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Advanced echocardiography in characterization and management of patients with secondary mitral regurgitation

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Citation

Namazi, F. (2022, May 10). *Advanced echocardiography in characterization and management of patients with secondary mitral regurgitation*. Retrieved from https://hdl.handle.net/1887/3303481

Version:	Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).

Part II

Echocardiography and prognosis in secondary mitral regurgitation

Chapter three

Prognostic Value of Left Ventricular Global Longitudinal Strain in Patients With Secondary Mitral Regurgitation

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J Am Coll Cardiol. 2020 Feb 25;75(7):750-758.

Abstract

Background
Left ventricular (LV) systolic function may be overestimated in patients with secondary mitral regurgitation (MR) when using LV ejection fraction (EF). LV global longitudinal strain (GLS) is a less load-dependent measure of LV function. However, the prognostic value of LV GLS in secondary MR has not been evaluated.

Objectives
This study sought to demonstrate the prognostic value of LV GLS over LVEF in patients with secondary MR.

Methods
A total of 650 patients (mean 66 ± 11 years of age, 68% men) with significant secondary MR were included. The study population was subdivided based on the LV GLS value at which the hazard ratio (HR) for all-cause mortality was >1 using a spline curve analysis (LV GLS <7.0%, impaired LV systolic function vs. LV GLS ≥7.0%, preserved LV systolic function). The primary endpoint was all-cause mortality.

Results
During a median follow-up of 56 (interquartile range: 28 to 106 months) months, 334 (51%) patients died. Patients with a more impaired LV GLS showed significantly higher mortality rates at 1-, 2-, and 5-year follow-up (13%, 23%, and 44%, respectively) when compared with patients with more preserved LV systolic function (5%, 14%, and 31%, respectively). On multivariable analysis, LV GLS <7.0% was associated with increased mortality (HR: 1.337; 95% confidence interval: 1.038 to 1.722; p = 0.024), whereas LVEF ≤30% was not (HR: 1.055; 95% confidence interval: 0.794 to 1.403; p = 0.711).

Conclusions
In patients with secondary MR, impaired LV GLS was independently associated with an increased risk for all-cause mortality, whereas LVEF was not. LV GLS may therefore be useful in the risk stratification of patients with secondary MR.

Introduction

The results of current landmark randomized trials evaluating the prognostic impact of transcatheter mitral valve repair therapy (using the MitraClip device [Abbott Vascular, Menlo Park, California]) in patients with secondary mitral regurgitation (MR) have underscored the relevance of patient selection for this treatment (1,2). MitraClip therapy did not confer a survival benefit compared with optimal medical therapy in the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial (1), whereas in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, patients randomized to the MitraClip arm had significant reduction in the composite endpoint of heart failure hospitalization and all-cause mortality (2). One of the factors underlying these discrepant results is the difference in left ventricular (LV) volumes between the study populations. Besides differences in grading MR between the 2 trials, patients enrolled in the MITRA-FR trial had larger LV volumes as compared with patients included in the COAPT trial. In contrast, LV ejection fraction (LVEF) was comparable in the 2 study populations. These facts suggest that patients included in the MITRA-FR trial had more advanced LV remodeling status as compared with patients included in the COAPT trial and that LVEF may not be an appropriate parameter to identify the patients who will benefit from mitral valve intervention. However, current guidelines base the recommendation to perform mitral valve surgery in heart failure patients with secondary MR on LVEF (3). In light of the available evidence, the method to assess LV systolic function in severe secondary MR that will identify the patients who will improve their prognosis with mitral valve intervention remains an unmet clinical need (4). Two-dimensional (2D) LV global longitudinal strain (GLS) measured with speckle tracking echocardiography has demonstrated more advanced LV damage (myocardial fibrosis) than LVEF in patients with nonischemic cardiomyopathy and severe secondary MR (5). However, the prognostic implications of LV GLS in patients with secondary MR have not been investigated. Accordingly, the aim of the present study was to evaluate the prognostic value of LV GLS over LVEF in a large cohort of patients with significant secondary MR.

Methods

Patient population

Patients with moderate and severe secondary MR, of both ischemic and nonischemic etiology, were identified retrospectively from the departmental clinical database (EPD-Vision 11.8.4.0, Leiden University Medical Center, Leiden, the Netherlands) and

echocardiographic database. The first echocardiogram performed with the patient in hemodynamic stable conditions and showing moderate and severe secondary MR defined the time point of entry in the analysis. Patients with previous invasive mitral valve intervention and patients with echocardiographic data not analyzable with 2D speckle-tracking echocardiography were excluded (Online Figure 1). The Institutional Review Board approved this retrospective analysis of clinically acquired data and waived the need of written patient informed consent.

Clinical variables included the New York Heart Association (NYHA) functional class, etiology of heart failure, heart rhythm, comorbidities, and medications. Ischemic etiology was defined by the presence of coronary artery disease diagnosed on invasive coronary angiography or a history of coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting (CABG). Mitral valve intervention included surgical therapy (i.e., surgical mitral valve repair, mitral valve replacement) and percutaneous edge-to-edge mitral valve repair.

Echocardiography

Transthoracic echocardiography was performed with patients at rest in the left lateral decubitus position, using a commercially available system (GE Vingmed Ultrasound, General Electric, Milwaukee, Wisconsin). Parasternal, apical, and subcostal views were acquired using 3.5 MHz or M5S transducers. Two-dimensional, M-mode, and Doppler data were stored for offline analysis (EchoPAC 201.0.0, GE Vingmed Ultrasound). LV volumes (end-systolic and end-diastolic) were measured in the apical 2- and 4-chamber views and LVEF was calculated according to Simpson's biplane method and indexed for body surface area (6). MR severity was graded according to current recommendations using an integrative approach that includes qualitative, semiquantitative, and quantitative data: mild (grade 1), moderate (grade 2), moderate to severe (grade 3), and severe (grade 4) (7, 8, 9). Significant MR was defined by a grade of ≥2+. Parameters for LV diastolic function included peak early diastolic wave and late diastolic wave measured on pulsed wave Doppler of mitral inflow, and the peak early diastolic wave-to-late diastolic wave ratio was calculated. Using tissue Doppler imaging, the septal and lateral peak early diastolic mitral annular velocities were measured in the apical 4-chamber view (10). As a measure of LV filling pressures, the ratio between peak early diastolic transmitral flow velocity and peak early diastolic mitral annular tissue velocity ratio was calculated. The tricuspid regurgitation was assessed on continuous-wave Doppler and tricuspid regurgitation velocity was calculated. To evaluate right ventricular function, tricuspid annular plane systolic excursion was measured on the apical 4-chamber view using the M-mode (11). LV GLS was measured from standard

2D transthoracic echocardiography using the apical 4-chamber, 2-chamber, and long-axis views of the LV (12). LV GLS was determined offline using commercially available software (EchoPAC 201.0.0). LV GLS measures the shortening of the myocardial fibers and is presented as negative values conventionally: more negative values indicate better systolic function (shortening), whereas less negative values, closer to 0, indicate more impaired systolic function. However, in this study, absolute values of LV GLS are presented (Figure 1). The intraclass correlation coefficients for the interobserver and intraobserver reproducibility of LV GLS measurements in this population was 0.89 (95% confidence interval [CI]: 0.63 to 0.96; p < 0.001) and 0.93 (95% CI: 0.84 to 0.97; p < 0.001), respectively.

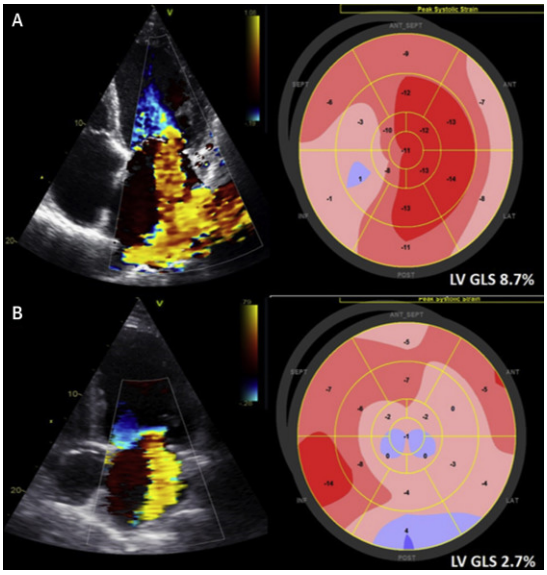


Figure 1. Measurement of LV GLS in Patients With Secondary MR
(A) A 59-year old patient with ischemic cardiomyopathy, in New York Heart Association functional class IV with severe mitral regurgitation (MR) and a left ventricular ejection fraction (LVEF) of 21%. (B) A patient with severe MR and an LVEF of 20%. Despite having the same degree of MR and a comparable LVEF, the LV global longitudinal strain (GLS) was highly different, which demonstrates that patient in A had a better LV systolic function when compared with the patient in B.

Follow-up

Patients were followed-up for the primary endpoint of all-cause mortality. Data on mortality were obtained from the departmental cardiology information system (EPD-Vision 11.8.4.0), which is linked to the governmental death registry database. Follow-up data were complete for all patients.

Statistical analysis

Categorical data are presented as absolute numbers and percentages. Continuous data are presented as mean ± SD when normally distributed or as median with interquartile range, when not normally distributed. To compare baseline characteristics between 2

groups, chi-square tests were used for categorical data and the unpaired Student's t-test or Mann-Whitney U test, as appropriate, for continuous data. Changes in hazard ratio (HR) for all-cause mortality across the LV GLS values (as a continuous variable) were investigated by fitting a spline curve (Figure 2). A threshold of LV GLS to dichotomize the population was derived from the spline curve (i.e., in which the predicted HR is ≥1). Cumulative survival rates were estimated by the Kaplan-Meier method for all-cause mortality, and a log-rank test was used to compare groups. Cox proportional hazards regression analysis was performed to investigate the association between clinical and echocardiographic parameters with all-cause mortality. The HR and 95% CI were calculated and reported. In the univariable analysis, p values <0.05 were considered statistically significant and were included in the multivariable model. To investigate the incremental value of LV GLS over clinical and conventional echocardiographic parameters to predict outcome, the likelihood ratio test was performed. The change in global chi-square values was calculated and reported. A 2-tailed p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows, version 23.0 (IBM Corporation, Armonk, New York) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

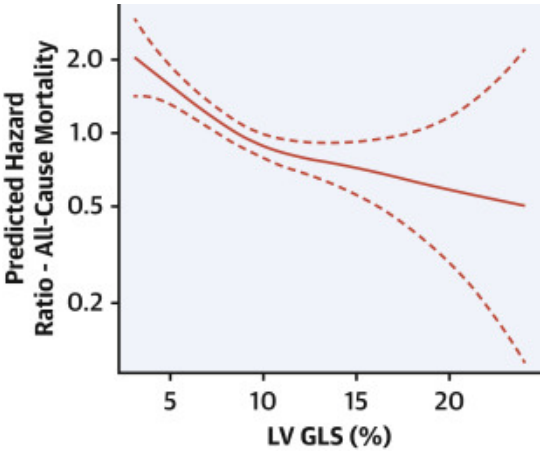


Figure 2. Spline Curve for All-Cause Mortality According to LV GLS

Prediction of all-cause mortality across a range of LV GLS, plotted as a fitted spline model on a log-hazard scale with overlaid confidence intervals. Red dashed lines represent 95% confidence intervals. Abbreviations as in Figure 1.

Results

Patient population

A total of 650 patients (mean 66 ± 11 years of age, 68% men) were included. The majority of patients were in NYHA functional class II and III, and 52% of patients had ischemic heart failure (Table 1). Table 2 summarizes the echocardiographic data for the overall population. The median LV GLS was 7.2% (interquartile range: 5.2% to 9.9%) in

the overall population, while the mean LVEF was 29 ± 10%. The majority of patients (83%) had grade 3 to 4 MR.

Table 1. Clinical Characteristics at Baseline

	Total Population (N = 650)	GLS ≥7.0% (n = 349)	GLS <7.0% (n = 301)	p Value
Age, yrs	66 ± 11	67 ± 11	65 ± 11	0.009
Male	439 (68)	225 (65)	214 (71)	0.072
BSA, m²	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.512
Atrial fibrillation	269 (41)	152 (44)	117 (39)	0.227
Hypertension	255 (39)	153 (44)	102 (34)	0.010
Diabetes mellitus	147 (23)	85 (24)	62 (21)	0.254
Creatinine level, mmol/l	102 (83–133)	97 (82–126)	106 (87–142)	0.002
NYHA functional class				
I	32 (5)	16 (5)	16 (5)	0.667
II	156 (24)	93 (27)	63 (21)	0.089
III	386 (59)	208 (60)	178 (59)	0.905
IV	76 (12)	32 (9)	44 (15)	0.031
Heart failure etiology				
Ischemic	340 (52)	190 (54)	150 (50)	0.241
Nonischemic	310 (48)	159 (46)	151 (50)	0.241
Medication				
Beta-blockers	455 (70)	257 (74)	198 (66)	0.029
Diuretics	543 (84)	274 (79)	269 (89)	<0.001
ACE inhibitor/ARB	529 (81)	286 (82)	243 (81)	0.691

Values are mean ± SD, n (%), or median (interquartile range). Patients were divided according to less impaired LV GLS (≥7.0%) vs. more impaired LV GLS (<7.0%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; GLS = global longitudinal strain; LV = left ventricular; NYHA = New York Heart Association.

Follow-up

After a median follow-up of 56 (interquartile range: 28 to 106) months, 334 (51.4%) patients died. Cardiac resynchronization therapy (CRT) was received by 453 (70%) patients (before mitral valve intervention). In 270 (42%) patients, mitral valve intervention was performed after a median follow-up of 35 (interquartile range: 17 to 65) months. Invasive treatment performed after baseline echocardiography is summarized in Table 3.

To investigate the association between LV GLS and all-cause mortality, spline curve analysis was performed. The assumption of linearity for all-cause mortality, predicted from the baseline LV GLS, was not violated (chi-square = 3.0489; p = 0.23) (i.e.,

demonstrating a nonlinear relation of LV GLS vs. all-cause mortality). After an initial plateau and slow rise of HR, there was an increase in the HR for more impaired values of LV GLS (<7.0%) (Figure 2). Based on the spline curve, a value of LV GLS 7.0% was used to dichotomize the population. Patients with more impaired LV systolic function (LV GLS <7.0%) were younger, had more impaired renal function, were more symptomatic (NYHA functional class IV), used less frequently beta-blockers and more often received CRT before invasive mitral valve intervention as compared with patients with more preserved LV systolic function (LV GLS ≥7.0%) (Tables 1, 2, and 3). Patients with more preserved LV GLS (≥7.0%) had a significantly higher prevalence of hypertension. In terms of echocardiographic data, patients with more impaired LV GLS (<7.0%) had significantly larger LV volumes and lower LVEF, compared with the group of patients with more preserved LV GLS (≥7.0%) (Table 2). During follow-up, patients with more preserved LV GLS (≥7.0%) underwent more frequently surgical mitral valve repair with concomitant CABG, whereas those with more impaired LV GLS (<7.0%) were less likely to undergo any invasive mitral valve intervention (Table 3).

Table 2. Echocardiographic Characteristics at Baseline

	Total Population (N = 650)	GLS ≥7.0% (n = 349)	GLS <7.0% (n = 301)	p Value
LVEDVi, ml	107 ± 41	92 ± 31	124 ± 45	<0.001
LVESVi, ml	79 ± 37	63 ± 27	96 ± 40	<0.001
LVEF, %	29 ± 10	33 ± 11	23 ± 7	<0.001
LV GLS, %	7.2 (5.2–9.9)	9.6 (8.0–11.7)	5.1 (3.4–6.0)	<0.001
MR grade				
2	113 (17)	57 (16)	56 (19)	0.446
3	290 (45)	165 (47)	125 (42)	0.141
4	247 (38)	127 (36)	120 (40)	0.362
LAVI, ml/m²	34 (26–45)	33 (24–45)	35 (27–46)	0.047
E′	4.5 ± 2.0	5.0 ± 2.1	4.0 ± 1.7	<0.001
E/E′ ratio	25 ± 22	23 ± 27	26 ± 16	0.084
TR velocity, m/s	2.7 ± 0.6	2.6 ± 0.6	2.7 ± 0.6	0.021
SPAP, mm Hg	40 ± 13	39 ± 13	42 ± 14	0.020
TAPSE, mm	16 ± 5	16 ± 5	15 ± 4	<0.001

Values are mean ± SD, median (interquartile range), or n (%). Patients were divided according to less impaired LV GLS (≥7.0%) vs. more impaired LV GLS (<7.0%).

E = peak early diastolic transmitral flow velocity; E′ = peak early diastolic mitral annular tissue velocity; LAVI = left atrial volume index; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; MR = mitral regurgitation; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; other abbreviations as in Table 1.

Table 3. Data on Device and Invasive Mitral Valve Treatment Received During Follow-Up

	Total Population (N = 650)	GLS ≥7.0% (n = 349)	GLS <7.0% (n = 301)	p Value
Device therapy				
CRT	453 (70)	221 (63)	232 (77)	<0.001
Valvular intervention				
None	380 (59)	186 (53)	194 (65)	0.004
MVr	177 (27)	110 (32)	67 (22)	0.008
MVR	3 (1)	2 (1)	1 (<1)	0.651
Percutaneous edge-to-edge mitral valve repair	90 (14)	51 (15)	39 (13)	0.542
Concomitant procedure				
CABG	47 (7)	34 (10)	13 (4)	0.008
TVP	117 (18)	71 (20)	46 (15)	0.094
LV reconstruction, Dor procedure	16 (3)	6 (2)	10 (3)	0.188
CorCap	60 (9)	24 (7)	36 (12)	0.026
Surgical MAZE	23 (4)	12 (3)	11 (4)	0.882

Values are n (%). Patients were divided according to less impaired LV GLS (≥7.0%) vs. more impaired LV GLS (<7.0%).

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; GLS = global longitudinal strain; MVr = surgical mitral valve repair; MVR = mitral valve replacement; TVP = tricuspid valvuloplasty.

∗ Device implanted before invasive mitral valve treatment. † With mitral valve treatment.

Survival analysis

Patients with more impaired LV GLS (<7.0%) experienced significantly higher mortality rates as compared with patients with more preserved LV GLS (≥7.0%) (13%, 23%, and 44% vs. 5%, 14%, and 31% at 1-, 2-, and 5-year follow-up, respectively; $p < 0.001$) (Figure 3). To investigate the association between LV GLS and all-cause mortality, a Cox proportional hazards model was constructed (Table 4). LVEF was introduced as categorical variable, taking the threshold of LVEF of 30% proposed by current guidelines (3). In addition, LV GLS was also introduced as a categorical variable, taking the threshold derived from the spline curve analysis. On multivariable analysis, age, impaired renal function, diabetes mellitus, the use of diuretics, and LV end-diastolic volume index were independently associated with all-cause mortality. Furthermore, more impaired LV GLS (<7.0%) remained independently associated with all-cause mortality (HR: 1.337; 95% CI: 1.038 to 1.722; $p = 0.024$), whereas LVEF ≤30% was not associated with the outcome (HR: 1.055; 95% CI: 0.794 to 1.403; $p = 0.711$).

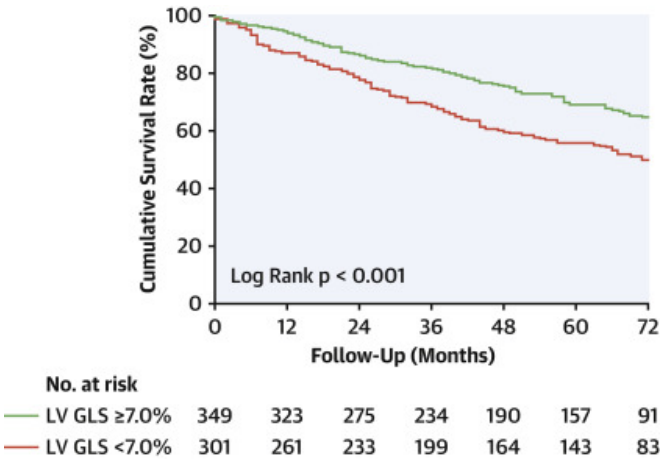


Figure 3. Kaplan-Meier Curves for All-Cause Mortality

Time to all-cause mortality, according to baseline LV GLS: ≥7.0% (less impaired, green) and LV GLS <7.0% (more impaired, red). Abbreviations as in Figure 1.

Table 4. Univariable and Multivariable Cox Regression Analyses to Identify Associates of All-Cause Mortality

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.030	1.018–1.041	<0.001	1.031	1.018–1.044	<0.001
Male	1.530	1.201–1.948	0.001	1.256	0.954–1.654	0.104
Creatinine	1.004	1.003–1.004	<0.001	1.003	1.002–1.004	<0.001
Hypertension	0.899	0.719–1.123	0.348			
Atrial fibrillation	1.187	0.956–1.475	0.121			
Diabetes mellitus	1.329	1.031–1.712	0.028	1.397	1.070–1.826	0.014
Ischemic etiology	1.344	1.082–1.669	0.008	1.105	0.864–1.414	0.425
NYHA functional class ≥II	1.122	0.644–1.955	0.685			
Beta-blockers	0.803	0.641–1.007	0.057			
Diuretics	1.994	1.411–2.818	<0.001	1.614	1.128–2.309	0.009
CRT	1.171	0.904–1.517	0.231			
Invasive mitral treatment	1.071	0.854–1.342	0.554			
LAVI	1.010	1.004–1.016	0.001	1.006	1.000–1.013	0.065
TAPSE	0.966	0.943–0.991	0.007	1.002	0.975–1.029	0.905
LVEDVi	1.005	1.003–1.008	<0.001	1.004	1.000–1.007	0.030
E′	0.941	0.886–0.999	0.046	0.956	0.895–1.022	0.188
LVEF ≤30%	1.392	1.096–1.769	0.007	1.055	0.794–1.403	0.711
LV GLS <7.0%	1.548	1.246–1.922	<0.001	1.337	1.038–1.722	0.024

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1, 2, and 3.

∗ Device implanted before invasive mitral valve treatment. † Combined surgical MVr, MVR, and percutaneous edge-to-edge MVr.

Incremental prognostic value of LV GLS for all-cause mortality

To determine the incremental value of impaired LV GLS (<7.0%) in addition to clinical and conventional echocardiographic parameters, a likelihood ratio test was performed. A baseline model comprised parameters associated with all-cause mortality in univariable Cox regression analysis. After the addition of LVEF ≤30% to the baseline model, no significant increase in the chi-square value was observed (chi-square difference = 0.1; p = 0.443). However, sequential addition of LV GLS <7.0% to the model including baseline parameters and LVEF ≤30% did show a significant increase in the chi-square value (chi-square difference = 3.6; p = 0.024), demonstrating the incremental prognostic value of LV GLS in patients with secondary MR (Figure 4).

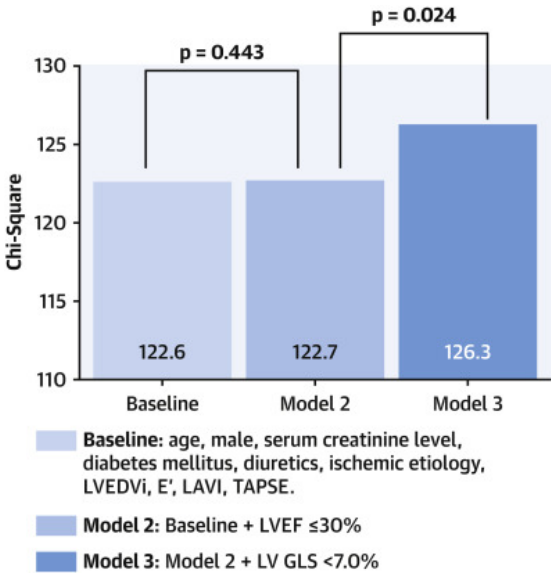


Figure 4. Incremental Value of LV GLS
The incremental value of LV GLS over clinical and traditional echocardiographic parameters for the prediction of all-cause mortality. E′ = peak early diastolic mitral annular tissue velocity; LAVI = left atrial volume index; LVEDVi = left ventricular end-diastolic volume index; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Figure 1.

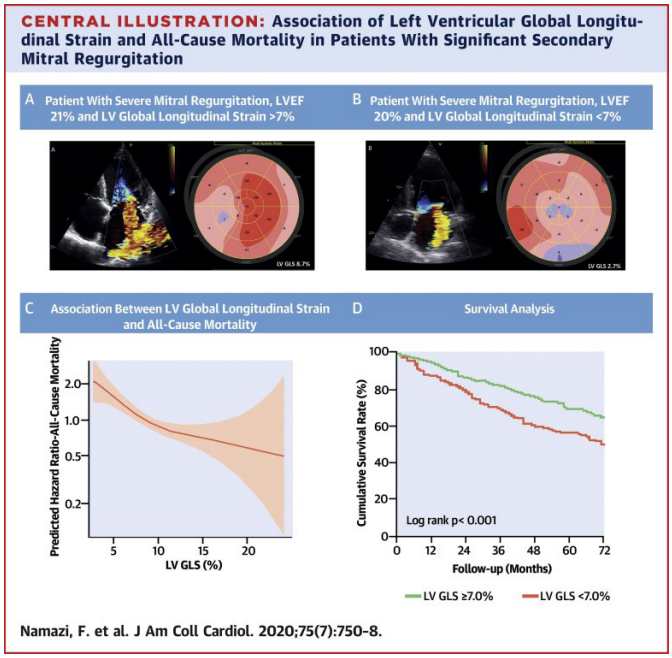
Discussion

The present study demonstrated that in patients with secondary MR, impaired LV GLS was independently associated with an increased risk for all-cause mortality, whereas LVEF was not (Central Illustration).

LVEF: Role in prognosis and intervention of secondary MR

According to current guidelines, patients with secondary MR are considered for mitral valve surgery when there is indication for coronary revascularization (3,13). When revascularization is not indicated, LVEF is one of the main variables to weigh

the indication of surgical mitral valve repair or replacement (3). Heart failure patients who remain symptomatic despite optimal medical therapy (including CRT) and who have a LVEF >30% may be considered for mitral valve surgery if the surgical risk is low (Class IIb) or percutaneous edge-to-edge repair if the surgical risk is high or there are contraindications (Class IIb) (3). The prognostic benefit of reducing secondary MR remains controversial due to a lack of convincing evidence showing improved survival with any intervention (14, 15, 16). Although it is well known that patients with secondary MR have a poor prognosis (17,18), it is less well known if secondary MR affects prognosis independently of LV systolic dysfunction (19). Recently, a long-term observational study demonstrated that secondary MR has an adverse prognostic impact in patients with heart failure and reduced LVEF, but it was only independently associated with all-cause mortality in those with a LVEF of 30% to 40% (20). This intriguing finding suggests that the benefit of mitral valve intervention may be limited to a certain range of LVEF.



Central Illustration. Association of Left Ventricular Global Longitudinal Strain and All-Cause Mortality in Patients With Significant Secondary Mitral Regurgitation

(A) Example of a patient with severe secondary mitral regurgitation (MR) and a left ventricular ejection fraction (LVEF) of 21%. (B) Example of another patient with severe secondary MR and an LVEF of 20%. Despite having the same degree of MR and a comparable LVEF, it is shown that the LV global longitudinal strain (GLS) is highly different, indicating that patient in panel A had a better LV systolic function when compared with the patient in panel B. (C) Prediction of all-cause mortality across a range of LV GLS, plotted as a fitted spline model on a log-hazard scale with overlaid confidence intervals. Dashed lines represent 95% confidence intervals. (D) Kaplan-Meier curves for all-cause mortality according to baseline LV GLS: ≥7.0% (less impaired, green) and LV GLS <7.0% (more impaired, red). It is shown that patients with an impaired LV GLS have higher mortality rates.

Deja et al. (21) showed a trend toward improved survival in patients with a LVEF ≤35% and moderate-to-severe MR when adding mitral valve surgery to CABG versus CABG or medical treatment alone. Two randomized trials, evaluating the prognostic effect of transcatheter mitral valve treatment in patients with secondary MR, were recently published (1,2). Patients in the MITRA-FR trial did not benefit from transcatheter mitral valve treatment in terms of the combined endpoint of heart failure hospitalization and all-cause mortality, whereas in the COAPT trial, patients experienced a significantly lower rate of heart failure hospitalization and all-cause mortality as compared with patients receiving guideline-directed medical therapy. In the MITRA-FR trial, patients had larger LV volumes at baseline (LV end-diastolic volume index 136.2 ± 37.4 ml/m2 in the intervention group vs. 134.5 ± 33.1 ml/m2 in the control group) than did those included in the COAPT trial (LV end-diastolic volume 194.4 ± 69.2 ml in the intervention group vs. 191.0 ± 72.9 ml in the control group). This might reflect more advanced baseline LV disease in the MITRA-FR trial, which was not evident when comparing only the baseline LVEF (similar in both study populations). This finding emphasizes the fact that LVEF may overestimate LV systolic function in patients with secondary MR, owing to its load-dependent nature (22). LVEF may therefore not be the optimal parameter to select patients with secondary MR for intervention. Even in the presence of advanced LV systolic dysfunction, LVEF may be preserved, leading to the unmasking of LV disease after intervention, with subsequent poor outcome (16,22). Novel, more sensitive parameters for assessing LV systolic function in the presence of secondary MR, are therefore required.

LV GLS and outcome in secondary MR

Kamperidis et al. (5) demonstrated that LV GLS is a more sensitive marker of LV systolic dysfunction than is LVEF in patients with nonischemic dilated cardiomyopathy and significant secondary MR. Despite having comparable LVEF, patients with severe MR had more impaired LV GLS values than did those with mild MR. This highlights the fact that LV systolic dysfunction is better reflected by LV GLS than by LVEF in secondary MR. LV GLS has shown incremental prognostic value in addition to LVEF in patients with heart failure (23,24) and can be used in the risk stratification and timing of surgery in patients with aortic regurgitation and primary MR (25,26). However, the prognostic value of LV GLS in patients with secondary MR remained unknown.

This is the first study evaluating the incremental prognostic value of LV GLS (in addition to LVEF) in secondary MR. Patients with a more impaired LV GLS (<7.0%) experienced higher mortality rates than did those with a more preserved LV GLS (≥7.0%). Because no clear consensus exists whether intervention for secondary MR translates into

prognostic benefit, it remains debatable whether mitral valve intervention at an earlier stage of LV systolic dysfunction could impact outcome (3,13). The results of the current study suggest that LV GLS, likely reflecting LV myocardial damage and fibrosis, is a better prognostic marker than LVEF. LV GLS could therefore aid further risk stratification of patients with secondary MR and help to identify those who will benefit from earlier mitral valve intervention.

Study limitations

The single-center, retrospective nature of this study may limit the generalizability of results; however, it represents a large, unselected cohort. The severity of secondary MR depends on prevailing hemodynamic conditions, but only stable patients were included. It should be acknowledged that LV GLS measurement is vendor-specific, although the difference with other platforms has been demonstrated to be moderate (27). In this study, vendor-specific software was used, and this must be taken into consideration when assessing LV GLS with different software. Quantitative measurements such as effective regurgitant orifice area were only feasible in 67% of the patients; therefore, this parameter was not included in the present analysis.

Conclusions

In patients with significant secondary MR, impaired LV GLS was independently associated with an increased risk of all-cause mortality. LV GLS may therefore be useful in the risk stratification of patients with secondary MR, as well as in the candidate selection and timing of mitral valve intervention.

References

1. Obadia JF, Messika-Zeitoun D, Leurent G et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. The New England journal of medicine 2018.
2. Stone GW, Lindenfeld J, Abraham WT et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. The New England journal of medicine 2018.
3. Baumgartner H, Falk V, Bax JJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European heart journal 2017;38:2739-2791.
4. Lee R, Marwick TH. Assessment of subclinical left ventricular dysfunction in asymptomatic mitral regurgitation. Eur J Echocardiogr 2007;8:175-84.
5. Kamperidis V, Marsan NA, Delgado V, Bax JJ. Left ventricular systolic function assessment in secondary mitral regurgitation: left ventricular ejection fraction vs. speckle tracking global longitudinal strain. European heart journal 2016;37:811-6.
6. 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. European heart journal cardiovascular Imaging 2015;16:233-70.
7. Grayburn PA, Carabello B, Hung J et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. Journal of the American College of Cardiology 2014;64:2792-801.
8. Lancellotti P, Tribouilloy C, Hagendorff A et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. European heart journal cardiovascular Imaging 2013;14:611-44.
9. Foster E, Wasserman HS, Gray W et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. The American journal of cardiology 2007;100:1577-83.
10. 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. European heart journal cardiovascular Imaging 2016;17:1321-1360.
11. Rudski LG, Lai WW, Afilalo J et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2010;23:685-713; quiz 786-8.
12. Negishi K, Negishi T, Kurosawa K et al. Practical guidance in echocardiographic assessment of global longitudinal strain. JACC Cardiovascular imaging 2015;8:489-492.

13. Nishimura RA, Otto CM, Bonow RO et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. The Journal of thoracic and cardiovascular surgery 2014;148:e1-e132.
14. Michler RE, Smith PK, Parides MK et al. Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation. The New England journal of medicine 2016;374:1932-41.
15. Nishimura RA, Otto CM, Bonow RO et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology 2017;70:252-289.
16. Trichon BH, Glower DD, Shaw LK et al. Survival after coronary revascularization, with and without mitral valve surgery, in patients with ischemic mitral regurgitation. Circulation 2003;108 Suppl 1:Ii103-10.
17. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759-64.
18. Rossi A, Dini FL, Faggiano P et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart 2011;97:1675-80.
19. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. Journal of the American College of Cardiology 2015;65:1231-1248.
20. Goliasch G, Bartko PE, Pavo N et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. European heart journal 2018;39:39-46.
21. Deja MA, Grayburn PA, Sun B et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. Circulation 2012;125:2639-48.
22. Magne J, Pibarot P. Left ventricular systolic function in ischemic mitral regurgitation: time to look beyond ejection fraction. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2013;26:1130-1134.
23. Bertini M, Ng AC, Antoni ML et al. Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy. Circulation Cardiovascular imaging 2012;5:383-91.
24. Sengelov M, Jorgensen PG, Jensen JS et al. Global Longitudinal Strain Is a Superior Predictor of All-Cause Mortality in Heart Failure With Reduced Ejection Fraction. JACC Cardiovascular imaging 2015;8:1351-1359.
25. Alashi A, Mentias A, Abdallah A et al. Incremental Prognostic Utility of Left Ventricular Global Longitudinal Strain in Asymptomatic Patients With Significant Chronic Aortic Regurgitation and Preserved Left Ventricular Ejection Fraction. JACC Cardiovascular imaging 2018;11:673-682.
26. Kim HM, Cho GY, Hwang IC et al.

Myocardial Strain in Prediction of Outcomes After Surgery for Severe Mitral Regurgitation. JACC Cardiovascular imaging 2018;11:1235-1244.
27. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2015;28:1171-1181, e2.