrillation (AF) recurrence after CPVA in PAF patients has good predictive efficacy, high specificity and accuracy.

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5.Informed consents of all patients were obtained from the patients themselves.

6.Conflict of Interest Disclosure

All authors declare that: (1) they have not received any support from any organization having an interest in the submitted works, whether financial or otherwise; (2) there are no other relationships or activities that may affect the submitted works.

【**Abstract**】**Aim** To construct a prediction model based on functional mitral regurgitation (FMR) in patients with paroxysmal atrial fibrillation (PAF) for predicting atrial fibrillation recurrence after the post-circular pulmonary vein radiofrequency ablation (CPVA).**Methods** We retrospectively analyzed 289 patients with PAF who underwent CPVA for the first time . The patients were randomly divided into modeling group and verification group at the ratio of 75:25. In the modeling group, the multivariate logistic regression was used to analyze and construct a prediction model for post-CPVA recurrence in PAF patients, which was then validated in the verification group.**Results** (1) After 3-6 months of follow-up, the patients were divided into sinus rhythm group (252 cases) and recurrence group (24 cases); (2) In the modeling group, the age, LAD(left atrial diameter) and degree of MR (mild, moderate, severe) were higher in recurrence group than that of the sinus rhythm group, and the left atrial appendage emptying velocity (LAAV) was lower in recurrence group (all$P$ <0.05). (3) A model for predicting the recurrence of PAF after radiofrequency ablation was constructed in the modeling group. The equation was: Logit(P) = -3.253 + 0.092 × age + 1.263 × mild MR + 2.325 × moderate MR + 5.111 ×severe MR - 0.113 × LAAV. The area under the curve (AUC) of the model was 0.889 in modeling group and 0.866 in verification group, and the difference was not statistically significant (P >0.05).

Conclusion: The prediction model of atrial fibrillation (AF) recurrence after CPVA in PAF patients has good predictive efficacy, high specificity and accuracy.

Key words: atrial fibrillation, prediction model, circular pulmonary vein radiofrequency ablation, echocardiography, recurrence

Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia in clinic. Patients with atrial fibrillation have an increased risk of stroke, heart failure, and depression, which seriously affects the patient's life quality[1] and increases social burden. For patients with paroxysmal atrial fibrillation (PAF), circular pulmonary vein radiofrequency ablation (CPVA) is recommended as a category I treatment[2]. Ablation therapy can improve the left atrium remodeling in AF patients[3]. Some observational studies suggest that successful AF catheter ablation and maintenance of sinus rhythm are associated with a decrease in stroke risk. However, the recurrence rate after atrial fibrillation ablation procedure is high (8%-40%)[4,5,6]. The results of ablation are affected by many factors, such as left size, serum Galectin-3, serum matrix metalloproteinase-9, etc [7-10], and the mechanism of recurrence as well as the related factors are still unclear, especially for PAF patients whose left atrium does not change significantly. Identification of the indicators that can predict recurrence after CPVA can help to develop more precise clinical strategies.

During the progression of atrial fibrillation, AF patients often have atrial remodeling, which is mainly manifested as atrial muscle degeneration, fibrosis of atrial muscle and extracellular matrix; the echocardiography

often shows normal left ventricular ejection fraction (LVEF) and left ventricle inner diameter, but the atrium is enlarged[9], accompanied by varying degrees of mitral regurgitation (MR). Normal mitral valve function depends on the structural and functional integrity of the atria and ventricles. In patients with isolated left atrial (LA) enlargement, when the mitral valve annulus is not significantly expanded, the mitral valve closure can be maintained by reducing the closure area and fornix height. But after decompensation, atrial-related MR will occur. Ring et al. believed that the percentage of systolic mitral valve antagonist area to the overlapping area of front and rear leaves of the mitral valve <13%, as measured by three-dimensional transesophageal echocardiography, can be used to predict the occurrence of functional MR (A/VF-MR)[11]. In 2017, the American Society of Echocardiography and the Society of Cardiovascular Magnetic Resonance issued the latest recommendations for non-invasive assessment of the severity of MR[12], which better guides and standardizes the imaging evaluation of MR.

The clinical management of AF should be individualized. The prediction of risk factors is important for comprehensive management of atrial fibrillation. Previous studies on post-radiofrequency prediction mostly focused on methods assessing the left atrial structure and function of AF patients. There was not any predictive model based on the degree of mitral regurgitation in patients with AF. This study further combined the parameters of left atrial structure, function, and degree of MR. We constructed a joint prediction model by using real-time three-dimensional echocardiography (RT-3DE) to evaluate the volume of LA, using transesophageal echocardiograghy (TEE) to obtain the left atrial appendage function parameters, and referring to the evaluation criteria of MR recommended by the latest guidelines. We developed a prediction model for the recurrence of PAF patients after CPVA based on echocardiographic and clinical characteristics, and verify its diagnostic efficacy in the verification group. This study provided a basis for designing clinical management strategies for AF patients.

We present the following article in accordance with the PRISMA reporting checklist.

Materials and Methods

1. Study objects

This study retrospectively analyzed 289 patients with non-valvular PAF who were treated at the Department of Cardiology, Changzhou First People's Hospital and Wu Jin Hospital from January 2017 to December 2020. All patients received CPVA treatment for the first time. There were 177 male patients and 112 female patients. PAF was defined as the AF occurrence that terminated spontaneously within 7 days, most of which could terminate within 24 hours. Exclusion criteria: (1) Patients with history of organic heart diseases such as coronary heart disease, hypertensive heart disease, cardiomyopathy, congenital heart disease, etc.; (2) Patients with clinical signs and symptoms of cardiac insufficiency and evidence of cardiac insufficiency in preoperative echocardiography [left ventricular ejection fraction less than 53%]; (3) Patients with primary mitral valve involvement, such as endocarditis , rheumatic valvular disease, chordae or papillary muscle rupture, congenital malformation or mitral valve ring calcification; (4) Patients were <18 or > 80 years old; (5) Patients with left atrial appendage emptying velocity (LAAV) <40cm/s, as measured by transesophageal echocardiography; (6) Patients with worsened MR after postoperative sinus rhythm was recovered; (7) Patients with history of thoracotomy; (8) Patients with bleeding diathesis or intolerance to heparin and anticoagulant drugs; (9) Patients with liver and kidney dysfunction, respiratory diseases, hyperthyroidism, and electrolyte disorders. All patients signed written informed consent. This study was in compliance with the "Declaration of Helsinki" and was approved by the Scientific Ethics Committee of Soochow University.

2. Equipment and methods

Routine transthoracic and transesophageal echocardiography: All patients received transthoracic echocardiograghy (TTE) and TEE with Philips Epiq 7C echocardiography machine (Philips Netherlands) before CPVA during sinus rhythm. The patient was laid in left side decubitus position and connected to the 12-lead ECG; the transthoracic image acquisition used the ultrasound probe (X5-1) to operate at the sternum side and apex. The degree of MR was measured by 2 experienced doctors. They collected the patient's sinus rhythm for 5 consecutive cardiac cycles. Doctors observed the structure and function of the mitral valve leaflets,

annulus, chordae tendineae, and papillary muscles to rule out primary mitral valve diseases. The two-plane Simpson method was used to calculate ejection fraction. The LAAV of patients was measured by TEE pulse Doppler. The TTE and TEE data were collected from all patients. All parameters were analyzed by two attending doctors or above, and the average value was taken. The two doctors were blinded to each other.

3. Echocardiographic evaluation of mitral regurgitation (MR) using comprehensive multi-parameter method

The evaluation of MR was based on the diagnostic criteria for heart valve disease published by American College of Cardiology (AHA) in 2017[6] and the Chinese expert consensus on echocardiographic evaluation of interventional treatment of MR[7]. Within 24 hours before CPVA, MR was evaluated during sinus rhythm and under stable clinical conditions (blood pressure control, optimal medical treatment).The vena contracta width (VCW, cm) on the parasternal long-axis plane under ZOOM mode was used as the main evaluation index of the degree of MR, the effective regurgitant orifiice area (EROA) and the regurgitant volume (RVol)measured by PISA method was used as the second reference index, (1)VCW<3 mm means mild MR; (2)VCW[?]3,¡7mm means moderate MR;(3)VCW>7 mm imeans severe MR(Table 1). All patients received echocardiography within 3 months after the operation.

4. Percutaneous catheter radiofrequency ablation

A three-dimensional endocardial electroanatomical mapping system (Johnson & Johnson, USA) was used to create and verify radio frequency injuries for all patients. Computed tomography can help to optimize the three-dimensional reconstruction. The ablation catheter and the circular catheter (BiosenseWebster, USA) used for recording and stimulation were both percutaneously punctured into the femoral vein and entered left atrium through the atrial septal. The radiofrequency signal was transmitted through an irrigation needle catheter (3.5 mm) equipped with a thermocouple. The target temperature was 45degC, and the power was 40W, which caused localized damage to the myocardium with a diameter and depth of 3 to 4 mm. As mentioned above, the radiofrequency injury was around the ipsilateral pulmonary vein, and the purpose was to establish a bidirectional conduction block between the left atrium and pulmonary vein, and reduce the local myocardial voltage to <0.15 mV, which could eliminate the pulmonary vein potential.

5. Postoperative follow-up and grouping

All patients routinely took the previous antiarrhythmic drugs for at least 3 months after the operation, and took the new anticoagulants for 2 months. The patients were followed up for 3-6 months. The ECG was followed up every month, and a 24-hour Holter examination was performed at least once a month. Telephone follow-up was also set up. Symptomatic patients were asked to take ECG examination at hospital. Recurrence was defined as: rapid atrial arrhythmia (including atrial fibrillation, atrial flutter, and atrial tachycardia) that occurred after a 3-month blank period of CPVA, confirmed by ECG or Holter, and lasted for [?]30 s. AF recurrence occurring in the first 3 months after the ablation (blanking period) were not counted for the purpose of the present analysis.

6. Statistical methods

Continuous variables were represented as mean +- standard deviation (SD) when following normal distribution, and were represented by P50 (P25, P75) otherwise. Categorical variables were expressed as frequency (%). Unpaired Student-t test or Mann-Whitney nonparametric test was used to compare between groups for continuous variables, and Pearson chi-square test or Fisher's exact test was used for categorical variables. The intra-class correlation coefficient (ICC) was used to analyze the agreement of measurements between two observers.

The split sample function automatically divided the original dataset into a modeling group and verification group at a ratio of 75:25. The multi-factor logistic regression method was used to establish a prediction model, and the best model parameters were selected according to the minimum Akaike's information criterion (AIC). The variable introduction standard was P <0.3. The independent variable was screened by collinearity (variation inflation factor, VIF), and the elimination criterion was VIF >10. The odds ratio (OR) and

95% confidence interval (CI) were calculated. The nomogram of the prediction model was plotted, which could visually display the prediction result of post-CPVA recurrence for each PAF patient. In addition, a calibration curve was plotted to show the prediction accuracy of the nomogram. The receiver operating characteristic (ROC) curve of the prediction model was plotted, and the area under the curve (AUC) and its 95% CI were obtained. The z statistic and Hanley and McNeil procedures[14] were used to compare the AUCs of modeling group and verification group. All statistical analysis was performed using R3.4.3 (http://www.R-project.org). All statistical tests were two-sided tests, and P <0.05 was considered statistically significant.

Results

1. Comparison of clinical data and echocardiographic parameters between the modeling group and validation group

5 PAF patients did not undergo CPVA due to left atrial appendage thrombosis, and 8 patients did not undergo CPVA due to targeted non-pulmonary venous disease. The study finally included 276 PAF patients, including 169 males and 107 females. 103 cases (37.7%) patients had MR before the operation. All patients completed the CPVA and converted to sinus rhythm during the operation. All patients showed reduced degree of MR regurgitation after the operation, no patients with severe MR 3 months after CPVA. The patients were divided into recurrence group (24 persons) and sinus rhythm group (252 persons) according to the follow-up results at 3-6 months after operation. The PAF patients were randomly divided into modeling group (203 cases) and verification group (73 cases) by statistical software at a ratio of 75:25. The comparison of clinical data and echocardiographic parameters between the two groups is shown in Table 2. There was no statistical difference between the two groups (P >0.05) in these parameters. The two observers exhibited perfect consistency in the results of echocardiographic parameter measurement (ICC:0.912–0.977, all$P$ <0.001).

2. Single factor analysis of clinical data and echocardiographic parameters in the modeling group

Univariate logistic analysis showed that, after radiofrequency ablation, the age, left atrial diameter (LAD), mild MR, moderate MR, and severe MR in the recurrence group were all higher than those in the sinus rhythm group, and LAAV was lower in the recurrence group. The other parameters were not significantly different between the two groups (P >0.05, Table 3).

3. Establishment and verification of the prediction model for post-CPVA recurrence in patients with PAF

In the modeling group, by using AF recurrence after radiofrequency ablation as the dependent variable, and using the patient's gender, age, body mass index (BMI), LAD, LVEF, left ventricular end-diastolic dimension (LVEDD), LAAV, degree of MR, B-type brain natriuretic peptide (BNP), CHA_2DS_2-Vasc as independent variables, we performed multivariate logistic regression analysis. The results showed that the age of PAF patients, the degree of MR, and LAAV were all independent risk factors for recurrence after CPVA, Table 4. The equation for predicting AF recurrence after radiofrequency was: Logit(P)= -3.253 +0.092xage+1.263xmild MR +2.325xmoderate MR +5.111xsevere MR -0.113xLAAV.

The ROC curve of the prediction model in the modeling group was plotted. The AUC was 0.889 (95%CI: 0.793-0.986), the sensitivity was 76.5%, the specificity was 94.6%, the positive likelihood ratio was 14.224, and the negative likelihood ratio was 0.249. The AUC of the prediction model was better than the single-factor parameters LAD, LVEF, LVEDD, LAAV, BNP, CHA_2DS_2-Vasc (all$P$ <0.05) (Figure 1A).

The ROC curve of the prediction model in the verification group was plotted. The AUC was 0.866 (95%CI: 0.711-1.000), the sensitivity was 71.4%, the specificity was 97.0%, the positive likelihood ratio was 23.571, and the negative likelihood ratio was 0.295. There was no significant difference in AUC between the modeling group and verification group (0.889 vs 0.866, P >0.05) (Figure 1B).

The nomogram (Figure 2) and calibration curve (Figure 3) of the prediction model were plotted. The

calibration curve showed that the prediction model had good consistency between the predicted value and observed value in both modeling group and verification group.

Discussion

In this study, we established a joint model based on MR degree and left atrial appendage function assessed by preoperative echocardiogram in PAF patients, in order to predict the risk of recurrence after CPVA. The diagnostic efficiency of the model was validated. Atrial fibrillation has caused increasing burden on patients and the medical system. Catheter ablation has more advantages over drug therapy in the treatment of AF patients to maintain sinus rhythm[15], and has become the first-line treatment for patients with PAF[16]. The maintenance of sinus rhythm after ablation is related to reverse remodeling, which can reduce LA size and improve left ventricular (LV) function. However, because atrial fibrillation is more likely to recur after CPVA, early and late recurrences require multiple operations and drug adjustments, and the scar after ablation can aggravate the structural remodeling of the left atrium. Therefore, we need to find some preoperative non-invasive indicators to identify patients at high-risk of recurrence after ablation, which will facilitate the adjustment of individualized treatment plans and precision medicine.

Many diagnostic techniques have been proven to help predict the recurrence of atrial fibrillation, including blood tests, echocardiography, computed tomography, and electrophysiological examinations. In addition, researchers have established multiple prediction models through the multiple indicators, including APPLE, ATLAS, CAAP-AF scores, etc[17-19]. The detection echocardiography is cost effective, convenient, and widely accepted in daily workup[20]. Previous studies have shown that the recurrence after catheter ablation (CA) in AF patients is largely dependent on the changes in the structure and function of the left atrium[21, 22]. The PAF patients selected in this study were mostly in the early stages of AF, with normal or slightly enlarged left atrium inner diameter. Their changes in left atrial structure were not significant. Since the PAF patients selected in this study were mostly in the early stages of AF, it is necessary to further search for indicators that can reflect atrial function and remodeling. These indicators are easy to detect and can provide valuable information.

The left atrium plays a vital role in the normal operation of the mitral valve, and timely atrial contraction is very important for mitral valve closure[23]. The MR of patients with AF is mostly functional type I MR, which may be caused by dilation of the mitral valve annulus due to atrial remodeling. In addition, MR is also related to the patient's age and the type of atrial fibrillation[24]. MR is easy to detect. The advances in equipment and clinical research have promoted more accurate methods for quantifying the degree of MR. Echocardiogram is particularly important in the evaluation of MR regurgitation. Other than the primary valvular disease and left ventricular insufficiency, 7.4% to 29% of AF patients have significant FMR[25-27], and 7.4% of the patients qualified for atrial fibrillation ablation have moderate or higher FMR. Recovering sinus rhythm can improve atrial function[24]. About 10.9% of PAF patients in this study had moderate or above FMR. Previous studies have shown that AF patients with MR are more likely to have recurrent AF after ablation. LZ et al. showed that the severity of MR in PAF patients was positively correlated with the incidence of recurrence after radiofrequency ablation[28]. Qiao et al. found that FMR was closely related to the matrix remodeling of the left atrium in PAF patients, and FMR was an independent risk factor for recurrence after radiofrequency ablation[29]. In this study, the risk of recurrence after radiofrequency in PAF patients gradually increased with the aggravation of mitral valve regurgitation. Previous research showed that the left atrial matrix remodeling , corresponding mitral valve annulus (MVA) expansion , mitral valve compensatory growth restriction, and decreased dynamic changes of the valve leaflets were important factors causing mitral valve regurgitation[26, 30]. After remodeling, the left atrium enlarges, the posterior leaflet annulus of the mitral valve shifts outward, and the anterior leaflet annulus shifts upwards by passive counterclockwise twisting; these changes lead to increased distance between the annulus papillary muscles, which limits the movement of mitral valve leaflet. In addition, the expansion of the mitral valve annulus is particularly obvious in the expansion of the posterior leaflet annulus[31]. The posterior leaflet of the mitral valve continues with the posterior wall of left atrium. The enlargement of left atrium causes the posterior leaflet of mitral valve to shift backward and downward. In addition, factors from left atrium, left

ventricle, and annulus cause or aggravate the functional mitral valve regurgitation, which further promotes the enlargement of left atrium, leading to the occurrence and maintenance of atrial fibrillation[32]. Therefore, for PAF patients with insignificant left atrium enlargement, MR can be used as a predictor for LA matrix remodeling[29]. These studies all provide evidence for using MR as a potential marker of left atrial matrix remodeling in AF patients.

The left atrial appendage is an extremely important accessory structure of the left atrium. Its morphology and structure are more complex[33]. The loss of coordination between contraction and diastole of the left atrial appendage in AF patients results in slow internal blood flow. The transesophageal echocardiography before AF radiofrequency ablation allows the observation of patient's left atrial appendage (LAA) hemodynamic changes from multiple angles, and yields the maximum emptying velocity of left atrial appendage. In addition, this study also used LAAV to rule out the effect of left atrial stunning on atrial function during the conversion of atrial fibrillation[34]. Therefore, LAAV plays an important role in clinical evaluation of left atrial appendage function. Melduni et al. found that, in patients with persistent AF after successful electrical cardioversion, the ones with reduced LAAV had increased risk of AF recurrence, stroke and death[35]. LAAV >40 cm/s could independently predict sinus rhythm persistence at 1 year[36]. In this study, the AUC of predicting AF recurrence based on LAAV alone was only 0.731, which may be related to the effects from heart function, heart rate, acquisition time and other factors on left atrial appendage function.

In this study, the degree of MR and LAAV were both independent predictors of atrial fibrillation recurrence after CPVA, but the diagnostic power of univariate indicator was still insufficient. Thus, we performed multivariate logistic regression on the observed indicators to establish a predictive model, which integrated clinical and echocardiographic parameters, and had more advantages over single-factor prediction. The calibration curve showed that the model had good prediction accuracy in both the modeling group and verification group. Many predicting models for recurrence after radiofrequency also showed similar results. He et al. found that a model constructed with LAAV could predict the risk of recurrence in PAF patients at 12 months after radiofrequency[37]. Yang et al. found that: the combined model integrating LA function and blood BNP level had good predictive value for the recurrence of early persistent AF after CPVA[38]. For the treatment of secondary MR, the management of primary disease is the most important; For severe cases, the MR guidelines recommend mitral valvuloplasty, mitral replacement, and percutaneous mitral valve repair. In this study, although the AF patients had moderate or higher MR before operation, their valve function was significantly improved after the recovery of sinus rhythm, and the degree of MR regurgitation was less than before. There was no patient with severe MR after radiofrequency.

This study still has limitations: (1) Although this study is a multi-center retrospective study, the number of cases included is small, and the small sample size may lead to selection bias; (2) All patients received 24-hour Holter monitoring during the follow-up, but they were not implanted with ring recorder, which may underestimate the recurrence rate of AF.

In summary, this study constructed and verified a model for predicting the recurrence of atrial fibrillation after CPVA in patients with PAF. The model took into account clinical and echocardiographic parameters and had good predictive performance. The model can identify high-risk patients with atrial fibrillation recurrence, and help doctors to optimize patient selection, inform patients of the recurrence risk, and design personalized treatment plans.

List of the terms

CPVA: circular pulmonary vein radiofrequency ablation

PAF: paroxysmal atrial fibrillation

MR: mitral regurgitation

LAAV: left atrial appendage emptying velocity

ROC: receiver operating characteristic

AUC: area under the curve

AF: atrial fibrillation

LVEF: left ventricular ejection fraction

LA: left atrial

RT-3DE: real-time three-dimensional echocardiography

TEE: transesophageal echocardiograghy

TTE: ansthoracic echocardiograghy

AHA: American College of Cardiology

VCW: vena contracta width

EROA: effective regurgitant orifiice area

LAD: left atrial diameter

BMI: body mass index

SBP: systolic blood pressure

DBP: diastolic blood pressure

LVEDD: left ventricular end-diastolic dimension

BNP:B-type brain natriuretic peptide

LV: left ventricular

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