

A novel predictive model of recurrence after surgical ablation of valvular atrial fibrillation

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Abstract

Background: Radiofrequency ablation(RFA) has emerged as a common approach to treatment of atrial fibrillation(AF) coupled with valve surgery. However, risk factors were rarely reported on recurrence after RFA of valvular atrial fibrillation . Methods: Retrospective study of a single-center database was performed in patients underwent valvular surgery combined with radiofrequency ablation. Follow-up was conducted from 3 months to 1 year after procedure. AF recurrence was defined as any episode of atrial arrhythmia lasting more than 30 seconds. Risk factors were analysis using Logistic regression and a predictive model was established. Results: 3-month follow-up was completed in 319 patients, 195 patients (61.1%) had AF recurrence. During the 1-year follow-up, 74 /166 patients(44.6%) had AF recurrence. Compared with sinus rhythm maintenance group, overweight($p=0.022$), high BMI($p=0.024$), large preoperative LAD($p<0.001$), small MI area($p=0.019$), large MI diameter($p<0.001$) and other liver function parameter like low ALT level($p=0.023$), high total bilirubin($p=0.013$) and direct bilirubin level($p=0.033$) were significantly correlated with AF recurrence after RF. In multivariate analysis, BMI(OR 1.12, 95% CI 1.04-1.21, $p=0.003$), LAD(OR 1.49, 95% CI 1.09-2.07, $p=0.015$), MI area(OR 0.41, 95% CI 0.18-0.85, $p=0.023$), MI diameter(OR 2.45, 95% CI 1.16-5.34, $p=0.021$), ALT(OR 0.98, 95% CI 0.97-0.99, $p=0.002$) and eGFR(OR 1.01, 95% CI 1.09-1.02, $p=0.042$) were significantly independent risk predictors of AF early recurrence. A predictive model was created with AUC of 0.720. Conclusions: BMI、LAD、MI area、MI diameter、ALT and eGFR were risk predictors of AF early recurrence. We established a predictive model and it devote to preoperative clinical health management of individual with valvular AF.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia defined as a rapid and irregular contraction of the atrial, with a consistent increased hospitalization by approximately 1% per year in USA¹. A typical electrocardiogram in AF shows no P waves and an irregular ventricular rate. It has been estimated that the worldwide incidence of AF was increased around 403 new cases per million person and the worldwide death of AF was increased by 48% in the past 10 years. According to the growing tendency, the estimated death rate of AF by the year 2050 is twice as much as now^{2, 3}. Among them, structural changes caused by valvular diseases are more likely to increase the occurrence of AF, and atrial fibrillation has seriously interfere with stroke events among patients with valve disease⁴. Absolutely, it has a serious impact on people's quality of life. The surgical treatment of atrial fibrillation is often performed with cox maze produce in conjunction with valvular heart diseases. Cox-maze IV procedure⁵, which was the most common maze procedure performed in the surgical treatment of AF and proven to be more efficient and convenient in

abolishing AF, but the recurrence rate of atrial fibrillation after maze procedure is still high. A total of 16% to 29% of those undergoing the cox maze procedure showed recurrent AF during the short term follow-up period as yet⁶⁻¹⁰. Thus, its also extremely important to prevent early recurrence of atrial fibrillation besides improve surgical success rate.

In previous studies^{4, 11, 12}, AF has become an independent risk factor of stroke, was related to increased mortality. Patients who have failed to restore sinus rhythm after treatment would be troublesome to appropriately rate and rhythm control which causes the loss of the quality of life, aggravate the occurrence of thromboembolic events. Long-term and continuous anticoagulant management is required. And it resulted in increasing greater disability and even mortality. Hence, more and more researchers focus on the prediction of atrial fibrillation recurrence on purpose for early intervention or even avoiding those adverse consequences.

To this end, several studies were designed to build predictive model to predicted the recurrence of AF. For example, Mesquita et al¹³ developed and recognized a risk score model of AF recurrence after pulmonary vein isolation(PVI) procedure blanking period(after first 3-month), including five predictors such as age $\geq$ 60years; female; non-paroxysmal AF; smoking; indexed left atrial volume. Thus, we aimed to perform a prediction model using inexpensive and widely available assay to investigate early recurrence at first 3 months of the valvular AF after the RF maze procedure with valvular surgery at our single center.

Methods

Study population

This was a retrospective analysis. Clinical data of all patients were collected and enrolled from the department of Cardiothoracic Surgery of Affiliated Drum Tower Hospital of Nanjing University Medical School between September 2018 and November 2019. All patients were preoperatively diagnosed with persistent valvular AF and valvular disease by a pre-ablation Holter and comprehensive transthoracic echocardiographic examination. Persistent AF was defined as any AF episode lasting longer than 7 days and requiring termination by cardioversion. The current study was approved by the institutional review board of Nanjing Drum Tower Hospital (2020-281-01).

The flowchart of the research were as follows(figure 1): (1) a total of 359 patients were collected from September 2018 to November 2019 in our department who underwent cardiac valve surgery combined with RF maze produce.(2) 29 patients were excluded because of lack of clinical data; 3 case died of heart failure after discharge; 2 case died of pulmonary infection after discharge; 1 case died of cancer after discharge; and another 5 patients were lost at follow-up.(3) Finally, 319 patients eventually achieved complete clinical data and follow-ups.

Data collection and Scoring standards

Baseline information for all patients was collected on admission such as age, sex, height, weight, body mass index[BMI], smoking, alcohol status, medical history(hypertension, coronary heart disease[CHD], diabetes mellitus[DM], chronic kidney disease[CKD]) and preoperative echocardiography. Blood sampling as laboratory tests was collected the morning after hospitalization and use to measure preoperative routine blood analyses or hematologic predictors. The CHA2DS2-VASc score was calculated as follows¹⁴: Congestive heart failure(1 points), Hypertension(1 points), Age $\geq$ 75 years(2 points), Diabetes mellitus(1 points), Prior Stroke or TIA or thromboembolism(2 points), Vascular disease(1 points), Age 65 to 74 years(1 points), female gender(1 points), which is recommended in guidelines. The duration of AF was calculated based on the time of patient's first onset of symptoms prior to admission or the first electrocardiogram diagnosis.

Amiodarone was discontinued at least 3 months before the procedure; all other antiarrhythmic drugs (AADs) were discontinued at least 5 half-lives before the ablation.

Bioprosthetic valve replacement and repairs patients were required oral anticoagulants(OACs) such as warfarin at least 3 months post-procedure, and mechanical valve replacement patients were prescribed OACs all their life. Check INR(international normalized ratio) at regular intervals and targeting INR range 2.5-3.0.

Surgical Radiofrequency Procedure

All procedures were performed under conventional cardiopulmonary bypass, hypothermia and cardioplegic arrest. Patients underwent radiofrequency ablation(Cox Maze IV) as a concomitant procedure during valvular surgery. Cardioblate surgical ablation system(Medtronic, Minneapolis, USA) were applied for radiofrequency ablation. The energy delivered by unipolar catheter to transmural atrium was approximately 25-30 Walt. Marshall ligament was resected and left atrial appendage(LAA) was resected or ligated during the operation.

Follow-up and end-point

All patients were followed up for first 3 months after operation. During the follow up. 24-hour Holter monitoring were prescribed for evaluate the postoperative sinus maintenance. We considered to have postoperative arrhythmias if patients had self-reported AF episodes and Holter changes. The early AF recurrence was defined as any episode of atrial arrhythmia lasting more than 30 seconds, which was confirmed by Holter during the first blank period of 3 month after RF maze surgery. The late AF recurrence is defined as non-sinus maintenance begin 6 months or 1 year after surgery. All outcome events were obtained via telephone or WeChat official account or outpatient follow up for 3 months after surgery.

Statistical analysis

All data are presented as n (%) for categorical variables and continuous variables are presented as median (interquartile range, IQR) and mean $\pm$ SD. Normality distribution were tested with the Kolmogorov-Smirnov test. Independent t-tests were performed for normally distributed variables, or Mann-Whitney U tests for non-normal distribution. Categorical variables were analyzed by Chi-square test or Fisher's exact test, as appropriate. Multivariate analysis was performed using a binary logistic regression model after best subset feature selection to discriminate independent risk factors for AF recurrence.

R software (version 4.0.3) was used for data analysis. R packages "tableone" were used for basic statistics and to make table one. The package "glmnet", "rms", "caret" and "leaps" was used for data reshape, best subset feature selection and logistic regression. Bootstrap was used to identify the robustness of the final model. Brief steps of feature selection in multiple regression analysis model using best subset selection: A) select variables using best subset selection and the optimum fitting predicted model is identified by comparing the RSS(residual sum of squares), adjusted R square, Cp(Mallow's Cp) and BIC(Bayesian information criterion). B) adjusted the R square, Cp and BIC are three statistics used to evaluate the model. A p-value of less than 0.05 was considered statistically significant.

Results

Follow-up Result and patient' characteristics

The data were available for 319 of 359 (88.9%) discharged patients. During the follow-up period, there were 11 patients were lost to or rejected follow-up, Heart failure was documented in 3 patients; 2 cases died of pulmonary infection after discharge and 1 patients died of cancer. In the remaining patients, 124 cases maintain sinus rhythm(SR) after 3 months and 195 were AF recurrence. The clinical characteristic of patients are shown in Table 1. There were no statistically differences in the baseline characteristics($p < 0.05$), including age, sex, height and preoperative basic disease, such as hypertension, diabetes mellitus(DM), coronary artery disease(CAD), chronic kidney disease(CKD) and stoke, patients who smoked or drink, CHA2DS2 score between the patients with or without AF recurrence. However, weight(60.00(53.75-70.00) versus 63.00(55.25-72.50) kg; $p = 0.040$) and BMI(22.92 (20.43-24.91) versus 23.73(21.24-26.10)kg/m²; $p = 0.038$) were higher in the AF recurrence group, while patients with recurrent AF had longer duration of AF(1.00(0.08-6.00) versus 2.50(0.19-10.00) years; $P = 0.022$). And among the preoperative echocardiographic parameters, the left atrial diameter (LAD) (5.10(4.60-5.50) versus 5.27(4.96-6.14)cm; $p < 0.001$) and mitral diameter(3.75(3.53-3.91) versus 3.87(3.66-4.10) cm; $p < 0.001$) were also more increased than the sinus rhythm maintain group (Table 2). In addition, higher total bilirubin(12.15(8.90-16.12)versus 13.40(9.90-19.25) $\mu\text{mol/L}$; $p = 0.027$) were in the AF recurrence group, but we found that other preoperative liver enzymes including ALT(21.35(15.73-36.60)versus

19.90(13.30-29.25) U/L; $p=0.026$), AST(23.80(18.35-31.15) versus 21.85(17.33-28.10) U/L; $p=0.048$) were higher in non-recurrence AF group(Table 3).

Univariable analysis of AF recurrence

In univariate logistic regression analysis (Table 4), the baseline characteristics weight(odds ratio, 1.024; 95% CI, 1.004-1.045; $p=0.022$), BMI(odds ratio, 1.081; 95% CI, 1.011-1.159; $p=0.024$), preoperative LAD(odds ratio, 1.651; 95% CI,1.273-2.182; $p<0.001$) ,MI area(odds ratio, 0.429; 95% CI,0.204-0.844; $p=0.019$), MI diameter(odds ratio, 3.091; 95% CI,1.69-5.907; $p<0.001$) and other liver function parameter like ALT(odds ratio, 0.989; 95% CI,0.98-0.998; $p=0.023$), Total bilirubin(odds ratio, 1.037; 95% CI,1.009-1.069; $p=0.013$) and Direct bilirubin(odds ratio, 1.085; 95% CI,1.013-1.176; $p=0.033$) were significantly correlated with AF recurrence after RF. However, none of the AF duration and AST level were associated with the recurrence of AF. Besides, we found that PASP(odds ratio, 1.017; 95% CI, 0.997-1.037; $p=0.099$) and eGFR(odds ratio, 1.009; 95% CI, 0.999-1.019; $p=0.090$) were also considered to be associated with recurrent of AF when p values was less than 0.10. All those variables above were showed in a forest plot(Figure 2.)

Feature selection using best subset selection

Multiple regression analysis model shown that there were three different combinations of variables to form the best prediction of fit degree by best subset selection(Figure 3A). The selected variables are shown in Figure 3B. The first model includes seven features which are BMI, LAD, MI area, MI diameter, ALT, TBil and eGFR. Second one has three features including BMI, LAD and ALT levels. And the last model also selects seven features which are the same as model one.

Discrimination and robustness final model

In multivariate analysis, BMI(OR 1.12, 95% CI 1.04-1.21, $p=0.003$), LAD(OR 1.49, 95% CI 1.09-2.07, $p=0.015$), MI area(OR 0.41, 95% CI 0.18-0.85, $p=0.023$), MI diameter(OR 2.45, 95% CI 1.16-5.34, $p=0.021$), ALT(OR 0.98, 95% CI 0.97-0.99, $p=0.002$) and eGFR(OR 1.01, 95% CI 1.09-1.02, $p=0.042$) were significantly independent risk predictors of AF early recurrence(Table 4). Meanwhile, ROC analysis was used to demonstrated the association between models and AF recurrence. We realized that the model which contains seven variables has a significant predictive value with AUC of 0.720, the second model including BMI, LAD and ALT levels variables demonstrated a predictive value with AUC of 0.715. and the last model consists of six variables without TBil showed a predictive value with AUC of 0.679(Figure 4A). Obviously, the figure 4B shows that the model has good robustness. The robustness of the final model(Model1) was examined by repeatedly refitting the model to 1000 differently sampled training and test sets (ratio 80:20) via the bootstrap procedure. The mean AUC is 0.687 with a 95% bootstrap CI of 0.683–0.691.

Discussion

The major findings of this follow-up study are as follow: 1) patients with AF recurrence had higher weight and BMI, most of them undergoing longer AF duration. but there was no statistically significant difference between gender and age. 2) pre-echocardiography revealed that patients with AF recurrence had a larger LAD and mitral anulus diameter with a smaller preoperative mitral orifice area , suggesting that these patients in our center were often accompanied by mitral stenosis or mitral regurgitation which was also the clinical characteristics of valvular AF patients. 3) other variables that were strongly associated with recurrence of AF was liver-derived parameter such as higher total bilirubin(TBil), direct bilirubin levels(DB) and lower ALT level. To the best of our knowledge, liver enzymes have never been reported to be involved in the prediction of AF recurrence. And a novel and simple predictive model was established with an AUC of 0.720 to predict short-term recurrence of valvular AF.

Till now, a number of studies have been used to predict long-term outcome after catheter ablation, but few have been studied for surgical radiofrequency ablation. RFA has emerged as a common approach on treatment of persistent valvular AF coupled with valve surgery which can effectively restore sinus rhythm⁹. Some prior studies suggest that the blanking period(first 3month) after RFCA might be a transient phenomenon couldn't considered recurrences¹⁵, since the results of long-term follow-up are helpful to determine

whether atrial fibrillation has recurs and to modify the anticoagulants management in timely to improve the quality of life of patients, recent studies have focused on the late recurrence and even very late arrhythmia recurrence (more than 12 months follow-up) after RFCA^{16, 17}. However, current studies suggest that early recurrence (define as the first 3 month) is associated with late recurrence (>1 years). Therefore, we are more devoted ourselves to the prediction of early recurrence than long-term recurrence. In our study, six independent risk factors related to recurrence of valvular AF after radiofrequency were analyzed: BMI, LAD, MI area, MI diameter, ALT and eGFR.

In clinical practice, LAD is well-established predictor when predicting the recurrence rate of AF. It has been known that large LA size is related to outcome of AF¹⁸ and leading to severe hemodynamic disorders, however, assessment of LAD using echocardiographic has heterogeneity among different observers and it's not accurate to use only one LAD indicator for recurrence prediction¹⁹. In this study, we found that recurrence after RFA is affected by several other factors as well. For example, the internal diameter and the area of the mitral valve annulus, which have not been reported in previous studies, have also shown to be related to valvular AF recurrence in this study. when AF recurs, patients with valvular disease in our study required TTE and TEE evaluation preoperatively and intraoperatively, and we can evaluate LAD, mitral valve diameter, and degree of stenosis by comparing multiple echocardiographic parameters to reduce errors. Yang et al²⁰ also aimed to develop a model based on BNP levels and LA function parameters which contains left atrial appendage peak emptying velocity (LAAV), minimum LA volume index (LAVImin) and diastolic emptying index (DEI) to predicting short-term recurrence of persistent AF after RFA. Our study found that these factors couldn't be validated in patients with valvular AF. It's possible that patients with long-term valvular heart disease have poorer cardiac function and are more prone to atrial remodeling than patients without valvular AF. Previous studies²¹ have indicated that structural remodeling of LA is the potential mechanisms for the occurrence of atrial fibrillation, while valvular AF is a progressive disease, hence, it's not surprising that MI diameter and MI area are associated with recurrence of valvular AF.

In addition to the risk factors associated with echocardiography parameters, eGFR as a marker of renal dysfunction has been associated with the prognosis of AF. Although the research on the prediction of AF recurrence after RFA is sparse, eGFR has been involved in many other predictive model (SCALE-CryoAF score²², APPLE score²³ etc) after catheter ablation²⁴. While APPLE and SCALE-CryoAF describes risk factors for AF recurrence after CBA, these score systems don't specifically assess radiofrequency ablation (RFA). these studies suggest that aggravation of renal function was associated with failure of restore sinus rhythm^{25, 26}. As well as our analysis, patients who underwent AF recurrence after RFA has higher baseline eGFR. And Raymond et al²⁷ demonstrates that obesity and high BMI are risk factor of AF recurrence, which is consistent with our analysis. And then, in a large scale long-term recurrence prediction study after radiofrequency catheter ablation (RFCA), the author²⁸ divided the BMI into 3 levels in detail (BMI<25kg/m²; 25[?]BMI<29kg/m²; BMI[?]30kg/m²) proving that patients with higher baseline BMI were easier to relapsed AF after RFCA, especially in BMI[?]30kg/m². Many research has been proved that age is a predictor of AF recurrence. Bunch et al²⁹ showed that elder population, particularly over 70 years of age, notable impacts outcomes of ablation with long-term follow-up. However, Average age in our patients is normally about 61 years-old, there is no statistical difference among our group.

Furthermore, of note in our report, this model is the first to confirm the association between liver enzymes and postoperative recurrence of valvular AF. In several studies, abnormal liver function was significantly correlation with the onset of AF³⁰⁻³², but the research on valvular atrial fibrillation and the outcome of postoperative recurrence and serum liver enzyme levels is sparse. Jiang et al³³ summarized some circulating blood markers that have been published so far related to the recurrence of AF, including inflammation-related serum markers and those involved in atrial remodeling, such as CRP, IL-6, BNP and TIMP-2 etc. However, our results also suggested that the simple laboratory test of serum liver function parameters was associated with outcome of valvular AF after RF.

In comparison, only one published study³⁴ has noted that serum bilirubin could be a biomarker to predicted AF recurrence. This view is consistent with our results from patients who concomitant valvular disease. Even

though TBil is not an independent risk factor for valvular AF recurrence in the multivariate analysis, we found that the AUC area increased after adding TBil variable to the model(model1 AUC 0.720 versus model3 AUC 0.679) which indicating that there may becomes more statistically significant differences between TBil and valvular AF recurrence in larger cohorts. In addition, liver injury parameters (ALT, AST, GGT), mainly GGT, has been considered as a significantly risk factor of cardiovascular diseases, including myocardial infarction, stroke and atrial fibrillation(AF)^{32, 35-37}. Although GGT level is reasonable to assume related to the elevated occurrence of AF in previous studies, we found no statistically difference in AF recurrence. Remarkably, in our study, univariable analysis indicated that decrease alanine transaminase(ALT) levels as a potential factor contributing to assess AF recurrence. Increases in ALT levels sever as an indicator of liver damage and hepatitis in clinical practice, the significant impacts on tumor postoperative recurrence-related events has been confirmed in recent studies³⁸. But less is known about the clinical value related with low ALT levels and the role of this serum liver enzyme in AF is poor studied. Dong et al³⁹proposed a new concept that ALT might to be an novel independent biomarker of aging and presumably independent of liver function. it's well known that aging involved in the mechanisms of myocardial remodeling contribute to the occurrence of AF⁴⁰. And preoperative AF associated with valvular disease compares to non-valvular AF is more prone to atrial remodeling, fibrosis and increased risk of thromboembolic events, among them, fibrosis has a negative effect on the maintenance of sinus rhythm⁴¹. Low ALT, aging and AF share interacting relationships. Therefore, an assumption for decrease ALT levels may lead to cellular and tissue aging which indicate fibrosis and oxidative stress damage environment that accelerates the recurrence of valvular AF. However, The underlying mechanism of short-term recurrence in patients with preoperative low serum ALT levels should be investigated in future studies. And all of the elements in this model are readily available and inexpensive which is particularly convenient for clinical use.

Conclusions

A new framework of early recurrence from persistent valvular AF was introduced. This study remedy knowledge gap and first established the link between recurrence of valvular AF and liver enzymes. It also provides an indication to clinicians that normal liver function before surgery may be effective in preventing postoperative AF recurrence. However, there are several limitations in our study. Small sample sizes and short-term follow-up time is the primary deficiency might be the reason why some of the characteristics were differ from other authors in long-term follow-up. it's necessary to tested further for our prediction model in larger samples and external validation. Secondly, this is a retrospective study, and some data were lacking when collecting data. Ultimately, our findings demonstrated a predicts value model that could devote to preoperative clinical health management of individual with valvular AF.

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Tables

Table1. Characteristics of Preoperative Patients for Atrial Fibrillation

Abbreviations: BMI, body mass index; CAD, Coronary artery disease ;CKD, Chonic kidney disease; NYHA, New York Heart Association;

* Statistically significant value($p < 0.05$)

Table2. Preoperative Echocardiographic parameters of Patients

Abbreviations: MI, mitral insufficiency; MS, Mitral Stenosis; IVSTD, Interventricular Septum Thickness Diastolic; LVDs, left ventricular end systole diameter; LVDd, Left ventricular end diastolic diameter; LAD, left atrial diameter; LVEF, left ventricular ejection function; PASP, pulmonary arterial systolic pressure.

Graded by severity: I, Mild; II, Mild-moderate; III, Moderate; IV, Moderate severe; V, Severe.

* Statistically significant value($p < 0.05$)

Table3. Preoperative Laboratory Characteristics of Patients

Abbreviations: WBC, White Blood Cell; PLT, Platelets; ALT, Alanine transaminase; AST, Aspartate aminotransferase; GGT, γ -glutamyl transpeptidase; TBil, Total bilirubin; DB, Direct bilirubin; CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate

* Statistically significant value($p < 0.05$)

Table 4. Univariable and Multivariate analysis of recurrence in AF patients following RF

* Statistically significant value($p < 0.05$)

Figure legends

Figure 1. Details chart of the study participants.

Figure 2. Univariate analysis of arrhythmia recurrence in AF patients following RF

Figure 3. Feature selection in Multiple regression analysis model(3A and 3B)

Figure 4. Three prediction model to predict AF early recurrence by receiver operating characteristic(ROC) analysis(A) and rubust control(B).

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