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Diagnostic Value of Combining Left Atrial Stiffness Index with sST2 for Heart Failure in Patients with Atrial Fibrillation

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Abstract

Objective: To obtain the derived parameter left atrial stiffness index (LASI) using two-dimensional speckle tracking imaging (2D-STI) and evaluate the diagnostic value of LASI combined with soluble suppression of tumorigenicity 2 (sST2) in atrial fibrillation (AF) patients with heart failure (HF). **Methods:** A retrospective analysis was conducted on 106 AF patients admitted to the Affiliated Hospital of Youjiang Medical University for Nationalities between March 2024 and March 2025. The patients were divided into an AF group (n = 60) and an AF with HF group (n = 46) based on the presence of HF. General clinical data, laboratory indicators, conventional echocardiographic parameters, 2D-STI strain parameters, and derived parameters were compared between the two groups. Multivariate binary logistic regression was used to identify independent risk factors for HF in AF patients, and receiver operating characteristic (ROC) curve analysis was performed to assess diagnostic efficacy. **Results:** Compared with the AF group, the AF with HF group showed significantly higher age, proportion of persistent AF, NT-proBNP, sST2, LVEDd, LVEDs, LAD, septal e', E/lateral e', and LASI levels, while hypertension, systolic blood pressure, LVEF, lateral e', absolute LASr, absolute LASed, and absolute LASst values were significantly lower (all $P < 0.05$). Binary logistic regression identified LASI (OR: 68.021; 95% CI: 4.008 - 1154.410; $P = 0.003$), LAD (OR: 1.145; 95% CI: 1.020 - 1.286; $P = 0.021$), and sST2 (OR: 1.087; 95% CI: 1.027 - 1.151; $P = 0.004$) as independent risk factors for HF in AF patients. ROC curve analysis revealed that the area under the curve (AUC) ranked as follows: combined model > LASI > sST2 > LAD (AUC: 0.935, 0.865, 0.857, 0.813; cutoff values: 0.675, 0.5, 35, 39; sensitivity: 82.61%, 82.61%, 78.26%, 76.09%; specificity: 98.33%, 80%, 85%, 80%, respectively). **Conclusion:** In patients with atrial fibrillation complicated with heart failure, elevated left atrial stiffness index (LASI) and increased expression of soluble suppres-

sion of tumorigenicity 2 (sST2) may serve as auxiliary diagnostic biomarkers, demonstrating certain clinical value.

Keywords

Atrial Fibrillation, Heart Failure, Left Atrial Stiffness Index, Soluble Suppression of Tumorigenicity 2

1. Introduction

Atrial fibrillation (AF) is a common clinical arrhythmia whose prevalence and incidence are increasing annually [1]. AF can lead to numerous clinical complications, such as stroke, thromboembolism, and heart failure (HF). For a long time, the thromboembolic risk of AF, particularly stroke, has received significant attention, with relatively comprehensive research on its prevention and management. In contrast, the complications related to heart failure have been comparatively underemphasized and less thoroughly investigated. Studies have indicated that approximately 30% of AF patients eventually progress to chronic HF, significantly increasing the risk of cardiovascular death and rehospitalization [2]. Therefore, identifying risk factors for the development of HF in AF patients and enabling the early recognition of high-risk individuals is crucial for optimizing treatment strategies and improving prognosis. However, traditional indicators of cardiac function assessment, such as left ventricular ejection fraction (LVEF) and brain natriuretic peptide (BNP), while possessing certain diagnostic value, can be influenced by factors like heart rate variability and volume load in AF patients, potentially limiting their diagnostic efficacy. AF originates from structural and/or functional remodeling of the left atrium, suggesting that left atrial structure and/or function could serve as early diagnostic indicators for AF-related heart failure. Timely intervention in AF may delay the progression of HF [3]. Two-dimensional speckle-tracking echocardiography (2D-STE) overcomes the angle-dependency limitations of conventional ultrasound, allowing for a more convenient and precise assessment of left atrial function throughout the cardiac cycle, thereby facilitating the identification of early-stage left atrial pathologies [4], The derived parameter, the left atrial stiffness index (LASI), has garnered increasing attention for its ability to non-invasively evaluate left atrial function and compliance. Concurrently, soluble suppression of tumorigenicity 2 (sST2), a novel biomarker reflecting myocardial fibrosis and inflammatory response, has demonstrated significant potential in predicting and risk-stratifying heart failure [5]. Nevertheless, its diagnostic value specifically in patients with AF and concomitant HF remains unclear. This study aims to investigate the diagnostic value of combining the 2D-STE-derived left atrial stiffness index (LASI) with serum soluble suppression of tumorigenicity 2 (sST2) for heart failure in patients with atrial fibrillation, hoping to provide a reference for clinical practice.

According to the Chinese Guidelines for the Diagnosis and Management of Atrial Fibrillation, patients with heart failure are classified into: heart failure with reduced ejection fraction (HFrEF, LVEF ≤40%), heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 41% - 49%), and heart failure with preserved ejection fraction (HFpEF, LVEF ≥50%).

2. Materials and Methods

2.1. Study Patients

This study is a retrospective study that selected 106 patients with atrial fibrillation admitted to the Affiliated Hospital of Youjiang Medical University for Nationalities from March 2024 to March 2025 as the research subjects. Inclusion criteria: 1) Patients with atrial fibrillation meet the diagnostic criteria specified in the Chinese Guidelines for the Diagnosis and Management of Atrial Fibrillation [6]: Electrocardiogram (ECG) examination indicates atrial fibrillation rhythm, with no repetitive P waves, unequal RR intervals, and basically normal QRS wave morphology. For atrial fibrillation patients, all parameters were measured during relatively regular cardiac cycles: before acquisition, the ECG was simultaneously connected, and five consecutive R-R intervals were observed. Cardiac cycles with an R-R interval variability rate of <15% were selected as valid cycles. The variability rate was calculated using the formula: (maximum R-R interval - minimum R-R interval)/average R-R interval ×100%. Cardiac cycles at the end of expiration were preferentially selected for acquisition to avoid interference from respiratory movement on the measurement of cardiac structure and strain. The ventricular rate of the patients was between 60 and 100 beats per minute. 2) Patients with heart failure meet the diagnostic criteria specified in the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2024 [7]: (a) Presence of symptoms or signs of heart failure, such as orthopnea, peripheral edema, jugular vein distension, etc.; physical examination reveals pulmonary rales, lateral displacement or diffusion of the apical beat, etc. (b) Left ventricular ejection fraction <40%. (c) Abnormal ECG, chest X-ray indicating pulmonary edema/congestion, cardiac enlargement, elevated B-type natriuretic peptide (BNP) levels, and echocardiography showing structural or functional abnormalities of the heart, etc. 3) Complete clinical data. 4) Age >18 years.

Exclusion criteria: 1) Concomitant severe hepatic or renal dysfunction; 2) Pregnancy or lactation; 3) Coexisting autoimmune disease, active infection, or malignancy; 4) Presence of severe structural heart disease (e.g., congenital heart disease, valvular heart disease, etc.); 5) Recent (within 3 months) cardiac surgery or interventional therapy; 6) Incomplete clinical data or difficulty in follow-up.

All patients with atrial fibrillation (AF) complicated by heart failure (HF) included in this study were diagnosed with stable chronic heart failure. Patients with acute decompensated heart failure were excluded based on the following criteria: no acute HF exacerbation within 48 hours prior to admission (*i.e.*, absence of resting dyspnea, pulmonary edema, or need for intravenous inotropic agents or diu-

retics), and no acute cardiac load abnormalities requiring urgent intervention (e.g., severe hypertension, uncontrolled rapid AF, etc.). In accordance with the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2024, patients with heart failure were classified into the following categories: heart failure with reduced ejection fraction (HFrEF, LVEF ≤ 40%), heart failure with mildly reduced ejection fraction (HFmrEF, 41% ≤ LVEF ≤ 49%), and heart failure with preserved ejection fraction (HFpEF, LVEF ≥ 50%).

A total of 106 patients were divided into two groups based on the presence or absence of heart failure: the atrial fibrillation group (AF group, n = 60) and the atrial fibrillation with heart failure group (AF + HF group, n = 46). All participants provided informed consent.

2.2. Instruments and Methods

1) Clinical Data Collection Demographic and clinical characteristics were collected, including gender, age, height, weight, history of hypertension, diabetes, coronary artery disease, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body mass index (BMI), and body surface area (BSA).

2) Serological Biomarker Assays Peripheral venous blood samples were collected from all patients under fasting conditions on the morning following admission. Blood samples for sST2 measurement were drawn into standard serum tubes, while those for N-terminal pro-B-type natriuretic peptide (NT-proBNP) were collected in EDTA-anticoagulated tubes. After collection, samples were allowed to clot (for sST2) for 30 minutes and then centrifuged at 3000 rpm for 10 minutes to separate serum or plasma. sST2 Measurement: Serum sST2 levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Presage® ST2 Assay). Serum samples were stored at 2˚C - 8˚C and analyzed within 24 hours; for long-term storage, samples were kept at −20˚C. NT-proBNP Measurement: Plasma NT-proBNP levels were measured using an electrochemiluminescence immunoassay (ECLIA) on a Roche Cobas e601 analyzer. Samples were processed immediately. All assays were performed following strict quality control procedures, and samples with hemolysis were excluded from the analysis.

3) Transthoracic Echocardiography A Philips EPIQ 7C ultrasound system equipped with an S5-1 phased-array transducer (frequency range 2 - 2.5 MHz) was used for all examinations. Participants were placed in the left lateral decubitus position while breathing quietly, with simultaneous electrocardiographic monitoring. Standard parameters were acquired: Left atrial diameter (LAD) was measured in the parasternal long-axis view. M-mode echocardiography in the parasternal long-axis view was used to measure left ventricular end-diastolic internal dimension (LVIDd), left ventricular end-systolic internal dimension (LVIDs), end-diastolic interventricular septal thickness (IVSd), and end-diastolic left ventricular posterior wall thickness (LVPWd). Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson's method. In the apical four-chamber view, pulsed-wave Doppler was used to acquire the early (E-wave) and

late (A-wave) diastolic mitral inflow velocities. Tissue Doppler imaging was used to measure the early diastolic mitral annular velocities at the septal (septal e') and lateral (lateral e') sites. The average e' (e' avg) was calculated, and the E/e' ratio were derived. Tissue Doppler e' velocity measurement method: Dynamic images containing five or more consecutive cardiac cycles were stored. At end-expiration, e' velocity was measured over five consecutive cardiac cycles with stable R-R intervals, clear spectral waveforms, and no waveform fusion. The final e' value for the interventricular septum or lateral wall was calculated as the average of the e' velocities measured across these multiple cardiac cycles.

4) Two-Dimensional Speckle-Tracking Echocardiography (2D-STE) 2D-STE was performed in accordance with the 2018 EACVI/ASE Expert Consensus on the Clinical Use of Speckle-Tracking Echocardiography [8], Using the same Philips EPIQ 7C system, dynamic images focused on the left atrium were acquired from the apical four-chamber view. Five consecutive cardiac cycles (R-R intervals) were recorded at a frame rate of >60 frames per second and stored in DICOM format for offline analysis. Subsequent analysis was performed using the AutoStrain LA module in the Philips QLAB software (version 13.0). The system automatically traced the left atrial endocardial border, excluding the left atrial appendage and pulmonary veins. If the automated tracking was suboptimal (tracking index <90%), manual adjustments were made to the region of interest to ensure accurate tracking throughout the cardiac cycle. All strain analyses used the end-diastolic phase as the reference point. The software automatically generated left atrial strain-time curves and derived the following parameters: left atrial reservoir strain (LASr), left atrial contractile strain (LASct), and left atrial conduit strain (LAScd). The left atrial stiffness index (LASI) was calculated using the formula: LASI = (E /e' avg)/LASr [9]. All the aforementioned 2D-STI parameters were independently acquired and analyzed offline by three sonographers, each with over five years of experience in 2D-STI operation, with the final values derived from the average of their measurements. In accordance with the pre-specified analysis protocol of this study, only left atrial reservoir longitudinal strain (LASr) was acquired and reported, and this parameter was used to calculate the left atrial stiffness index. Although this technique can also generate left atrial contraction strain (LASct) and left atrial conduit strain (LAScd), these parameters were not within the scope of analysis in this study.

2.3. Statistical Analysis

Statistical analyses were performed using SPSS software (version 27.0). Categorical data are presented as numbers and percentages (n, %) and were compared between groups using the Chi-square test or Fisher's exact test, as appropriate. Normally distributed continuous data are expressed as mean ± standard deviation ($\overline{x} \pm s$) and were compared using the independent samples *t*-test. Non-normally distributed continuous data are expressed as median with interquartile range (M [Q1, Q3]) and were compared using the Mann-Whitney U test. Variables that showed a statistically significant difference (P-value < 0.05) in the uni-

variate analyses were subsequently included in a multivariate binary logistic regression model to identify independent risk factors. The correlation between LASI and sST2 was assessed using Pearson correlation analysis. Furthermore, Receiver Operating Characteristic (ROC) curve analysis was conducted using MedCalc software (version 20.010) to evaluate the diagnostic performance of the identified independent factors. The area under the curve (AUC), optimal cutoff value, specificity, and sensitivity were calculated for each variable and for their combination.

3. Results

3.1. Comparison of Clinical Characteristics and Laboratory Findings between the Two Groups

Compared to the AF-alone group, the AF with HF group showed statistically significant differences in age, NT-proBNP levels, sST2 levels, the prevalence of persistent AF, the prevalence of hypertension, and systolic blood pressure (SBP) (all $P < 0.05$). No significant differences were observed between the two groups in terms of gender, body mass index (BMI), history of diabetes, history of coronary artery disease (CAD), diastolic blood pressure (DBP), heart rate (HR), body surface area (BSA), or C-reactive protein (CRP) levels (all $P > 0.05$). Details are presented in Table 1.

Table 1. Comparison of clinical characteristics and laboratory findings between the two groups.

Item	AF group (n = 60)	AF with HF group (n = 46)	Statistic	P-value
Age (years)	64.00 (55.00, 69.00)	68.50 (60.00, 72.75)	Z = −2.19	0.029
Male, n (%)	37 (61.67)	32 (69.57)	$\chi^2 = 0.71$	0.398
Hypertension, n (%)	34 (56.67)	16 (34.78)	$\chi^2 = 5.00$	0.025
Diabetes, n (%)	7 (11.67)	1 (2.17)	$\chi^2 = 2.14$	0.144
Coronary artery disease, n (%)	26 (43.33)	25 (54.35)	$\chi^2 = 1.27$	0.261
Persistent AF, n (%)	22 (36.67)	27 (58.70)	$\chi^2 = 5.08$	0.024
Systolic BP (mmHg)	136.50 (118.00, 149.25)	120.50 (102.25, 129.00)	Z = −2.95	0.003
Diastolic BP (mmHg)	82.00 (71.00, 90.25)	74.50 (63.00, 94.00)	Z = −1.00	0.317
Heart rate (bpm)	82.00 (74.00, 100.00)	90.00 (78.50, 100.75)	Z = −1.19	0.236
BMI (kg/m^2)	23.60 (21.98, 25.77)	24.10 (21.52, 26.55)	Z = −0.34	0.731
BSA (m^2)	1.74 (1.62, 1.85)	1.77 (1.59, 1.90)	Z = −0.48	0.628
NT-proBNP (pg/ml)	393.95 (122.58, 1019.00)	607.05 (470.17, 1035.58)	Z = −2.22	0.026
sST2 (ng/ml)	22.00 (13.00, 32.12)	42.00 (36.00, 56.00)	Z = −6.27	<0.001
CRP (mg/L)	7.05 (3.44, 10.90)	10.30 (3.80, 14.67)	Z = −1.85	0.064

Note: Data are presented as median (interquartile range) for continuous variables and as number (percentage) for categorical variables. AF = atrial fibrillation; HF = heart failure; BMI = body mass index; BSA = body surface area; BP = blood pressure; bpm = beats per minute; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sST2 = soluble suppression of tumorigenicity 2; CRP = C-reactive protein.

3.2. Comparison of Echocardiographic and Hemodynamic Parameters between the Two Groups

Univariate analysis of the imaging data revealed significant differences between the two groups in the following parameters (all $P < 0.05$): left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVIDd), left ventricular end-systolic dimension (LVIDs), left atrial diameter (LAD), septal e' velocity, lateral e' velocity, E/lateral e' ratio, absolute value of left atrial reservoir strain (LASr), absolute value of left atrial conduit strain (LAScd), absolute value of left atrial contractile strain (LASct), and left atrial stiffness index (LASI). No significant differences were observed between the groups in the following parameters (all $P > 0.05$): end-diastolic interventricular septal thickness (IVSd), end-diastolic left ventricular posterior wall thickness (LVPWd), mitral inflow E-wave velocity (E), mitral inflow A-wave velocity (A), E/A ratio, and average E/e' ratio. Detailed results are presented in Table 2.

Table 2. Comparison of echocardiographic parameters between the two groups.

Parameter	AF group (n = 60)	AF with HF group (n = 46)	Statistic	P-value
LVEF (%)	64.65 (59.00, 69.20)	42.50 (33.25, 57.83)	Z = −5.71	<0.001
LVIDd (mm)	46.00 (42.75, 48.25)	54.00 (47.00, 60.75)	Z = −4.29	<0.001
LVIDs (mm)	29.00 (26.00, 32.00)	40.50 (31.25, 50.75)	Z = −5.04	<0.001
IVSd (mm)	9.00 (8.75, 10.00)	9.00 (9.00, 10.00)	Z = −0.27	0.789
LVPWd	9.00 (8.00, 11.00)	10.00 (8.00, 11.00)	Z = −0.463	0.643
LAD (mm)	34.00 (32.00, 39.00)	41.50 (39.92, 47.75)	Z = −5.50	<0.001
E (cm/s)	83.10 (74.00, 97.00)	86.00 (79.12, 98.75)	Z = −0.94	0.349
A (cm/s)	81.50 (66.75, 96.00)	78.00 (57.00, 98.00)	Z = −0.50	0.614
E/A	1.10 (0.80, 1.30)	1.20 (1.02, 1.37)	Z = −1.16	0.245
Septal e' (cm/s)	7.00 (5.97, 8.00)	8.21 (7.10, 9.35)	Z = −3.78	<0.001
Lateral e' (cm/s)	9.45 (7.97, 10.42)	7.85 (6.15, 8.75)	Z = −4.17	<0.001
E/e' avg	10.79 ± 2.22	11.83 ± 3.17	t = −1.98	0.050
|LASr| (%)	25.30 (19.52, 30.95)	15.50 (12.48, 19.95)	Z = −5.72	<0.001
LASI	0.40 (0.30, 0.50)	0.80 (0.62, 1.00)	Z = −6.47	<0.001

Note: Data are presented as median (interquartile range) or mean ± standard deviation, as appropriate. AF = atrial fibrillation; HF = heart failure; LVEF = left ventricular ejection fraction; LVIDd = left ventricular end-diastolic dimension; LVIDs = left ventricular end-systolic dimension; IVSd = end-diastolic interventricular septal thickness; LVPWd = end-diastolic left ventricular posterior wall thickness; LAD = left atrial diameter; E = early diastolic mitral inflow velocity; A = late diastolic mitral inflow velocity; Septal e' = septal mitral annular early diastolic velocity; Lateral e' = lateral mitral annular early diastolic velocity; E/e' avg = average E/e' ratio; LASr| = absolute value of left atrial reservoir strain; LAScd| = absolute value of left atrial conduit strain; LASct| = absolute value of left atrial contractile strain; LASI = left atrial stiffness index.

Among the 46 patients with atrial fibrillation complicated by heart failure in this study, 21 cases (46%) were classified as HFrEF, 8 cases (17%) as HFmrEF, and 17 cases (37%) as HFpEF, indicating that heart failure with reduced ejection fraction was the predominant subtype.

3.3. Binary Logistic Regression and Receiver Operating Characteristic (ROC) Curve Analyses

In this study, the left atrial stiffness index was calculated from its components: the peak early diastolic mitral inflow velocity (E), the average of the peak early diastolic myocardial velocities at the septal and lateral mitral annulus (e′), and the left atrial reservoir longitudinal strain (LASr), using the formula: LASI = (E/e′) / LASr. Although septal e′ and lateral e′ also showed statistically significant differences between groups in the comparative analysis, we included only the left atrial stiffness index in the subsequent univariable and multivariable logistic regression analyses. This decision was made in order to focus on an index that more comprehensively reflects atrial mechanical function. Multivariate binary logistic regression analysis identified the left atrial stiffness index (LASI), soluble ST2 (sST2), and left atrial diameter (LAD) as significant independent risk factors for the development of heart failure in patients with atrial fibrillation (all $P < 0.05$). The results of the regression analysis are detailed in Table 3. ROC curve analysis was performed to evaluate the diagnostic efficacy of these independent factors. The areas under the curve (AUC) for predicting HF in AF patients were as follows: 0.865 (95% CI: 0.795 - 0.934) for LASI, 0.857 (95% CI: 0.784 - 0.929) for sST2, 0.813 (95% CI: 0.723 - 0.902) for LAD, and 0.935 (95% CI: 0.885 - 0.985) for the combination model. The corresponding optimal cutoff values, sensitivities, and specificities were: LASI: cutoff >0.5, sensitivity 82.61%, specificity 80.00%, sST2: cutoff >35 ng/mL, sensitivity 78.26%, specificity 85.00%, LAD: cutoff >39 mm, sensitivity 76.09%, specificity 80.00%, Combination: cutoff >0.675, sensitivity 82.61%, specificity 98.33%. Detailed results of the ROC analysis are presented in Table 4 and Figure 1.

Table 3. Logistic regression analysis of factors influencing heart failure in patients with atrial fibrillation.

Variable	Univariate analysis				Multivariate analysis			
	β	S.E	*P*	OR (95%CI)	*β*	S.E	*P*	OR (95%CI)
Hypertension	−0.897	0.405	0.027	0.408 (0.185 - 0.901)	−0.423	0.791	0.593	0.655 (0.139 - 3.090)
Persistent AF	0.898	0.402	0.025	2.455 (1.117~ 5.395)	0.431	0.729	0.555	1.538 (0.369 - 6.416)
Age	0.026	0.019	0.178	1.026 (0.988 - 0.065)				
Systolic BP	−0.022	0.009	0.011	0.978 (0.961 - 0.995)	−0.016	0.016	0.315	0.984 (0.953 - 1.016)
NT-proBNP	0.000	0.000	0.376	1.000 (1.000 - 0.000)				
LVEF	−0.124	0.025	<0.001	0.883 (0.841 - 0.927)	−0.067	0.072	0.356	0.936 (0.812 - 1.078)

Continued

LVEDd	0.133	0.033	<0.001	1.142 (1.071 - 0.218)	−0.193	0.133	0.149	0.825 (0.635 - 1.071)
LVEDs	0.156	0.035	<0.001	1.169 (1.093 - 0.252)	0.123	0.164	0.453	1.131 (0.820 - 1.559)
LAD	0.193	0.042	<0.001	1.213 (1.117 - 1.317)	0.136	0.059	0.021	1.145 (1.020 - 1.286)
LASI	5.928	1.201	<0.001	375.243 (35.668 - 3947.681)	4.220	1.445	0.003	68.021 (4.008 - 1154.410)
sST2	0.112	0.023	<0.001	1.119 (1.069 - 1.170)	0.084	0.029	0.004	1.087 (1.027 - 1.151)

Table 4. Predictive value of sST2, LASI, LAD, and their combination for atrial fibrillation with chronic heart failure.

Variable	AUC	95%CI	Cut-off value	Sensitivity (%)	Specificity (%)	Youden's index	P-value
ST2	0.857	0.784 - 0.929	35	78.26	85.00	0.633	<0.001
LASI	0.865	0.795 - 0.934	0.5	82.61	80.00	0.626	<0.001
LAD	0.813	0.723 - 0.902	39	76.09	80.00	0.561	<0.001
Combination	0.935	0.885 - 0.985	0.675	82.61	98.33	0.809	<0.001

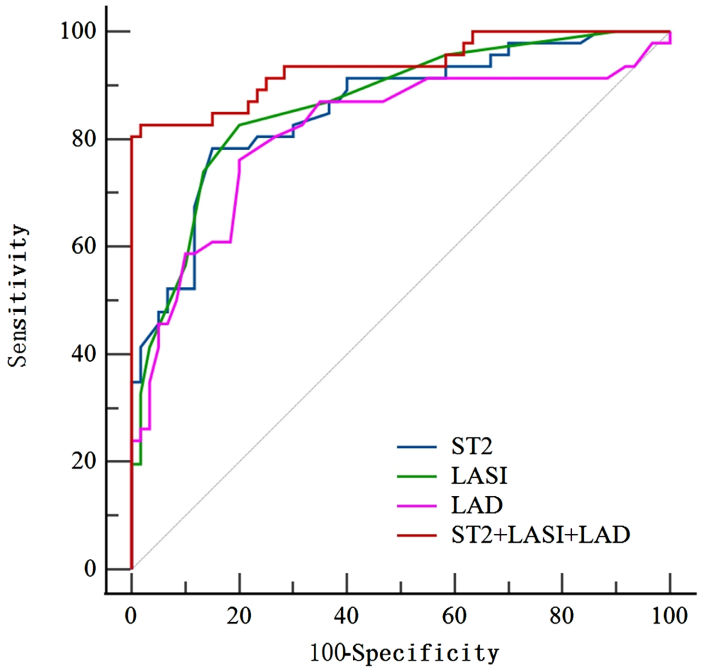

Figure 1. Receiver operating characteristic (ROC) curves of sST2, LASI, and LAD for predicting heart failure in patients with atrial fibrillation.

3.4. Correlation between LASI and sST2

Pearson correlation analysis revealed a significant weak positive correlation between LASI and sST2 among the 106 study participants ($r = 0.336$, $P < 0.001$), suggesting that as sST2 expression levels increase, the left atrial stiffness index exhibits a synchronous upward trend, indicating a clear positive association between the two variables.

4. Discussion

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia with increasing annual incidence and prevalence rates. Heart failure (HF), a common complication of AF, engages in a complex bidirectional relationship with it, wherein each condition potentiates the other, forming a vicious cycle that significantly elevates the risk of adverse cardiovascular events [10]. Identifying risk factors for the development of HF in AF patients is therefore of paramount clinical importance.

From an echocardiographic perspective, this study utilized the left atrial stiffness index (LASI), a parameter derived from two-dimensional speckle-tracking imaging (2D-STI), as an objective indicator to assess left atrial (LA) function in patients with AF and concomitant HF, exploring its diagnostic value in AF-related cardiac dysfunction. LASI quantifies the relationship between LA filling pressure and myocardial deformation characteristics [11], providing a novel biomechanical parameter for clinical assessment of LA function. A study by Khurram *et al*. involving 219 AF patients undergoing catheter ablation demonstrated that the 40 patients with recurrence during a median follow-up of 10 months had significantly higher LA stiffness than those without recurrence ($P < 0.01$). Multivariate analysis confirmed LA stiffness as an independent predictor of post-ablation recurrence (OR = 3.21, 95% CI: 1.87 - 5.52) [12]. Furthermore, a prospective cohort study by Ibadete *et al*. revealed that LA stiffness was significantly positively correlated with the incidence of major adverse cardiovascular events in patients with heart failure with reduced ejection fraction (HR = 2.15, 95% CI: 1.46 - 3.17) [13] [14]. These findings collectively underscore the prognostic value of LA stiffness. LA myocardial fibrosis constitutes the pathological basis of structural remodeling in AF patients, playing a pivotal role in both the initiation and perpetuation of AF [15]. As a novel imaging biomarker, LASI assesses the degree of myocardial fibrosis by quantifying LA mechanical properties, thereby offering an objective basis for evaluating AF progression. It achieves a comprehensive evaluation of LA hemodynamics and mechanical function primarily by integrating the diastolic parameter E/e' with the reservoir strain (LASr). Chronic AF leads to atrial fibrosis and collagen deposition, significantly increasing atrial wall stiffness. This structural remodeling, accompanied by decreased LA compliance, forces a compensatory rise in filling pressure to maintain ventricular filling [16]. As atrial contractile function declines, the retrograde transmission of pulmonary venous pressure causes hemodynamic disturbances, manifesting as increased pulmonary capillary wedge pressure, significantly elevated BNP levels, and worsened HF symptoms, forming an "AF-atrial remodeling-HF" vicious cycle. In this study, the left atrial stiffness index (LASI) was significantly lower in the AF with HF group than in the AF-only group ($P < 0.05$). Multivariable logistic regression analysis identified LASI as an independent predictor of AF with HF (OR = 68.021, 95% CI: 4.008 - 1154.410), further confirming that reduced LASI is closely associated with the risk of HF in patients with AF. The wide 95% confidence interval observed for LASI in this study is likely attributable to the limitations of a single-center design with

a relatively small sample size, as well as quasi-complete separation in the regression model, rather than reflecting genuine extreme variability in the effect of LASI. Despite the wide confidence interval, the P value for LASI remained < 0.01, indicating a statistically robust association as an independent risk factor. Moreover, ROC curve analysis demonstrated favorable diagnostic performance (AUC = 0.865). In light of the underlying pathophysiological mechanisms, the association between elevated LASI and left atrial remodeling and the development of heart failure is well-grounded. Future studies with larger sample sizes are warranted to obtain more precise estimates of the effect size.

Our results showed that left atrial diameter (LAD) had lower diagnostic sensitivity as a risk factor compared to other functional parameters. This finding may suggest that structural changes lag behind functional alterations. In the early stages of AF and HF, the left atrium undergoes electrical remodeling and functional compensation (e.g., myocardial fibrosis, impaired diastolic function), during which LAD may not yet be significantly enlarged. Research by Bao Lilian *et al.* [17] confirmed that changes in LA function often precede structural changes under various physiological and pathological conditions, indicating that functional parameters possess higher clinical sensitivity than traditional morphological indicators. Furthermore, an enlarged LAD is not specific to AF with HF but is also common in hypertension, mitral valve disease, and obesity, reducing its specificity for HF. Therefore, functional indices (like LASI) and biomarkers (like sST2) hold greater clinical advantage for the early diagnosis of AF with HF, while LAD is more suitable for assessing advanced structural changes or as an auxiliary reference.

From a serological perspective, soluble ST2 (sST2), an immunomodulatory protein, participates in the regulation of myocardial fibrosis by blocking the IL-33/ST2 signaling pathway, leading to reduced myocardial compliance and ventricular diastolic dysfunction. In AF patients, atrial electrical remodeling and hemodynamic abnormalities further exacerbate myocardial stress, stimulating increased sST2 release. Its elevated serum level directly reflects the degree of myocardial fibrosis and the progression of ventricular remodeling, showing a significant correlation with HF severity. Compared to the traditional biomarker NT-proBNP, sST2 is less influenced by renal function and volume status, offering better specificity. This study demonstrated that sST2 was significantly elevated in AF patients with HF (AUC = 0.857) and was an independent risk factor for HF occurrence. This result validates that myocardial fibrosis is a key pathological mechanism in AF-related HF and confirms sST2 as a reliable serological biomarker for clinical diagnosis. Multiple studies have confirmed the critical role of sST2 in the development and progression of heart failure. Research by Roy *et al.* [18] indicated that sST2, by mediating oxidative stress responses, directly participates in the process of myocardial remodeling, promoting the occurrence of HF with preserved ejection fraction (HFpEF). Simultaneously, elevated sST2 levels are significantly associated with coronary microvascular dysfunction, specifically manifested as microvascular damage, myocardial fibrosis, and abnormal blood perfusion [19]

[20], these pathological changes collectively constitute important mechanisms in HFpEF pathogenesis.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a biologically active peptide secreted by myocardial cells in response to volume or pressure overload. Its elevated levels sensitively reflect ventricular wall stress, dilation, and functional impairment, making it an important biomarker for heart failure. In this study, although NT-proBNP levels were significantly higher in the AF with HF group, multivariate analysis showed it was not an independent risk factor. This may be attributed to confounding factors inherent to AF itself, renal dysfunction, and volume status [7]. NT-proBNP is synthesized and released by ventricular cardiomyocytes under pressure or volume overload, directly reflecting ventricular wall tension. The irregular ventricular rate in AF causes varying diastolic filling times, potentially leading to intermittent volume overload and stimulating NT-proBNP release. Thus, even in the absence of HF, AF patients can exhibit elevated NT-proBNP due to atrioventricular dyssynchrony or rapid ventricular rates. Furthermore, NT-proBNP is primarily cleared by renal excretion, and its plasma levels are inversely correlated with glomerular filtration rate (GFR). Renal impairment can therefore reduce clearance and elevate plasma NT-proBNP concentrations independently of cardiac function.

C-reactive protein (CRP), a systemic inflammation marker, holds significant value in cardiovascular risk assessment. Although AF primarily manifests as an atrial disorder, its nature may fall within the spectrum of systemic diseases [21]. The lack of a significant difference in CRP in this study might be because both AF and HF are often comorbid with metabolic diseases like hypertension, diabetes, and obesity, which themselves can elevate CRP levels. Additionally, AF itself can cause elevated CRP, which limits its specificity for diagnosing HF in this population.

This study found that the prevalence of hypertension in the atrial fibrillation group (56.67%) was higher than in the atrial fibrillation with heart failure group (34.78%), which contradicts the clinical understanding that hypertension is a major risk factor for heart failure. This discrepancy reflects a clinical characteristic bias within the study cohort and can be explained from three perspectives: Firstly, inclusion bias and baseline characteristics: this study excluded patients with severe cardiac structural abnormalities or recent interventions/surgeries. Long-term hypertension is often associated with conditions such as mitral valve disease and left ventricular hypertrophy, which were likely excluded. The atrial fibrillation with heart failure group was older, and some elderly patients had undiagnosed hypertension due to low baseline blood pressure or orthostatic hypotension, resulting in a lower reported prevalence. Secondly, therapeutic intervention effects: Patients with atrial fibrillation and heart failure are more actively treated with antihypertensive medications such as RAAS inhibitors and beta-blockers due to cardiac dysfunction. Even patients with a history of hypertension may have their blood pressure controlled to normal levels and thus not be recorded as hypertensive dur-

ing follow-up. In contrast, patients with atrial fibrillation alone receive less intensive blood pressure management, leading to poorer control and a higher recorded prevalence. Thirdly, pathophysiological changes: Severe heart failure leads to reduced cardiac output and peripheral hypoperfusion, which can lower blood pressure to normal levels in previously hypertensive patients—a phenomenon described as "heart failure masking hypertension"—thereby reducing the diagnostic rate. It should be noted that this inverse association is a characteristic of this single-center, small-sample study and does not negate the clinical value of hypertension. Future multicenter, large-sample studies with adjustment for confounding factors are needed for further validation.

The atrial fibrillation with heart failure group in this study included three phenotypes: HFrEF, HFmrEF, and HFpEF, accounting for 46%, 17%, and 37% of cases, respectively. The pathophysiological relationship between LASI and sST2 varies across heart failure phenotypes with different ejection fractions: In HFrEF, myocardial fibrosis and impaired ventricular systolic function jointly drive increased left atrial stiffness, whereas in HFpEF, left atrial diastolic dysfunction is the core pathological change. Therefore, the diagnostic value of combining LASI and sST2, as demonstrated in this study, is applicable to patients with atrial fibrillation and heart failure across different ejection fraction phenotypes, providing a unified reference indicator for the auxiliary diagnosis of various heart failure phenotypes. However, whether the diagnostic performance of these two markers differs among phenotypes requires further stratified analysis for validation.

Based on a univariate significance threshold of $P < 0.05$, this study incorporated clinically meaningful indicators such as age and NT-proBNP into multivariate regression to adjust for confounding factors and validate the independent role of core clinical indicators. Furthermore, non-parametric testing in Table 1 showed that NT-proBNP levels were significantly higher in the atrial fibrillation with heart failure group than in the atrial fibrillation group ($P = 0.026$). However, NT-proBNP did not reach statistical significance in univariate logistic regression ($P = 0.376$), likely due to high inter-individual variability in NT-proBNP levels and the diluting effect of unadjusted confounders such as age, atrial fibrillation type, and systolic blood pressure. Therefore, NT-proBNP was included in multivariate regression for further validation of its independent role. The results showed that it remained a non-independent risk factor for atrial fibrillation with heart failure ($P > 0.05$), suggesting that NT-proBNP may not be an independent influencing factor in this context, and its level changes may be mediated by other factors.

Notably, this study is the first to explore the combined diagnostic value of sST2 and LASI, finding that the AUC for their combination (0.935) was significantly higher than that of any single indicator ($P < 0.05$). Their synergistic mechanism lies in providing a comprehensive assessment of the disease process from complementary pathophysiological dimensions: sST2 reflects the chronic structural change of myocardial fibrosis via the IL-33/ST2 pathway, while LASI quantifies real-time LA functional abnormality and hemodynamic impairment by integrat-

ing E/e' and LASr. This combination of a molecular biomarker and a functional index covers both the pathological basis of myocardial fibrosis (sST2) and captures the immediate manifestation of atrio-ventricular coupling dysfunction (LASI), resulting in higher specificity (98.33%) and comprehensiveness for diagnosis.

This study has several limitations: 1) Limited Sample Size: This study is a single-center retrospective analysis with a relatively small sample size. For certain indicators (e.g., LASI), the wide confidence intervals of the logistic regression parameters indicate insufficient statistical stability. Future research with larger sample sizes is required to validate the conclusions. 2) Follow-up duration: The follow-up period was insufficient to evaluate the long-term prognostic value of LASI and sST2. Extended follow-up is warranted. 3) Confounding factors: Other factors influencing HF (such as coronary artery disease and hypertension) could not be entirely excluded as potential confounders.

5. Conclusion

In summary, this study confirms that patients with atrial fibrillation complicated by heart failure exhibit a significant elevation in the left atrial stiffness index and a marked increase in sST2 expression levels. The combined detection of these two biomarkers can provide valuable auxiliary reference for the clinical diagnosis of atrial fibrillation with comorbid chronic heart failure.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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