Impact of Left Atrial Geometric Remodeling on Late Atrial Fibrillation Recurrence After Catheter Ablation

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Abstract

Purpose: To quantitatively investigate the impact of left atrial (LA) geometric remodeling on atrial fibrillation (AF) recurrence after catheter ablation (CA).

Methods: A retrospective analysis of 105 patients with AF who underwent coronary computed tomographic angiography before CA. Risk factors for AF recurrence were identified by multivariable logistic regression analysis and used to create a nomogram.

Results: After at least 12 months of follow-up, 30 patients (29%) developed recurrent AF. Patients with recurrence had a higher LA volume, LA sphericity, and a lower LA ejection fraction (LAEF) ($P < 0.05$). There was no significant difference in asymmetry index between the two groups ($P = 0.121$). Multivariable regression analysis showed that LA minimal volume index (LAVImin) (OR: 1.280, 95% CI: 1.027–1.594, $P = 0.028$), LA sphericity (OR: 1.268, 95% CI: 1.071–1.500, $P = 0.006$) and CHA2DS2-VASc score (OR: 1.326, 95% CI: 1.016–1.732, $P=0.038$) were independent predictors of AF recurrence. The combined model of the LA sphericity to the LAVImin substantially increased the predictive power for AF recurrence (area under the curve [AUC] = 0.736, 95% CI: 0.627–0.844, $P < 0.001$), with a sensitivity of 80% and a specificity of 61%. A nomogram was generated based on the contribution weights of the risk factors; the AUC was 0.769 (95% CI: 0.666–0.872) and had good internal validity.

Conclusion: The CHA2DS2-VASc score, LA sphericity, and LAVImin were significant and independent predictors of AF recurrence after CA. Furthermore, the nomogram had a better predictive capacity for AF recurrence.

Introduction

Atrial fibrillation (AF) is associated with a high risk of thromboembolic stroke, heart failure, and premature death. It is the commonest cardiac arrhythmia and is also associated with high cost burdens on healthcare systems.[1]Although catheter ablation (CA) is a widely accepted treatment for drug-refractory AF with a success rate of 50%–80%,[2,3] AF recurrence remains an important issue. Beyond pulmonary vein–associated triggers, it has been suggested that the underlying mechanisms instigating AF recurrence are complex. Various imaging modalities, including echocardiography, computed tomography (CT), and cardiac magnetic resonance imaging (CMRI), have been used to demonstrate the important role of left atrial (LA) geometry in assessing AF incidence.[4,5] Recent research has focused on precise assessments of the LA shape, which may prove to be a more precise marker than size alone.[6]

This study aimed to investigate whether LA geometric remodeling has a prognostic impact on AF recurrence after CA and to develop a precise predictive nomogram.

Methods

Study Population

This study retrospectively analyzed 105 consecutive AF patients who underwent CT angiography (CTA) before AF ablation in the Department of Medical Imaging at the Second Hospital of Hebei Medical University, Shijiazhuang, China, between October 2017 and September 2018. According to the 2019 AHA/ACC/HRS guidelines,[2] paroxysmal AF was self-limiting within 7 days of onset, and persistent AF lasted longer than 7 days or required cardioversion. Patients were eligible for inclusion if they had documented symptomatic AF and no previous ablation treatment. The exclusion criteria were valvular heart disease, cardiomyopathy, congenital cardiac abnormalities, presence of LA thrombus. The institutional review board of the Second Hospital of Hebei Medical University granted ethical approval. Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements.

Image Acquisition

All images were generated using a 256-slice CT scanner (Brilliance iCT, Philips Healthcare, Cleveland, OH, USA) and retrospective electrocardiography (ECG)-gated spiral data acquisition. Metoprolol (50–100 mg) was given 30-60 minutes before CCTA to patients with a mean heart rate ≥65 beats /min. The scan parameters were as follows: tube voltage, 120 kV; automatic tube current, 280–350 mA; detector collimation, 128 × 0.625 mm; slice thickness, 0.67 mm; section interval, 0.33 mm; gantry rotation time, 330 ms; beam pitch, 0.18. The contrast material of iohexol (Omnipaque 350; 1.0 mL/kg) was injected into the ulnar vein at the rate of 4–5 mL/s.

Image Analysis

Retrospective ECG-gated reconstruction generated ten phases with an interval of 10% over a R–R interval at 5%–95%, and then image data were transferred to the Philips EBW4.5 workstation for post-processing. Three-dimensional images of the left atrium and pulmonary vein were automatically or semi-automatically segmented with the workstation. The LA volume was obtained after the atrial appendage and the pulmonary veins were excluded. LA maximum volume (LAVmax), LA minimum volume (LAVmin), and LA appendage volume (LAAV) were automatically calculated. Body surface area (BSA) correction was used to determine LA maximum volume index (LAVImax) and LA minimum volume index (LAVImin). LA ejection fraction (LAEF) was calculated with cardiac function software. According to guidance by Wadell, [7] the maximal LA diameter was assessed on the rendered image, assuming that the volume of the sphere was the same as that of LA, and then the diameter of the corresponding sphere was calculated. The LA sphericity was the ratio of the diameter of the corresponding sphere to the maximum LA diameter (Fig. 1A). Next, LAV was divided into anterior (LA-A) and posterior (LA-P) volumes using a section parallel to the posterior wall between the pulmonary vein ostia and the LAA. The asymmetry index (ASI) was the ratio of LA-A to LAV (Fig.1 B).[8] All the parameters were observed and measured from multiple angles by two radiologists after relevant training.

Ablation Procedure

According to the uniform standard of circumferential isolation of the pulmonary vein, CA was performed with a 3.5 mm tip irrigated ablation catheter (Navistar Thermocool, Biosense-Webster, Diamond Bar, CA, USA) placed at the ostia of pulmonary veins to record pulmonary vein potentials. The LA geometry reconstruction was guided by electroanatomic mapping (CARTO-3 system, Biosense-Webster, Diamond Bar, CA, USA). The bidirectional conduction block from the atrium to the pulmonary veins was the endpoint of the pulmonary vein isolation, as confirmed by Lasso catheter (Biosense-Webster, Diamond Bar, CA, USA). If AF was not terminated, additional linear ablation and complex fractionated atrial electrogram ablation were performed.

Follow-up

Follow-up was performed at 3, 6, and 12 months by telephone interviews with patients and/or family members regarding the condition of the heart. AF recurrence, defined as any episode >30 seconds identified by 12-lead ECG or Holter after a 3-month blank period, signified the end of follow-up.

Statistical Analysis

Normally distributed continuous variables are expressed as means ± standard deviations, and skewed data are expressed as medians with interquartile ranges. Categorical variables are expressed as frequencies and percentages. Chi-square analysis was used for categorical variables, and Student's t-test or the Mann–Whitney U-test was used for continuous variables.

Multivariable logistic regression analysis with a backward stepwise procedure were performed to evaluate risk factors for AF recurrence. The criteria used for variables in the model were $P < 0.05$ for inclusion and $P > 0.10$ for removal, and odds ratio (OR) and 95% confidence interval (CI) calculations were performed. Receiver operating characteristic (ROC) curve analysis determined the optimal cut-off values with the highest sensitivity and specificity for predicting AF recurrence.

Multivariable logistic regression analysis informed the construction of a nomogram. The discriminating ability of the nomogram was evaluated using concordance index calculation and calibration plots.

All statistical analyses were performed using SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) and R, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). All P-values were two-sided, and P-values <0.05 were considered statistically significant.

Results

Study Sample

The baseline patient characteristics are summarized in Table 1. We enrolled 105 patients, including 66 men (63%), with a mean age of 59.8 ± 10.5 years. After at least 12 months of follow-up, 30 patients (29%) experienced recurrent AF. There were no significant differences between the patients who experienced AF recurrence (recurrence group) and those who did not (non-recurrence group) in terms of age, sex, AF duration, body mass index, hypertension status, diabetes mellitus status, vascular disease status, coronary artery disease status, or history of stroke/transient ischemic attack. However, the recurrence group had significantly higher proportions of patients with heart failure ($P = 0.013$) and persistent AF ($P=0.045$) and a higher median CHA2DS2-VASc score ($P = 0.009$).

LA Structure Parameters and Recurrent AF

CTA parameters are summarized in Table 2. The recurrence group had higher LAVmax, LAVImax, LAVmin, LAVImin, and LA sphericity values, and a lower LAEF ($P < 0.05$). Additionally, partial volume differed significantly between the recurrence and non-recurrence groups ($P < 0.05$). However, there was no significant difference in ASI between the two groups ($P = 0.121$). There was a weak correlation between LA sphericity and LAVmin/LAVmax ($r = 0.280$, $P = 0.004$; $r = 0.198$, $P = 0.043$, respectively).

Univariable and multivariable logistic analysis of clinical and CTA parameters for recurrent AF are summarized in Table 3. The univariable analysis identified persistent AF, heart failure, CHA2DS2-VASc score, LAEF, LAVImax, LAVImin, and LA sphericity as risk factors for AF recurrence ($P < 0.05$). Multivariable logistic regression analysis revealed LAVImin, LA sphericity, and CHA2DS2-VASc score as independent predictors. According to the ROC curve analysis, the optimal LAVImin cut-off value for predicting AF recurrence was 46.43 mL/m^2; the area under the curve (AUC) was 0.660 (95% CI: 0.531–0.789, $P = 0.011$), with a 63% sensitivity and a 75% specificity. The optimal LA sphericity cut-off value was 81.04%, with an AUC of 0.669 (95% CI: 0.549–0.789, $P = 0.007$), a 67% sensitivity, and a 64% specificity. The combined model of LA sphericity and LAVImin could reach a greater AUC of 0.736 (95% CI: 0.627–0.844, $P < 0.001$, sensitivity 80%, specificity 61%) than the individual models for LAVImin and LA sphericity (Table 4).

In the nomogram (Fig. 2) based on the contribution weights of the selected variables in the regression model, each predictive value was assigned a point on the corresponding variables line and added to form a scale from 0%–100% to find out the corresponding risk of AF recurrence. LA sphericity was the strongest predictor of recurrence after ablation, followed by LAVImin and CHA2DS2-VASc score. The nomogram model could accurately predict AF recurrence with an AUC of 0.769 (95% CI 0.666–0.872) (Fig. 3) and had good internal validity (Fig. 4).

Discussion

We investigated the impact of LA structural remodeling on outcomes of CA for AF. The main study findings were as follows: (1) LAVImin, LA sphericity, and CHA2DS2-VASc score were independent predictors of AF recurrence after CA, (2) LAVImin >46.4 mL/m^2 and LA sphericity >81% were associated with a high risk of AF recurrence, (3) the integration of LA sphericity data with the LAVImin data provided additional prognostic information regarding AF recurrence, (4) we devised a nomogram combining LA sphericity, LAVImin, and CHA2DS2-VASc score data to predict the risk of AF recurrence. Our findings may help improve AF therapy by facilitating more appropriate and earlier patient selection.

Atrial remodeling, known as structural and functional remodeling, is a response to increased pressure and volume overload, resulting in changes in the myocardium (myocyte hypertrophy and interstitial fibrosis). A more fibrotic left atrium would trigger areas of slow conduction and altered repolarization dynamics, shifting the focus of AF initiation and maintenance to the left atrium from the pulmonary veins and requiring additional substrate ablation.[9] Radiofrequency ablation in such patients may be insufficient, leading to increased recurrence rates. Furthermore, a high fibrotic burden is associated with LA dysfunction,[10] and an impaired LA emptying fraction has been correlated with recurrent AF.[11]

Sustained AF is associated with heart failure,[12-14] which, in turn, increases LA pressure and dilatation, further aggravating the development and progression of AF. In other words, AF and heart failure frequently coexist synergistically.[15,16] It is exactly for this reason that in our study, the prevalence of heart failure in the recurrence group was higher than that in the non-recurrence group.

The CHA2DS2-VASc score, combined with the clinical parameters of congestive heart failure, hypertension, advanced age, diabetes, prior stroke/transient ischemic attack/thromboembolism, vascular disease, and sex, is a risk stratification marker for predicting stroke. In our study, the CHA2DS2-VASc score was an independent predictor of AF recurrence following CA, which was consistent with previous findings.[17]

LA enlargement is regarded as an independent predictor of AF onset[18]and AF recurrence after radiofrequency ablation.[19] However, given the asymmetrical nature of atrial enlargement, the LA diameter is no longer regarded to reflect the true LA volume. Lang et al. demonstrated that the LA volume (and not anterior–posterior LA diameter) was associated with AF recurrence after radiofrequency ablation.[20] In a meta-analysis, the authors demonstrated that higher LAV and LAVI were associated with AF recurrence, and these factors emerged as independent predictors.[4] Our findings aligned with this observation.

Recently, several researchers have shifted their focus from LA size to shape, which can be assessed as a marker of maladaptive remodeling in AF and is associated with poor ablation outcomes and prognosis.[6,21-23] Bisbal et al. propose a novel quantity termed LA sphericity index to describe the morphological remodeling of the left atrium and suggest that the shape of the left atrium changes from disk-shaped to spherical in response to AF.[24] They offered a physiological explanation for this phenomenon that the sphere has the best volume-to-surface ratio and a more stable form; therefore, the LA wall accommodates the increased volume and pressure by spherical expansion under low stress.[25] They also presented evidence that patients with a higher sphericity index had an 11-fold higher risk of recurrence than patients with discoid left atria.[26] However, in contrast to previous work, den Uijl et al. studied the effects of LA volume, LA sphericity, and fibrosis on the prognosis of AF recurrence after CA in 83 patients and demonstrated LA volume as the strongest predictor.[27] Moon et al. observed that the prognosis of spherical remodeling was better among patients with LAV <125 ml, while patients with LAV ≥ 125 ml, LA volume had a better prognosis.[7] In our study, LA volume and sphericity were both stronger predictors of AF recurrence after CA, and we further found that the integration of the LA volumetric and geometric quantification provided better prognostic information to predict AF recurrence beyond that obtainable using LA minimum volume or sphericity individually.

Nedios et al.[28] demonstrated that AF progression led to asymmetrical dilatation, mainly at the anterior part of the atrium. They claimed that an ASI >60% was associated with a low success rate after CA, but the ASI was less pronounced in association with persistent AF, which already had facilitated asymmetric atrial dilatation. In contrast, we found that ASI was not a strong prognostic predictor of AF ablation outcomes. One explanation for our results could be that asymmetrical deformities may occur before chamber dilatation.

A nomogram is a kind of graphical model that can estimate specific outcomes or survival in association with certain risk factors. Nomograms are widely used in oncology and medicine.[29] Our model was composed of LA size, shape, and clinical findings, which played different roles and interacted with each other. The nomogram could provide a precise probability of AF recurrence. To our knowledge, ours was the first attempt to establish a nomogram to calculate the likelihood of AF recurrence after ablation.

Limitations

This study had a few limitations. First, this single-center, retrospective study had a small sample size. Second, patients with common concomitant diseases were not excluded. Third, since AF recurrence may be asymptomatic and cannot be detected by regular and occasional ECG recordings, our findings need to be confirmed by continuous rhythm monitoring during long-term follow-up. Furthermore, this nomogram model needs further external validation.

Conclusion

The CHA2DS2-VASc score, LAVImin, and LA sphericity are strongly associated with recurrent AF after CA. The integration of LA size and shape could substantially increase certainty when predicting AF recurrence. A novel nomogram could potentially provide better prognostic information, improve patient selection, and avoid unnecessarily aggressive medical therapy.

Declarations

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Availability of data and material: Data are available on request to the authors.

Code availability: software: Philips EBW4.5 workstation.

Authors' contributions: Caiying Li contributed to the conception of the study; Fuqian Guo performed image analysis ,data analyses and wrote the manuscript; Lan Yang and Chen Chen performed image analysis; Material preparation and data collection were performed by, Yi-Cheng Chen, Ji-Qiong Ni, Rong Fu, Yang Jiao, Yuan-Yuan Meng. All authors read and approved the final manuscript.

Ethics approval :The institutional review board of the Second Hospital of Hebei Medical University granted ethical approval (No. 2018-R245).

Consent to participate: Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements

Consent for publication: Written informed consent for publication was obtained from all participants.

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Tables

Table 1 Clinical characteristics of the recurrence and non-recurrence groups

	No recurrence (N=75)	Recurrence (N=30)	P
Age (y)	59.15±10.27	61.26±10.98	0.351
Male[n,(%)]	47(63%)	19(63%)	0.949
Persistent AF[n,(%)]	10(13%)	9(30%)	0.045
Duration of AF(month)	24(4,60)	36(11,63)	0.319
Risk factors			
BMI(kg/m^2)	26.79±3.49	26.47±3.78	0.685
BSA(m^2)	1.84±0.17	1.85±0.15	0.761
Hypertension[n,(%)]	37(49%)	20(67%)	0.107
Diabetes mellitus[n,(%)]	9(12%)	5(17%)	0.751
Vascular disease[n,(%)]	23(31%)	15(50%)	0.063
Cardiac artery disease[n,(%)]	27(36%)	11(37%)	0.949
Hyperlipidemia[n,(%)]	10(13%)	6(20%)	0.577
Congestive heart failure[n,(%)]	5(7%)	8(27%)	0.013
Previous stroke/ TIA[n,(%)]	12(16%)	8(27%)	0.209
CHA_2DS_2-VASc score	2(1,3)	3(2,4)	0.009

AF atrial fibrillation, BMI body mass index, BSA body surface area, TIA transient ischemic attack

Table 2 Comparison of left atrial parameters between the recurrence and non-recurrence groups

	No recurrence (N=75)	Recurrence (N=30)	P
LAVmax(ml)	114.36±27.81	135.09±39.50	0.012
LAVImax(ml/m^2)	62.26±15.16	72.97±20.74	0.014
LAVmin(ml)	68.30(53.4,87.9)	98.56±47.01	0.013
LAVImin(ml/m^2)	36.01(28.59,46.77)	53.28±24.96	0.011
LA sphericity(%)	79.44(77.38,82.10)	81.32±3.51	0.007
LA-A(ml)	84.10±20.82	96.60±28.14	0.033
LA-P(ml)	30.26±8.76	35.62(30.2,46.09)	0.004
ASI(%)	74(71,76)	72.5(69.75,75.0)	0.121
LAEF(%)	41.54(28.58,46.71)	30.29±16.54	0.023
LAAV(ml)	8.41±3.09	9.72±5.01	0.423

LAVmax left atrial maximum volume, LAVImax left atrial maximum volume index, LAVmin left atrial minimum volume, LAVImin left atrial minimum volume index, LA-A left atrial anterior volume, LA-P left atrial posterior volume, ASI asymmetry index, LAEF left atrial ejection fraction, LAAV left atrial appendage volume

Table 3 Univariable and multivariable logistic analysis for associations with recurrent atrial fibrillation

Variables	UV			MV		
	OR	95%CI	P	OR	95%CI	P
Age	1.020	(0.978,1.064)	0.348	-	-	-
Male	0.972	(0.404,2.338)	0.949	-	-	-
Persistent AF	3.143	(1.104,8.948)	0.032	-	-	-
Congestive heart failure	5.091	(1.509,17.170)	0.009	-	-	-
CHA2DS2-VASc	1.340	(1.066,1.686)	0.012	1.326	(1.016,1.732)	0.038
LAEF	0.966	(0.938,0.996)	0.027	1.159	(0.999,1.345)	0.051
LAVImax	1.036	(1.010,1.063)	0.007	-	-	-
LAVImin	1.033	(1.011,1.055)	0.004	1.280	(1.027,1.594)	0.028
LA sphericity	1.207	(1.042,1.397)	0.006	1.268	(1.071,1.500)	0.006

AF atrial fibrillation, UV univariable logistic analysis , MV multivariable logistic analysis, OR odds ratio, CI confidence interval, LAVImax left atrial maximum volume index, LAVImin left atrial minimum volume index, LAEF left atrial ejection fraction.

Table 4 Comparison of areas under the receiver operating characteristic curves of measured left atrial parameters for predicting atrial fibrillation recurrence

Characteristics	AUC(95%CI)	P
LAVImin	0.660(0.531~0.789)	0.011
LA sphericity	0.669(0.549~0.789)	0.007
LAVImin and LA sphericity	0.736(0.627~0.844)	0.000

AUC area under the curve, CI confidence interval, LAVImin left atrial minimum volume index

Figures

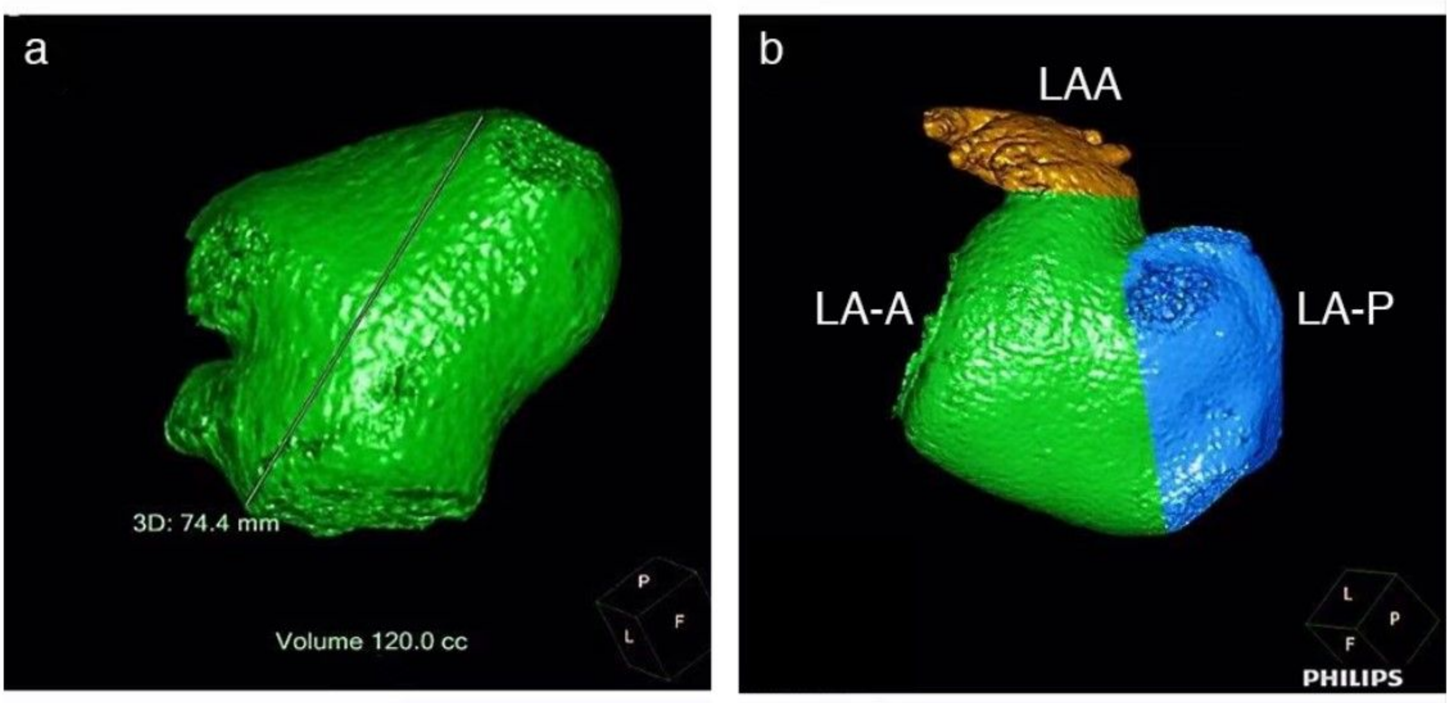

Figure 1

Measurements of left atrial (LA) sphericity and LA asymmetry index (ASI). The maximum LA diameter was 7.44 cm. The given LA volume in the three-dimensional rendered image is 120.0 ml (A). The corresponding sphere with a volume of 120.0 ml has a diameter of 3.72 cm. The LA sphericity was calculated as the ratio of the diameter of the corresponding sphere to the maximum LA length diameter (3.72/7.44=0.82). A section parallel to the posterior wall between the pulmonary vein ostia and the LAA was used to divide LAV into anterior (LA-A) (green area) and posterior (LA-P) (blue area) volumes. The ASI was calculated as the ratio of LA-A to LAV（B）.

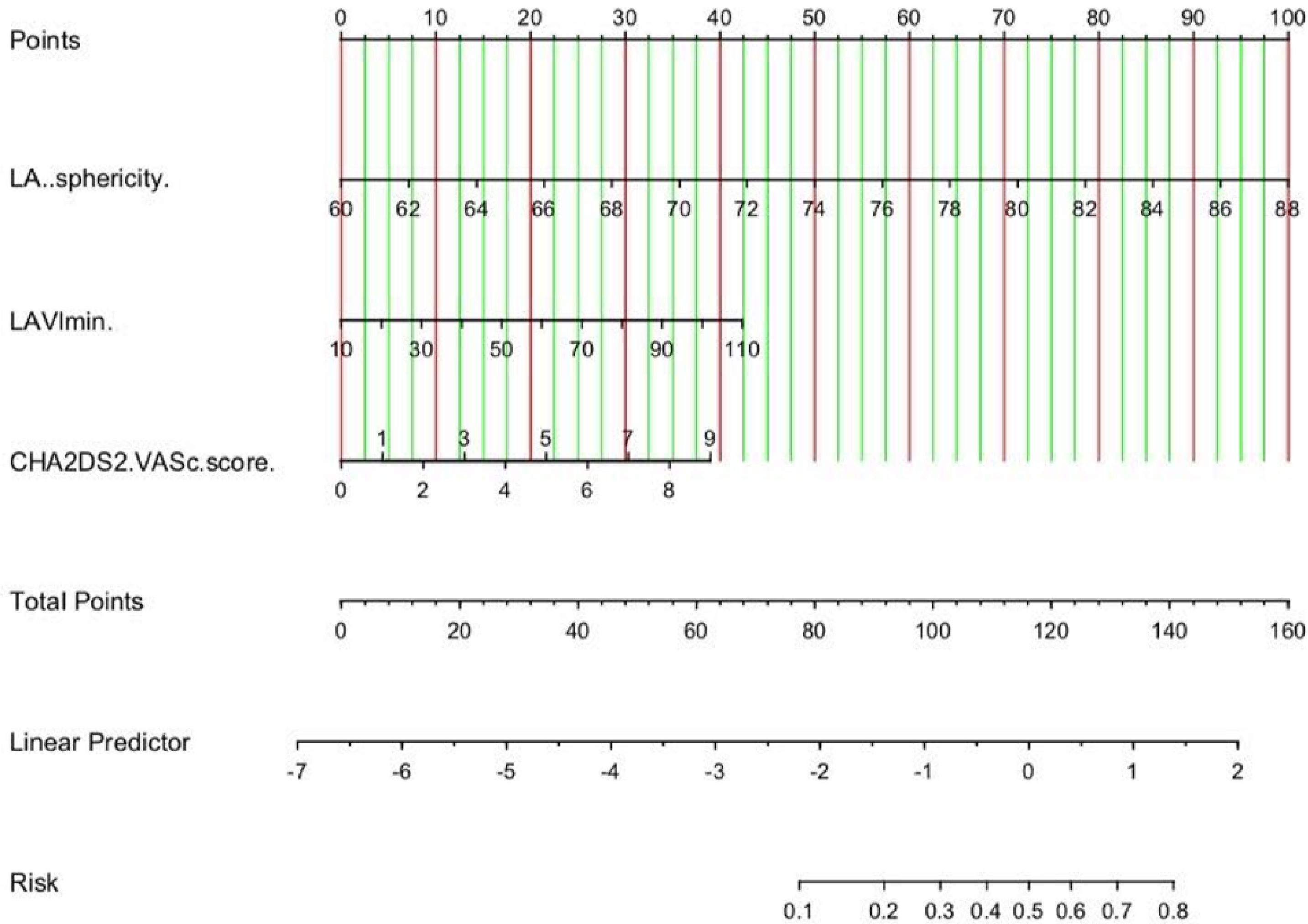

Figure 2

Nomogram for predicting the atrial fibrillation (AF) recurrence. To estimate the probability of AF recurrence, draw an upward vertical line to the “Points” bar from each variable, according to the sum of all variables points, or draw a downward vertical line from the “Total Points.”

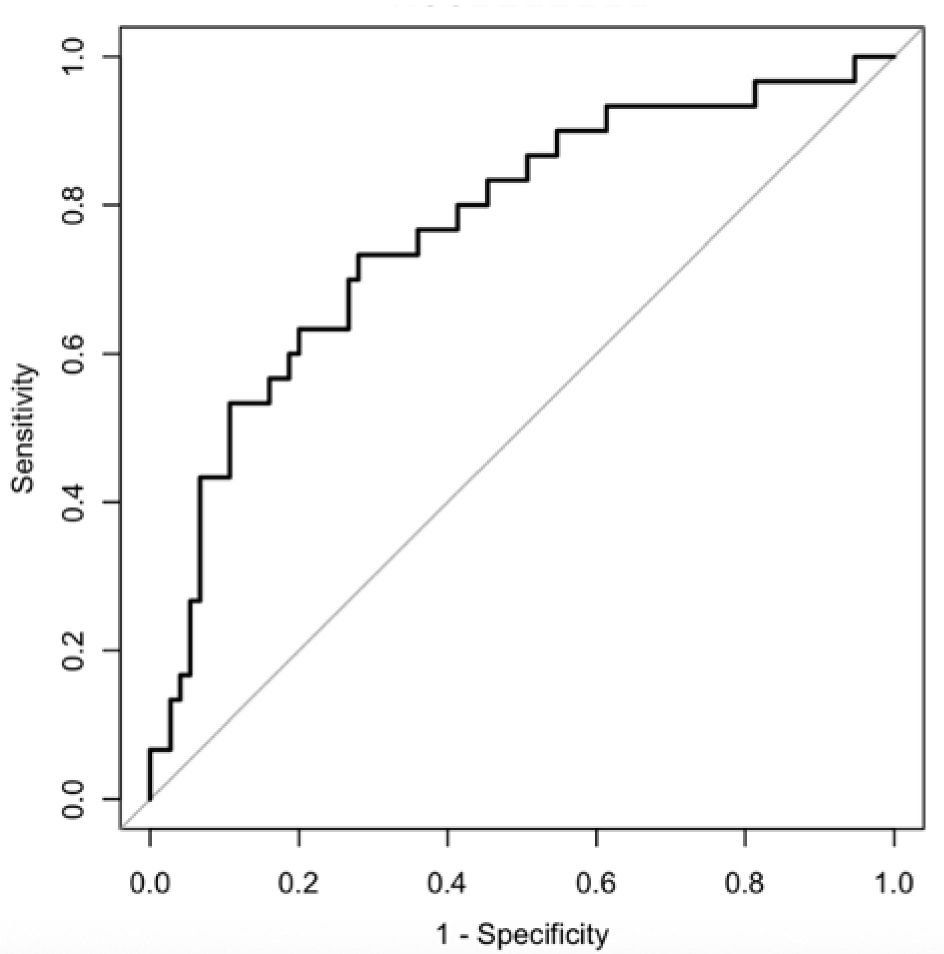

Figure 3

Receiver operating characteristic curve of the nomogram. The area under the curve was 0.769 (95% confidence interval 0.666–0.872).

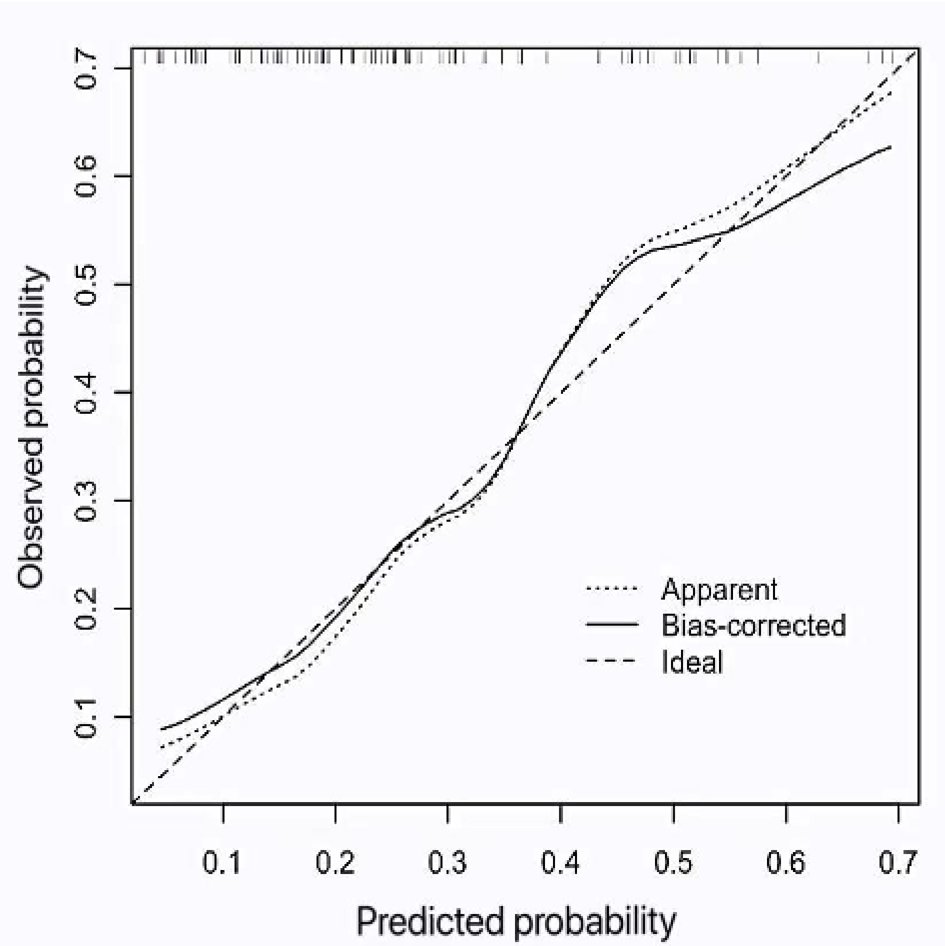

Figure 4

Calibration plots of the nomogram for AF recurrence The X-axis represents the predicted probability of atrial fibrillation (AF) recurrence, and the Y-axis represents the observed probability.