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Incremental predictive value of left atrial strain and left atrial appendage function in rhythm outcome of non-valvular atrial fibrillation patients after catheter ablation

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ABSTRACT

Objective The purpose of this study was to develop a non-invasive and convenient nomogram based on speckle tracking echocardiography, left atrial appendage function and clinical factors to predict the risk of atrial fibrillation (AF) recurrence after catheter ablation.

Methods A total of 124 prospectively consecutive patients with AF treated with catheter ablation in our hospital was retrospectively analysis. Baseline echocardiographic parameters were measured by using transthoracic and transesophageal echocardiography before ablation. Multivariate analysis was performed for selecting predictors for a nomogram and internal validation and calibration were evaluated by the bootstep method.

Results During the follow-up of 12±3 months, 41 patients (33.1%) occurred AF recurrence after catheter ablation, while 83 patients (66.9%) had maintained sinus rhythm. Four predictors (AF type, left atrial appendage emptying flow velocity, left Atrial maximal volumes index and global longitudinal strain) with the P<0.5 was selected into the nomogram according to multivariate findings. Internal validation by bootstrapping with 1000 resamples was determined C-index of the nomogram for prediction AF recurrence was 0.901, which showed optimal discrimination and calibration of the established nomogram.

Conclusions Nomogram based on echocardiography and clinical characteristics had good predictive performance for the possibility of AF recurrence, which providing practical guidance for individualised management of patients with AF after catheter ablation.

Key questions

What is already known about this subject?

- Global longitudinal strain (GLS) of left atrial has previously been shown to predict atrial fibrillation (AF) recurrences after ablation in patients with AF.

What does this study add?

- Left atrial appendage emptying flow velocity (LAAFV) measured by transesophageal echocardiography in patients with AF has incremental predictive value for AF recurrence after ablation.
- Nomogram based on AF type, LAAFV, Left Atrial Maximal Volumes Index and GLS had good predictive performance for the possibility of AF recurrence.

How might this impact on clinical practice?

- The findings allow for a diversified assessment of the possibility of AF recurrence.
- Nomogram in our study providing practical guidance for individualised management of patients with AF after catheter ablation.

INTRODUCTION

Non-valvular atrial fibrillation (AF) is an atrial arrhythmia characterised by uncontrolled, rapid, disorganised excitation of the atria, which is associated with cardiovascular and cerebrovascular complications and morbidity, especially the risk and mortality of thromboembolic.[1 2] It was reported that AF leads to a fivefold increase in the risk of ischaemic stroke.[3] Catheter ablation, eliminating the initiating foci of AF, has been demonstrated to be an effective and well-established treatment strategy in restoring sinus rhythm and appears to be superior to antiarrhythmic therapy in symptomatic patients with drug-refractory AF.[4 5] Although recent advances in techniques for catheter ablation, the recurrence of AF after ablation still to be observed in one third of AF patients and often requires repeated ablation procedures.[6] Therefore, assessing the risk of individual recurrence is important for optimising the benefits of catheter ablation and selecting appropriate patients, which helps to identify those patients who are most likely to benefit from AF ablation.[7] Patients with low success rate usually need to enlarge the ablation lesions according to additional left atrial (LA) substrate modification. Meanwhile, it also provides guidance and suggestions for the management of patients post-AF ablation.

Many prior studies have reported that AF type, LA volume index (LAVI) and plasma brain natriuretic peptide, etc, were strong predictors for AF recurrence (AFR) after catheter ablation.[8 9] Ultrasound based on speckle-tracking echocardiography (STE), as non-invasive quantification of the LA myocardial deformation properties, can identify subclinical myocardial dysfunction during the cardiac cycle, and impaired LA global longitudinal strain (GLS) are related to the degree of structural LA remodelling and fibrosis of atria in patients with AF.[10] Recently, lower GLS was recognised as an independent predictor of AFR after catheter ablation.[11 12] However, GLS based nomogram by comminating with LA volume and LA appendage (LAA) function have not been proposed. Thus, the present study was performed to establish a predictive model based on GLS and known predictors, and evaluate the predictive value of the proposed model.

METHODS

Study population

We prospectively enrolled 124 non-valvular AF patients who underwent their first-time ablation procedure between September 2017 and January 2020. Exclusion criteria were (1) history of moderate or greater structural heart disease, (2) active coronary artery disease or cardiomyopathy, (3) history of cardiac surgery and/or cardiac device implantation, (4) previous ablation procedure, (5) severe system chronic disease or reduced left ventricle (LV) systolic function on baseline echocardiography (LV ejection fraction, LVEF <40%), (6) patients with atrial or ventricular arrhythmias during the echocardiographic examination, (7) patients with thrombus in LAA, (8) uninterpretable images quality and (9) unavailable of clinical follow-up data.

The baseline characteristics of patients were comprehensively assessed, including age, sex, body mass index, AF type, prevalence of the most common cardiovascular risk factors (hypertension, smoking, type 2 diabetes, dyslipidaemia), history of stroke, coronary heart disease and transient ischaemic attack/stroke, and finally current medical treatment. Plasma N-terminal pro-brain natriuretic peptide (NT-pro-BNP) concentrations were measured by a highly sensitive latex turbidimetric immunoassay before ablation. The concentrations of serum uric acid (sUA) in were quantified using enzymatic assays.

Echocardiography

Standard echocardiography

All patients underwent transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) study prior to ablation procedure by experienced sonographers, using a Philips iE33 ultrasound machines (Philips Medical Systems, Eindhoven, Netherlands) and EPIQ 7C (Philips Healthcare, Eindhoven, Netherlands), connecting limb lead ECG during TTE and TEE examination. Standard echocardiographic views were obtained and all measurements were performed according to the guidelines of American Society of Echocardiography.[13] Tricuspid annular plane systolic excursion (TAPSE) was obtained via M-mode and measured. LVEF was obtained from the apical four-chamber and two-chamber views (4 CV, 2CV) by Simpson's biplane method. LA maximal volumes during diastolic phase were calculated from the apical 4CV and 2CV of the LA by the biplane method of the discs, and were indexed to body surface area, total LA Maximal Volumes Index (LAVImax).

Two-dimensional STE

Three cine loops from 4CV and 2CV acquired with at least 60 frames per second were digitised and stored for offline analysis. LA strain analysis was performed offline using commercially available software (TomTec Imaging Systems, Munich, Germany). We selected the P wave onset of the ECG as the reference point for paroxysmal AF, and the QRS wave onset of the ECG as the reference point for persistent AF, as previously proposed.[10] LA endocardium boundary was traced manually in the end-systolic frame, and additional epicardial boundary were automatically marked by the software, generating a region of interest (ROI). After manually adjusting and calibrating the ROI of LA, the software automatically divided the region into six segments, and generated average time-strain curves. The software calculated LA average mean values for six segments obtained from the 4CV and 2CV. We identified the LA reservoir strain as the sum values of peak positive longitudinal strain during ventricular systole and LA negative longitudinal strain during ventricular diastole, LA GLS (figure 1).

Each subject underwent TEE examination prior to catheter ablation by qualified sonographer, to observe if there were thrombus in LAA. Five-consecutive cardiac cycles were acquired in cine loop format and stored for

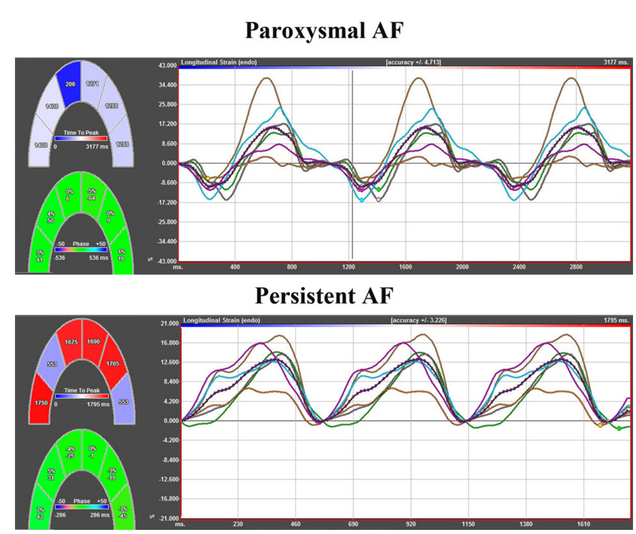

Figure 1 Screenshot of offline LA deformation analysis with 2D-speckle tracking software for paroxysmal and persistent AF. 2D, 2 dimensional; AF, atrial fibrillation; LA, left atrial.

further analysis. LAA emptying flow velocity (LAAFV) was measured by pulse-wave Doppler with the sample volume placed at 1 cm away from the LAA orifice. The subjects were blindly evaluated by two experienced sonographers.

Radiofrequency catheter ablation procedure

The ablation procedure protocol at our institution was implemented as previously described.[14 15] In brief, anti-arrhythmic drugs (AADs) were stopped five half-lives before ablation procedure. Pulmonary vein (PV) angiography was performed to verify the ostia and antrum of PV, CARTO mapping system (Biosense Webster, Irvine, California, USA) was constructed for building a LA three-dimensional electroanatomic map and intracardiac electrogram recordings. The integration module of CARTO system was used to integrate of PV CT images with the constructed eletroanatomy to navigate the ablation catheter in real time. The endpoint of extensive circumferential PV isolation was the abolition or dissociation of PV potential or failure to induce AF. Patients with persistent AF received the additional ablation procedures, including linear ablation of the LA roof and isolation of superior vena cava.

Follow-up

All patients were monitored in the hospital for at least 12 hours. Oral anticoagulation was continued after the procedure and AAD therapy for 3 months. Follow-up was conventionally performed at 3, 6 and 12 months after ablation. At each clinical visit, patients received a questionnaire regarding any arrhythmia-related symptoms, and followed by a 12-lead ECG and continuous 24-hour Holter monitoring. AFR was defined as a recording of AF or any other atrial tachyarrythmias lasting at least 30 s during electrocardiography or 24-hour Holter monitoring. However, recurrence of AF within only the first 3 months during the follow-up were defined as blanking period.

Statistical analysis

Continuous variables were expressed as mean±SD. Categorical data were summarised as percentages. Differences between groups were performed by using the independent-samples Student's t-test, χ^2 statistics or Fisher's exact test if applicable. Univariate and multivariate binary logistic regression analysis were used to determine the predictors of AFR after catheter ablation, and the OR and 95% CI were calculated. Receiver operating characteristic (ROC) curve analysis were generated to assess the ability of different variables in predicting AFR, and the cut-off value was used to assess the sensitivity and specificity for prediction of AFR. The prediction model validation of nomogram was performed using bootstrap with 1000 resamples to quantify and predict future performance. Intraobserver and interobserver variability for GLS were calculated in 10 randomly chosen patients by two independent investigators, both investigators were blinded to the study background. Values of $p<0.05$ were considered to be statistically significant. Statistics were conducted using SPSS V.19.0 software (SPSS) and R Studio (V.3.6.1; R studio, Boston, Massachusetts, USA).

Table 1 Baseline clinical, demographic and echocardiographic characteristics between the atrial fibrillation recurrence (AFR) and maintenance of sinus rhythm (MSR) groups in all subjects

Variables	AFR group (n=41)	MSR group (n=83)	P value
Age (years)	65.5±6.0	62.6±7.3	0.033
Male sex (%)	28 (68.3%)	47 (56.6%)	0.216
Body mass index (kg/m^2)	27.8±5.6	26.5±4.9	0.645
AF type			0.114
Persistent AF	26 (63.4%)	40 (48.2%)	
Paroxysmal AF	15 (36.6%)	43 (51.8%)	
AF duration (months)	38.7±35.5	36.5±33.7	0.743
Hypertension (%)	29 (70.7%)	53 (63.9%)	0.290
Smoking (%)	14 (34.1%)	32 (38.6%)	0.633
Type 2 diabetes (%)	12 (29.3%)	21 (25.3%)	0.638
Dyslipidaemia (%)	23 (56.1%)	43 (51.8%)	0.652
History of TIA/stroke (%)	11 (26.8%)	14 (16.9%)	0.144
History of CAD (%)	8 (19.5%)	12 (14.5%)	0.317
Antiplatelets (%)	10 (24.4%)	25 (30.1%)	0.328
ACEI/ARB (%)	22 (53.7%)	46 (55.4%)	0.502
Beta-blockers (%)	29 (70.7%)	64 (77.1%)	0.288
NT-pro-BNP (pg/mL)	1046.0±1044.2	527.8±564.9	0.000
sUA (µmol/L)	345.8±106.6	326.3±78.6	0.254
TAPSE (mm)	20±4	19±4	0.185
LVMI (g/m^2)	85.8±16.6	80.4±16.8	0.093
LVEF (%)	59.2±7.1	60.8±5.6	0.161
LAVImax (mL/m^2)	44.1±11.4	37.2±12.4	0.001
LAAFV (cm/s)	36.2±12.0	50.3±16.9	0.000
GLS (%)	19.8±4.5	26.6±5.5	0.000

Values are expressed as mean±SD or frequency (%).
ACEI/ARB, ACE inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; CAD, coronary artery disease; GLS, global longitudinal strain; LAAFV, left atrial appendage emptying flow velocity; LAVImax, left atrial maximal volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; sUA, serum uric acid; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack.

RESULT

Study population

Table 1 summarises the baseline clinical and echocardiographic parameters of 128 patients that met the inclusion criteria and were followed for an average of 12±9 months. Overall, patients were divided into two groups according to whether there was a clinical AFR, 41 patients (33.1%) experienced AFR were defined as AFR group, while 83 patients (66.9%) were in sinus rhythm on last follow-up and demonstrated maintenance sinus rhythm (MSR group). There were no significant differences with respect to gender, body mass index, AF type, AF

Table 2 Univariate and multivariate logistic regression analysis of AF recurrence

Variables	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age	1.065 (1.005 to 1.128)	0.033	0.988 (0.886 to 1.068)	0.974
NT-pro-BNP	1.001 (1.000 to 1.002)	0.003	0.881 (0.999 to 1.001)	0.906
AF type	1.863 (0.865 to 4.015)	0.112	0.387 (0.102 to 1.392)	0.143
LVMI	1.020 (0.997 to 1.043)	0.094	0.996 (0.961 to 1.021)	0.531
LAVImax	1.047 (1.012 to 1.083)	0.008	1.025 (0.977 to 1.076)	0.311
LVEF, %	0.958 (0.900 to 1.019)	0.173	1.010 (0.927 to 1.101)	0.802
LAAFV	0.933 (0.902 to 0.965)	0.000	0.940 (0.896 to 0.987)	0.011
GLS	0.758 (0.680 to 0.845)	0.000	0.689 (0.528 to 0.772)	0.000

AF, atrial fibrillation; GLS, global longitudinal strain; LAAFV, left atrial appendage emptying flow velocity; LAVImax, left atrial maximal volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; ;OR, odd ratio.

duration, common cardiovascular risk factors, current clinical medical treatment, sUA, TAPSE, LVMI and LVEF between the two groups at baseline. However, AFR group were older (65.5±6.0 vs . 62.6±7.3, p=0.03), had higher NT-pro-BNP level (1046.0±1044.2 vs . 527.8±564.9, p<0.001), larger LAVImax (44.1±11.4 vs . 37.2±12.4, p=0.001), lower LAAFV (36.2±12.0 vs . 50.3±16.9, p<0.001) and lower GLS (19.8±4.5 vs . 26.6±5.5, p<0.001) when compared with MSR group. GLS showed a good intraobserver and interobserver variability, the intraobserver variation coefficient of GLS was 4.6%±1.5% and the interobserver variation was 5.2%±1.6%.

Development of predicted model and validation

Univariate and multivariable predictors of AFR were shown in tables 2 and 3. Univariate logistic regression analysis identified that age (OR: 1.065, 95% CI 1.005 to 1.128, p=0.033), NT-pro-BNP (OR: 1.001, 95% CI 1.000 to 1.002, p=0.003), LAVImax (OR: 1.047, 95% CI 1.012 to 1.083, p=0.008), LAAFV (OR: 0.933, 95% CI 0.902 to 0.965, p<0.001) and GLS (OR: 0.758, 95% CI 0.680 to 0.845, p<0.001) were significant contributors to AFR after ablation and were included in the multivariate analysis. Multivariate logistic regression analysis found LAAFV (OR: 0.940, 95% CI 0.896 to 0.987, p=0.011) and GLS (OR: 0.689, 95% CI 0.528 to 0.772, p<0.001) were independent factors for prediction the possibility of AFR after ablation.

Then, the variables in multivariable logistic analysis with significant level≤0.5 were selected for development of prediction nomogram model, including AF type (OR: 0.394, 95% CI 0.114 to 1.368, p=0.142), LAAFV (OR: 0.941, 95% CI 0.899 to 0.984, p=0.008), LAVImax (OR: 0.643, 95% CI 0.538 to 0.769, p=0.253) and GLS (OR:1.023, 95% CI 0.984 to 1.064, p<0.001). Bootstrapping with 1000 resamples was performed to quantify and predict future performance for internal validation. The C-index of the nomogram for prediction AFR was 0.901. The calibration plot demonstrated good agreement between prediction and actual recurrence (figures 2 and 3).

The most predictive variables entered comparative ROC analysis, which identified that the area under

Table 3 Multivariable logistic regression analysis of AF recurrence and nomogram construction

Variables	Multivariable OR (95% CI)	P value	Selected for model OR (95% CI)	P value
Age	0.988 (0.886 to 1.068)	0.974		
NT-pro-BNP	0.881 (0.999 to 1.001)	0.906		
AF type	0.387 (0.102 to 1.392)	0.143	0.394 (0.114 to 1.368)	0.142
LVMI	0.996 (0.961 to 1.021)	0.531		
LAVImax	1.025 (0.977 to 1.076)	0.311	0.643 (0.538 to 0.769)	0.253
LVEF, %	1.010 (0.927 to 1.101)	0.802		
LAAFV	0.940 (0.896 to 0.987)	0.014	0.941 (0.899 to 0.984)	0.008
GLS	0.689 (0.528 to 0.772)	0.000	1.023 (0.984 to 1.064)	0.000

AF, atrial fibrillation; GLS, global longitudinal strain; LAAFV, left atrial appendage emptying flow velocity; LAVImax, left atrial maximal volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.;

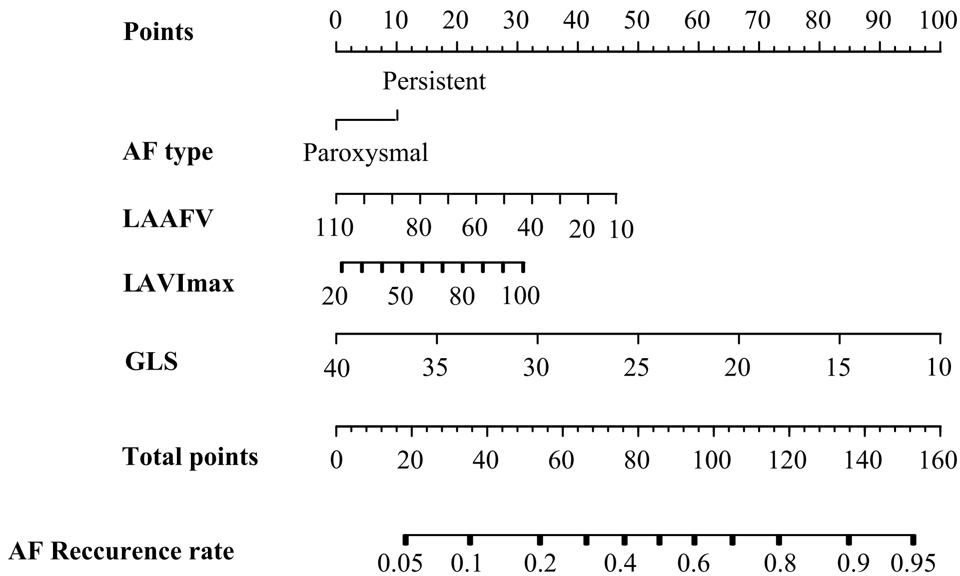

Figure 2 Nomogram for prediction patients with AF recurrence. It can be easily used to following steps: (1) affirm the AF type, the value of LAAFV, LAVImax and GLS; (2) Sum up all the points of each patient and locate the calculated total number on the total points axis; (3) The total points determine final probabilities of AF recurrence. AF, atrial fibrillation; GLS, global longitudinal strain; LAAFV, left atrial appendage emptying flow velocity; LAVImax, Left Atrial Maximal Volumes Index.

curve (AUC) of combined index (GLS+LAAFV + LAVImax+AF type) to be superior compared with lonely AF type, LAVImax, LAAFV and GLS for the prediction of AFR, suggesting that combined index has the highest diagnostic performance (AUC 0.880, 95% CI 0.812 to 0.947 vs AUC 0.576, 95% CI 0.470 to 0.683, AUC 0.684, 95% CI 0.585 to 0.784, AUC 0.744, 95% CI 0.654 to

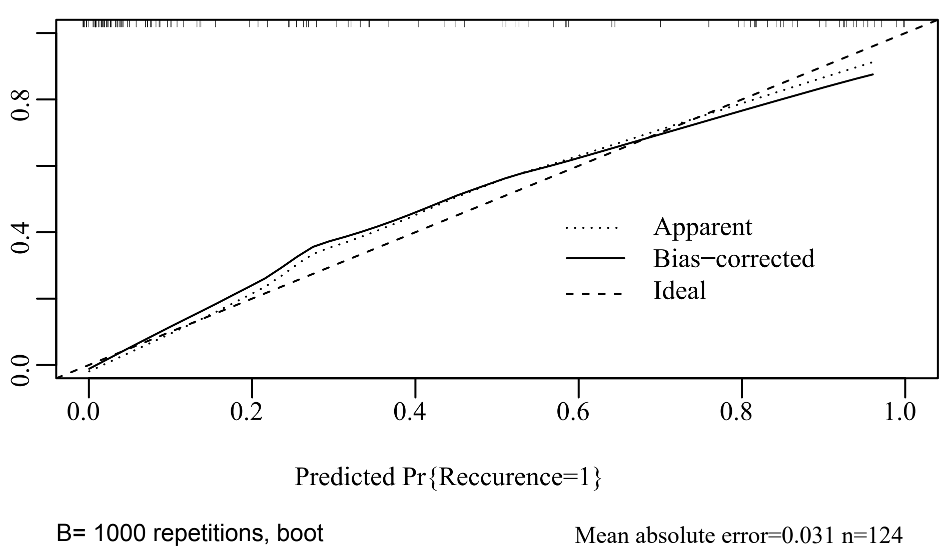

Figure 3 The calibration curve was used to evaluate the prediction performance of AF recurrence after ablation therapy of the non-invasive nomogram with C-index of 0.901, indication a good performance. The short line represented an ideal evaluation, the dotted line represented apparent evaluation and the solid line stand for bias-corrected evaluation. AF, atrial fibrillation.

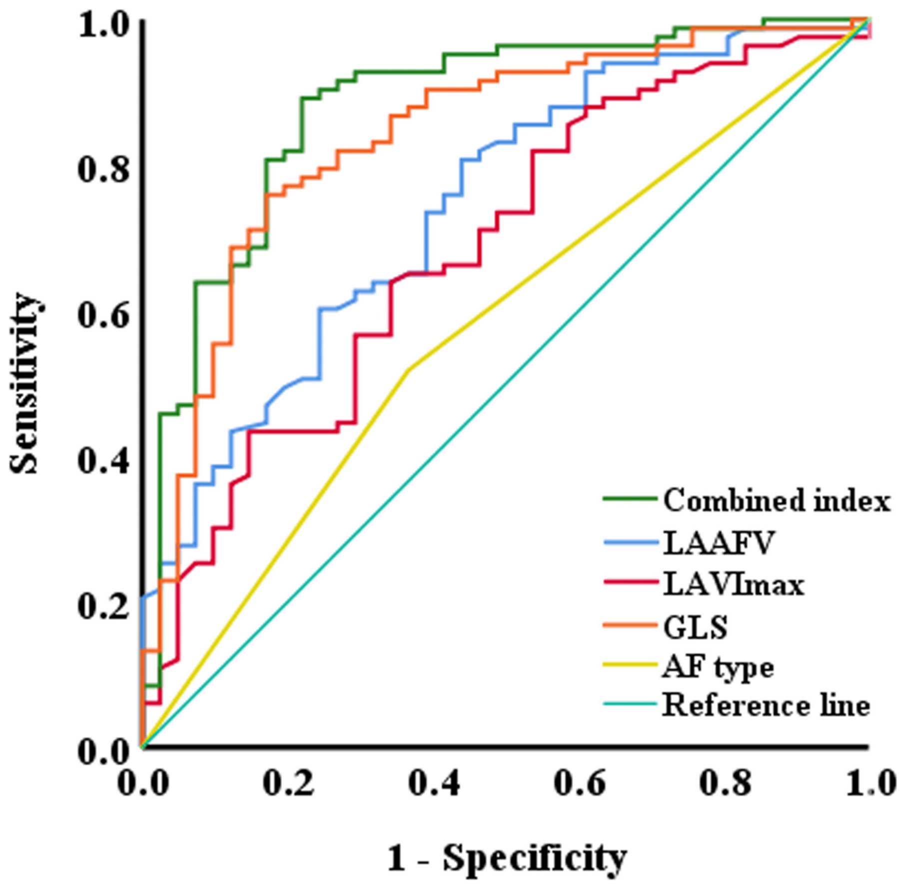

Figure 4 ROC curves for the prediction of sinus rhythm maintenance. The area under the curve (AUC) for combined index was greater than for left atrial global longitudinal strain (GLS), left atrial appendage emptying flow velocity (LAAFV), maximal LA Volume Index (LAVImax) and AF type. AF, atrial fibrillation.

0.834, AUC 0.839, 95% CI 0.470 to 0.683, respectively) (figure 4).

DISCUSSION

This study developed an easy-to-use score system based on AF type, LAVImax, LAAFV and GLS for predict of AFR postablation. The major findings in the current study were as follows. First, AFR patients showed a significantly decreased GLS and LAAFV as compared with MSR group indicating a functional remodelling occur to LA in patients with AF. Second, GLS and LAAFV were independent predictor of AFR after ablation after adjustment for clinical characteristics and conventional echocardiographic parameters, which allows identification of patients with high risk for AFR after ablation. Third, an integrated scoring model that combined AF type, LAVImax, and LAAFV and GLS showed excellent discriminatory performance (C-index: 0.901).

With the development of non-invasive assessment techniques of LA function and LA fibrosis, LA function (such as LA volume, LVEF and LA strain) and LA fibrosis degree assessed by delayed enhancement MRI become good predictive factors of AFR in patients post-AF ablation.[9 16–19] These studies were based on the same concept: LA structural and functional remodelling may be the possible pathogenesis of AFR following catheter ablation.[20] Thus, LA strain, a sensitive indicator of LA function, combined with LA volume, a structural parameter of LA, will help to predict the recurrence of AF after ablation. The nomogram we proposed in our study included the above two indicators and provided an easy-to-use predictive model to identify who had high possibility of AFR. Patients with an estimated value of more than 88 points with the AFR more than 50% in our model, so more reasonable decisions such as additional LAA isolation or intensive drug treatment and frequent follow-up should be considered for those patients.

The nomogram included four predictors from baseline clinical data, TEE, TTE and STE analysis prior to ablation. GLS and LAAFV were the important independent risk factors of AFR in the multivariate model. The nomogram established based on this multivariate regression model showed optimal discrimination (C-index 0.901), indicating a good performance for predict of rhythm outcome post-AF ablation. In this study, we attempted to evaluate the combination predictive value of AF type, LAVImax, LAAFV and GLS. Interestingly, the discriminant ability of the predictive model was greatly improved by adding GLS to the model involving clinical variables, TTE and TEE parameters.

Our analysis results were accordance with the previous findings. Notably, persistent AF has been reported as a significant predictor for higher rates of recurrent AF, which may be due to a higher degree of atrial remodelling in patients with persistent AF. A long-term process of reverse remodelling initiated by ablation might be essential to restore and MSR.[21 22] Therefore, the inducibility of AF was also identified as a significant predictor of recurrent AF.[23] Current international guidelines suggested that LA volume should be instead of assessing the LA size and remodelling, particularly in patients with dilated atria, due to the asymmetrical nature of enlargement atria.[24] Recent trials have demonstrated that increased LAVI was associated with occult AFR postablation.[25 26] In addition, the experimental evidence also implied that patients with decreased LAA function prior to ablation are more likely to relapse.[27] LAAFV reflects the comprehensive LA function and severity of LA remodelling and has been considered as a reliable predictor of AFR.[28] GLS measured by STE for the assessment of LA reservoir function has showed its prognostic value in predicting the recurrent of AF, as it provides characterisation and quantification of LA myocardial deformation, including the compliance of the atrial wall as well as myocardial fibrosis.[29 30] One might hypothesise that a lower GLS may mean a subclinical impairment of the LA myocardium, which can be linked to a higher risk of recurrence of AF post-AF ablation. Therefore, it is reasonable to include these important predictors in the nomogram.

When compared with the univariate and multivariate prediction models including clinical variables, echocardiographic parameters and strain values, this nomogram model showed better prediction accuracy. The findings of this study suggest that our nomogram scoring system can be used as a useful model for identifying the high AFR rate after catheter ablation, which is superior to the predictive value of a single parameter. Thus, the assessment of GLS and LAAFV may help clinicians to identify patients at relatively higher risk for recurrent of AF. Since the structural and functional remodelling of LA is partially reversible, the evaluation of GLS and LAAFV may provide more treatment recommendations for patients with AF ablation on the basis of drug therapy.

Study limitations

The present study has several main limitations. First, this is a single-centre study with a small sample size, so a prospective multicentre study needs to confirm the predictive value of GLS in predicting the rhythmic outcome of AF. Second, although patients were followed up through regular outpatient appointments, electrocardiograms and 24-hour Holter, asymptomatic episodes of AF may not be detected. Thus, the AFR rate may be underestimated in the study. In addition, obstructive sleep apnea (OSA) is a known risk factor for recurrent AF, We will explore the effect of OSA on recurrence after ablation of AF in future studies. Finally, nomogram should be applied and validated in external cohorts with larger prospective studies. Therefore, more research is needed to test the validity of the nomogram we have established.

CONCLUSION

In conclusion, we have constructed an easy-to-use nomogram based on echocardiography features and clinical characteristics, which allowed physicians to identify patients who potentially benefit from catheter ablation, and provided practical guidance for individualised management of patients with AF after catheter ablation.

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Competing interests None declared.

Patient consent for publication Not required.

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