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Original Article

Left atrial stiffness index predicts atrial fibrillation risk in heart failure with preserved ejection fraction: a nomogram model

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Abstract: Objective: Develop a LASI-based nomogram for predicting atrial fibrillation (AF) risk in heart failure with preserved ejection fraction (HFpEF). Methods: This retrospective study analyzed 275 HFpEF patients (160 AF, 115 controls). Echocardiography measured LASI (E/e' divided by peak atrial longitudinal strain), left atrial volumes, strains (AP2%, AP4%), and electromechanical delays (SD2: inter-atrial; SD4: intra-left atrial). Multivariate logistic regression identified AF predictors. Nomogram performance was validated by ROC analysis and DCA. Results: Compared to controls, the AF group had significantly larger LVDD/LVSD (P<0.001 both), lower 3D-LAEF% (P<0.001), lower E/e' (P<0.001), higher LASI (P<0.001), larger BSA (P<0.001), higher AP2% (P<0.001), lower AP4% (P<0.001), and longer SD4 (P<0.001). Multivariate analysis identified positive associations with AF risk for: BSA (OR=9.167, P<0.001), AP4% (OR=1.033, P=0.008), SD2 (OR=1.003, P=0.001), and LASI (OR=1.043, P<0.001). Negative associations were found for E/e' (OR=0.889, P=0.002) and SD4 (OR=0.997, P<0.001). ROC AUCs were: LASI=0.666, E/e'=0.707, BSA=0.682, SD2=0.615, AP4=0.666, SD4=0.705. The combined model AUC was 0.801. DCA identified LASI as the optimal single predictor (net benefit 0.3184). Conclusion: LASI independently predicted AF risk in HFpEF. The validated nomogram, integrating LASI, BSA, and electromechanical markers (SD2, SD4, AP4%, E/e'), enables precise AF risk stratification, aiding early identification of high-risk patients for targeted intervention.

Keywords: LASI, HFpEF, AF, prediction model, nomogram, cardiac remodeling

Introduction

Heart failure with preserved ejection fraction (HFpEF) represents a major and growing public health burden, accounting for nearly 50% of all heart failure cases [1]. Its prevalence increases dramatically with age, exceeding 4% in adults over 75 years [2]. Characterized by impaired left ventricular relaxation and increased diastolic stiffness, HFpEF pathophysiology involves complex interactions between myocardial fibrosis, microvascular dysfunction, and chronic inflammation [3]. This results in elevated left ventricular filling pressures and the classic presentation of exertional dyspnea and exercise intolerance, despite preserved systolic function.

A critical determinant of poor outcome in HFpEF is its strong bidirectional association with atrial fibrillation (AF) [4]. This relationship forms a self-perpetuating pathophysiological cycle: HFpEF-induced ventricular stiffness elevates left atrial (LA) pressure, triggering structural remodeling (fibrosis) and electrical alterations that promote AF initiation and maintenance [5]. In turn, AF causes loss of atrial contractility and irregular ventricular rates, further impairing diastolic filling in the stiffened ventricle [6]. This synergistic interaction leads to substantially worsened prognosis; patients with concomitant AF and HFpEF face 2-3 times higher risks of all-cause mortality, cardiovascular death, and heart failure hospitalizations compared to those with either condition alone [7].

Age-related changes, including cardiomyocyte senescence, increased myocardial collagen deposition, and neurohumoral activation (especially RAAS overactivity), disproportionately

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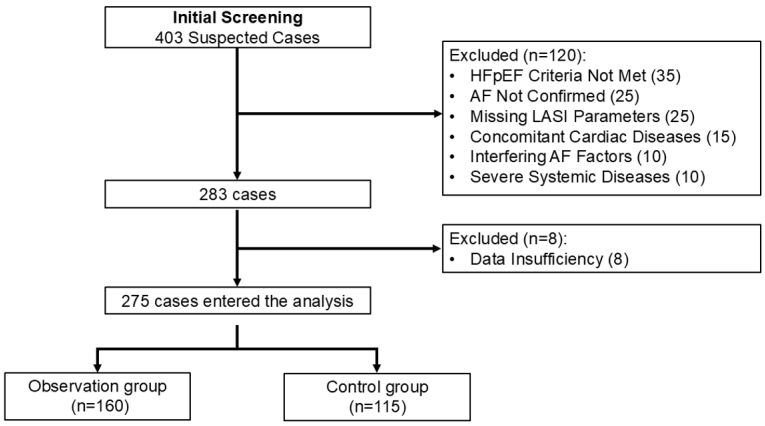

Figure 1. Flow diagram detailing the selection of patients included in the retrospective analysis.

exacerbate LA dysfunction in HFpEF [8]. The resulting increase in LA stiffness, quantifiable through pressure-volume relationships, serves as both a critical substrate for AF and a key mediator of HFpEF progression [9]. Consequently, elderly patients with AF-HFpEF comorbidity experience alarmingly reduced survival, with 5-year mortality rates 25-30% higher than age-matched HFpEF patients without AF [7].

Despite this profound clinical effect, significant diagnostic and prognostic challenges persist [10-12]. Conventional assessment tools inadequately characterize the severity of LA myopathy in this comorbid state, and no validated risk stratification models exist specifically for elderly AF-HFpEF patients [1, 13, 14]. This gap often delays therapeutic intervention and hinders personalized management.

The left atrial stiffness index (LASI) has emerged as a promising biomarker to address these challenges. Calculated non-invasively as the ratio of Doppler-derived E/e' (surrogate of LV filling pressure) to peak atrial longitudinal strain (PALS, measure of LA reservoir function), LASI integrates dynamic pressure-volume characteristics to quantify LA fibrotic remodeling and compliance [15]. Elevated LASI strongly predicts adverse outcomes across cardiovascular conditions, with multicenter data demonstrating its superior predictive value for major adverse cardiac events (MACE) compared to traditional biomarkers like NT-proBNP (sensitivity 80% at LASI ≥0.76) [16].

However, two critical knowledge gaps limit LASI's clinical translation in elderly patients with AF-HFpEF. 1) Pathophysiologic specificity: The hemodynamic interplay and fibrotic crosstalk unique to AF-HFpEF comorbidity may confer distinct diagnostic and prognostic significance to LASI. Yet, this remains poorly characterized [17]. 2) Prognostic modeling: No validated LASI-incorporated risk prediction tools exist for this high-risk demographic, leading to continued reliance on clinician gestalt and non-specific biomarkers [18].

To address these critical gaps, we conducted a retrospective cohort study specifically focused on elderly AF-HFpEF patients. Our research aimed to elucidate the pathophysiologic significance of LASI within the AF-HFpEF comorbidity phenotype and develop the first LASI-integrated prognostic nomogram for individualized risk stratification in this high-risk population.

Materials and methods

Study design and participants

In this study, clinical data of 275 patients with AF complicated HFpEF who were treated at the Affiliated Hospital of Nantong University between August 2021 and October 2024 were retrospectively reviewed. Initial screening identified 403 potential cases, of which 128 were excluded for failing inclusion criteria (e.g., protocol deviations, incomplete clinical data) and 8 due to insufficient echocardiographic records. The final cohort of 275 patients was divided into an atrial fibrillation group (AF+ HFpEF, n=160) and a control group (HFpEF without AF, n=115) based on their clinical status at enrollment. The study flow chart is shown in **Figure 1**. This retrospective study was approved by the Medical Ethics Committee of Affiliated Hospital of Nantong University prior to data analysis, in accordance with the Declaration of Helsinki (2013 revision).

Inclusion criteria

Eligible participants were adults (≥18 years) with a confirmed diagnosis of HFpEF, defined by

concurrent satisfaction of these criteria: LVEF ≥50%, clinical manifestations consistent with NYHA class II-IV heart failure symptoms or structural cardiac abnormalities (e.g., left ventricular hypertrophy, left atrial enlargement), and objective evidence of diastolic dysfunction (E/e' ratio ≥13 or NT-proBNP elevation). Participants also required comprehensive LASI-related measurements (2D/3D left atrial volumes, strain metrics, electromechanical timing parameters), documented AF status verified through ECG or Holter monitoring, and baseline clinical information, including body surface area (BSA), blood pressure readings, and laboratory test results.

Exclusion criteria

Patients were excluded if they had significant cardiovascular comorbidities, including valvular heart disease with ≥ moderate stenosis or regurgitation, structural myocardial disorders such as hypertrophic/restrictive cardiomyopathy, or congenital heart defects, or a history of acute coronary syndrome and previous coronary revascularization (bypass surgery or interventional procedures). Exclusion also applied to those with confounding factors for atrial fibrillation evaluation, such as inadequately managed hyperthyroidism (serum TSH <0.1 mU/L), cardiac interventions within the previous six months (surgical or ablative), ongoing ventricular arrhythmias, or the presence of a pacemaker/implantable cardioverter-defibrillator (ICD) devices. Data integrity issues requiring exclusion included missing critical measurements (e.g., left atrial strain, E/e' ratio, or documented AF status) and suboptimal echocardiographic imaging quality precluding reliable left atrial function quantification. Additional exclusions were advanced systemic pathologies like end-stage renal failure (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2), active malignancies with a limited life expectancy (<1 year), or acute infectious conditions and systemic inflammatory disorders in active phases.

Data collection

Main observation indicators: The findings associated with the LASI were assessed via transthoracic echocardiography (TTE). Key metrics included two-dimensional and three-dimensional left atrial volumes, calculated as maximum left atrial volume (LAVmax), minimum left atrial volume (LAVmin), and left atrial ejection fraction (LAEF) derived from the formula (LAVmax - LAVmin)/LAVmax × 100%. Left atrial mechanical properties were quantified using strain and strain rate parameters, specifically AP2 (reservoir phase strain) and AP4 (active contraction phase strain). Electromechanical timing features encompassed SD2 (left atrial electromechanical delay in milliseconds) and SD4 (mechanical contraction duration in milliseconds). AF diagnosis was established based on electrocardiographic evidence of AF lasting ≥30 seconds, confirmed by 12-lead ECG or 24-hour Holter monitoring, while excluding other arrhythmias such as atrial flutter or supraventricular tachycardia. Outcome categorization distinguished between newly diagnosed AF (first detected during the study period) and prior AF history, with detailed documentation required for duration and therapeutic interventions in the latter group.

HFpEF-related evaluation criteria: According to ESC guidelines, the diagnosis of HFpEF should fulfill three key criteria: a LVEF ≥50%, symptoms consistent with NYHA class II-IV heart failure or structural abnormalities such as left ventricular hypertrophy or atrial enlargement, and objective evidence of diastolic dysfunction, defined by at least one of the following: E/e' ratio ≥13, NT-proBNP >220 pg/mL (sinus rhythm) or >660 pg/mL (AF), or elevated left ventricular filling pressure. Supporting indices, such as left ventricular mass index (LVMI) and left atrial volume index (LAVI), were also used to comprehensively assess cardiac structure and function.

Confounders and covariates: The study recorded demographic and clinical data, including age, gender, BMI, BSA. Comorbidities such as hypertension, diabetes mellitus, chronic kidney disease [eGFR <60 mL/min/1.73 m^2] were also documented. Laboratory values included NT-proBNP, hs-CRP, serum creatinine, uric acid, and lipid profiles (LDL-C, HDL-C).

Measurement of cardiac function markers

Examinations were completed by two experienced echocardiologists using the SC2000 ultrasound diagnostic instrument (Siemens) and the eSieLVA left heart quantitative analysis software. The 4V1C probe (with a frequency of

3 MHz to 5 MHz) and the 4Z1C volume probe (with a frequency of 1 MHz to 4 MHz) were selected for image acquisition. The images were stored and analyzed using the Siemens workstation and 3D-Mechanics software. During the examination, participants were positioned either in the left lateral decubitus or supine position and instructed to hold their breath at end-expiration to facilitate image acquisition. Standard views, including the parasternal long-axis view and apical two-, three-, and four-chamber views, were obtained to record spectral Doppler images of the mitral valve and left ventricular outflow tract. Tissue Doppler imaging was used to capture three cardiac cycles from each of the apical views. Measurements included LVEF, left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), and the E/e' ratio. All measurements were averaged over three cardiac cycles. Left atrial volume, measured by the biplane Simpson method, was indexed to body surface area (BSA) to yield LAVI.

LASI

Two experienced sonographers applied ultrasound spot tracking imaging technology to obtain images of the basal, middle, and fundal segments of the second-, third-, and fourth-chamber cardiac sections of the apex. The longitudinal peak of the left atrium during systole was recorded for each segment of the atrial wall. The peak atrial longitudinal strain (PALS) of the left atrium was obtained by using myocardial quantitative motion analysis software. The left atrial strain index (LASI) was calculated as the average of the SD2 and SD4 values using the formula: LASI = (SD2 + SD4)/2.

Statistical analysis

Statistical analysis was conducted using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA), with all procedures validated by a statistics specialist. Non-normally distributed continuous variables were analyzed using the Kruskal-Wallis and Mann-Whitney U tests. Multivariate logistic regression was performed to determine adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Model discrimination was evaluated using the area under the receiver operating characteristic curve (AUC). The DeLong test was used to compare AUCs of different indicators, and ROC curves for combined indicators were plotted to illustrate their joint predictive performance. $P<0.05$ was considered significant. Data are presented as mean ± standard deviation unless otherwise specified.

Results

Comparison of general, clinical, and biochemical characteristics between control and atrial fibrillation groups

The atrial fibrillation group had a mean age of 56.47±0.67 years and a BMI of 21.55±0.31 kg/m^2, while the control group had a mean age of 57.33±0.46 years and a BMI of 22.13±0.29 kg/m^2. No significant differences were found in baseline characteristics between the two groups ($P>0.05$), indicating good comparability. However, statistically significant differences were observed in BNP ($t=6.243$, $P<0.01$) and uric acid levels ($t=2.801$, $P=0.005$). No significant differences were found for age, disease duration, LDL-C, HDL-C, TC, TG, creatinine, hs-CRP, TBIL, RDW, MYOG, SBP, or BMI ($P>0.05$), with creatinine showing borderline non-significance ($t=1.760$, $P=0.081$) (**Table 1**).

Comparison of cardiac structure and function findings between control and atrial fibrillation groups

The atrial fibrillation group exhibited increased LVDD ($t=11.091$, $P<0.05$) and LVESD ($t=15.155$, $P<0.05$), along with a higher BSA ($t=4.255$, $P<0.05$). LVEF was significantly elevated ($t=-23.881$, $P<0.05$), while LADD was reduced ($t=7.356$, $P<0.05$) in atrial fibrillation group. Two-dimensional assessments showed higher left atrial maximum volume (2D_LAVmax; $t=6.662$, $P<0.05$) but lower left atrial volume index (2D_LAVI; $t=6.172$, $P<0.05$). Three-dimensional echocardiography revealed increased 3D_LAVmax ($t=7.018$, $P<0.05$), 3D_LAVmin ($t=7.454$, $P<0.05$), and 3D left atrial ejection fraction (3D_LAEF%; $t=-10.566$, $P<0.05$), yet a lower 3D_LAVI ($t=6.19$, $P<0.05$) and higher left atrial stiffness index (LASI; $t=-10.492$, $P<0.05$). Diastolic function values showed a reduced E/e' ratio ($t=7.016$, $P<0.05$). Electromechanical delay indices indicated elevated AP2% ($t=-4.054$, $P<0.05$), reduced AP4% ($t=-5.706$, $P<0.05$), and increased SD4 ($t=6.149$, $P<0.05$) in the atrial fibrillation group (**Table 2**; **Figures 2**-**5**).

Table 1. Differences in general data, clinical and biochemical indexes between the two groups

	Atrial fibrillation group (N=160)	Control group (N=115)	t	P
Age	56.47±0.67	57.33±0.46	-1.102	0.271
Course	1.28±0.02	1.24±0.02	1.455	0.147
BNP (pg/mL)	1310.25±90.36	1300.18±85.42	0.942	0.348
LDL-C (mmol/L)	3.11±0.06	3.18±0.06	-0.726	0.469
HDL-C (mmol/L)	1.10±0.04	1.08±0.03	0.386	0.700
Cr (μmol/L)	145.03±3.58	136.78±3.04	1.760	0.081
UA (μmol/L)	488.32±20.15	485.17±18.63	1.301	0.195
TC (mmol/L)	4.32±0.10	4.20±0.08	0.951	0.343
TG (mmol/L)	1.95±0.03	1.88±0.03	1.404	0.162
hs-CRP (mg/L)	1.52±0.04	1.54±0.03	-0.368	0.713
TBIL (μmol/L)	13.99±0.20	13.76±0.22	0.739	0.461
RDW (%)	12.94±0.13	12.91±0.10	0.157	0.875
MYOG (ng/mL)	90.06±2.04	87.05±1.62	1.169	0.244
SBP (mmHg)	120.66±2.12	122±1.56	-0.523	0.602
BMI (kg/m^2)	21.55±0.31	22.13±0.29	-1.359	0.175

Note: BNP, Brain Natriuretic Peptide; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; TC, Total Cholesterol; TG, Triglyceride; Cr, Creatinine; UA, Uric Acid; TBIL, Total Bilirubin; RDW, Red Blood Cell Distribution Width; MYOG, Myoglobin; SBP, Systolic Blood Pressure; BMI, Body Mass Index.

Univariate logistic regression analysis

In the univariate logistic regression analysis, several clinical and echocardiographic data showed significant associations with the outcome event (**Table 3**). BNP (OR: 0.998, 95% CI: 0.997-1.0, P=0.025) and LVEF (OR: 0.978, 95% CI: 0.959-0.998, P=0.033) demonstrated protective effects, as higher BNP levels and lower LVEF were inversely associated with the event risk. Conversely, elevated LVDD (OR: 1.028, 95% CI: 1.001-1.054, P=0.039), LVSD (OR: 1.027, 95% CI: 1.004-1.05, P=0.022), and LADD (OR: 1.04, 95% CI: 1.005-1.075, P= 0.025) indicated increased risk. Among left atrial data, 2D_LAVmax (OR: 1.006, P=0.019), 2D_Lmax (OR: 1.31, P=0.021), 2D_LAVmin (OR: 1.007, P=0.018), 2D_Lmin (OR: 1.291, P=0.017), 2D_LAVI (OR: 1.012, P=0.013), 3D_LAVmax (OR: 1.007, P=0.017), 3D_LAVmin (OR: 1.008, P=0.022), and 3D_LAVI (OR: 1.013, P=0.013) all showed significant positive associations. Notably, LASI (OR: 0.417, 95% CI: 0.184-0.942, P=0.035) emerged as a strong protective factor. Other variables, including E/e', BSA, AP2, AP4, and SD4, did not show statistical significance (P>0.05).

Multivariate logistic regression results of left atrial function-related parameters and atrial fibrillation risk in HFpEF patients

Multivariate logistic regression results are presented that BSA was independently associated with an increased risk of AF (OR=9.167, 95% CI: 3.325, 25.218, P<0.001), indicating that each 1-unit increase in BSA was linked to a more than 9-fold rise in AF risk. In contrast, higher values of the left ventricular diastolic function value E/e' ratio (OR=0.889, 95% CI: 0.820-0.963, P=0.002) and the left atrial electromechanical function index SD4 (OR=0.997, 95% CI: 0.996-0.998, P<0.001) were associated with a significantly lower risk of AF, suggesting their protective roles. Furthermore, parameters reflecting left atrial contractile function - LASI (OR=1.043, 95% CI: 1.022, 1.065, P<0.001), AP4 (OR=1.033, 95% CI: 1.009-1.059, P= 0.008) and SD2 (OR=1.003, 95% CI: 1.001-1.004, P=0.001) were both independently linked to elevated AF risk, demonstrating their predictive value for AF development (**Table 4**).

Evaluation of the diagnostic efficacy of different indicators for the risk of atrial fibrillation in patients with HFpEF

ROC curve analysis showed that the AUCs for LASI, E/e', BSA, SD2, AP4, SD4 were 0.666, 0.707, 0.682, 0.615, 0.666, and 0.705, respectively. Among them, the AUCs of E/e' and SD4 were relatively high, indicating that these two indicators have good diagnostic efficacy in distinguishing whether patients with HFpEF are at risk of AF. The prognostic performance of individual marker was moderate. However, their combined detection yielded an AUC of 0.801,

Table 2. Comparison of indicators related to cardiac structure and function

	Atrial fibrillation group (N=160)	Control group (N=115)	t	P
LVDD	65.66±1.055	55.63±1.761	11.091	<0.001
LVSD	62.48±0.689	51.53±0.707	15.155	<0.001
LVEF (%)	51.80±1.102	52.30±1.250	-1.630	0.104
LADD	37.20±0.548	59.03±0.732	7.356	<0.001
2D_LAVmax	46.71±0.51	40.35±0.70	6.662	<0.001
2D_Lmax	116.91±4.15	78.04±4.1	6.964	<0.001
2D_Smax	6.52±0.08	5.63±0.10	7.329	<0.001
2D_LAVmin	30.23±0.70	22.39±0.80	6.837	<0.001
2D_Lmin	78.37±3.35	46.75±3.18	7.573	<0.001
2D_Smin	6.04±0.07	4.96±0.12	0.339	0.735
2D_LAEF (%)	24.38±0.65	22.70±4.93	-10.399	<0.001
2D_LAVI	34.12±0.56	47.23±1.127	6.172	<0.001
3D_LAVmax	106.56±3.77	70.01±3.60	7.018	<0.001
3D_LAVmin	64.48±2.29	44.90±2.188	7.454	<0.001
3D_LAEF (%)	75.15±3.13	43.04±2.96	-10.566	<0.001
3D_LAVI	31.10±0.54	44.05±1.09	6.19	<0.001
LASI	58.63±2.07	40.65±2.03	-10.492	<0.001
E/e'	0.47±0.01	0.87±0.03	7.016	<0.001
BSA	19.48±0.44	14.25±0.60	4.255	<0.001
AP2 (%)	1.82±0.01	1.72±0.02	-4.054	<0.001
AP4 (%)	-3.15±0.98	6.69±2.22	-5.706	<0.001
SD2 (ms)	-3.02±0.88	9.95±2.09	0.049	0.961
SD4 (ms)	846.15±26.97	839.28±138.76	6.149	<0.001

Note: LVDD, Left Ventricular End-Diastolic Diameter; LVSD, Left Ventricular End-Systolic Diameter; LVEF, Left Ventricular Ejection Fraction; LAVmax, Maximum Left Atrial Volume; LAVmin, Minimum Left Atrial Volume; LAEF, Left Atrial Ejection Fraction; AP2, Left Atrial Reservoir Phase Strain; AP4, Left Atrial Active Contraction Phase Strain; SD2, Left Atrial Electromechanical Delay Time; SD4, Left Atrial Mechanical Contraction Time; LASI, left atrial stiffness index.

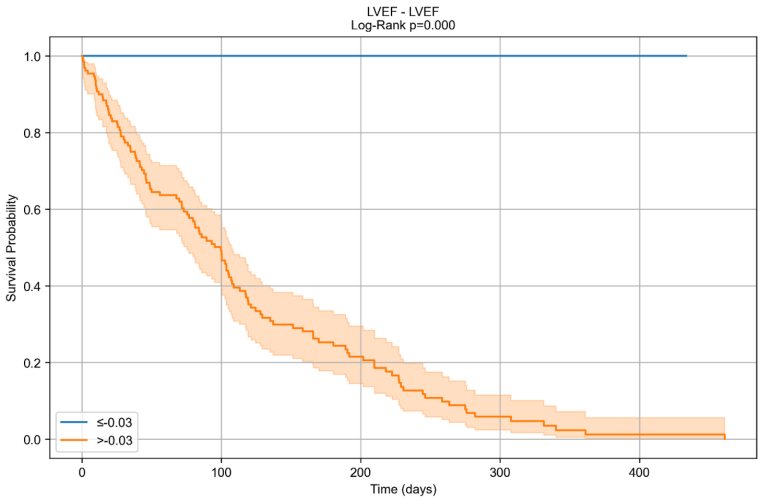

Figure 2. KM curves for patients stratified by LVEF. Intuitively, patients with LVEF - related indicator ≤ -0.03 maintain a relatively high survival probability throughout the observation. In contrast, those with the indicator > -0.03 see a marked decline in survival probability over time. The Log - Rank test (P<0.001) confirms a statistically significant difference between the two groups' survival curves. This implies the LVEF - related indicator may act as a key factor influencing patient survival. Note: LVEF, Left Ventricular Ejection Fraction.

demonstrating superior predictive accuracy in prognostic discrimination (**Figure 6**).

Decision curve analysis (DCA) of diagnostic variables in decision-making regarding the risk of atrial fibrillation in patients with HFpEF

The DCA for the diagnostic variable figure shows diagnostic variables such as LASI, E/e', BSA, AP4, SD2 and SD4, as well as two reference curves: "Diagnosis None" (a non-diagnostic strategy with a net benefit basically being 0) and "Diagnosis All" (a strategy of diagnosing all cases, where the net benefit sharply drops to a negative value at a high threshold probability). Within

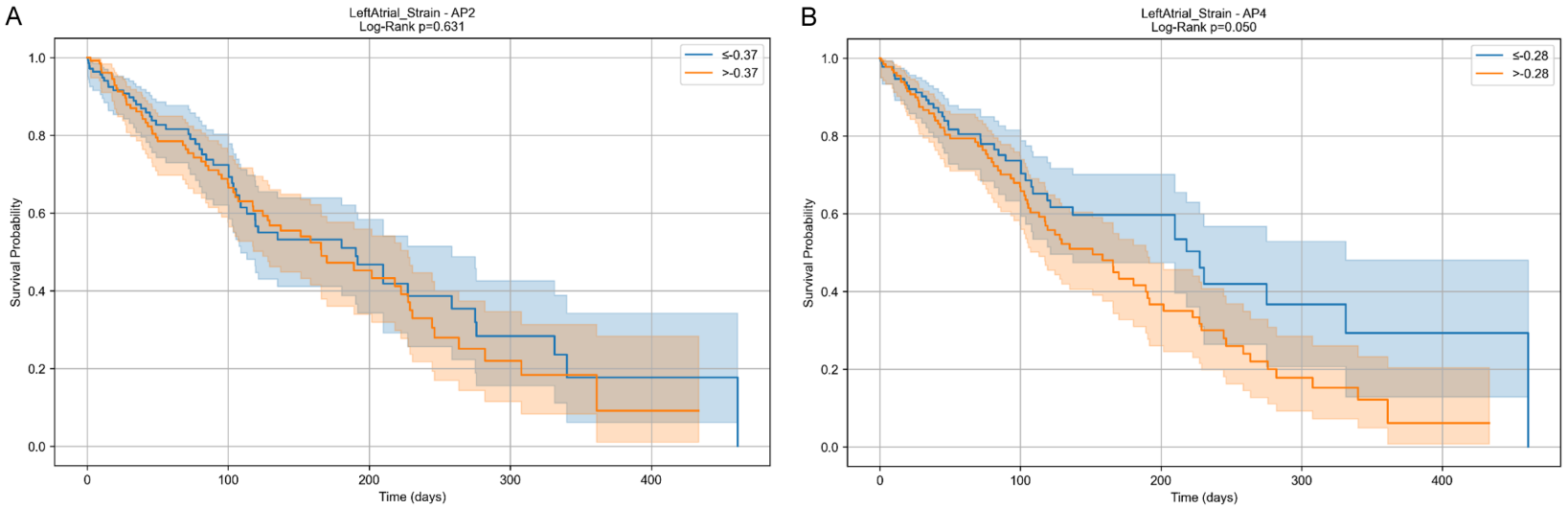

Figure 3. KM curves for patients stratified by left atrial strain (AP2 and AP4). A. Kaplan-Meier curves for HFpEF patients stratified by Left Atrial Strain - AP2; B. Kaplan-Meier curves for HFpEF patients stratified by Left Atrial Strain - AP4.

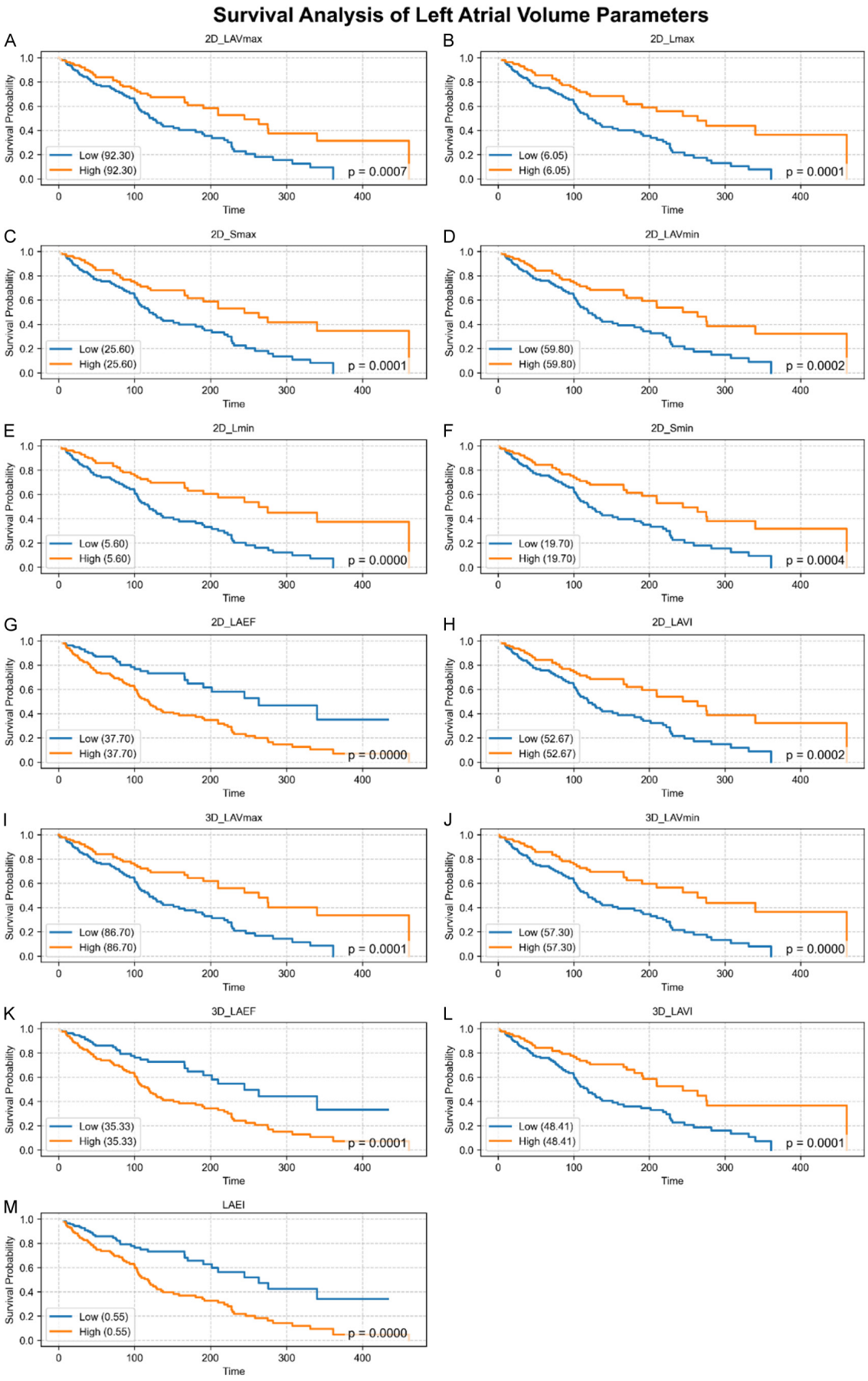
Survival Analysis of Left Atrial Volume Parameters
A
2D_LAVmax
Low (92.30)
High (92.30)
p = 0.0007
B
2D_Lmax
Low (6.05)
High (6.05)
p = 0.0001
C
2D_Smax
Low (25.60)
High (25.60)
p = 0.0001
D
2D_LAVmin
Low (59.80)
High (59.80)
p = 0.0002
E
2D_Lmin
Low (5.60)
High (5.60)
p = 0.0000
F
2D_Smin
Low (19.70)
High (19.70)
p = 0.0004
G
2D_LAEF
Low (37.70)
High (37.70)
p = 0.0000
H
2D_LAVI
Low (52.67)
High (52.67)
p = 0.0002
I
3D_LAVmax
Low (86.70)
High (86.70)
p = 0.0001
J
3D_LAVmin
Low (57.30)
High (57.30)
p = 0.0000
K
3D_LAEF
Low (35.33)
High (35.33)
p = 0.0001
L
3D_LAVI
Low (48.41)
High (48.41)
p = 0.0001
M
LAEI
Low (0.55)
High (0.55)
p = 0.0000
Survival Probability
Time

Figure 4. KM curves for patients stratified by LEFT Atrial Volume measurements. A. Kaplan-Meier curves illustrating the relationship between Left Atrial Stiffness Index and atrial fibrillation risk in HFpEF patients. B. Kaplan-Meier curves showing the impact of Left Atrial Stiffness Index on atrial fibrillation outcomes in HFpEF patients. C. Kaplan-Meier curves depicting the association between Left Atrial Stiffness Index and atrial fibrillation incidence in HFpEF patients. D. Kaplan-Meier curves highlighting the predictive value of Left Atrial Stiffness Index for atrial fibrillation in HFpEF patients. E. Kaplan-Meier curves demonstrating the role of Left Atrial Stiffness Index in predicting atrial fibrillation events in HFpEF patients. F. Kaplan-Meier curves illustrating the influence of Left Atrial Stiffness Index on atrial fibrillation risk stratification in HFpEF patients. G. Kaplan-Meier curves showing the correlation between Left Atrial Stiffness Index and atrial fibrillation occurrence in HFpEF patients. H. Kaplan-Meier curves depicting the prognostic significance of Left Atrial Stiffness Index for atrial fibrillation in HFpEF patients. I. Kaplan-Meier curves highlighting the predictive utility of Left Atrial Stiffness Index for atrial fibrillation in HFpEF patients. J. Kaplan-Meier curves illustrating the relationship between Left Atrial Stiffness Index and atrial fibrillation prognosis in HFpEF patients. K. Kaplan-Meier curves showing the impact of Left Atrial Stiffness Index on atrial fibrillation risk assessment in HFpEF patients. L. Kaplan-Meier curves depicting the association between Left Atrial Stiffness Index and atrial fibrillation prediction in HFpEF patients. M. Kaplan-Meier curves highlighting the role of Left Atrial Stiffness Index in identifying atrial fibrillation risk in HFpEF patients.

most of the threshold probability intervals, the curves of each diagnostic variable exhibit advantages to varying degrees compared with the "Diagnosis All" curve, suggesting that these variables have value in assisting the decision-making for diagnosing the risk of AF in patients with HFpEF. The event rate of LASI was 0.32, with LASI identified as the optimal predictive factor (maximum net benefit: 0.3184) in decision curve analysis (**Figure 7**).

Discussion

With the increased elderly population, heart failure (HF) has become an increasingly serious public health problem. Especially for elderly patients with chronic heart failure over 80 years old, as factors such as slowed body metabolism and declining organ function, the risk of adverse cardiac events and the difficulty of rehabilitation have significantly increased [2, 17-19]. Among these patient populations, the coexistence of HFpEF and AF is notably prevalent [5]. Research indicates that over half of newly diagnosed HF patients show some degree of AF, while around 30% of individuals with AF also have underlying heart failure [20]. Given this strong clinical association, identifying reliable prognostic markers for patients with both HFpEF and AF, as well as developing effective therapeutic strategies, has become a key focus in contemporary cardiology research [21].

In recent years, growing evidence has highlighted the intricate bidirectional relationship between AF and HFpEF [16]. AF is not only a consequence of impaired cardiac function but also can actively contribute to the progression of HFpEF through various pathophysiologic mechanisms [4]. For instance, AF has been associated with increased activation of the renin-angiotensin-aldosterone system (RAAS), heightened myocardial inflammation, and elevated oxidative stress levels [20], all of which can further impair cardiac structure and function. Conversely, the presence of HFpEF can worsen AF symptoms, creating a self-perpetuating cycle that accelerates disease progression [1]. Therefore, understanding the complex interplay between these two conditions is essential for developing more targeted and effective therapeutic approaches [22].

The LASI serves as a valuable marker for assessing the extent of myocardial fibrosis [15]. Research has demonstrated that LASI is closely linked to the presence of AF, hypertension-related target organ damage, and clinical outcomes in heart failure [23]. This study seeks to investigate the association between LASI and the risk of adverse cardiovascular events in elderly patients with chronic heart failure, particularly those with HFpEF complicated by AF. Furthermore, we aim to develop a nomogram-based predictive model incorporating LASI to offer new insights and tools for improving risk stratification and prognosis evaluation in this patient population [24].

This study focused on elderly patients with chronic heart failure to identify key factors influencing the occurrence of adverse cardiac events. Using multivariate logistic regression analysis, we determined significant predictors, which were then incorporated into a nomogram-based prediction model. Particular emphasis was placed on the role of the LASI in

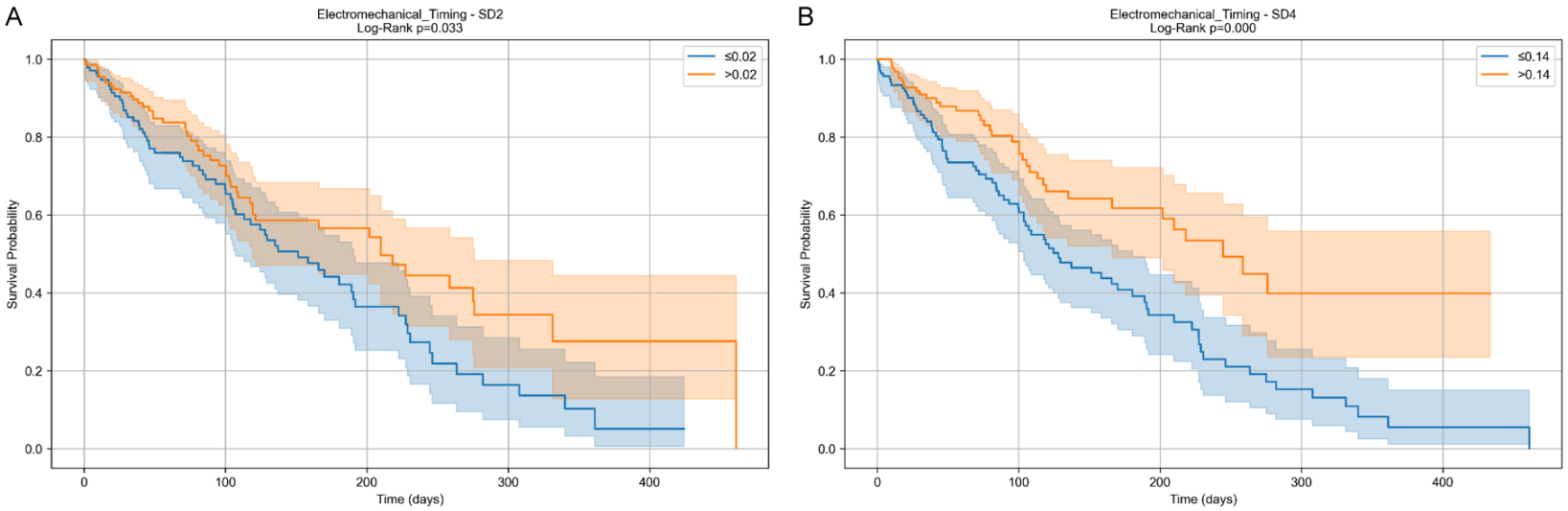

Figure 5. KM curves for patients stratified by electromechanical timing. A. Kaplan-Meier curves illustrating the relationship between Electromechanical Timing - SD2 and atrial fibrillation risk in HFpEF patients; B. Kaplan-Meier curves showing the effect of Electromechanical Timing - SD4 on atrial fibrillation outcomes in HFpEF patients.

Table 3. Univariate logistic regression analysis of factors associated with the outcome event

Variable	B	Wald χ^2	*P*-value	OR (95% CI)
BNP	-0.002	5.053	0.025	0.998 (0.997-1.0)
LVDD	0.027	4.26	0.039	1.028 (1.001-1.054)
LVSD	0.027	5.255	0.022	1.027 (1.004-1.05)
LVEF	-0.022	4.543	0.033	0.978 (0.959-0.998)
LADD	0.039	5.054	0.025	1.04 (1.005-1.075)
2D_LAVmax	0.006	5.539	0.019	1.006 (1.001-1.011)
2D_Lmax	0.27	5.363	0.021	1.31 (1.042-1.646)
2D_Smax	0.029	4.761	0.029	1.03 (1.003-1.057)
2D_LAVmin	0.007	5.641	0.018	1.007 (1.001-1.014)
2D_Lmin	0.255	5.701	0.017	1.291 (1.047-1.592)
2D_LAEF	-0.027	5.088	0.024	0.974 (0.951-0.997)
2D_LAVI	0.012	6.162	0.013	1.012 (1.003-1.022)
3D_LAVmax	0.007	5.719	0.017	1.007 (1.001-1.012)
3D_LAVmin	0.008	5.218	0.022	1.008 (1.001-1.014)
3D_LAEF	-0.023	3.524	0.06	0.978 (0.955-1.001)
3D_LAVI	0.013	6.134	0.013	1.013 (1.003-1.024)
LASI	-0.875	4.426	0.035	0.417 (0.184-0.942)
E/e'	0.009	0.226	0.635	1.009 (0.971-1.049)
BSA	-0.273	0.155	0.694	0.761 (0.195-2.966)
AP2	0.005	0.469	0.493	1.005 (0.991-1.018)
AP4	-0.006	0.613	0.434	0.994 (0.98-1.009)
SD4	0.001	1.245	0.264	1.0 (1.0-1.001)

Note: LVDD, Left Ventricular End-Diastolic Diameter; LVSD, Left Ventricular End-Systolic Diameter; LVEF, Left Ventricular Ejection Fraction; LAVmax, Maximum Left Atrial Volume; LAVmin, Minimum Left Atrial Volume; LAEF, Left Atrial Ejection Fraction; AP2, Left Atrial Reservoir Phase Strain; AP4, Left Atrial Active Contraction Phase Strain; SD2, Left Atrial Electromechanical Delay Time; SD4, Left Atrial Mechanical Contraction Time; LASI, left atrial stiffness index.

Table 4. Multivariate logistic regression of indices related to left atrial function and the risk of atrial fibrillation in patients with HFpEF

Variable	Coef	Std Err	Wald χ^2	*P*-value	OR	95% CI
Age	-0.016	0.011	2.094	0.148	0.984	(0.963, 1.006)
2D_Smin	0.005	0.005	1.059	0.303	1.005	(0.996, 1.014)
LASI	0.042	0.010	17.643	<0.001	1.043	(1.022, 1.065)
E/e'	-0.118	0.039	9.152	0.002	0.889	(0.820, 0.963)
BSA	2.215	0.523	17.864	<0.001	9.167	(3.325, 25.218)
AP2 (%)	-0.003	0.013	0.052	0.819	0.997	(0.973, 1.022)
AP4 (%)	0.033	0.012	7.06	0.008	1.033	(1.009, 1.059)
SD2 (ms)	0.003	0.001	10.936	0.001	1.003	(1.001, 1.004)
SD4 (ms)	-0.003	0.001	18.762	<0.001	0.997	(0.996, 0.998)

Note: BSA, Body Surface Area; AP2, Left Atrial Reservoir Phase Strain; AP4, Left Atrial Active Contraction Phase Strain; SD2, Left Atrial Electromechanical Delay Time; SD4, Left Atrial Mechanical Contraction Time; LASI, left atrial stiffness index.

predicting cardiovascular outcomes. The results revealed that LASI values demonstrated moderate predictive performance in the AF group compared to the control group. Furthermore, the event rate of LASI was 0.32, elevated LASI identified as the optimal predictive factor (maximum net benefit: 0.3184) in decision curve analysis in this population.

In conclusion, as an important indicator for evaluating the degree of myocardial fibrosis, LASI has shown great potential in predicting

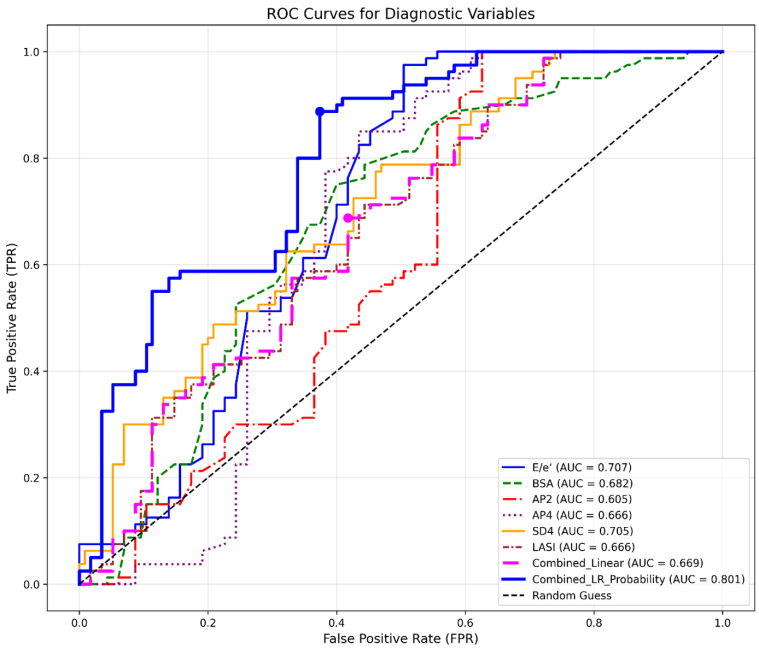

Figure 6. ROC curve analysis for LASI, E/e', BSA, AP4, SD2 and SD4 and their combination for predicting AF risk. Note: ROC, Receiver Operating Characteristic; BSA, Body Surface Area; SD2, Left Atrial Electromechanical Delay Time; SD4, Left Atrial Mechanical Contraction Time; AF, atrial fibrillation; LASI, left atrial stiffness index.

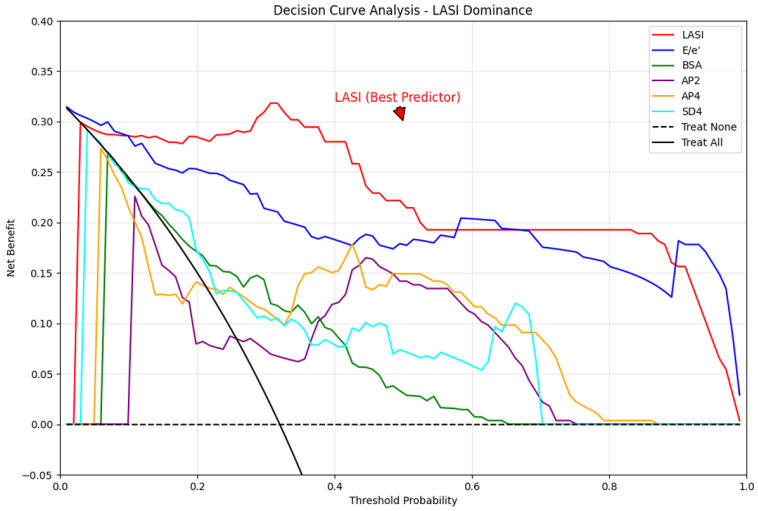

Figure 7. DCA of LASI, E/e', BSA, AP4, SD2 and SD4. Note: DCA, Decision Curve Analysis; BSA, Body Surface Area; SD4, Left Atrial Mechanical Contraction Time; LASI, left atrial stiffness index.

the prognosis of elderly patients with chronic heart failure, especially those with HFpEF complicated by AF. The nomogram predictive model established based on LASI can not only quantitatively or predict the prognosis of patients from an overall perspective but also help medical staff directly obtain the risk weights of relevant factors in predicting the occurrence of adverse cardiac events in patients. This can help formulate long-term intervention plans and follow-up programs. Although this study still has certain limitations, for example, there is currently no software specifically for analyzing left atrial function indicators, and the accuracy of the non-invasive LASI calculation method still needs to be improved. Overall, as a reliable prognostic prediction tool, LASI provides a new direction and hope for future research.

Future research can further explore how to optimize the calculation method of LASI and develop specialized imaging techniques to more accurately evaluate the functional status of the left atrium. In addition, conducting more research on different types of angiotensin receptor-neprilysin inhibitor (ARNI) drugs and other possible combination treatment methods will also help to better understand and manage the condition of patients with HFpEF complicated by AF, thereby improving the prognosis and quality of life of patients. In short, as an emerging prognostic prediction indicator, LASI provides us with a new perspective for a deeper understanding and treatment of patients with HFpEF complicated by AF.

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Disclosure of conflict of interest

None.

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