

Left Atrial Appendage Circular RNAs Are New Predictors of Atrial Fibrillation Recurrence After Surgical Ablation in Valvular Atrial Fibrillation Patients: a Case Control Study

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Research Article

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Abstract

Background: Atrial fibrillation recurrence after surgical ablation in valvular atrial fibrillation patients will increase the mortality and morbidity during follow-up. In this study, we attempted to evaluate the relationship between circular RNAs in left atrial appendage and atrial fibrillation recurrence to establish a predictive model for early intervention.

Methods: A retrospective case control study of all patients who underwent surgical ablation during valve surgery was performed. The expression level of circular RNAs were detected in the left atrial appendage tissue after surgery. 24 hours Holter examination was used to evaluate the status of heart rhythm during follow-up. The independent risk factors of atrial fibrillation recurrence were analyzed by multivariate analysis. The predictive model of atrial fibrillation recurrence was visualized by Nomogram and was tested by receiver operating characteristic curve analysis. Kaplan-Meier analysis was performed to compare the rate of freedom from atrial fibrillation recurrence after surgery.

Results: A total of 136 patients completed the research strategy from September 2018 to June 2019, 81 (59.6%) patients restored sinus rhythm and 55 (40.4%) patients experienced atrial fibrillation recurrence. Increased age ($P=0.002$), longer AF duration ($P<0.001$) and increased expression of *circ 81906-RYR2* ($P<0.001$), *circ 44782-LAMA2* ($P=0.002$), *circ 418-KCNN2* ($P=0.011$) and *circ 35880-ANO5* ($P<0.001$) were detected in atrial fibrillation recurrence group. Multivariate analysis revealed that increased age (odds ratio=1.072, $P=0.006$), longer AF duration (odds ratio=1.007, $P=0.036$) and increased expression of *circ 81906-RYR2* (odds ratio=2.210, $P<0.001$) were independent risk factors for recurrence. The area under the curve was 0.77 and the cut-off value was 70 points of the predictive model. The results of Kaplan-Meier plots showed that patients over 70 points were more likely to suffer from atrial fibrillation recurrence during the follow-up.

Conclusions: *Circ 81906-RYR2* could be a new predictor of atrial fibrillation recurrence after surgical ablation. A predictive model consists of age, atrial fibrillation duration and expression of *circ 81906-RYR2* was alternative for early intervention of atrial fibrillation recurrence.

Trial registration: Retrospectively registered.

Background

Surgical ablation combined with valve surgery is an effective method to maintain sinus rhythm (SR) during follow-up in valvular atrial fibrillation (AF) patients [1]. Restoration of sinus rhythm is helpful to decrease the incidence of heart failure, re-hospitalization and thrombotic events after surgery [2]. However, the restoration rate after surgery varied among different centers (65%-95%) [3–6]. A real-world nationwide study also showed the rate of AF recurrence range from 31–45% [7]. The outcome of patients with persistent or permanent AF was worse than patients with paroxysmal AF. Several risk factors have been identified in the former studies, such as advanced age, concomitant cardiovascular disease and the length of AF duration [8, 9] to predict the possibility of post-operative AF recurrence. It is helpful to find

some new biomarkers to predict AF recurrence after surgical ablation in AF patients with valvular heart disease (VHD) and make the early therapeutic intervention for those who suffered from AF recurrence. Circular RNA (CircRNA) is a kind of non-coding RNA and which was first described in the early 1990s [10]. Basic researches have revealed that circRNAs can be used as clinical predictors for central nervous disease [11] and cancers [12], our former study have found several differentially expressed circRNAs in AF patients with VHD [13], however whether these circRNAs can be used as clinical biomarkers for outcome of surgical ablation still need further evaluation. The aim of this study was to evaluate the prognostic value of circRNAs for the outcome of surgical ablation in persistent AF patients with VHD. We present the following article in accordance with the STROBE reporting checklist.

Methods

Patients enrollments

A total of 150 persistent AF patients with VHD were continuously enrolled in this study from September 2018 to June 2019. Preoperative transthoracic echocardiography (TTE) was performed to evaluate the subtype of valve diseases, the degree of valve diseases, left atrial diameter (LAD) and the left ventricular ejection fraction (LVEF). Persistent AF was diagnosed by the preoperative 24 hours Holter examination in patients with continuous AF over 3 months. Patients over 50 years old need to finish coronary angiography to evaluate the coronary artery lesion. Demographic data (including age, gender and body mass index), cardiovascular risk factors (hypertension, diabetes mellitus, chronic kidney disease, smoke or alcohol abuse), concomitant diseases, results of TTE and intro-operative data (operation time, cardiopulmonary bypass time, aortic crossclamp time, valve repair or replacement and type of artificial valve) were recorded for further exploration. The exclusion criteria were listed as follow: 1) age of patients was less than 18 or more than 75 years old, 2) patients with aortic diseases, infective endocarditis, congenital heart diseases or acute myocardial infraction, 3) non-valvular AF, 4) patients died during perioperative period. Remote ECG monitoring was settled for all patients in the first 5 days after operation. Beta blocker or amiodarone was used to maintain the heart rate between 60 and 70 bpm. All patients discharged without complications and received more than 1 year follow up. Telephone interviews were performed monthly and all patients required to finish the 24 hours Holter examination during visit to the outpatient clinic 3 months, 6 months and 1 year after operation to evaluate the arrhythmia events during follow-up. Patients were divided into two groups as sinus rhythm maintenance (SRM) and atrial fibrillation recurrence (AFR) according to the results of the 24 hours Holter in 3 months and 1 year separately. Patients who experienced AF events in 3 months received at least once cardioversion and following antiarrhythmic drugs therapy.

Surgical procedures

Surgical ablation also known as Cox-Maze IV procedure [14] was performed in all patients. Cardioblade surgical ablation system (Medtronic, Minneapolis, USA) was selected to finish the radiofrequency ablation. Bi-atrial ablations were achieved, left atrial appendage (LAA) and Marshall ligament were

resected during the operation. Valve replacement or repair were performed in patients with valve diseases. Coronary artery bypass graft was operated in patients with coronary artery lesions. In brief, after cardiopulmonary bypass (CPB) establishment, pulmonary vein isolation and the ablation of right atrium was performed before ascending aorta clamping, then the ablation of left atrium was performed according to the procedure of Cox-Maze IV. The ablation energy was settled range from 25 Walt to 30 Walt. There were 40 mitral valve repair, 10 aortic valve repair, 125 tricuspid valve repair, 66 mitral valve replacement, 26 aortic valve replacement, 1 tricuspid valve replacement and 13 coronary artery bypass graft performed as the concurrent surgery.

Examination of circRNAs in LAA tissue

LAA was resected in all patients enrolled in this study. The specimen was divided into two parts after resection, of which, one was immediately frozen into liquid nitrogen for RNA isolation and further experiments, the other was prepared for pathological analysis.

The expression level of circRNAs in LAA were detected by using quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR). Total RNA was extracted from LAA sample using TRIzol Reagent (Cat. No 15596018, ThermoFisher Scientific) according to the manufacturer. The concentration of total RNA was measured by NanoDrop One (ThermoFisher Scientific) and then it was reverse transcribed to synthesize cDNA using HiScript II Q Select RT SuperMix for qRT-PCR (Cat. No R232-01, Vazyme). The expression of specific circRNA (*circ 81906-RYR2*, *circ 44782-LAMA2*, *circ 418-KCNN2*, *circ 35880-ANO5* and *circ 255-ITGA7*) was measured by qRT-PCR with ChamQ Universal SYBR qPCR Master Mix (Cat. No Q711-02, Vazyme) and LightCycler 480 Instrument II (Roche Molecular System, Inc). *GAPDH* was selected as the internal reference and the relative expression level of circRNA was calculated with the $2^{-\Delta\Delta CT}$ method. The primers used in this study were listed in Supplementary Table 1.

Statistical analysis

Numerical variables were described as mean \pm standard deviation (SD), categorical variables were described as case numbers. Statistical analysis was performed by using SPSS version 23.0. Differences of continuous variables between groups were measured by Student's *t* test or Mann-Whitney *U* test. Chi-square test was used to analyze the categorical variables, fisher's exact was used when sample size was less than five. Kaplan-Meier analysis was used to compare the rate of freedom from AF. Multivariate logistic regression analysis was performed to find the predictors of AF recurrence. Rms package was used to visualize the predictive model and nomogramFormula package was used to calculate the total score of each patient by using the R language (version 4.0.3). Receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity of the prediction model. Youden's index was calculated by the formula $J = \text{sensitivity} + \text{specificity} - 1$. Kaplan-Meier analysis was performed to compare the rate of freedom from AF recurrence after surgery. P value less than 0.05 was considered significantly different.

Results

150 persistent AF patients with VHD were continuously enrolled in this study from September 2018 to June 2019. According to the exclusion criteria, seven patients were excluded from this study. Four patients were due to overage, two patients were excluded because of the diagnosis of aortic disease, another one patient was excluded because the valve disease was aroused by acute myocardial infraction. The remained 143 patients were put forward to receive the surgical ablation procedure during operation. There were seven cases lost follow-up. Finally, data of 136 patients were remained for further analysis. The mean follow-up period was 19.8 ± 2.9 months. The clinical characters were listed in Tables 1 and 2.

Table 1
Clinical characteristics of valvular PeAF patients in 3 months follow-up

	SRM1 N = 72	AFR1 N = 64	P value
Age (year)	58.9 ± 9.6	61.4 ± 8.0	0.098
Gender (Male/Female)	36/36	29/35	0.610
BMI (kg/m ²)	23.3 ± 3.6	24.4 ± 3.3	0.055
AF duration (month)	41.0 ± 60.6	61.2 ± 77.6	0.023
Cardiovascular risk factors			
Hypertension (n/%)	22 (30.6%)	25 (39.1%)	0.367
Diabetes mellitus (n/%)	3 (4.2%)	5 (7.8%)	0.475
CKD (n/%)	1 (1.4%)	2 (3.1%)	0.601
Smoke abuse (n/%)	7 (9.7%)	5 (7.8%)	0.769
Alcohol abuse (n/%)	5 (6.9%)	2 (3.1%)	0.447
Coronary artery disease (n/%)	10 (13.9%)	11 (17.2%)	0.640
Stroke (n/%)	4 (5.6%)	3 (4.7%)	1.000
Transthoracic echocardiography			
LAD (cm)	5.1 ± 0.9	5.5 ± 1.1	0.024
EF (%)	52.4 ± 6.9	53.0 ± 7.8	0.403
Rheumatic valvular disease (n/%)	40 (55.6%)	32 (50.0%)	0.606
NYHA Class			
Class I	1	4	0.343
Class II	34	24	
Class III	36	34	
Class IV	1	2	
BNP (pg/mL)	345.5 ± 301.7	319.2 ± 301.3	0.769
CRP (mg/L)	7.2 ± 20.9	8.2 ± 15.5	0.346

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; LAD, left atria diameter; EF, ejection fraction; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate

	SRM1	AFR1	P value
	N = 72	N = 64	
eGFR (mL/(min*1.73m ²))	93.5 ± 23.7	95.1 ± 21.6	0.675
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; LAD, left atria diameter; EF, ejection fraction; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate			

Table 2
Clinical characteristics of valvular PeAF patients in one-year follow-up

	SRM2 N = 81	AFR2 N = 55	P value
Age (year)	58.2 ± 9.3	62.8 ± 7.7	0.002
Gender (Male/Female)	43/38	22/33	0.163
BMI (kg/m ²)	23.9 ± 3.6	23.7 ± 3.4	0.849
AF duration (month)	35.2 ± 54.8	67.2 ± 72.9	< 0.001
Cardiovascular risk factors			
Hypertension (n/%)	26 (32.1%)	21 (38.2%)	0.582
Diabetes mellitus (n/%)	6 (7.4%)	2 (3.6%)	0.473
CKD (n/%)	2 (2.5%)	1 (1.8%)	1.000
Cholesterol (n/%)	1.35 ± 0.69	1.63 ± 3.57	0.051
Triglyceride (n/%)	3.80 ± 0.91	3.65 ± 0.78	0.314
Smoke abuse (n/%)	7 (8.6%)	5 (9.1%)	1.000
Alcohol abuse (n/%)	6 (7.4%)	1 (1.8%)	0.241
Coronary artery disease (n/%)	9 (11.1%)	12 (21.8%)	0.098
Stroke (n/%)	4 (4.9%)	3 (5.5%)	1.000
Transthoracic echocardiography			
LAD (cm)	5.18 ± 0.86	5.39 ± 1.12	0.400
EF (%)	53.1 ± 6.7	52.0 ± 8.1	0.385
Rheumatic valvular disease (n/%)	43 (53.1%)	29 (52.7%)	1.000
NYHA Class			
Class I	3	2	0.511
Class II	38	20	
Class III	39	31	
Class IV	1	2	

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; LAD, left atria diameter; EF, ejection fraction; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; CPB, cardiopulmonary bypass time; ACC, aortic crossclamp; CABG, coronary artery bypass graft

	SRM2	AFR2	P value
	N = 81	N = 55	
BNP (pg/mL)	316.5 ± 264.0	357.2 ± 347.8	0.980
CRP (mg/L)	7.26 ± 20.08	8.24 ± 16.10	0.304
eGFR (mL/(min*1.73m ²))	93.2 ± 22.8	96.1 ± 22.5	0.558
Intraoperative data			
Operation time (hour)	4.40 ± 0.99	4.30 ± 0.98	0.610
CPB time (min)	153.0 ± 44.2	144.7 ± 41.5	0.242
ACC time (min)	117.4 ± 43.3	109.2 ± 40.3	0.235
Mitral valve repair (n)	23	17	0.691
Mitral valve replacement (n)	35	31	
Aortic valve repair (n)	7	3	1.000
Aortic valve replacement (n)	17	10	
Tricuspid valve repair (n)	74	51	1.000
Tricuspid valve replacement (n)	1	0	
CABG (n)	7	5	1.000
Bioprosthetic valve	37	27	0.107
Mechanical valve	23	7	
Types of arrhythmia			
Persistent atrial fibrillation (n/%)		41 (74.5%)	
Paroxysmal atrial fibrillation (n/%)		6 (10.9%)	
Atrial flutter (n/%)		8 (14.5%)	
Total score > 70 points (n/%)	26 (32.1%)	40 (72.7%)	< 0.001
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; LAD, left atria diameter; EF, ejection fraction; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; CPB, cardiopulmonary bypass time; ACC, aortic crossclamp; CABG, coronary artery bypass graft			

Patients were split up into two groups at 3 months or 1 year after operation. There were 64 patients (47.1%) suffered from recurrent AF (AFR1 group) during the first 3 months follow-up. LAD (5.1 ± 0.9 vs

5.5 ± 1.1, P = 0.024) and AF duration (41.0 ± 60.6 vs 61.2 ± 77.6, P = 0.023) were significantly different between two groups (Table 1).

According to the Holter examination in one-year follow-up, there were 81 patients getting a result of SR (SRM2 group), other 55 patients were diagnosed AF (AFR2 group). 74.5% of the recurrent patients were persistent AF. The preoperative clinical characters showed that patients in SRM2 group was 4.6 years younger (58.2 ± 9.3 vs 62.8 ± 7.7, P = 0.002) than AFR2 group. The AF duration was shorter in SRM2 group patients (35.2 ± 54.8 months vs 67.2 ± 72.9 months, P < 0.001). None difference was found in other variables (Table 2). Compared to the follow-up results of three months, 21 patients in AFR1 group restored sinus rhythm and 12 patients in SRM1 group progressed to persistent AF in one-year examination.

Based on the one-year follow up results, the relative expression of *circ 81906-RYR* (0.0160 ± 0.008 vs 0.0245 ± 0.0141, P < 0.001), *circ 44782-LAMA2* (0.00564 ± 0.00290 vs 0.00754 ± 0.00384, P = 0.002), *circ 418-KCNN2* (0.00760 ± 0.00475 vs 0.01071 ± 0.00812, P = 0.011) and *circ 35880-ANO5* (0.0242 ± 0.0111 vs 0.0341 ± 0.0178, P < 0.001) were significantly increased in AFR2 group patients compared with SRM2 group (Fig. 1 and Table 3).

Table 3
Expression of circRNA in left atria appendage

	SRM1 N = 72	AFR1 N = 64	P value	SRM2 N = 81	AFR2 N = 55	P value
circ 81906-RYR2	0.0171 ± 0.009	0.0220 ± 0.0140	0.013	0.0160 ± 0.008	0.0245 ± 0.0141	< 0.001
circ 44782-LAMA2	0.00595 ± 0.00287	0.00662 ± 0.00379	0.069	0.00564 ± 0.00290	0.00754 ± 0.00384	0.002
circ 418-KCNN2	0.00976 ± 0.0120	0.00923 ± 0.00635	0.107	0.00760 ± 0.00475	0.01071 ± 0.00812	0.011
circ 35880-ANO5	0.0266 ± 0.0165	0.0302 ± 0.0174	0.009	0.0242 ± 0.0111	0.0341 ± 0.0178	< 0.001
circ 255-ITGA7	0.00582 ± 0.00358	0.00863 ± 0.0133	0.881	0.00542 ± 0.00353	0.00621 ± 0.00399	0.230

Data of the one-year follow up were used to evaluate the risk factor of AF recurrence. Univariate analysis demonstrated that the advanced age (P = 0.004), longer AF duration (P = 0.007), increased expression of *circ 81906-RYR2* (P < 0.001), *circ 44782-LAMA2* (P = 0.003), *circ 418-KCNN2* (P = 0.013) and *circ 35880-ANO5* (P = 0.001) were risk factors for AF recurrence (Table 4). Multivariate analysis revealed that age (OR 1.071 95% CI 1.019–1.125 P = 0.007), AF duration (OR 1.007 95% CI 1.000-1.013 P = 0.040) and *circ 81906-RYR2* (OR 2.213 95% CI 1.428–3.429 P < 0.001) were significantly independent predictors for AF

recurrence (Table 4). A nomogram was established to visualize the predictive model from logistics regression analysis (Fig. 2).

Table 4

Univariate and multivariate analysis of risk factors for recurrence of AF after surgical ablation

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.065	1.020–1.112	0.004	1.072	1.020–1.127	0.006
AF duration	1.008	1.002–1.014	0.007	1.007	1.000–1.013	0.036
circ 81906-RYR2	2.283	1.502–3.470	< 0.001	2.210	1.425–3.427	< 0.001
circ 44782-LAMA2	1.772	1.207–2.601	0.003			
circ 418-KCNN2	1.603	1.103–2.328	0.013			
circ 35880-ANO5	1.997	1.336–2.983	0.001			

Furthermore, ROC curve was used to evaluate the relationship between *circ 81906-RYR2* and AF recurrence. The area under the curve (AUC) value of *circ 81906-RYR2* was 0.699 (95% CI 0.609–0.789, $P < 0.001$) (Fig. 3A). After combined with two clinical characters, age and AF duration, the AUC value was 0.77 (95% CI 0.690–0.849, $P < 0.001$) (Fig. 3B). The Youden's index of the total score of the predictive model was 70 points with sensitivity of 87.3% and specificity of 55.6%. Clinical data of all patients was regrouped by the Youden's index. Kaplan-Meier analysis demonstrated that patients with total score more than 70 points showed high recurrence rate of AF in one year after surgery (50% vs 20% $P < 0.001$) (Fig. 4).

Discussion

Surgical ablation should be recommended in patients with symptomatic AF during valve surgery. LAA excision is suggested to reduce the incidence of AF induced thrombotic events [1]. Surgical techniques improvements were achieved to decrease the postoperative AF recurrence, however, the outcome of surgical ablation is still not satisfactory in AF patients with VHD, especially those with rheumatic valvular diseases [15]. Limited number of studies have reported that AF duration, left atrial size and the severity of mitral regurgitation were independent risk factors for AF recurrence in valvular AF patients [16, 17].

CircRNA is a kind of non-coding RNA and is derived from the process of alternative splicing of pre-mRNAs [18, 19]. The 5'ends and 3'ends of the spliced RNA act as the upstream splice acceptor and the downstream splice donor and are finally covalently linked to each other which is known as back-splicing. Researchers have demonstrated that circRNAs can act as a microRNA sponge to regulate miRNA function [20], bind with proteins to regulate the interaction between proteins [21] and form peptide to participate

different biological process [22]. Recent years, circRNAs as clinical biomarkers have been proved in the central nervous disease [11] and cancers [12], however, the function of circRNAs in AF remain poorly understood. In our former study, we have described the expression profile of circRNAs in AF patients with VHD and validated ten differentially expressed circRNAs in patients LAA tissue [13]. To our knowledge, this was the first study to evaluated the relationship between LAA circRNAs and AF recurrence after surgical ablation.

According to our previous study [13], the five most differentially expressed circRNAs were selected in this study. We found the recurrence rate of valvular persistent AF patients was 40.4% in our center. The recurrence rate was higher than other studies because of the larger preoperative left atrial diameter of patients enrolled in this study (the average left atrial diameter was 5.2cm) and the large amount of rheumatic valvular disease patients (52.9%). We found that increased age ($P = 0.002$) and longer AF duration ($P < 0.001$) were common in AF recurrence group. The expression of the circRNAs showed that there were four circRNAs (*circ 81906-RYR2*, *circ 44782-LAMA2*, *circ 418-KCNN2* and *circ 35880-ANO5*) increased significantly in AF recurrence patients. Furthermore, multivariate analysis showed that increased expression of *circ 81906-RYR2* was an independent risk factor for AF recurrence besides advanced age and longer AF duration which were reported in previous study [16, 23]. Nomogram was used to visualize the predictive model and the total score of each patient was calculated by the formula of the predictive model. The results of ROC curve showed that the expression of *circ-81906 RYR2* alone was not accurately enough to predict AF recurrence. It was more effective to make the prediction of AF recurrence by the predictive model. The Kaplan-Meier plot also proved that patients with total score over 70 points was high risk to experience AF recurrence during follow-up, in the other hand, patients under 70 points could be considered as low risk of AF recurrence after surgery.

Themistoclakis et al. reported that recurrence of atrial tachycardias after 2 months were associated with AF recurrence after the blanking period [8]. In this study, 64 patients were found AF recurrence in 3 months after surgery, and 43 patients (67.2%) among them remain AF till one year after surgery. We also found that 21 patients in AFR1 group restored sinus rhythm and 12 patients in SRM1 group relapsed into AF one-year after surgery. After calculated the predicted points of the AFR1 patients, there were 28 patients under 70 points, and in those patients, who restored sinus rhythm in one year, there were 16 patients under 70 points. In a word, for those low risk patients (total score less than 70 points) who experienced AF 3 months after surgery, early interventions, such as cardioversion and antiarrhythmic drugs therapy, were effective to help restore sinus rhythm in one year.

Several limitations of this study should be mentioned. First, the patient amount and the follow-up length of this study is limited, more AF patients with VHD and longer length of follow-up are needed to make the validation of the predictive model. Second, LAA tissue is necessary for the detection of *circ 81906-RYR2*, therefore, such kind of detection is restricted to surgical ablation. For those patients received catheter ablation, extra LAA section is needed to get the LAA tissue. Third, AF recurrence is always asymptomatic and undetectable, long term heart rhythm monitor is recommended.

Conclusion

Left atrial appendage circular RNA *circ 81906-RYR2* was an independent risk factor for AF recurrence after surgical ablation. A predictive model which consist of age, AF duration and *circ 81906-RYR2* could be alternative for prediction of AF recurrence. What's more, early intervention for those low recurrent risk patients is helpful to maintain sinus rhythm during follow up.

Abbreviations

SR: sinus rhythm; AF: atrial fibrillation; VHD: valvular heart disease; circRNA: circular RNA; TTE: transthoracic echocardiography; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; SRM: sinus rhythm maintenance; AFR: atrial fibrillation recurrence; LAA: left atrial appendage; CPB: cardiopulmonary bypass; qRT-PCR: quantitative real-time reverse transcription polymerase chain reaction; SD: standard deviation; ROC: Receiver operating characteristic; AUC: area under the curve.

Declarations

Ethics approval and consent to participate:

This study was approved by the ethics committee of the Nanjing Drum Tower Hospital (approval number: 2016-151-01). Written informed consents was obtained from all patients enrolled in this study.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets generated and analyzed during the current study are not publicly available because a series of studies are related to the current study in our project and need to be continued, but are available from the corresponding authors on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

QZ and DW conceived the study design; HCao and FF finished the surgical procedure; XZ and YW performed the laboratory experiments and made the follow-up. HChong collected clinical data. XZ and RM completed the data analysis and interpretation. XZ, YW and RM wrote the manuscript. All authors made the approval of the final manuscript.

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Figures

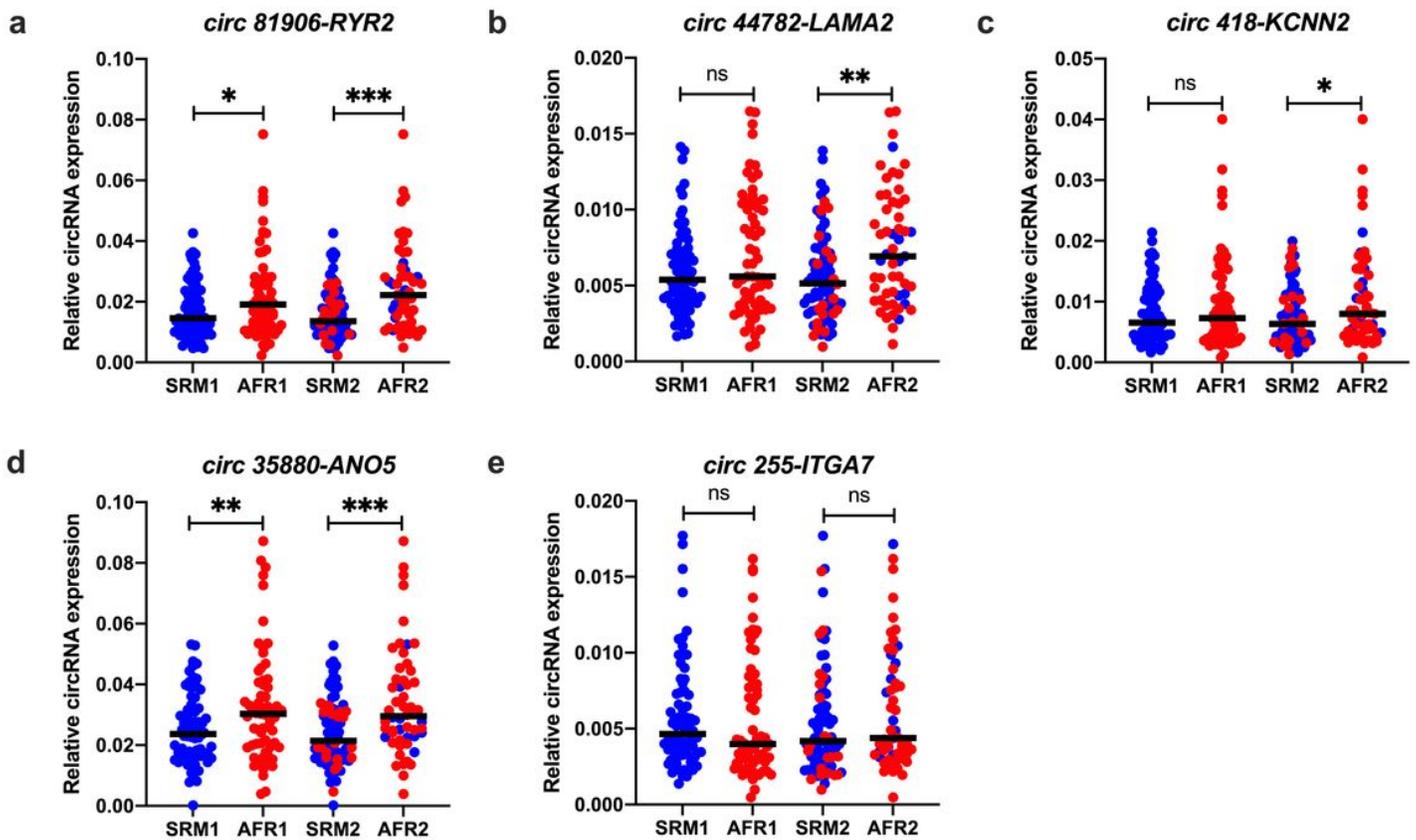


Figure 1

Relative expression of circRNAs in left atrial appendage in valvular PeAF patients. a. The relative expression of circ 81906-RYR2 was increased in both AFR1 (P=0.013) and AFR2 group (P<0.001). b. The relative expression of circ 44782-LAMA2 was increased in AFR2 group (P=0.002). c. The relative expression of circ 418-KCNN2 was increased in AFR2 group (P=0.011). d. The relative expression of circ 35880-ANO5 was increased in both AFR1 (P=0.009) and AFR2 group (P<0.001). e. The relative expression of circ 255-ITGA7 was not significantly different between both groups. Blue dots mean patients in SRM1 group and red dots mean patients in AFR1 group. *P<0.05 **P<0.01 ***P<0.001 Abbreviations: AFR: atrial fibrillation recurrence; SRM: sinus rhythm maintainness.

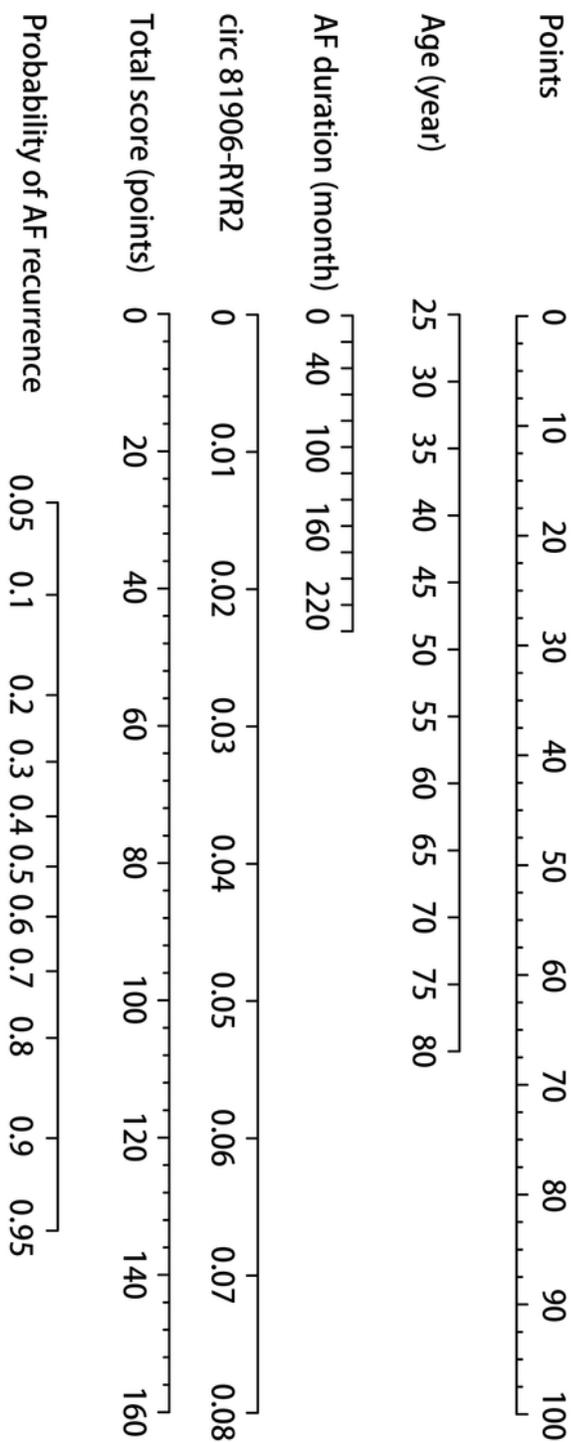


Figure 2

Nomogram of independent risk factors of atrial fibrillation recurrence after surgical ablation. Each value of risk factor could be converted into a detail point and the total score would reflect the probability of atrial fibrillation recurrence in one-year follow up. Abbreviations: AF: atrial fibrillation.

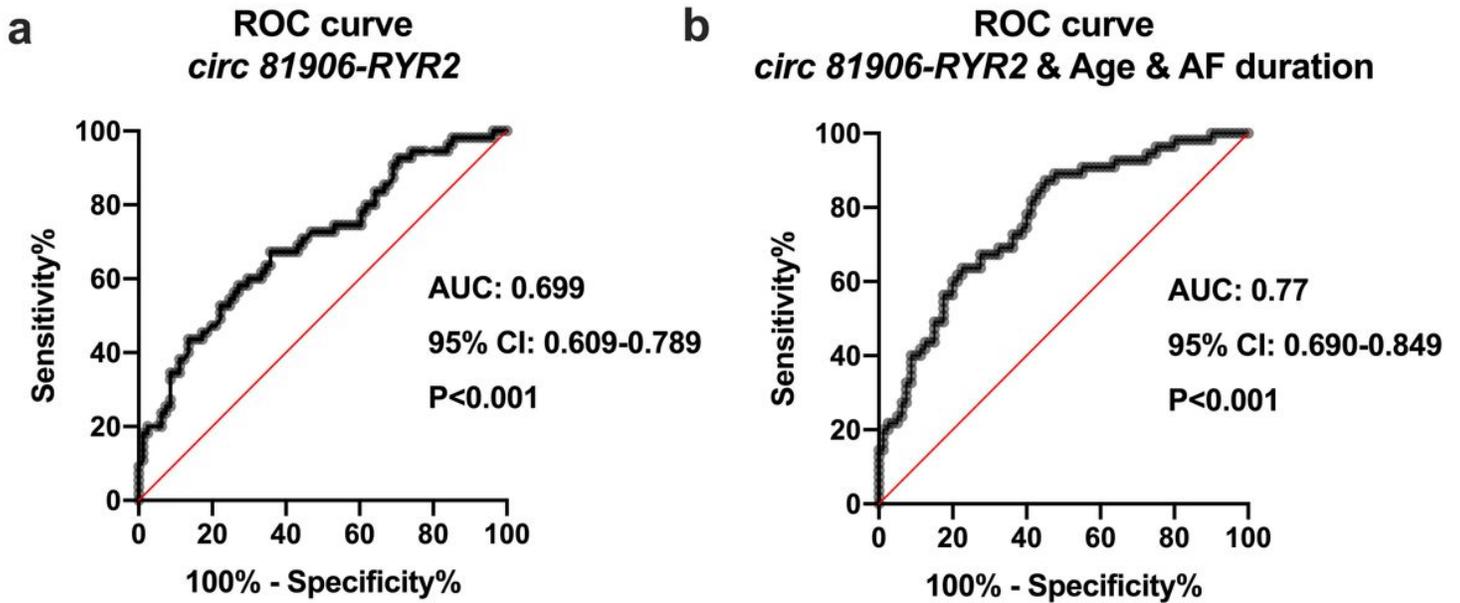


Figure 3

ROC curve of risk factors for predicting AF recurrence after surgical ablation. a. ROC curve of *circ 81906-RYR2*. b. ROC curve of *circ 81906-RYR2* combined with age and AF duration. Abbreviations: AF: atrial fibrillation; ROC: receiver operating characteristic.

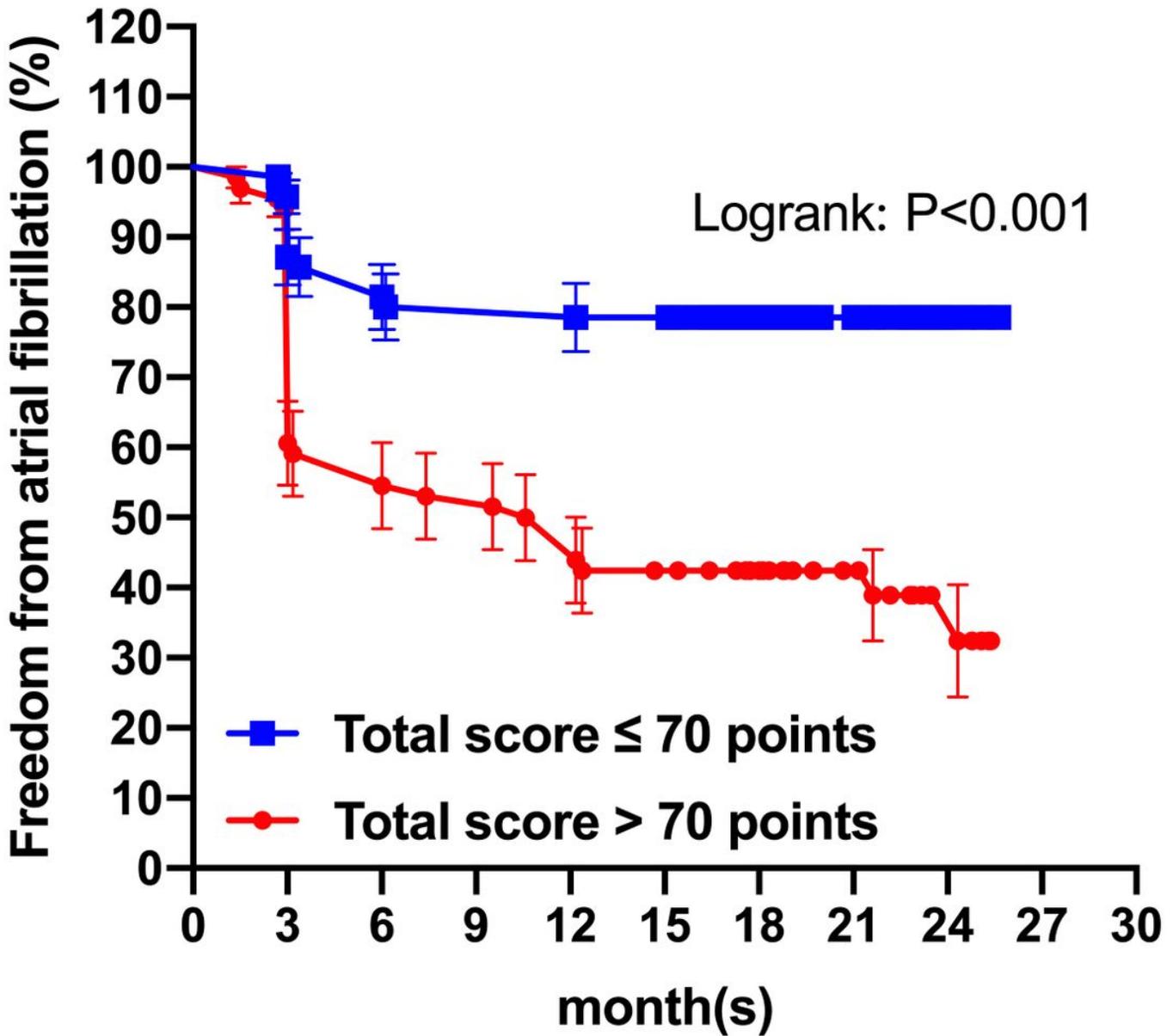


Figure 4

Kaplan-Meier plots of freedom from atrial fibrillation recurrence according to the predictive model. Patients with total score less than 70 points showed high rate of freedom from AF recurrence in one-year follow up (80% vs 50%, $P < 0.001$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1.docx](#)