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Research article

Left atrial strain predicts risk and prognosis in patients with acute coronary syndrome: A retrospective study with external validation

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HIGHLIGHTS

- LA function parameters significantly correlate with the GRACE score.
- Impaired LASr has high specificity in identifying high-risk patients with ACS.
- LASr may be superior to Max LAVI in predicting an adverse prognosis following ACS.

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Keywords:
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ABSTRACT

Objectives: To explore the association between left atrial (LA) strain and the GRACE score in patients with acute coronary syndrome (ACS) and to investigate the utility of LA function in predicting short-term adverse cardiovascular events post ACS.

Methods: This retrospective study included ACS patients who underwent coronary angiography (CAG) in two independent cohorts from October 2020 to July 2022. The patients were classified into low-intermediate risk group and high-risk group based on the GRACE score. All participants underwent a transthoracic echocardiogram, with LA strain analysis before CAG. Correlation analysis was used to determine the relationship between LA strain and the GRACE score. The predictive value of LA strain was examined utilizing the area under the curve (AUC). Participants were followed for 10.5 ± 2.9 months for the primary endpoint of major adverse cardiovascular events (MACE).

Results: A total of 229 patients were included in this study, including 196 in the primary group and 33 in the validation group. Spearman's correlation analysis showed there was a moderate negative correlation between the GRACE and left atrial reservoir strain (LASr) in both the primary ($r = -0.63$, $P < 0.001$) and validation ($r = -0.73$, $P < 0.001$) cohorts. Receiver operator characteristic (ROC) curve analysis showed that the AUC of LASr for prediction of the high-risk group was 0.86. Taking LASr 19.6% as the cut-off value, the sensitivity and specificity were 0.71 and 0.92, respectively. The cut-off value of 19.6% remains good at identifying high-risk group in the validation group (AUC = 0.87, sensitivity: 77.8%, specificity: 95.8%). Furthermore, 49 patients reached the endpoint in the primary cohort during the follow-up. On multivariable regression analysis, LASr ($P = 0.03$) was the independent echocardiographic predictor for the primary endpoint, rather than left atrial volume index (LAVI).

Conclusions: LASr can identify high-risk patients with ACS as defined by the GRACE score and may be superior to Max LAVI in predicting incidents of MACE in the short-term following ACS.

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1. Introduction

Acute coronary syndrome (ACS) encompasses a wide range of diagnoses, from unstable angina to myocardial infarction (MI) with significant myocardial damage, and it is still one of the leading causes of morbidity and mortality worldwide [1, 2, 3]. Despite advances in ACS care, the incidence of major adverse cardiovascular event (MACE) remains high [4]. The routine invasive strategy (coronary angiography within 24–72 h) has been shown to improve clinical outcomes compared to the selectively invasive strategy [5]. In particular, an early (<24 h) invasive strategy can significantly reduce mortality in high-risk patients [6, 7, 8]. As a result, early individual risk assessment of ACS patients is clinically critical. A number of prognostic models have been developed to estimate the future risk of all-cause mortality or MI. These models have been transformed into clinical risk scores, with the GRACE risk score providing the best discriminative performance [9, 10]. According to recent European Society of Cardiology (ESC) guidelines, the GRACE score provides the most accurate risk stratification of inpatients and discharges. And the patients whose GRACE risk score > 140 are regarded as a high-risk population [8, 11]. However, the GRACE risk score includes some biochemical indicators such as high-sensitivity troponin, which are not suitable for rapid assessment of pre-examination and triage.

The left atrium (LA), as the chamber that communicates with the left ventricle (LV) and the pulmonary veins, coordinates with the LV function throughout the whole cardiac cycle and plays an important role in cardiac performance [12, 13, 14]. Interestingly, deterioration of LA structure and function contributes to the development of LV disorders and has a strong prognostic value in cardiovascular disease [15]. The left atrial volume index (LAVI), the only parameter of LA function recommended in current ultrasound guidelines, can be widely used to predict adverse cardiovascular outcomes [16, 17, 18]. However, it reflects a cumulative overload of chronically elevated filling pressure over time and thus fails to reflect the abrupt reduction in cardiac function in the short-term period [19, 20]. LA strain, a high-profile new parameter for evaluating LA intrinsic function in real-time, has been shown to correlate with LV filling pressure more strongly than LAVI [21, 22]. Importantly, it can detect functional impairment of the LA in the early stages, even if the LA volume has not yet changed [23, 24]. Increasing evidence has suggested that LA strain analysis obtained via two-dimensional speckle tracking carries additional prognostic value in patients with ischemic heart disease [14, 17, 25, 26]. As a result, it is possible that LA strain is superior to LAVI as a marker of cardiac function in the short-term following ACS.

The aim of this study was to evaluate the correlation between echocardiographic parameters related to LA, specifically LA strain, and the GRACE score in ACS patients. Additionally, we sought to determine the utility of LA strain in predicting short-term MACE post ACS.

2. Materials and methods

This study obtained approval from two institutional review boards (site 1: The Second Affiliated Hospital of Harbin Medical University, site 2: Guangdong Provincial People's Hospital) and was exempt from obtaining informed consent from patients (reference number: sydwgzr2020-030 and KY-Z-2022-043-03). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.1. Study design and population

We retrospectively included 220 consecutive patients admitted for ACS between October 2020 and April 2021 from site 1. Diagnosed ACS based on the clinical setting (i.e., symptoms, vital signs), the 12-lead ECG, and the cardiac troponin concentration determined at presentation to the emergency department and serially thereafter, according to the latest guidelines [11]. We excluded patients with atrial fibrillation, idiopathic cardiomyopathy, valvular disease, and advanced stage of nephropathy. Patients with suboptimal image quality on transthoracic echocardiography were also excluded. Furthermore, we intend to follow the enrolled patients for one year. Patients with an expected survival time of fewer than 12 months were excluded as well. Finally, a total of 196 patients comprised the primary study cohort. Then we retrospectively incorporated 33 ACS patients between March 2022 to July 2022 from site 2. Inclusion and exclusion criteria were the same as for the original cohort. The final 33 patients formed a validation group to test the results from the primary cohort.

All patients underwent clinical evaluation on admission, which comprised demographics and baseline clinical characteristics, as well as the determinants of the GRACE risk score (i.e., age, heart rate, systolic blood pressure, serum creatinine concentration, the presence of ST-segment deviation, cardiac arrest during admission, elevated serum cardiac biomarkers, and Killip class) [27]. We calculated individual GRACE scores and this algorithm is available online (https://qxmd.com/calculate/calculator_262/grace (accessed on 9 May 2021)). According to the calculated GRACE score, we classified the patients into two groups: high-risk group (>140) and low-intermediate risk group (≤140) [11]. In a subsequent analysis, we further divided the patients into three groups: low-risk group (<109), intermediate-risk group (109–140), and high-risk group (>140) for better subgroup analysis. The affected vessel was defined as anyone coronary artery with >50% stenosis among left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). A comprehensive transthoracic echocardiogram was performed before undergoing an invasive intervention (median 1 day, IQR, 0–2 days). The patient's follow-up was conducted for up to 12 months through telephone interviews or medical records. The primary outcome was the occurrence of MACE including atrial fibrillation, heart failure, recurrent unstable angina or myocardial infarction, coronary revascularization, nonfatal stroke, and cardiovascular death.

2.2. Conventional echocardiography

All patients underwent routine transthoracic echocardiography in the left lateral decubitus position using commercially available equipment (EPIQ5c, Philips Ultrasound) according to the American Society of Echocardiography guidelines [16]. Optimized views of the LV and LA were acquired at 50–70 frames per second. Images were stored digitally for offline analysis.

From the parasternal long-axis view, we recorded the LV end-diastolic diameter (LVIDd), LV end-systolic diameter (LVISd), interventricular septum diameter (IVSd), LV posterior wall diameter (LVPWd), and LA diameter (LAd) at end-systole. LV end-diastolic and end-systolic volumes were obtained by Simpson's biplane method, and then LV ejection fraction (LVEF) was calculated. Diastolic function was quantitated using early diastolic (E) and late diastolic (A) transmitral velocities, E/A ratio, an average of the septal and lateral annular e′ velocities, and E/e′ ratio.

Biplane LA volume was evaluated from apical four-and two-chamber views by the modified method of discs. Two-dimensional LA maximal and minimal volumes were measured at ventricular end-systole and end-diastole, respectively. Two-dimensional LA pre-A volume was measured at the onset of the electrocardiographic P wave. LAVI was defined as the LA volume divided by the body surface area. LAEF was calculated as (maximal LA volume – minimal LA volume)/maximal LA volume, passive LAEF was calculated as (maximal LA volume – pre-A LA volume)/maximal LA volume and active LAEF was calculated as (pre-A LA volume – minimal LA volume)/pre-A LA volume.

2.3. Speckle-tracking echocardiography

Speckle-tracking echocardiography was performed using customized software (QLAB13.0 Philips Andover, MA), which allows LA strain analysis. According to the current Europe Society of Echocardiography consensus on standardization of LA myocardial deformation imaging, LA strain was assessed in the apical four-chamber view, with the commencement of the QRS complex utilized as the zero-reference point

[28]. The endocardium of the LA wall was manually traced and adjusted by modifying the region of interest or contour width, taking care to keep the appendage and pulmonary veins out of the LA cavity. Then a global LA strain-time curve was generated. For patients in the high-risk (Figure 1A) and low-intermediate risk (Figure 1B) groups, we obtained the corresponding strain-time curves and strain values of three phases, respectively. LA reservoir strain (LASr) was measured from the maximal inflection point on the LA strain-time curve, LA contractile strain (LASct) was measured at the onset of the electrocardiographic P wave, and LA conduit strain (LAScd) was obtained from the difference between LASr and LASct. Original digitized echocardiographic data were reanalyzed by one experienced sonographer, blinded to clinical outcomes. All the strain measurements were repeated three times to obtain the average measured value in the analysis. To test intra- and inter-observer reproducibility of LA strain analyses by Speckle-tracking technology, we randomly selected 20 patients among both cohorts. LA strain was analyzed by two different individuals 30 days apart, who were blinded to study outcomes (inter--observer variability), and by the first individual 30 days later (intra--observer variability).

2.4. Statistical analysis

Data are presented as mean ± SD. Categorical variables are presented as frequencies and percentages. According to the different types of data obtained for each parameter, a suitable analysis was selected. Comparison between the two groups was performed by the Student's *t*-test (normally distributed) and the Mann Whitney *U*-test (non-normally distributed) for continuous variables, and the Chi-squared test for categorical variables. Comparisons between the three groups were performed by ANOVA with Bonferroni's correction for multiple comparisons. Correlation tests between the GRACE score and ultrasound parameters were performed using Spearman's rank correlation coefficient. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to evaluate the performance of LASr as a predictor of the high-risk group. We also performed logistic regression analyses to determine the predictors of the high-risk group. The Kaplan-Meier method was used to calculate cumulative survival rates, and the log-rank test was used to examine differences between groups. A restricted linear spline was employed to test for a possible non-linear relationship between LASr and the research outcomes. Cox proportional hazards models were used to identify the independent predictors of the study endpoints. The estimated hazard ratios (HR) and their 95% CIs quantify the strength of the association. Inter- and intrarater reliability were calculated using the intraclass correlation coefficient (ICC). Statistical analyses were performed using SPSS version 28.0 (IBM Corporation, Armonk, NY, USA) and R version 3.6.3 (R Development Core Team). A comparison with a *P*-value < 0.05 in two-tailed tests was considered statistically significant.

3. Results

3.1. Clinical characteristics

The characteristics of the two cohorts are shown in Table 1. In total, 196 patients (median age, 59 years; range, 25–84 years) were from the primary cohort. Of these, 152 (77.6%) were in the low-intermediate risk group, and 44 (22.4%) were in the high-risk group. The 33 patients (median age, 58 years; range, 39–77 years) from the validation cohort, among which 24 (72.7%) were in the low-intermediate risk group, and 9 (27.3%) were in the high-risk group. Significant differences were found between low-intermediate risk and high-risk groups for age, anti-platelet drugs, and diuretics ($P < 0.05$) in both cohorts, and only in the primary cohort was a significant difference in diabetes, creatinine, and BNP prevalence observed. Furthermore, these individuals were more probably to have a higher rate of multi-vessel disease ($P < 0.001$) and easier to reach endpoints ($P < 0.001$) in the primary cohort.

3.2. Echocardiography characteristics

Table 2 shows the echocardiography characteristics of the study population. In the primary cohort, mean LVEF was 64 ± 9%, mean Max LAVI was 32.3 ± 13.1 mL/m^2, and mean LARS was 25.4 ± 7.7%. In the validation cohort, mean LVEF was 60 ± 11%, mean Max LAVI was 25.6 ± 6.2 mL/m^2, and mean LARS was 26.7 ± 6.7%. Compared with the low-intermediate risk group, the high-risk group had larger LAd, larger Min LAVI, lower LAEF as well as lower LASr, LAScd, and LASct ($P < 0.01$ for all) in both cohorts. We also noticed that there were no significant differences in LV structure and function indicators such as LVIDd, E/A, E/e′ ratio, and so on in the primary cohort.

3.3. Correlations between the GRACE score and LA function parameters

In the primary cohort, the correlation coefficient of the LASr was the highest (Figure 2) among other variables, showing a moderate negative correlation ($r = -0.63$, $P < 0.001$), followed by LAScd ($r = -0.58$, $P < 0.001$) and LASct ($r = -0.40$, $P < 0.001$). These results were confirmed in

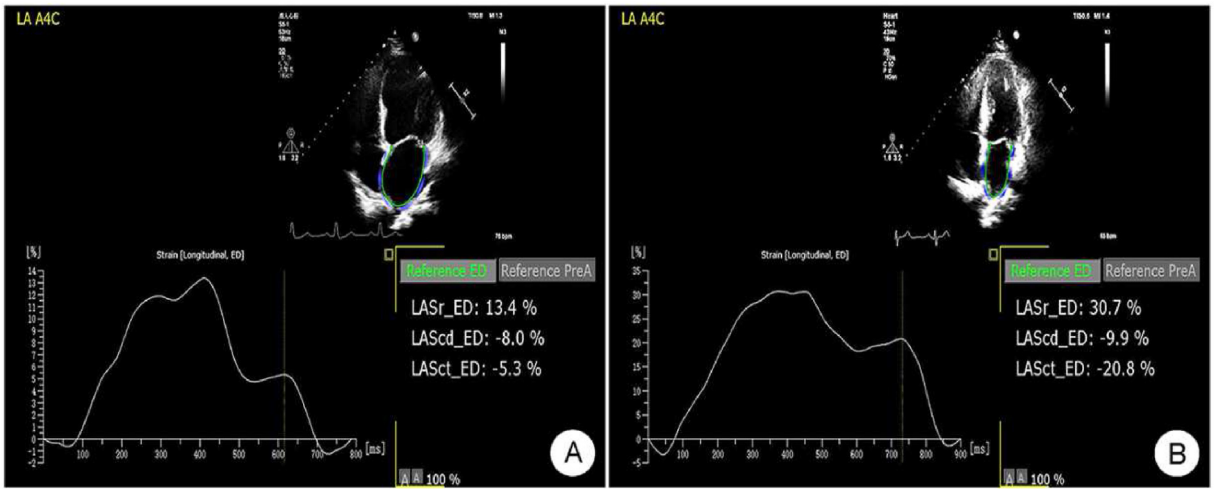

Figure 1. LA strain analyses in apical four-chamber view. A. An example of the high-risk group. B. An example of the low-intermediate risk group. Significantly reduced values of LA strain for the high-risk group are noted.

Table 1. Baseline characteristics of the study sample.

Variables	The primary cohort			The validation cohort		
	Low-intermediate risk group	High-risk group	*P*-value	Low-intermediate risk group	High-risk group	*P*-value
N	152	44		24	9	
Age, years	57.8 ± 9.2	62.9 ± 7.8	**<.001**	54.7 ± 8.9	66.1 ± 5.2	**<.001**
Male, n (%)	94 (61.8)	32 (72.7)	0.185	17 (70.8)	7 (77.8)	1.000
Heart rate, bpm	75.8 ± 10.7	79.8 ± 13.7	0.078	79.7 ± 15.8	74.2 ± 9.0	0.336
Body mass index, kg/m2	1.79 ± 0.17	1.77 ± 0.16	0.405	24.7 ± 2.9	23.2 ± 2.7	0.186
Systolic blood pressure, mmHg	135.3 ± 17.2	133.6 ± 17.7	0.581	126.8 ± 15.3	126.7 ± 21.6	0.985
Chest pain, n (%)	142 (93.4)	39 (88.6)	0.293	14 (58.3)	5 (55.6)	1.000
Dyspnea, n (%)	84 (55.3)	34 (77.3)	**0.009**	6 (25.0)	4 (44.4)	0.400
Killip class, n (%)			**<.001**			**<.001**
1	140 (92.1)	7 (15.9)		24 (100.0)	3 (33.3)	
2	7 (4.6)	14 (31.8)		0 (0)	3 (33.3)	
3	5 (3.3)	6 (13.6)		0 (0)	1 (11.1)	
4	0 (0)	17 (38.6)		0 (0)	2 (22.2)	
ST-segment deviation, n (%)	20 (13.2)	17 (38.6)	**<.001**	2 (8.3)	6 (66.7)	**0.002**
Elevated serum cardiac biomarkers, n (%)	13 (8.6)	29 (65.9)	**<.001**	3 (12.5)	6 (66.7)	**0.005**
Background						
Diabetes, n (%)	27 (17.8)	15 (34.1)	**0.020**	12 (50.0)	5 (55.6)	1.000
Dyslipidemia, n (%)	39 (25.7)	9 (20.5)	0.480	11 (45.8)	4 (44.4)	1.000
Hypertension, n (%)	76 (50.0)	19 (43.2)	0.425	11 (45.8)	7 (77.8)	0.134
Smoking, n (%)	57 (37.5)	15 (34.1)	0.680	6 (25.0)	0 (0)	0.156
Medications						
Aspirin, n (%)	143 (94.1)	39 (88.6)	0.217	21 (87.5)	9 (100.0)	0.545
Clopidogrel, n (%)	136 (89.5)	32 (72.7)	**0.005**	14 (58.3)	9 (100.0)	**0.032**
Statins, n (%)	129 (84.9)	34 (77.3)	0.236	23 (95.8)	9 (100.0)	1.000
Beta-blocker, n (%)	46 (30.3)	13 (29.5)	0.927	21 (87.5)	8 (88.9)	1.000
Antidiabetics, n (%)	25 (16.4)	13 (29.5)	0.053	12 (50.0)	6 (66.7)	0.458
Diuretics, n (%)	8 (5.3)	10 (22.7)	**<.001**	0 (0)	4 (12.1)	**0.003**
ACEI/ARB, n (%)	24 (15.8)	11 (25.0)	0.160	14 (58.3)	7 (77.8)	0.429
Number of affected vessels, n (%)						
1	42 (85.7)	7 (14.3)	0.114	6 (25.0)	0 (0)	0.156
2	38 (76.0)	12 (24.0)	0.761	6 (25.0)	5 (55.6)	0.121
3	21 (13.8)	20 (45.5)	**<.001**	4 (16.7)	4 (44.4)	0.170
Laboratory assessment						
cTNI(μg/L)	0.36 ± 3.2	1.86 ± 6.2	0.127	0.02 ± 0.04	0.10 ± 0.16	0.187
CK(u/l)	106.3 ± 154.6	105.5 ± 99.6	0.973	104.6 ± 61.0	118.1 ± 121.1	0.673
Creatinine (mg/dL)	76.9 ± 18.1	87.5 ± 31.7	**0.005**	73.7 ± 15.9	104.2 ± 65.9	0.206
BNP(pg/ml)	109.1 ± 199.3	2175.4 ± 3945.6	**0.001**	35.5 ± 23.9	1656.9 ± 3453.6	0.197
MACE, n (%)	28 (18.4)	21 (47.7)	**<.001**	-	-	-

Bold values denote statistical significance.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; CK = creatine kinase; cTNI = the C-terminal domain of troponin I; MACE = major adverse cardiac events.

the validation cohort, LASr still had the highest correlation coefficient ($r = -0.73$, $P < 0.001$, Table S1). In the primary cohort, logistic regression analysis revealed that LASr was the only echocardiographic variable that was independently associated with a higher risk of having a GRACE score greater than 140 (OR:0.79, 95%CI: 0.72–0.87, $P < 0.001$, Table 3). On categorizing patients into three risk groups, mild-risk group (GRACE score < 109), intermediate-risk group (GRACE score 109–140), and high-risk group (GRACE score > 140), LASr showed significant attenuation ($P < 0.001$) with increasing GRACE score (Figure 3A). Inverse trends were seen for Max LAVI, although they were not statistically significant between the mild-risk group and the intermediate-risk group ($P = 0.509$, Figure 3B).

The ROC curves demonstrated that the LASr has a significant discriminative ability to predict high-risk ACS patients (GRACE score > 140), with an AUC of 0.86 (Figure 4). LASr of 19.6% was found to be the best cutoff for predicting the GRACE score > 140 in patients with ACS (sensitivity: 70.5% and specificity: 92.1%). This cutoff value was also demonstrated to have a good ability to identify high-risk patients in the validation cohort, with an AUC of 0.87 (sensitivity: 77.8% and specificity: 95.8%, Figure S1).

3.4. Primary outcomes

Because of insufficient follow-up time for patients in the validation group, we only obtained complete follow-up records for patients in the primary cohort. After a mean of 10.5 ± 2.9 months of follow-up, there were 49 patients reached the endpoint event. Of 196 subjects, 25 had recurrent unstable angina or MI, 13 had heart failure admissions, 5 had coronary revascularization, 2 developed AF and 4 died from cardiovascular disease.

Event-free survival rates of LA function parameters are evaluated by Kaplan-Meier curves. The study population was dichotomized according

Table 2. Baseline Echocardiographic Parameters of the study sample.

Variables	The primary cohort			The validation cohort		
	Low-intermediate risk group	High-risk group	*P*-value	Low-intermediate risk group	High-risk group	*P*-value
LVEF, %	66.1 ± 6.1	57.6 ± 14.0	**<.001**	62.7 ± 7.8	52.2 ± 15.3	0.079
LVEF <45%, n (%)	0 (0)	8 (18.2)	**<.001**	1 (4.2)	3 (33.3)	0.052
LVIDd, mm	45.1 ± 6.4	48.3 ± 13.0	0.111	44.1 ± 2.5	52.7 ± 10.1	**0.035**
LVISd, mm	27.4 ± 4.7	34.3 ± 12.7	**<.001**	26.5 ± 4.7	35.3 ± 11.4	0.051
IVSd, mm	11.3 ± 4.1	12.5 ± 7.1	0.310	9.5 ± 1.2	10.7 ± 1.8	**0.028**
LVPWd, mm	10.8 ± 2.1	10.5 ± 3.7	0.479	8.9 ± 0.9	9.8 ± 1.1	**0.029**
E, m/s	0.8 ± 0.1	0.9 ± 0.2	**0.031**	0.7 ± 0.2	0.8 ± 0.2	0.263
A, m/s	0.9 ± 0.2	0.9 ± 0.2	0.522	0.7 ± 0.2	1.0 ± 0.3	**0.021**
e′, cm/s	9.3 ± 10.5	8.8 ± 2.6	0.739	8.9 ± 2.0	6.9 ± 1.6	**0.013**
E/A	0.9 ± 0.3	1.1 ± 0.5	0.061	1.0 ± 0.4	0.9 ± 0.4	0.360
E/e′	9.8 ± 2.5	10.7 ± 4.7	0.099	8.2 ± 1.8	11.9 ± 3.4	**0.012**
E/e′ > 14, n (%)	10 (6.6)	4 (9.1)	0.812	1 (4.2)	3 (33.3)	0.052
LAd, mm	34.5 ± 4.2	38.0 ± 8.1	**0.009**	32.7 ± 3.8	37.8 ± 3.8	**0.002**
Max LAVI, mL/m2	30.0 ± 9.3	40.2 ± 19.9	**0.002**	24.8 ± 6.5	27.8 ± 5.1	0.220
pre-A LAVI, mL/m2	21.4 ± 7.3	31.7 ± 18.3	**<.001**	16.2 ± 5.2	19.7 ± 6.9	0.133
Min LAVI, mL/m2	11.9 ± 5.3	21.8 ± 17.9	**<.001**	8.4 ± 3.6	12.3 ± 5.0	**0.019**
LAEF, %	61.1 ± 9.1	50.0 ± 15.6	**<.001**	66.5 ± 8.6	56.2 ± 11.9	**0.010**
active LAEF, %	45.3 ± 10.7	35.8 ± 15.4	**<.001**	48.0 ± 11.3	37.0 ± 12.0	**0.019**
passive LAEF, %	28.8 ± 10.7	22.8 ± 10.1	**0.001**	35.2 ± 9.1	29.7 ± 18.4	0.409
LASr, %	27.7 ± 6.0	17.3 ± 7.5	**<.001**	29.8 ± 4.4	18.6 ± 4.6	**<.001**
LAScd, %	14.4 ± 5.5	7.9 ± 4.9	**<.001**	14.7 ± 5.7	8.8 ± 4.0	**0.008**
LASct, %	16.7 ± 6.6	11.1 ± 5.5	**<.001**	15.1 ± 3.7	9.9 ± 5.2	**0.003**

Bold values denote statistical significance.
A = peak late diastolic transmitral flow velocities; E = peak early diastolic transmitral flow velocities; e′ = peak early diastolic mitral annular velocities; E/A = peak early and late diastolic transmitral flow velocities ratio; E/e′ = peak early diastolic transmitral flow velocities and peak early diastolic mitral annular velocities ratio; LAd = left atrium diameter; LAEF = left atrial emptying fraction; LAScd = left atrial conduit strain; LASct = left atrial contractile strain; LASr = left atrial reservoir strain; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVIDd = left ventricular end-diastolic diameter; LVISd = left ventricular end-systolic diameter; LVPWd = left ventricular posterior wall in diastole; IVSd = interventricular septum diameter.

to the calculated cutoff value of LASr. According to the Kaplan-Meier analysis, patients with impaired LASr (<19.6%) had significantly higher incident rates of endpoints than those with LARS ≥ 19.6% (P = 0.004, Figure 5A). It is worth noting that survival rates also showed significant differences when we divided the patients into two groups based on the median value of Max LAVI during the 12-month follow-up (P = 0.001, Figure 5B). Using the restricted cubic splines for LASr, there was not a significant non-linear association between LASr and primary outcomes (P = 0.073, Figure 6).

We also performed multivariate Cox regression models using univariate variables identified on log-rank tests. To avoid overfitting, we performed nested models (Table 4) with clinical variables (model 1), echocardiographic variables (model 2), and independent clinical and echocardiographic variables (model 3) derived from models 1 and 2. Multivariate analysis demonstrated that DM (P = 0.009), age (P = 0.017), and LASr (P = 0.032) were significantly associated with MACE.

3.5. Reproducibility

The intraclass correlation coefficients for inter- and intra-observer variability for the randomly selected group of 20 subjects in all patients were 0.74 (95% CI, 0.45–0.89, P < 0.001) and 0.90 (95% CI, 0.76–0.96, P < 0.001) for LASr, respectively. For LAScd, the intraclass correlation coefficients for inter- and intra-observer variability were 0.76 (95% CI, 0.49–0.90, P < 0.001) and 0.82 (95% CI, 0.60–0.92, P < 0.001), respectively. For LASct, the intraclass correlation coefficients for inter- and intra-observer variability were 0.45 (95% CI, 0.02–0.73, P < 0.001) and 0.68 (95% CI, 0.35–0.86, P < 0.001), respectively.

4. Discussion

To the best of our knowledge, this is the first study to establish a link between LA function parameters and the clinical risk of poor prognosis as measured by the GRACE score. We also confirmed this hypothesis with an external validation group. The results of our study have shown that there was a moderate and significant negative correlation between the GRACE score and LASr in ACS patients. Moreover, reduced LASr was associated with poor prognosis in ACS patients and was an independent predictor of MACE.

4.1. Risk stratification in patients with ACS

ACS is one of the leading causes of death in the modern world. Prognosis varies greatly depending on the severity of the myocardial injury. If coronary angiography is performed within 24 h to determine the optimal revascularization strategy, the prognosis of high-risk ACS patients may be improved. Therefore, early risk stratification of such patients is essential. Currently, the GRACE scoring was recommended by the ESC guidelines for risk assessment of patients with ACS and it is widely used in clinical practice. It is generally accepted that a high GRACE score is associated with a poor prognosis [11]. In our study, compared with the low-intermediate risk group, a higher incidence of MACE was found (P < 0.001), and the incidence of three-vessel affected was higher in the high-risk group. Meanwhile, the LVEF values in the high-risk group were lower than those of the low-intermediate risk group. These findings also suggest that patients with a higher GRACE score have worse cardiac function, more complex coronary lesions, and a worse prognosis. Several previous studies have discovered that patients

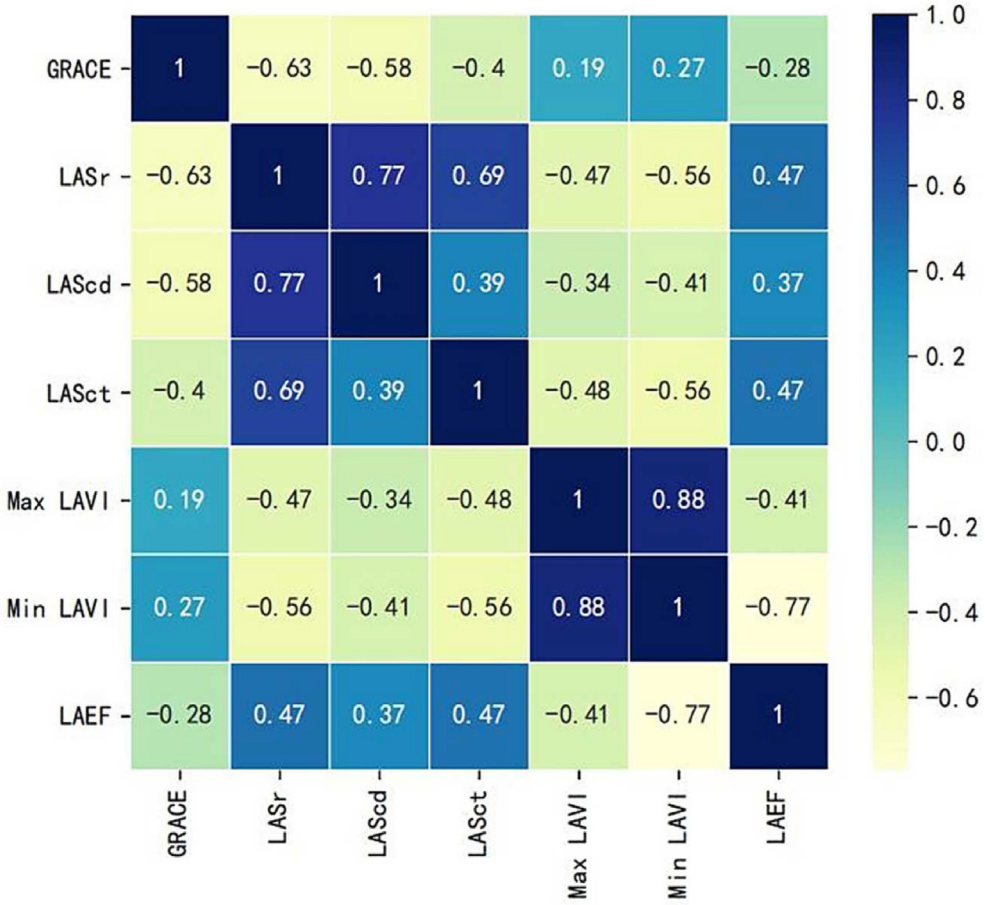

Figure 2. Spearman's correlation coefficient analysis to assess the strength of association between the GRACE score and LA function parameters. The correlation coefficient was shown on each small grid. LASr had the highest correlation coefficient among them.

Table 3. Multivariate regression analysis for predictors of GRACE score>140.

Variable	OR	95%CI	*P*-value
LVEF	0.97	0.90–1.05	0.460
LVISd	1.02	0.94–1.11	0.610
E/e′	1.11	0.95–1.28	0.180
Max LAVI	1.00	0.96–1.04	0.950
LAEF	1.01	0.95–1.06	0.860
LASr	0.79	0.72–0.87	**<.001**

Bold values denote statistical significance.
CI = confidence interval; E/e′ = peak early diastolic transmitral flow velocities and peak early diastolic mitral annular velocities ratio; LAEF = left atrial emptying fraction; LASr = left atrial reservoir strain; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVISd = left ventricular end-systolic diameter; OR = odds ratio.

with high-risk coronary anatomy had a higher GRACE score, which is consistent with our findings [29, 30].

4.2. Correlations between the GRACE score and LA function parameters

Our findings found that the LAVI and LA strains representing the function of LA were increased and decreased in the high-risk group, respectively. And in the subgroup analysis from the primary cohort, LASr varied in parallel with changes in GRACE risk scores, while LAVI varied was not significantly different (Figure 3). In the correlation analysis, LASr had the highest correlation coefficient with the GRACE score, both in the primary and validation cohorts. Therefore, we suggest that LASr was more closely to disease burden and risk factors in ACS.

In patients with ACS, pathophysiological LV-LA disturbances are often exaggerated. Because acute loss of partial myocardial function abounded to cause an early delay in active relaxation and loss of LV compliance, resulting in an acute rise in diastolic and LA pressures. Gradually accumulated pressure leads to pulmonary congestion symptoms, as well as LA remodeling and dysfunction without immediate treatment [31]. As a result, early evaluation of diastolic functions is critical. As a component of the multiparametric diagnosis and grading of diastolic dysfunction, LAVI has been shown to be a strong predictor of cardiovascular outcomes both in healthy individuals and in various cardiovascular conditions [12, 18]. However, due to its irregular geometry and variable-sized appendage and pulmonary veins, measuring LA size is an unavoidable challenge, and more importantly, deterioration in LA function occurs before structural changes [20, 32]. Speckle-tracking echocardiography can precisely evaluate LA function with good reproducibility due to its excellent performance of semi-automated, less angle-dependent, and less affected by artifacts [18]. A consensus document for standardization of LA strain analysis has been recently published [28]. Several centers have made available normal speckle tracking strain data of LA from healthy individuals [33, 34, 35]. All of these efforts contribute to a more in-depth understanding of LA function. The advancement of speckle-tracking technology has enabled us to detect LA subclinical myocardial dysfunction even before structural remodeling of the LA occurs. This also confirms the feasibility of predicting high-risk populations using LASr obtained by speckle-tracking technology in ACS patients.

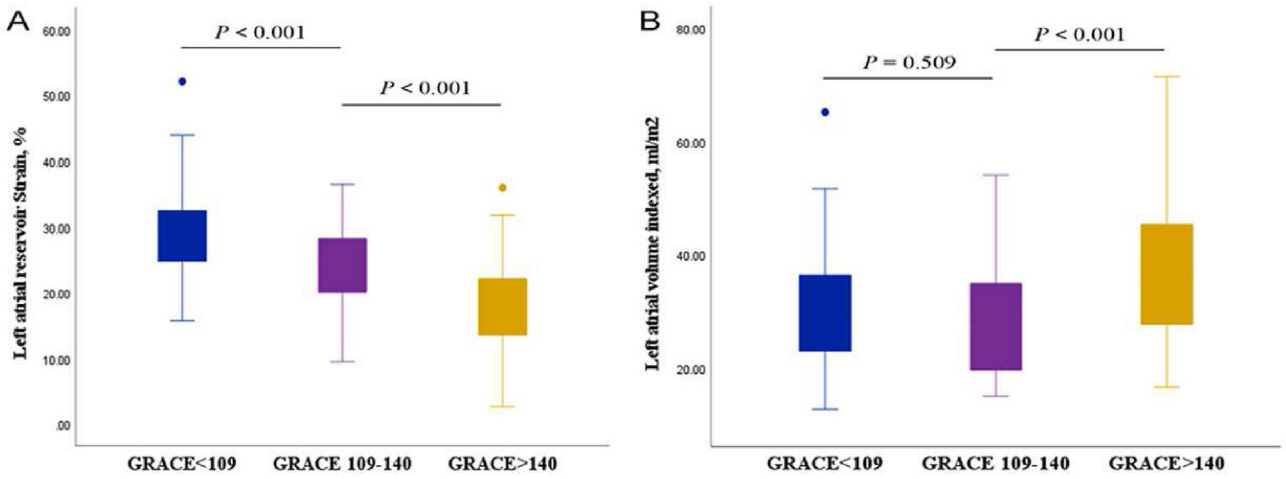

Figure 3. Box plots of the LA parameters under groups based on the GRACE score. A. The distribution of LASr for mild-risk (GRACE score < 109), intermediate-risk (GRACE score 109–140), and high-risk (GRACE score > 140) group. B. The distribution of LAVI for mild-risk (GRACE score <109), intermediate-risk (GRACE score 109–140), and high-risk (GRACE score > 140) group. The central box represents the values from the lower to upper quartile (25th to 75th percentile). The whiskers extend from the minimum to the maximum value, excluding an outlying value, which is displayed as a separate point.

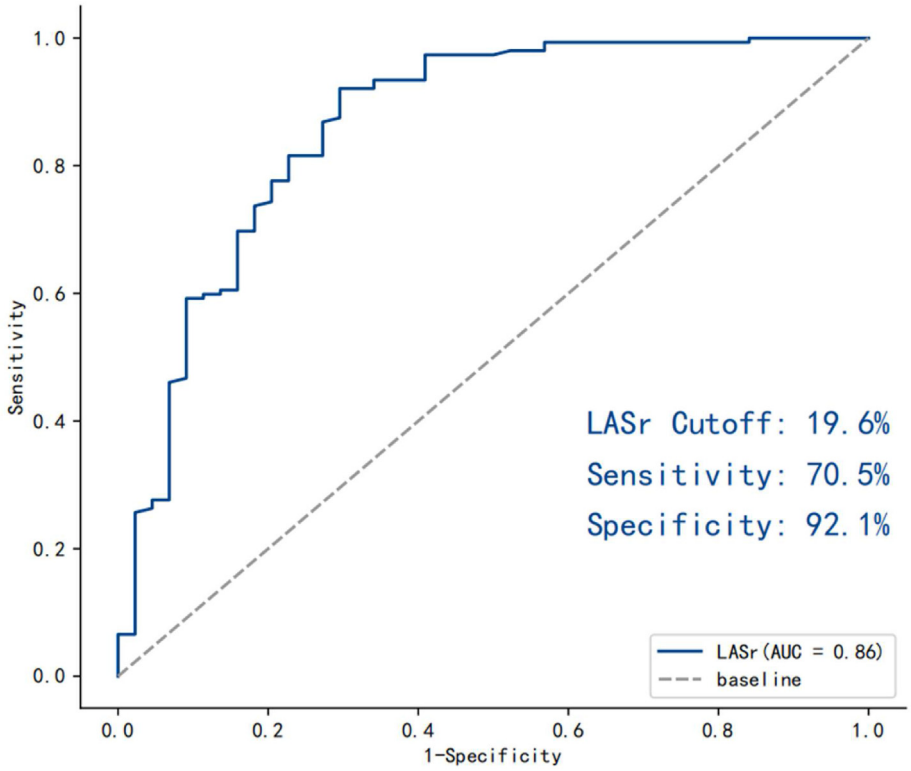

Figure 4. ROC curve on the predictive significance of the LASr for high-risk ACS patients (GRACE > 140).

Besides, we found that an impaired LASr (<19.6%) could indicate a higher GRACE score from the primary cohort. This cut-off value also displayed a great capacity to discriminate against high-risk patients in the validation cohort, with a sensitivity of 77.8% and a specificity of 95.8%. Notably, the population of these two cohorts is respectively from the northern and the southern region. This may indicate the general applicability of this value. Hence, during a clinical assessment of ACS patients in the emergency department, assessing LA strain may afford a new way to quickly identify high-risk patients, enabling clinicians to provide more aggressive therapeutic earlier.

4.3. The utility of LASr in the short-term prognosis of ACS patients

Our study demonstrated that LASr is the only LA function index that is independently associated with the GRACE score as well as the primary endpoints of MACE in the multivariate regression models. Hence, in the short term, LASr may be superior to LAVI for assessing the prognosis after ACS. We postulated several reasons for this. First, LA structural and mechanical remodeling is inconsistent. Volumetric indices are load-dependent and subject to geometrical assumptions, whereas LA reservoir strain better reflects intrinsic LA function. Lnborg et al. demonstrated that LAVI is

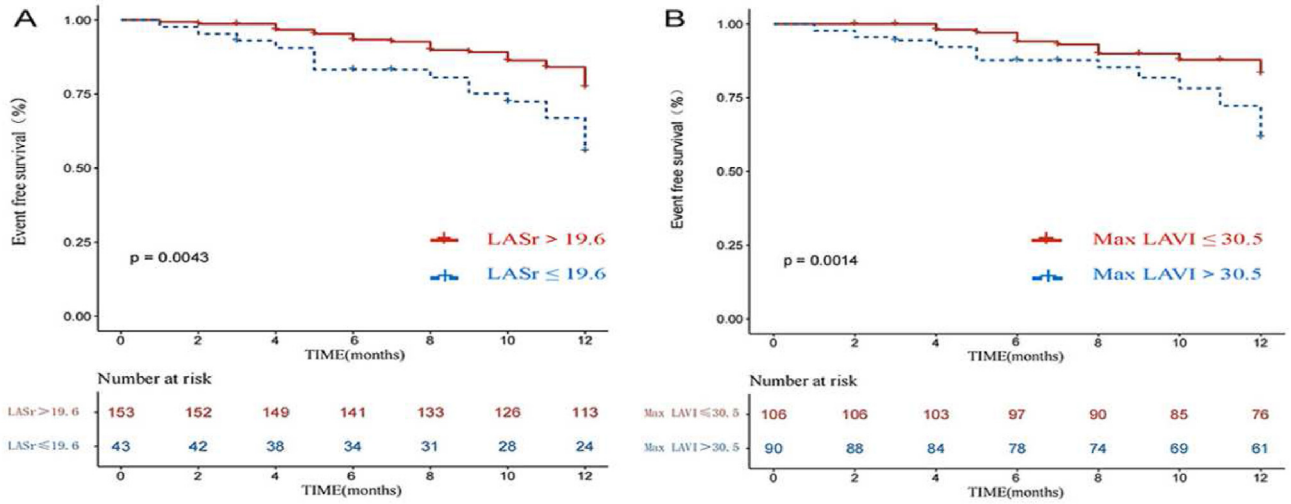

Figure 5. The Kaplan-Meier curves of LA parameters for the primary outcome of MACE. A. The Kaplan-Meier curves of LASr by reference cut-off value of 19.6% for the primary outcome of MACE. B. The Kaplan-Meier curves of Max LAVI by the median value of 30.5 mL/m^2 for the primary outcome of MACE.

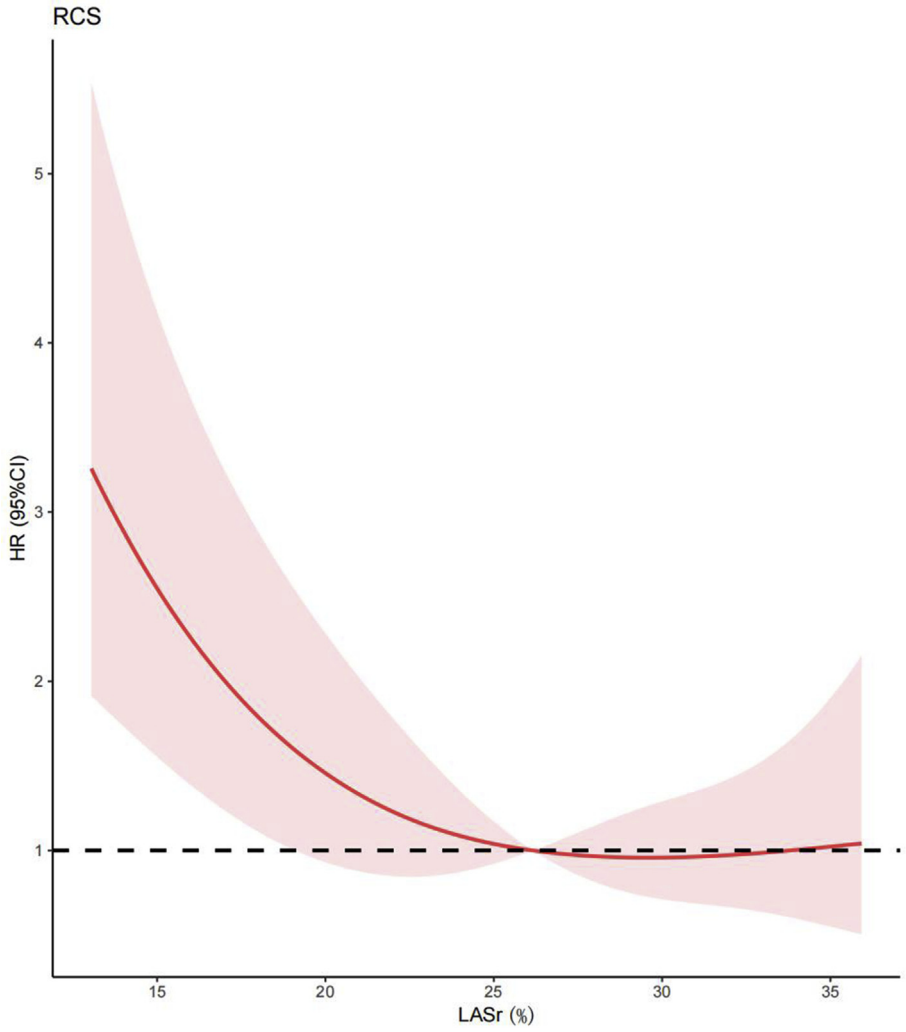

Figure 6. Spline curve demonstrating the HR for the occurrence of MACE at follow-up according to LASr. The line of best fit (red line) and 95% confidence intervals (red hashed line) are shown. For primary outcomes, the non-linear association depicted is not statistically significant ($P = 0.073$).

Table 4. Multiple Cox proportional hazards model for the primary outcome of cardiovascular death and MACE.

Covariates	HR (95%CI)	*P*-value
Nested model 1: clinical variables		
Age, years	1.05 (1.02–1.09)	**0.004**
Diabetes mellitus	2.25 (1.25–4.04)	**0.007**
Elevated serum cardiac biomarkers	2.33 (1.29–4.22)	**0.005**
Nested model 2: echocardiographic variables		
E/e′	1.03 (0.96–1.09)	0.416
Max LAVI, mL/m2	1.00 (0.99–1.02)	0.866
LAEF	0.98 (0.96–1.01)	0.286
LASr, %	0.96 (0.91–1.00)	0.078
Nested model 3: clinical and echocardiographic variables		
Age, years	1.05 (1.01–1.08)	**0.017**
Diabetes mellitus	2.19 (1.22–3.94)	**0.009**
Elevated serum cardiac biomarkers	1.84 (0.98–3.47)	0.059
LASr, %	0.96 (0.92–1.00)	**0.032**

Bold values denote statistical significance.
CI = confidence interval; E/e′ = peak early diastolic transmitral flow velocities and peak early diastolic mitral annular velocities ratio; HR = hazard ratio; LAEF = left atrial emptying fraction; LASr = left atrial reservoir strain; LAVI = left atrial volume index.

determined by preexisting conditions rather than acute LV function [36]. LAVI as a surrogate for chronically elevated filling pressure failed to accurately reflect the abrupt hemodynamic change, which may partly explain the lack of prognostic value in predicting the primary outcome observed in this study. However, LASr, which reflects atrial compliance, was modulated by a descent of the LV base during systole [37]. It may be more closely related to the change caused by impaired myocardium and therefore has a stronger association with prognosis. Second, the close relationship between strain and the degree of fibrosis in atrial tissue underscores that this parameter reflects better than others [38, 39]. Myolysis and an imbalance in collagen synthesis and degradation reduce the stretch force of the atria [40]. However, the precise underlying pathophysiological explanation for the link between LA remodeling and adverse outcomes is unknown. There is increasing evidence that abnormalities in LA function are caused by changes in the extracellular matrix, which are reflected in pathophysiological changes in renin secretion, levels of angiotensin II, aldosterone, transforming growth factor-β1, sympathetic stimulation, and markers of systemic inflammation such as C-reactive protein, all of which are known pathways in ACS patients [41, 42, 43, 44, 45]. Previous studies have demonstrated that the synthesis of an atrial natriuretic peptide is disrupted in parallel with LA fibrosis, resulting in sodium retention and volume overload, which increases the risk of heart failure [46]. Therefore, lower atrial strain is associated with a poorer outcome.

4.4. Prospects

As of today, only the measurement of LAVI is recommended in current echocardiographic guidelines [16]. However, the above considerations and the findings of our study demonstrate that LASr may be a brilliant indicator that cannot be ignored in the short period following ACS. Furthermore, LA function could be a therapeutic target, and LASr is expected to become a clinical indicator of monitoring improvement with therapy, with previous studies showing an improvement in LASr with early treatment with vasoactive medications such as ACEi [47, 48]. Further research into the underlying value of LASr in ACS patients is warranted, and may ultimately improve risk stratification and treatment strategy.

4.5. Limitations

The current study had several limitations. Firstly, due to the insufficient follow-up time for patients in the validation group, we only obtained complete follow-up records for patients in the primary cohort. This prevents us from validating the prognostic role of LASr in the short-term following ACS in the validation group yet. We expect to fill this regret in the future study. Second, in the absence of a definitive Killip rating, we used a class based on the BNP lever to replace the Killip class. Considering the characteristics of our study, BNP may provide a more objective and appropriate judgment compared with the Killip class. Third, the LA volume was calculated using the two-dimensional method. Due to the complex geometry of the LA, studies have shown that its measurement by a three-dimensional method is the most accurate [49]. Fourth, we did not follow up with an ultrasound after treatment. Several studies found that LA reservoir function had the potential to recover in weeks if decongestive therapy was performed [31]. Impaired LASr after decongestion has been linked to an increased risk of heart failure and all-cause death. This also provides a direction for further research.

5. Conclusions

LASr, as an integrated marker of dynamic LA function, has the potential to identify high-risk patients as defined by the GRACE score. Furthermore, LASr measured by echocardiography may be superior to Max LAVI in predicting incident MACE in the short-term following ACS.

Declarations

Author contribution statement

Yi-Tong Li: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Wen-Qian Shen: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Xin Duan; Yang Li; Yan-Xia Wang; Xing-Xing Ren; Qi-Qi Liu: Contributed reagents, materials, analysis tools or data.

Jia-Wei Tian: Conceived and designed the experiments.

Guo-Qing Du: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

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