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ORIGINAL ARTICLE

Left atrial function in patients with rheumatic mitral stenosis: addressing prognostic insights beyond atrial fibrillation prediction

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Abstract

Aims

Rheumatic mitral stenosis (MS) frequently leads to impaired left atrial (LA) function because of pressure overload, highlighting the underlying atrial pathology. Two-dimensional speckle tracking echocardiography (2D-STE) offers early detection of LA dysfunction, potentially improving risk assessment in patients with MS. This study aims to evaluate the predictive value of LA function assessed by 2D-STE for clinical outcomes in patients with MS.

Methods and results

Between 2011 and 2021, patients with MS underwent LA function assessment using 2D-STE, with focus on the reservoir phase (LASr). Atrial fibrillation (AF) development constituted the primary outcome, with death or valve replacement as the secondary outcome. Conditional inference trees were employed for analysis, validated through sample splitting. The study included 493 patients with MS (mean valve area 1.1 ± 0.4 cm^2, 84% female). At baseline, 166 patients (34%) had AF, with 62 patients (19%) developing AF during follow-up. LASr emerged as the primary predictor for new-onset AF, with a threshold of 17.9%. Over a mean 3.8-year follow-up, 125 patients (25%) underwent mitral valve replacement, and 32 patients (6.5%) died. A decision tree analysis identified key predictors such as age, LASr, severity of tricuspid regurgitation (TR), net atrioventricular compliance (C_n), and early percutaneous mitral valvuloplasty, especially in patients aged ≤49 years, where LASr, with a threshold of 12.8%, significantly predicted adverse outcomes.

Conclusion

LASr emerged as a significant predictor of cardiovascular events in this MS cohort, validated through a decision tree analysis. Patients were stratified into low- or high-risk categories for adverse outcomes, taking into account LASr, age, TR severity, and C_n.

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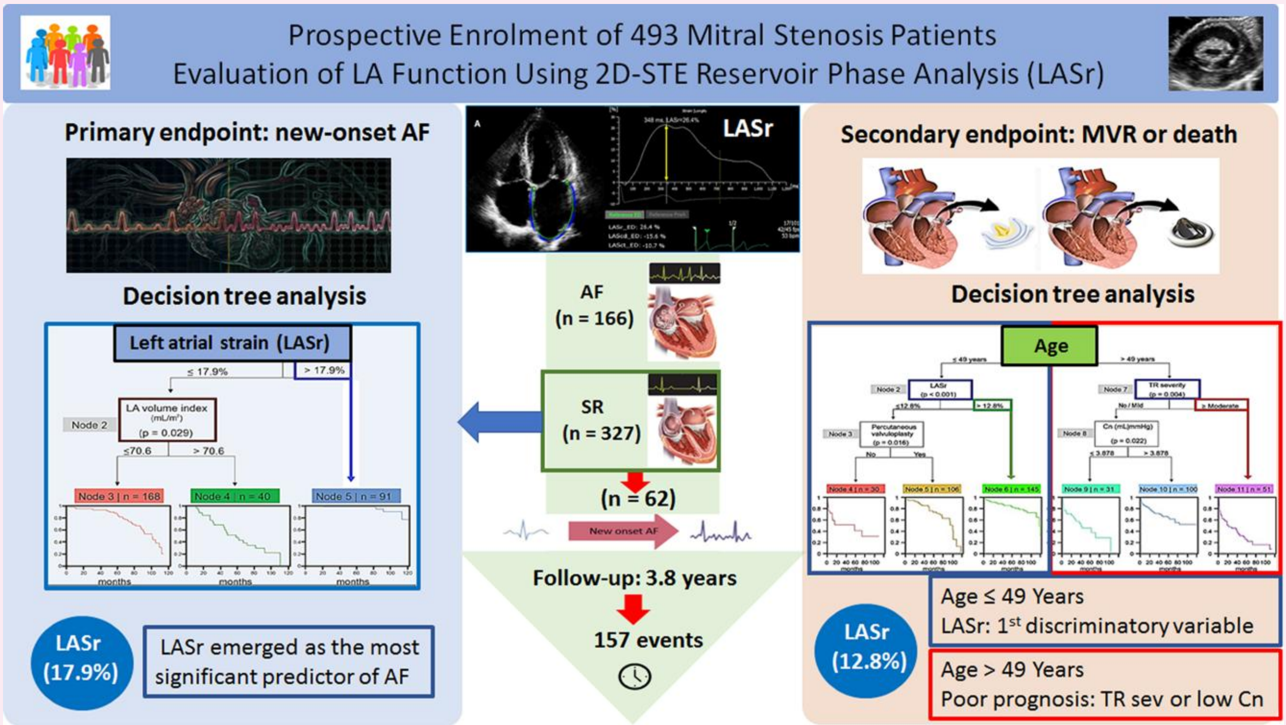
Graphical Abstract



Left atrial function in patients with rheumatic mitral stenosis. A total of 493 patients with mitral stenosis, age 46.4 ± 12.5 years, were prospectively recruited between 2011 and 2021. Left atrial function was assessed using two-dimensional speckle tracking echocardiography during the reservoir phase (LASr). The primary outcome was the new onset of atrial fibrillation (AF), and the secondary outcome was a composite of death or valve replacement. Based on the decision tree analysis, LASr was the most important predictor of new-onset AF, establishing a cut-off point of 17.9%. Age emerged as the primary predictor for the secondary outcome. However, in patients aged ≤49 years, LASr was the first discriminatory variable with a cut-off point of 12.8% for predicting adverse outcome. 2D-STE, two-dimensional speckle tracking echocardiography; C_n, net atrioventricular compliance; LA, left atrial; LASr, left atrial strain during the reservoir phase; MVR, mitral valve replacement; SR, sinus rhythm; TR, tricuspid regurgitation.

Keywords left atrial reservoir strain • rheumatic mitral stenosis • atrial fibrillation • risk prediction • decision tree analysis

Introduction

Rheumatic heart disease (RHD) is a serious health concern, especially in low- and middle-income countries, where it accounts for over a million premature deaths annually.[1] Mitral stenosis (MS) is almost exclusively caused by RHD and remains a major cause of valvular heart disease worldwide.[2–4]

Chronically left atrial (LA) pressure overload leads to a range of adaptive changes with interstitial fibrosis and atrial remodelling. Impaired LA function in rheumatic MS may represent atrial pathology with progressive fibrosis, increased LA stiffness with a progressive reduction in compliance, and abnormal atrial contractility.[5] This underlying atrial remodelling also predisposes to atrial fibrillation (AF), which triggers the development of symptoms and is associated with an increased risk of adverse cardiovascular events.[6,7] Approximately 80% of strokes in patients with RHD occur in the presence of MS and AF, significantly impacting their quality of life and functional abilities.[8] Considering the significant impact of LA function on the progression and management of rheumatic MS, including the necessity for anticoagulation therapy, identifying patients with LA adverse remodelling who are at risk for worse outcomes may help guide therapeutic strategies.

Two-dimensional speckle tracking echocardiography (2D-STE) is an emerging tool utilized for assessing LA phasic function. A previous study revealed a strong correlation between LA reservoir function, LA compliance, and fibrosis observed on cardiac magnetic resonance imaging.[9] In addition, LA reservoir function by 2D-STE has been reported to have an incremental prognostic value for cardiovascular events over LA volume in patients with a variety of disease states, such as post-cryptogenic stroke, recurrence of AF after ablation, and prediction of AF onset in heart failure.[5,10,11] Furthermore, LA reservoir function correlates with cardioembolic events and, therefore, has the potential to enhance risk stratification in patients with a low CHA_2DS_2-VASc score.[12]

In the setting of rheumatic MS, utilizing 2D-STE enables early detection of impaired LA reservoir capacity, indicating atrial stiffness and potentially improving risk stratification and intervention timing. However, there is a scarcity of available data regarding the predictive value of atrial function in determining cardiovascular events in this specific population. Previous studies[13,14] have demonstrated an association between LA strain and AF in patients with MS, but their retrospective design presents limitations, highlighting the need for further prospective research. Additionally, the proposed LA reservoir strain cut-off values for other cardiac conditions may not be applicable to MS due to its unique characteristics, emphasizing the necessity for target studies to establish accurate cut-off values.

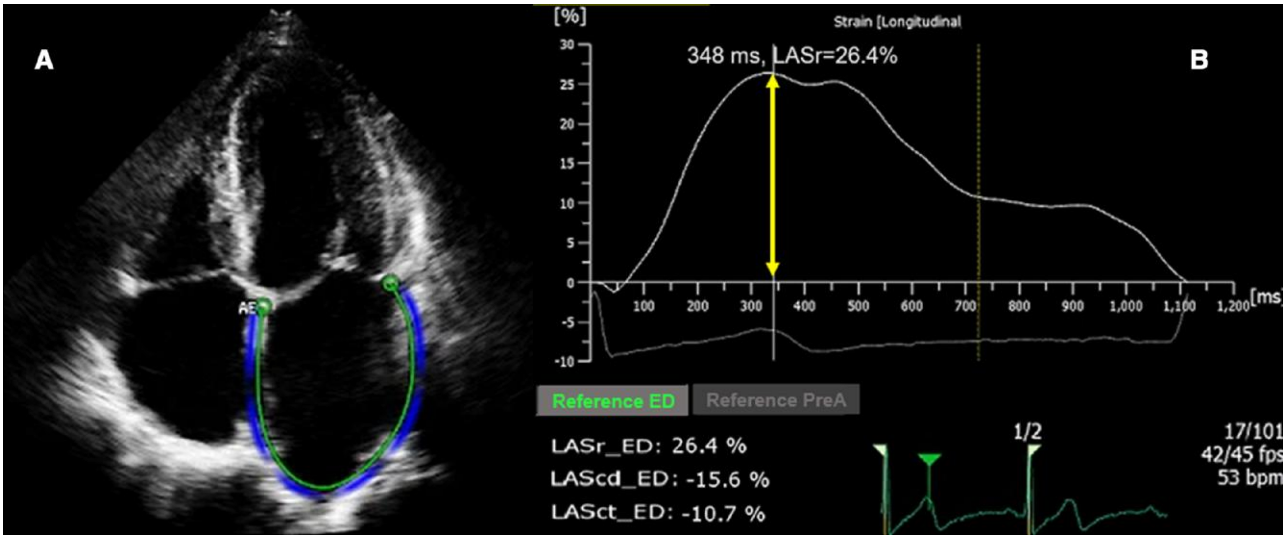


Figure 1 Assessment of LA strain by 2D speckle-tracking echocardiography. (*A*) An echocardiographic apical four-chamber view with a colour-coded region of interest for LA strain trace. (*B*) Measurement of LA strain during the reservoir phase (LASr) at end-diastole, as indicated by the arrow.

Therefore, our objective was to evaluate the prognostic significance of LA reservoir strain in patients with MS using a machine learning approach based on decision tree methods and to establish its optimal cut-off values for predicting adverse events.

Methods

Study population

Patients with MS who were referred to a tertiary-care referral centre between 2011 and 2021 were eligible for the study. To be included in the study, patients had to have morphological features indicating rheumatic valvular disease with MS confirmed by transthoracic echocardiography. Patients with mitral prosthesis or non-rheumatic concomitant cardiac diseases, such as ischaemic or degenerative valve disease, were not included. Patients with inadequate echocardiographic imaging for strain analysis and the lack of electrocardiographic data for determining heart rhythm were excluded (*Figure 2*). The date of enrolment was defined as the date on which an echocardiogram with LA measurement was performed.

Patients were classified based on rhythm status [sinus rhythm (SR) or AF] according to their electrocardiogram at enrolment into the study. After the follow-up period, for further analysis, patients were categorized into three groups based on their cardiac rhythm: (i) those in SR at baseline (SR group), (ii) those in persistent AF at baseline (persistent AF group), and (iii) those who were initially in SR but developed AF during the follow-up period (new-onset AF group).

The study protocol was approved by the institutional ethics committee.

Echocardiographic evaluation

A standard transthoracic echocardiogram was performed according to the recommendations of the American Society of Echocardiography[15] using commercially available machines (iE33 and EPIQ7; Philips, Andover, MA, USA). All measurements were performed by two investigators blinded to the clinical data. Echocardiographic views were obtained from the left lateral position.

Left ventricular (LV) global systolic function was measured using the biplane Simpson's method.[15] Right ventricular (RV) systolic function was evaluated using several echocardiographic parameters, including peak systolic velocity at the tricuspid annulus using tissue Doppler imaging, tricuspid annular plane systolic excursion, and RV myocardial performance index. The continuous-wave Doppler tricuspid regurgitant (TR) velocity was used to determine systolic pulmonary artery pressure using the simplified Bernoulli equation.[15]

Mitral inflow was obtained by continuous-wave Doppler echocardiography placing the sample volume between the mitral leaflet tips during diastole. Peak and mean transmitral diastolic pressure gradients were measured from Doppler profiles recorded in the apical four-chamber view. Mitral valve area was measured using planimetry and concurrently calculated using the pressure half-time method. Net atrioventricular compliance (C_n) was also determined non-invasively using Doppler echocardiography.[16,17]

Assessment of LA strain

For LA strain measurements, the LA-focused four-chamber view was obtained by electrocardiogram (ECG)-gated two-dimensional echocardiography, as recomendaded.[18] This analysis provided normal reference values for LA strain across different phases (reservoir, conduit, and contraction).

LA strain parameters were measured offline using QLAB 15 (*Figure 1*) with dedicated LA strain measurement software. The endocardium of the LA was manually traced at end systole with automatic tracking throughout the cardiac cycle using R-to-R gating,[19] which allows automatic detection through software and its applicability to patients with AF.[12] The strain values were derived from the strain curves obtained. The peak strain during the reservoir (LASr), conduit (LAScd), and contractile (LASct) phases was measured.[18]

Clinical outcomes

The primary outcome was the development of new-onset AF, documented on standard 12-lead ECG or 24 h Holter monitor recording in those patients in SR at baseline. A 24 h Holter monitor recording was performed if the patient had symptoms suggestive of AF. The date of enrolment was defined as the date on which an echocardiogram with LA measurement was performed.

The secondary outcome was a composite of cardiovascular death or the need for mitral valve replacement, evaluated in all patients, regardless of whether they were in SR or AF at the time of study enrolment. Follow-up data were obtained at the outpatient clinic basis every 6–12 months or less, according to symptoms or valve disease severity. The present study utilized conditional inference trees to analyse primary and secondary outcomes, which help establish connections between outcome variables and explanatory factors.

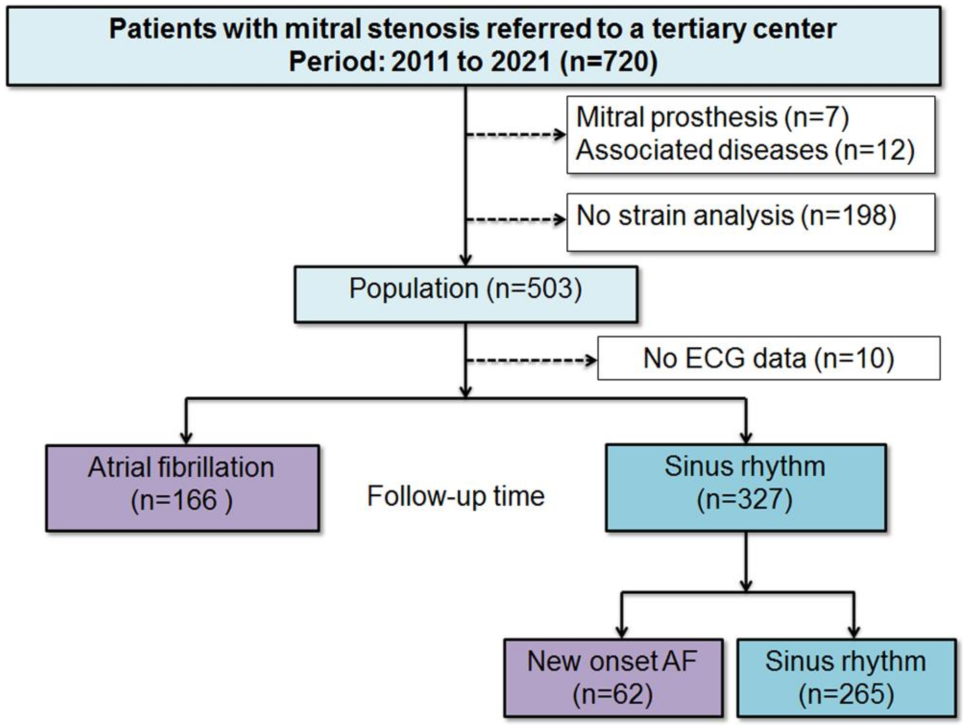


Figure 2 A flow chart of the study population.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as numbers and percentages. For the comparison of three groups, analysis of variance was used when normally distributed and Wilcoxon when not normally distributed. The categorical variables were compared using the χ^2 test.

The primary and secondary outcomes were analysed through conditional inference trees,[20] which allows to determine the relationship between an outcome variable, including primary and secondary outcomes, and a set of explanatory variables with a well-established role in rheumatic MS prognosis. Specifically, key prognostic variables for MS were selected to enter the model: age, New York Heart Association (NYHA) functional class, indexed LA volume, LV ejection fraction, RV function, mitral valve area, pressure gradients, pulmonary artery systolic pressure, net atrioventricular compliance, percutaneous mitral valvuloplasty (PMV), and TR severity.

The original sample (initial node) was divided into two subsamples (nodes) by applying some efficient rule based on the values of the exploratory variables. The composed nodes should be similarly partitioned, looking for discriminate groups.

The remarkable difference between conditional inference trees and other tree-based regression models is that the partitions are based on the statistical significance of appropriate tests, while the other algorithms are not based on inferential background. For a particular node, in the context of conditional inference trees, the first step is identifying the explanatory variable strongly associated with the outcome. Then, the best cut-off value for this variable should be obtained to separate the original node observations into two groups that differ the most in terms of the outcome variable. This implementation utilizes a unified framework for conditional inferences, or permutation tests.[21]

We defined some additional parameters to derive the conditional inference trees. The minimum number of observations in the final nodes was 15, while to admit a partition, the node should have at least 30 sample units. The maximum number of layers for a tree was set at four, and all partitions were based on the 5% significance level. Both adverse cardiovascular events and new-onset AF were analysed by considering the time until the new-onset AF and adverse events (survival trees).

To validate our model, we split the original sample randomly into two parts: 80% for training the model and 20% for validation. Using the training data, we created an inferential conditional tree and then used the validation data for prediction. Assessing the decision tree performance on the validation set, we compared Kaplan–Meier curves for both training and validation samples in each terminal node.

Statistical analyses were performed employing SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) and R 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) using the party and party kit packages[20] available in the R software for statistical computation.[22] All tests were two sided, with a *P*-value <0.05 considered statistically significant.

Reproducibility analysis

Intra- and inter-observer variability was assessed by repeating LASr in 15% of patients randomly selected from the study population in SR, at least 3 months apart by the same investigator and by a second independent investigator. The second round of intra-observer measures was blinded to the results from the initial measures. The reproducibility of these measurements was represented by the intra-class correlation coefficient and the coefficient of variation.

Results

Baseline characteristics of the study population

Out of the initial 720 patients recruited for the study, 503 patients had valid LA strain measurements and were included in the analysis (*Figure 2*). Ten patients were excluded from the analysis due to missing ECG data leaving a final total of 493 patients for the analysis. The demographic, clinical characteristics, and echocardiographic parameters of

Table 1 Baseline characteristics of the study population

Clinical features	
Age (years)	46.4 ± 12.5
Women	412 (84)
Heart rate (bpm)	70.6 ± 13.9
Systolic blood pressure (mmHg)	116 ± 16
Diastolic blood pressure (mmHg)	75 ± 11
NYHA functional Class III/IV	185 (37.2)
Previous embolic events	102 (20.7)
Previous valvuloplasty[a]	159 (32.2)
Anticoagulation therapy	204 (41.4)
Sinus rhythm	327 (66.3)
Atrial fibrillation	166 (33.7)
Echocardiographic data	
LV end-diastolic diameter (mm)	48.4 ± 6.4
LV end-systolic diameter (mm)	31.8 ± 5.7
LV ejection fraction (%)	62 ± 7.9
LA volume (mL/m^2)	62 ± 27
Mitral valve area (cm^2)	1.11 ± 0.4
Mean gradient (mmHg)	10.2 ± 4.9
SPAP (mmHg)	44.7 ± 18.1
RV-FAC (%)	46.1 ± 10.3
TR moderate/severe	82 (16.6)
Net atrioventricular compliance (C_n) (mL/mmHg)	5.1 ± 1.9
LA strain	
LASr (%)	12.5 ± 7.1
LAScd (%)	6.7 ± 4.1
LASct (%)	6.0 ± 4.2

Data are expressed as absolute numbers (percentage) or the mean value ± standard deviation.
FAC, right ventricular fractional area change; LA, left atrial; LAScd, left atrial strain during the conduit phase; LASct, Left atrial strain during the contractile phase; LASr, left atrial strain during the reservoir phase; LV, left ventricular; NYHA, New York Heart Association; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.
[a]Surgical commissurotomy or percutaneous valvuloplasty in the past [85 patients (16.9%) percutaneous valvuloplasty, 58 patients (11.5%) surgical commissurotomy; 16 patients (3.2%) both surgical and percutaneous valvuloplasty].

the study population are presented in *Table 1*. The mean age of the participants was 46.4 ± 12.5 years, with 84% being female. Among the included patients, 37.2% were classified as NYHA functional Class III or IV heart failure symptoms. Additionally, 20.7% had a history of previous embolic events, 41.4% were using anticoagulants, and 32.2% had undergone prior mitral valve intervention.

At baseline, 327 (66.3%) were in SR, while 166 (33.7%) were in AF. Regarding echocardiographic parameters, the mean transmitral valve gradient was 10.2 ± 4.9 mmHg, with a mitral valve area of 1.11 ± 0.4 cm^2. The most of the patients (86%) had severe MS with a valve area ≤1.5 cm^2.

Assessing LA strain, it was found to be impaired in all patients, with a mean LA strain during reservoir phase (LASr) of 12.5 ± 7.1%, LA strain during conduit phase (LAScd) of 6.7 ± 4.1%, and LA strain during contraction phase (LASct) of 6.0 ± 4.2%. For further analysis, patients were categorized into three groups based on their cardiac rhythm: (i) those in SR at baseline (SR group), (ii) those in persistent AF at baseline (persistent AF group), and (iii) those who were initially in SR but developed AF during the follow-up period (new-onset AF group). The characteristics of the study population in terms of new-onset AF, persistent AF, and SR are provided in *Tables 2* and *3*, allowing for a detailed comparison between these groups.

Significant differences were observed among the groups in terms of age, with the persistent AF group having the highest mean age (53.9 years) followed by the new-onset AF group (45.8 years) and the SR group (41.8 years). Furthermore, the proportion of male patients was higher in the AF group compared to the SR group (24 vs. 12%, respectively).

The baseline measurements of heart rate, systolic blood pressure, and diastolic blood pressure were significantly higher in the group with AF at baseline compared to the other groups. As expected, the use of anticoagulation therapy was significantly more common in the AF at baseline group (91%), followed by the new-onset AF group (31%), and much less frequent in the SR group (13%) ($P < 0.001$). There were no significant differences observed among the three groups regarding the NYHA functional class and the presence of right-sided heart failure.

In terms of echocardiographic parameters, the LA volume index (LAVi) was found to be higher in the group of patients with AF at baseline, followed by the new-onset AF group, and the lowest in patients with SR (77.2 ± 34.8 vs. 62.4 ± 22.2 vs. 53.1 ± 16.4, respectively; $P <$ 0.001). Similarly, LA strain parameters, including LASr, LAScd, and LASct, were impaired in all patients, with a gradual reduction across the groups.

Value of LA reservoir strain in predicting new-onset AF

In the subset of 327 patients in SR at enrolment, 62 (19%) developed new-onset AF during the follow-up. In the decision tree analysis to predict new-onset AF including potential variables associated with AF, LASr was identified as the most important predictor of new-onset AF with a cut-off point of 17.9%. In patients with LASr ≤ 17.9%, the occurrence of new-onset AF was 24.3%. On the other hand, in the group with LASr > 17.9%, AF developed in only 4.5% of patients (*Figure 3A*).

For those who had LASr ≤ 17.9%, the LAVi was identified as the second important predictive factor. Specifically, patients with LASr ≤ 17.9% and LAVi > 70.6 mL/m^2 exhibited the worst AF-free survival (*Figure 3B*).

The conditional tree fitted based on the training sample was quite similar to that obtained from the whole sample, with slightly different cut-off values for the predictors (see Supplementary data online, *Figure S1A and B*). Comparing the Kaplan–Meier curves derived from the training and test samples in each terminal node revealed a notable similarity, suggesting that the fitted model was adequate to predict new data.

Value of LA reservoir strain in predicting adverse outcomes

During a mean follow-up period of 3.8 years (range, 0.2–10 years), 125 patients (25%) underwent mitral valve replacement, and 32 patients (6.5%) died. Death or need for valve replacement occurred in 56% of patients with new-onset AF compared with 26% in patients who remained in SR.

At the time of enrolment into the study, patients with severe MS who were eligible for PMV underwent the procedure within a short time frame (<2 months) from the baseline date. Consequently, PMV was considered as an explanatory variable rather than an event in the analysis. This distinction allows for the examination of the impact of PMV on patient outcomes and its association with other variables in the study.

According to the decision tree analysis, age, LASr, TR severity, C_n, and valve intervention were the most important predictors of adverse outcomes (*Figure 4A*). The first variable that provided the best division

Table 2 Clinical characteristics of the study population according to cardiac rhythm at baseline and during the follow-up

Clinical data[a]	SR at baseline ($n = 265$)	AF at baseline ($n = 166$)	New-onset AF ($n = 62$)	*P*-value
Age (years)	41.8 ± 11.6	53.9 ± 10.5	45.8 ± 11.5	<0.001
Women	233 (88)	127 (76)	52 (84)	0.008
Body surface area (m^2)	1.67 ± 0.2	1.74 ± 0.2	1.67 ± 0.2	0.002
NYHA Classes III and IV	96 (36)	64 (39)	21 (34)	0.223
Chest pain	132 (50)	55 (33)	21 (34)	0.001
Right-sided heart failure[b]	59 (22)	43 (26)	15 (24)	0.642
Ischaemic cerebrovascular events[c]	30 (11)	47 (28)	16 (26)	<0.001
Diabetes	1 (0)	7 (4)	2 (3)	0.008
Diuretics	161 (61)	142 (86)	40 (64)	<0.001
β-Blockers	199 (75)	140 (84)	50 (81)	0.045
ACE inhibitors	26 (10)	46 (28)	12 (19)	<0.001
Angiotensin receptor blockers	25 (9)	30 (18)	5 (8)	0.010
Penicillin benzathine	90 (34)	23 (14)	17 (27)	<0.001
Anticoagulation therapy	33 (12)	149 (90)	19 (31)[d]	<0.001
Heart rate (bpm)	69.4 ± 14.1	74 ± 14.3	67.3 ± 10.1	<0.001
Systolic blood pressure (mmHg)	114.2 ± 15.1	120.4 ± 16.2	117.3 ± 16.1	<0.001
Diastolic blood pressure (mmHg)	73.5 ± 10.4	77.4 ± 10.6	76.1 ± 7.1	0.002

ACE, angiotensin-converting inhibitors; AF, atrial fibrillation; SR, sinus rhythm; NYHA, New York Heart Association.
[a]Data are expressed as the mean value ± standard deviation or absolute numbers (percentage).
[b]Clinical syndrome of right heart failure (jugular vein distention, hepatomegaly, ascites, and lower limb oedema).
[c]Stroke or transient ischaemic attack at baseline.
[d]Number of patients on anticoagulation therapy at baseline, before new-onset AF was diagnosed.

Table 3 Echocardiographic characteristics of the study population according to cardiac rhythm

Echocardiographic parameters[a]	SR at baseline ($n = 265$)	AF at baseline ($n = 166$)	New-onset AF ($n = 62$)	*P*-value
LV end-diastolic diameter (mm)	48.0 ± 5.4	49.3 ± 7.9	47.7 ± 6.0	0.075
LV end-systolic diameter (mm)	30.7 ± 4.5	33.8 ± 6.8	30.7 ± 5.1	<0.001
LV ejection fraction (%)	64.1 ± 6.6	57.8 ± 8.4	64.5 ± 7.0	<0.001
LA volume (mL/m^2)	53.1 ± 16.4	77.2 ± 34.8	62.4 ± 22.2	<0.001
Mitral valve area (cm^2)[b]	1.12 ± 0.4	1.12 ± 0.3	1.05 ± 0.4	0.459
Peak gradient (mmHg)	18.8 ± 7.5	17.4 ± 6.1	19.1 ± 8.2	0.105
Mean gradient (mmHg)	10.7 ± 5.4	9.0 ± 3.5	11.1 ± 5.9	0.001
SPAP (mmHg)	44.9 ± 19.6	41.5 ± 12.7	52.8 ± 22.0	<0.001
RV-FAC (%)	47.9 ± 9.6	43.7 ± 9.8	43.6 ± 12.8	<0.001
TAPSE (mm)	19.1 ± 3.5	15.2 ± 4.0	18.1 ± 3.9	0.009
RV systolic annular velocity (cm/s)[c]	11.2 ± 2.0	8.7 ± 1.8	10.6 ± 2.0	<0.001
TR moderate/severe	21 (8)	50 (30)	10 (16)	<0.001
C_n (mL/mmHg)	5.1 ± 2.0	5.0 ± 1.7	5.1 ± 2.4	0.800
LASr (%)	15.7 ± 7.4	7.7 ± 3.9	11.4 ± 5.0	<0.001
LAScd (%)	7.7 ± 4.5	5.2 ± 3.1	6.2 ± 3.5	<0.001
LASct (%)	−8.1 ± 4.2	−2.7 ± 2.0	−5.3 ± 3.1	<0.001

C_n, net atrioventricular compliance; LA, left atrial; LASr, left atrial strain during the reservoir phase; LAScd, left atrial strain during the conduit phase; LASct, left atrial strain during the contractile phase; LV, left ventricular; RV, right ventricular; SPAP, systolic pulmonary artery pressure; RV-FAC, right ventricular fractional area change; TAPSE, tricuspid annular motion; TR, tricuspid regurgitation.
[a]Data are expressed as the mean value ± standard deviation or absolute numbers (percentage).
[b]Mitral valve area measured by planimetry.
[c]Peak systolic velocity at the tricuspid annulus.

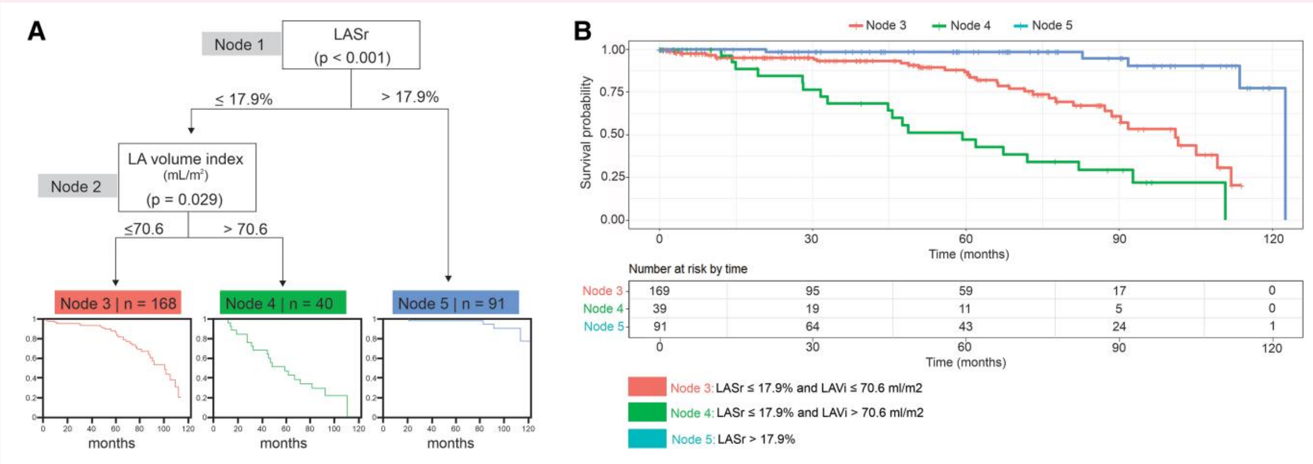


Figure 3 (*A*) A survival conditional inference tree for new-onset AF. LASr was identified as the most important predictor of new-onset AF. For those with LASr ≤ 17.9%, LA volume was a discriminatory variable. (*B*) Estimated survival curves for the final nodes provided by the conditional inference tree for new-onset AF. Node 5 is of patients with LASr > 17.9%, Node 3 is of those with LASr ≤ 17.9% and LAVi ≤ 70.6 mL/m^2, and Node 4 is of those with LASr ≤17.9% and LAVi >70.6 mL/m^2.

of the sample was age, with a cut-off point of 49 years. In patients aged 49 years or younger, LASr emerged as the second discriminatory variable, while in those aged over 49 years, TR severity became the second discriminatory variable.

Within the group of patients aged 49 years or younger and LASr ≤ 12.8%, the decision tree analysis revealed that undergoing successful PMV at enrolment (Node 5) was associated with better event-free survival compared with those who did not undergo the procedure (Node 4). For patients with mild TR, C_n served as a discriminatory variable with a cut-off value of 3.88 mL/mmHg. Within the group of patients with $C_n \leq 3.88$ mL/mmHg, event-free survival was significantly lower compared with the group with $C_n > 3.88$ mL/mmHg.

Overall, Nodes 5, 6, and 10 were identified as the low-risk groups (*Figure 4B*). Low-risk groups according to this decision tree consisted of young patients with LASr > 12.8% (Node 6) or LASr ≤ 12.8% who underwent PMV (Node 5) and those with age >49 years with mild TR and $C_n > 3.88$ mL/mmHg (Node 10). Also, the highest risk group based on this tree consisted of those who had LASr ≤ 12.8% and did not undergo PMV (Node 4), patients with mild TR and low C_n (Node 9), and patients with significant TR (Node 11). *Figure 5* illustrates the LA strain parameters in two patients who had similar LA enlargement and severity of MS at baseline but had different outcomes based on their LA strain values.

The conditional tree derived from the training sample differed slightly from the original tree (see Supplementary data online, *Figure S1C and D*), featuring only five terminal nodes. Yet, the predictors used in both the original and validation models exhibited considerable similarity, notably with C_n emerging as the second discriminating variable among patients over 49 years old. While the Kaplan–Meier curves for the training and test samples showed similarity in most terminal nodes, Nodes 4 and 8 displayed more prominent differences due to the limited number of observations in the test sample predicted by these nodes (10 and 15, respectively), which produces higher variability for the estimation of the survival curves.

Reproducibility analysis

The intra-observer variability of LASr measurements demonstrated a high level of agreement, with an intra-class correlation of 0.94 [95% confidence interval (CI) 0.83–0.97] and a coefficient of variation of 8.4% (95% CI 4.0–12.8%). Similarly, the inter-observer variability showed a strong agreement, with an intra-class correlation of 0.94 (95% CI 0.80–0.98) and a coefficient of variation of 30.4% (95% CI 20.4–40.3%).

Discussion

This study included a large cohort of rheumatic MS to assess the predictors of adverse outcomes using a machine learning approach. Our study showed that LA strain was able to accurately identify patients at high risk for the development of incident AF who may benefit from timely anticoagulation. Additionally, based on the decision tree analysis, LASr played important role in predicting clinical outcomes in young patients, taking into account well-known prognostic variables. Our study expands the understanding of LA strain prognostic implications beyond new-onset AF, incorporating additional clinical outcomes. The decision tree analysis provides insights into how these variables interact and influence patient prognosis, allowing for more targeted risk stratification and potentially guiding treatment decisions.

LA strain has been shown to be a valuable predictor of new-onset AF and other cardiovascular events in various diseases, as highlighted in previous studies.[10,23,24] However, the unique nature of MS sets it apart from other cardiac conditions. In MS, there is a specific increase in LA afterload while having a lesser impact on the LV. The increase in LA afterload, combined with the presence of significant inflammation in the atrial musculature due to rheumatic carditis, results in atrial myocardial fibrosis, electrical inhomogeneity, and abnormal conduction velocities, all of which contribute to an increased risk of developing AF.[13,25] The analysis of LA strain shows different values between AF and SR measurements, with lower strain values seen during AF.[26]

New-onset AF worsens the prognosis of patients with MS as it leads to a sudden increase in atrial pressure, generating pulmonary venous capillary congestion, pulmonary hypertension, and further RV dysfunction. Our findings indicate that death or need for valve replacement occurred in 56% of patients with new-onset AF compared with 26% in patients who remained in SR, despite similar NYHA functional class at baseline. This suggests that the onset of arrhythmia contributes to a worsened prognosis. Additionally, new-onset AF can also lead to the

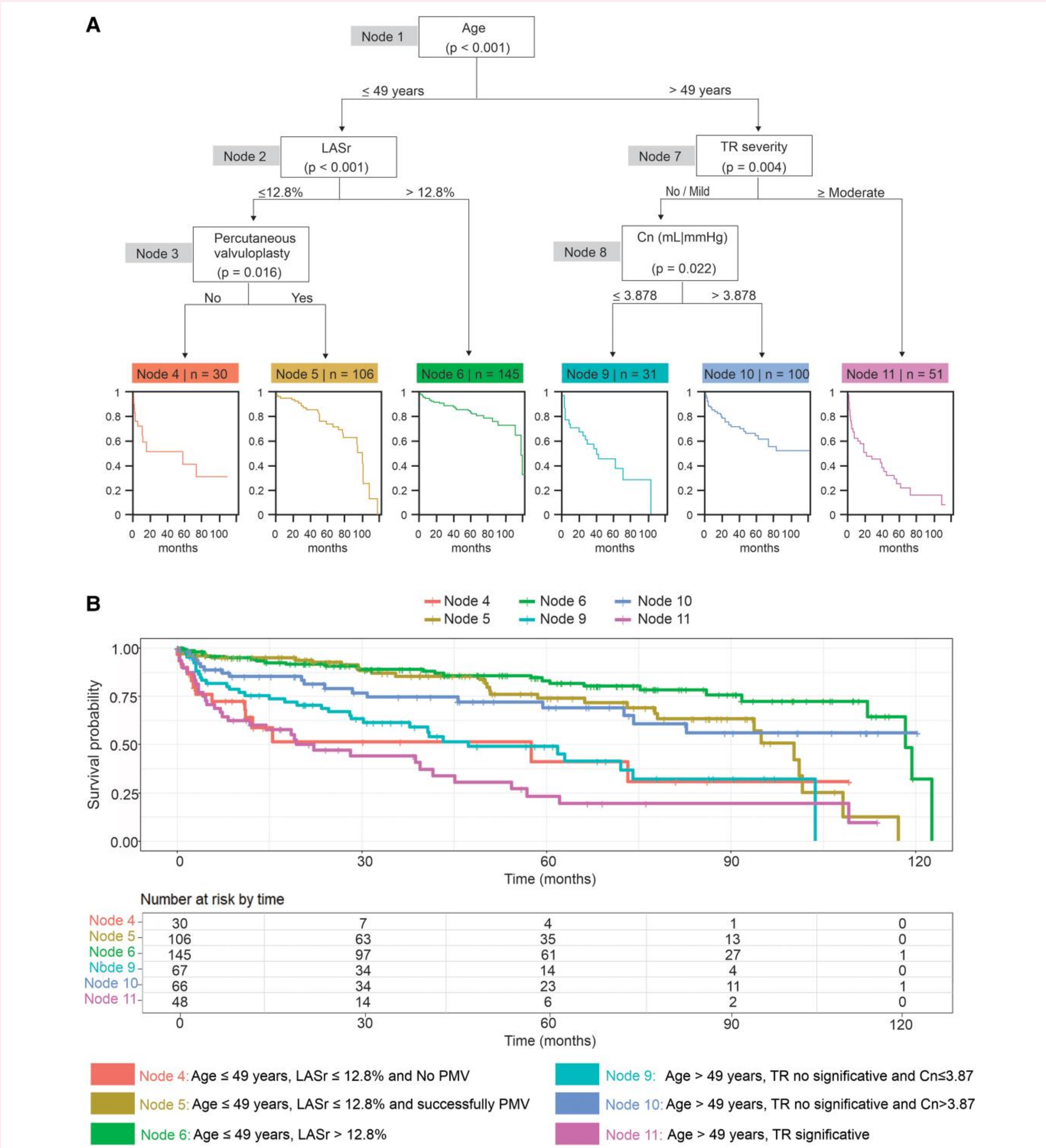


Figure 4 (*A*) A survival conditional inference tree for event-free survival prediction. The first variable, which best divided the sample, was age with a cut-off point of 49 years. (*B*) Estimated survival curves for the final nodes provided by the conditional inference tree for cardiovascular events defined as death or the need of mitral valve replacement.

occurrence of thromboembolic events, particularly in those patients who were not taking oral anticoagulants.

Although previous studies have shown the association of LA strain with new-onset AF, these studies have important limitations, mainly related to small sample sizes and a few events.[13,25] Stassen *et al.*[13] demonstrated that LA strain was a predictor of new-onset AF in a retrospective study where the patients were selected from an echocardiographic database. Ancona *et al.*[27] included 101 patients, with only 20 experiencing new-onset AF, which restricts the appropriate analysis for developing a prediction model. Similarly, Caso *et al.*[25] included 53 asymptomatic patients with mild or

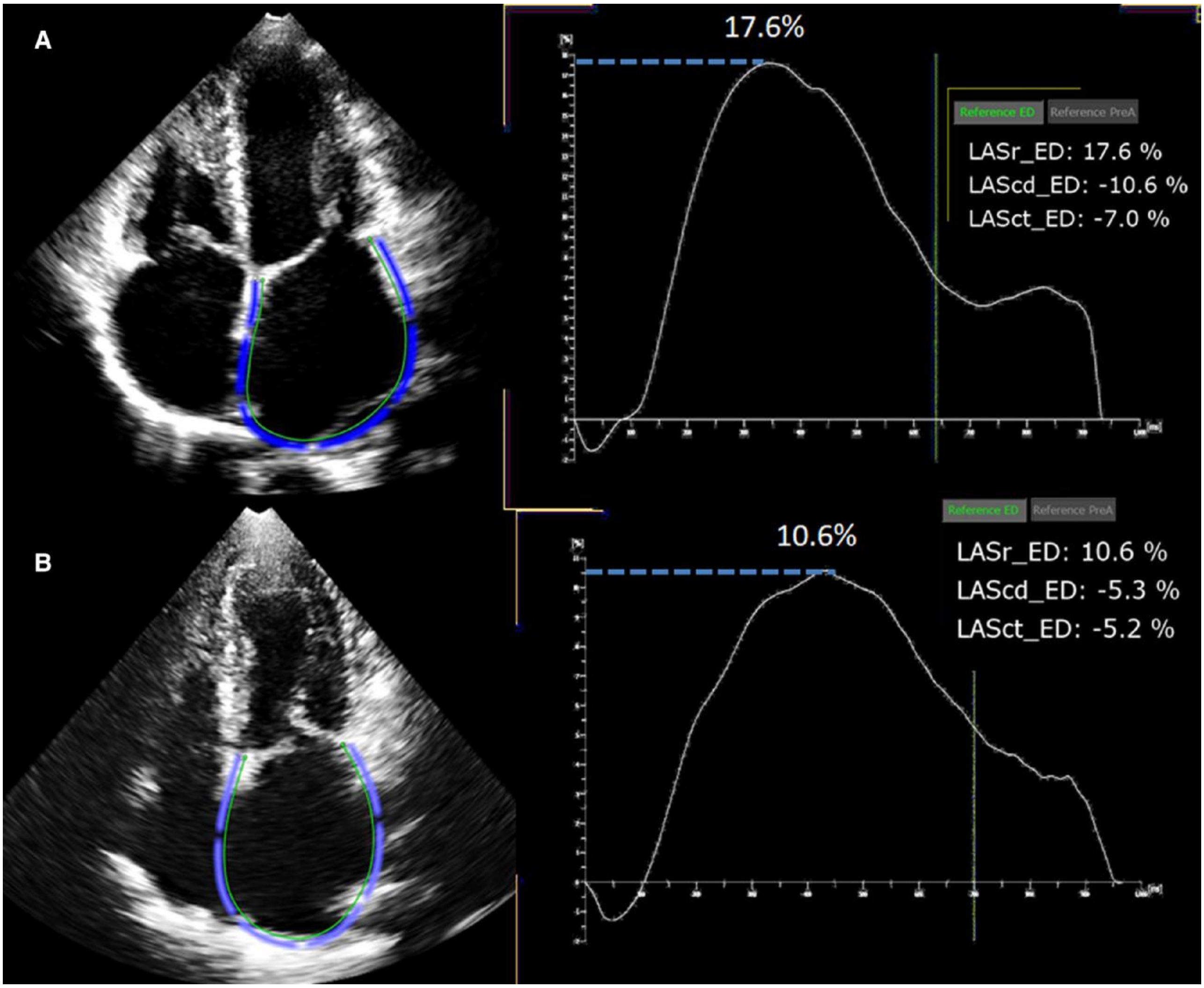


Figure 5 LA strain measurements in two patients with similar LA size and MS severity. (*A*) LA strain in a patient with MS with favourable outcome overtime, without events. (*B*) LA strain in another patient who progressed with a worsening of functional class and underwent mitral valve replacement.

moderate MS, with adverse events occurring in only 22 patients. Other studies in the field either have a retrospective design[14] or cross-sectional design,[28–33] which pose limitations for conducting robust prediction analyses and are susceptible to selection bias.

Our current study contributes substantially to the knowledge in this field by presenting robust evidence of the predictive value of LA strain extending beyond new-onset AF. In our study, including a substantial population with wide spectrum of MS severity, we employed an advanced statistical analysis technique based on the decision tree method through machine learning. This approach enables the identification of predictors for adverse events by categorizing patients into homogeneous groups and exploring interactions among well-established prognostic variables. Furthermore, our study establishes a specific cut-off value for LA strain, predicting not only new-onset AF but also mortality and the necessity for valve replacement. Our findings have clinical relevance, providing valuable insights that can guide decision-making strategies regarding treatment approaches, differing from those presented in the previous studies.

Role of LA strain in predicting events in patients with MS

Accurately identifying risk factors for adverse outcomes in MS is of utmost importance for informed clinical decision-making, particularly considering the availability of various interventional procedures. In our study, we employed the decision tree method to assess the predictors of adverse events. This method allows for the classification of patients into homogenous categories based on their observed characteristics, facilitating the exploration of interactions between variables, and enabling the identification of subgroups of patients at different risks of adverse events. The decision tree method is a powerful tool that can effectively uncover nonlinear relationships and interactions between variables.

Impaired LA reservoir capacity, as specified by reduced LA strain, may reflect atrial myocardial fibrosis, and increased atrial stiffness, which in turn predicts the development of symptoms and subsequent cardiovascular events. Nevertheless, early PMV alters the typical progression of the disease in patients with diminished LA strain by increasing LA compliance, hence improves LA function. Our previous study provided evidence that this improvement in LA compliance played a crucial role in predicting functional status at the 6-month follow-up, independent of other haemodynamic data.[34]

In contrast, in older patients with long-standing disease, the severity of TR emerged as the most prominent prognostic variable. Previous studies have consistently linked the presence of significant TR with increased mortality,[35,36] regardless of the severity of MS, pulmonary pressure, or RV dysfunction.[37] Severe TR can persist even after PMV intervention, contributing to progressive RV dysfunction and a poor prognosis.[38] In patients without significant TR, C_n emerged as a crucial predictor of adverse events. LA compliance plays a significant role in determining the overall severity of MS and serves as a powerful predictor of death and other clinical outcomes. Low C_n is a key determinant of pulmonary hypertension and contributes to progressive RV remodelling, which further exacerbates TR. Our findings indicate that C_n has the highest discriminatory power in patients without significant TR. In this subset of patients, C_n modulates the impact of obstruction on the pulmonary vasculature, playing a major role in disease progression before the development of severe RV remodelling and significant TR. This highlights the role of C_n in early disease stages and its contribution to the pulmonary vasculature response to obstruction.

There is a growing recognition of the significance of LA function as a prognostic determinant in various cardiovascular diseases. While LA volume has been extensively studied as a predictor of cardiovascular risk, its utility in the setting of MS is limited due to common LA enlargement resulting from increased atrial pressure, which is a marker of disease severity. However, impairment of LA reservoir function, primarily governed by atrial compliance, can be detected early using LA strain. This measurement provides valuable information about the contractile and relaxation properties of the LA, reflecting its ability to accommodate blood during ventricular systole and refill during ventricular diastole.

Study limitations

The study has some limitations. First, despite a comprehensive follow-up for new-onset AF, the absence of continuous ECG monitoring may have led to missed cases of asymptomatic AF. However, given that diastolic filling time is significantly reduced with new-onset AF, it is unlikely that many patients with significant MS would have remained asymptomatic. Secondly, the LA images in which the atrial strain was measured were not recorded specifically for performing the LA strain in terms of orientation, depth, gain, and frame rate. Nevertheless, strain computation was feasible in 87% of echocardiograms. There is variability in strain measurement, a lack of standardization between vendors, and few dedicated atrial strain packages. This study was conducted at a single reference centre, and therefore, the results may not be generalizable to the overall population. Further studies are needed to validate the optimal cut-off value in predicting new-onset AF and adverse cardiovascular outcomes in an MS population.

Clinical implications

The pathophysiology of rheumatic MS predominantly depends on the LA function, where pressure overload induces both anatomical and functional changes that ultimately lead to atrial dysfunction. Assessing LA strain is useful for early diagnosis of impaired reservoir function, indicating increased atrial stiffness and thereby improving risk stratification. In a large cohort of patients with a broad range of MS severity, LA strain adds value to current prognostic factors. Reduced LA reservoir strain is the major predictor of mortality and the need for valve replacement, in addition to new-onset AF. Using decision tree analysis, our study establishes a precise threshold value for LA strain and provides clinical insights for guiding patient care strategies, specifically in determining the need for anticoagulant treatment and timely valve intervention.

Conclusion

In a large cohort of patients with a range of MS severity, LA strain emerged as a significant predictor of cardiovascular events using decision tree analysis. Patients were categorized as low or high risk for unfavourable outcomes based on characteristics such as LASr, age, TR severity, and net atrioventricular compliance. The use of a machine-based decision tree technique revealed its potential for improving risk stratification in patients with MS, giving useful insights for therapeutic decision-making in this population.

Supplementary data

Supplementary data are available at *European Heart Journal – Imaging Methods and Practice* online.

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Consent

The written informed consent was obtained from all patients at the time of enrolment into the study.

Conflict of interest: None declared.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

F.d.A.F. and L.M.T.C. performed the measurements and wrote the first draft of the manuscript. W.A.M.E., M.C.P.N., J.H., and R.A.L. conceived the study. All authors contributed to the analysis of results and reviewed and approved the final manuscript.

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