

Original Article

Predictive value of soluble growth stimulated expression gene 2 (sST2) for recurrence after radiofrequency ablation in patients with atrial fibrillation

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Abstract: Objectives: To assess the prognostic utility of preoperative soluble growth stimulated expression gene 2 (sST2) for post-ablation Atrial fibrillation (AF) recurrence and develop a multi-marker nomogram to optimize pre-procedural risk assessment. Methods: This monocentric retrospective study enrolled 517 AF patients undergoing radiofrequency ablation (RFA) between January 2020 and December 2024, with a 12-month postprocedural follow-up. We collected baseline clinical characteristics, left atrial diameter (LAD), and serum biomarkers including high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), and sST2. Multivariable logistic regression revealed the independent risk factors for recurrence after ablation; we then constructed a nomogram and performed internal validation. Results: AF recurrence occurred in 172 patients (33.27%). LAD, hs-CRP, NT-proBNP, IL-6, and sST2 were confirmed as independent predictors of recurrence. sST2 demonstrated the strongest individual predictive performance, with an optimal cutoff value of 32.69 ng/mL and an area under the curve (AUC) of 0.825. The combined nomogram achieved AUCs of 0.950 in the training set and 0.935 in the validation set, which was significantly better than the traditional CHA₂DS₂-VASc and HATCH scores. Calibration curves and decision curve analysis confirmed excellent model fit and substantial clinical net benefit. Conclusions: Preoperative sST2 is a robust independent predictor of AF recurrence after RFA. The novel nomogram integrating sST2 with LAD and inflammatory/neurohormonal biomarkers enables more accurate risk stratification and supports personalized perioperative management.

Keywords: Atrial fibrillation, radiofrequency ablation, recurrence, soluble growth stimulated expression gene 2, biomarker

Introduction

The incidence of atrial fibrillation (AF) is rising worldwide, placing a substantial burden on public health. AF is closely associated with stroke, heart failure, and death [1, 2]. The incidence of new AF cases and AF-related mortality are linked to socioeconomic development, indicating that AF has become a major cardiovascular disease challenge in the 21st century [3, 4]. For patients with AF symptoms that is refractory to drug therapy, catheter-based radiofrequency ablation (RFA) is a common clinical intervention. RFA can restore normal sinus rhythm, mainly by electrically isolating the pulmonary veins [5, 6].

However, AF recurrence after ablation is not uncommon [7]. A key underlying cause is progressive atrial structural remodeling, including atrial fibrosis. Fibrosis refers to excessive extracellular matrix accumulation, which alters the electrical properties of the heart and promotes the formation of reentrant circuits that sustain AF [8]. The extent of pre-existing fibrosis and ongoing fibrotic activity after ablation are critical determinants of procedural success. Hence, identifying reliable biomarkers that reflect atrial fibrotic and inflammatory activity is crucial for pre-procedural risk stratification and predicting long-term outcomes.

Soluble growth stimulated expression gene 2 (sST2), a member of the interleukin-1 receptor family, is released into the circulation in response to cardiac stress and strain [9]. As a decoy receptor for interleukin-33 (IL-33), sST2 blocks the cardioprotective IL-33/ST2 signaling pathway that normally exerts anti-fibrotic and anti-hypertrophic effects. Elevated sST2 levels thus promote a pro-fibrotic and pro-inflammatory state in the myocardium [10]. In AF populations, higher sST2 concentrations have been consistently associated with the presence, persistence, and recurrence of the arrhythmia [11-13].

Although recent meta-analyses have confirmed the prognostic value of sST2 for AF recurrence, most existing studies focus on single-factor associations without translating findings into clinically applicable risk-stratification tools [14-16]. Notably, post-ablation recurrence arises from complex interactions between atrial structural remodeling, inflammation, neurohormonal activation, and fibrotic activity-pathological processes reflected by distinct but interrelated biomarkers. To address this gap, this study not only validates preoperative sST2 as an independent predictor of AF recurrence after RFA in a large cohort, but also constructs a novel nomogram integrating sST2 with left atrial diameter (LAD), high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and interleukin-6 (IL-6). The primary objective is to develop a comprehensive, easy-to-use prediction model that outperforms individual biomarkers and provides actionable guidance for pre-procedural risk assessment and personalized postoperative management.

Materials and methods

Research subjects

A cohort of 517 patients diagnosed with AF and treated with RFA at Guangdong Medical University Affiliated Dongguan Songshan Lake Central Hospital from January 2020 to December 2024 was enrolled in this study. The inclusion criteria were: (1) Meeting the diagnostic criteria for AF [17]; (2) Age $\geq$ 18 years; (3) Complete clinical data. The exclusion criteria were: (1) A history of previous RFA or other car-

diac surgeries; (2) Preoperative esophageal ultrasound indicating intracardiac thrombus; (3) Presence of congenital heart disease, severe valvular heart disease, end-stage liver or kidney failure, severe chronic obstructive pulmonary disease, acute coronary events, autoimmune diseases, or cancers; (4) Active infection within the past two weeks; (5) Pregnancy or lactation.

The study protocol was approved by the Ethics Committee of Guangdong Medical University Affiliated Dongguan Songshan Lake Central Hospital, and all procedures adhered to the Declaration of Helsinki. Since this study only involved retrospective analysis of existing clinical data without extra interventions or direct contact with participants, the ethics committee granted a waiver of informed consent. All patient records were anonymized and de-identified before analysis to ensure confidentiality.

Surgical methods

Patients underwent routine blood tests, transthoracic echocardiography, and transesophageal echocardiography prior to the procedure to estimate cardiac function and exclude left atrial thrombi. Under local anesthesia, the right femoral vein was punctured, and a decapolar coronary sinus electrode (DECA NAV, Biosense Webster, USA) was inserted. Two transseptal punctures were performed using an 8F Swarts sheath (St. Jude Medical, USA), and a star-shaped mapping catheter (Pentaray, Biosense Webster, USA) was advanced to the ostia of each pulmonary vein to map pulmonary vein potentials. A three-dimensional (3D) electro-anatomical mapping system (CARTO 3 system, Biosense Webster, USA) was used to continuously sample points on all walls of the left atrium and reconstruct its 3D structure. Based on the CARTO 3 3D reconstruction, pulmonary vein antrum sites were marked: the anterior wall ablation site was approximately 0.5 cm outside the pulmonary vein ostium, and the posterior wall ablation site was approximately 1 cm outside the pulmonary vein ostium. An irrigated-tip contact force sensing ablation catheter (SmartTouch, Biosense Webster, USA) was used for ablation. The endpoint of pulmonary vein ablation was defined as either the disap-

pearance of pulmonary vein potentials or electrical isolation between the pulmonary veins and the left atrium. After completing circumferential ablation around both pulmonary veins and achieving isolation endpoints, further mapping or ablation was conducted based on the patient's cardiac rhythm at that time (AF, atrial tachycardia, or sinus rhythm). If AF could not be terminated after circumferential pulmonary vein ablation, linear ablation was sequentially performed along the left atrial roof line, mitral isthmus line, and tricuspid isthmus line. If the patient remained in AF after the above ablations, bidirectional synchronized direct current cardioversion (150-200 J) was performed to restore sinus rhythm.

Postoperative follow-up

All patients were followed up for at least 12 months post-procedure. Follow-up visits were scheduled at 3, 6, 9, and 12 months postoperatively, during which 24-hour ambulatory electrocardiography (ECG) (DigiTrak XT, Philips, USA) and 12-lead ECG (MAC-1200, GE Healthcare, USA) were performed. Patients were instructed to return to the hospital for ECG evaluation if they experienced arrhythmia-related symptoms such as palpitations, chest tightness, or dizziness. The first 3 months post-procedure were defined as a blanking period, during which any detected arrhythmias were not considered recurrence. AF recurrence was defined as the presence of atrial tachyarrhythmia (atrial tachycardia, flutter, or fibrillation) lasting more than 30 seconds, as documented by 24-hour ECG or 12-lead ECG after the 3-month blanking period.

Based on whether AF recurred within 12 months postoperatively, the 517 patients were categorized into a non-recurrence cohort ($n = 345$) and a recurrence cohort ($n = 172$). According to the chronological order of RFA procedures, the 517 patients were further divided into a training set ($n = 362$) and a validation set ($n = 155$).

Data collection

We retrospectively extracted patient data from the hospital's electronic health records, covering the following categories: (1) General information: gender, age, body mass index (BMI), smoking history, past medical history (diabetes mellitus, hypertension, stroke), AF type, AF

duration, intraoperative electrical cardioversion, and CHA₂DS₂-VASc score. (2) Echocardiographic parameters: before RFA, a IE33 color Doppler ultrasound diagnostic system (Philips, Netherlands) was used to measure left ventricular ejection fraction (LVEF), LAD, left ventricular end-systolic diameter (LVESD), and left ventricular end-diastolic diameter (LVEDD). (3) Serum biomarkers: before RFA, an AU5800 automated biochemical analyzer (Beckman Coulter, USA) was used to measure serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), serum creatinine (Scr), hs-CRP, apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB) levels. Additionally, a Cobas e601 fully automated chemiluminescence immunoassay system (Roche Diagnostics, Switzerland) was used to measure serum NT-proBNP and IL-6 levels. Serum sST2 level was measured using an ASPECT reader (Critical Diagnostics, USA).

Statistical processing

All statistical analyses were performed using SPSS version 25.0. Continuous data were reported as mean $\pm$ standard deviation ($M \pm SD$), and between-group comparisons were conducted using independent samples t-tests. Categorical data were presented as counts (percentages) [n (%)] and compared between groups using χ^2 tests. To select candidate predictors for multivariable logistic regression, univariate analyses were first performed with a threshold of $P < 0.10$. Subsequently, a forward stepwise procedure (likelihood ratio) was employed, with entry and removal criteria of $P < 0.05$ and $P < 0.10$, respectively, to identify independent predictors of AF recurrence. Multicollinearity among independent variables was assessed by calculating variance inflation factors (VIFs). VIF values > 5 indicated moderate collinearity, and VIF values > 10 indicated severe collinearity, which warranted exclusion or combination of the affected variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of independent factors for post-RFA AF recurrence. Independent factors identified by logistic regression were incorporated into R software (version 4.3.3) to construct and validate a clinical prediction model for AF recurrence after RFA. Model calibration was evalu-

ated using the Hosmer-Lemeshow test and calibration plots, where predicted probabilities were divided into 10 equal deciles and compared with observed recurrence rates. Decision curve analysis (DCA) was also conducted to estimate the net clinical benefit of the nomogram. Statistical significance was defined as a two-sided $P < 0.05$.

Results

Data consistency of the two cohorts

First, to ensure the comparability of the two temporally divided cohorts, we compared all data between the training set and the validation set (**Table 1**). There were no significant differences in general information, echocardiographic parameters, and serum biomarkers between the two cohorts (all $P > 0.05$). These findings confirm that the training and validation sets were well-balanced across all measured parameters, supporting the validity of our internal validation approach.

Training set

Comparison of clinical data in the training set: Baseline characteristics of the training set (**Table 2**) showed that patients who later experienced recurrence were more likely to have persistent AF (67.74% vs. 53.36%, $P = 0.008$), a longer AF duration (26.52 vs. 23.84 months, $P = 0.002$), and a $\text{CHA}_2\text{DS}_2\text{-VASc}$ score ≥ 2 (54.84% vs. 40.34%, $P = 0.009$). Intraoperative electrical cardioversion was also more frequent in the recurrence group (32.26% vs. 20.59%, $P = 0.014$). No significant differences were observed in age, BMI, smoking history, diabetes, hypertension, or stroke history between the two groups (all $P > 0.05$). These data suggest that a more advanced AF substrate, rather than traditional cardiovascular risk factors, drives early post-ablation recurrence.

Echocardiographic measurements (**Figure 1**) further distinguished the two groups. As shown in panel A, the mean LVEF was significantly lower in the recurrence group ($58.12 \pm 9.04\%$ vs. $60.84 \pm 10.27\%$, $P = 0.013$). Panel B reveals that the recurrence group had a significantly larger LAD (42.57 ± 6.12 vs. 38.36 ± 5.48 mm, $P < 0.001$). In contrast, panels C and D indicate that LVESD (31.86 ± 3.74 vs. 31.18 ± 3.44 mm, $P = 0.083$) and LVEDD

(48.04 ± 4.86 vs. 47.25 ± 4.59 mm, $P = 0.131$) did not differ between groups. Thus, reduced systolic function and left atrial enlargement, but not ventricular cavity size, emerged as the key echocardiographic predictors.

Analysis of serum biomarkers (**Table 3**) showed that several inflammatory and cardiac stress markers were elevated in the recurrence group. Specifically, patients with recurrence had higher levels of UA (342.81 ± 72.43 vs. 319.63 ± 66.25 $\mu\text{mol/L}$, $P = 0.002$), hs-CRP (4.58 ± 1.62 vs. 3.06 ± 1.38 mg/L, $P < 0.001$), NT-proBNP (218.45 ± 94.83 vs. 154.23 ± 72.61 pg/mL, $P < 0.001$), IL-6 (14.32 ± 2.14 vs. 12.08 ± 1.85 pg/mL, $P < 0.001$), and sST2 (39.28 ± 9.36 vs. 28.46 ± 7.12 ng/mL, $P < 0.001$). No differences were observed in lipid levels, Scr, ApoA1, or ApoB between the two groups (all $P > 0.05$). Collectively, these data indicate that a pro-inflammatory and neurohormonally active state is associated with AF recurrence.

Influencing factors of AF recurrence after RFA: Univariate logistic regression (**Table 4**) confirmed that most of the above factors were significantly associated with recurrence. Persistent AF (odds ratio [OR] = 1.835, 95% confidence interval [CI] 1.171-2.910, $P = 0.009$), AF duration (OR = 1.055, 95% CI 1.023-1.090, $P < 0.001$), intraoperative cardioversion (OR = 1.837, 95% CI 1.122-2.999, $P = 0.015$), $\text{CHA}_2\text{DS}_2\text{-VASc}$ score ≥ 2 (OR = 1.796, 95% CI 1.160-2.792, $P = 0.009$), LAD (OR = 1.136, 95% CI 1.091-1.185, $P < 0.001$), UA (OR = 1.005, 95% CI 1.002-1.008, $P = 0.003$), hs-CRP (OR = 1.974, 95% CI 1.665-2.374, $P < 0.001$), NT-proBNP (OR = 1.010, 95% CI 1.007-1.013, $P < 0.001$), IL-6 (OR = 1.782, 95% CI 1.557-2.067, $P < 0.001$), and sST2 (OR = 1.180, 95% CI 1.139-1.227, $P < 0.001$) were all univariate predictors, whereas higher LVEF was a protective factor (OR = 0.972, 95% CI 0.951-0.994, $P = 0.014$). These results confirm the broad involvement of structural, inflammatory, and fibrotic pathways in AF recurrence.

To ensure the reliability of multivariate regression estimates, we assessed multicollinearity among all candidate predictors using VIF. The VIF values for all variables included in the final multivariate model were as follows: LAD = 1.84, hs-CRP = 1.96, NT-proBNP = 1.62, IL-6 = 2.11, sST2 = 2.35, persistent AF = 1.28, AF duration = 1.45, intraoperative cardioversion = 1.19,

sST2 predicts AF recurrence after RFA

Table 1. Comparison of data consistency between training and validation sets

Indicator	Training set (n = 362)	Validation set (n = 155)	t/ χ^2	P
General information				
Gender [n (%)]			0.005	0.947
Male	230 (63.54%)	98 (63.23%)		
Female	132 (36.46%)	57 (36.77%)		
Age (years)	57.87 $\pm$ 10.05	57.75 $\pm$ 9.75	0.130	0.896
BMI (kg/m ²)	26.80 $\pm$ 3.28	26.73 $\pm$ 3.19	0.255	0.799
Smoking history [n (%)]	116 (32.04%)	50 (32.26%)	0.002	0.962
Past medical history [n (%)]				
Diabetes mellitus	62 (17.13%)	27 (17.42%)	0.007	0.936
Hypertension	150 (41.44%)	65 (41.94%)	0.011	0.916
Stroke	20 (5.52%)	8 (5.16%)	0.028	0.867
Type of AF [n (%)]			0.008	0.929
Persistent AF	211 (58.29%)	91 (58.71%)		
Paroxysmal AF	151 (41.71%)	64 (41.29%)		
Duration of AF (months)	24.76 $\pm$ 7.18	24.90 $\pm$ 6.88	0.208	0.835
Intraoperative electrical cardioversion [n (%)]	89 (24.59%)	39 (25.16%)	0.019	0.889
CHA ₂ DS ₂ -VASc score [n (%)]			0.027	0.869
$\geq$ 2 points	164 (45.3%)	69 (44.52%)		
< 2 points	198 (54.7%)	86 (55.48%)		
Echocardiographic parameters				
LVEF (%)	59.91 $\pm$ 9.93	60.13 $\pm$ 7.46	0.273	0.785
LAD (mm)	39.80 $\pm$ 6.04	39.61 $\pm$ 5.92	0.330	0.741
LVESD (mm)	31.41 $\pm$ 3.56	31.40 $\pm$ 3.45	0.035	0.972
LVEDD (mm)	47.52 $\pm$ 4.69	47.49 $\pm$ 4.55	0.069	0.945
Serum biomarkers				
TC (mmol/L)	4.35 $\pm$ 1.10	4.35 $\pm$ 1.06	0.041	0.968
TG (mmol/L)	1.26 $\pm$ 0.49	1.26 $\pm$ 0.40	0.096	0.924
LDL-C (mmol/L)	2.66 $\pm$ 1.00	2.64 $\pm$ 0.95	0.207	0.836
HDL-C (mmol/L)	1.14 $\pm$ 0.31	1.14 $\pm$ 0.29	0.109	0.913
UA (μ mol/L)	327.57 $\pm$ 69.21	325.92 $\pm$ 68.02	0.250	0.803
Scr (μ mol/L)	72.55 $\pm$ 21.16	72.25 $\pm$ 20.47	0.151	0.880
hs-CRP (mg/L)	3.58 $\pm$ 1.63	3.52 $\pm$ 1.61	0.388	0.698
ApoA1 (g/L)	1.39 $\pm$ 0.47	1.39 $\pm$ 0.38	0.011	0.992
ApoB (g/L)	0.90 $\pm$ 0.24	0.88 $\pm$ 0.23	0.891	0.373
NT-proBNP (pg/mL)	176.23 $\pm$ 86.35	172.43 $\pm$ 93.59	0.446	0.656
IL-6 (pg/mL)	12.85 $\pm$ 2.22	12.74 $\pm$ 2.24	0.529	0.597
sST2 (ng/mL)	32.17 $\pm$ 9.46	31.65 $\pm$ 9.54	0.580	0.562

Notes: AF, atrial fibrillation; BMI, body mass index; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; Scr, serum creatinine; hs-CRP, high-sensitivity C-reactive protein; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; NT-proBNP, N-terminal pro-brain natriuretic peptide; IL-6, interleukin-6; sST2, soluble growth stimulated expression gene 2.

CHA₂DS₂-VASc $\geq$ 2 = 1.33, LVEF = 1.57, and UA = 1.41. All VIF values were well below the conventional threshold of 5 (and far below 10), indicating that multicollinearity was not a significant issue in our dataset.

After adjusting for confounders in multivariate logistic regression (**Table 5**), only five factors remained independent predictors: LAD (OR = 1.148, 95% CI 1.070-1.232, P < 0.001), hs-CRP (OR = 1.806, 95% CI 1.406-2.320,

sST2 predicts AF recurrence after RFA

Table 2. Comparison of general information between two groups in the training set

Indicator	Non-recurrence group (n = 238)	Recurrence group (n = 124)	t/ χ^2	P
Gender [n (%)]			0.547	0.459
Male	148 (62.18%)	82 (66.13%)		
Female	90 (37.82%)	42 (33.87%)		
Age (years)	57.24 $\pm$ 9.86	59.08 $\pm$ 10.34	1.654	0.099
BMI (kg/m ²)	26.68 $\pm$ 3.14	27.04 $\pm$ 3.52	1.000	0.318
Smoking history [n (%)]	72 (30.25%)	44 (35.48%)	1.025	0.311
Past medical history [n (%)]				
Diabetes mellitus	38 (15.97%)	24 (19.35%)	0.659	0.417
Hypertension	94 (39.50%)	56 (45.16%)	1.078	0.299
Stroke	11 (4.62%)	9 (7.26%)	1.085	0.297
Type of AF [n (%)]			6.934	0.008
Persistent AF	127 (53.36%)	84 (67.74%)		
Paroxysmal AF	111 (46.64%)	40 (32.26%)		
Duration of AF (months)	23.84 $\pm$ 6.37	26.52 $\pm$ 8.26	3.158	0.002
Intraoperative electrical cardioversion [n (%)]	49 (20.59%)	40 (32.26%)	5.988	0.014
CHA ₂ DS ₂ -VASc score [n (%)]			6.920	0.009
≥ 2 points	96 (40.34%)	68 (54.84%)		
< 2 points	142 (59.66%)	56 (45.16%)		

Notes: AF, atrial fibrillation; BMI, body mass index.

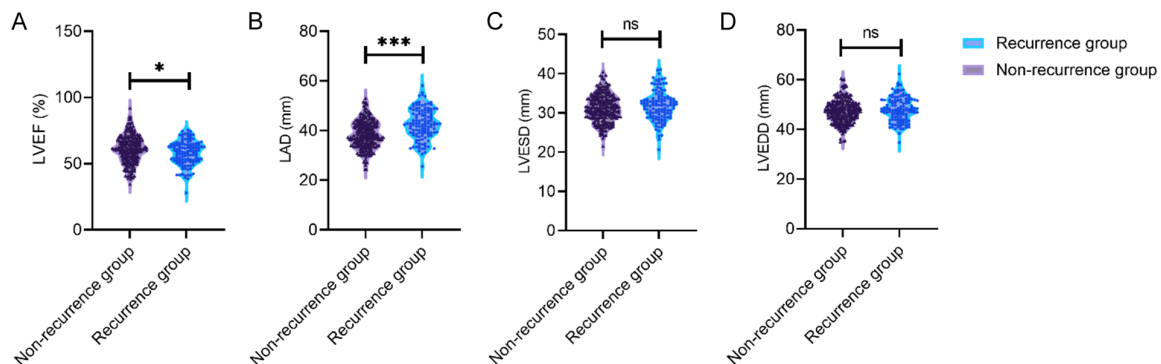


Figure 1. Comparison of echocardiographic parameters between two groups in the training set. A. LVEF (%); B. LAD (mm); C. LVESD (mm); D. LVEDD (mm). Notes: LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; *, $P < 0.05$; ***, $P < 0.001$; ns, no significance.

$P < 0.001$), NT-proBNP (OR = 1.008, 95% CI 1.004-1.013, $P < 0.001$), IL-6 (OR = 1.822, 95% CI 1.451-2.288, $P < 0.001$), and sST2 (OR = 1.154, 95% CI 1.098-1.212, $P < 0.001$). Persistent AF, AF duration, intraoperative cardioversion, CHA₂DS₂-VASc score, LVEF, and UA lost statistical significance after adjustment. Therefore, left atrial size, systemic inflammation, neurohormonal activation, and sST2 constitute the core independent risk profile for post-ablation recurrence.

The predictive performance of independent factors was quantified by ROC analysis (Table 6). Among all single indicators, sST2 achieved the highest AUC (0.825), with a best cutoff of 32.69 ng/mL, yielding a sensitivity of 81.5% and a specificity of 75.2%. IL-6 (AUC = 0.785), hs-CRP (AUC = 0.773), NT-proBNP (AUC = 0.703), and LAD (AUC = 0.693) also showed good discriminatory ability.

Given the distinct atrial remodeling profiles between persistent AF and paroxysmal AF, we

sST2 predicts AF recurrence after RFA

Table 3. Comparison of serum biomarkers between two groups in the training set

Variables	Non-recurrence group (n = 238)	Recurrence group (n = 124)	t	P
TC (mmol/L)	4.31 ± 1.08	4.42 ± 1.13	0.882	0.378
TG (mmol/L)	1.24 ± 0.51	1.32 ± 0.44	1.470	0.142
LDL-C (mmol/L)	2.62 ± 0.96	2.74 ± 1.05	1.092	0.275
HDL-C (mmol/L)	1.16 ± 0.33	1.11 ± 0.27	1.527	0.128
UA (μmol/L)	319.63 ± 66.25	342.81 ± 72.43	3.058	0.002
Scr (μmol/L)	71.44 ± 20.86	74.69 ± 21.65	1.388	0.166
hs-CRP (mg/L)	3.06 ± 1.38	4.58 ± 1.62	8.846	< 0.001
ApoA1 (g/L)	1.37 ± 0.51	1.43 ± 0.38	1.230	0.220
ApoB (g/L)	0.91 ± 0.24	0.87 ± 0.22	1.590	0.113
NT-proBNP (pg/mL)	154.23 ± 72.61	218.45 ± 94.83	6.600	< 0.001
IL-6 (pg/mL)	12.08 ± 1.85	14.32 ± 2.14	10.337	< 0.001
sST2 (ng/mL)	28.46 ± 7.12	39.28 ± 9.36	11.293	< 0.001

Notes: TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; Scr, serum creatinine; hs-CRP, high-sensitivity C-reactive protein; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; NT-proBNP, N-terminal pro-brain natriuretic peptide; IL-6, interleukin-6; sST2, soluble growth stimulated expression gene 2.

Table 4. Univariate logistic regression analysis of factors influencing AF recurrence after RFA

Indicator	Coefficient	Std Error	Wald	P	OR	95% CI
Persistent AF	0.607	0.232	2.618	0.009	1.835	1.171-2.910
Duration of AF	0.054	0.016	3.313	< 0.001	1.055	1.023-1.090
Intraoperative electrical cardioversion	0.608	0.250	2.430	0.015	1.837	1.122-2.999
CHA ₂ DS ₂ -VASc score ≥ 2 points	0.586	0.224	2.618	0.009	1.796	1.160-2.792
LVEF	-0.028	0.011	2.450	0.014	0.972	0.951-0.994
LAD	0.127	0.021	5.986	< 0.001	1.136	1.091-1.185
UA	0.005	0.002	2.992	0.003	1.005	1.002-1.008
hs-CRP	0.680	0.090	7.533	< 0.001	1.974	1.665-2.374
NT-proBNP	0.010	0.002	6.274	< 0.001	1.010	1.007-1.013
IL-6	0.578	0.072	8.011	< 0.001	1.782	1.557-2.067
sST2	0.165	0.019	8.645	< 0.001	1.180	1.139-1.227

Notes: AF, atrial fibrillation; RFA, radiofrequency ablation; OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; UA, uric acid; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; IL-6, interleukin-6; sST2, soluble growth stimulated expression gene 2.

performed additional ROC analyses to derive subgroup-specific optimal sST2 cutoff values for recurrence prediction in the overall training cohort (**Table 7**). The optimal sST2 cutoff was 32.690 ng/mL for persistent AF patients (AUC = 0.824, sensitivity 82.1%, specificity 76.4%), and 33.435 ng/mL for paroxysmal AF patients (AUC = 0.822, sensitivity 80.0%, specificity 77.5%).

Joint prediction: A nomogram integrating the five independent predictors (LAD, hs-CRP, NT-proBNP, IL-6, sST2) was constructed (**Figure 2A**). In the training set, the combined model achieved an excellent AUC of 0.950, with a sensitivity of 84.9% and a specificity of 91.3%

(**Figure 2B**). This multi-marker approach substantially improved predictive accuracy compared with any single variable, highlighting its potential for clinical risk stratification. The calibration curve closely aligned with the ideal 45° reference line, and the Hosmer-Lemeshow test yielded no significant difference ($\chi^2 = 7.24$, $P = 0.621$), indicating no meaningful deviation between predicted and observed recurrence risks (**Figure 2C**). DCA demonstrated that across a clinically relevant threshold probability range of 10%-80%, the nomogram provided substantially higher net benefit than both the “treat all” and “treat none” strategies (**Figure 2D**).

Table 5. Multivariate logistic regression analysis of factors influencing AF recurrence after RFA

Indicator	Coefficient	Std Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
Persistent AF	0.521	0.391	1.332	0.183	1.684	0.782	3.628
Duration of AF	0.043	0.028	1.509	0.131	1.044	0.987	1.104
Intraoperative electrical cardioversion	0.753	0.418	1.801	0.072	2.123	0.936	4.816
CHA ₂ DS ₂ -VASc score $\geq$ 2points	0.127	0.383	0.332	0.740	1.136	0.536	2.404
LVEF	-0.025	0.021	-1.207	0.227	0.975	0.935	1.016
LAD	0.138	0.036	3.826	< 0.001	1.148	1.070	1.232
UA	0.005	0.003	1.757	0.079	1.005	0.999	1.010
hs-CRP	0.591	0.128	4.630	< 0.001	1.806	1.406	2.320
NT-proBNP	0.008	0.002	3.481	< 0.001	1.008	1.004	1.013
IL-6	0.600	0.116	5.165	< 0.001	1.822	1.451	2.288
sST2	0.143	0.025	5.657	< 0.001	1.154	1.098	1.212

Notes: AF, atrial fibrillation; RFA, radiofrequency ablation; OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; UA, uric acid; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; IL-6, interleukin-6; sST2, soluble growth stimulated expression gene 2.

Table 6. Predictive value of the independent influencing factors for AF recurrence after RFA

Indicator	Best threshold	Sensitivity	Specificity	AUC	Youden index	F1 score
LAD	38.860	0.750	0.559	0.693	0.309	0.578
hs-CRP	3.755	0.726	0.727	0.773	0.453	0.645
NT-proBNP	208.540	0.532	0.786	0.703	0.318	0.548
IL-6	13.705	0.645	0.824	0.785	0.469	0.650
sST2	32.690	0.815	0.752	0.825	0.567	0.711

Notes: AF, atrial fibrillation; RFA, radiofrequency ablation; ROC, receiver operating characteristic; AUC, area under the curve; LAD, left atrial diameter; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; IL-6, interleukin-6; sST2, soluble growth stimulated expression gene 2.

Comparison with established clinical risk scores: To contextualize the clinical utility of our nomogram, we compared its performance with established clinical scoring systems for AF (**Table 8**). The AUCs of the CHA₂DS₂-VASc score and HATCH score were 0.612 (95% CI: 0.556-0.668) and 0.583 (95% CI: 0.526-0.640), respectively-both significantly lower than the nomogram's AUC of 0.950 (DeLong's test, $P < 0.001$ for both comparisons).

Validation set

Finally, the clinical prediction model was validated in the independent validation set (**Figure 3**). The combined nomogram (LAD, hs-CRP, NT-proBNP, IL-6, sST2) yielded an AUC of 0.935, with a sensitivity of 80.6% and a specificity of 97.5%. These values were nearly identical to those obtained in the training set, demonstrat-

ing that the model is robust and not overfitted. In summary, the five-factor panel reliably predicts AF recurrence after RFA in both the training and validation cohorts.

Discussion

In this retrospective cohort study of 517 patients undergoing AF ablation, we not only confirmed that sST2 is an independent predictor of 12-month post-procedural AF recurrence, but also developed a novel nomogram combining sST2 with LAD, hs-CRP, NT-proBNP, and IL-6 that achieved excellent discriminative performance in both the training and independent validation cohorts. While prior meta-analyses have established the association between elevated sST2 and increased recurrence risk, our study extends this knowledge in three key ways. First, we provide a population-specific optimal sST2 cutoff (32.69 ng/mL) with high sensitivity (81.5%) and specificity (75.2%), offering direct clinical utility for risk classification. Second, our multi-marker model captures complementary pathological pathways: LAD reflects established structural remodeling, hs-CRP and IL-6 indicate active systemic inflammation, NT-proBNP signals myocardial wall stress, and sST2 uniquely represents ongoing atrial fibrotic activity via inhibition of the cardiopro-

sST2 predicts AF recurrence after RFA

Table 7. Subgroup analysis of optimal sST2 cutoff values for predicting AF recurrence after RFA

Subgroup	Best threshold	Sensitivity	Specificity	AUC	Youden index	F1 score
Persistent AF	32.690	0.821	0.764	0.824	0.585	0.754
Paroxysmal AF	33.435	0.800	0.775	0.822	0.575	0.660

Notes: sST2, soluble growth stimulated expression gene 2; AF, atrial fibrillation; RFA, radiofrequency ablation; AUC, area under the curve.

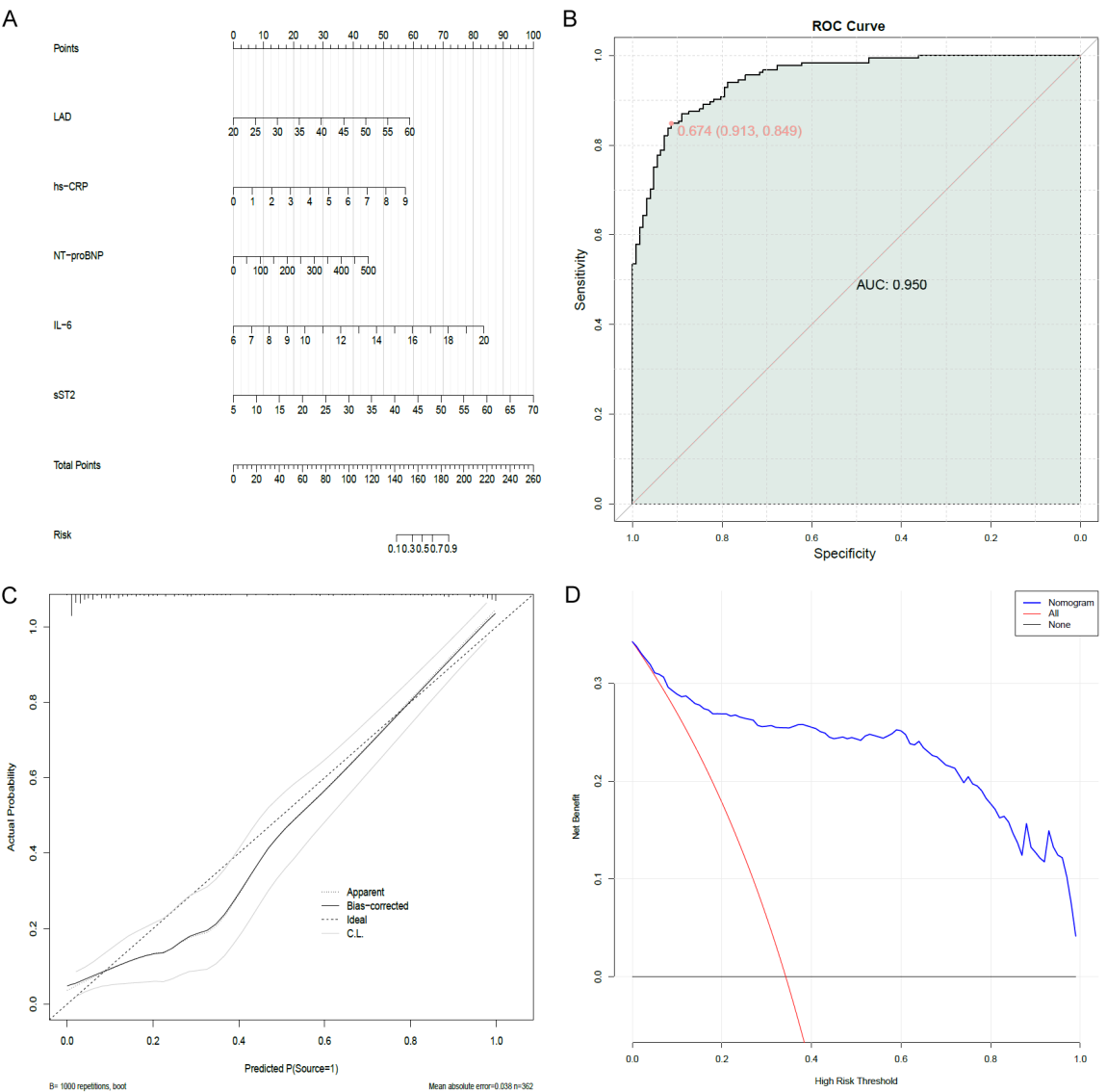


Figure 2. A clinical prediction model for AF recurrence after RFA in the training set (A) Nomogram prediction model; (B) ROC analysis; (C) Calibration curve; (D) DCA. Notes: AF, atrial fibrillation; RFA, radiofrequency ablation; ROC, receiver operating characteristic; DCA, decision curve analysis; AUC, area under the curve; LAD, left atrial diameter; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; IL-6, interleukin-6; sST2, soluble growth stimulated expression gene 2.

tective IL-33/ST2 signaling pathway. This integrated approach addresses the multifactorial nature of recurrence far more effectively than

single-biomarker analyses. Third, the model was rigorously validated in an independent cohort, minimizing overfitting bias and support-

Table 8. Comparative performance of the nomogram model vs. classic scoring systems

Model	AUC (95% CI)	Sensitivity	Specificity	P (vs. Nomogram)
Nomogram (LAD + hs-CRP + NT-proBNP + IL-6 + sST2)	0.950 (0.928-0.972)	0.849	0.913	-
CHA ₂ DS ₂ -VASc score	0.612 (0.556-0.640)	0.548	0.597	< 0.001
HATCH score	0.583 (0.526-0.640)	0.419	0.723	< 0.001

Notes: AUC, area under the curve; CI, confidence interval; LAD, left atrial diameter; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; IL-6, interleukin-6; sST2, soluble growth stimulated expression gene 2.

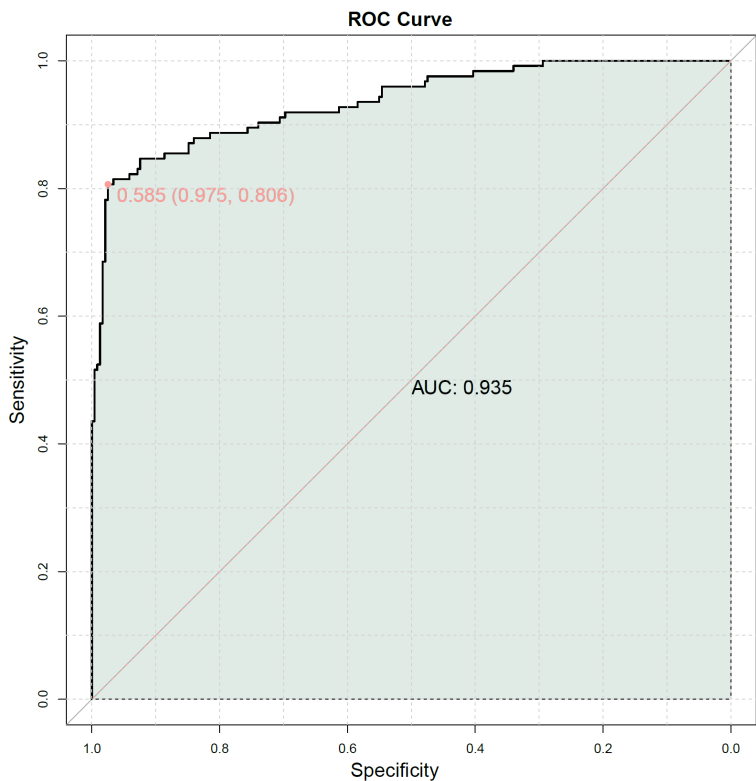


Figure 3. The clinical prediction model for AF recurrence after RFA in the validation set. Notes: AF, atrial fibrillation; RFA, radiofrequency ablation; ROC, receiver operating characteristic; AUC, area under the curve.

ing its generalizability to similar clinical populations. These features distinguish our work from prior studies and provide a practical tool to identify high-risk patients who may benefit from intensified monitoring, adjunctive anti-inflammatory or antifibrotic therapies, and shared decision-making prior to RFA.

Our finding that persistent AF and longer AF duration were associated with recurrence in univariate analysis is consistent with the well-established concept that longer arrhythmia exposure promotes more advanced atrial remodeling [18-20]. However, these factors lost

independent predictive power after adjustment for biomarkers such as LAD and sST2 [21-23]. This suggests that their effect is largely mediated by structural and fibrotic changes already captured by echocardiography and circulating markers. Similar observations have been reported by Falasconi et al. [12], who noted that the clinical type of AF becomes less predictive once objective measures of atrial substrate are considered.

Left atrial enlargement was a strong independent predictor of recurrence in our study. This aligns with the widely accepted view that LAD reflects chronic atrial pressure overload and structural remodeling, which provide a substrate for reentrant circuits [24-26]. Patients with larger left atria are more likely to have extensive low-voltage areas and fibrosis, both of which undermine the durability of

pulmonary vein isolation [27-29]. Conversely, LVEF was lower in the recurrence group in univariate analysis but did not remain in the multivariate model. This indicates that while global systolic dysfunction may accompany recurrent AF, it is not as directly linked to post-ablation outcomes as left atrial remodeling [29].

Among the inflammatory markers, both hs-CRP and IL-6 were elevated in patients with recurrence and retained independent predictive value. Systemic inflammation can promote atrial fibrosis and electrical instability [30-32]. High IL-6 levels can activate fibro-

blasts, increasing extracellular matrix deposition. Hs-CRP is a marker of inflammatory activity. A meta-analysis by Chen et al. [16] found that higher IL-6 levels are associated with increased AF recurrence after ablation, which is consistent with our results. After multivariable adjustment, our results still showed that a pro-inflammatory state contributes to recurrence, independent of atrial size or neurohormonal activation.

NT-proBNP, a marker of myocardial stretch and wall stress, was also higher in the recurrence group and independently predicted recurrence. In AF patients, elevated NT-proBNP may reflect underlying atrial or ventricular dysfunction, but it can also result from rapid and irregular ventricular rates that increase cardiac workload [33-35]. Fan et al. [12] found that NT-proBNP levels correlate with the extent of left atrial low-voltage areas, suggesting that this biomarker captures the severity of atrial remodeling. Our results support the notion that neurohormonal activation, as reflected by NT-proBNP, provides complementary information to structural and inflammatory markers.

The central finding of our study is the strong and independent predictive value of sST2 for AF recurrence after RFA. sST2 is released from cardiomyocytes under mechanical stress and acts as a decoy receptor for IL-33, thereby inhibiting the cardioprotective IL-33/ST2 signaling pathway that normally counteracts fibrosis and hypertrophy [36, 37]. Higher sST2 levels therefore promote a pro-fibrotic milieu in the atria. In our cohort, patients who later developed recurrence had higher pre-ablation sST2 concentrations, and sST2 outperformed all other individual biomarkers in ROC analysis. These observations are consistent with the meta-analysis by Chen et al. [16], which concluded that increased sST2 is associated with a higher risk of AF recurrence, and with the study by Fan et al. [12], who demonstrated that elevated sST2 correlates with increased left atrial low-voltage areas. Mechanistically, sST2 may serve as a circulating readout of atrial fibroblast activation and extracellular matrix turnover, both of which are critical determinants of the arrhythmogenic substrate. Unlike LAD, which reflects established structural changes, sST2 may indicate ongoing fibrotic activity, which explains its superior predictive performance [12, 22].

In univariate analysis, UA was higher in the recurrence group, but it was not an independent predictor after adjustment. This suggests that UA may be linked to recurrence through inflammation or kidney function, rather than directly causing arrhythmia. Intraoperative electrical cardioversion and CHA₂DS₂-VASc score were also not independent predictors. One possible reason is that their effects are already captured by more direct measures of atrial remodeling and systemic inflammation.

The combined nomogram, which included LAD, hs-CRP, NT-proBNP, IL-6, and sST2, achieved high AUCs in both the training and validation sets, and its predictive performance was far better than that of any single variable. A major strength of this study is the demonstration that our biomarker-based nomogram provides incremental predictive value beyond traditional clinical risk scores. Both the CHA₂DS₂-VASc and HATCH scores are invaluable for assessing stroke risk and AF progression; however, as shown in our comparative analysis, they exhibit poor discriminatory power for predicting post-ablation recurrence. This limitation likely stems from their reliance on demographic and comorbidity data that do not directly reflect the active atrial remodeling processes responsible for arrhythmia recurrence. In contrast, our model integrates LAD (structural remodeling), hs-CRP and IL-6 (inflammation), NT-proBNP (wall stress), and sST2 (active fibrosis). By capturing these complementary mechanistic pathways, the nomogram offers a more precise tool for identifying patients at high risk of failed ablation, enabling tailored therapeutic strategies that conventional scoring systems cannot provide.

From a clinical perspective, our risk model may help identify patients at high risk of recurrence before ablation. For patients with elevated sST2 (e.g., above 32.69 ng/mL) combined with left atrial enlargement and high inflammatory markers, clinicians could consider more intensive post-ablation surveillance, including frequent outpatient visits, extended Holter monitoring, or even the use of implantable loop recorders. Additionally, these patients might benefit from a more aggressive rhythm-control strategy during the blanking period, such as prophylactic antiarrhythmic drugs, although this remains to be tested. Moreover, since sST2 reflects active fibrotic processes, it raises the

hypothesis that therapies targeting fibrosis or the IL-33/ST2 pathway could potentially improve outcomes in these high-risk individuals. However, we emphasize that these suggestions are hypothesis-generating and not derived from our data. Future prospective interventional trials are urgently needed to evaluate whether biomarker-guided management improves long-term success rates after ablation.

Several limitations must be acknowledged. This study was a single-center retrospective analysis, which may introduce selection bias and limit its generalizability. The results need to be validated in prospective, multi-center studies. We only measured sST2 once before ablation. Serial measurements may provide more prognostic information and help monitor patient response to therapy. We did not perform invasive left atrial voltage mapping, which can directly measure fibrosis. Thus, we could not examine the relationship between sST2 levels and low-voltage areas in our patients. For follow-up, we used 24-hour ambulatory ECG and 12-lead ECG, but did not use continuous rhythm monitoring, which may have missed some asymptomatic recurrences. Future studies should consider using implantable loop recorders or continuous telemetry to more accurately detect recurrences. The optimal sST2 cutoff may vary by assay platform and population, which requires further standardization. Whether targeting sST2 or the IL-33/ST2 pathway can improve post-ablation outcomes remains unknown; interventional studies are needed to explore this possibility.

Conclusion

This study provides evidence that preoperative sST2 levels are independently associated with AF recurrence after RFA and may serve as a blood biomarker for pro-fibrotic atrial remodeling. Combining sST2 with other clinical and laboratory parameters, including left atrial size, inflammatory markers, and neurohormonal indices, may improve the comprehensiveness and accuracy of risk assessment. However, this study has limitations, including its retrospective design and single-center setting, so these findings should be interpreted with caution. Future prospective, multi-center studies with standardized protocols are needed to validate whether sST2 can be used for risk stratification in clinical practice.

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Disclosure of conflict of interest

None.

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References

- [1] Rafaqat S, Sharif S, Majeed M, Naz S, Saqib M and Manzoor F. Association of adiponectin gene expression with atrial fibrillation in a Pakistani populace. *Sci Rep* 2023; 13: 22589.
- [2] Zou F, Levine H, Mohanty S, Natale A and Di Biase L. Atrial fibrillation-induced cardiomyopathy. *Card Electrophysiol Clin* 2025; 17: 13-18.
- [3] Sandberg EL, Halvorsen S, Berge T, Grimsø J, Atar D, Leangen Grenne B and Jortveit J. Digital recruitment and compliance to treatment recommendations in the Norwegian Atrial Fibrillation self-screening pilot study. *Eur Heart J Digit Health* 2024; 5: 371-378.
- [4] Karamitanha F, Ahmadi F and Fallahabadi H. Difference between various countries in mortality and incidence rate of the atrial fibrillation based on human development index in worldwide: data from global burden of disease 2010-2019. *Curr Probl Cardiol* 2023; 48: 101438.
- [5] Falasconi G, Penela D, Soto-Iglesias D, Francia P, Teres C, Saglietto A, Jauregui B, Viveros D, Bellido A, Alderete J, Meca-Santamaria J, Franco P, Gaspardone C, San Antonio R, Huguet M, Cámara Ó, Ortiz-Pérez JT, Martí-Almor J and Berrueto A. Personalized pulmonary vein antrum isolation guided by left atrial wall thickness for persistent atrial fibrillation. *Europace* 2023; 25: euad118.
- [6] Falasconi G, Penela D, Soto-Iglesias D, Latini AC, Landra F, Curti E, Francia P, Saglietto A, Turturiello D, Viveros D, Bellido A, Alderete J, Zaraket F, Franco-Ocaña P, Valcher S, Amata F, Valeriano C, Gigante C, Teresi L, Tonello B, Mea R, Sánchez-Mollá L, De Lucia C, Huguet M, Cámara Ó, Ortiz-Pérez JT, Martí-Almor J and Berrueto A. Personalized pulmonary vein isolation guided by left atrial wall thickness for persistent atrial fibrillation ablation: the PeAF-by-

- LAWT randomized trial. *Europace* 2025; 27: euaf163.
- [7] Ahn HJ, Cha MJ, Lee E, Lee SR, Choi EK, Han S, Nam GB, Choi JI, Pak HN, Oh IY, Shin DG, On YK, Park SW, Kim YH and Oh S; KARA investigators. The higher recurrence rate after catheter ablation in younger patients with atrial fibrillation suggesting different pathophysiology. *J Interv Card Electrophysiol* 2023; 66: 1609-1619.
- [8] Vlachakis PK, Theofilis P, Apostolos A, Karakasis P, Ktenopoulos N, Boulmpou A, Drakopoulou M, Leontsinis I, Xydis P, Kordalis A, Koniari I, Gatzoulis KA, Sideris S and Tsioufis C. Beyond pulmonary vein reconnection: exploring the dynamic pathophysiology of atrial fibrillation recurrence after catheter ablation. *J Clin Med* 2025; 14: 2919.
- [9] Chida A, Sato H, Shintani M, Nakayama T, Kawamura Y, Furutani Y, Inai K, Saji T, Matsuo-ka R, Nonoyama S and Nakanishi T. Soluble ST2 and N-terminal pro-brain natriuretic peptide combination. Useful biomarker for predicting outcome of childhoodpulmonary arterial hypertension. *Circ J* 2014; 78: 436-442.
- [10] Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN and Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *J Clin Invest* 2007; 117: 1538-1549.
- [11] Gizatulina TP, Mamarina AV, Martyanova LU, Belonogov DV, Kolunin GV, Petelina TI, Shirokov NE and Gorbatenko EA. The soluble ST2 level predicts risk of atrial fibrillation recurrences in long-term period after radiofrequency ablation. *BMC Cardiovasc Disord* 2024; 24: 460.
- [12] Fan J, Li Y, Yan Q, Wu W, Xu P, Liu L, Luan C, Zhang J, Zheng Q and Xue J. Higher serum sST2 is associated with increased left atrial low-voltage areas and atrial fibrillation recurrence in patients undergoing radiofrequency ablation. *J Interv Card Electrophysiol* 2022; 64: 733-742.
- [13] Liu H, Wang K, Lin Y, Liang X, Zhao S, Li M and Chen M. Role of sST2 in predicting recurrence of atrial fibrillation after radiofrequency catheter ablation. *Pacing Clin Electrophysiol* 2020; 43: 1235-1241.
- [14] Waranugraha Y, Rizal A and Yuniadi Y. The role of soluble ST2 in atrial fibrillation development and its recurrence after catheter ablation: a systematic review and meta-analysis study. *Acta Cardiol* 2026; 81: 146-155.
- [15] Shi Y, Zhang Z, Zhang T, Zhang L, An S and Chen Y. Circulating soluble suppression of tumorigenicity-2 and the recurrence of atrial fibrillation after catheter ablation: a meta-analysis. *Biomol Biomed* 2024; 24: 1470-1481.
- [16] Chen P, Zhang J, Du J, Shi D and Zhang H. Predictive value of soluble suppression of tumorigenicity 2 in atrial fibrillation: a systematic review and meta-analysis. *Front Cardiovasc Med* 2023; 10: 1308166.
- [17] January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM and Yancy CW. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the american college of Cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation* 2019; 140: e125-e151.
- [18] Goette A, Corradi D, Dobrev D, Aguinaga L, Cabrera JA, Chugh SS, de Groot JR, Soulat-Dufour L, Fenelon G, Hatem SN, Jalife J, Lin YJ, Lip GYH, Marcus GM, Murray KT, Pak HN, Schotten U, Takahashi N, Yamaguchi T, Zoghbi WA, Nattel S, Mont L, Akar JG, Akoum N, Althoff T, Diaz JC, Guichard JB, Jadidi A, Kalman J, Lim H and Teixeira RA. Atrial cardiomyopathy revisited: evolution of a concept: a clinical consensus statement of the European Heart Rhythm Association (EHRA) of the ESC, the Heart Rhythm Society (HRS), the Asian Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS). *Europace* 2024; 26: euae204.
- [19] Grigoriou K, Karakasis P, Theofilis P, Pamporis K, Vlachakis PK, Apostolos A, Ktenopoulos N, Fyntanidou B, Karagiannidis E, Patoulis D, Antoniadis AP and Fragakis N. Lifestyle modification in atrial fibrillation: mechanisms, phenotypes and ablation outcomes. *Exp Physiol* 2026; [Epub ahead of print].
- [20] D'Ambrosio P, Claessen G, Kistler PM, Heidbuchel H, Kalman JM and La Gerche A. Ventricular arrhythmias in association with athletic cardiac remodelling. *Europace* 2024; 26: euae279.
- [21] Ureche C, Dodi G, Covic A, Nedelcu A, Volovăţ SR, Sascău RA, Stătescu C and Covic A. Connection between cardiac fibrosis biomarkers and echocardiography parameters in advanced chronic kidney disease patients. *J Clin Med* 2023; 12: 3003.
- [22] Andreasova T, Malek F, Jiraskova Zakostelska Z, Neuzil P and Vranova J. Association of biomarkers of cardiac remodeling, myocardial fibrosis and inflammation with parameters of heart function and structure in patients with arterial hypertension. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2025; 169: 272-280.

- [23] Beltrami M, Galluzzo A, Bonacchi G, Checchi L, Ricciardi G, Perrotta L, Garofalo M, Paoletti Perini A, Mattesini A, Pieragnoli P and Palazzuoli A. Combination between biomarkers and echocardiographic data for prediction of left ventricular reverse remodelling in cardiac resynchronization therapy. *J Clin Med* 2025; 14: 3496.
- [24] Iwamiya S, Ihara K, Nitta G and Sasano T. Atrial fibrillation and underlying structural and electrophysiological heterogeneity. *Int J Mol Sci* 2024; 25: 10193.
- [25] Zhou J, Zhou E, He Q, Zhang K, Zhang T, Mao C, Zhang J and Zhang Z. Association between insulin resistance and incomplete endothelialization of LAAC devices in patients with atrial fibrillation: a retrospective study. *Cardiol Ther* 2025; 14: 463-475.
- [26] Boehmer AA, Ninni S, Heijman J, Dobrev D and Nattel S. The clinical pathophysiology of atrial fibrillation: outstanding questions from bedside to bench and back. *Physiol Rev* 2026; 106: 1055-1121.
- [27] Pegoraro N, Chiarello S, Bisi R, Muscogiuri G, Bertini M, Carnevale A, Giganti M and Cossu A. Cardiac magnetic resonance in the assessment of atrial cardiomyopathy and pulmonary vein isolation planning for atrial fibrillation. *J Imaging* 2025; 11: 143.
- [28] Lepillier A, Pineau J, Otmani A, Durand C, Waintraub X, Zakine C, Niro M, Moubarak G, Zhao A, Bars C, Badenco N, Escande W, Macaluso G and Piot O. Pulmonary vein isolation and low-voltage area ablation in sinus rhythm for persistent atrial fibrillation: the SCAR-AF randomized trial. *Heart Rhythm* 2025; 22: e858-e865.
- [29] Serban T, Mannhart D, Abid QU, Höchli A, Lazar S, Krisai P, Bettelini AS, Knecht S, Kühne M, Sticherling C, du Fay de Lavallaz J and Badertscher P. Durability of pulmonary vein isolation for atrial fibrillation: a meta-analysis and systematic review. *Europace* 2023; 25: euad335.
- [30] Karakasis P, Pamporis K, Theofilis P, Milaras N, Vlachakis PK, Grigoriou K, Patoulas D, Karamitsos T, Antoniadis AP and Fragakis N. Inflammasome signaling in cardiac arrhythmias: linking inflammation, fibrosis, and electrical remodeling. *Int J Mol Sci* 2025; 26: 5954.
- [31] Pang Z, Ren Y and Yao Z. Interactions between atrial fibrosis and inflammation in atrial fibrillation. *Front Cardiovasc Med* 2025; 12: 1578148.
- [32] Murakata Y, Yamagami F, Murakoshi N, Xu D, Song Z, Li S, Okabe Y, Aonuma K, Yuan Z, Mori H, Aonuma K, Tajiri K and Ieda M. Electrical, structural, and autonomic atrial remodeling underlies atrial fibrillation in inflammatory atrial cardiomyopathy. *Front Cardiovasc Med* 2023; 9: 1075358.
- [33] Kerr B and Brandon L. Atrial Fibrillation, thromboembolic risk, and the potential role of the natriuretic peptides, a focus on BNP and NT-proBNP - a narrative review. *Int J Cardiol Heart Vasc* 2022; 43: 101132.
- [34] Werhahn SM, Becker C, Mende M, Haarmann H, Nolte K, Laufs U, Zeynalova S, Löffler M, Dagres N, Husser D, Dörr M, Gross S, Felix SB, Petersmann A, Herrmann-Lingen C, Binder L, Scherer M, Hasenfuß G, Pieske B, Edelmann F and Wachter R. NT-proBNP as a marker for atrial fibrillation and heart failure in four observational outpatient trials. *ESC Heart Fail* 2022; 9: 100-109.
- [35] Bayes-Genis A, Docherty KF, Petrie MC, Januzzi JL, Mueller C, Anderson L, Bozkurt B, Butler J, Chioncel O, Cleland JGF, Christodorescu R, Del Prato S, Gustafsson F, Lam CSP, Moura B, Pop-Busui R, Seferovic P, Volterrani M, Vaduganathan M, Metra M and Rosano G. Practical algorithms for early diagnosis of heart failure and heart stress using NT-proBNP: a clinical consensus statement from the Heart Failure Association of the ESC. *Eur J Heart Fail* 2023; 25: 1891-1898.
- [36] Thanikachalam PV, Ramamurthy S, Mallapu P, Varma SR, Narayanan J, Abourehab MA and Kesharwani P. Modulation of IL-33/ST2 signaling as a potential new therapeutic target for cardiovascular diseases. *Cytokine Growth Factor Rev* 2023; 71-72: 94-104.
- [37] Yaseen X, Aikebaier R, Maimaiti A and Mushajiang M. IL-33/soluble ST₂ axis is associated with radiation-induced cardiac injury. *Open Life Sci* 2024; 19: 20220841.