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SPECIAL ISSUE: FOCUS ON LV STRAIN FOR PREDICTING HARD OUTCOMES

ORIGINAL RESEARCH

Prognostic Value of Global Longitudinal Strain and Etiology After Surgery for Primary Mitral Regurgitation

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ABSTRACT

OBJECTIVES This study sought to investigate whether left ventricular (LV) global longitudinal strain (GLS) is associated with long-term outcome after mitral valve (MV) surgery for primary mitral regurgitation (MR) and assess the differences in outcome according to MR etiology: Barlow's disease (BD), fibroelastic deficiency (FED), and forme fruste (FF).

BACKGROUND Appropriate timing of MV surgery for primary MR is still challenging and may differ according to the etiology. In these patients, LV-GLS has been proposed as more sensitive measure to detect subtle LV dysfunction as compared with LV ejection fraction.

METHODS Echocardiography was performed in 593 patients (64% men, age 65 $\pm$ 12 years) with severe primary MR who underwent MV surgery, including assessment of LV-GLS. The etiology (BD, FED, or FF) was defined based on surgical observation. During follow-up, primary endpoint was all-cause mortality and a secondary endpoint included cardiovascular death, heart failure hospitalizations, and cerebrovascular accidents.

RESULTS During a median follow-up of 6.4 (interquartile range: 3.6 to 10.4) years, 146 patients died (16 within 30 days after surgery), 46 patients were hospitalized for heart failure, and 13 patients had a cerebrovascular accident. Age (hazard ratio [HR]: 1.08; 95% confidence interval [CI]: 1.05 to 1.11; $p < 0.001$) and LV-GLS (HR: 1.13; 95% CI: 1.06 to 1.21; $p < 0.001$) were independently associated with all-cause mortality. Patients with LV-GLS >–20.6% (more impaired) showed significant worse survival than did patients with LV-GLS ≤–20.6%; of interest, patients with BD showed similar prognosis compared with FED and FF. In addition, previous atrial fibrillation (HR: 1.70; 95% CI: 1.01 to 2.86; $p = 0.045$) and LV-GLS (HR: 1.01; 95% CI: 1.01 to 1.15; $p = 0.019$) were independently associated with the secondary endpoint.

CONCLUSIONS LV-GLS is independently associated with all-cause mortality and cardiovascular events after MV surgery for primary MR and might be helpful to guide surgical timing. Importantly, patients with BD showed similar prognosis when corrected for age, compared with patients with FED or FF. (J Am Coll Cardiol Img 2020;13:577–85) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BD = Barlow's disease

CI = confidence interval

EDD = end-diastolic diameter

EF = ejection fraction

ESD = end-systolic diameter

FED = fibroelastic deficiency

FF = forme fruste

GLS = global longitudinal strain

HR = hazard ratio

IQR = interquartile range

LA = left atrial

LV = left ventricular

MR = mitral regurgitation

MV = mitral valve

Untreated severe primary mitral regurgitation (MR) is associated with increased morbidity and mortality, but prognosis in these patients can be significantly improved with mitral valve (MV) surgery (1,2). However, timing of surgery is still a matter of debate. According to most recent guidelines (3,4), MV surgery is recommended for symptomatic patients with severe primary MR, or in asymptomatic patients with severe primary MR when left ventricular (LV) systolic dysfunction or dilatation occurs (based on left ventricular ejection fraction [LVEF] and LV diameters), in the presence of pulmonary arterial hypertension or in case of new onset atrial fibrillation (AF) and when the likelihood of repair is high and the surgical risk is low. Despite these recommendations, appropriate timing of surgery remains a clinical challenge, since identification of symptoms might be difficult, LVEF and LV dimension may not reliably reflect LV dysfunction and the likelihood of MV repair is dependent of MR etiology and expertise of the surgical center. LV global longitudinal strain (GLS) has been introduced as a more sensitive and accurate measurement of LV function (5) and current guidelines mention the potential incremental value of LV-GLS over LVEF for risk stratification in patients with severe primary MR (3). Although few studies have shown the association of LV-GLS with outcome after surgery for primary MR, evidence of the prognostic value of LV-GLS in these patients remains limited (6-8). Therefore, the present study aimed at further investigating the prognostic value of pre-operative LV-GLS in a large contemporary population of patients who underwent MV surgery for primary MR and with a long-term follow-up. Additionally, despite the fact that the likelihood of MV repair plays a significant role in the management of these patients, only a very limited number of studies reported long-term outcome after MV surgery systematically differentiating the MR etiology, including Barlow's disease (BD) and fibroelastic deficiency (FED), which are characterized by different MV lesions (9). Therefore, the present study also aimed at investigating the impact of MR etiology over the long-term outcome after MV surgery (10).

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METHODS

PATIENT POPULATION. Patients who underwent MV surgery for severe primary MR in our center between 2000 and 2015 were identified. Patients were excluded if transthoracic echocardiography was not available before surgery. Furthermore, patients with rheumatic valve disease, active endocarditis, connective tissue disorders, or hypertrophic cardiomyopathy were excluded. Included patients were divided in 3 groups according to the etiology of MR, based on echocardiographic findings and surgical observations (11,12): 1) FED, defined when thin leaflets or thickening limited to a single prolapsed segment of the MV were observed, with or without chordal rupture or flail; 2) BD, defined when a bileaflet prolapse with excess tissue, elongated chordae, and annular abnormalities, such as annular displacement and curling of the annulus, were observed; and 3) forme fruste (FF), defined when myxomatous changes in more than compared with segment of a single leaflet were observed, but without significant annular abnormalities. All patients underwent clinical and echocardiographic evaluation before MV surgery. Patient data were 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, New York Heart Association functional class, comorbidities and EuroSCORE (European System for Cardiac Operative Risk Evaluation) II. Duration of cardiopulmonary bypass and aortic cross-clamp time were noted, as were other concomitant surgical procedures. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board. Due to the retrospective design of this study, the Medical Ethical Committee waived the need of written informed consent.

ECHOCARDIOGRAPHY. Standard transthoracic echocardiography was performed with commercially available ultrasound machines (Vivid 7 and E9, GE-Vingmed, Milwaukee, Wisconsin). Images were digitally stored and analyzed offline using EchoPAC version 112 (GE Medical Systems, Horten, Norway). LV end-diastolic diameter (EDD), LV end-systolic diameter (ESD), and left atrial (LA) diameter were measured from the parasternal long-axis view. LV volumes, LVEF, and LA volumes were measured using Simpson's method and indexed for body surface area (13). Stroke volume was measured by determining the velocity time integral at the level of the LV outflow tract and the LV outflow tract diameter ($\pi \times$ [LV outflow tract diameter/2]^2 $\times$ velocity time integral). MR severity was quantitatively assessed according to current recommendations using a multiparametric approach and including the effective regurgitant orifice area (using proximal isovelocity surface area method) and regurgitant volume measurements, when feasible (14). Systolic pulmonary artery pressure was estimated by measuring maximal tricuspid regurgitant jet velocity with the simplified Bernoulli equation in combination with an estimation of the right atrial pressure, as recommended (15).

Speckle tracking analysis was performed from the apical views (2-, 3-, and 4-chamber) at a frame rate >40 fps (mean 60 fps) to assess LV-GLS. The region of interest was automatically created and manually adjusted to the myocardial thickness when necessary. LV-GLS was then calculated by averaging the peak longitudinal strain values of the 17 segments, excluding segments that could not be traced correctly.

OUTCOME ANALYSIS. The date of MV surgery was set as the beginning of the observational period. The primary endpoint of this study was all-cause mortality >30 days after surgery. The occurrence of death during follow-up was obtained by medical charts review and through the municipal civil registries for survival status. In case cause of death was unclear from the medical charts, the general practitioner or local hospital was contacted. The secondary endpoint was a combined endpoint of cardiovascular events, including cardiac death, heart failure hospitalization and cerebrovascular accidents. Heart failure hospitalization was defined when the patient was admitted because of signs and symptoms of decompensated heart failure. Patients who underwent reoperation were censored at that time.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD when normally distributed and as median (interquartile range [IQR]) when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Differences in baseline clinical and echocardiographic characteristics between the groups based on etiology were assessed using analysis of variance, Kruskal-Wallis or chi-square tests, when appropriate. To evaluate which variables were associated with the endpoints, univariable Cox proportional hazards regression analysis was performed and hazard ratio (HR) with 95% confidence interval (CI) was calculated. To identify independent prognosticators of the primary and secondary endpoint, separate multivariable analysis was performed including all variables with a $p < 0.10$ at univariable analysis.

Survival curves were constructed according to the Kaplan-Meier method to estimate cumulative survival and compared using log-rank tests. The cutoff value for LV-GLS was based on the median value

TABLE 1 Baseline Clinical Characteristics of the Total Population and Divided in 3 Groups According to the MR Etiology

	All Patients (N = 593)	FED (n = 365)	Barlow (n = 164)	Forme Fruste (n = 64)	p Value
Clinical characteristics					
Age, yrs	65 ± 12	68 ± 10	59 ± 13	64 ± 11	<0.001
Men	380 (64)	233 (64)	102 (62)	45 (70)	0.729
Hypertension	259 (46)	150 (44)	83 (52)	26 (43)	0.203
Diabetes	23 (4)	13 (4)	9 (5)	1 (2)	0.572
Atrial fibrillation	219 (37)	131 (36)	61 (37)	27 (42)	0.627
NYHA functional class					<0.001
I	169 (29)	87 (24)	64 (39)	18 (28)	
II	282 (48)	163 (45)	82 (50)	37 (58)	
III	133 (22)	107 (30)	17 (10)	9 (14)	
IV	7 (1)	6 (2)	1 (1)	0 (0)	
Serum creatinine, μmol/l	89 ± 26	92 ± 29	83 ± 17	89 ± 29	0.002
eGFR, ml/min/1.74 m^2	79 ± 27	74 ± 25	88 ± 27	83 ± 31	<0.001
EuroSCORE II, %	2.0 (1.1–3.8)	2.4 (1.3–4.5)	1.4 (0.9–2.7)	2.1 (1.0–3.6)	<0.001
MV surgery					
Type of surgery					0.240
MV repair	584 (98)	360 (99)	160 (97)	64 (100)	
MVR (mechanical)	4 (1)	1 (0.3)	3 (2)	0 (0)	
MVR (bioprosthetic)	5 (1)	4 (1)	1 (0.6)	0 (0)	
Aortic cross-clamp time, min	200 ± 67	188 ± 63	217 ± 62	222 ± 85	<0.001
CPB time, min	151 ± 52	142 ± 51	167 ± 49	167 ± 54	<0.001
Concomitant procedures					
CABG	121 (20)	85 (23)	17 (10)	19 (30)	0.003
TVP	274 (46)	161 (44)	87 (53)	26 (47)	0.103
MAZE	168 (28)	90 (25)	54 (33)	24 (38)	<0.001
Aortic surgery	45 (8)	37 (10)	6 (4)	2 (3)	<0.001

Values are mean ± SD, n (%), or median (interquartile range).

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FED = fibroelastic deficiency; MR = mitral regurgitation; MV = mitral valve; MVR = mitral valve replacement; NYHA = New York Heart Association; TVP = tricuspid valve annuloplasty.

(-20.6%) of the study population which is in concordance with previously suggested cutoff value for normal range (6,7). To provide more insight into the relation between LV-GLS and mortality, also Kaplan-Meier curves according to tertiles of LV-GLS were constructed. To assess the additional prognostic value of LV-GLS on top of other clinical variables, likelihood-ratio testing was performed and Harrell's C-statistic (16) was calculated. A p value <0.05 was considered significant. SPSS software package version 20 (IBM Corporation, Armonk, New York) was used for statistical analysis.

RESULTS

PATIENT POPULATION. A total of 593 patients were included (age 65 ± 12 years, 64% men) of a cohort of 684 patients who underwent surgery for organic MR in our center. Of these, 91 patients were excluded due to the lack of echocardiographic examinations (or of

TABLE 2 Echocardiographic Characteristics of the Total Population and Divided in 3 Groups According to MR Etiology

	All Patients (N = 593)	FED (n = 365)	Barlow (n = 164)	Forme Fruste (n = 64)	p Value
LVEDD, mm	54 ± 7	54 ± 7	55 ± 7	54 ± 7	0.034
LVEDD index, mm/m^2	29 ± 4	28 ± 4	29 ± 4	28 ± 4	0.190
LVESD, mm	33 ± 7	33 ± 7	34 ± 7	33 ± 7	0.481
LVESD index, mm/m^2	18 ± 4	18 ± 4	18 ± 4	17 ± 4	0.752
LVEDV, ml	135 ± 42	132 ± 42	141 ± 41	135 ± 42	0.082
LVEDV index, ml/m^2	71 ± 20	69 ± 20	73 ± 17	70 ± 19	0.144
LVESV, ml	45 (34-59)	44 (32-58)	48 (37-60)	44 (36-61)	0.055
LVESV index, ml/m^2	23 (19-30)	23 (18-30)	25 (20-31)	23 (19-31)	0.064
LVEF, %	65 ± 8	65 ± 8	64 ± 8	64 ± 8	0.742
Forward SV, ml	59 (48-72)	59 (48-73)	58 (45-71)	62 (48-74)	0.849
LA diameter, mm	45 ± 8	45 ± 7	45 ± 9	47 ± 8	0.153
LAVI, ml/m^2	51 (39-63)	48 (38-61)	53 (42-69)	52 (41-70)	0.063
MR grade					0.014
III	186 (31)	98 (27)	67 (40)	21 (33)	
IV	407 (69)	267 (73)	97 (60)	43 (67)	
EROA, mm^2	41 (29-54)	41 (31-55)	38 (28-53)	42 (28-55)	0.186
RVol, ml	57 ± 24	60 ± 22	51 ± 28	60 ± 23	0.004
TR grade					0.851
0	66 (12)	41 (12)	18 (11)	7 (11)	
1-2	468 (81)	286 (81)	131 (80)	51 (84)	
3-4	38 (7)	26 (7)	9 (5)	3 (5)	
sPAP, mm Hg	32 (27-43)	35 (28-48)	30 (25-35)	30 (25-42)	<0.001
LV-GLS, %	-21 ± 4	-20 ± 4	-22 ± 4	-21 ± 4	0.003

Values are mean ± SD, median (interquartile range), or n (%).

EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; EROA = effective regurgitant orifice area; ESD = end-systolic diameter; ESV = end-systolic volume; GLS = global longitudinal strain; LA = left atrial; LAVI = left atrial volume index; LV = left ventricular; RVol = regurgitant volume; sPAP = systolic pulmonary artery pressure; SV = stroke volume; other abbreviations as in Table 1.

sufficient quality) before surgery. A total of 365 patients were classified as FED, 164 were classified as BD, and 64 as FF. Baseline clinical characteristics and the differences between the 3 groups are shown in Table 1. Patients with BD were significantly younger than patients with FF or FED (age 59 ± 13 years vs. 64 ± 11 years and 68 ± 10 years, respectively). No differences were observed for cardiovascular risk factors and the incidence of AF (either paroxysmal or persistent) among the 3 groups. However, patients with BD were more often asymptomatic which was shown by the percentage of patients in New York Heart Association functional class I (39% vs. 28% and 24%; $p < 0.001$). Furthermore, patients with BD had a better renal function and a lower EuroSCORE II. However, patients with BD had longer surgery times, as reflected by a longer cardiopulmonary bypass time and longer aortic cross-clamp time, but they underwent less frequently concomitant coronary artery bypass grafting, whereas no differences were observed for concomitant tricuspid valve annuloplasty (Table 1).

ECHOCARDIOGRAPHIC CHARACTERISTICS. Baseline echocardiographic characteristics and differences among the 3 groups are shown in Table 2. Median time between the echocardiography and MV surgery was 40 (IQR: 7 to 135) days, which was not significantly different between groups. Mean LVEF was 65 ± 8%, and only 113 (19%) patients had LVEF between 50% and 60%; no differences in LVEF were noted between groups. Patients with BD had slightly larger LVEDD compared with patients with FF and FED (55 ± 7 mm vs. 54 ± 7 mm and 54 ± 7 mm for LVEDD; $p = 0.034$); however, when LVEDD was indexed for body surface area, it was not significantly different among the groups. Similarly, LVESD, LA dimension and LV and LA volumes were not significantly different between groups. The effective regurgitant orifice area was not significantly different among the 3 groups, but the regurgitant volume was slightly lower in patients with BD compared with FED and FF (51 ± 28 ml for BD, vs. 60 ± 22 ml and 60 ± 24 ml for FF and FED, respectively; $p = 0.004$). Of interest, the systolic pulmonary artery pressure was significantly higher in FED patients compared with FF and BD (35 [IQR: 28 to 48] mm Hg vs. 32 [IQR: 27 to 43] mm Hg and 30 [IQR: 25 to 35] mm Hg; $p < 0.001$). Furthermore, mean LV-GLS was within the normal ranges in the overall population (-20.7 ± 4.0%). Interestingly, LV-GLS was better in BD patients as compared with FF and FED (-22 ± 4% vs. -21 ± 4% and -20 ± 4%, respectively; $p = 0.003$).

OUTCOME. During median follow-up of 6.4 (IQR: 3.6 to 10.4) years, 146 deaths occurred, of which 16 occurred <30 days after surgery (1 gastrointestinal bleeding, 7 multiorgan failure, 2 acute myocardial infarction, 5 heart failure, and 1 ventricular arrhythmia). A total of 31 patients underwent second MV surgery, of whom 10 died during further follow-up, they were censored at time of reoperation. For the remaining 120 deaths, cause of death was cardiac in 28 patients, unknown in 36 patients, and noncardiac in 56 patients. Furthermore, 46 patients were admitted to the hospital because of heart failure and 13 patients had a cerebrovascular accident.

Survival analysis. Univariable Cox hazard regression analysis showed that age, New York Heart Association functional class ≥II, previous AF, estimated glomerular filtration rate, LVEDD, LVEF, systolic pulmonary artery pressure, LV-GLS, and MR etiology (BD being protective) were associated with the all-cause mortality endpoint. However, multivariable analysis showed that only age and LV-GLS were independently associated with all-cause mortality (HR: 1.08; 95% CI: 1.05 to 1.11; $p < 0.001$ for age; HR: 1.13; 95% CI:

1.06 to 1.21; p < 0.001 for LV-GLS) (Table 3). In Table 4, the results of the Cox cause-specific hazard analysis are shown for the secondary endpoint. The multivariable analysis showed that previous AF and LV-GLS were independently associated with cardiovascular events (HR: 1.08; 95% CI: 1.01 to 1.15; p = 0.019 for LV-GLS; HR: 1.70; 95% CI: 1.01 to 2.86; p = 0.045 for previous AF).

Patients with more preserved LV-GLS showed significant better survival in terms of all-cause mortality than patients with more impaired LV-GLS, when divided based on the median LV-GLS of -20.6% (log-rank 22.6; p < 0.001) (Central Illustration). In particular, cumulative survival for all-cause mortality was 94% and 85% at 5 and 10 years, respectively, for patients with preserved LV-GLS <-20.6% and 81% and 60% for patients with impaired LV-GLS (≥-20.6%). In addition, when dividing the population in 3 groups according to tertiles of LV-GLS, patients with most preserved LV-GLS (≤-22.3%) showed better outcome in terms of all-cause mortality than did patients with mildly impaired LV-GLS (between -22.3% and -19.5%), while patients with most impaired LV-GLS (≥-19.5% showed worst survival (log-rank 36.1; p < 0.001) (Central Illustration).

Incremental value of LV-GLS. Figure 1 shows the incremental value for predicting all-cause mortality of LV-GLS on top of other clinical and echocardiographic variables evaluated by the likelihood-ratio testing and the Harrell's C-statistic. The addition of LV-GLS to a clinical model (including: age, AF, New York Heart Association functional class ≥II, estimated glomerular filtration rate, LVEDD, LVEF, systolic pulmonary artery pressure), provided significant improvement of the prognostic model (p < 0.001) with an increase of C-statistic 0.74 to 0.77.

DISCUSSION

The main findings of this study can be summarized as follows: 1) LV-GLS is independently associated with all-cause mortality and cardiovascular events in patients undergoing MV surgery for severe primary MR; 2) LV-GLS has incremental prognostic value over clinical risk factors for long-term survival; and 3) when corrected for age, patients with BD showed similar prognosis compared with FED and FF despite more complex MV involvement and challenging MV repair.

PROGNOSTIC MARKERS FOR LONG-TERM OUTCOME AFTER MITRAL VALVE SURGERY. Development of LV dilatation and dysfunction is one of the most important factors considered in current guidelines to refer patients with severe primary MR for surgery. In particular, current European guidelines recommend MV surgery (3), even when patients are asymptomatic, if LVEF is ≤60% and/or LVESD ≥45 mm. Most recent American guidelines (4) consider MV surgery also reasonable in these patients when a decrease in

TABLE 3 Univariable and Multivariable Cox Regression Analysis to Identify Independent Predictors for All-Cause Mortality After MV Surgery (Primary Endpoint)

	Univariable HR (95% CI)	p Value	Multivariable HR (95% CI)	p Value
Age, yrs	1.09 (1.07-1.11)	<0.001	1.08 (1.05-1.11)	<0.001
NYHA functional class ≥II	2.12 (1.32-3.39)	0.002	1.20 (0.70-2.06)	0.504
Atrial fibrillation	1.77 (1.24-2.53)	0.002	0.92 (0.56-1.50)	0.726
eGFR, ml/min/1.74 m^2	0.97 (0.96-0.98)	<0.001	0.99 (0.98-1.01)	0.447
LVEDD, mm	0.96 (0.93-0.99)	0.005	0.98 (0.95-1.02)	0.389
LVESD, mm	1.01 (0.98-1.03)	0.571		
LVEF, %	0.97 (0.95-0.99)	0.009	1.00 (0.97-1.03)	0.891
LA diameter, mm	1.02 (1.00-1.04)	0.081	1.01 (0.98-1.04)	0.614
EROA, mm^2	1.00 (0.99-1.01)	0.729		
LVGLS, %	1.16 (1.11-1.21)	<0.001	1.13 (1.06-1.21)	<0.001
sPAP, mm Hg	1.02 (1.00-1.03)	0.016	0.99 (0.98-1.01)	0.530
TVP	0.88 (0.61-1.27)	0.494		
CABG	1.03 (0.66-1.61)	0.901		
MVR	0.91 (0.13-6.51)	0.203		
Diagnosis				
Forme fruste		<0.001		0.257
FED	1.14 (0.65-2.00)	0.655	0.58 (0.29-1.15)	0.117
Barlow	0.41 (0.21-0.83)	0.013	0.56 (0.25-1.24)	0.557

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

TABLE 4 Univariable and Multivariable Cox Cause-Specific Hazard Analysis to Identify Independent Predictors for Cardiovascular Events (Secondary Endpoint Including Cardiac Death, HF Hospitalizations, and CVA) After MV Surgery

	Univariable HR (95% CI)	p Value	Multivariable HR (95% CI)	p Value
Age, yrs	1.06 (1.03-1.08)	<0.001	1.03 (0.99-1.07)	0.076
NYHA functional class ≥II	1.85 (1.07-3.19)	0.027	1.01 (0.55-1.85)	0.971
Atrial fibrillation	2.57 (1.66-3.96)	<0.001	1.70 (1.01-2.86)	0.045
eGFR, ml/min/1.73 m^2	0.98 (0.97-0.99)	<0.001	0.99 (0.98-1.01)	0.621
LVEDD, mm	0.98 (0.94-1.00)	0.129		
LVESD, mm	1.02 (0.99-1.05)	0.261		
LVEF, %	0.98 (0.96-1.01)	0.115		
LA diameter, mm	1.02 (0.99-1.05)	0.153		
EROA, mm^2	1.00 (0.99-1.02)	0.909		
LV-GLS, %	1.12 (1.06-1.19)	<0.001	1.08 (1.01-1.15)	0.019
sPAP, mm Hg	1.02 (1.00-1.03)	0.016	1.01 (0.99-1.02)	0.452
TVP	1.10 (0.72-1.69)	0.665		
CABG	1.39 (0.85-2.26)	0.187		
MVR	1.97 (0.27-14.16)	0.502		
Diagnosis				
Forme fruste		0.013		0.208
FED	1.19 (0.59-2.39)	0.629	0.72 (0.33-1.56)	0.403
Barlow	0.48 (0.21-1.13)	0.094	0.44 (0.17-1.12)	0.085

CVA = cerebrovascular accident; HF = heart failure; other abbreviations as in Tables 1 to 3.

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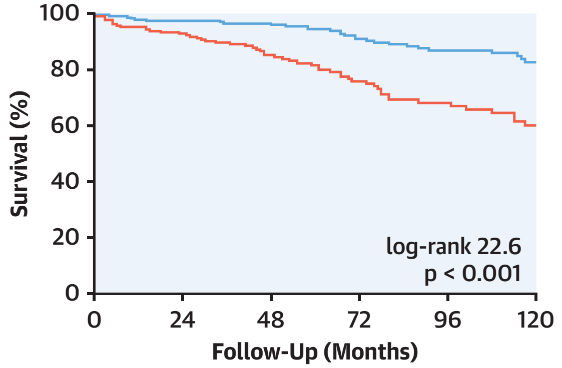
CENTRAL ILLUSTRATION Kaplan-Meier Survival Curves According to LV-GLS

A **All-Cause Mortality**

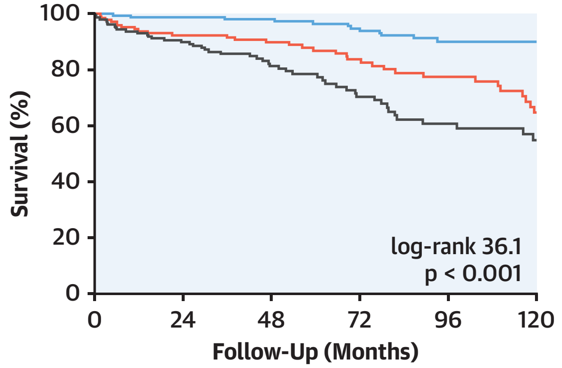


Number at risk

LV GLS < -20.6%					
249	223	192	150	109	69
LV GLS ≥ -20.6%					
229	182	124	89	59	37

LV-GLS < -20.6% LV-GLS ≥ -20.6%

B **All-Cause Mortality**

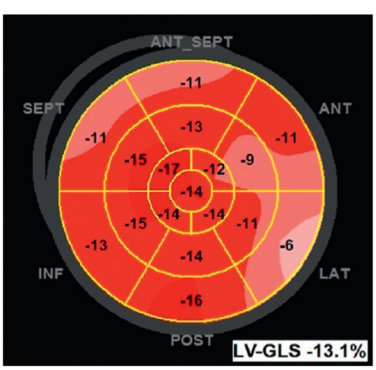


Number at risk

LV-GLS ≤ -22.3%					
161	150	128	110	81	53
LV-GLS > -22.3%, <-19.5%					
152	124	100	75	53	33
LV-GLS ≥ -19.5%					
165	134	89	59	38	26

LV-GLS ≤ -22.3% LV-GLS ≥ -19.5%
LV-GLS > -22.3%, < -19.5%

C



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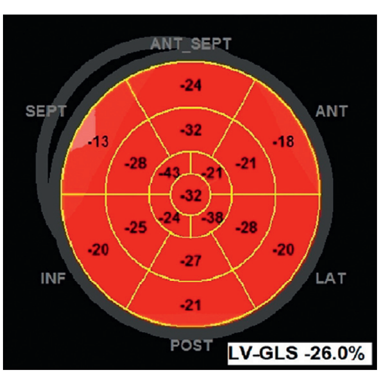

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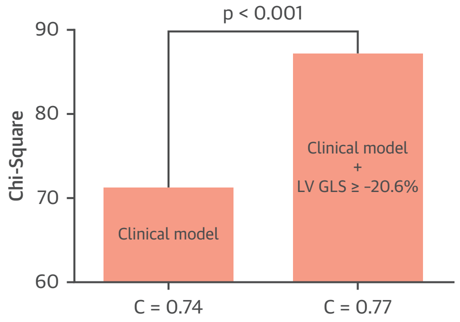
In the **upper panel**, survival curves for all-cause mortality are shown **(A)** according to the median left ventricular global longitudinal strain (LV-GLS) (-20.6%) and **(B)** according to the tertiles of LV-GLS (≤-22.3%; -22.3% to -19.5%; ≥-19.5%). In the **lower panel**, examples of bullseye plot of LV-GLS are shown: **(C)** a 69-year-old patient, with impaired LV-GLS (-13.1%), who died of heart failure 1.5 year after the echocardiography, and **(D)** a 46-year-old patient, with preserved LV-GLS (-26.0%), who did not experience an event during 12.3 years of follow-up. ANT = anterior; INF = inferior; LAT = lateral; POST = posterior; SEPT = septum.

FIGURE 1 Likelihood Ratio Test for the Incremental Prognostic Value of LV-GLS



The bar graphs show the incremental value of left ventricular global longitudinal strain (LV-GLS) to the standard clinical and echocardiographic variables associated with all-cause mortality. Harrell's C-statistic represents overall adequacy of risk prediction.

LVEF or increase in LVESD is observed during serial echocardiographic examinations, based on the increasing evidence that patients benefit most from surgery when LV function is still preserved. It is, however, challenging to measure LV systolic function accurately in these patients because LVEF might not properly reflect LV function in the presence of severe MR and, importantly, structural and functional alterations of LV myocardium may occur before a decline in LVEF can be detected (17). Therefore, studies have focused on identifying other parameters which are able to better detect subclinical LV systolic dysfunction. Brain natriuretic peptide is one of the parameters proposed as a marker of LV dysfunction in these patients. Pizarro et al. (18) showed that elevated plasma brain natriuretic peptide levels were associated with the combined endpoint of heart failure symptoms, LV dysfunction or death in patients with severe organic MR and LVEF >60%. Mentias et al. (19) demonstrated that higher levels of plasma brain natriuretic peptide are associated with worse survival in a cohort of 548 patients with asymptomatic severe organic MR. In addition, GLS has been proposed as a sensitive and reliable marker of subtle LV dysfunction in patients with severe primary MR and initial studies showed that in these patients, impaired LV-GLS at baseline was associated with worse LV function after MV surgery (20-22). The prognostic value of LV-GLS was shown in 2 studies which showed that LV-GLS was associated with long-term mortality together with reduced exercise capacity and elevated brain natriuretic peptide in asymptomatic patients with severe MR and preserved LVEF (6,7). However, current guidelines emphasize the potential limitation of intervendor differences in the software algorithms for LV-GLS measurement (3) and in these studies only vector velocity imaging was applied to measure LV-GLS. The present study confirmed the independent prognostic value of LV-GLS when measured with another widely available speckle tracking-based software and in a large population of patients undergoing MV repair with a long-term follow-up. Recently, also Kim et al. (8) studied the prognostic value of LV-GLS after MV surgery in 506 patients with severe primary MR and showed that LV-GLS, measured with another widely used software, was associated with worse outcome in terms of cardiac events and all-cause mortality with a median follow-up of 3.5 years; however, more than 10% of the patients had rheumatic or congenital MR and more than 40% in the outcome group underwent MV replacement (instead of repair), which was also significantly associated with the outcome. The present study confirms these results in a more homogenous population of 593 patients with only degenerative MR, who underwent solely MV repair, and with longer follow-up duration.

DIFFERENCES BETWEEN ETIOLOGIES: BD VERSUS FD. BD and FED are the most common forms of primary MR (14). BD is characterized by thickened MV leaflets, multisegmental prolapse, chordal elongation or rupture, and typical annular abnormalities, such as dilatation, abnormal motion, and posterior displacement of the annulus. In turn, patients with FED typically show thin, or normal thickened, MV leaflets, single segment prolapse, or chordal rupture (11). The correct etiologic classification is important for patient management, having an impact in the decision making for timing of surgery and surgical approach. Several studies showed that MV repair surgery for BD is usually longer, more complex and has a lower success rate than in FED if not performed in experienced centers. On the other hand, patients with BD are normally younger, with less comorbidities and less symptoms at first presentation (11). Although the clinical need for differentiation between BD and FED has already been recognized in current guidelines (3,9), there are only few data available focused on the prognostic value of MR etiology for patients undergoing MV surgery. A study by Coutinho et al. (23) evaluated long-term outcome (reoperation and mortality) after MV surgery in patients with FED or myxomatous valves: no differences were observed in mortality or reoperation between those groups. However, the study analyzed only patients with anterior or bileaflet prolapse. The present study showed, in line with previous literature, that patients with BD are usually younger, have less comorbidities and a lower logistic EuroSCORE II, compared with patients with FED or FF. When corrected for age, patients with BD showed similar prognosis as compared with FED and FF despite more complex MV involvement and challenging MV repair. In addition, MR etiology was included in the multivariate analysis when assessing the prognostic value of LV-GLS in primary MR but was not independently associated with long-term mortality or with cardiovascular events.

CLINICAL IMPLICATIONS. Appropriate timing for surgery and risk stratification in patients with severe primary MR is still challenging and therefore research has focused on identifying new and reliable prognostic parameters. The present study confirmed the prognostic value of LV-GLS in patients with severe primary MR and specifically showed that patients with normal LV-GLS have a significantly better outcome. Particularly in asymptomatic patients with severe primary MR, without signs of LV dysfunction according to conventional criteria, or any other clinical indications for surgery according to current guidelines, presence of impaired LV-GLS could possibly lead to early surgery in experienced centers, instead of watchful waiting until overt LV dysfunction develops. In these patients, MV surgery at this early stage might protect for developing LV dysfunction, possibly irreversible, and subsequent adverse events during the follow-up after surgery. This hypothesis, however, needs to be demonstrated in a prospective study. Also, in patients who already have indication for surgery according to current guidelines based on other parameters, LV-GLS can optimize risk stratification reflecting more accurately myocardial dysfunction. Furthermore, the present study showed that complex MV lesions, as seen in BD, do not influence the long-term outcome specifically in patients with normal LV-GLS, and therefore absence of myocardial dysfunction.

STUDY LIMITATIONS. Because this study has been performed in a tertiary referral center, highly experienced in MV surgery, the results from this cohort might not be generalizable to other centers. Similarly, recurrence of MR during follow-up was not considered, being the aim of the study to identify baseline characteristics associate with the long-term outcome after surgery. Furthermore, although relatively large, patient population was not large enough to perform robust multivariable analyses separately for the 3 MR etiologic groups. Also, brain natriuretic peptide was not routinely measured and could therefore not be included in this analysis. Finally, further large prospective studies are needed to confirm the results and to assess how LV-GLS can tailor treatment and optimize surgical management for the different etiologies of primary MR.

CONCLUSIONS

LV-GLS, as a sensitive marker of LV systolic dysfunction, is independently associated with long-term all-cause mortality and cardiovascular events after MV surgery for primary MR and can therefore be helpful in optimizing timing of surgery and risk stratification. Importantly, despite more complex involvement of the MV apparatus and therefore surgical operation, patients with Barlow's disease showed similar prognosis compared with patients with FED or FF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The present study confirms the independent association of LV-GLS and long-term adverse events in a large cohort of patients who underwent MV surgery for severe primary MR. In addition, it shows that MR etiology does not have a significant influence on outcome in an experienced surgical center.

TRANSLATIONAL OUTLOOK: Complex MV lesions should not delay surgery when patients could be operated in an experienced surgical center. Furthermore, LV-GLS could be used as a new parameter to optimize timing for surgery in these patients, but large prospective studies are needed to evaluate how this could be implemented in daily practice.

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