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Left Atrial Reservoir Function and Outcomes in Secondary Mitral Regurgitation



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Background: Left atrial (LA) size is a marker of disease severity and is related to worse outcomes in secondary mitral regurgitation (MR). The prognostic value of LA function assessed by LA reservoir strain (LARS), however, remains unknown. The aim of this study was to investigate the prognostic implications of LARS in patients with significant secondary MR.

Methods: LARS was evaluated using speckle-tracking echocardiography in patients with more than mild (grade ≥ 2) secondary MR. The population was divided into two groups according to the median LARS value (9.8%). The primary end point was all-cause mortality.

Results: A total of 666 patients (mean age, 66 ± 11 years; 68% men) were included. On multivariable analysis, more severe MR was independently associated with more impaired LARS (LARS $< 9.8\%$; odds ratio, 0.419; 95% CI, 0.249-0.704; $P = .001$). During a median follow-up period of 5 years (interquartile range, 2-10), 383 patients (58%) died. Patients with LARS $< 9.8\%$ had significantly lower survival rates at 1-, 2-, and 5-year follow-up (85%, 70%, and 45%, respectively) compared with patients with LARS $\geq 9.8\%$ (96%, 93%, and 78%, respectively; $P < .001$). After multivariable adjustment (including LA volume and left ventricular global longitudinal strain), more preserved LARS ($\geq 9.8\%$; hazard ratio, 0.499; 95% CI, 0.386-0.645; $P < .001$) was independently associated with lower all-cause mortality. LARS provided incremental prognostic value over LA volume and left ventricular global longitudinal strain.

Conclusions: LARS is independently associated with all-cause mortality in patients with significant secondary MR and has incremental prognostic value over LA volume and left ventricular global longitudinal strain. LARS may improve risk stratification of patients with secondary MR. (*J Am Soc Echocardiogr* 2022;35:477-85.)

Keywords: Secondary mitral regurgitation, Left atrium, Left atrial reservoir strain, Mortality

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Significant secondary mitral regurgitation (MR) is frequently observed in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF)¹ and is strongly associated with decreased quality of life and increased risk for HF hospitalization and all-cause mortality.^{2,3} Significant efforts have been undertaken to reduce MR severity and improve long-term prognosis.⁴⁻⁶ Recent results of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated that percutaneous edge-to-edge repair may improve outcomes in selected patients with secondary MR.⁵ Still, almost half of the patients who underwent transcatheter mitral valve repair were hospitalized for HF or died within 2 years after therapy.⁵ These results emphasize the need for further research to improve risk stratification and timing of intervention in these patients. Although current research has mainly focused on left ventricular (LV) systolic dysfunction to risk-stratify patients with secondary MR,^{3,7,8} MR-associated remodeling affects the not only left ventricle but also the left atrium.^{9,10} The left atrium plays an important role in HF by modulating LV cardiac output (augmenting LV preload), preventing pulmonary congestion (by buffering pressure oscillations between the left ventricle and pulmonary vasculature), and helping prevent sodium retention and volume overload (by regulating the secretion of atrial natriuretic peptide).¹¹ Left

Abbreviations

AF = Atrial fibrillation
COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation
GLS = Global longitudinal strain
HF = Heart failure
HR = Hazard ratio
IQR = Interquartile range
LA = Left atrial
LARS = Left atrial reservoir strain
LAVi = Left atrial volume index
LV = Left ventricular
LVEF = Left ventricular ejection fraction
MR = Mitral regurgitation

atrial (LA) reservoir function, measured using speckle-tracking echocardiography, is an important prognostic marker in patients with HF with reduced LVEF, showing incremental prognostic value over LA volume.¹² However, the prognostic implications of LA reservoir function in patients with secondary MR have not been thoroughly evaluated. Accordingly, the aim of the present study was to investigate the association between LA reservoir strain (LARS), measured using speckle-tracking echocardiography, and long-term outcomes in a large cohort of patients with moderate to severe secondary MR.

METHODS**Patient Population**

Patients who presented between January 2000 and December 2018 with moderate to severe secondary MR at the Leiden University Medical Center in the Netherlands were retrospectively identified. Secondary MR was defined as MR resulting from an alteration in LV geometry (i.e., dilated left ventricle with tethering of both leaflets or isolated inferobasal myocardial infarction leading to posterior leaflet tethering) with structurally normal valve leaflets and chordae. The first echocardiogram obtained with the patient in a hemodynamically stable state and showing moderate to severe secondary MR defined the time point of entry in the analysis. Both patients with ischemic and those with nonischemic HF were included. An ischemic etiology was defined by the presence of significant coronary artery disease on invasive coronary artery angiography. Patients with previous mitral valve interventions, mixed etiology (i.e., primary and secondary MR), and echocardiographic data that were not analyzable using two-dimensional speckle-tracking echocardiography were excluded. All patients underwent complete clinical and echocardiographic evaluation at the time of the first echocardiographic examination. Patient information was prospectively collected in the departmental cardiology information system (EPD-Vision; Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. Clinical data included demographic characteristics, cardiovascular risk factors, comorbidities, etiology of HF, New York Heart Association functional class, and medications. Mitral valve intervention at follow-up included surgical therapy (i.e., mitral valve repair, mitral valve replacement) and percutaneous edge-to-edge mitral valve repair. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for written patient informed consent.

Echocardiography

All patients underwent transthoracic echocardiography in the left lateral decubitus position using commercially available ultrasound

equipment (Vivid 7 and E9; GE-Vingmed Ultrasound, Horten, Norway). Electrocardiographically triggered echocardiographic data were stored digitally in cine-loop format for offline analysis using EchoPAC version 203 (GE Medical Systems, Little Chalfont, United Kingdom). LV volumes, LVEF, and LA volumes were measured using the biplane Simpson method and indexed to body surface area.¹³ Using Doppler tissue imaging of the mitral annulus in the apical four-chamber view, e' was measured at both the lateral and septal sides and averaged to calculate the E/e' ratio for estimation of LV filling pressures.¹⁴ Peak systolic pulmonary artery pressure was derived from the peak velocity of the tricuspid regurgitant jet according to the Bernoulli equation, adding right atrial pressure (estimated according to the inspiratory collapse and diameter of the inferior vena cava).¹³ For the evaluation of right ventricular systolic function, anatomical M-mode was applied to the focused apical four-chamber view of the right ventricle to measure tricuspid annular plane systolic excursion.¹³ MR severity was graded according to current recommendations using an integrative approach that includes qualitative, semi-quantitative, and quantitative data and was graded on a four-point scale: mild (grade 1), moderate (grade 2), moderate to severe (grade 3), and severe (grade 4).¹⁵ Significant MR was defined by a grade of $\geq 2+$. Speckle-tracking LV global longitudinal strain (GLS) was averaged from 17 LV segments and measured from apical views (two-, three-, and four-chamber).¹⁶ The region of interest was traced manually and adjusted to the myocardial thickness. LA speckle-tracking strain was measured in the apical four-chamber view, with the onset of the QRS complex used as the zero-reference point.^{17,18} Original digitized echocardiographic data were reanalyzed by one of the authors (J.S.), blinded to clinical outcome. The endocardium of the LA wall was traced manually and corrected by adjusting the region of interest or the width of the contour, excluding the pulmonary vein ostia and LA appendage. LARS was measured directly from the LA strain-versus-time curve. LARS was chosen over LA conduit strain and LA contractile strain because it shows a good correlation with LA wall fibrosis on cardiac magnetic resonance imaging¹⁹ and can be measured in patients with atrial fibrillation (AF).¹⁷ Both LV GLS and LARS are represented as absolute (i.e., positive) values.

Clinical End Points

Patients were followed up for the primary end point of all-cause mortality. Data on mortality were obtained from the departmental cardiology information system (EPD-Vision), which is linked to the governmental death registry database. Follow-up data were complete for all patients.

Statistical Analysis

Continuous variables are reported as mean \pm SD when normally distributed and as median (interquartile range [IQR]) when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Continuous variables were compared using the independent-samples Student's t test when normally distributed, and the Mann-Whitney U test was used to compare continuous variables that did not adhere to a normal distribution. Categorical variables were compared using the Fisher exact test. The inter- and intraobserver variability of LARS measurements was assessed by calculating the intraclass correlation coefficient on 20 randomly selected patients. The intraclass correlation coefficients for inter- and intraobserver variability were 0.92 (95% CI, 0.85-0.97; $P < .001$) and 0.94 (95% CI, 0.87-0.98; $P < .001$), respectively.

HIGHLIGHTS

- LARS is associated with MR severity in patients with more than mild secondary MR.
- LARS is associated with mortality in patients with more than mild secondary MR.
- LARS provides incremental prognostic value over LA volume and LV GLS.

The association between MR severity and LARS was evaluated using logistic regression analysis including as independent variables clinical and echocardiographic parameters associated in the univariable analysis with P values < 0.05 . Patients were divided into two groups according to the median value of LARS (9.8%) and into three groups according to LARS tertiles. In a subsequent analysis, patients were divided into four groups according to the median value of LARS (9.8%) and a history of AF (group 1, LARS $\geq 9.8\%$ and no AF; group 2, LARS $\geq 9.8\%$ and AF; group 3, LARS $< 9.8\%$ and no AF; group 4, LARS $< 9.8\%$ and AF). Patients were also divided into four groups according to the median value of LARS (9.8%) and the median value of LA volume index (LAVi; 50 mL/m²; group 1, LARS $\geq 9.8\%$ and LAVi < 50 mL/m²; group 2, LARS $\geq 9.8\%$ and LAVi ≥ 50 mL/m²; group 3, LARS $< 9.8\%$ and LAVi < 50 mL/m²; group 4, LARS $< 9.8\%$ and LAVi ≥ 50 mL/m²). Changes in hazard ratio (HR) for all-cause mortality across LARS values (as a continuous variable) were investigated by fitting a spline curve. Cumulative survival rates for all-cause mortality were estimated using the Kaplan-Meier method, and differences between groups were analyzed using the log-rank test. Uni- and multivariable analyses of time to events were performed using Cox proportional-hazard models with LARS as an independent variable (as a continuous and as a categorical variable). The occurrence of surgical or transcatheter mitral valve repair or replacement was entered as a time-dependent covariate. The HR and 95% CI were calculated and reported. In the univariable analysis, variables with P values < 0.05 were considered statistically significant and entered in the multivariable model. To investigate the incremental value of LARS over clinical and conventional echocardiographic parameters to predict outcome, a likelihood ratio test was performed. The change in global χ^2 value was calculated and reported. A two-tailed P value $< .05$ was considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows version 25.0 (IBM, Armonk, NY).

RESULTS

Patient Population

A total of 666 patients (mean age, 66 ± 11 years; 68% men) were included (Supplemental Figure 1). Baseline clinical and echocardiographic characteristics are shown in Table 1. The majority of patients ($n = 473$ [71%]) were in New York Heart Association functional class III or IV, and 348 patients (52%) had ischemic HF. Most of the patients had grade 3 to 4 MR ($n = 545$ [82%]). Mean LVEF was $29 \pm 11\%$, median LV GLS was 7.2 (IQR, 5.2%-9.9%), and median LARS was 9.8% (IQR, 6.6%-14.5%). There were 329 patients with LARS $< 9.8\%$ and 337 with LARS $\geq 9.8\%$. Patients with LARS $< 9.8\%$ were older, were more often male, were more symptomatic (according to New York Heart Association functional class), had higher body surface areas, more often had AF, had more impaired

renal function, and more often had undergone cardiac resynchronization therapy at baseline. In addition, patients with LARS $< 9.8\%$ had larger LA volumes, more impaired LVEFs and LV GLS, more severe MR with higher pulmonary artery pressures, and more impaired right ventricular systolic function.

Independent Association between MR Severity and LARS

Table 2 summarizes the results of the uni- and multivariable logistic regression analyses to assess the association between MR severity and LARS as a categorical variable (i.e., LARS $< 9.8\%$ vs LARS $\geq 9.8\%$). On multivariable analysis, more severe MR was independently associated with more impaired LARS (odds ratio, 0.419; 95% CI, 0.249-0.704; $P = .001$).

LARS in Secondary MR: Prognostic Implications

During a median follow-up period of 5 years (IQR, 2-10 years), 383 patients (58%) died. In 278 patients (42%), mitral valve intervention was performed after a median follow-up duration of 2 months (IQR, 0-4 months). Of these 278 patients who underwent mitral valve intervention, 182 (65%) had surgical mitral valve repair, three (1%) had surgical mitral valve replacement, and 93 (33%) underwent percutaneous edge-to-edge mitral valve repair. There was no difference in the percentage of patients with LARS $\geq 9.8\%$ undergoing mitral valve intervention at follow-up compared with patients with LARS $< 9.8\%$ (40% vs 43%, $P = .488$). Patients with LARS $< 9.8\%$ experienced significantly higher mortality rates compared with those with LARS $\geq 9.8\%$ (85%, 70%, and 45% vs 96%, 93%, and 78% at 1-, 2-, and 5-year follow-up, respectively; $P < .001$; Figure 1). The Kaplan-Meier curve for time to cumulative survival according to tertiles of LARS is shown in Supplemental Figure 2. In addition, Kaplan-Meier curve analysis was performed when dividing the population into four groups according to LARS and history of AF (Figure 2A), demonstrating significantly higher cumulative mortality rates in patients with more impaired LARS ($P < .001$). Particularly for patients with LARS $< 9.8\%$ (groups 3 and 4), significantly higher event rates were observed compared with patients with LARS $\geq 9.8\%$ (groups 1 and 2), independent of a history of AF ($P < .001$ for all), demonstrating the importance of LARS assessment, despite the presence of AF. Kaplan-Meier curve analysis was also performed by dividing the population into four groups according to LARS and LAVi (Figure 2B), again demonstrating significantly higher cumulative mortality rates in patients with more impaired LARS ($P < .001$). Particularly for patients with LARS $< 9.8\%$ (groups 3 and 4), significantly higher event rates were noted compared with patients with LARS $\geq 9.8\%$ (groups 1 and 2), independent of LA volume ($P < .001$ for all), demonstrating the importance of LARS assessment, even when taking LAVi into account. To investigate the association between LARS as a continuous variable and all-cause mortality, a spline-curve analysis was performed, showing the HR for the occurrence of all-cause mortality at follow-up according to LARS (Supplemental Figure 3). Of interest, the curve showed that the predicted HR for all-cause mortality was ≥ 1 at a LARS threshold value of $\pm 10\%$ (which is close to the median value of 9.8%). A Cox proportional-hazards model was constructed with LARS introduced as a continuous variable. On multivariable analysis, age (HR, 1.029; 95% CI, 1.017-1.042; $P < .001$), New York Heart Association functional class III or IV (HR, 1.404; 95% CI, 1.084-1.819; $P = .010$), serum creatinine (HR, 1.006; 95% CI, 1.004-1.008; $P < .001$), MR grade 3 (HR, 2.384; 95% CI, 1.639-3.468; $P < .001$) and grade 4 (HR, 2.665; 95% CI,

Table 1 Baseline clinical and echocardiographic characteristics

Variable	Overall study population	LARS < 9.8%	LARS ≥ 9.8%	P
	(N = 666)	(n = 329)	(n = 337)	
Age, y	66.2 ± 10.8	67.1 ± 10.4	65.4 ± 11.2	.041
Sex, male	452 (67.9)	250 (76.0)	202 (59.9)	<.001
BSA, m ²	1.92 ± 0.21	1.95 ± 0.21	1.90 ± 0.21	.004
Arterial hypertension	262 (39.3)	128 (38.9)	134 (39.8)	.821
Diabetes mellitus	155 (23.3)	85 (25.8)	70 (20.8)	.122
AF	274 (41.1)	179 (54.4)	95 (28.2)	<.001
COPD	76 (11.4)	47 (14.3)	29 (8.6)	.021
Creatinine level, mmol/L	101 (83-134)	110 (90-143)	95 (79-121)	<.001
NYHA functional class III or IV	473 (71.0)	255 (77.5)	218 (64.7)	<.001
Ischemic etiology of HF	348 (52.3)	162 (49.2)	186 (55.2)	.124
Previous CRT device implantation	59 (8.9)	37 (11.2)	22 (6.5)	.032
β-blocker	464 (69.7)	213 (64.7)	251 (74.5)	.006
ACE inhibitor/ARB	542 (81.4)	251 (76.3)	291 (86.4)	.001
Diuretic	557 (83.6)	290 (88.1)	267 (79.2)	.002
LVEDVi, mL/m ²	107 ± 41	107 ± 41	106 ± 42	.615
LVESVi, mL/m ²	79 ± 37	80 ± 37	77 ± 37	.187
LVEF, %	28.5 ± 10.5	26.8 ± 10.0	30.2 ± 10.7	<.001
LV GLS, %	7.2 (5.2-9.9)	6.2 (4.3-8.5)	8.2 (6.3-11.0)	<.001
MR grade				.001
2	121 (18.2)	42 (12.8)	79 (23.4)	<.05
3	293 (44.0)	148 (45.0)	145 (43.0)	NS
4	252 (37.8)	139 (42.2)	113 (33.5)	<.05
Vena contracta, mm	6.0 (5.0-7.0)	6.0 (5.0-7.0)	5.0 (4.0-6.0)	.003
E/e' ratio	20 (15-27)	22 (16-30)	19 (14-27)	.002
PASP, mm Hg	40 ± 13	43 ± 13	37 ± 13	<.001
TAPSE, mm	16 ± 5	15 ± 5	17 ± 4	<.001
LAVi, mL/m ²	55 ± 25	62 ± 26	48 ± 28	<.001
LARS, %	9.8 (6.6-14.5)	6.6 (4.7-8.1)	14.2 (11.7-18.8)	<.001

Data are expressed as mean ± SD, number (percentage), or median (interquartile range). Bold values indicates statistical significant.

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BSA, body surface area; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; LVEDVi, LV end-diastolic volume index; LVESVi, LV end-systolic volume index; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

1.799-3.948; $P < .001$), LV GLS (HR, 0.957; 95% CI, 0.919-0.997; $P = .037$), and LARS (HR, 0.953; 95% CI, 0.930-0.975; $P < .001$) were independently associated with all-cause mortality (Table 3). When LARS was introduced as a categorical variable (i.e., LARS ≥ 9.8%), it remained independently associated with all-cause mortality (HR, 0.499; 95% CI, 0.386-0.645; $P < .001$), whereas LV GLS did not (Supplemental Table 1). The association also remained significant when LARS was entered as tertiles into the multivariable analysis (HR, 0.737 [95% CI, 0.569-0.956; $P = .021$] for tertile 2; HR, 0.504 [95% CI, 0.363-0.699; $P < .001$] for tertile 3; Supplemental Table 2). The Kaplan-Meier curves for time to cumulative survival according to the subgroup of patients who underwent surgical or percutaneous intervention are shown in Supplemental Figure 4. On multivariable analysis, adjusting for the same covariables used in Table 3 (except mitral valve intervention), LARS remained independently associated with outcome (HR, 0.902; 95% CI, 0.852-0.955; $P < .001$). There was no interaction between the type of intervention (surgical vs percutaneous) and LARS with outcome ($P = .270$).

Incremental Prognostic Value of LARS for All-Cause Mortality

To determine the incremental prognostic value of LARS (as a continuous variable) over other clinical and echocardiographic parameters, a likelihood ratio test was performed. The addition of LAVi to the baseline model showed no significant increase in the χ^2 value ($P = .138$). However, the addition of LARS to the model showed a significant increase in the χ^2 value (χ^2 difference = 11.1, $P < .001$), demonstrating the incremental prognostic value of LARS in patients with secondary MR (Figure 3). The likelihood ratio test with LAVi and LARS entered as categorical variables is shown in Supplemental Figure 5.

DISCUSSION

The main findings of the present study can be summarized as follows: (1) LARS is independently associated with MR severity in patients

Table 2 Parameters associated with LARS as a categorical variable (i.e., LARS < 9.8% vs ≥ 9.8%) in patients with significant secondary MR

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.985 (0.971-0.999)	.042	0.998 (0.979-1.017)	.821
Male sex	0.473 (0.339-0.660)	<.001	0.569 (0.377-0.857)	.007
Arterial hypertension	1.037 (0.760-1.415)	.821		
Diabetes mellitus	0.753 (0.525-1.080)	.123		
Serum creatinine	0.993 (0.990-0.997)	<.001	0.999 (0.995-1.003)	.628
Ischemic cardiomyopathy	1.268 (0.931-1.726)	.132		
AF	0.329 (0.239-0.454)	<.001	0.337 (0.222-0.510)	<.001
LV GLS	1.188 (1.132-1.247)	<.001	1.245 (1.176-1.319)	<.001
PASP	0.967 (0.955-0.980)	<.001	0.977 (0.962-0.991)	.002
LAVi	0.968 (0.957-0.978)	<.001	0.976 (0.965-0.988)	<.001
MR severity	0.424 (0.276-0.653)	<.001	0.419 (0.249-0.704)	.001

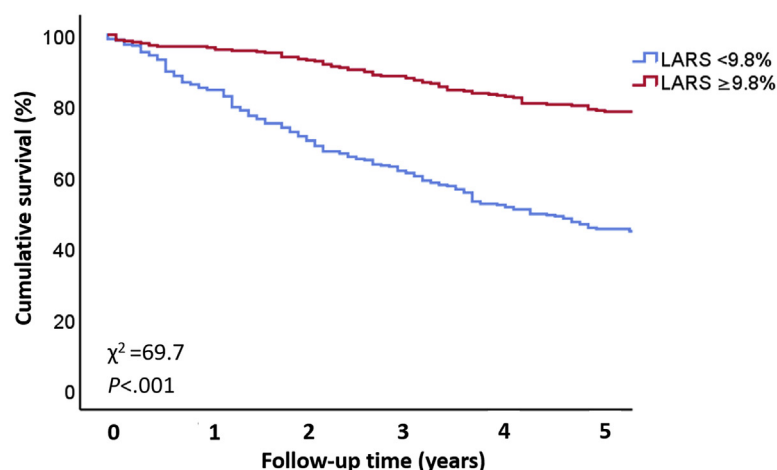
OR, Odds ratio; PASP, pulmonary artery systolic pressure.
Bold values indicates statistical significant.

with at least moderate secondary MR, (2) LARS is independently associated with all-cause mortality in patients with significant secondary MR; and (3) LARS provides incremental prognostic value over LA volume and markers of LV systolic function (LVEF and LV GLS) for long-term survival.

LA Remodeling in Secondary MR

Significant secondary MR is frequently observed in patients with HF and reduced LVEF, with a prevalence of up to 55%.¹ In these patients, secondary MR occurs as a complication of mitral annular dilatation and tethering of the mitral valve leaflets caused by displacement of the papillary muscles due to LV geometric distortion and dilatation.²⁰ The effects of additional volume overload on an already failing left

ventricle can be deleterious, as it increases diastolic wall stress and accelerates the process of LV adverse remodeling with progressive LV dilatation and failure.^{21,22} However, MR-associated cardiac remodeling affects not only the left ventricle but also the left atrium,^{9,10} and assessment of LA function may help better understand the pathophysiologic consequences of secondary MR in patients with HF. In patients with HF and reduced LVEF, LA afterload is increased because of the concomitant presence of LV diastolic dysfunction (i.e., an increase in LV end-diastolic pressure). Significant secondary MR imposes an additional volume overload on the thin-walled left atrium, thereby accelerating LA remodeling.^{23,24} Previous studies have demonstrated that the extent of LA remodeling provides a reliable estimate of the regurgitant volume in MR.²⁵ LA remodeling is also accompanied by a range of maladaptive processes that finally lead



Number at risk						
	0	1	2	3	4	5
— LARS <9.8%	329	278	231	201	162	138
— LARS ≥9.8%	337	325	312	293	261	231

Figure 1 Kaplan-Meier curve for time to cumulative survival, according to LARS. Time to all-cause mortality according to baseline LARS < 9.8% (blue) versus LARS ≥ 9.8% (red).

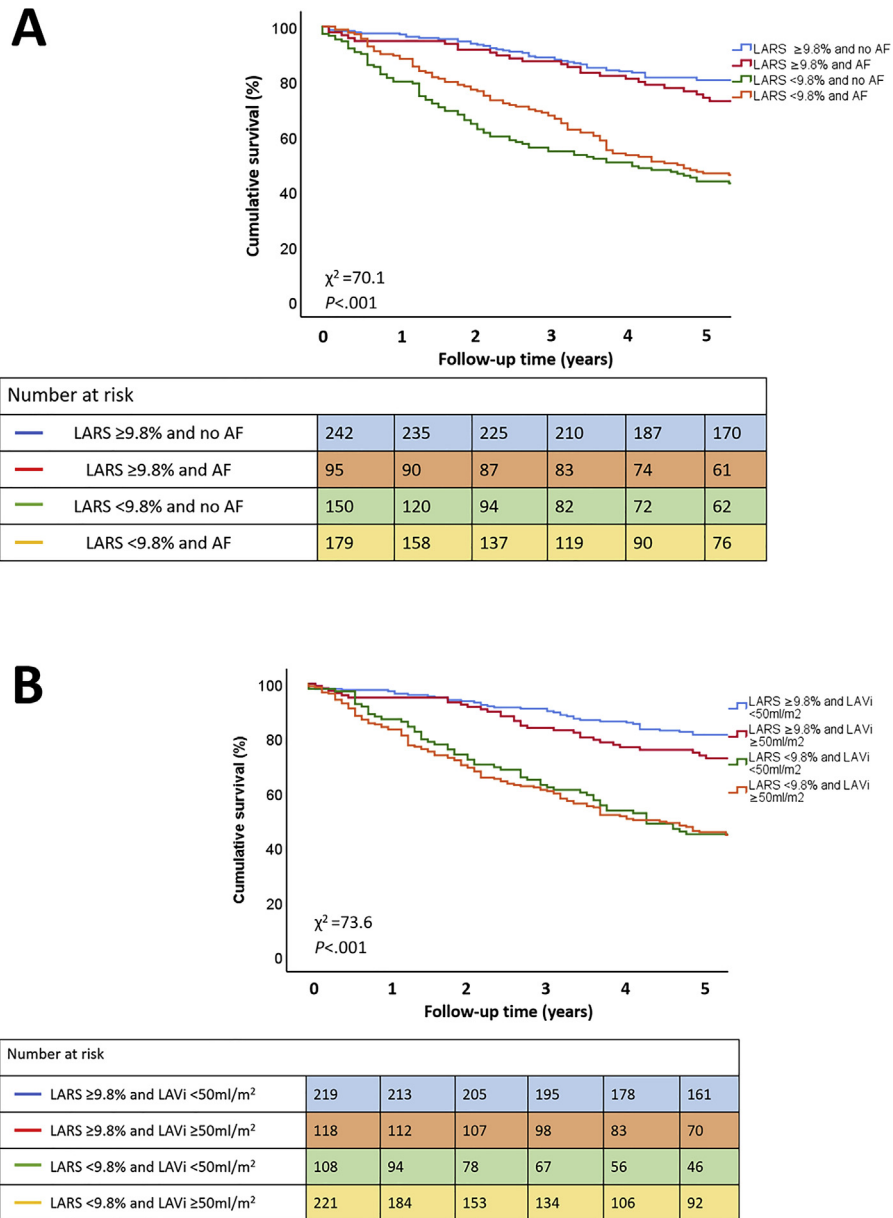


Figure 2 Kaplan-Meier curve for time to cumulative survival, according to **(A)** LARS and presence of AF and **(B)** LARS and LAVi. **(A)** Time to all-cause mortality, according to baseline LARS and presence of AF: LARS ≥ 9.8% and no AF (blue curve), LARS ≥ 9.8% and AF (red curve), LARS < 9.8% and no AF (green curve), and LARS < 9.8% and AF (orange curve). **(B)** Time to all-cause mortality, according to baseline LARS and LAVi: LARS ≥ 9.8% and LAVi < 50 mL/m² (blue curve), LARS ≥ 9.8% and LAVi ≥ 50 mL/m² (red curve), LARS < 9.8% and LAVi < 50 mL/m² (green curve), and LARS < 9.8% and LAVi ≥ 50 mL/m² (orange curve).

to interstitial fibrosis of the atrial wall,²⁶⁻²⁸ causing a progressive reduction in LA compliance.²⁸ Because the left atrium functions as a buffer between the left ventricle and the pulmonary vasculature, reduced LA compliance unfavorably increases the pulsatile load on the pulmonary circulation, leading to pulmonary hypertension and right ventricular–pulmonary arterial uncoupling.^{29,30} Moreover, reduced LA compliance decreases LV preload and therefore LV cardiac output.³¹ The left atrium also has an important endocrine function,³¹ and previous studies have demonstrated that synthesis of atrial natriuretic peptide becomes disrupted in parallel with LA fibrosis, leading to sodium retention and volume overload in patients with HF.¹¹ Finally, atrial remodeling enhances the risk for developing

atrial arrhythmias,³² which have been associated with worse outcomes in patients with HF.³³ Assessment of LA structural changes could therefore have important prognostic implications and may improve risk stratification in patients with secondary MR.

Prognostic Implications of LARS in Secondary MR

LA dilatation is associated with worse outcomes in patients with HF and reduced LVEF.¹¹ Results from a large meta-analysis, including 1,157 patients with HF, showed that LA size was a powerful predictor of outcomes and provided prognostic information beyond LV systolic and diastolic dysfunction.³⁴ LA enlargement also carries important

Table 3 Uni- and multivariable Cox regression analyses to identify associates of all-cause mortality in patients with moderate to severe secondary MR with LARS as a continuous variable

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.033 (1.022-1.044)	<.001	1.029 (1.017-1.042)	<.001
Male sex	1.646 (1.308-2.071)	<.001	1.304 (0.993-1.711)	.056
Arterial hypertension	0.945 (0.769-1.162)	.592		
Diabetes mellitus	1.379 (1.093-1.740)	.007	1.175 (0.905-1.525)	.227
Serum creatinine	1.004 (1.003-1.004)	<.001	1.006 (1.004-1.008)	<.001
NYHA functional class III or IV	1.705 (1.340-2.170)	<.001	1.404 (1.084-1.819)	.010
Ischemic cardiomyopathy	1.340 (1.094-1.641)	.005	0.978 (0.769-1.244)	.855
AF	1.223 (1.000-1.498)	.050	0.811 (0.629-1.044)	.104
Mitral valve surgery (time- dependent covariate)	1.140 (0.923-1.407)	.224		
LVESVi	1.005 (1.003-1.008)	<.001	1.002 (0.998-1.006)	.270
LV GLS	0.927 (0.898-0.957)	<.001	0.957 (0.919-0.997)	.037
TAPSE	0.965 (0.943-0.988)	.003	0.993 (0.967-1.019)	.584
PASP	1.019 (1.011-1.027)	<.001	1.005 (0.997-1.014)	.239
MR severity		<.001		<.001
Grade 2	Reference		Reference	
Grade 3	2.299 (1.673-3.161)	<.001	2.384 (1.639-3.468)	<.001
Grade 4	2.751 (1.990-3.802)	<.001	2.665 (1.799-3.948)	<.001
LAVi	1.008 (1.004-1.012)	<.001	1.000 (0.995-1.005)	.992
LARS	0.938 (0.921-0.955)	<.001	0.958 (0.935-0.981)	<.001

NYHA, New York Heart Association; PASP, pulmonary systolic pressure; TAPSE, tricuspid annular plane systolic excursion. Bold values indicates statistical significant.

prognostic implications in patients with significant MR.³⁵ However, LA size reflects the chronic effects of LV filling pressures over time (which could already have been normalized), whereas LARS more accurately reflects dynamic LV filling pressures.³⁶ In addition, LARS may also be a better marker of LA fibrosis than LA size.¹⁹ Finally, LA functional changes occur well before LA dilatation occurs and may therefore represent an earlier stage of LA remodeling.³⁷ In 405 patients with HF and reduced LVEF, Carluccio *et al.*¹² demonstrated that LARS allowed powerful prognostication, independent

of LA volume and LV longitudinal function. Although previous studies have shown the prognostic value of LARS in primary MR,³⁸⁻⁴⁰ the relationship between LARS and prognosis has not been evaluated in patients with HF and secondary MR. The present data demonstrate that LARS is independently associated with MR severity and show a strong, independent link with mortality in a large HF population with moderate to severe MR. In addition, and in contrast to LA volume and the presence of AF, LARS remained independently associated with all-cause mortality after adjusting for various clinical and echocardiographic variables and provided incremental prognostic value over parameters of LV systolic dysfunction (LVEF and LV GLS).

Clinical Implications

The results of the present study show that LARS, reflecting LA compliance, is a strong prognostic marker in patients with secondary MR. The measurement of LARS could therefore help risk-stratify patients with secondary MR and identify those who might benefit from closer follow-up. The COAPT trial demonstrated that percutaneous edge-to-edge mitral valve repair improves outcomes in selected patients with secondary MR.⁵ However, a significant percentage of the patients who underwent transcatheter mitral valve repair were hospitalized for HF or died within 2 years after therapy,⁵ underscoring the need for further research to optimize timing of intervention in these patients. Toprak *et al.*⁴¹ demonstrated that successful transcatheter edge-to-edge mitral valve repair improved LARS within 12 months after the procedure.⁴¹ Whether improvement in LA function after transcatheter mitral valve repair translates into better outcomes requires prospective evaluation.

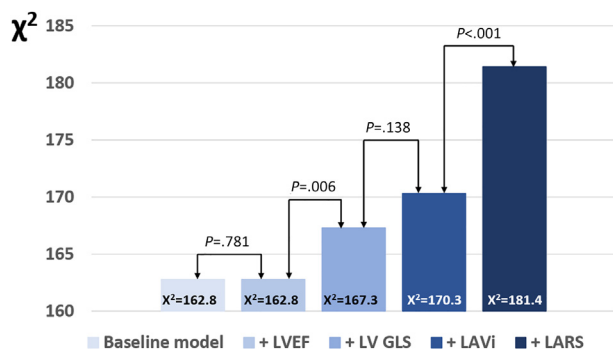


Figure 3 Likelihood ratio test for the incremental prognostic value of LARS. The incremental value of LARS over clinical and traditional echocardiographic parameters for the prediction of all-cause mortality. *The baseline model included age, sex, diabetes mellitus, serum creatinine, New York Heart Association functional class III or IV, ischemic etiology of HF, AF, LV end-systolic volume index, tricuspid annular plane systolic excursion, and systolic pulmonary artery pressure.

Study Limitations

This study was subject to the limitations of its single-center, retrospective design. MR severity may be influenced by loading conditions, which often vary over time. However, only hemodynamically stable patients were included. Although we show an association between LARS and MR severity, a control group including patients with no or mild secondary MR is missing. Assessment of right ventricular function with tricuspid annular plane systolic excursion is angle dependent and measures only the displacement of the lateral annulus, thereby extrapolating the motion of a single point to the entire right ventricle. Assessment of LARS is vendor specific, and values cannot be compared directly across different ultrasound platforms. HF hospitalization as an end point was not available. Mortality was ascertained by review of hospital records (linked to the governmental death registry database), and it was not possible to separate cardiac and noncardiac causes of death.

CONCLUSION

In patients with significant secondary MR, impaired LARS is associated with an increased risk for all-cause mortality. Assessment of LARS improves risk stratification of patients with significant secondary MR and may identify patients who may benefit from closer follow-up.

SUPPLEMENTARY DATA

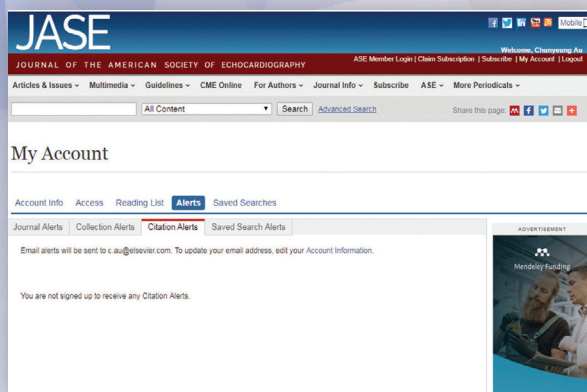
Supplementary data related to this article can be found at <https://doi.org/10.1016/j.echo.2022.01.007>.

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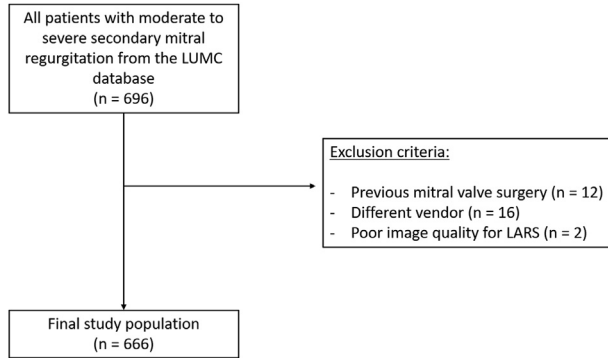
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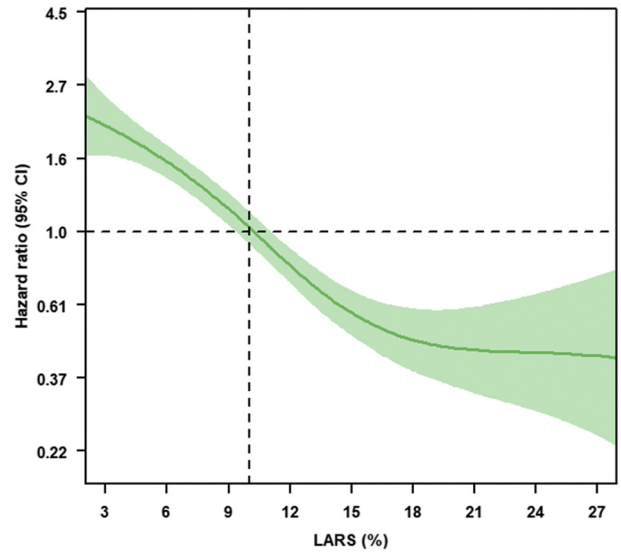
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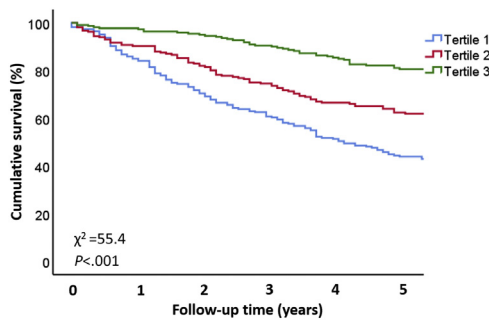
SUPPLEMENTARY DATA



Supplemental Figure 1 Flowchart of the study population. LUMC, Leiden University Medical Center.

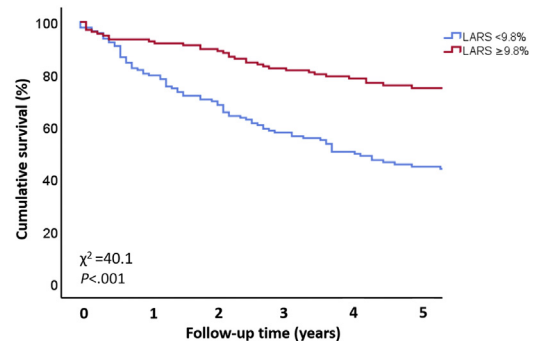


Supplemental Figure 3 Spline curve demonstrating the HR for the occurrence of all-cause mortality at follow-up according to LARS. The curve shows the HR change for the occurrence of all-cause mortality with 95% CIs (shaded green areas) across a range of values of LARS at the time of index echocardiography. The curve shows that the predicted HR for all-cause mortality is ≥ 1 at a LARS threshold value of $\pm 10\%$ (which is close to the median value of 9.8%).



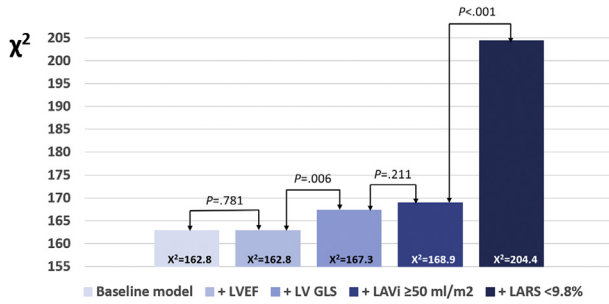
Number at risk						
	0	1	2	3	4	5
— Tertile 1	227	191	157	137	110	93
— Tertile 2	217	196	176	159	133	117
— Tertile 3	222	216	210	198	180	159

Supplemental Figure 2 Kaplan-Meier curve for time to cumulative survival, according to tertiles of LARS.



Number at risk						
	0	1	2	3	4	5
— LARS < 9.8%	142	130	97	82	63	52
— LARS $\geq 9.8\%$	136	126	121	110	92	71

Supplemental Figure 4 Kaplan-Meier curve for time to cumulative survival, according to LARS in the subgroup of patients who received surgical or percutaneous intervention. Time to all-cause mortality according to baseline LARS < 9.8% (blue) versus LARS $\geq 9.8\%$ (red).



Supplemental Figure 5 Likelihood ratio test for the incremental prognostic value of LARS as a categorical variable. The incremental value of LARS as a categorical variable over clinical and traditional echocardiographic parameters (with LAVi also expressed as a categorical variable) for the prediction of all-cause mortality. *The baseline model included age, sex, diabetes mellitus, serum creatinine, New York Heart Association functional class III or IV, ischemic etiology of HF, AF, LV end-systolic volume index, tricuspid annular plane systolic excursion, and systolic pulmonary artery pressure.

Supplemental Table 1 Univariable and multivariable Cox regression analyses to identify associates of all-cause mortality in patients with moderate to severe secondary MR with LARS as a categorical variable

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.033 (1.022-1.044)	<.001	1.029 (1.016-1.042)	<.001
Male sex	1.646 (1.308-2.071)	<.001	1.253 (0.953-1.647)	.106
Arterial hypertension	0.945 (0.769-1.162)	.592		
Diabetes mellitus	1.379 (1.093-1.740)	.007	1.188 (0.917-1.541)	.192
Serum creatinine	1.004 (1.003-1.004)	<.001	1.006 (1.004-1.008)	<.001
NYHA functional class III or IV	1.705 (1.340-2.170)	<.001	1.378 (1.063-1.785)	.015
Ischemic cardiomyopathy	1.340 (1.094-1.641)	.005	0.975 (0.766-1.240)	.837
AF	1.223 (1.000-1.498)	.050	0.783 (0.610-1.006)	.056
Mitral valve surgery (time-dependent covariate)	1.140 (0.923-1.407)	.224		
LVESVi	1.005 (1.003-1.008)	<.001	1.003 (0.999-1.006)	.163
LV GLS	1.079 (1.045-1.114)	<.001	0.964 (0.926-1.005)	.082
TAPSE	0.965 (0.943-0.988)	.003	0.995 (0.970-1.021)	.705
PSAP	1.019 (1.011-1.027)	<.001	1.005 (0.996-1.013)	.288
MR severity		<.001		<.001
Grade 2	Reference		Reference	
Grade 3	2.299 (1.673-3.161)	<.001	2.307 (1.584-3.358)	<.001
Grade 4	2.751 (1.990-3.802)	<.001	2.613 (1.762-3.876)	<.001
LAVi	1.008 (1.004-1.012)	<.001	1.000 (0.994-1.005)	.944
LARS ≥ 9.8%	0.425 (0.345-0.522)	<.001	0.499 (0.386-0.645)	<.001

LVESVi, LV end-systolic volume index; NYHA, New York Heart Association; PSAP, pulmonary systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Bold values indicates statistical significant.

Supplemental Table 2 Univariable and multivariable Cox regression analyses to identify associates of all-cause mortality in patients with moderate to severe secondary MR with tertiles of LARS

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.033 (1.022-1.044)	<.001	1.028 (1.016-1.041)	<.001
Male sex	1.646 (1.308-2.071)	<.001	1.314 (1.001-1.724)	.050
Arterial hypertension	0.945 (0.769-1.162)	.592		
Diabetes mellitus	1.379 (1.093-1.740)	.007	1.188 (0.916-1.541)	.194
Serum creatinine	1.004 (1.003-1.004)	<.001	1.006 (1.004-1.008)	<.001
NYHA functional class III or IV	1.705 (1.340-2.170)	<.001	1.394 (1.076-1.807)	.012
Ischemic cardiomyopathy	1.340 (1.094-1.641)	.005	0.972 (0.764-1.237)	.820
AF	1.223 (1.000-1.498)	.050	0.797 (0.618-1.026)	.079
Mitral valve surgery (time-dependent covariate)	1.140 (0.923-1.407)	.224		
LVESVi	1.005 (1.003-1.008)	<.001	1.002 (0.999-1.006)	.235
LV GLS	1.079 (1.045-1.114)	<.001	0.960 (0.921-1.000)	.051
TAPSE	0.965 (0.943-0.988)	.003	0.992 (0.967-1.018)	.565
PSAP	1.019 (1.011-1.027)	<.001	1.004 (0.996-1.013)	.342
MR severity		<.001		<.001
Grade 2	Reference		Reference	
Grade 3	2.299 (1.673-3.161)	<.001	2.414 (1.660-3.510)	<.001
Grade 4	2.751 (1.990-3.802)	<.001	2.734 (1.844-4.054)	<.001
LAVi	1.008 (1.004-1.012)	<.001	1.000 (0.995-1.005)	.977
LARS tertiles		<.001		<.001
Tertile 1	Reference		Reference	
Tertile 2	0.696 (0.552-0.877)	.002	0.737 (0.569-0.956)	.021
Tertile 3	0.388 (0.300-0.501)	<.001	0.504 (0.363-0.699)	<.001

LVESVi, LV end-systolic volume index; NYHA, New York Heart Association; PSAP, pulmonary systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Bold values indicates statistical significant.