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# Left atrial geometric and functional remodeling parameters by cardiac magnetic resonance imaging and outcome prediction in patients with severe aortic stenosis

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## ABSTRACT

**Background**: Emerging studies are beginning to shape the role of afflicted left atrium's (LA) function and strain in cardiovascular diseases including aortic stenosis (AS), especially for risk stratification and outcome prediction. Cardiac magnetic resonance imaging (CMR) is becoming increasingly useful in determining parameters of LA, however, in patients with AS, this has not been yet approached.

**Aims**: The study sought to evaluate the role of CMR in characterizing LA geometry and function in patients with severe AS.

**Methods**: We prospectively evaluated 70 patients with symptomatic severe AS and 70 controls. LA volumes, function and strain were determined using CMR. A composite outcome (cardiac death, ventricular tachyarrhythmias, and heart failure hospitalization) was evaluated over a median of 13 months. Time-to-event outcomes were analyzed accordingly.

**Results**: Besides increased LA volumes (LAVs) and LA sphericity index (LASI) ($P$ <0.001), LA phasic functions and strain were considerably defective in patients with AS (all $P$ <0.001). LV mass (LVM), end-diastolic and end-systolic volumes were also significantly associated withal LA strain parameters ($P$ <0.001). Regarding outcome prediction, decreased total (LA-εt), active (LA-εa) and passive strain (LA-εp), along with enhanced LASI were independently associated with outcome ($P$ <0.001). Time-to-event analysis showed significantly higher risk to reach the composite outcome for LA-εt <31.1% (hazard ratio [HR], 6.981; 95% confidence interval [CI], 2.74–17.77; $P$ <0.001), LA-εp <14.5% (HR, 2.68; 95% CI, 1.00–7.18; $P$ <0.01), and LA-εa <21.2% (HR, 2.02; 95% CI, 1.07–3.83, $P$ <0.03).

**Conclusion**: Patients with severe AS have significantly remodelled LA, with impaired phasic function and strain. Amongst all CMR parameters, LAVmin, LASI, LAPF and LA-εp appear to be independent predictors for outcome.

**Key words:** aortic stenosis; cardiac magnetic resonance imaging; left atrial sphericity index; left atrial phasic functions; left atrial strain

## BACKGROUND

Aortic stenosis (AS) is the most common valvular heart disease, having paramount consequences on life quality and survival [1]. Given that aortic valve replacement is the only effective therapy, the continuous seek of non-invasive parameters which could improve risk stratification and prognosis prediction is a necessity [2]. Left atrium (LA) plays decisive roles in maintaining the integrity of heart's physiology, while its impairment has been proved to be considerably associated with mortality and poor outcomes in cardiovascular diseases [3, 4]. The constant development of cardiac magnetic resonance imaging (CMR) has widened its uses, and recent studies endorsed its ability to properly evaluate LA structure and function. Nonetheless, studies to characterize LA by CMR and to ascertain its utility in patients with AS are still lacking.

LA's physiology comprises three successive phases which have primary roles in preserving the cardiac output, even in those with left ventricular (LV) dysfunction, and it includes: LA reservoir function, conduit function, and booster pump functions [5–7].Contrariwise, it has been suggested that LV dysfunction promotes LA damage and dilation [3], however in patients with AS, O'Connor et al. [8] have shown that LA enlargement is not always accompanied by its dysfunction. Moreover, LA phasic dysfunction is closely related to the progression of LV dysfunction, being also able to independently predict cardiovascular outcome [9]. Furthermore, LA strain by CMR has been shown to identify LV impaired relaxation [10]. However, the prognosticating capacity of these parameters in patients with AS has not been yet approached.

With regard the LA geometry, LA volumes (LAV) have been shown to be important predictors of outcome and mortality [11]. In patients with AS, Rusinaru et al have proved that echocardiography based LAV was an independent predictor of mortality [12]. As for LA sphericity index (LASI), its importance in characterizing LA shape and remodelling, and in predicting atrial fibrillation's recurrence has been recently endorsed by several studies [13]. Nevertheless, in patients with AS, the role of LASI is still unknown.

The aim of our study was to appraise the role of LA geometry and function determined by CMR in patients with severe AS.

## METHODS

### Study population

We conducted a prospective study on 70 patients with symptomatic severe AS and 70 controls (patients with cardiovascular risk factors and without clinically overt cardiovascular diseases) matched for age and gender, who were examined in the 2$^{nd}$ Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania, between March 2018 and May 2021. Severe AS was defined as peak aortic jet velocity ≥4 m/s, and/or mean transvalvular gradient ≥40 mm Hg, and/or [3] aortic valve area ≤1.0 cm$^2$ (indexed aortic valve area≤0.6 cm2/m2) determined by standard transthoracic echocardiography [14]. Patients with severe AS were considered symptomatic if they experienced dyspnoea, angina, palpitation and/or syncope. Figure 2 represents the study's flow-chart which includes the exclusion criteria, as well.

The research was approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca. The study was conducted in accordance with the Declaration of Helsinki. All patients were informed about the investigation protocol and signed a consent form.

**CMR imaging**

CMR images were performed using a Siemens 1.5 T Open Bore scanner (Magnetom Altea, Siemens Medical Solutions, Erlangen, Germany). According to international recommendations, a standard scanning protocol was used for the acquisition of fast imaging employing steady-state free precession (SSFP) sequences was performed to detect ventricular function and mass in short-axis and long-axis planes, to enclose both ventricles from base to apex [15]. Scanning parameters included: repetition time (TR) 3.6 ms; echo time (TE) 1.8 ms; flip angle 60°; slice thickness 6 mm; field of view 360 mm; image matrix of 192 × 192 pixels; voxel size 1.9 × 1.9 × 6 mm; 25–40 ms temporal resolution reconstructed to 30 cardiac phases. LGE was acquired 10 minutes after intravenous administration of 0.2 mmol/kg gadoxetic acid (Clariscan, GH Healthcare AS, Oslo, Norway) in long- and short axis sequences, using a segmented inversion-recovery gradient-echo sequence (TR, 4.8 ms; TE, 1.3 ms; inversion time, 200–300 ms). LA-LGE sequenced was performed during mid-ventricular diastole using an ECG-triggered and navigator-gated, fat-saturated 3D gradient echo inversion recovery sequence, 15–25 min after administration of gadolinium contrast agent (Figure 1).

**Evaluation of LV systolic and diastolic function**

All images were evaluated by two experienced observers, blinded to all clinical data. LVEDV and LV end-systolic volume (LVESV), LVEF and end-diastolic LV mass (LVM) were measured on short-axis cine-SSFP images. Epicardial and endocardial borders were traced semi-automatically at end-diastole and end-systole using specialized software (Syngo Virtual Cockpit). All volumes were indexed to body surface area. The presence, distribution, and mass of LV-LGE were assessed from short-axis images, using the 17-segments model, and we used a threshold of 5SD above the signal intensity of normal myocardium. The extent of LV-LGE was expressed by gram (g) and as percentage of LVM. Because the LGE quantification with the threshold of 5SD demonstrated the best agreement with visual assessment and best reproducibility among different technique thresholds, we used a threshold of 5SD above the signal intensity of normal myocardium [16, 17].

LV longitudinal function was assessed by LAS, defined as the difference in mitral annular displacement at end-systole vs. end-diastole, and expressed in percentages [16].

With regard to LV diastolic function, blood flow and myocardial velocity PC-CR images were used to acquire: (1) transmitral through-plane flow velocity (encoding velocity Venc, 180cm/s; TE, 3.1ms; TR, 7.6 ms; views per segment, 2; temporal resolution, 15 ms), and (2) longitudinal myocardial velocity (Venc, 15cm/s or 20 cm/s; TE, 5 ms; TR, 9.5 ms; views per segment, 2; temporal resolution, 20 ms). To minimize background offsets and so that acquisition duration remained compatible with breath holding, a 50% rectangular field of view was used [16]. Each PC-CMR dataset included a dynamic modulus series (providing information about the variation in mitral valve orifice geometry during the cardiac cycle) and the associated velocity-encoded dynamic series, acquired during an entire cardiac cycle. These contours were then superimposed on velocity PC-CMR images for flow analysis.

Three basic waveforms were obtained which allowed measurements of the following parameters: Transmitral early (E, in cm/s) and late (A, in cm/s) peak velocities and early (EQ, in mL/s) and late (AQ, in mL/s) peak flow rates; filling volume (FV), deceleration time (DT, in ms) and isovolumic relaxation time (IVRT, in ms).Myocardial longitudinal early (E', in cm/s) and late (A', in cm/s) peak velocity on LV lateral wall.

LA parameters were determined by CMR using a dedicated software (cvi42, Circle Cardiovascular Imaging Inc., Calgary, CA), in accordance with international guidelines, comprising: maximum LA volume (LAVmax), pre-atrial contraction LA volume (LAVpre-A), and minimum LA volume (LAVmin); LA reservoir function was evaluated using LA total emptying fraction (LATF), the LA conduit function using LA passive emptying fraction (LAPF), and the atrial booster pump function using LA active emptying fraction (LAAF), along with their specific LA strain: LA-εt, LA-εp, and LA-εa, respectively [6, 18, 19]. The LA sphericity index (LASI) was calculated using this formula: LA volume = maximum LA volume/ $(4\pi/3)$(maximum LA length/2) [20, 21].

**Clinical outcomes**

Patients were followed-up over a median time interval of 13 months (3 to 19 months) by completing a query either on hospital visits, telephone house-calls, or both. The composite endpoint comprised major adverse cardiac events (MACE), including cardiac death, ventricular

tachyarrhythmias and heart failure (HF) hospitalization. Hospitalization due to non-cardiac causes were not considered in the analysis.

### Statistical analysis

The analysis was performed using MedCalc (Version 19.1.7, MedCalc Software, Belgium), *P*-values <0.05 were considered statistically. Data were presented as mean (SD), median with interquartile range (IQR) or percentage. Categorical data was assessed using Chi square test. Continuous data was tested using t-test or Mann-Whitney U test, in accordance to normality of data. Pearson's correlation (parametric) or Spearman's correlation (non-parametric) was performed to investigate the potential relationship between LV conventional parameters, baseline parameters and LA function. Cohen's Kappa inter- and intra-observer coefficients were determined to assess the reproducibility of CMR parameters. The Cox regression model was used to evaluate event predictions and the results were presented as hazard ratios (HR). For each outcome, we considered all the significant variables in the univariate analysis and sought the best overall multivariable models for the composite end point, by stepwise-forward selection. Event-free survival was generated by the Kaplan-Meier method and statistical significance was determined by the log-rank test.

## RESULTS

### Baseline characteristics and LV function measurements

Eventually, 70 patients with severe AS (mean [standard deviation, SD], 67 [8.8] year-old; 57.1% males) and 70 controls (mean [SD], 65 [8.6] year-old; 58.5% males), were included in the study, and their baseline clinical characteristics are presented in Table 1). Within the diseased group, 47.1% [n = 33] of patients with severe AS presented with dyspnoea, 34.2% (n = 24) with typical angina and only 18.5% (n = 13) had syncope. Regarding the etiology of the AS, 80% had degenerative disease, 10% presented with bicuspid aortic valve, 6% had rheumatic valvular disease and 4% could not be determined.

CMR conventional parameters are presented in Supplementary material, *Table S1*. LVEDV, LVESV, LVM, LVEF and LAS were significantly impaired in those with AS, as compared to controls (all *P* <0.001). Furthermore, several LV diastolic parameters such as A, DT, E', E/A ratio, E/E ratio (*P* <0.001) were also notably impaired. LGE was found in 34 patients with AS (48.5%).

LGE was distributed mid-wall in 14 patients (20%), in the sub-epicardial myocardium in 5 patients (7.1%), was focal in 12 patients (17.1%), and diffuse in 3 patients (4.3%).

Regarding the agreements of the CMR parameters, LAVmax, LAVmin, LAVpre-A, LASI and E/E' ratio, had kappa coefficients for inter-observer agreements of 0.92, 0.94, 0.92, 0.94, and 0.91 respectively, and for intra-observer coefficients of 0.93, 0.95, 0.93, 0.94, and 0.91.

**Characterization of LA phasic function and geometry**

LA volumes were significantly increased in AS group (all $P$ <0.001). LASI was considerably impaired in the diseased group (mean [SD], 0.50 [0.09] vs. 0.40 [0.05]; $P$<0.001), while 31.4% of them were positive for LA-LGE. As for LA phasic function, all three were significantly defective in the diseased group: LATF, LAPF, LAAF (all $P$ <0.001). Furthermore, LA strain CMR parameters (LA-εt, LA-εp, and LA-εa; $P$ <0.001) were also substantially afflicted in those with AS, as compared to controls.

**Associations of LA phasic function and strain with LV functional parameters, LA volumes and geometry**

The most fitting correlations between LA phasic functions and strain, LV parameters and LA geometry are summarized in Supplementary material, *Table S2*. LA phasic functions and strains parameters were inversely associated with LA volumes and LASI. Hence, LAVmax, LAVpre-A, LAVmin had the strongest correlations with LAAF, LA-εt, LA-εp and LA-εa proved (all $P$ <0.001), while LASI proved the best associations mainly with LA-εt and LA-εa ($P$ <0.001).

Furthermore, LAAF, LA-εt, LA-εp and LA-εa had the best correlations with conventional LV functional parameters (all $P$ <0.001). The most significant associations were between LVM, LVEDV and LVESV, and LA-εt, LA-εp and LA-εa ($P$ <0.001).

**The ability of LA parameters to predict composite endpoint in patients with AS**

Patients with AS were followed-up for a median of 13 months. Of all, 1 experienced cardiac death, 3 ventricular tachyarrhythmias, and 11 HF hospitalization. In multivariable analysis, only a few remained independent predictors for outcome: LAVmin ($P$ <0.001), LASI ($P$ <0.001), LAPF ($P$ <0.001), LA-εp ($P$ <0.001), LA-LGE ($P$ <0.001), LV-LGE ($P$ <0.001) and E/E' ratio ($P$ <0.001) (Table 3).

Time-to-event analysis was performed to test their ability to predict the composite outcome (Figure 4). Thus, a threshold of >22 ml/m$^2$ for LAVmin (HR, 1.75; 95% CI, 1.04–4.07, *P* <0.001), >34% for LAPF (HR, 4.13; 95% CI, 1.32–12.21; *P* <0.001), >0.5 for LASI (HR, 2.24; 95% CI, 1.06–3.99; *P* = 0.04) significantly predicted the outcome. As for LA strain parameters, LA-εt<31.1% (HR, 6.981; 95% CI, 2.74–17.77; *P* <0.001), LA-εp <14.5% (HR, 2.68; 95% CI, 1.00–7.18; *P* = 0.01), and LA-εa <21.2% (HR, 2.02; 95% CI, 1.07–3.83; *P* = 0.03) also predicted the outcome. As for cardiac fibrosis, the presence of both LA-LGE (HR, 2.78; 95% CI, 1.07–7.16; *P* = 0.01) and LV-LGE (HR, 2.58; 95% CI, 1.11–5.97; *P* = 0.03) significantly predicted the outcome.

## DISCUSSION

This is the first CMR study to characterize the predictive ability of LA geometry and function in patients with AS. Hence, the main findings of this study encompass: (1) LA volumes, phasic functions, strain, and geometry were considerably impaired; (2) LA strains were strongly related to LA volumes, LASI and LV function; (3) LAVmin, LAPF, LA-εp, and E/E' ratio were independently associated with outcome; (5) LASI and LA strains were notably related with higher risk of composite endpoint.

As a direct response to LV impairment, LA dilates and becomes defective [3]. Studies have shown that regardless of cardiovascular disease, LA's phasic functions commonly become impaired [3, 9, 22], being firmly associated with HF, LV dysfunction, and atrial fibrillation [8, 22, 23]. LA reservoir function often becomes impaired even before LV hypertrophy and dilation, being closely related to LV diastolic dysfunction. Additionally, LA reservoir dysfunction independently predicted HF hospitalization and cardiac mortality [24].

We proved that LA parameters were significantly impaired in those with AS and these findings were confirmed using healthy volunteers. Hence, LA volumes, phasic functions and strains were considerably defective in patients with AS. Thus far, some studies have shown the utility of CMR in the assessment of LA parameters [9, 24, 25], however in patients with AS such research has never been yet conducted. Echocardiography-based studies have concluded that patients with severe AS had all three LA phasic functions defective and, moreover, LA reservoir and conduit functions were associated with impaired LV filling pressures and relaxation, and with AS's severity [26, 27]. Additionally, Ferreira et al have shown that defective LA emptying fraction was a strong predictor for all-cause mortality [28]. As for LA strain, studies have shown that LA strain

was related to LV dysfunction and AS severity, being also an independent predictor for HF hospitalization, all-cause mortality, and new-onset atrial fibrillation, regardless of LA dilation [29, 30]. Recently, Kim et al. have conducted a CMR study in which they have suggested that LA peak longitudinal strain might predict cardiovascular events in AS, but several studies have shown that traditional CMR methods might have questionable reliability, requiring further adjustments [31, 32]. Taken together, more work is still required to properly assess the prognosis ability of CMR-based LA parameters.

Furthermore, all three LA volumes proved to have the strongest associations with LAAF, LA-εt, LA-εp and LA-εa, strengthening even more the pathogenetic duality of which LA dilation and dysfunction are two complementary processes. These measurements were also closely related with parameters of LV systolic dysfunction, thus suggesting the mutuality of LA and LV impairment. Similar results have been found in other cardiovascular diseases, but so far there is no such study conducted in patients with AS. Recent published data has proved similar associations between LV systolic dysfunction and LA enlargement and impairment [9, 33]. Moreover, in our diseased group, LVEF's deterioration was closely related with LA dysfunction, similar to other reports [34].

What is more, in the actual study, the predictive ability of relevant LA parameters was tested. In univariate analysis, all LA volumes, LA phasic functions, LA strains and LASI were associated with the composite endpoint, however, after adjustment for confounders, only a few remained significant. Hence, LAVmin, LA conduction function, LA passive strain, and LASI were independent predictors for cardiovascular outcome in patients with AS. Furthermore, we performed Kaplan-Meier analysis to test the ability of time-to-event prediction for these LA parameters, and all of them reached statistical significance. Similarly, some studies have shown the predictive ability of LA volumes, phasic functions, and strain for outcome in various cardiovascular diseases [25, 35]. Nonetheless, as we are aware, this is the first research article which evaluates the comprehensive predictive ability of LA parameters by CMR in patients with AS.

Lastly, regarding LASI, in comparison with other LA parameters, this was significantly associated with parameters of LA strain only. Moreover, time-to-event analysis has shown that it significantly increases the risk of outcome for a threshold of >0.5. Lately, LASI determined by both echocardiography and CMR has been proved to be a marker of LA remodelling, atrial fibrillation recurrence and HF hospitalization [36–38]. These findings suggest a more intimate relation

between LASI as a marker of LA remodelling and dysfunction and defective LA strains, thereby indicating that although LA dilation and dysfunction are at some point co-dependent, these pathogenetic processes are also independent one from another. Additionally, this is the first study to assess the predictive ability of LASI in patients with AS.

Regarding the limitations, firstly, this was a single centre study; Secondly, more advanced LA parameters such as atrial displacement weren't approached. Finally, a second diagnosis method, such as cardiac catheterization or echocardiography, was not performed.

## CONCLUSIONS

Patients with severe AS have significantly remodelled LA, with impaired phasic function and strain. Amongst all CMR parameters, LAVmin, LASI, LAPF and LA-εp are independent predictors for outcome.

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**Supplementary material**

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

**Article information**

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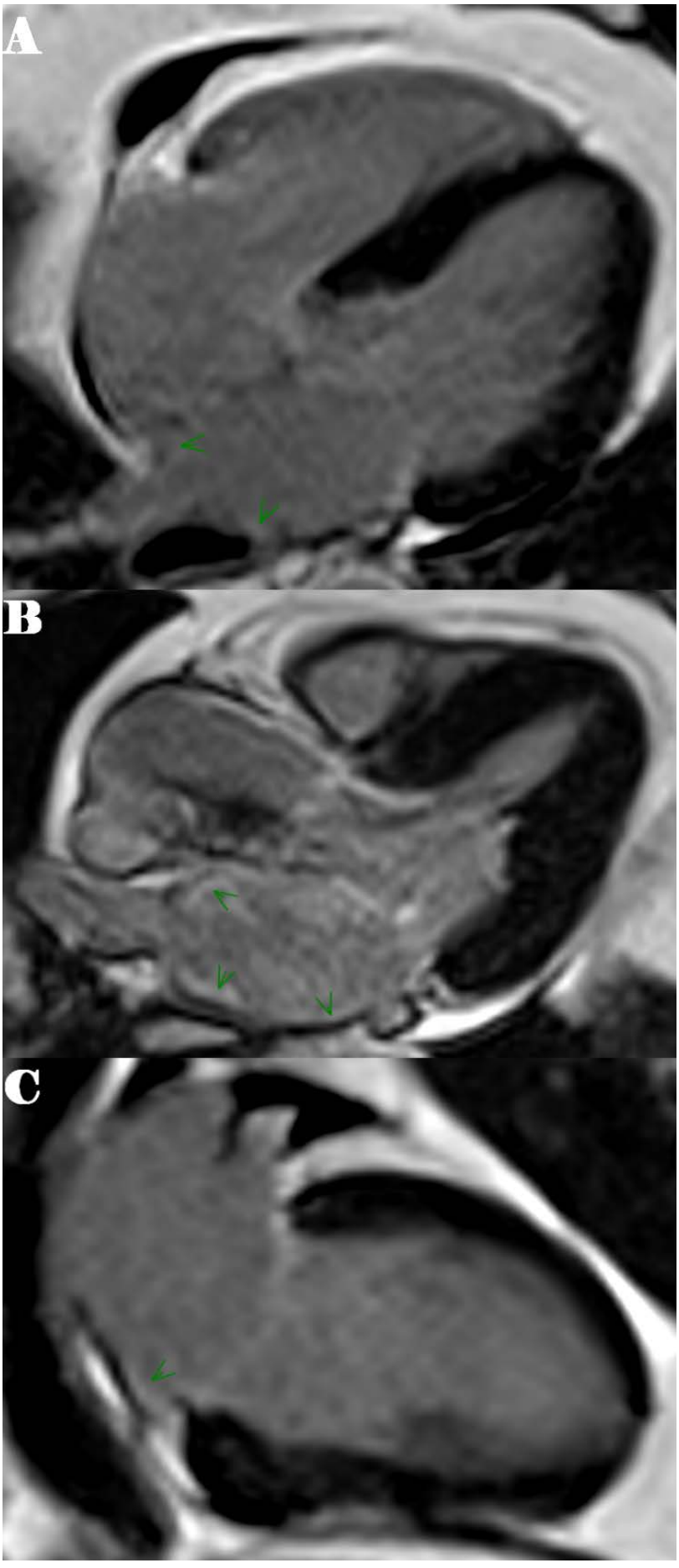
A
B
C

**Figure 1.** Cardiac magnetic resonance images representing patients left atrial late-gadolinium enhancement in 4-(**A**), 3-(**B**), and 2-(**C**)chambers views

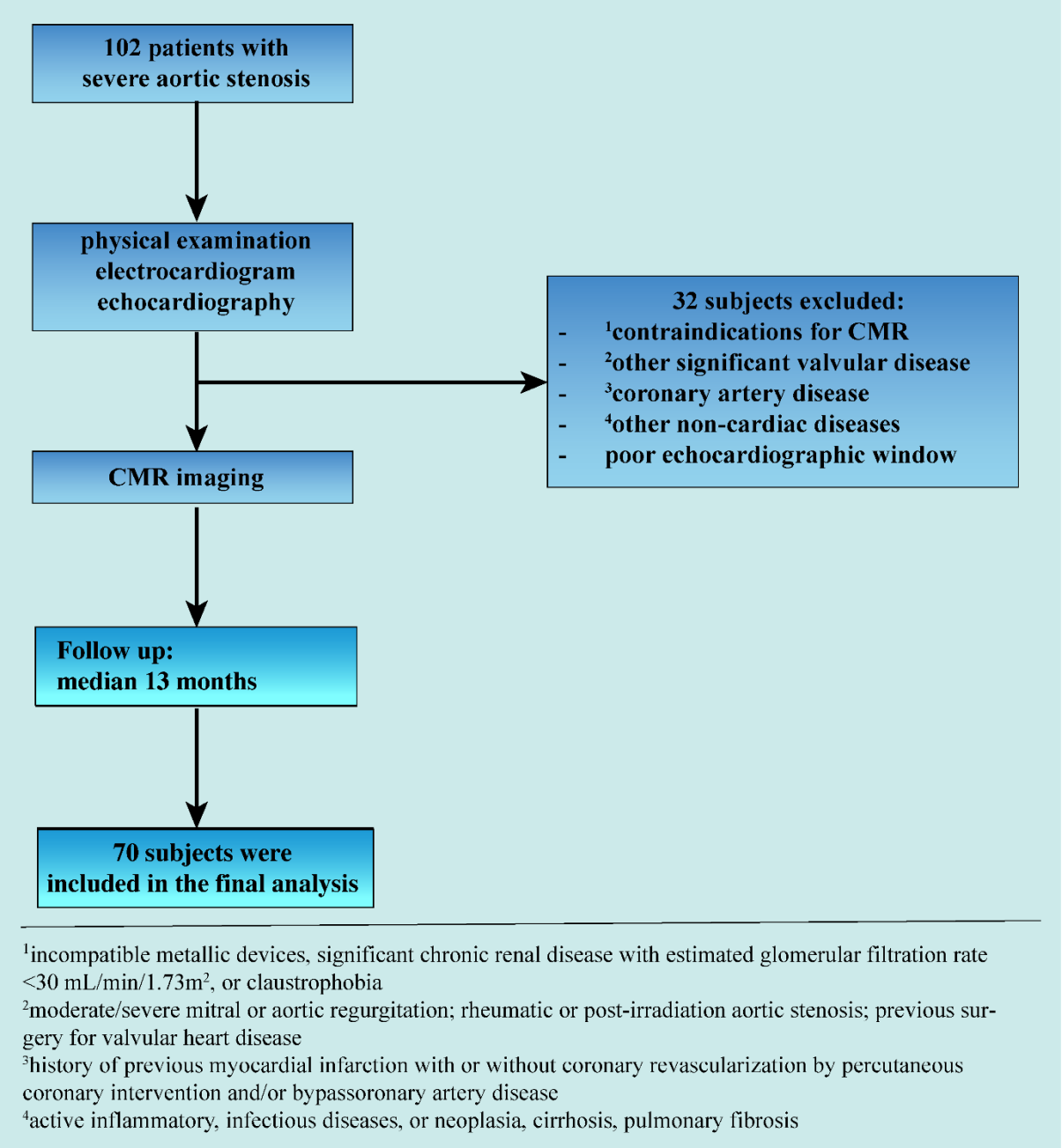


**Figure 2**. Flow-chart of the study

Abbreviations: CMR, cardiac magnetic resonance

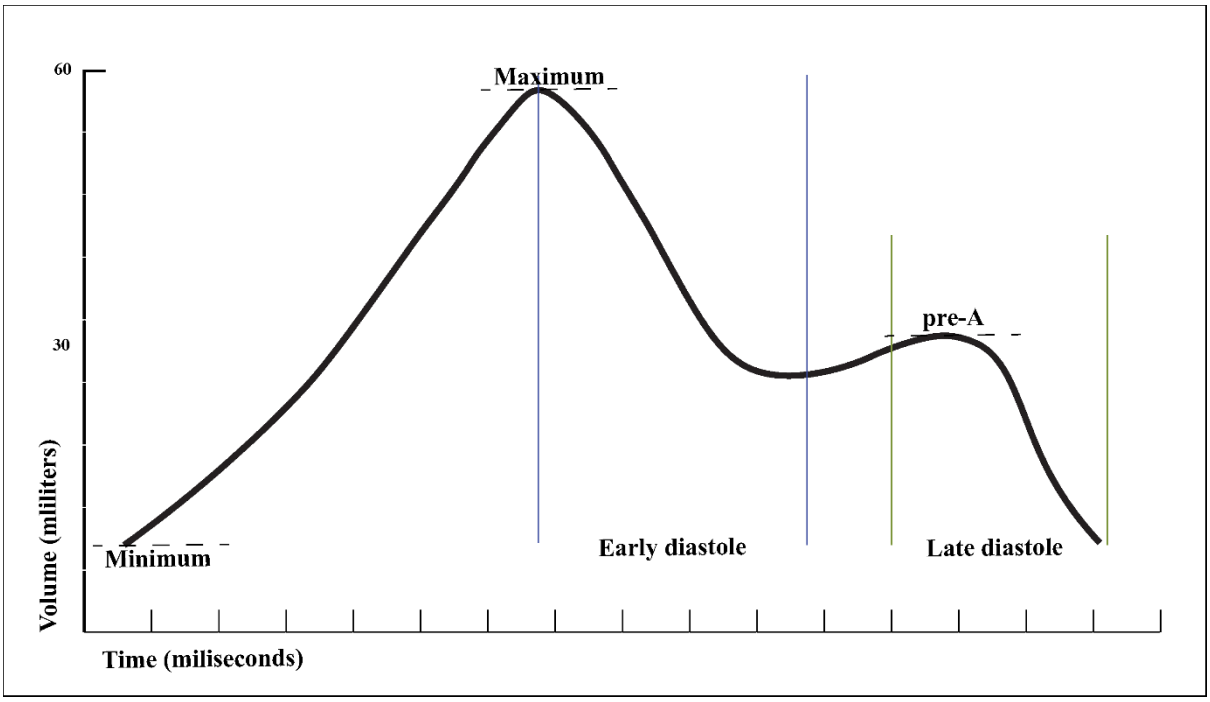


**Figure 3**. Left atrial volume curves during cardiac cycle

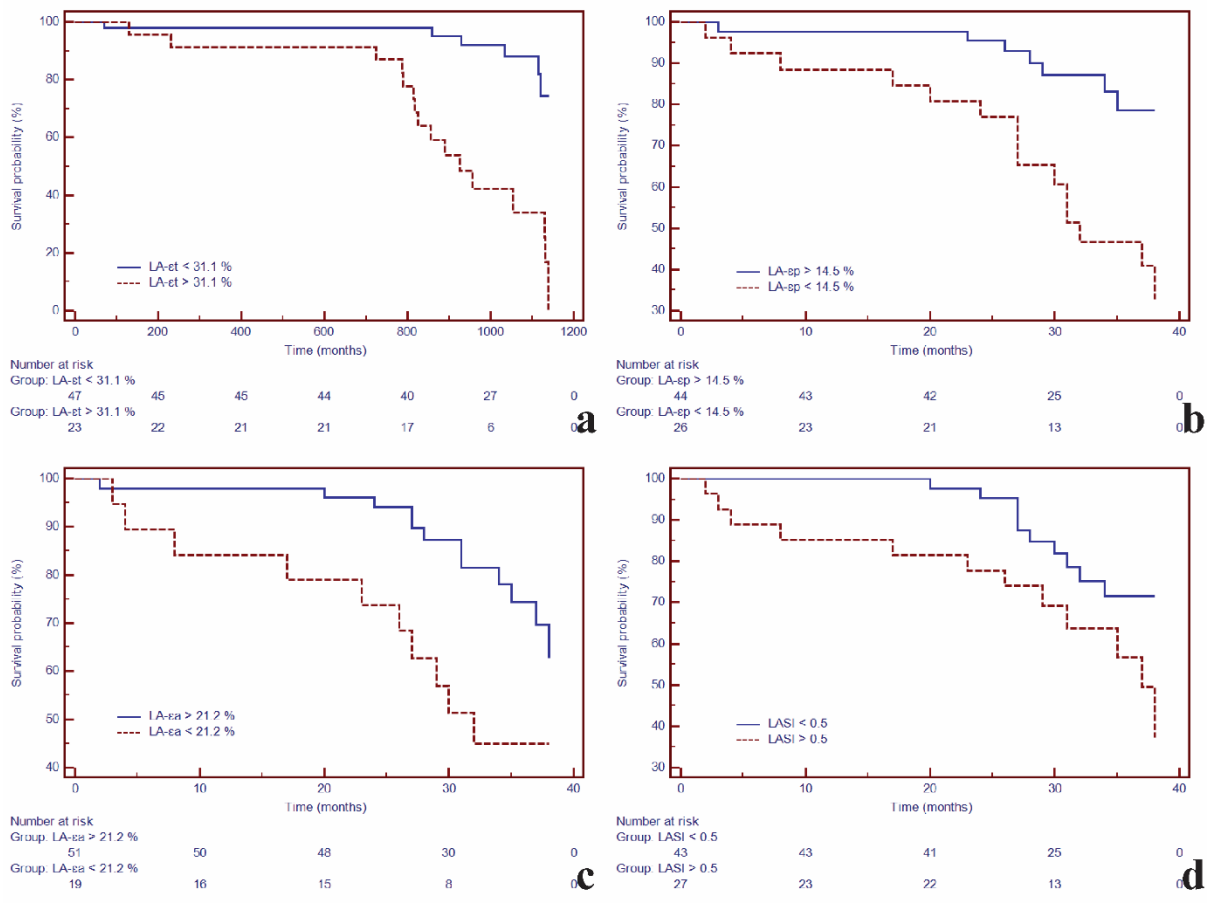


**Figure 4.** Log-rank analyses for left atrial parameters in determining the outcome.

Abbreviations: LA-εa, left atrial active strain; LA-εp< left atrial passive strain; LA-εt, left atrial total strain; LASI, left atrial sphericity index

**Table 1.** Baseline characteristics of patients in study

| Variables | **AS All patients n = 70** | **Controls n = 70** | ***P*-value** |
|---|---|---|---|
| **Clinical characteristics** | | | |
| Age, mean (SD), years | 67 (8.8) | 65 (8.6) | 0.110 |
| Male gender, n (%) | 40 (57.1) | 41 (58.5) | 0.102 |
| Body-mass index, mean (SD), kg/m$^2$ | 30.5 (4.9) | 28.4 (4.2) | 0.05 |
| Hypertension, n (%) | 49 (70) | 37 (52.8) | 0.05 |
| Diabetes mellitus, n (%) | 32 (45.7) | 18 (25.7) | 0.05 |
| **Electrocardiogram** | | | |
| Atrial fibrillation paroxysmal, n (%) | 6 (8.5) | – | NA |
| Left bundle branch block, n (%) | 11 (15.7) | 2 (2.8) | <0.001 |
| Right bundle branch block, n (%) | 10 (14.2) | 1 (1.4) | <0.001 |
| Significant Q waves, n (%) | 3 (4.2) | – | NA |
| **Echocardiography** | | | |
| Peak aortic velocity, mean (SD), m/s | 4.46 (0.46) | 1.35 (0.33) | <0.001 |
| Peak transaortic gradient, mean (SD), mm Hg | 82.2 (17.8) | 7.7 (2.31) | <0.001 |
| Mean transaortic gradient, mean (SD), mm Hg | 53.1 (14.6) | 3.7 (0.74) | <0.001 |
| AVA index, mean (SD), cm$^2$/m$^2$ | 0.51 (0.08) | 3.2 (0.07) | <0.001 |
| **Medication** | | | |
| Beta-blockers, n (%) | 53 (75.7) | 4 (5.7) | <0.001 |
| ACEIs or ARBs, n (%) | 47 (67.1) | 10 (14.2) | <0.001 |
| Calcium channel blockers, n (%) | 23 (32.8) | 5 (7.1) | <0.001 |
| Diuretics, n (%) | 43 (61.4) | 6 (8.5) | <0.001 |
| Antiarrhythmic, n (%) | 15 (21.4) | — | NA |
| Anticoagulant, n (%) | 13 (18.5) | — | NA |
| **Sera Biomarkers** | | | |
| NT-proBNP, median (IQR), pg/ml | 634.3 (172–1329) | 215.7 (66–372) | <0.001 |
| Galectin-3, median (IQR), | 16.4 (2.2–23.6) | 5.6 (1–12.6) | <0.001 |
| PICP, median, (IQR), ng/ml | 1.16 (0.38–7.32) | 0.75 (0.38–4.6) | 0.05 |
| PIIINP, median (IQR), ng/ml | 10.7 (2.5–68.3) | 8.1 (2.4–29.7) | 0.05 |
| eGFR, mean (SD), ml/min/1.73 m$^2$ | 82.1 (17.9) | 89.3 (23.3) | 0.05 |

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVA, aortic valve area; eGFR, estimated glomerular filtration rate; IQR, interquartile range; n, number of patients; NT-proBNP, N-terminal pro-brain natriuretic peptide; PICP, procollagen type I C-terminal propeptide; PIIINP, procollagen type III N-terminal propeptide; SD, standard deviation

**Table 2.** Comparison between left atrial function and geometry parameters between AS and healthy volunteers

| **Variables** | **AS patients n = 70** | **Controls n = 70** | ***P*-value** |
|---|---|---|---|
| **LA volumes indexed** | | | |
| $LAV_{max}$ index, mean (SD), $ml/m^2$ | 42.2 (4.8) | 26.9 (3.5) | <0.001 |
| $LAV_{min}$ index, mean (SD), $ml/m^2$ | 20.3 (5.9) | 10.5 (1.3) | <0.001 |
| $LAV_{pre-A}$ index, mean (SD), $ml/m^2$ | 31.7 (6.2) | 18.9 (2.4) | <0.001 |
| **LA geometry and fibrosis** | | | |
| LASI, mean (SD) | 0.50 (0.09) | 0.40 (0.05) | <0.001 |
| LA-LGE, n, mean (SD) | 22 (31.4) | — | N/A |
| **LA phasic functions** | | | |
| LATF, mean (SD) % | 58.2 (2.1) | 60.7 (1.8) | <0.001 |
| LAPF, mean (SD) % | 34.9 (2.8) | 29.6 (4.9) | <0.001 |
| LAAF, mean (SD) % | 36.3 (4.1) | 43.9 (3.9) | <0.001 |
| **LA strain parameters** | | | |
| LA-$\varepsilon_t$, mean (SD) (%) | 31.1 (2.4) | 39.8 (3.3) | <0.001 |
| LA-$\varepsilon_p$, mean (SD), (%) | 14.5 (1.9) | 18.3 (3.0) | <0.001 |
| LA-$\varepsilon_a$, mean (SD) (%) | 21.2 (2.8) | 28.8 (4.1) | <0.001 |

Abbreviations: AS, aortic stenosis; n, number of patients; LA-$\varepsilon_t$, left atrial total strain; LA-$\varepsilon_p$, left atrial passive strain; LA-$\varepsilon_a$, left atrial active strain; LAV, left atrial volume; LASI, left atrial sphericity index; LA-LGE, left atrial late gadolinium enhancement; LAPF, left atrial passive emptying fraction; LAAF, left atrial active emptying fraction; LATF, left atrial total emptying fraction

**Table 3. Univariate and Multivariate Cox Analysis testing between studied parameters and MACEs**

| | **Univariable analysis** | | **Multivariable analysis** | |
|---|---|---|---|---|
| | **Unadjusted HR (95% CI)** | ***P*-value** | **Adjusted HR (95% CI)** | ***P*-value** |
| Age, years | 1.02 (0.97–1.07) | 0.516 | | |
| Gender, male | 1.01 (0.45–2.19) | 0.612 | | |
| Body mass index, $kg/m^2$ | 1.01 (0.93–1.09) | 0.090 | | |
| LVEDV index, $ml/m^2$ | 1.01 (1.00–1.03) | 0.047 | | |
| LVESV index, $ml/m^2$ | 1.02 (1.00–1.04) | 0.018 | | |
| LVEF, % | 1.01 (0.93–1.07) | 0.721 | | |

| | | | | |
|---|---|---|---|---|
| LVM index, g/m$^2$ | 1.09 (1.07–1.33) | <0.001 | | |
| LV-LGE | 2.75 (1.25–7.97) | <0.001 | 1.73 (1.02–5.91) | <0.001 |
| LAS, % | 1.28 (1.13–2.12) | <0.001 | | |
| LAV max index, ml/m$^2$ | 1.12 (1.01–1.17) | 0.019 | | |
| LAV min index, ml/m$^2$ | 1.45 (1.23–1.89) | <0.001 | 1.37 (1.08–1.66) | <0.01 |
| LAV preA index, ml/m$^2$ | 1.31 (1.17–1.37) | <0.001 | | |
| LASI | 1.20 (1.18–1.43) | <0.001 | 1.13 (1.01–1.43) | <0.01 |
| LA-LGE | 3.36 (1.35–9.35) | <0.001 | 3.56 (1.02–12.47) | <0.001 |
| LATF, % | 1.66 (1.44–1.72) | <0.001 | | |
| LAPF, % | 2.16 (1.73–2.64) | <0.001 | 1.76 (1.09–2.34) | <0.01 |
| LAAF, % | 1.61 (1.52–1.81) | <0.001 | | |
| LA-$\varepsilon_t$, % | 1.25 (1.19–1.43) | <0.001 | | |
| LA-$\varepsilon_p$, % | 1.54 (1.35–1.86) | <0.001 | 1.31 (1.12–2.01) | <0.01 |
| LA-$\varepsilon_a$, % | 1.43 (1.32–1.61) | <0.001 | | |
| E /E'ratio | 1.59 (1.19–2.22) | <0.001 | 1.20 (1.00–1.44) | <0.01 |
| DT, ms | 1.13 (1.01–1.26) | 0.012 | | |
| NP-proBNP, pg/ml | 1.01 (0.81–1.02) | 0.978 | | |
| Galectin-3, ng/ml | 0.99 (0.94–1.05) | 0.254 | | |

Abbreviations: cMRI, cardiac magnetic resonance imaging; LV, left ventricle; LVEDV; left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LV-LGE, left ventricularlate gadolinium enhancement; LAV, left atrial volume; LASI, left atrial sphericity index; LA-LGE, left atrial late gadolinium enhancement; LAPF, left atrial passive emptying fraction; LAAF, left atrial active emptying fraction; LATF, left atrial total emptying fraction;-$\varepsilon_t$, left atrial total strain; LA-$\varepsilon_p$, left atrial passive strain; LA-$\varepsilon_a$, left atrial active strain; E, early peak mitral flow velocity; E', myocardial longitudinal early diastolic peak myocardial velocity; MACEs, major adverse cardiovascular events; NT-proBNP, N-terminal pro-brain natriuretic peptide

Adjustment models: age, gender with the addition of significant parameters of univariable analysis