Left Atrial Functional Assessment and Mortality in Patients with Severe Aortic Stenosis

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Abstract

Background: Aortic valve stenosis (AS) is the most common primary valvular heart disease leading to surgical or percutaneous aortic valve replacement (AVR) in Europe and its prevalence is growing. While other risk factors in severe AS are well documented, less is known about the association between left atrial (LA) function and prognosis in AS. Our aim is to clarify the relationship between LA function measured at severe AS diagnosis (evaluated by means of volumetric assessment) and all-cause mortality during follow-up.

Methods: We retrospectively evaluated patients diagnosed with severe AS for the first time at our echocardiography laboratory. We evaluated LA reservoir, conduit and pump function by measuring LA volumes at different timings of cardiac cycle. Treatment strategy was decided according to heart team consensus and patient decision. We divided patients into groups according to terciles of LA reservoir, conduit and pump function. Primary outcome was defined by the occurrence of all-cause mortality during follow-up.

Results: A total of 451 patients were included in the analysis, with a median follow-up time of 73 months (interquartile range 44.5). 55.8% of patients underwent AVR and 45.5% of patients registered the primary outcome during follow-up. Left atrial emptying fraction (LAEF) was the best LA functional parameter and the best overall parameter in discriminating primary outcome (AUC 0.840, 95% CI 0.803-0.872, p<0.001). After adjustment for clinical, demographic and echocardiographic variables, cumulative survival of patients with LAEF <37% and LAEF 37 to 53% relative to patients with LAEF ≥54% remained significantly lower (hazard ratio 19.04, 95% CI 8.30-43.67, P<0.001 and hazard ratio 4.09, 95% CI 1.85-9.06, *p*=0.001, respectively). After adjustment for AVR, excess risk of LAEF <37% and LAEF 37 to 53% relative to LAEF ≥54% remained significant (hazard ratio 13.95, 95% CI 5.98-32.54, P<0.001 and hazard ratio 3.97, 95% CI 1.80-8.78, P=0.001, respectively).

Conclusions: In patients with a first diagnosis of severe AS, LA function, evaluated by means of volumetric assessment, is an independent predictor of all-cause mortality and a more potent predictor of death compared to classical severity parameters. These data can be useful to identify high-risk patients who might benefit of AVR.

Introduction

Aortic valve stenosis (AS) is the most common primary valvular heart disease leading to surgical or percutaneous valve replacement in Europe and its prevalence is growing due to the generalized aging of population [1]. According to current recommendations, aortic valve replacement (AVR) is indicated in the presence of symptoms and/or left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) < 50%] [2]. However, both symptoms and systolic dysfunction can appear late in the course of the disease, being often synonym of irreversible damage to the myocardium when found [3]. On the other hand, structural changes can occur before symptom onset and are associated with worse prognosis, even

after AVR [4, 5]. With the increasingly widespread access to both surgical or transcatheter AVR, there is a necessity to find other sensitive markers present at an earlier stage of the disease.

In patients with AS, there is a background of chronically increased left ventricular afterload which is associated with structural and functional changes in the left atrium (LA). As such, LA enlargement is a common finding in these patients [6] and correlates with increased left ventricular filling pressures [7]. Also, the ongoing pressure overload leads to disturbance in the LA three functional phases: reservoir, conduit and contractile phase [8], particularly in the contractile phase. Reservoir and conduit phase impairment also seems to occur, but may be a late finding, associated with pulmonary hypertension [9].

LA functional assessment has been performed by means of volumetric method in a number of diseases, such as dilated cardiomyopathy [10], atrial fibrillation [11, 12], ventricular arrhythmias [13] and heart failure [14]. While much is known about LA structural damage as a predictor of mortality in different diseases such as dilated cardiomyopathy [15], myocardial infarction [16], mitral regurgitation [17] and more recently in AS [18], there is limited information regarding LA function as a predictor of prognosis in patients with AS.

Although there is recent data regarding the impact of LA mechanics, evaluated by speckle tracking echocardiography, in the outcome of patients with AS [19–21], the lack of standardisation between vendors and lack of validation for its use in thin-walled chambers should be taken into account when using this technique. Three-dimensional echocardiography has also been proved to be more strictly correlated to LA dimensions measured by cardiac magnetic resonance [22]. However, it is not available in every echocardiography laboratory and still has important issues with temporal resolution. Therefore, two-dimensional LA volumetric assessment remains a simple, reproducible and the routinely used method to measure LA function.

Thus, our primary aim is to assess the LA function, evaluated by means of volumetric assessment, in patients with severe AS diagnosis, and to study its potential impact on all-cause mortality during follow-up.

Methods

Study participants

In this study, we retrospectively evaluated 667 patients diagnosed with severe AS [$V_{max} \geq 4$ m/s, mean pressure gradient (MPG) ≥ 40 mmHg, or aortic valve area (AVA) ≤ 1.0 cm^2] for the first time at our echocardiography laboratory, between December 2010 and February 2020. The following patients were excluded: (1) those with prosthetic valves, previous cardiac surgery, congenital heart disease, supravalvular or subvalvular AS, dynamic left ventricular outflow tract obstruction; (2) those with mitral stenosis (defined as functional mitral valve area ≤ 2.5 cm^2; (3) those with atrial fibrillation (AF) at index echocardiogram or with previous history of AF and (4) those with poor acoustic window with suboptimal

imaging of left atrium. Clinical and demographic baseline characteristics, including presence of coronary artery disease, cardiovascular risk factors, functional status, normal cognition and other comorbidities were collected from the hospital medical records.

The study was approved by the institutional scientific and bioethical committees and was performed in accordance with the Declaration of Helsinki.

Echocardiographic measurements

All patients underwent comprehensive 2-dimensional and Doppler echocardiographic evaluation. Exams were conducted using a General Electric Vivid S6 or Vivid 7 Ultrasound system and 3Sc-RS tissue harmonics transducer operating with a frequency of 1.2/3.4 MHz. Obtained images were then exported to a computer database and processed with EchoPAC® Clinical Workstation Software version 113 (General Electric, Healthcare, Chicago, Illinois). AVA was calculated using the continuity equation [23], and indexed AVA (AVAi) was obtained after indexing AVA to body surface area (BSA). Left ventricular outflow tract (LVOT) diameter was measured in parasternal long-axis view in accordance with recent recommendations [24]. LVOT velocity-time integral (VTI) was measured in apical 5-chamber view. V_{max} and mean pressure gradient (MPG) were obtained using continuous-wave Doppler in the view in which cursor alignment with flow was the most appropriate, recording the highest value of V_{max} and aortic VTI. All pressure gradients were calculated using simplified Bernoulli equation. LVEF was measured with the Simpson biplane method. Wall thickness was measured at end-diastole in parasternal long-axis view. Left ventricular hypertrophy (LVH) was defined when left ventricular mass was > 115 g/m^2 for men and > 95 g/m^2 for women, measured by 2D-directed M-mode. LV diastolic function was assessed by measurement of mitral E velocity, mitral A velocity, mitral E/A ratio, mitral “L” velocity, pulsed-wave tissue Doppler-derived mitral annular early diastolic velocity measured at septum (septal e’), mitral E/e’ ratio, LA maximum volume index and tricuspid regurgitation velocity, in accordance to American Society of Echocardiography guidelines [25]. Valvular regurgitation severity was assessed following recommendations from European Society of Cardiology [26]. For each measurement, at least three cardiac cycles were averaged.

Left atrial volumetric assessment

The 3 LA functional phases can be evaluated non-invasively with echocardiography. For that effect, LA volumes were measured using the biplane method of disks (modified Simpson) in apical 2- and 4-chamber views, at different phases during the cardiac cycle, with the method described by O’Connor *et al* [8]. We measured the following LA volumes: (1) maximal LA volume (Vol_{max}), during ventricular end-systole right before mitral valve opening; (2) minimum LA volume (Vol_{min}), during ventricular end-diastole right after mitral valve closure and (3) Vol_{preA}, just before the start of the “P” wave on electrocardiogram. We excluded left atrial appendage and pulmonary vein orifices from measurement. LA reservoir function was evaluated by measuring LA total emptying volume (Vol_{max} - Vol_{min}) and LA emptying fraction (LAEF) [(LA total emptying volume/Vol_{max}) x 100]. LA conduit function was evaluated by measuring LA passive

emptying volume (Vol_{max} - Vol_{preA}) and LA passive emptying fraction (LAPEF) [(LA passive emptying volume/Vol_{max}) x 100]. LA pump function was evaluated by measuring LA active emptying volume (Vol_{preA} - Vol_{min}) and LA active emptying fraction (LAAEF) [(LA active emptying volume/Vol_{preA}) x 100]. All volumes were then indexed for BSA.

Treatment decision and follow-up

Treatment strategy (conservative, percutaneous, surgical, or conservative and then percutaneous or surgical) was decided according to patient's cardiologist and own patient decision. The majority of study patients were observed and followed-up in outpatient setting at our center. Other patients were diagnosed with AS after hospital admission, and then followed up in outpatient setting. A minority of patients were diagnosed with AS after hospital admission and underwent surgery during the same hospitalization. Information on follow-up was obtained by assessing patient registries at our institution. The end-point was overall survival after diagnosis, with conservative, percutaneous or surgical treatment. During follow-up patients were observed by their assigned cardiologist. Decisions regarding treatment were made in heart team, with the approval of patient's cardiologist and according to patient's will.

Statistical analysis

Study population was divided into groups according to terciles of LA functional assessment (LAEF, LAPEF and LAAEF). Normality of continuous variables was evaluated by histogram observation and Kolmogorov-Smirnov test. Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as adequate, and categorical variables as frequencies or percentages. Group comparison was made with Student *t*, Wilcoxon rank-sum, unidirectional ANOVA or Kruskal-Wallis tests according to normality. Individual variables were assessed for homogeneity of variance using Levene's test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Relationship between different variables were assessed by correlation analysis: Pearson's method for normally distributed variables and Spearman's method for skewed variables.

A receiver operating characteristic (ROC) curve analysis was performed to assess the discriminative power of the different measures of LA function and volumes, LVEF, E/e' ratio, septal e', AVA, tricuspid annular plane systolic excursion (TAPSE), or right ventricle/right atrium (RV/RA) gradient. We compared ROC curves using the Delong method.

Survival rates were estimated using Kaplan-Meier method and compared with 2-sided log-rank test. Date of entry into the study was defined as the date of diagnosis (index transthoracic echocardiogram). Univariate and multivariable analysis were used to identify predictors of outcome using Cox proportional hazard models. We used clinically relevant risk-adjusting variables (very severe AS, surgical or percutaneous treatment, age at diagnosis, gender, body mass index (BMI), arterial hypertension, coronary artery disease, diabetes, history of malignancy, chronic lung disease, previous symptomatic stroke/transient ischemic attack, Katz index of independence ≤ 4, dementia, AF appearance during follow-up, LVEF, right ventricular enlargement, TAPSE and severe mitral or tricuspid regurgitation) in order

to adjust for differences in baseline characteristics. We treated age at diagnosis, LVEF, TAPSE and BMI as continuous variables in Cox hazard model. Risk was expressed as hazard ratio (HR) and their 95% confidence interval (CI). In order to check Cox model assumptions were respected, we used statistics based on Schoenfeld residuals. To assess nonlinearity, we used Martingale residuals. In every Cox model, we tested for first-order interactions between covariables and each prognosis variable being tested.

Analysis was conducted using IBM® SPSS® Statistics (SPSS for Windows, version 26.0, Armonk, New York) and MedCalc® statistical software (MedCalc software for Windows, version 19.2.0, Ostend, Belgium). All reported p-values were 2-sided and P values < 0.05 were considered statistically significant.

Interobserver and intraobserver variability

Interobserver and intraobserver variability of LA volumetric assessment were assessed by means of coefficient of variation (CoV), Bland-Altman method[27] and intraclass correlation coefficient (ICC)[28]. Detailed analysis is depicted in Supplementary Table 1.

Results

Baseline characteristics

At a first stage, a total of 667 patients were enrolled. We excluded 132 patients with AF at index echocardiography, 15 for previous cardiac surgery, 4 for dynamic LVOT obstruction, 16 for unsatisfactory image quality and 49 for having at least mild mitral stenosis. After exclusion criteria were applied, a total of 451 patients were included in the analysis. Our cohort was followed-up during a median period of 73 months (interquartile range 44.5). There were no patients lost to follow-up.

The median (interquartile range) LAEF values were 46 (27) % for the entire cohort, 24 (12) % for patients with LAEF < 37%, 45 (9) % for patients with LAEF 37–53% and 61 (9) % for patients with LAEF ≥ 54%; median (interquartile range) LAPEF values were 23 (14) % for the entire cohort, 13 (8) % for patients with LAPEF < 19%, 23 (5) % for patients with LAPEF 19–28% and 34 (8) for patients with LAPEF ≥ 29%; median (interquartile range) LAAEF values were 26 (27) % for the entire cohort, 9 (9) % for patients with LAAEF < 17%, 26 (9) % for patients with LAAEF 17 to 34% and 46 (13) for patients with LAAEF ≥ 35%.

Clinical and demographic characteristics of the 451 patients were significantly different between LAEF groups, as presented in Table 1. Patients with LAEF < 37% were older, had lower BSA, a higher degree of dependence on daily activities, higher prevalence of coronary artery disease, and developed significantly more often AF during follow-up.

Table 1
Baseline clinical and demographic characteristics, global and stratified by left atrial emptying fraction

Variable	All patients (n = 457)	LAEF < 37% (n = 146)	LAEF 37–53% (n = 148)	LAEF ≥ 54% (n = 157)	*P* Value
Male gender, n (%)	244 (54.1)	68 (46.6)	78 (52.7)	98 (62.4)	0.020
Age, y	74.3 ± 10.8	77.9 ± 11.1	74.9 ± 8.8	70 .1 ± 10.9	< 0.001
Body surface area, m^2	1.78 ± 0.18	1.72 ± 0.17	1.76 ± 0.19	1.84 ± 0.17	< 0.001
Hypertension, n (%)	326 (74.4)	97 (68.8)	106 (73.1)	123 (80.9)	0.054
AF during follow-up, n (%)	64 (14.4)	41 (28.7)	17 (11.6)	6 (3.9)	< 0.001
Coronary artery disease, n (%)	151 (45.9)	48 (59.3)	47 (40.5)	56 (42.4)	0.020
Dyslipidemia, n (%)	295 (67.4)	78 (55.3)	102 (70.3)	115 (75.7)	0.001
Diabetes mellitus, n (%)	133 (30.3)	43 (30.5)	47 (32.2)	43 (28.3)	0.763
Previous malignancy, n (%)	66 (15.1)	21 (14.9)	27 (18.6)	18 (11.8)	0.263
Chronic lung disease, n (%)	40 (9.1)	16 (11.3)	15 (10.3)	9 (5.9)	0.225
Previous stroke/TIA, n (%)	47 (10.7)	17 (12.1)	11 (7.6)	19 (12.5)	0.324
Katz index ≤ 4*, n (%)	68 (15.5)	41 (28.7)	16 (11.0)	11 (7.3)	< 0.001
Dementia, n (%)	23 (5.2)	12 (8.4)	6 (4.1)	5 (3.3)	0.114

AF denotes atrial fibrillation; TIA, transient ischemic attack

* Katz index of independence in activities of daily living, ranging from 6 (patient independent) to 0 (patient very dependent)

Regarding echocardiographic variables, patients with LAEF < 37% registered lower values in all LA volumetric measures, had lower LVEF, lower AVA and AVAi, greater RV disfunction, higher pulmonary pressures and greater degree of diastolic disfunction with higher LV filling pressures and more commonly shown diastolic L wave. The same group also had greater prevalence of other concomitant severe valvular disease. Differences in echocardiographic measures between groups can be seen in Table 2.

Table 2
Echocardiographic parameters, global and stratified by left atrial emptying fraction

Variable	All patients (n = 457)	LAEF < 37% (n = 146)	LAEF 37–53% (n = 148)	LAEF ≥ 54% (n = 157)	*P* Value
LAPEF	23.8 ± 10.6	14.9 ± 7.4	25.0 ± 7.9	30.9 ± 9.3	< 0.001
LAPEVi	11.1 ± 5.3	8.7 ± 5.2	12.1 ± 5.0	12.2 ± 4.9	< 0.001
LAAEF	27.3 ± 17.1	9.5 ± 6.8	26.7 ± 9.2	44.1 ± 11.8	< 0.001
LAAEVi	9.0 ± 5.1	4.7 ± 3.4	9.7 ± 4.0	12.0 ± 4.7	< 0.001
LVEF, %	56.6 ± 11.9	49.2 ± 15.2	58.6 ± 8.8	61.5 ± 6.5	< 0.001
LVEF ≥ 50%, n (%)	365 (81.3)	85 (58.6)	131 (88.5)	149 (95.5)	< 0.001
Aortic valve area, cm^2	0.74 ± 0.33	0.62 ± 0.19	0.75 ± 0.19	0.85 ± 0.46	< 0.001
Aortic valve indexed to BSA, cm^2/m^2	0.44 ± 0.36	0.37 ± 0.11	0.42 ± 0.10	0.51 ± 0.56	0.004
Transaortic mean pressure gradient, mmHg	49.4 ± 14.8	48.8 ± 17.7	49.9 ± 14.1	49.6 ± 14.8	0.811
Peak aortic jet velocity, m/s	4.46 ± 0.62	4.40 ± 0.79	4.47 ± 0.55	4.50 ± 0.62	0.334
Very severe aortic stenosis*, n (%)	109 (24.3)	39 (27.1)	35 (23.8)	35 (22.3)	0.616
LVOT VTI / AV VTI ratio	0.22 ± 0.07	0.20 ± 0.06	0.22 ± 0.06	0.25 ± 0.07	< 0.001
Enlarged right ventricle, n (%)	66 (14.7)	39 (26.7)	13 (8.8)	14 (9.0)	< 0.001
TAPSE, mm	20.1 ± 4.1	19.5 ± 4.3	21.5 ± 3.7	22.0 ± 3.7	< 0.001
TAPSE < 16 mm, n (%)	30 (6.7)	23 (15.9)	3 (2.0)	4 (2.6)	< 0.001
RV/RA gradient, mmHg	32.9 ± 13.1	39.1 ± 14.8	27.8 ± 9.5	28.2 ± 9.1	< 0.001
SPAP, mmHg	37.2 ± 14.8	44.6 ± 16.6	31.7 ± 10.7	32.1 ± 10.6	< 0.001

Variable	All patients (n = 457)	LAEF < 37% (n = 146)	LAEF 37–53% (n = 148)	LAEF ≥ 54% (n = 157)	*P* Value
Left ventricular hypertrophy, n (%)	242 (55.1)	89 (62.2)	83 (57.2)	70 (46.4)	0.019
Severe left ventricular hypertrophy, n (%)	14 (3.2)	11 (7.7)	2 (1.4)	1 (0.7)	< 0.001
Mitral E velocity, m/s	0.85 ± 0.26	0.95 ± 0.26	0.83 ± 0.28	0.79 ± 0.22	< 0.001
Mitral A velocity, m/s	0.95 ± 0.36	0.78 ± 0.43	1.04 ± 0.35	0.98 ± 0.26	< 0.001
Septal e' velocity, cm/s	4.78 ± 1.72	3.82 ± 1.32	4.80 ± 1.77	5.52 ± 1.60	< 0.001
Septal a' velocity, cm/s	6.94 ± 2.35	4.89 ± 1.85	7.02 ± 1.86	8.41 ± 1.92	< 0.001
E/A ratio	1.10 ± 0.85	1.71 ± 1.27	0.89 ± 0.46	0.84 ± 0.38	< 0.001
E/e' ratio	19.77 ± 8.44	27.34 ± 10.02	18.59 ± 5.77	15.12 ± 4.42	< 0.001
Diastolic L wave, n (%)	26 (7.1)	20 (19.0)	4 (3.2)	2 (1.5)	< 0.001
Severe tricuspid regurgitation, n (%)	6 (1.3)	4 (2.7)	2 (1.4)	0 (0.0)	< 0.001
Severe aortic regurgitation, n (%)	28 (6.2)	18 (12.3)	6 (4.1)	4 (2.5)	0.003
Severe mitral regurgitation, n (%)	17 (3.8)	15 (10.3)	2 (1.4)	0 (0.0)	< 0.001

AV denotes aortic valve; LAEF, left atrial emptying fraction; LAAEF, left atrial active emptying fraction; LAAEVi, indexed left atrial active emptying volume; LAPEF, left atrial passive emptying fraction; LAPEVi, indexed left atrial passive emptying volume; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; RV/RA, right ventricle/right atrium; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; VTI, velocity time integral

* Defined as transaortic mean pressure gradient ≥ 60 mmHg or peak aortic jet velocity ≥ 5 m/s

Clinical outcomes

A total of 208 (45.6%) out of 456 patients died during follow-up. A total of 249 patients (55.8%) underwent AVR, the vast majority surgical AVR (98.4%). Cumulative incidence of AVR during follow-up was greater in tercile 2 and 3 (65.3% and 71.1% versus 31.9%, respectively, P < 0.001). Among the 249 patients referred to AVR, 30 (12.0%) had depressed LVEF, 10 (4.0%) had severe concomitant valvular lesions, 13 (14.6% of available information) had > 50 mmHg of SPAP and 62 (25.1%) had very severe AS

(MPG ≥ 60 mmHg or V_{max} ≥ 5 m/s). A total of 149 (75.6%) of 197 patients that did not undergo AVR died during follow-up. On the other hand, a total of 56 (22.5%) of 249 patients that underwent AVR died during follow-up.

Outcome impact of LA reservoir function

Mean total LA emptying volume was 34.6 (± 13.4) mL, mean indexed total LA emptying volume was 19.7 (± 7.0) mL/m^2 and mean LAEF was 44.0 (± 17.2) %. Survival during follow-up was progressively higher with increasing LAEF from LAEF < 37% to LAEF ≥ 54% (17.1%, 58.8% and 85.9%, respectively, *P* < 0.001). Patients with LAEF < 37% had a significantly higher all-cause mortality during follow-up compared with patients with LAEF ≥ 37% (82.9% versus 27.3%, *P* < 0.001; Fig. 1A). After adjustment for clinical and demographic variables, cumulative survival of patients with LAEF < 37% and LAEF 37 to 53% compared to patients with LAEF ≥ 54% remained significantly lower (adjusted HR 19.04, 95% CI 8.30-43.67, *P* < 0.001 and adjusted HR 4.09, 95% CI 1.85–9.06, *P* = 0.001; Table 3). Survival was also higher in patients with LAEF 37 to 53% when compared to patients with LAEF < 37% (adjusted HR 0.22, 95% CI 0.13–0.37, *P* < 0.001). When treated as a continuous variable, LAEF remained independently associated with all-cause mortality, with a significant increase in survival with increasing LAEF (adjusted HR 0.92, 95% CI 0.90–0.94, per % increase, *P* < 0.001).

All associations remained true after adjustment for AVR, as LAEF impact on mortality during follow-up was still significant (LAEF < 37% versus LAEF 37 to 53% and LAEF ≥ 54%, respectively, adjusted HR 3.97, 95% CI 1.80–8.78, *P* = 0.001 and adjusted HR 13.95, 95% CI 5.98–32.54, *P* < 0.001, respectively; Fig. 1B). The incidence of all-cause mortality when starting follow-up at time of AVR still tended to be higher in patients with LAEF < 37% when compared to patients with LAEF 37 to 53% and patients with LAEF ≥ 54% (58.7% versus 26.6% and 3.7%, *P* < 0.001).

Subgroup analysis

We found no interaction between age at diagnosis, BSA, BMI, arterial hypertension, presence of coronary artery disease, diabetes mellitus, previous symptomatic stroke/transient ischemic attack, Katz index of independence ≤ 4, atrial fibrillation appearance during follow-up, LVEF, right ventricular enlargement, TAPSE, severe mitral or tricuspid regurgitation, very severe AS, E/e', septal e' velocity and the outcome impact of different LAEF terciles (all variables *P* for interaction > 0.05). As we found gender to interact with different terciles of LAEF, we performed a separate analysis for each gender, and we observed that predictive power of different terciles was greater in females (LAEF < 37% versus LAEF ≥ 54% in females, HR 14.46, 95% CI 7.15–29.25, *P* < 0.001; LAEF < 37% versus LAEF ≥ 54% in males, HR 8.59, 95% CI 4.65–15.87, *P* < 0.001). Mortality during follow-up was progressively higher as AVA was smaller, both in LAEF < 37% (AVA > 0.8 cm^2, 75.9%, AVA 0.6 to 0.8 cm^2, 77.1% and AVA < 0.6 cm^2, 94.3%, *P* = 0.026) and LAEF ≥ 37% (AVA > 0.8 cm^2, 22.0%, AVA 0.6 to 0.8 cm^2, 28.9% and AVA < 0.6 cm^2, 46.4%, *P* = 0.023). In patients with preserved LVEF, mortality during follow-up was consistently higher in patients with LAEF < 37% compared with patients with LAEF ≥ 37% (88.2% versus 25.8%, *P* < 0.001) as well as in patients with

depressed LVEF (75.0% versus 41.7%, $P = 0.005$). The impact of LAEF < 37% in prognosis was still observed in patients with LVH (92.1% versus 32.2%, $P < 0.001$) and without LVH (66.7% versus 20.3%, $P < 0.001$).

Outcome impact of LA conduit function

A detailed analysis of outcome impact of LA conduit function can be seen in Supplementary material.

Outcome of LA pump function

A detailed analysis of outcome impact of LA pump function can be seen in Supplementary material.

Table 3
Relative risk of all-cause mortality associated with left atrial functional assessment

Variable	All-cause mortality	
	HR (95% CI)	P value
LAEF		
Unadjusted		
> 53%	Reference	
37–53%	3.36 (2.06–5.47)	< 0.001
< 37%	11.26 (7.12–17.80)	< 0.001
Model 1*		
> 53%	Reference	
37–53%	4.09 (1.85–9.06)	0.001
< 37%	19.04 (8.30-43.67)	< 0.001
Model 2Ŧ		
> 53%	Reference	
37–53%	3.97 (1.80—8.78)	0.001
< 37%	13.95 (5.98–32.54)	< 0.001
LAPEF		
Unadjusted		
> 28%	Reference	
19–28%	1.52 (0.99–2.31)	0.052
< 19%	3.89 (2.63–5.74)	< 0.001
Model 1*		
> 28%	Reference	
19–28%	1.50 (0.77–2.93)	0.231
< 19%	3.16 (1.68–5.94)	< 0.001
Model 2Ŧ		
> 28%	Reference	
19–28%	1.39 (0.72–2.70)	0.331

Variable	All-cause mortality	
	HR (95% CI)	P value
< 19%	2.17 (1.13–4.19)	0.020
LAAEF		
Unadjusted		
> 34%	Reference	
17–34%	3.34 (1.96–5.69)	< 0.001
< 17%	8.88 (5.38–14.68)	< 0.001
Model 1*		
> 34%	Reference	
17–34%	2.21 (1.00-4.87)	0.049
< 17%	6.05 (2.62–13.96)	< 0.001
Model 2Ŧ		
> 34%	Reference	
17–34%	2.08 (0.95–4.56)	0.069
< 17%	4.87 (2.08–11.42)	< 0.001

CI denotes confidence interval; HR, hazard ratio; LAAEF, left atrial active emptying fraction; LAEF, left atrial emptying fraction; LAPEF, left atrial passive emptying fraction.

*Model 1 was adjusted for very severe aortic stenosis, age at diagnosis, gender, body mass index (BMI), arterial hypertension, coronary artery disease, diabetes, history of malignancy, chronic lung disease, previous symptomatic stroke/transient ischemic attack, Katz index of independence ≤ 4, dementia, atrial fibrillation appearance during follow-up, LVEF, right ventricular enlargement, TAPSE and severe mitral or tricuspid regurgitation.

ŦModel 2 was adjusted for variables used in model 1 and aortic valve replacement during follow-up.

Comparison between LA volumetric parameters and other echocardiographic features as predictors of mortality

We entered different LA volumetric parameters into ROC analysis in order to estimate the probability of death at follow-up. Different variables and respective AUCs are depicted in Table 4 and Fig. 4. Compared to classical echocardiographic AS severity parameters (V_{max}, AVA and MPG), LAEF at AS diagnosis emerged as the best discriminator of all-cause mortality. Between LA volumetric parameters, LAEF also persisted as the most accurate predictor of mortality during follow-up, with an AUC of 0.84, which was greater than LAPEF (0.84 versus 0.72, *P* < 0.001), LAAEF (0.84 versus 0.82, P = 0.0082), indexed LA total emptying volume (0.84 versus 0.79, *P* = 0.001), indexed LA passive emptying volume (0.84 versus 0.63, *P*

< 0.001) and indexed LA active emptying volume (0.84 versus 0.75, *P* < 0.001). Optimal cut-off values to identify higher mortality were 37% for LAEF, 19% for LAPEF and 23% for LAAEF. The best cut-off value of LAEF in order to identify increased mortality had a sensitivity of 61% and a specificity of 89%.

Table 4. Discriminative power of echocardiographic parameters

Variables	AUC	95% CI	P-value	Sensitivity (%)	Specificity (%)	Criterion
LAEF (%)	0.840	0.803–0.872	< 0.001	61	89	37
LAAEF (%)	0.816	0.775–0.853	< 0.001	73	81	23
LATEVi (mL)	0.789	0.747–0.828	< 0.001	63	83	17
E/e' ratio	0.759	0.710–0.804	< 0.001	63	77	20
LAAEVi (mL)	0.746	0.699–0.789	< 0.001	61	78	7
LVEF (%)	0.745	0.703–0.785	< 0.001	47	96	51
Septal e' velocity (cm/s)	0.728	0.677–0.775	< 0.001	69	65	4
LAPEF (%)	0.715	0.669–0.759	< 0.001	47	87	17
AVA (cm^2)	0.685	0.638–0.729	< 0.001	70	57	0.7
LAPEVi (mL)	0.629	0.578–0.678	< 0.001	52	71	9
LAVi (mL)	0.628	0.574–0.682	< 0.001	69	52	44
TAPSE (mm)	0.614	0.567–0.659	< 0.001	37	81	18
RV/RA gradient (mmHg)	0.616	0.550–0.678	0.002	46	72	32
Aortic MPG (mmHg)	0.541	0.494–0.588	0.136	17	96	34
V_{max} (m/s)	0.541	0.493–0.587	0.143	38	72	4.2

AUC denotes area under the curve; AVA, aortic valve area; LAAEF, left atrial active emptying fraction; LAAEVi, indexed left atrial active emptying volume; LAEF, left atrial emptying fraction; LAPEF, left atrial passive emptying fraction; LAPEVi, indexed left atrial passive emptying volume; LATEVi, indexed left atrial total emptying volume; LAVi, indexed left atrial maximum volume; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; TAPSE, tricuspid annular plane systolic excursion; RV/RA, right ventricle/right atrium

Discussion

In the present study, we focused on the impact of LA function on outcome in patients with severe AS. To the best of our knowledge, this is the first study to extensively evaluate the prognostic value of LA functional assessment using classic volumetric parameters in current era severe AS patients. We found that LA function, evaluated by echocardiographic volumetric parameters, is a strong predictor of all-cause mortality, not only in patients who underwent AVR but also in patients who remained on conservative treatment. When compared to other classical prognostic factors in AS such as AVA, V_{max}, MPG and LVEF, LA function was a better predictor of mortality during follow-up. Also, this effect of LA function on prognosis remains true even after adjustment for other factors that are known to affect prognosis in AS, such as age, LVEF, AVA, other concomitant valvular disease and comorbidities. Diminished LAEF (LAEF ≤ 53%) was associated with increased risk of all-cause death during follow-up, and was the best echocardiographic predictor in our study. Other LA functional parameters were still powerful predictors of adverse outcome, mainly LAAEF. Also, the impact of LA functional assessment remained significant across different AVA and LA volumes, in patients with preserved or depressed left ventricular systolic function and different degrees of left ventricular hypertrophy. Additionally, our results show that LA functional parameters remain good predictors of mortality after AVR, despite the important impact of the procedure on mortality of these patients. We also found that LA functional assessment is reproducible, easy and fast to obtain, as different phasic volumes were measured by the biplane method of disks, routinely used in the majority of echocardiography laboratories and the recommended method of measuring left atrial volume [29]. Thus, based on the aforementioned findings, we suggest that LA functional evaluation should be performed in all patients evaluated for severe aortic stenosis and the results should be taken into consideration for the management of these patients.

The background of chronically increased left ventricular afterload in AS is associated with structural and functional changes in the LA. LA enlargement, the most common macroscopic LA structural change, has been considered the most direct noninvasive proof of increased LV filling pressure and diastolic dysfunction [6, 7]. Also, it has been recently associated with higher mortality, even after AVR [18, 30]. Besides LA dilatation, the ongoing pressure overload leads to disturbance in the LA three functional phases: reservoir, conduit and contractile phase [8], particularly in the contractile phase. In our study, we found a reduction in all phasic LA performances, when compared to control groups of patients without cardiac disease [8, 14, 31] and the results from NORRE study, in which 371 healthy subjects were enrolled in order to obtain normal ranges for echocardiographic measures of LA function [32]. As reported in previous studies, the intrinsic left atrial myopathic disease can precede visible LA structural changes, being an early marker of increased LV filling pressures [8, 33]. This finding can explain the patients with normal LA volume and depressed LA function found in our cohort, which showed higher echocardiographic measures of diastolic dysfunction such as elevated septal e' velocity and higher E/e' ratios. As AS is a disease in which elevated intracavitary pressures play a very important role in its progression, the finding of LA functional change may represent an important milestone in which AVR may

play an important role in its modification. As such, LA volume and function best capture the cardiac remodelling associated with AS, contrary to other echocardiographic variables.

While much is known about LA structural damage as a predictor of death in different diseases such as dilated cardiomyopathy [15], myocardial infarction [16], mitral regurgitation [17] and more recently in AS [18], there is limited information regarding LA function as a predictor of prognosis in patients with AS. There have been some reports showing that LA function assessed by speckle-tracking echocardiography can predict worse outcomes in AS patients. In a study conducted in our center, Marques-Alves *et al*. found that, in a population of patients with moderate and severe AS, LA global strain was the best discriminator of AS severity and a significant predictor of a composite of heart failure, death and AVR [19]. The same study also found that atrial mechanics were better predictors of prognosis that LV global longitudinal strain, which was not a significant predictor of outcome. In another study by Todaro *et al*., which recruited 89 asymptomatic patients with severe AS and normal LVEF and 40 age- and gender-matched controls, in which LA and LV mechanics were measured by speckle-tracking echocardiography, LV global longitudinal strain, LA reservoir and LA stiffness were found to be strong predictors of adverse events during follow-up [20]. However, on multivariate analysis only LV global longitudinal strain remained a significant predictor of events recurrence. Galli *et al*. also found that in a population of 128 patients with severe AS, global peak LA strain measured by speckle-tracking echocardiography was a significant independent predictor major adverse cardiac events [21]. No study has evaluated the impact of volumetric assessment of LA function on outcome of severe AS patients, as in all LA function was assessed by speckle-tracking echocardiography. This technique has some advantages compared to volumetric methods, as it makes no geometric assumptions, does not need to make multiple plane acquisition and is, theoretically, less time consuming. Although the risk of LA foreshortening and the assumption of a geometric model of a non-symmetric chamber are real, we found LA volumetric assessment to be an easy, reproducible and fast method of LA evaluation. Besides, if the intention is to measure LA emptying fractions, the problem of foreshortening and eventual underestimation of LA volumes is less important, as it would not impact on the emptying fraction values. STE also has some limitations, as it is prone to suboptimal tracking of the endocardial border, is sensible to acoustic shadowing and reverberations, is not absolutely angle-independent and relies on good image quality. Moreover, each provider has his own software package and it is not available in every echocardiography laboratory.

Other published studies that addressed the impact of LA function on prognosis used as outcome a composite of heart failure, death and AVR [19], occurrence of symptoms and death [20] and major adverse cardiac events [21], outcomes that can be broad. In our study, the measured outcome was all-cause mortality, still, the best predictor of outcome found (LAEF representing LA reservoir function) showed very good predictive value. Also, our study had a long follow-up period compared to other studies, which is important not only to reduce immortality bias but also to better understand the clinical course of AS patients.

Limitations

Our study had a retrospective design and, as such, has the inherent limitations of such studies. We did not record the specific indications for AVR, however, all decisions for AVR were taken in a heart team with extensive experience in valvular heart disease and who assures good practice according to guidelines. We included only patients with severe AS, so we can not extrapolate our findings to moderate or mild AS or even to other valvular diseases. Also, we excluded all patients with AF at the baseline exam and with previous history of the disease. This criterion excluded many patients from analysis. However, we registered the development of AF during follow-up, which gave us the possibility to evaluate its impact on patient prognosis. We did not record any analytical parameters such as natriuretic peptides or serum creatinine, thus, we did not know in what measure they could influence our results. Finally, we did not record the reason for conservative management, so we do not know the extent of patient AVR refusal or what led our heart team to make that decision.

Conclusion

In patients with a first diagnosis of severe AS in hospital setting, LA function assessed by volumetric parameters is an independent predictor of all-cause mortality. Compared to classical severity parameters, different LA functional parameters were found to be more potent predictors of death. These data can be useful in clinical practice for risk stratification and therefore for decision of timing for AVR.

Declarations

Ethics approval: All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. As this is an observational study, the local ethics committee has confirmed that no ethical approval is required.

Availability of data and materials: the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest/Competing interests: The authors declare that they have no competing interests.

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Consent to participate: Consent was not obtained as procedures were part of patient standard care and there was no concern about identifying information.

Authors' contributions: JF conceptualized the research, performed transthoracic echocardiograms, elaborated the database, analysed the data and wrote the manuscript. VG performed transthoracic echocardiograms, elaborated the database and analysed the data. PA performed transthoracic echocardiograms, elaborated the database and analysed the data. RM performed transthoracic echocardiograms, elaborated the database and analysed the data. RT performed transthoracic echocardiograms, analysed the data, actively discussed the results and reviewed the draft manuscript.

SM, and LG actively discussed the results and reviewed the draft manuscript. JF and RT elaborated the revised manuscript. All the authors have read and approved the manuscript version submitted.

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34. Declarations.

Figures

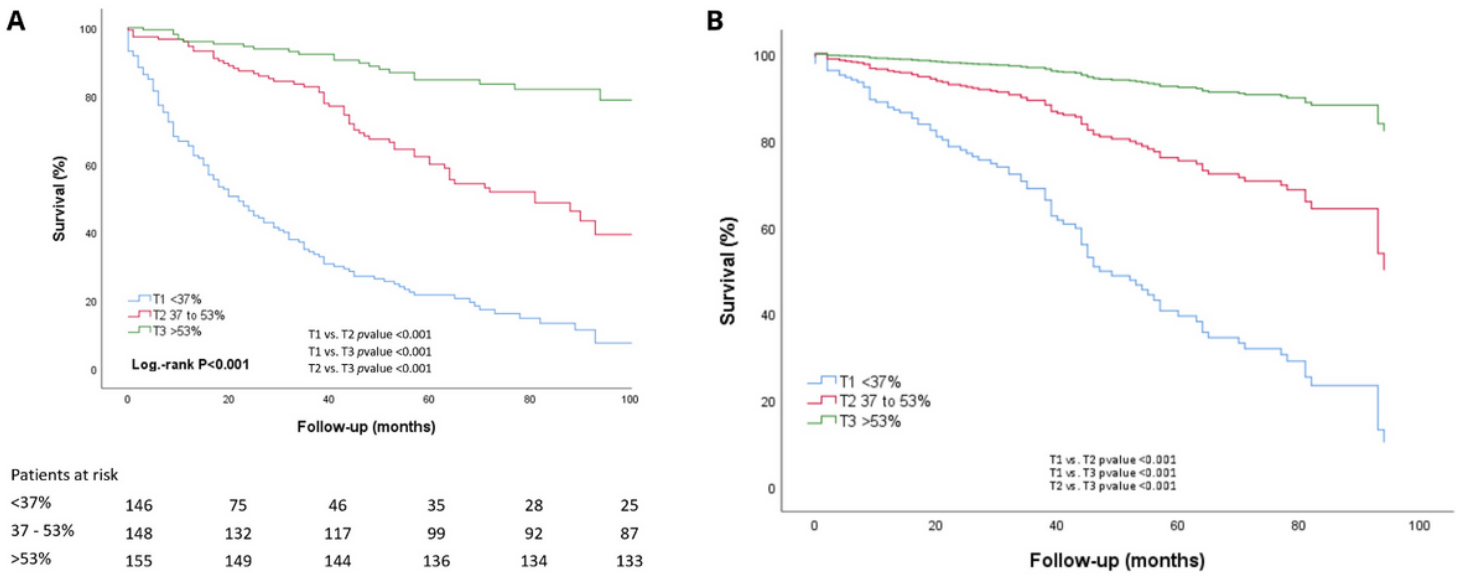

Figure 1

A, Kaplan-Meier curves of patients with severe aortic stenosis according to left atrial emptying fraction (LAEF) terciles. B, Adjusted survival curves of patients with severe aortic stenosis according to LAEF terciles. Adjustment variables can be seen in Statistics section. T1, T2 and T3 indicate first, second and third tercile.

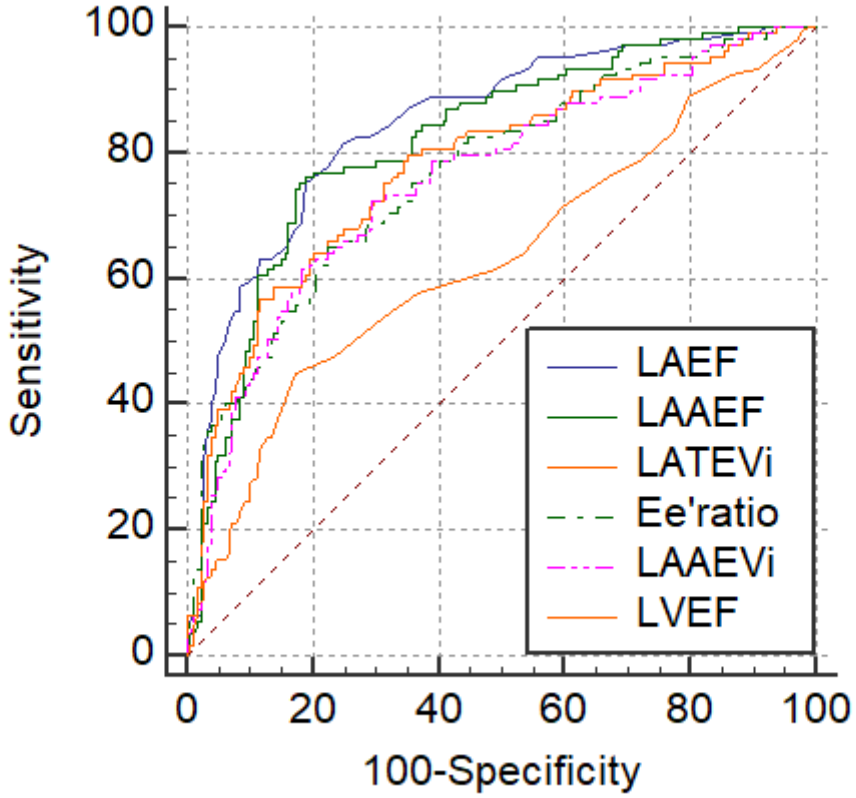

Figure 2

ROC analysis curves of LAEF, LAAEF, LATEVi, E/e' ratio, LAAEVI and LVEF for all-cause mortality. LAAEF, left atrial active emptying fraction; LAAEVi, indexed left atrial active emptying volume; LAEF, left atrial emptying fraction; LATEVi, indexed left atrial total emptying volume; LVEF, left ventricular ejection fraction

Supplementary Files

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