

Original Research



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Prognostic Impact of Left Atrial Strain After Mitral Valve Repair Surgery in Patients With Severe Mitral Regurgitation

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AUTHOR'S SUMMARY

The prognostic impact of left atrial (LA) function on long-term clinical outcomes in patients with chronic severe mitral regurgitation (MR) after mitral valve (MV) repair surgery remains unclear. In patients with chronic severe MR who received successful MV repair surgery, baseline LA global longitudinal strain (LAGLS) is an independent predictor of postoperative outcomes. Patients with high baseline LAGLS had better long-term outcomes compared to those with low LAGLS regardless of whether the patient had a LA volume index <60 mL/m². Assessment of the preoperative LAGLS can be used to predict postoperative outcomes and determine the optimal timing for MV surgery.

ABSTRACT


Background and Objectives: The prognostic value of left atrial (LA) function in terms of long-term clinical outcomes after mitral regurgitation (MR) surgery remains unclear. Therefore, we investigated the impact of preoperative LA global longitudinal strain (LAGLS) on the long-term postoperative clinical outcomes in chronic severe MR patients who underwent mitral valve (MV) repair surgery.

Methods: From January 2012 to December 2017, we analyzed 338 patients (mean age, 51.9±12.5 years; 218 males [64.5%]) treated with MV repair surgery for severe MR. The primary outcome was cardiovascular events, defined as the composite of all-cause death, newly developed atrial fibrillation (AF), and re-hospitalization for cardiovascular causes.


Results: During a median follow-up of 45 months (interquartile range, 26–65), 30 (8.9%) cardiovascular events, 5 (1.5%) all-cause death, 8 (2.4%) newly developed AF, and 26 (7.7%) re-hospitalizations occurred. On multivariable analysis, baseline LAGLS was an independent predictor of cardiovascular events (adjusted hazard ratio [HR], 0.91; 95% confidential interval [CI], 0.85–0.97; p=0.004) and re-hospitalization (adjusted HR, 0.93; 95% CI,

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Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions

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0.86–1.00; $p=0.037$). According to the optimal cutoff value of LAGLS, patients with low LAGLS ($<23.6\%$) had a significantly higher risk of cardiovascular events (adjusted HR, 2.70; 95% CI, 1.04–7.00; $p=0.041$) than those with high LAGLS ($\geq 23.6\%$). In a subgroup analysis, patients with high LAGLS had better clinical outcomes regardless of whether the patient had a LA volume index <60 mL/m².

Conclusions: In patients with chronic severe MR who received successful MV repair surgery, preoperative LAGLS is an independent predictor of long-term postoperative outcomes.

Keywords: Mitral regurgitation; Mitral annuloplasty; Surgery; Prognosis; Strain echocardiography

INTRODUCTION

Mitral regurgitation (MR) is the most frequent valvular heart disease requiring surgical intervention.^{1,2} Optimal timing of surgical treatment of severe MR is crucial for preventing adverse clinical outcomes. Current guidelines recommend mitral valve (MV) surgery for patients with severe MR and overt symptoms, left ventricular (LV) systolic dysfunction, atrial fibrillation (AF), or pulmonary hypertension.³ Significant dilation of the left atrial (LA) is also a poor prognostic marker and is included as a class IIa indication for surgery, even in asymptomatic patients with severe MR.³ During the early phase of MR, LA compensates for the increase in regurgitant volume by augmenting its reservoir function.^{4,5} However, LA no longer compensates for chronic volume overload that occurs in advanced phase; consequently, LA adverse remodeling occurs, manifesting as LA dilatation and dysfunction. LA dilatation may be accompanied by cellular hypertrophy and interstitial fibrosis, with increased vulnerability to the development of AF and LA dysfunction.⁶ Recently published studies have shown decreased LA reservoir function even in the early stage of LA structural changes. Thus, decreased LA reservoir function may indicate the hemodynamic implications of severe MR at an earlier stage than that of overt LA structural changes.^{7,8} Furthermore, decreased LA function is associated with a poor long-term prognosis in patients with several cardiovascular diseases.^{9,10} However, the prognostic significance of LA function in patients with severe MR remains unclear. The assessment of LA reservoir function by speckle-tracking echocardiography can provide an objective marker of LA function and may have prognostic implications in patients with severe MR after MV surgery. Therefore, we assessed the LA global longitudinal strain (LAGLS) by speckle-tracking echocardiography and evaluated its prognostic impact in patients with chronic severe MR requiring MV repair surgery.

METHODS

Ethical statement

The study protocol was approved by the Asan Medical Center Institutional Review Board (2019-0553) and performed in accordance with the Declaration of Helsinki. The need for informed consent was waived due to the retrospective nature of the study.

Study population

The study population comprised consecutive patients with chronic severe MR who underwent successful MV repair surgery at Asan Medical Center (Seoul, South Korea) from January 2012 to December 2017. A diagnosis of severe MR required more than 4 of the following criteria: (1) flail leaflet; (2) vena contracta width >0.7 cm; (3) proximal isovelocity surface area (PISA)

radius >1.0 cm at an aliasing velocity of about 40 cm/s; (4) regurgitant jet area >50% of the LA; and (5) pulmonary vein systolic flow reversal. If only 2–3 criteria were met, ≥ 1 qualitative parameter were necessary, especially with an effective regurgitant orifice area ≥ 0.4 cm² or regurgitant volume ≥ 60 mL, using the PISA method. Patients with a baseline LV ejection fraction (LVEF) <50%, AF/flutter rhythm at baseline, significant concomitant aortic valve disease, previous MV surgery, and more than a moderate degree of residual MR after surgery were excluded.

Echocardiographic evaluation

Conventional echocardiographic analysis

Transthoracic echocardiography was performed as routine clinical practice and baseline study was performed within 7 days before MR surgery, using commercially available echocardiographic systems (iE33 and Epiq7, Philips Healthcare, Andover, MA, USA; Vivid 7 and E9, General Electric Healthcare, Waukesha, WI, USA). Digitally stored images were retrospectively analyzed by an experienced cardiologist specialized in valvular heart diseases. MR severity was assessed using the following parameters: valve morphology, jet area, vena contracta width, pulmonary vein flow pattern, and proximal convergence method with a multi-parametric integrative approach.¹¹ LV and LA chamber quantification were performed following the recommendations of the American Society of Echocardiography,¹² LA anteroposterior linear diameter was measured at the end-systole along the parasternal long-axis view using M-mode echocardiography. LV and LA volumes were assessed from apical 4- and 2-chamber views using Simpson's biplane method and indexed by the body surface area. LA maximal and minimal volumes were measured just before MV opening (Vol_{max}) and at MV closure (Vol_{min}), respectively. The LA expansion index was calculated as $(Vol_{max} - Vol_{min}) / Vol_{min} \times 100$.¹³ The diastolic properties of the LV were analyzed by the mitral inflow pattern, including the early mitral inflow velocity (E), deceleration time, and late mitral inflow velocity (A).¹⁴ Doppler tissue interrogation of the early diastolic mitral annular relaxation velocity (E') and late diastolic velocity (A') were recorded at the septal annulus, and the E/E' ratio was used to estimate the LV filling pressure.¹⁵ The systolic pulmonary artery pressure (SPAP) was assessed by the maximal velocity of the tricuspid regurgitation (TR) jet using the modified Bernoulli equation,¹⁶ and right atrial pressure was estimated by the inferior vena cava diameter and its response to inspiration.¹⁷ Significant pulmonary hypertension was defined as an estimated SPAP ≥ 50 mmHg. Right ventricle (RV) systolic function was estimated by the systolic velocity of the lateral annulus of the tricuspid valve, with a velocity <9.5 cm/sec indicating RV systolic dysfunction.¹²

Speckle-tracking echocardiographic analysis

Speckle-tracking echocardiography was used to evaluate LA myocardial function. An experienced investigator analyzed the LA strain using off-line software (TomTec Imaging Systems 2D Cardiac Performance Analysis, Germany) and greyscale LA images obtained in both apical 4- and 2-chamber views (frame rate, 60–80 frames/s).¹⁸ After importing digitally stored cine echocardiographic images to the software, the LA endocardial border was manually drawn using a point-and-click approach. Then, the software automatically performed endocardial border tracking. If the entire cardiac wall was not covered from the endocardium to the epicardial border, manual adjustments were performed to optimize the tracking. After segmental tracking quality analysis and final manual corrections, longitudinal strain and strain rate curves were generated in all segments, and the average value was calculated for the corresponding time points.¹⁹ We used R-R gating in the strain analysis, with the onset of the QRS complex as the reference point. Two peaks representing

LA reservoir function (first peak) and LA contractile function (starting at the P wave onset) were obtained. The LAGLS was calculated by averaging the first peak-positive LA strain values observed in all LA segments from apical 4- and 2-axis views.²⁰⁾

Outcomes and follow-up

Postoperatively, patients regularly visited physicians in the outpatient clinic at 3- to 6-month intervals. Clinical follow-up data, including postoperative clinical events, until the end of December 2019, were obtained by a review of the registry data and medical records. The primary study endpoint was adverse cardiovascular events, defined as the composite of all-cause death, newly developed AF (persisting 5 days after MV repair), and re-hospitalization for cardiovascular causes (nonfatal stroke, MV reoperation, and heart failure). Stroke of any type was defined using clinical documentation, with confirmatory imaging findings. Heart failure was defined according to the Framingham criteria, with the presence of two major, or one major and two minor criteria.²¹⁾ Dates and causes of death were obtained from medical records for patients with regular clinical follow-up, or from the Korean National Registry of Vital Statistics for patients without regular follow-up.

Statistical analysis

Continuous variables are presented as the mean \pm standard deviation or median (interquartile range); categorical variables are presented as numbers and percentages. Group comparisons were evaluated using the chi-square or Fisher exact test for categorical variables, and the Student *t*-test or Mann-Whitney *U* test for continuous variables, as appropriate. Cox proportional hazard analysis was used to identify prognostic factors significantly associated with study outcomes, with adjustment for the effects of covariates in a multivariate analysis. Clinically relevant covariates with $p < 0.1$ on univariate analysis were added in the multivariate model. Time-dependent receiver-operating characteristic (ROC) curve analysis was performed, and area under the curve (AUC) was calculated for the prognostic value of baseline LAGLS to predict cardiovascular events. The most accurate cutoff value (i.e., the best compromise between sensitivity and specificity) was obtained using the Kaplan-Meier (KM) estimation method at 5 years after MV surgery. To examine the effect of baseline LAGLS in different subsets of patients, subgroup analyses were conducted according to the echocardiographic variables which were significant in the multivariable model (age, sex, LV end-systolic dimension, LA maximal volume index (LAV_i_{max}), and estimated SPAP). Adjusted hazard ratios (HRs) were calculated using the Cox proportional-hazards model. Time-to-event curves were constructed using KM estimates, and group comparisons were performed using the log-rank test. All reported *p* values are 2-sided, and $p < 0.05$ were considered statistical significance. All statistical analyses were performed using the SPSS version 21.0 (IBM, Chicago, IL, USA) and R software version 3.4.0 (R Foundation, Vienna, Austria).

RESULTS

During the study period, 718 patients with chronic severe MR underwent MV repair surgery in the Asan Medical Center (Seoul, South Korea). Among them, 380 patients were excluded for several reasons including AF/flutter at the baseline ($n=253$ patients), significant concomitant aortic valve disease ($n=53$ patients), LVEF $< 50\%$ ($n=32$ patients), previous MV surgery ($n=16$ patients), with moderate or severe residual MR after the surgery ($n=6$ patients), and concomitant LA reduction or Maze operation ($n=12$ patients). Finally, 338 patients (mean age, 51.9 ± 12.5 years; 218 male) were analyzed (**Supplementary Figure 1**). During a median

Table 1. Comparison of baseline characteristics between patients with and without cardiovascular events

Variables	All patients (n=338)	Cardiovascular event (+) (n=30)	Cardiovascular event (-) (n=308)	p value
Age (years)	51.9±12.5	50.7±13.0	52.0±12.5	0.607
Male gender	218 (64.5)	21 (70.0)	197 (64.0)	0.556
Body surface area (m ²)	1.74±0.19	1.76±0.16	1.74±0.19	0.564
Comorbidities				
Hypertension	132 (39.2)	10 (33.3)	122 (39.6)	0.561
Diabetes mellitus	22 (6.5)	3 (10.0)	19 (6.2)	0.429
Hyperlipidemia	29 (8.6)	3 (10.0)	26 (8.4)	0.732
Coronary artery disease	5 (1.5)	1 (3.3)	4 (1.3)	0.374
Cerebrovascular disease	9 (2.7)	1 (3.3)	8 (2.6)	0.571
Renal failure*	3 (0.9)	0	3 (1.0)	1.000
Operative profiles				
Mitral valve repair				
Annuloplasty	333 (98.5)	28 (93.3)	305 (99.0)	0.064
Ring annuloplasty	332 (98.2)	28 (93.3)	304 (98.7)	
Sliding annuloplasty	23 (6.8)	4 (13.3)	19 (6.2)	
Leaflet plication	209 (61.8)	20 (66.7)	189 (61.4)	0.695
Tri-/Quadrangular resection	185 (54.7)	16 (53.3)	169 (54.9)	
McGoon technique	7 (2.1)	0	7 (2.3)	
Alferi stitch	6 (1.8)	1 (3.3)	5 (1.6)	
Cleft repair	17 (5.0)	3 (10.0)	14 (4.5)	
Direct suture	13 (3.8)	1 (3.3)	12 (3.9)	
Leaflet augmentation	2 (0.6)	1 (3.3)	1 (0.3)	
Commissural repair	74 (21.9)	7 (23.3)	67 (21.8)	0.819
New chordae formation	138 (40.8)	16 (53.3)	122 (39.6)	0.174
Chordae transfer	12 (3.6)	1 (3.3)	11 (3.6)	1.000
Concomitant procedure				
Tricuspid anuloplasty	36 (10.7)	6 (20.0)	30 (9.7)	0.281
Coronary artery bypass grafting	6 (1.8)	1 (3.3)	5 (1.6)	
ASD closure	3 (0.9)	0	3 (1.0)	

Data are expressed as number (%) or mean ± standard deviation.

ASD = atrial septal defect.

*Renal failure was defined as an estimated glomerular filtration ratio of <30 mL/min/1.73 m² or dialysis.

follow-up of 45 months (interquartile range, 26–65 months), there were 30 (8.9%) adverse cardiovascular events, 5 (1.5%) all-cause deaths, 8 (2.4%) newly developed AF, and 26 (7.7%) re-hospitalizations for cardiovascular causes. Patients with and without cardiovascular events had similar clinical and operative characteristics (**Table 1**). Annuloplasty was performed in 333 (98.5%) patients, and 209 (61.8%) received a leaflet plication. Concomitant procedures, including tricuspid valve annuloplasty, coronary artery bypass graft surgery, and atrial septal defect closure were performed in 45 (13.3%) patients.

Echocardiographic data before and after mitral valve repair surgery

Baseline echocardiographic data are summarized in **Table 2**. Most patients showed primary MR (98.8%), including MV prolapse/flail (96.4%) and rheumatic disease (2.4%). The two groups did not significantly differ in LV dimensions, LVEF, diastolic properties of the LV, and degree of MR. Baseline LA anteroposterior dimension and volume index were larger in patients with cardiovascular events than in those without events. In addition, the LAGLS and expansion index were lower in patients with cardiovascular events than in those without events. The estimated RA pressure, SPAP, and presence of RV dysfunction were greater in patients with cardiovascular events than in those without events. Follow-up echocardiographic data obtained in the immediate postoperative period and 1-year postoperatively are shown in the **Supplementary Table 1**. After MV repair surgery, all patients showed considerable reductions in the LA diameter (baseline, 48.0±6.8 mm; immediately postoperatively, 42.5±6.0 mm; 1-year postoperatively, 39.3±5.8 mm) and LAV_i_{max} (baseline,

Table 2. Comparison of baseline echocardiographic parameters between patients with and without cardiovascular events

Variables	All patients (n=338)	Cardiovascular event (+) (n=30)	Cardiovascular event (-) (n=308)	p value
Mitral regurgitation etiology				0.356
Flail/Prolapse	326 (96.4)	29 (96.7)	297 (96.4)	
Rheumatic	8 (2.4)	0	8 (2.6)	
Functional	4 (1.2)	1 (3.3)	3 (1.0)	
LV				
LV end-systolic diameter (mm)	37.1±5.5	38.8±8.0	36.9±5.2	0.198
LV end-diastolic diameter (mm)	60.0±6.1	61.7±8.4	59.9±5.8	0.111
LV ejection fraction (%)	65.8±5.1	65.5±6.6	65.8±5.0	0.842
LA				
LA anterior-posterior diameter, mm	48.0±6.8	50.9±8.1	47.7±6.6	0.014
LA maximal volume index (mL/m ²)	96.0±44.8	130.8±88.0	92.7±37.0	0.028
LA reservoir function				
Expansion index (%)	81.1±34.4	64.5±23.0	82.7±34.9	<0.001
Global longitudinal strain (%)	24.5±7.1	19.9±5.0	25.0±7.1	<0.001
Mitral E velocity (cm/s)	124.2±31.7	133.9±39.3	123.3±30.8	0.079
Mitral A velocity (cm/s)	66.0±23.9	67.1±37.7	65.9±22.2	0.793
E/A ratio	2.1±0.8	2.4±1.1	2.1±0.8	0.135
Deceleration time (ms)	191.3±39.4	183.8±35.1	192.1±39.8	0.283
Septal E' velocity (cm/s)	7.9±2.4	8.0±2.9	7.9±2.4	0.816
Mitral E/E' ratio	16.8±7.4	18.6±10.8	16.6±7.0	0.173
MR PISA radius (mm)	13.4±3.2	14.0±3.8	13.4±3.2	0.319
Moderate to severe AR	2 (0.6)	0	2 (0.6)	1.000
Moderate to severe TR	13 (3.8)	1 (3.3)	12 (3.9)	1.000
TR peak velocity (m/s)	2.8±0.6	3.1±0.7	2.8±0.6	0.014
Estimated RA pressure (mmHg)	6.1±3.4	5.8±3.0	6.1±3.5	0.662
Estimated SPAP (mmHg)	38.5±14.6	44.8±17.8	37.8±14.1	0.013
Significant pulmonary hypertension	66 (19.5)	10 (15.2)	56 (18.2)	0.055
RV dysfunction	33 (9.8)	7 (23.3)	26 (8.4)	0.018

Data are expressed as number (%) or mean ± standard deviation.

AR = aortic regurgitation; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; PISA = proximal isovelocity surface area; RA = right atrium; RV = right ventricle; SPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

96.0±44.8 mL/m²; immediately postoperatively, 68.0±34.9 mL/m²; 1-year postoperatively, 49.5±19.5 mL/m²). Although the LAGLS decreased immediately after surgery, it improved at 1-year postoperatively. Patients without cardiovascular events had smaller maximal LA diameter and LAVi_{max} values at baseline, immediately postoperatively, and 1-year after surgery compared to those with events (**Figure 1**). LAGLS values were significantly lower in patients with cardiovascular events before and after MV repair surgery compared to those in patients without events (**Figure 2**).

Left atrial function and clinical outcomes

On multivariate Cox-proportional hazard analysis with adjustment for age, sex, LV end-systolic dimension, LAVi_{max}, and estimated SPAP, baseline LAGLS was identified as an independent predictor of cardiovascular events (adjusted HR, 0.91; 95% confidential interval [CI], 0.85–0.97; p=0.005) and re-hospitalization for cardiovascular causes (adjusted HR, 0.93; 95% CI, 0.86–1.00; p=0.039) (**Table 3**). Using the time-dependent ROC curve analysis, the optimal cutoff value of LAGLS for predicting adverse cardiovascular events at 5 years was 23.6% (AUC, 0.736; 95% CI, 0.63–0.84; p<0.001), with a sensitivity and specificity of 83.9% and 56.7%, respectively. The patients were divided into the high LAGLS (≥23.6%) and low LAGLS (<23.6%) groups based on the cutoff value. A comparison of the baseline characteristics between two groups is shown in **Supplementary Table 2**. Both groups were similar in terms of gender, prevalence of diabetes mellitus and hypertension, and operative characteristics. However, compared to the high LAGLS group, the low LAGLS group was older (54.9±11.6 years vs. 49.1±12.7 years, p<0.001), with increased LV end-systolic

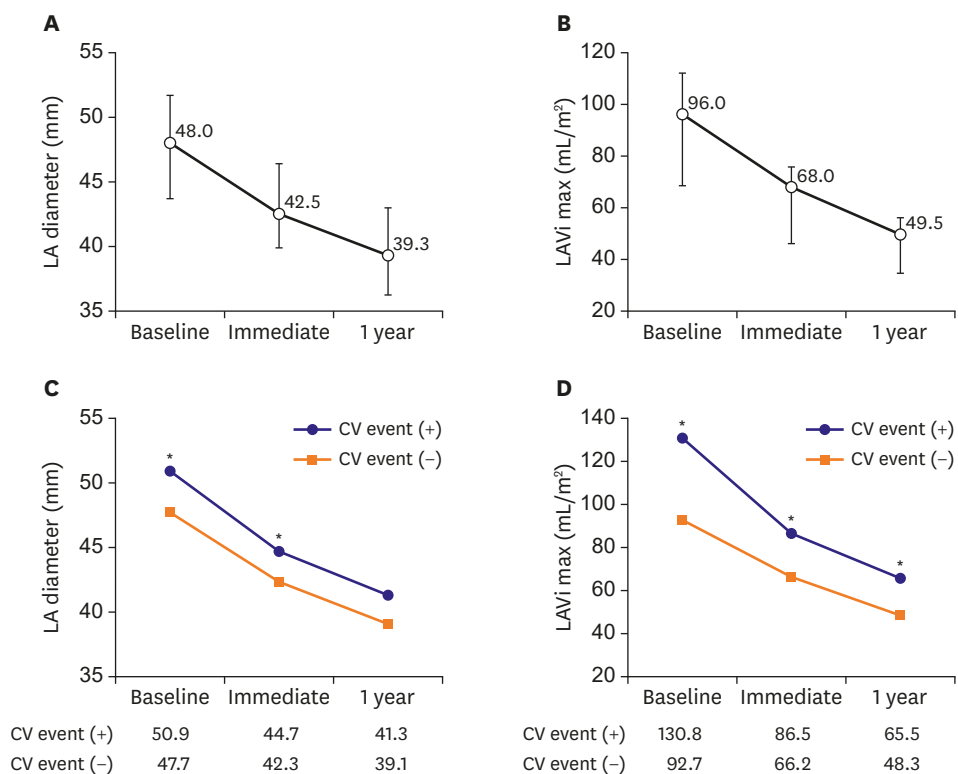


Figure 1. Change in LA size and volume before and after mitral valve repair surgery. LA anteroposterior diameter and LAVi_{max} are shown for all patients (A and B) and for patients with or without CV events (C and D). Data are displayed as the median value, with 25th and 75th percentiles (whiskers). CV = cardiovascular; LA = left atrial; LAVi_{max} = left atrial maximal volume index. *p < 0.05.

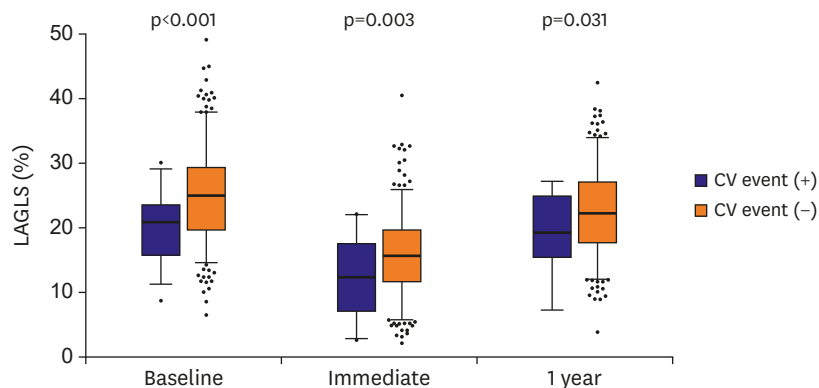


Figure 2. Time course of the LA global longitudinal strain before and after mitral valve repair surgery. The LA global longitudinal strain at baseline, immediately after surgery, and 1-year after surgery is shown according to presence of CV events. Box-plot indicates the median value, and the 25th and 75th percentiles; whiskers depict the 2.5th and 97.5th percentiles. CV = cardiovascular; LA = left atrial.

diameter and LAVi_{max}, higher estimated SPAP and RA pressure, and higher prevalence of RV dysfunction. However, there were no significant differences in LVEF, MR severity, and concomitant other valvular regurgitation. The high LAGLS group had a significantly lower rate of adverse cardiovascular events (adjusted HR, 0.37; 95% CI, 0.14–0.96; p=0.041) than low LAGLS group (**Figure 3** and **Supplementary Table 3**).

Table 3. Univariate and multivariable predictors of cardiovascular events after mitral valve repair surgery

Variables	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	1.00 (0.97–1.02)	0.717	0.99 (0.96–1.03)	0.613
Male gender	1.30 (0.59–2.83)	0.514	1.56 (0.66–3.68)	0.308
LV end-systolic diameter (mm)	1.05 (1.00–1.11)	0.063	0.98 (0.91–1.05)	0.559
LV end-diastolic diameter (mm)	1.05 (0.99–1.10)	0.109		
LV ejection fraction (%)	0.99 (0.92–1.07)	0.815		
LA maximal volume index (mL/m ²)	1.01 (1.01–1.01)	<0.001	1.01 (1.00–1.01)	0.045
LA Global longitudinal strain (%)	0.89 (0.84–0.94)	<0.001	0.91 (0.85–0.97)	0.005
Mitral peak E velocity (cm/s)	1.01 (1.00–1.12)	0.094		
Mitral A velocity (cm/s)	1.00 (0.99–1.02)	0.903		
Mitral E/E' ratio	1.03 (0.99–1.07)	0.206		
TR peak velocity (m/s)	1.92 (1.13–3.27)	0.017		
Estimated SPAP (mmHg)	1.03 (1.01–1.05)	0.015	1.01 (0.99–1.04)	0.310
RV dysfunction	3.14 (1.35–7.33)	0.008		

CI = confidential interval; HR = hazard ratio; LA = left atrium; LV = left ventricle; RV = right ventricle; SPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

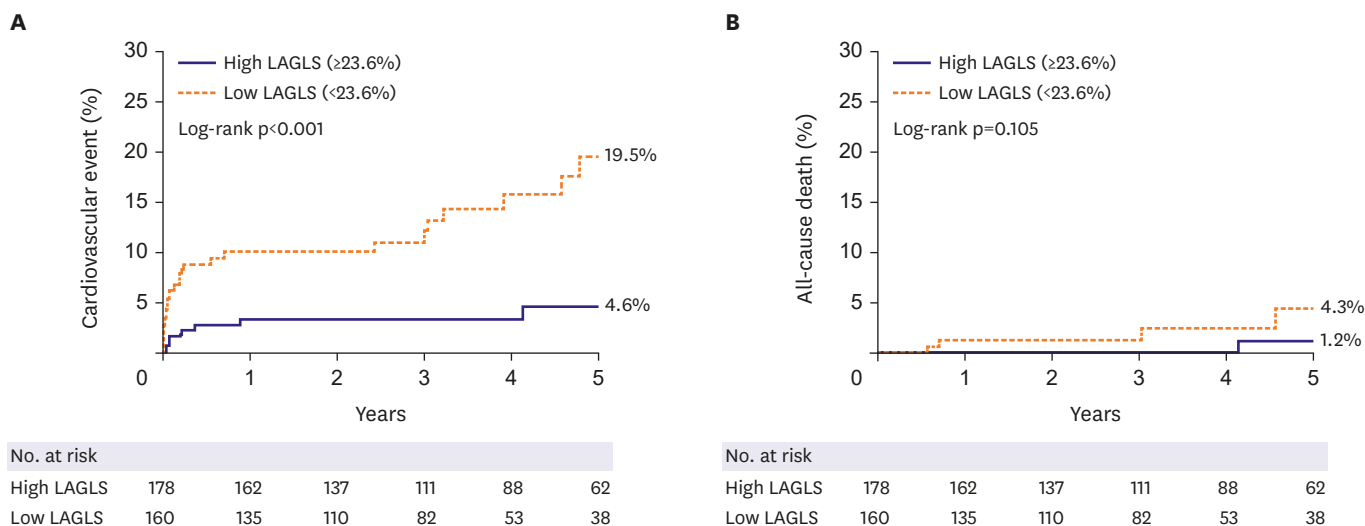


Figure 3. Comparison of outcomes between high and low baseline LAGLS groups. Cumulative incidence curves for cardiovascular events (A) and all-cause death (B) based on the optimal cutoff value of LAGLS (23.6%). High LAGLS: LAGLS \geq 23.6%. LAGLS = left atrial global longitudinal strain.

Subgroup analyses were performed with the adjustment of multiple variables which were identified as significant determinants for the primary outcome in the final multivariable model. Among the subgroup of patients with $LAVi_{max} \geq 60$ mL/m², high LAGLS was associated with a significantly lower rate of adverse cardiovascular events (adjusted HR, 0.35; 95% CI, 0.14–0.92; $p=0.033$). Similarly, in patients with $LAVi_{max} < 60$ mL/m², high LAGLS was associated with a significantly lower rate of adverse cardiovascular events (adjusted HR, 0.05; 95% CI, 0.00–0.69; $p=0.026$; **Figure 4**).

DISCUSSION

The major finding of our study is that preoperative LAGLS is an independent predictor of postoperative adverse cardiovascular events in patients with chronic severe MR who underwent successful MV repair surgery. There was a significantly higher rate of adverse

No. of events/total patients	LAGLS ($\geq 23.6\%$)	LAGLS ($< 23.6\%$)	Multivariable-adjusted HR for primary outcome	p for interaction
Gender				
Male	6/122	15/96		0.498
Female	1/56	8/64		
LV end-systolic diameter (mm)				
<45	7/171	20/146		-
≥ 45	0/7	3/14	NA	
LV ejection fraction (%)				
<60	2/23	5/23		0.555
≥ 60	5/155	18/137		
LV maximal volume index (mL/m²)				
<60	1/50	2/10		0.411
≥ 60	6/128	21/150		
Significant PH				
Yes	0/12	10/54	NA	-
No	7/166	13/106		
RV dysfunction				
Yes	1/5	6/28		0.333
No	6/173	17/132		

Figure 4. Subgroup analysis for cardiovascular events. HRs, adjusted by variables identified as significant determinants in the final multivariable model, are shown for the high LAGLS group in comparison with the low LAGLS group. HRs lower than 1 indicate a lower risk of cardiovascular events. CV = cardiovascular; HR = hazard ratio; LA = left atrium; LAGLS = left atrial global longitudinal strain; LV = left ventricle; PH = pulmonary hypertension; RV = right ventricle.

cardiovascular events in patients with a low preoperative LAGLS ($< 23.6\%$) than in those with high preoperative LAGLS ($\geq 23.6\%$). Additionally, the long-term clinical outcomes were better with high LAGLS regardless of whether the patient had an $LAV_{i_{max}} < 60$ mL/m².

MV surgery is considered as a definitive treatment for patients with symptomatic severe MR. Current European guidelines recommend MV surgery for patients with overt symptoms, LV dilatation, LV systolic dysfunction, AF, or pulmonary hypertension. Significant LA dilatation (≥ 60 mL/m²) with a sinus rhythm has also been found to be a predictor of poor clinical outcomes in patients with asymptomatic severe MR and is considered one of the surgical indications.³⁾ Increased LA size or volume is associated with adverse cardiovascular outcomes in both the general population and in patients with various cardiac diseases; thus, it is a powerful predictor of cardiovascular disease.²²⁾ However, increased LA volume itself cannot represent LA dysfunction, and normal LA function can be found even with enlarged LA, without an evidence of diastolic dysfunction.²³⁾ Recently, several studies have investigated the associations between LA volume, function, and clinical outcomes, and found that LA function reflected LA remodeling better than LA enlargement.²⁴⁾²⁵⁾ Unlike LA volume, LA strain is an objective marker of LA function,²⁶⁾ and it represents the extent of myocardial fibrosis in the LA.⁸⁾ The degree of LA fibrosis is a significant predictor of early and late LA reverse remodeling after MV surgery. In particular, LA longitudinal strain can detect subtle LA remodeling in the early stage, before structural changes, myocardial fibrosis, and chamber stiffness occur in the LA. Thus, the assessment of LA reservoir function is a more useful tool than LA volume for identifying patients whose outcomes may be improved with chronic severe MR surgery. Cameli et al.²⁷⁾ reported that decreased LAGLS ($< 35\%$) was a poor prognostic marker of adverse clinical events, including AF, stroke/transient ischemic attack, and cardiovascular death, in patients with moderate asymptomatic MR. In addition, Debonnaire et al.²⁸⁾ presented that patients with severe MR and decreased LAGLS ($\leq 24.0\%$) had worse survival during follow-up, regardless of their symptom status. In our study, we show that low baseline LAGLS ($< 23.6\%$) is

a poor prognostic marker of postoperative outcomes in chronic severe MR patients underwent MV repair surgery. Thus, the LAGLS may be a good marker for determining the optimal timing of MV surgery. Based on our findings, we propose that considering MV surgical correction before LAGLS decrease would be helpful in achieving good clinical outcomes even in patients without symptoms or a LAV_{imax} <60 mL/m².

In our study, compared to baseline values, LA dimensions and volume were significantly decreased after successful MR reduction; most of this reduction occurred during the early postoperative period, continuing over the 1-year postoperatively. On the other hand, the LAGLS decreased immediately after surgery, despite a significant decrease in LA volume. One year after MV repair surgery, the LA strain value improved compared to the immediately postoperative value, but did not fully recover and remained lower than the baseline LAGLS value. Decreased LA strain after surgery may be associated with reduced preload and decreased LA expansion due to MR correction; however, the possibility of LA function deterioration due to atriotomy after open surgery and manipulation of the LA cannot be ruled out. Mitral annuloplasty also had the potential to interfere with the basal movement of LA because the rigid complete ring directly fixes and stabilizes the mitral annulus. Patients without cardiovascular events had a smaller reduction in LA volume, but still maintained a high LAGLS after MV repair surgery, while patients with cardiovascular events had lower LA strain values despite a marked reduction in LA volume postoperatively. These findings suggest that low baseline LAGLS may be associated with increased LA stiffness and persistent LA dysfunction after MR repair surgery.

The present study has several limitations. First, there was heterogeneity in the baseline characteristics of the study population. To compensate for potential selection and baseline differences between study groups, covariate adjustment was performed. However, the results may still be biased by confounding variables that were not taken into account. Second, almost half of the screened patients were excluded due to AF. In patients with AF, LA strain was significantly lower than in non-AF patients even with the same MR severity. Therefore, AF patients were excluded to investigate the impact of LA strain affected by chronic volume overload caused by severe MR rather than AF on postoperative clinical outcomes. It is unclear whether the study results can be applied to patients with functional MR. Furthermore, in this present study, preoperatively LVGLS could not be assessed. Therefore, important additional factor, LVGLS, was not comprehensively integrated into this risk model. Third, in this study, we set the primary endpoint as a composite outcome, a cardiovascular event, because the event rate of each individual outcome was small. Cardiovascular events consisted of individual outcomes that were either already included in previous studies of valve disease or occurred frequently in MR patients. Finally, although our findings suggest an additional clinical role of LAGLS assessment in determining the optimal timing for surgery in patients with chronic severe MR, the study was single-center in nature, with a small registry; thus, a clinically directive conclusion is not feasible. The overall findings should be confirmed through a further large-scale clinical investigation.

In patients with chronic severe MR, preoperative LAGLS is an independent predictor of postoperative outcomes after MV repair surgery. Patients with high preoperative LAGLS had better long-term outcomes compared to those with low preoperative LAGLS, regardless of a LAV_{imax} <60 mL/m². Therefore, the evaluation of preoperative LAGLS can be used to predict postoperative outcomes and determine the optimal timing for MV surgery.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Echocardiographic data at baseline, immediate postoperation, and 1-year after mitral valve repair surgery

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Supplementary Table 2

Baseline clinical and echocardiographic parameters of high ($\geq 23.6\%$) and low LAGLS group ($< 23.6\%$)

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Supplementary Table 3

Comparison of long-term clinical outcomes between the high LAGLS and low LAGLS groups

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Supplementary Figure 1

Patient selection flow diagram.

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REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation* 2018;137:e67-492.
[PUBMED](#) | [CROSSREF](#)
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005-11.
[PUBMED](#) | [CROSSREF](#)
3. Falk V, Baumgartner H, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur J Cardiothorac Surg* 2017;52:616-64.
[PUBMED](#) | [CROSSREF](#)
4. Cameli M, Lisi M, Giacomini E, et al. Chronic mitral regurgitation: left atrial deformation analysis by two-dimensional speckle tracking echocardiography. *Echocardiography* 2011;28:327-34.
[PUBMED](#) | [CROSSREF](#)
5. Borg AN, Pearce KA, Williams SG, Ray SG. Left atrial function and deformation in chronic primary mitral regurgitation. *Eur J Echocardiogr* 2009;10:833-40.
[PUBMED](#) | [CROSSREF](#)
6. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation* 1995;92:835-41.
[PUBMED](#) | [CROSSREF](#)
7. Toprak C, Kahveci G, Kilicgedik A, et al. Left atrial remodeling in patients undergoing percutaneous mitral valve repair with the MitraClip system: an advanced echocardiography study. *Echocardiography* 2016;33:1504-11.
[PUBMED](#) | [CROSSREF](#)
8. Cameli M, Lisi M, Righini FM, et al. Usefulness of atrial deformation analysis to predict left atrial fibrosis and endocardial thickness in patients undergoing mitral valve operations for severe mitral regurgitation secondary to mitral valve prolapse. *Am J Cardiol* 2013;111:595-601.
[PUBMED](#) | [CROSSREF](#)

9. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail* 2015;8:295-303.
[PUBMED](#) | [CROSSREF](#)
10. Park JH, Hwang IC, Park JJ, Park JB, Cho GY. Prognostic power of left atrial strain in patients with acute heart failure. *Eur Heart J Cardiovasc Imaging* 2021;22:210-9.
[PUBMED](#) | [CROSSREF](#)
11. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303-71.
[PUBMED](#) | [CROSSREF](#)
12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-70.
[PUBMED](#) | [CROSSREF](#)
13. Vianna-Pinton R, Moreno CA, Baxter CM, Lee KS, Tsang TS, Appleton CP. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. *J Am Soc Echocardiogr* 2009;22:299-305.
[PUBMED](#) | [CROSSREF](#)
14. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277-314.
[PUBMED](#) | [CROSSREF](#)
15. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527-33.
[PUBMED](#) | [CROSSREF](#)
16. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984;70:657-62.
[PUBMED](#) | [CROSSREF](#)
17. Brennan JM, Blair JE, Goonewardena S, et al. Reappraisal of the use of inferior vena cava for estimating right atrial pressure. *J Am Soc Echocardiogr* 2007;20:857-61.
[PUBMED](#) | [CROSSREF](#)
18. Badano LP, Koliaas TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2018;19:591-600.
[PUBMED](#) | [CROSSREF](#)
19. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *J Am Soc Echocardiogr* 2011;24:277-313.
[PUBMED](#) | [CROSSREF](#)
20. Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. *J Am Soc Echocardiogr* 2017;30:59-70.e8.
[PUBMED](#) | [CROSSREF](#)
21. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.
[PUBMED](#) | [CROSSREF](#)
22. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol* 2003;41:1036-43.
[PUBMED](#) | [CROSSREF](#)
23. Park JH, Kim KH, Rink L, et al. Left atrial enlargement and its association with left atrial strain in university athletes participated in 2015 Gwangju Summer Universiade. *Eur Heart J Cardiovasc Imaging* 2020;21:865-72.
[PUBMED](#) | [CROSSREF](#)
24. Facchini E, Degiovanni A, Marino PN. Left atrium function in patients with coronary artery disease. *Curr Opin Cardiol* 2014;29:423-9.
[PUBMED](#) | [CROSSREF](#)
25. Appleton CP, Kovács SJ. The role of left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging* 2009;2:6-9.
[PUBMED](#) | [CROSSREF](#)

26. Park JH. Two-dimensional echocardiographic assessment of myocardial strain: important echocardiographic parameter readily useful in clinical field. *Korean Circ J* 2019;49:908-31.
[PUBMED](#) | [CROSSREF](#)
27. Cameli M, Pastore MC, Righini FM, et al. Prognostic value of left atrial strain in patients with moderate asymptomatic mitral regurgitation. *Int J Cardiovasc Imaging* 2019;35:1597-604.
[PUBMED](#) | [CROSSREF](#)
28. Debonnaire P, Leong DP, Witkowski TG, et al. Left atrial function by two-dimensional speckle-tracking echocardiography in patients with severe organic mitral regurgitation: association with guidelines-based surgical indication and postoperative (long-term) survival. *J Am Soc Echocardiogr* 2013;26:1053-62.
[PUBMED](#) | [CROSSREF](#)