JACC: CARDIOVASCULAR IMAGING VOL. 11, NO. 9, 2018

PUBLISHED BY ELSEVIER

Myocardial Strain in Prediction of Outcomes After Surgery for Severe Mitral Regurgitation

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ABSTRACT

OBJECTIVES We investigated whether global longitudinal strain (GLS) is a better predictor of clinical events after surgery for mitral regurgitation (MR) than conventional parameters.

BACKGROUND The optimal timing for surgery is guided by left ventricular (LV) dimension or left ventricular ejection fraction (LVEF), even though normal LVEF can mask depressed LV systolic function in severe mitral MR.

METHODS From 2006 to 2016, 506 patients (age 58.5 ± 13.7 years, 54.3% male) with severe primary MR who underwent mitral valve surgery were included. We measured GLS and global circumferential strain. Cardiac events included admission for worsening heart failure (HF), reoperation for failure of MV surgery, and cardiac death.

RESULTS During a median follow-up period of 3.5 years, 56 (11.1%) patients died, 41 (8.1%) were hospitalized for HF, and 10 (2.0%) underwent reoperation. In univariate analysis, LVEF, atrial fibrillation, left atrial dimension, age, previous ischemia, concomitant coronary artery bypass graft, and both GLS and global circumferential strain were predictive of cardiac events. On multivariate Cox models, age (hazard ratio [HR]: 1.429, 95% confidence interval [CI]: 1.116 to 1.831; p = 0.005), left atrial dimension (HR: 1.034, 95% CI: 1.006 to 1.063; p = 0.019) and GLS (HR: 1.229, 95% CI: 1.135 to 1.331; p < 0.001) were independent predictors of cardiac events. In subgroup analysis, LV GLS was a significant predictor of cardiac outcome, regardless of the presence of LV dysfunction, the presence of atrial fibrillation, and the type of surgery. Impaired GLS was associated with all-cause mortality (HR: 1.068, 95% CI: 1.003 to 1.136; p = 0.040).

CONCLUSIONS GLS appears to be a better predictor of cardiac events all-cause death than conventional parameters. Measuring preoperative GLS is helpful to predict post-operative outcome and determine optimal timing for surgery in patients with severe primary MR. (J Am Coll Cardiol Img 2018;11:1235–44)

Mitral regurgitation (MR) is the second most common cardiac valve disease in developed countries (1). Although the majority of patients diagnosed are asymptomatic, severe MR is associated with higher morbidity and mortality without surgical treatment (2,3). In contrast, successful surgical correction of MR results in good long-term outcomes (4). Therefore, it is important to identify patients whose outcome could be improved with surgery by considering the risks and benefits. Although surgical repair of primary MR has been remarkably successful and operative mortality has significantly decreased, the 2017 focused update guidelines for operative criteria retained the 2006 guidelines. The current guidelines recommend surgery in patients with symptomatic severe MR or in asymptomatic patients who develop early signs of left ventricular (LV) dysfunction as a result of the MR. LV dysfunction has been defined as LV ejection fraction (EF) 30% to 60% and/or LV end-systolic

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Manuscript received January 2, 2018; revised manuscript received February 20, 2018, accepted March 20, 2018.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2018.03.016

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BNP = brain natriuretic peptide

EDD = end-diastolic dimension

EDV = end-diastolic volume

EF = ejection fraction

ESD = end-systolic dimension

ESV = end-systolic volume

GCS = global circumferential strain

GLS = global longitudinal strain

HF = heart failure

LA = left atrium

LV = left ventricle

MR = mitral regurgitation

MV = mitral valve

NYHA = New York Heart Association

dimension (ESD) ≥40 mm or ≥45 mm (5–7). However, it remains difficult to determine optimal timing for surgery with the current guidelines. LVEF and LVESD, parameters proposed in the guideline, are difficult to interpret due to the influence of the hemodynamic milieu of MR. In asymptomatic patients who consider undergoing surgery LVESD is rarely more than 45 mm (4). In addition, LVEF in patients with severe MR often remains normal or higher, and subclinical LV dysfunction might be masked due to MR lowering of LV afterload (4,8–10). Early-stage LV dysfunction with normal LVEF predicts post-operative LV decompensation and poor prognosis (9). Therefore, it is a great challenge to identify potential LV dysfunction at an early stage and to perform surgery to prevent the development of irreversible LV dysfunction in patients with chronic severe MR.

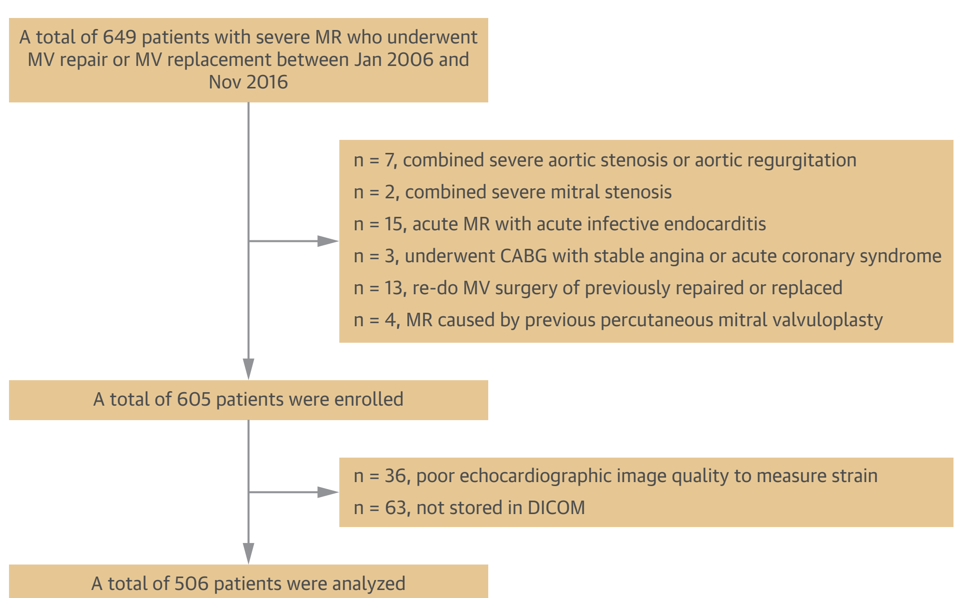
SEE PAGE 1245

Longitudinal myocardial function has been considered more sensitive than radial function, and is therefore suitable for detection of minor myocardial damage in patients with MR (11). Myocardial strain is one of the most suitable methods used to evaluate longitudinal contraction of LV, and recently introduced speckle-tracking strain analysis was shown to reflect LV myocardial function accurately with angle-independent assessment (12). Therefore, we sought to study the value of LV global longitudinal strain (GLS) to predict postoperative clinical outcomes after surgery for primary MR in comparison with conventional parameters.

METHODS

STUDY POPULATION. The medical records of 649 consecutive patients with severe primary MR who underwent surgical correction with either mitral valve (MV) repair or MV replacement were retrospectively reviewed. The patients were selected from a cohort treated in Seoul National University Bundang Hospital and Seoul National University Hospital between January 2006 and November 2016. Among the 649 patients, 143 patients were excluded due to combined severe aortic stenosis or regurgitation, severe mitral stenosis, acute MR with infective endocarditis, the history of coronary artery bypass graft (CABG) surgery with stable angina pectoris or acute coronary syndrome, re-do MV surgery, MR caused by previous percutaneous mitral valvuloplasty, images

FIGURE 1 Flow Chart of Study Population



Flow chart of study population to illustrate inclusion and exclusion criteria. CABG = coronary artery bypass graft; DICOM = Digital Imaging and Communication in Medicine; MR = mitral regurgitation; MV = mitral valve.

not stored in Digital Imaging and Communication in Medicine standard, and poor echocardiographic image quality used to measure strain. A total of 506 patients were included in the final analysis (Figure 1). The study was performed according to the principles of the Declaration of Helsinki and approved by the Clinical Research Institute of Seoul National University Bundang Hospital and Seoul National University Hospital.

TRANSTHORACIC ECHOCARDIOGRAPHY. Echocardiographic data were obtained with commercially available equipment. All subjects underwent conventional 2-dimensional, M-mode, and conventional and color Doppler ultrasonography conducted by experienced sonographer in accordance with American Society Echocardiography guidelines (13). MR was quantified by an integrated approach including valve morphology, measurement of the effective regurgitant orifice and the regurgitated volume using the proximal isovelocity surface area method, and pulmonary venous flow pattern. Severe MR was confirmed on the basis of an effective regurgitant orifice area of ≥0.40 cm² and regurgitant volume of ≥60 ml by using proximal isovelocity surface area methods. LV end-diastolic dimension and end-systolic dimension (ESD), and wall thickness were obtained using in M-mode or 2-dimensional images. The LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated from the apical 2-chamber and 4-chamber views and LVEF values were obtained by the Simpson's biplane method. Right ventricular systolic pressure was estimated from the peak velocity of tricuspid regurgitation.

STRAIN ANALYSIS. Speckle-tracking analysis enables angle-independent quantification of myocardial deformation by tracking, frame-to-frame, and natural acoustic speckles that are produced by the scatter of ultrasound beam by tissue. This method is a validated method that shows correlation through sonomicrometry and magnetic resonance imaging (14). For global strain analysis, 2-dimensional gray-scale images were acquired from a parasternal short axis view at the mid-papillary level, with apical 4-chamber, apical 3-chamber and apical 2-chamber views. Strain measurement was performed by using commercially available software. Digitally acquired images were downloaded from cardiac picture archiving and communication system and then uploaded to the TomTec system (Image Arena version 4.6, TomTec, Munich, Germany) for analysis. We manually traced along the LV endocardial border in the end-systolic frame. The software automatically extracted a strain curve from the gray-scale images. Peak strain was defined as the peak negative value on the strain curve during the entire cardiac cycle. GLS was calculated by averaging the peak value of 3 apical views. Reproducibility in measurement of strain was evaluated in 15 randomly selected patients using the interclass correlation coefficient. The interclass correlation coefficients for interobserver variability for

TABLE 1 Baseline Characteristics According to the Occurrence of Cardiac Event

	Cardiac Event		
	No (n = 443)	Yes (n = 63)	p Value
Age, yrs	57.8 ± 13.6	63.6 ± 13.3	0.001
Male	246 (55.5)	29 (46.0)	0.157
Systolic blood pressure, mm Hg	120.8 ± 18.9	124.1 ± 24.5	0.223
Diastolic blood pressure, mm Hg	73.0 ± 19.0	70.5 ± 16.2	0.178
Body surface area, m²	1.7 ± 0.2	1.6 ± 0.2	0.197
Body mass index, kg/m²	23.8 ± 3.7	23.4 ± 3.3	0.337
Underlying disease			
Hypertension	201 (45.4)	32 (50.8)	0.419
Diabetes mellitus	64 (14.4)	7 (11.1)	0.476
Hypercholesterolemia	64 (14.4)	8 (12.7)	0.710
Stroke	14 (3.2)	6 (9.5)	0.015
Atrial fibrillation	175 (39.5)	37 (58.7)	0.004
Myocardial infarction	4 (0.9)	3 (4.8)	0.014
Revascularization	8 (1.8)	4 (6.3)	0.027
Medication			
ACEI/ARB	218 (49.2)	29 (46.0)	0.637
Beta-blocker	112 (25.3)	18 (28.6)	0.576
Diuretics	260 (58.7)	38 (60.3)	0.806
Calcium-channel blocker	90 (20.3)	13 (12.6)	0.953
Digoxin	108 (24.4)	19 (30.2)	0.322
Laboratory exam			
Hemoglobin	13.3 ± 1.9	12.4 ± 2.1	0.001
Blood urea nitrogen	17.0 (14.0–22.0)	19.0 (15.0–25.0)	0.01
Creatinine	0.9 (0.8–1.1)	1.0 (0.9–1.4)	0.009
BNP* (n = 138)	193.0 (68.0–459.0)	202.0 (73.0–405.0)	0.954
Pro-BNP* (n = 74)	1,260.0 (480.5–2,173.5)	1,858.0 (1,016.7–4,745.1)	0.068
Cholesterol	168.6 ± 35.2	151.3 ± 47.8	0.001
NYHA functional class			0.008
I	150 (33.9)	14 (22.2)	
II	218 (49.2)	34 (54.0)	
III	68 (15.3)	10 (15.9)	
IV	7 (1.6)	5 (41.7)	
Etiology			0.323
Degenerative	399 (90.1)	54 (85.7)	
Rheumatic	40 (9.0)	9 (14.3)	
Congenital	4 (0.9)	0 (0)	
Type of surgery			0.002
MV replacement (mechanical)	53 (12.0)	10 (15.9)	
MV replacement (bioprosthetic)	49 (11.1)	16 (25.4)	
MV repair	341 (77.0)	37 (58.7)	
Concomitant CABG	19 (4.3)	7 (11.1)	0.022

Values are mean ± SD, n (%), or median (interquartile range). *BNP and Pro-BNP values were available in 138 (27.2%) and 74 (14.6%) patients, respectively.

ACEI = angiotensin-converting enzyme inhibitor; ARB = aldosterone receptor antagonist; BNP = brain natriuretic peptide; CABG = coronary artery bypass graft surgery; MV = mitral valve; NYHA = New York Heart Association.

TABLE 2 Comparison of Baseline Echocardiographic Parameters in Patients With and Without Cardiac Events After Mitral Valve Surgery

	Cardiac Event		
	No (n = 443)	Yes (n = 63)	p Value
LVEF, %	60.3 ± 7.9	57.3 ± 9.6	0.024
LVEDD, mm	59.8 ± 7.8	59.4 ± 10.4	0.760
LVESD, mm	38.6 ± 6.9	39.6 ± 9.5	0.458
LVEDV, ml	166.8 ± 54.7	161.6 ± 77.2	0.603
LVESV, ml	62.4 ± 28.6	66.1 ± 42.2	0.504
LVEDD index, mm/m^2	36.0 ± 5.2	35.7 ± 7.4	0.857
LVESD index, mm/m^2	23.3 ± 4.3	23.5 ± 6.3	0.890
LVEDV index, ml/m^2	99.0 ± 31.2	97.9 ± 42.5	0.852
LVESV index, ml/m^2	36.9 ± 16.2	40.0 ± 23.8	0.332
LA dimension, mm	55.6 ± 10.4	61.7 ± 13.3	0.001
RVSP, mm Hg	46.9 ± 16.8	49.1 ± 15.6	0.309
GLS, %	−20.0 ± 4.1	−16.5 ± 4.0	<0.001
GCS, %	−26.6 ± 6.8	−24.0 ± 6.9	0.010

Values are mean ± SD.

GCS = global circumferential strain; GLS = global longitudinal strain; LA = left atrium; LVEDD = left ventricular end diastolic diameter; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; LVESV = left ventricular end systolic volume; RVSP = right ventricular systolic pressure.

GLS and global circumferential strain (GCS) were 0.96 and 0.95, respectively.

OUTCOMES. The study population was followed until January 2017. Cardiac events and all-cause death were used for the assessment of outcome. Cardiac events were defined as admission for worsening heart failure (HF), reoperation for failure of MV surgery, and cardiac death during follow-up. The data on mortality were obtained from the Korean Ministry of Security and Public Administration. Death was classified as cardiac or noncardiac on the basis of medical records. When the cause of death was not known, records from the National Statistical Office of Korea were used. The cause of death was identified in all but 3 patients. We treated these patients as noncardiac death.

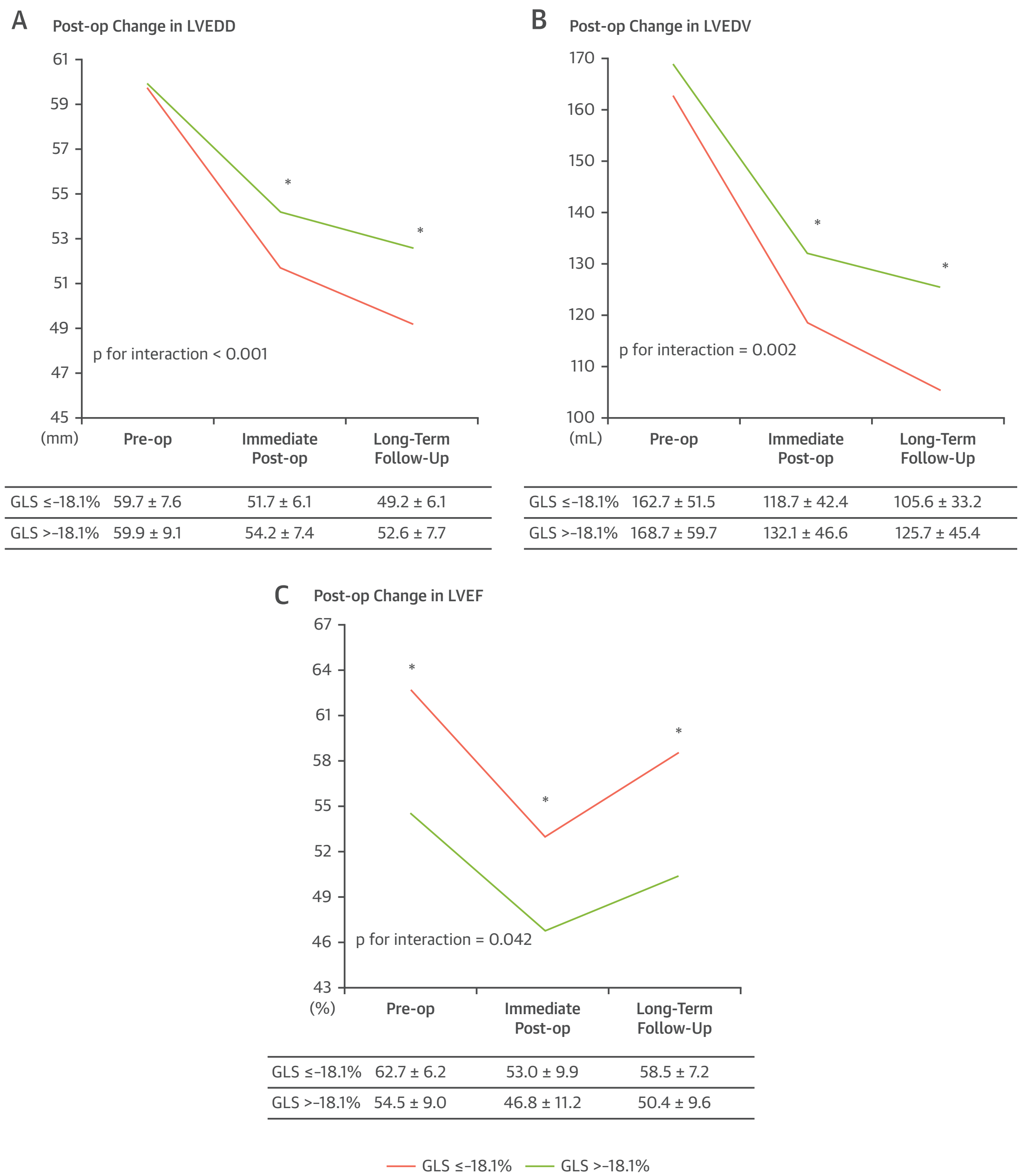
STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD, and categorical variables as n (%). Comparisons between the groups were performed with the Student's *t*-test, the Mann-Whitney *U* test, or the repeated-measures analysis of variance test. The chi-square test or Fisher exact test was used for categorical variables. The cutoff value of baseline GLS to predict cardiac events was set according to receiver-operating characteristic curve analysis with the highest sum of sensitivity and specificity. Event rates were estimated using event counts and exposure over time. Univariate Cox proportional hazard regression analyses were performed to evaluate the predictive values of each variable, and variables found to be significant were introduced into a multivariable Cox proportional hazards regression model. The multivariable Cox hazards models were performed with an incremental increase including confounding variables. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. Event-free survival analyses were conducted by Kaplan-Meier method with log-rank test and the Cox proportional hazard model. All statistical analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, Illinois), and a p value <0.05 was considered statistically significant.

RESULTS

STUDY POPULATION. Baseline characteristics of the patient population according to the occurrence of cardiac events are summarized in Table 1. The median follow-up after MV surgery was 3.5 years (interquartile range: 1.3 to 6.3 years). During the follow-up, there were 41 (8.1%) admissions for worsening HF, 10 (2.0%) reoperations for failure of MV surgery, 3 (0.6%) heart transplantations, and 56 (11.1%) deaths, including 23 (4.5%) cardiac deaths. When comparing groups with and without cardiac events, there were no significant differences in terms of sex, hypertension, diabetes mellitus, and hypercholesterolemia. However, the patients who had cardiac events were older and had higher proportions of patients with atrial fibrillation (AF), stroke, myocardial infarction, previous revascularization, concomitant CABG surgery, and MV replacement. Laboratory findings, including brain natriuretic peptide (BNP) and pro-BNP levels were not significantly different, but hemoglobin and total cholesterol levels were lower and creatinine was higher in the group with cardiac events. There were also no differences in cardiovascular medications including beta-blockers, renin-angiotensin system blockers, calcium channel blockers, diuretics, and digoxin, taken by the 2 groups at the time of surgery.

ECHOCARDIOGRAPHIC DATA BEFORE AND AFTER MV SURGERY. Pre-operative echocardiographic parameters are reported in Table 2. There were similar results for LVESD, and right ventricular systolic pressure in patients with and without cardiac events. However, the patient groups with cardiac events had lower LVEF (60.3 ± 7.9% vs. 57.3 ± 9.6%; p = 0.024) and greater left atrial (LA) dimension (55.6 ± 10.4 mm vs. 61.7 ± 13.3 mm; p = 0.001). The mean GLS was −19.6 ± 4.2% and the mean GCS was −26.3 ± 6.9% in the total study population. Both GLS (−20.0 ± 4.1% vs. −16.5 ± 4.0%; p < 0.001) and GCS (−26.6 ± 6.8% vs. −24.0 ± 6.9%;

FIGURE 2 Changes in LVEF and LV Reverse Remodeling After Surgery According to the GLS



	Pre-op	Immediate Post-op	Long-Term Follow-Up
GLS ≤-18.1%	59.7 ± 7.6	51.7 ± 6.1	49.2 ± 6.1
GLS >-18.1%	59.9 ± 9.1	54.2 ± 7.4	52.6 ± 7.7

	Pre-op	Immediate Post-op	Long-Term Follow-Up
GLS ≤-18.1%	162.7 ± 51.5	118.7 ± 42.4	105.6 ± 33.2
GLS >-18.1%	168.7 ± 59.7	132.1 ± 46.6	125.7 ± 45.4

	Pre-op	Immediate Post-op	Long-Term Follow-Up
GLS ≤-18.1%	62.7 ± 6.2	53.0 ± 9.9	58.5 ± 7.2
GLS >-18.1%	54.5 ± 9.0	46.8 ± 11.2	50.4 ± 9.6

(A) Changes in LVEDD. **(B)** Changes in LVEDV. **(C)** Changes in LVEF. *$p < 0.05$ between group with GLS ≤–18.1% and GLS >–18.1%. GLS = global longitudinal strain; LV = left ventricular; LVEDD = left ventricular end diastolic diameter; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction.

p = 0.01) were significantly impaired among those who had cardiac events during follow-up.

The cutoff value of GLS for predicting cardiac events was identified with a receiver-operating characteristic curve. The area under the curve of pre-operative GLS was 0.738 (95% CI: 0.673 to 0.803), with a best cutoff point of –18.1%. A cutoff value of >–18.1% could predict cardiac outcomes with a sensitivity and specificity of 71.4% and 70.7%, respectively.

In the echocardiographic evaluation during follow-up, LVEF recovery was relatively less in the group

TABLE 3 Unadjusted and Adjusted Cox Regression Analysis for Cardiac Events and All-Cause Mortality

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Cardiac events						
Age, decade	1.548	1.243–1.928	<0.001	1.429	1.116–1.831	0.005
LVEF, %	0.966	0.940–0.992	0.012	1.025	0.978–1.062	0.178
LVESD, mm	1.015	0.981–1.050	0.397			
LVESV, ml	0.995	0.979–1.012	0.582			
LA dimension, mm	1.048	1.026–1.070	<0.001	1.034	1.006–1.063	0.019
RVSP, mm Hg	1.008	0.994–1.022	0.287			
AF	2.162	1.309–3.573	0.003	1.195	0.650–2.195	0.567
History of ischemia	3.522	1.276–9.721	0.015	1.808	0.534–6.119	0.341
Concomitant CABG	2.797	1.271–6.153	0.001	1.399	0.494–3.956	0.527
GLS, %	1.200	1.131–1.273	<0.001	1.229	1.135–1.331	<0.001
GCS, %	1.048	1.009–1.090	0.017	0.987	0.936–1.040	0.615
All-cause mortality						
Age, decade	2.464	1.837–3.306	<0.001	2.372	1.759–3.199	<0.001
LVEF, %	1.008	0.975–1.041	0.639			
LVESD, mm	0.641	0.938–1.012	0.180			
LVESV, ml	0.979	0.955–1.003	0.081			
LA dimension, mm	1.038	1.015–1.061	0.001	1.031	1.005–1.058	0.019
RVSP, mm Hg	1.013	0.998–1.028	0.087			
AF	1.991	1.172–3.382	0.011	0.878	0.470–1.642	0.685
History of ischemia	1.453	0.354–5.959	0.604			
Concomitant CABG	2.630	1.124–6.154	0.026	1.785	0.756–4.214	0.186
GLS, %	1.102	1.035–1.173	0.002	1.068	1.003–1.136	0.040
GCS, %	1.031	0.990–1.074	0.136			

AF = atrial fibrillation; CABG = coronary artery bypass graft surgery; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

with a GLS of >−18.1% than in that with a GLS of ≤−18.1% in the long-term follow-up examination (Figure 2). Furthermore, LV reverse remodeling was more prominent in the patients with a GLS of ≤−18.1% than in those with a GLS of >−18.1%.

PREDICTORS OF CARDIAC OUTCOMES. Table 3 shows the results for the Cox proportional hazards models. On univariate survival analysis, age, LVEF, presence of AF, LA dimension, previous ischemia, concomitant CABG, GLS, and GCS showed significant associations with cardiac events during follow-up. In multivariate analyses, age (HR: 1.429; $p = 0.005$), LA dimension (HR: 1.034; $p = 0.019$) and GLS (HR: 1.229; $p < 0.001$) were significant determinants for cardiac events among the parameters significant in univariate analysis. Similar findings were observed for all-cause death. Older age (HR: 2.372; $p < 0.001$), greater LA dimension (HR: 1.031; $p = 0.019$), and impaired GLS (HR: 1.068; $p = 0.040$) independently predicted all-cause mortality. In the subgroup analysis, LV GLS showed significant predictive power for cardiac events, regardless of the presence of LV dysfunction (LVEF 30% to 60% and/or LVESD ≥40 mm, HR: 3.865, $p = 0.018$; LVEF > 60% and LVESD <40 mm, HR: 7.133; $p < 0.001$), the presence of AF (with AF, HR: 3.092; $p = 0.019$; without AF, HR: 7.213, $p = 0.001$), and the type of surgery (MV replacement, HR: 3.979; $p = 0.010$; MV repair, HR: 3.572; $p = 0.002$) (Figure 3). Risk-adjusted event-free survival shown by Cox proportional hazard model showed higher risk of composite events in the patients with a GLS >−18.1% than in those with GLS ≤−18.1% (Figure 4). GLS still showed a significant association with post-operative cardiac events in the patients who were asymptomatic or mildly symptomatic (New York Heart Association [NYHA] functional class I or II) (Online Figure 1).

MV repair showed a significant association with lower cardiac events (HR: 0.486, 95% CI: 0.294 to 0.803; $p = 0.003$) and all-cause death (HR: 0.462, 95% CI: 0.272 to 0.786; $p = 0.004$) in the univariate analysis (Online Figure 2). In the Cox regression survival analysis, MV repair was still a significant factor of cardiac events (HR: 0.561, 95% CI: 0.031 to 0.949; $p = 0.031$) after adjustment for age, LVEF, LA dimension, presence of AF, and concomitant CABG.

INCREMENTAL PROGNOSTIC VALUE OF GLS ON CARDIOVASCULAR EVENTS. To minimize correlation effects of LV EF and GLS, we also used global chi-square testing and analyzed LVEF and GLS separately. Model 1 was adjusted for age, LA dimension, and AF, which were significant in univariate analysis. In Model 2, in which LVEF was added to Model 1, the value increased from 31.926 to 36.008 ($p = 0.037$). Model 3 adjustments included the factors in Model 1 and GLS, and Model 4 used adjusted factors in Model 2 and GLS. GLS provided incremental prognostic value with regard to the prediction of cardiac events in both Model 3 (global chi-square from 31.926 to 59.246; $p < 0.001$) and Model 4 (global chi square from 36.008 to 60.467; $p < 0.001$) (Figure 5). Compared to LV EF, GLS offered more powerful incremental predictive power beyond the risk factors.

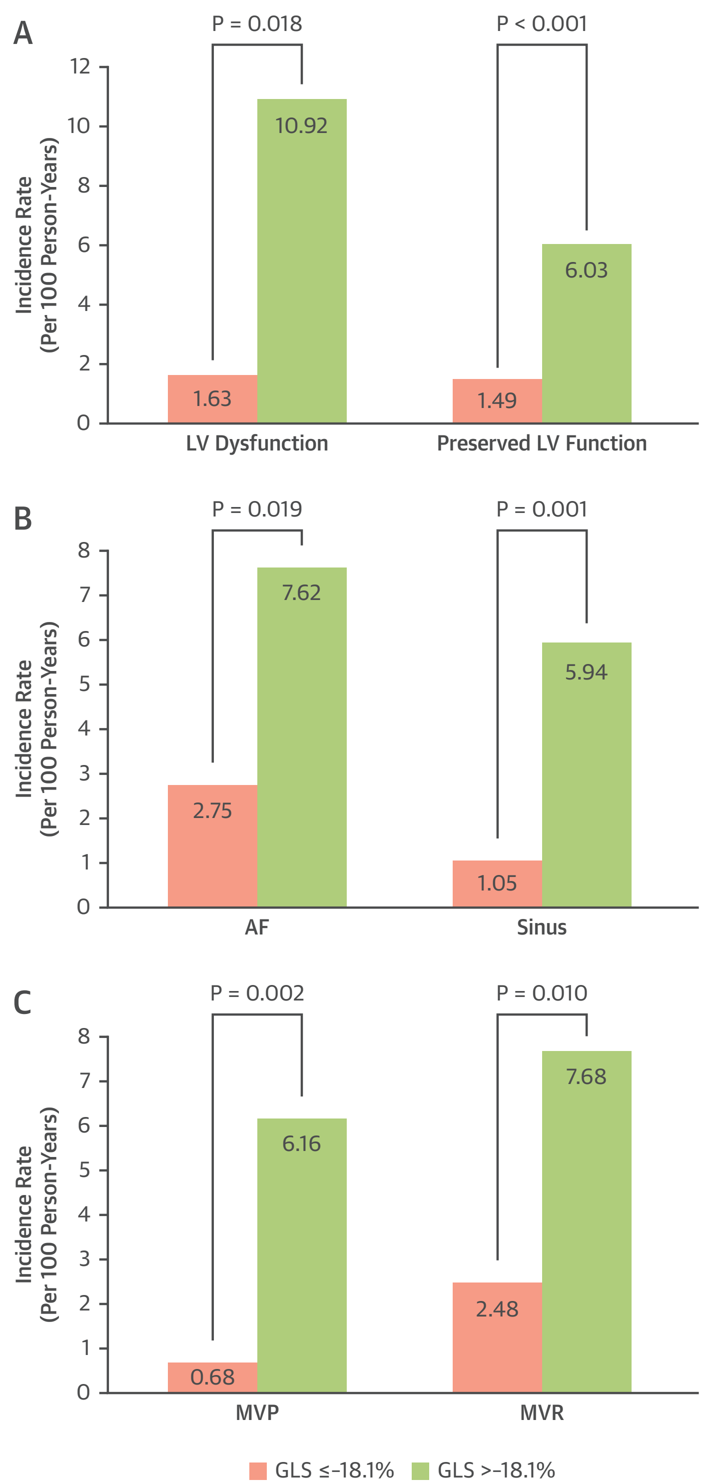
DISCUSSION

In this study, we showed that pre-operative GLS was the most powerful independent prognostic factors for prediction of cardiac events and all-cause death in patients with severe primary MR who underwent surgical correction. Subgroup analysis showed consistent results, regardless of LV dysfunction, presence of AF, and type of surgery. In addition, GLS showed superior incremental predictive effects regarding cardiac events beyond conventional risk factors, compared with LVEF. These findings show that GLS enables early detection of subtle LV dysfunction, so that measuring preoperative GLS is helpful in predicting postoperative outcome and determining the optimal timing for surgery in patients with severe MR.

Current guidelines recommended prompt MV surgery in patients with symptomatic severe MR to relieve of HF symptoms and preserve LV systolic function (5-7). However, it remains difficult to decide whether or not those with asymptomatic severe MR should undergo surgery (15,16). Based on several studies evaluating the effect of pre-operative parameters on post-operative outcomes, surgery in patients with asymptomatic severe MR is recommended when LV dysfunction occurs, as shown by LVEF ≤60% and/or LVESD ≥40 mm or ≥45 mm (5-7). However, assessment of LV dysfunction by LVEF is often overestimated due to severe MR providing lower impedance pathway for LV ejection (4,8-10). As backward LVEF is significant in severe MR, LVEF based on Simpson's method may not be accurate for evaluation of systolic function. Therefore, forward EF may be superior to total EF to predict outcome in patients with severe MR (17). A recent observational cohort study showed that LV GLS was independently associated with mortality and provided additive prognostic utility to previously known predictors in patients with asymptomatic significant MR, normal LV dimension, and preserved LVEF (18). Although both EF and strain are loading-dependent parameters, strain measures the myocardium itself. Furthermore, GLS is a better parameter than LVEF for detection of subclinical myocardial dysfunction (19,20). In the present study, 203 (40.1%) patients underwent MV surgery without LV dysfunction, as suggested by current guidelines (6,7). During the long-term follow-up, GLS-based criteria showed superior to LVEF criteria in predicting post-operative cardiac events (incidence rate: 1.56 vs. 6.87/100 person-years for GLS, 2.83 vs. 3.7/100 person-years for LVEF) (Online Figure 3). Additionally, net reclassification improvement showed that the use of GLS can provide a better risk stratification than the use of criteria from the current guidelines (overall net reclassification improvement of 31.9%) (Online Table 1). These results support the clinical usefulness of GLS in patients with severe MR undergoing surgery in comparison of LVEF and LVESD, the parameters used in current guidelines.

LV GLS is useful for evaluating LV long axis function, and speckle-tracking allows angle-independent evaluation (12). It has been suggested that longitudinal myocardial function is impaired sooner than

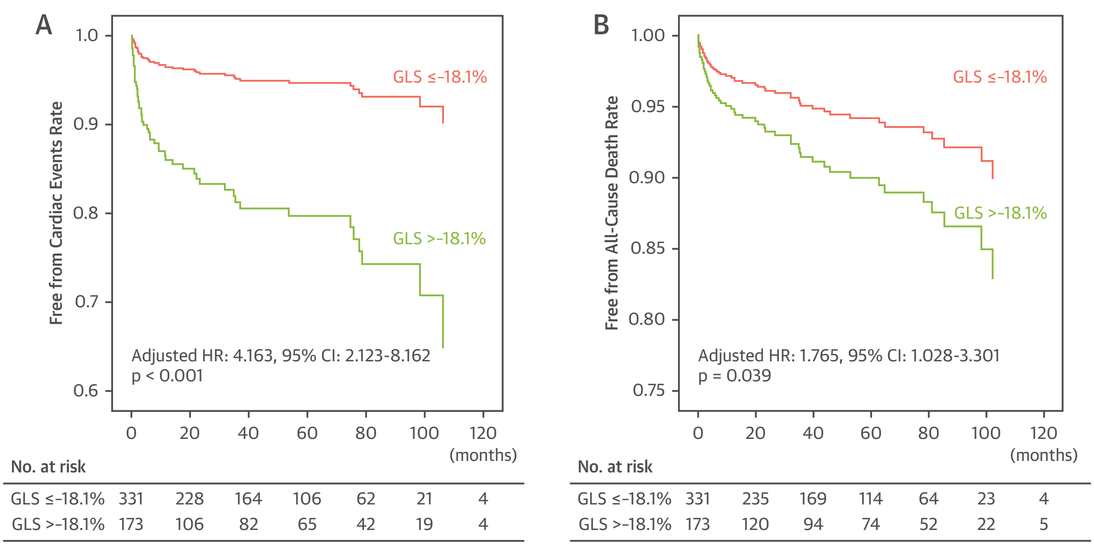
FIGURE 3 Annual Events Rates According to LV Dysfunction, AF, and Type of Surgery



The cutoff value of GLS was set by the highest sum of sensitivity and specificity using receiver-operating characteristic curve. AF = atrial fibrillation; MVP = mitral valve repair; MVR = mitral valve replacement; other abbreviations as in Figure 2.

JACC: CARDIOVASCULAR IMAGING, VOL. 11, NO. 9, 2018
SEPTEMBER 2018:1235-44

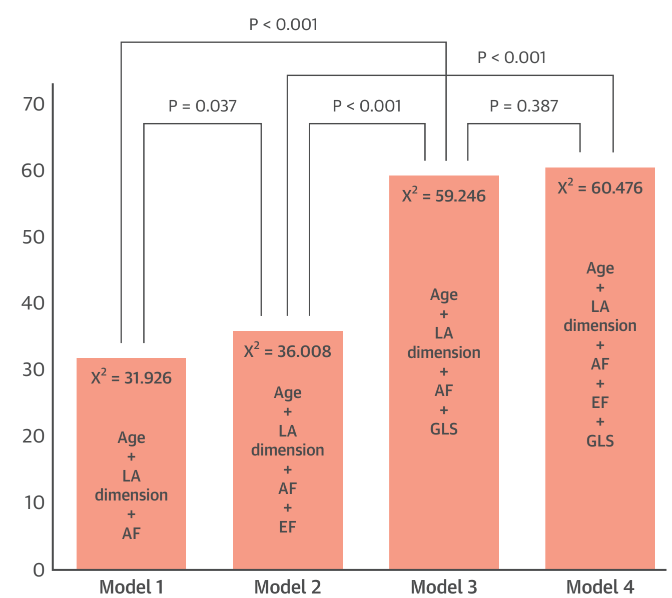
FIGURE 4 **Risk-Adjusted Event-Free Survival According to GLS**



Event-free survival curves are shown according to the GLS (−18.1%), adjusted for significant univariate predictors. **(A)** Event-free survival curve for cardiac events. **(B)** Event-free survival curve for all-cause death. CI = confidence interval; GLS = global longitudinal strain; HR = hazard ratio.

circular function in cardiac disorders because of the subendocardial localization (21,22). Therefore, assessment of longitudinal function could help in the early diagnosis of LV dysfunction (22). Earlier damaged longitudinal function also occurred in patients with MR. As the MR progresses, the LV dilates and becomes spherical; this change damages the longitudinal motion, which is more sensitive than radial contraction to detect minor LV dysfunction (11). In this study, GLS showed more powerful incremental predictive value for cardiac events than LVEF, which predominantly quantifies radial contraction.

FIGURE 5 **Incremental Prognostic Value of GLS**



Incremental prognostic value of global longitudinal strain was obtained from global chi-square testing. EF = ejection fraction; LA = left atrium; other abbreviations as Figures 2 and 3.

In follow-up echocardiography, we observed LV reverse remodeling as a result of loading condition changes. Before surgery, in compensated MR, increased preload and LV volume and decreased afterload maintain balance as normal LVEF. After MV surgery, the LV loading condition shifts to decreased preload and the LV adapts with a decrease in size. This and other studies (10,23,24) showed a reduction in LVEF after MV surgery; this is because afterload-dependent LVESV decreases relatively less than preload-dependent LVEDV (10,23-25). Some patients have significantly diminished LVEF, leading to LV dysfunction. Previous studies demonstrated that assessment of GLS has been shown to detect post-operative LV dysfunction in patients with severe MR who underwent surgery (24,26-28). In this study, we confirmed the predictive value of GLS for post-operative LV dysfunction, as well as for cardiac events. Additionally, we showed association with LV reverse remodeling and cardiac events, and post-operative LV dysfunction. LV reverse remodeling was more pronounced in the group with a GLS of ≤−18.1%. LVEF recovery was relatively less in the group with a GLS of >−18.1% than in that with a GLS of ≤−18.1%. LV dysfunction is useful as a surrogate marker for post-operative outcomes, but it might not sufficiently reflect the underlying goals of surgery. In this respect, our results advanced our understanding of the benefits of GLS for predicting real clinical outcomes after surgical treatment. Furthermore, compared with the LV dysfunction criteria, the cutoff value of GLS could predict the occurrence of cardiac events better (Online Figure 3), and GLS markedly improved the incremental prognostic value as compared with LVEF. Therefore, setting the surgery timing on a strain basis might be helpful. Further prospective clinical trials are needed to determine the critical role of GLS measurement in determining the optimal surgery timing.

STUDY LIMITATIONS. First, this was a retrospective study, and thus strain measurements were performed on stored images using dedicated software. Success in measuring strain depends on the quality of the images. In this study, we excluded patients with poor quality preoperative images (6.0%) to measure strain reliably. Second, we included severe MR patients with AF to address the prognostic value of GLS. Many clinical studies of GLS excluded patients with AF due to variable beat-to-beat ventricular cycle length. However, guidelines now recommend multiple measurements in patients with AF (13). In this study, we tried to quantify strain measurement in as many beats as possible from stored images, and GLS provided prognostic value for cardiac events regardless of the presence of AF. Third, patients with smaller body surface areas than Western patients were included. The current guidelines for surgery are based on the Western world. Previous studies on severe MR in Asia (29,30) showed that the baseline LV size in Asians was not smaller than that in white subjects (24), and so did our study. Finally, given that the cutoff value of GLS might be different in other populations of severe MR, external validation in larger patients would be warranted.

CONCLUSIONS

Pre-operative GLS showed a significant association with clinical events and appears to be a better predictor of cardiac events than conventional parameters in patients with severe primary MR who underwent MV surgery. Measuring pre-operative GLS is helpful for prediction of post-operative outcome and determination of optimal timing for surgery in patients with severe primary MR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Current guidelines recommend surgery in patients with symptomatic severe MR or in asymptomatic patients who develop early signs of LV dysfunction as a result of the MR. However, application of current guidelines derived insufficient outcome in some patients who might have subclinical LV dysfunction. We showed that preoperative GLS was the most powerful independent prognostic factor for prediction of cardiac events in patients with severe primary MR who underwent surgical correction. The better predictive value of GLS over conventional parameters could be attributable to the property of GLS that can recognize earlier damaged longitudinal myocardial function in patients with severe MR. LV GLS might become a useful tool for prediction of post-operative outcome and determination of optimal timing for surgery in patients with severe primary MR.

TRANSLATIONAL OUTLOOK: In patients with severe primary MR who underwent MV surgery, GLS enables early detection of subtle LV dysfunction, so that measuring pre-operative GLS is helpful in predicting post-operative outcome and determining the optimal timing for surgery. These findings need further prospective validation.

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KEY WORDS global longitudinal strain, mitral regurgitation, mitral valve repair, mitral valve replacement

APPENDIX For supplemental figures and table, please see the online version of this paper.