



Universiteit
Leiden
The Netherlands

Prognostic impact of left ventricular global longitudinal strain in atrial mitral regurgitation

Meucci, M.C.; Stassen, J.; Tomsic, A.; Palmen, M.; Crea, F.; Bax, J.J.; ... ; Delgado, V.

Citation

Meucci, M. C., Stassen, J., Tomsic, A., Palmen, M., Crea, F., Bax, J. J., ... Delgado, V. (2022). Prognostic impact of left ventricular global longitudinal strain in atrial mitral regurgitation. *Heart*, 109, 478-484. doi:10.1136/heartjnl-2022-321698

Version: Publisher's Version

License: [Creative Commons CC BY-NC 4.0 license](https://creativecommons.org/licenses/by-nc/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3515787>

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

Original research

Prognostic impact of left ventricular global longitudinal strain in atrial mitral regurgitation

Maria Chiara Meucci,^{1,2} Jan Stassen ,^{1,3} Anton Tomsic ,⁴ Meindert Palmen ,⁴ Filippo Crea,^{2,5} Jeroen J Bax,^{1,6} Nina Ajmone Marsan,¹ Victoria Delgado ^{1,7}

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/heartjnl-2022-321698>).

¹Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

²Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

³Department of Cardiology, Jessa Hospital, Hasselt, Belgium

⁴Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands

⁵Department of Cardiovascular and Pulmonary Sciences, Catholic University of the Sacred Heart, Rome, Italy

⁶Heart Center, University of Turku and Turku University Hospital, Turku, Finland

⁷Hospital University Germans Trias i Pujol, Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Spain

Correspondence to

Dr Victoria Delgado, Leiden University Medical Center, Leiden, Netherlands; videlga@gmail.com

Received 29 July 2022

Accepted 10 October 2022

Published Online First

21 October 2022



► <http://dx.doi.org/10.1136/heartjnl-2022-321945>



© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Meucci MC, Stassen J, Tomsic A, et al. *Heart* 2023;109:478–484.

ABSTRACT

Objective Left atrial (LA) and left ventricular (LV) mechanics are impaired in patients with atrial functional mitral regurgitation (AFMR), but their prognostic value in this subset of patients remains unknown. The present study aimed to evaluate the association between LA and LV longitudinal strain and clinical outcomes in patients with AFMR.

Methods A total of 197 patients (mean age 73±10 years, 44% men) with at least moderate AFMR were retrospectively identified. LV global longitudinal strain (GLS) and left atrial reservoir strain (LAS) were calculated by two-dimensional speckle tracking echocardiography. All-cause mortality was the primary endpoint of the study. The threshold value of LV GLS ($\leq 16.3\%$) to identify impaired LV mechanics was defined based on the risk excess of the primary endpoint described with a spline curve analysis.

Results Impaired LV GLS ($\leq 16.3\%$) was found in 89 (45%) patients. During a median follow-up of 69 months, 45 (23%) subjects experienced the primary endpoint. Patients with impaired LV GLS ($\leq 16.3\%$) had a significantly lower cumulative survival rate at 5 years, as compared with patients with LV GLS ($> 16.3\%$) (74% vs 93%, $p < 0.001$). On multivariable Cox regression analysis, LV GLS expressed as continuous variable was independently associated with the occurrence of all-cause mortality (HR 0.856, 95% CI 0.763 to 0.960; $p = 0.008$) after adjustment for age, LAS, pulmonary artery systolic pressure and severe tricuspid regurgitation. Conversely, LAS was not significantly associated with patients' outcome.

Conclusions In patients with significant AFMR, the impairment of LV GLS was independently associated with worse outcomes.

INTRODUCTION

Atrial functional mitral regurgitation (AFMR) has been recently recognised as a subcategory of secondary mitral regurgitation (MR), characterised by severe left atrial (LA) dilation and normal left ventricular (LV) dimensions and systolic function.^{1,2} AFMR typically occurs in patients with atrial fibrillation (AF) and/or heart failure with preserved ejection fraction (HFpEF). Mitral annular dilation caused by severe LA remodelling has been traditionally considered the key mechanism of AFMR.¹ Nevertheless, recent studies using advanced imaging techniques highlighted the role played by additional factors in AFMR pathogenesis, including insufficient leaflet growth for the magnitude of mitral

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial functional mitral regurgitation (AFMR) is a subcategory of secondary mitral regurgitation determined by left atrial (LA) enlargement and mitral annular dilation. Currently, there is little evidence regarding the role of echocardiographic tools to risk stratify this population. Particularly, an impairment of either atrial and ventricular mechanics has been reported in patients with AFMR, but the prognostic significance of this finding has not been investigated.

WHAT THIS STUDY ADDS

⇒ In this cohort study, we found that, among 197 patients with moderate or severe AFMR, the impairment of left ventricular (LV) global longitudinal strain (GLS) assessed by speckle-tracking echocardiography was associated with an increased risk of mortality. However, in the context of a predominantly atrial disease, LV GLS emerged as a better prognostic marker than LA reservoir strain.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The assessment of LV GLS in patients with AFMR might be useful for clinicians to identify patients with higher risk of adverse outcomes.

annulus dilation,^{3,4} atrioventricular leaflet tethering^{5,6} and impaired mitral annular mechanics.^{7,8} Furthermore, LA dysfunction and reduced LV mechanics have been suggested as potential triggers of AFMR in patients with LA dilatation, being the main determinants of mitral annular dynamics.^{1,8} Notably, in a study by Tang *et al*,⁸ the impairment of LV global longitudinal strain (GLS) solely was associated with the presence of significant AFMR among patients with AF, whereas left atrial reservoir strain (LAS) was not, thus challenging the concept of AFMR as a purely atrial consequence.

Current guidelines of valvular heart disease do not provide specific recommendations for the management of AFMR, and little is known about the prognostic determinants in this subset of patients.⁹ While the prognostic implications of altered LV mechanics have been demonstrated in the context of primary MR^{10,11} and functional MR

secondary to LV disease (VFMR),¹² they remain unexplored in AFMR.

Thus, the present study aimed at investigating (1) the clinical and echocardiographic associates of poor outcomes in patients with AFMR and (2) the prognostic value of LA and LV longitudinal strain, evaluated with two-dimensional speckle-tracking echocardiography (2D-STE).

METHODS

Patient population

All patients diagnosed with moderate or severe MR between January 2005 and December 2019 were retrospectively identified from the departmental cardiology information system (EPD-Vision 11.8.4.0; Leiden University Medical Centre, Leiden, the Netherlands) and patients with AFMR were selected. AFMR was defined as MR caused by isolated mitral annulus dilation, in the absence of leaflet abnormalities and LV dilation or systolic dysfunction.¹ Mitral annulus dilation was defined by an antero-posterior diameter of >35 mm or a ratio of annular diameter:anterior leaflet length of >1.3 (in diastole).¹³ Furthermore, patients with AFMR should have normal LV volumes and normal systolic function (indexed LV end-diastolic volume of <71 mL/cm² (women) or <79 mL/cm² (men) and left ventricular ejection fraction (LVEF) of ≥50%, in the absence of regional wall motion abnormalities).¹⁴ Patients with congenital heart disease, hypertrophic cardiomyopathy, significant calcification of mitral annulus, previous cardiac valve surgery or other significant valvular heart diseases (with the exception of secondary tricuspid regurgitation (TR)) were excluded (online supplemental figure S1). Additionally, patients in whom speckle-tracking analysis was not feasible, due to poor image quality, were also excluded.

The first echocardiographic examination performed with the patient in haemodynamic stable conditions and showing moderate or severe AFMR defined the time point of entry in the present analysis.

Clinical variables included the New York Heart Association (NYHA) functional class, cardiovascular risk factors, history of ischaemic heart disease and AF, comorbidities and medications.

The results of this work have been presented during the 71st Annual Scientific Session of the American College of Cardiology.¹⁵

Conventional echocardiographic examination

Comprehensive transthoracic echocardiograms were performed using a commercially available system (VIVID 7, E9 and E95; GE-Vingmed, Horten, Norway). All images were digitally stored for offline analysis (EchoPAC V.203; GE-Vingmed, Horten, Norway).

From the apical two-chamber and four-chamber views, the LV end-diastolic and end-systolic volumes were calculated and indexed for body surface area (BSA), and the LVEF was obtained by the biplane Simpson method.¹⁴ The end-systolic LA volume was measured from the apical two-chamber and four-chamber views using the biplane Simpson method and indexed for BSA (left atrial volume index (LAVI)).¹⁴

The assessment of LV diastolic function was performed according to international recommendations.¹⁶ Pulmonary artery systolic pressure (PASP) was calculated from the TR peak jet velocity and the right atrial pressure (estimated from the diameter and collapsibility of the inferior vena cava).¹⁷

Finally, MR and TR severity were graded as none/trivial, mild, moderate or severe, according to current guidelines, using an integrative approach that includes qualitative, semiquantitative

and quantitative parameters.^{9 13} The effective regurgitant orifice area of MR was estimated using the proximal isovelocity surface area method and, in patients with AF, averaging measurements obtained on three consecutive cardiac cycles.¹³

Speckle-tracking echocardiographic examination

LV GLS and LAS were measured offline by 2D-STE and using EchoPAC V.203 software (GE-Vingmed Ultrasound), as we previously described.¹⁸

LV GLS was calculated using images from the apical four-chamber and two-chamber and long-axis views zoomed on the LV and with a frame rate of ≥50 frames/s. The LV endocardial border was manually traced and then automatically tracked by the software through the cardiac cycle. The LV GLS was derived by averaging all segmental strain values and later by averaging values of all apical views.^{14 18}

LAS was assessed using the onset of the QRS wave as reference point (R–R gating). After the manual definition of LA endocardial border in the apical four-chamber view, the region of interest was adjusted to cover the entire LA wall and divided into six segments by the software. The average of peak values during the cardiac cycle of all six segments identifies the LAS.^{18 19}

In patients with AF at the time of the echocardiogram, measurements were obtained on three consecutive cardiac cycles, when available, and averaged, to obtain values of LV GLS and LAS. In the present study, strain measurements are presented as absolute values.

Follow-up

The occurrence of all-cause mortality was the primary endpoint of the present study. In addition, mitral valve interventions, including surgical mitral valve repair and transcatheter edge-to-edge mitral valve repair, as well as AF ablation procedures, were noted. Data were collected using the departmental cardiology information system (EPD-Vision 11.8.4.0), which is linked to the governmental death registry database. Follow-up data were available for all patients.

Patient and public involvement statement

It was not possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our study.

Statistical analysis

Continuous data are reported as mean±SD when normally distributed and as median (IQR) when not normally distributed. Categorical variables are presented as absolute numbers and percentages.

Unpaired Student's T test and Mann–Whitney U test (for continuous data, as appropriate) and Chi-square test or the Fisher's exact test (for categorical variables) were used to compare the baseline characteristics between two groups. The correlation between LV GLS and LA strain was assessed using the Spearman's method.

Spline curve analyses were performed to investigate the HR changes for the primary endpoint across the range of LV GLS and LAS values. The cut-off value of LV GLS associated with increased risk of all-cause mortality was estimated using the fitted spline curve (ie, in which the predicted HR is >1) and was used to define impaired LV mechanics. Kaplan-Meier survival analysis with a log-rank test was performed to calculate survival rates for the population, stratified by LV GLS with the spline curve-derived threshold value. The association between clinical and echocardiographic parameters and all-cause mortality was

Table 1 Clinical characteristics of the total population and subgroups stratified according to LV GLS

	Total population (n=197)	LV GLS ≤16.3% (n=89)	LV GLS >16.3% (n=108)	P value
Age (years)	73±10	75±10	72±10	0.026
Male gender, n (%)	86 (44)	41 (46)	45 (42)	0.535
Hypertension, n (%)	103 (52)	41 (46)	62 (57)	0.155
Diabetes, n (%)	16 (8)	8 (9)	8 (7)	0.644
Dyslipidaemia, n (%)	67 (34)	29 (33)	38 (35)	0.776
Coronary artery disease, n (%)	36 (18)	18 (20)	18 (17)	0.650
AF, n (%)				0.003
Paroxysmal AF	59 (30)	17 (19)	42 (39)	
Persistent or permanent AF	123 (62)	67 (75)	56 (52)	
No AF	15 (8)	5 (6)	10 (9)	
Previous AF ablation, n (%)	22 (11)	6 (7)	16 (15)	0.070
eGFR (mL/min/1.73 m ²)	68±21	69±22	67±20	0.573
NYHA functional class, n (%)				0.409
I	63 (31)	25 (28)	38 (35)	
II	80 (41)	36 (41)	44 (41)	
III–IV	54 (27)	28 (31)	26 (24)	
Medications, n (%)				
Oral anticoagulant	169 (86)	77 (87)	92 (85)	0.671
Beta blockers	131 (66)	59 (66)	72 (67)	0.873
ACEi/ARB	106 (54)	46 (52)	62 (56)	0.407
Diuretics	97 (49)	46 (52)	51 (47)	0.528
Antiarrhythmics	38 (19)	17 (19)	21 (19)	0.994
Digoxin	37 (19)	18 (20)	19 (18)	0.592

Values are expressed as mean±SD, median (IQR) or n (%).
ACEi, ACE inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LV, left ventricular; NYHA, New York Heart Association.

evaluated using Cox proportional hazards regression models. Exposure to mitral valve intervention was included in the model as a binary time-dependent term. Variables with a univariable value of $p < 0.05$ were incorporated into the multivariable models. In order to investigate the incremental prognostic value of LV GLS over clinical and conventional echocardiographic variables included in the multivariate analysis, the likelihood ratio test for nested models was performed. Additional multivariable models including potential confounders were performed as sensitivity analyses. The proportional hazards assumption was verified for all the Cox regression models through the assessment of scaled Schoenfeld residuals. Significant collinearity between any pairs of continuous variables that met the entry criteria for multivariable regression models was excluded by a correlation factor analysis (correlation coefficient < 0.70).

All p-values were two-sided and p-values < 0.05 were considered statistically significant. Data were analysed using the SPSS version 25.0 and the R software version 4.0.1.

RESULTS

Patient population

A total of 197 patients (mean age 73 ± 10 years, 44% men) were included (online supplemental figure S1). A history of AF was observed in the majority of participants (92%), while only 19% of patients had concomitant coronary artery disease (table 1).

Table 2 displays the echocardiographic characteristics of the overall cohort. The mean LV GLS was $16.4\% \pm 2.7\%$, whereas the mean LVEF was $58\% \pm 6\%$. In addition, the median LAS was 11.0% (IQR 8.8%–16.4%). At the time of diagnosis, 117 (59%) patients had moderate AFMR, while severe AFMR was observed in the remaining 80 (41%) participants. LV GLS was moderately correlated with LAS (correlation coefficient = 0.46, $p < 0.001$).

Follow-up

After a median follow-up of 69 (IQR 38–112) months, 45 (23%) patients died. Additionally, mitral valve intervention was performed in 60 (31%) patients after a median follow-up of 5 (IQR 3–10) months (online supplemental table S1).

Patients who reached the primary endpoint were more frequently symptomatic (NYHA class \geq II–IV), had lower values of LV GLS, higher values of PASP and a higher prevalence of severe TR compared with their counterparts (online supplemental table S2).

To evaluate the relationship between LV GLS and the occurrence of all-cause death, a spline curve was fitted, demonstrating that the HR for the primary endpoint was significantly higher with decreasing values of LV GLS (figure 1). Based on the spline curve, values of LV GLS below 16.3% were associated with increased risk of death. Thereby, this threshold was used to define impaired LV mechanics and divide the population. Similarly, a spline curve investigating the association between LA strain values and the risk of all-cause mortality is shown in online supplemental figure S2.

Impaired LV GLS was observed in 89 patients (45% of the overall population). Patients with impaired LV GLS ($\leq 16.3\%$) were older and had more often a history of persistent or permanent AF, as compared with patients with more preserved LV GLS ($> 16.3\%$) (table 1). In terms of echocardiographic data, patients with impaired LV GLS had significantly larger indexed LV end-systolic volume and lower LVEF, in comparison with patients with more preserved LV GLS (table 2 and figure 2). Moreover, subjects with impaired LV GLS were characterised by a larger LA dilation and a greater impairment of LAS. The prevalence of severe MR was also higher in patients with impaired LV GLS, as compared with individuals with more preserved LV GLS. During

Table 2 Echocardiographic characteristics of the total population and subgroups stratified according to LV GLS

	Total population (N=197)	LV GLS ≤16.3% (n=89)	LV GLS >16.3% (n=108)	P value
AF,* n (%)	127 (65)	72 (81)	55 (51)	<0.001
HR (beats/min)	76±18	81±18	72±18	<0.001
LVEDVI (mL/m ²)	52±11	52±11	51±10	0.514
LVESVI (mL/m ²)	21±6	22±6	19±5	<0.001
LVEF (%)	58±5	56±5	61±5	<0.001
LV GLS (%)	16.4±2.7	14.1±1.6	18.4±1.5	<0.001
LAVI (mL/m ²)	53 (43–68)	60 (49–74)	51 (40–61)	<0.001
LAS (%)	11.0 (8.8–16.4)	9.6 (8.3–12.5)	13.5 (9.2–19.5)	<0.001
E/A ratio†	1.6 (1.1–2.1)	1.9 (1.0–2.6)	1.4 (1.1–2.0)	0.253
E-wave DCT (ms)	156 (117–200)	140 (105–187)	178 (137–204)	0.002
E/e' ratio	10.1 (8.1–12.7)	10.1 (7.8–13.5)	10.0 (8.1–12.5)	0.802
MR VC (mm)	5.5±1.5	6.0±1.5	5.0±1.0	0.045
MR EROA (mm ²)	28±9	31±8	27±7	0.001
MR grade, n (%)				0.048
Moderate	119 (60)	47 (53)	72 (67)	
Severe	78 (40)	42 (47)	36 (33)	
TR grade, n (%)				0.054
None/mild	82 (42)	30 (34)	52 (48)	
Moderate	59 (30)	27 (30)	32 (30)	
Severe	56 (28)	32 (36)	24 (22)	
PASP (mm Hg)	32 (26–39)	32 (25–42)	31 (27–38)	0.542

Values are expressed as mean±SD, median (IQR) or n (%).

*AF at the time of echocardiography.

†Calculated only in patients in sinus rhythm.

AF, atrial fibrillation; DCT, deceleration time; E/A ratio, ratio between E-wave and A-wave velocities; E/e' ratio, ratio between E-wave velocity and the composite mean of E' velocity; EROA, effective regurgitant orifice area; GLS, global longitudinal strain; HR, heart rate; LA, left atrial; LAS, left atrial reservoir strain; LAVI, left atrial volume index; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MR, mitral regurgitation; PASP, pulmonary arterial systolic pressure; TR, tricuspid regurgitation; VC, vena contracta width.

follow-up, there were no significant differences in the rates of mitral valve intervention or AF ablation between the two groups (online supplemental table S1).

Prognostic value of LV GLS

Patients with impaired LV GLS had significantly lower cumulative survival rates at 1 and 5 years, as compared with patients with more preserved LV GLS (88% vs 98%; $p=0.006$ and 74% versus 93%; $p<0.001$, respectively; [figure 3](#)). On univariable Cox regression analysis ([table 3](#)), more impaired LV GLS was

significantly associated with the occurrence of all-cause mortality. In addition, age, LAVI, LAS, PASP and the presence of severe TR were also associated with a worse survival. Conversely, there

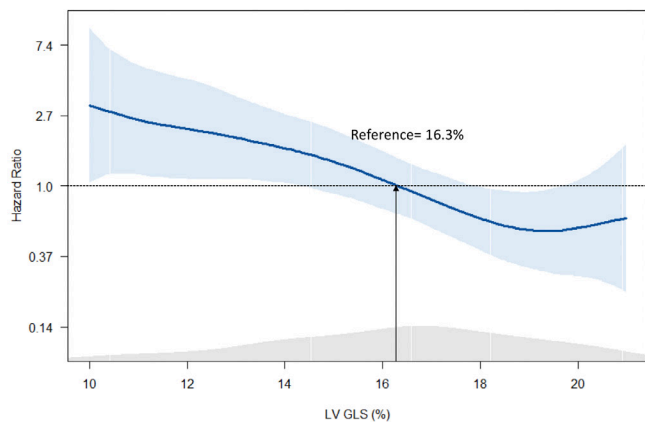


Figure 1 Penalized spline curve for the all-cause mortality according to LV GLS values. The spline curve describes the HR change for the primary endpoint with 95% CIs (shaded blue areas) across a range of values of LV GLS. GLS, global longitudinal strain; LV, left ventricular.

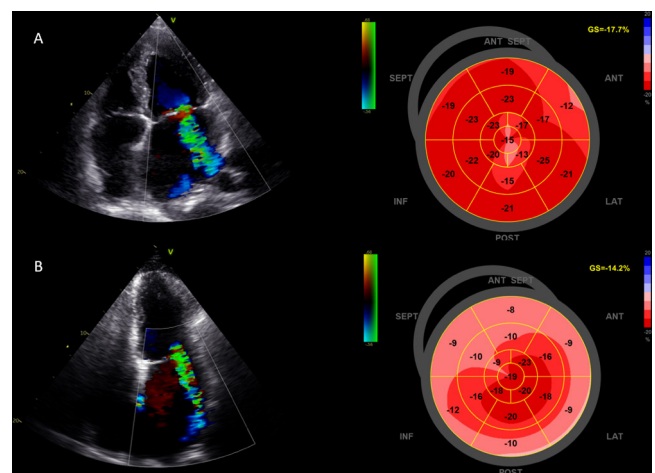


Figure 2 Examples of measurement of LV GLS in patients with AFMR. (A) Echocardiographic images from a patient with severe AFMR and preserved LVEF (63%). The bull's eye plot shows preserved LV GLS (17.7%). (B) Echocardiographic images from another patient with severe AFMR and preserved LVEF (55%). The bull's eye plot demonstrates an impairment of LV GLS (14.2%), particularly of the basal LV segments. AFMR, atrial functional mitral regurgitation; ANT, anterior; ANT-SEPT, antero-septal; GLS, global longitudinal strain; INF, inferior; LAT, lateral; LV, left ventricular; LVEF, left ventricular ejection fraction; POST, posterior; SEPT, septal.

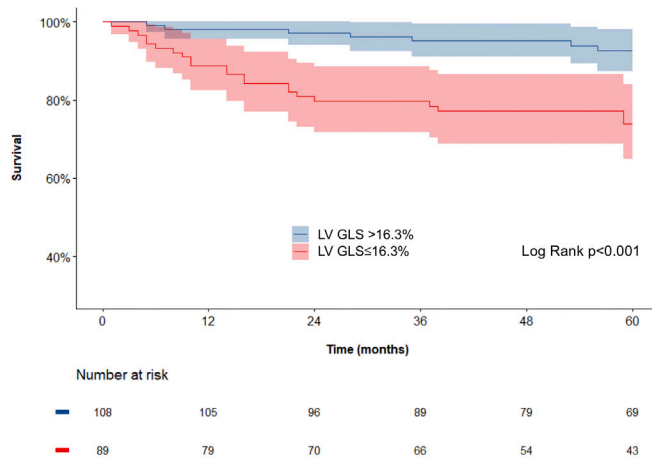


Figure 3 Kaplan-Meier curve at 5 years for all-cause mortality stratified by LV GLS ($\leq 16.3\%$). GLS, global longitudinal strain; LV, left ventricular.

was no significant association between mitral valve intervention and outcome. Since the relatively limited number of events and in order to minimise the collinearity effects between LAVI and LAS, these two variables were included alternatively in the multivariable models. The association between LV GLS and all-cause mortality remained significant, after adjustment for age, PASP, the presence of severe TR, and LAVI (model 1) or, alternatively, LAS (model 2) (table 3).

Notably, a significant improvement in the model power for predicting patients' outcome was observed following the

inclusion of LV GLS in the multivariable models (Chi-square difference=7.05 for the model one or Chi-square difference=7.02 for the model 2; both $p=0.008$). When LV GLS was introduced in the analyses as categorical variable (LV GLS $\leq 16.3\%$), it was consistently associated with a worse survival (online supplemental table S3). Other multivariable models were built incorporating potential confounders and with a maximum of 5 variables in each model. These analyses confirmed the significant association between LV GLS and all-cause mortality, after controlling for gender, the presence of symptoms (NYHA class \geq II–IV), AF during echocardiography and MR severity (online supplemental table S4). Conversely, the association between LAS and the primary endpoint had a borderline significance after controlling for age and gender and was not significant after further adjustment for each of the other relevant variables, included alternatively in the analysis (online supplemental table S5). Similarly, when expressed as dichotomous variable using the threshold derived from the spline curve (LAS $< 12\%$; as illustrated in online supplemental figure S2), LA strain did not retain an independent association with mortality in multivariable analyses (online supplemental table S5).

DISCUSSION

The present study demonstrated that, among patients with significant (moderate and severe) AFMR, the impairment of LV GLS was independently associated with worse outcomes, whereas LAS was not.

Secondary MR in patients with normal LV dimensions and preserved LVEF has increasingly been recognised. This entity, named AFMR, typically occurs in patients with AF and/or HFpEF with severe LA dilatation and normal LV dimensions and systolic

Table 3 Univariable and multivariable Cox regression analysis for all-cause mortality.

	Univariable analysis		Multivariable analysis 1		Multivariable analysis 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Clinical variables						
Age (years)	1.046 (1.011 to 1.082)	0.009	1.027 (0.992 to 1.064)	0.133	1.019 (0.985 to 1.054)	0.287
Male gender	1.713 (0.950 to 3.088)	0.073				
Diabetes	1.163 (0.357 to 3.791)	0.802				
Coronary artery disease	1.181 (0.567 to 2.462)	0.246				
eGFR (ml/m ²)	0.995 (0.980 to 1.011)	0.551				
NYHA class \geq II–IV	1.921 (0.844 to 4.369)	0.120				
MV intervention (time-dependent)	0.805 (0.399 to 1.624)	0.544				
Echocardiographic variables						
AF*	1.665 (0.859 to 3.225)	0.132				
LVEDVI (mL/m ²)	0.991 (0.964 to 1.020)	0.552				
LVESVI (mL/m ²)	1.011 (0.955 to 1.063)	0.962				
LVEF (%)	0.955 (0.906 to 1.007)	0.091				
LV GLS (%)	0.824 (0.741 to 0.917)	<0.001	0.856 (0.763 to 0.960)	0.008	0.850 (0.753 to 0.959)	0.008
LAVI (mL/m ²)	1.011 (1.002 to 1.020)	0.013	1.005 (0.994 to 1.017)	0.338		
LAS (%)	0.928 (0.869 to 0.990)	0.024			1.003 (0.934 to 1.077)	0.936
E/e' ratio	1.030 (0.973 to 1.098)	0.288				
Severe MR	1.760 (0.976 to 3.175)	0.060				
MR EROA (mm ²)	1.025 (0.996 to 1.056)	0.095				
Severe TR	2.728 (1.495 to 4.977)	0.001	1.779 (0.896 to 3.530)	0.100	1.967 (1.022 to 3.788)	0.043
PASP (mm Hg)	1.034 (1.011 to 1.057)	0.003	1.011 (0.984 to 1.039)	0.443	1.017 (0.992 to 1.044)	0.185

*AF at the time of echocardiography.

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; GLS, global longitudinal strain; LA, left atrial; LAS, left atrial reservoir strain; LAVI, left atrial volume index; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; RVoI, regurgitant volume; TR, tricuspid regurgitation.

function (based on LVEF).^{1,2} Although mitral annular dilatation has been traditionally considered the underlying mechanism, recent studies using advanced imaging techniques suggested several additional contributors in AFMR pathogenesis.¹⁸ Among them, LA dysfunction and reduced LV longitudinal mechanics have been described as potential triggers of AFMR in subjects with LA dilatation.^{1,8} Patients with AFMR showed impaired values of LV GLS and LAS, as compared with patients with AF but without AFMR.^{8,20} These differences remained in patients with comparable LA and LV dimensions and LVEF.⁸ Nevertheless, only the impairment of LV GLS was correlated with reduced systolic annular dynamics (ie, systolic annular area change) and with the presence of significant AFMR, among patients with AF,⁸ suggesting that AFMR may be not a purely atrial disorder.

In addition, little is known about the risk stratification and the therapeutic strategies for the management of patients with significant AFMR.^{1,9,21,22} Particularly, the prognostic value of impaired LA and/or LV mechanics, assessed by 2D-STE, has never been investigated in patients with AFMR.

Prognostic implications of LV GLS in AFMR

LVEF may overestimate LV systolic function in the context of MR due to its load-dependent nature, as well as the regurgitant fraction of the LV volume not contributing to the forward stroke volume.²³ On the contrary, LV GLS has emerged as sensitive and accurate marker of LV systolic dysfunction, with the advantage of being less influenced by the loading conditions in comparison to LVEF.²⁴ LV GLS has been demonstrated to detect subtle LV systolic dysfunction in patients with primary MR and preserved LVEF²³ and, of importance, was independently associated with adverse outcomes after mitral valve surgery in two large retrospective cohorts of patients with severe primary MR.^{10,11} Similarly, in individuals with moderate or severe VFMR, lower values of LV GLS predict a worse survival, while LVEF was not.¹² Accordingly, LV GLS has been proposed as an additional tool for the risk stratification and decision-making of patients with significant MR.^{10,12}

The present study showed for the first time that LV GLS was independently associated with the occurrence of all-cause mortality in patients with moderate or severe AFMR. An LV GLS of $\leq 16.3\%$ identified a cohort of patients with impaired LV mechanics, despite normal LVEF, who have a worse survival.

Of note, besides the detrimental effects of the chronic volume overload, a variety of factors may explain the impairment of LV GLS in patients with AFMR. AF negatively affects LV structure and function through several mechanisms including systemic inflammation, impaired microvascular perfusion, interference with the ventricular calcium handling and oxidative stress.²⁵ Moreover, reduced LV GLS assessed with 2D-STE is typically observed in patients with HFpEF and has been associated with a worse symptomatic status²⁶ and adverse cardiovascular events.²⁷ Thus, from a pathophysiological point of view, the relationship between AFMR and impaired LV GLS may be bidirectional, with reduced LV mechanics being either cause or consequence of the MR and need to be clarified in prospective series.

Other prognostic markers in AFMR

In the study by Abe *et al*,²⁸ the presence of concomitant significant MR and TR among 298 patients with AF and preserved LVEF identified a subset of patients ($n=11$) with worse outcome at a mean follow-up of 24 months. Similarly, TR grading was reported as an independent prognostic marker in a small cohort ($n=90$) of patients with at least moderate-to-severe AFMR,

together with age, renal function and LV end-systolic dimensions.²⁰ The present study confirmed this finding in a larger population of patients with significant AFMR and with longer follow-up duration.

MR may contribute to the atrial cardiomyopathy, which is a cause and/or consequence of AF. Whether LAS may be a useful marker of worse outcomes in these patients has not been explored. In the present study, in contrast to LV GLS, LAS was not independently associated with outcomes in patients with AFMR. Notably, this finding was also confirmed evaluating its prognostic value separately from LV GLS, since the latter is a major determinant of LAS.²⁹ This observation may seem surprising in the context of a primarily atrial disease but is possibly related to the presence of advanced LA remodelling with severe LA dysfunction in the vast majority of the subjects, thus making LAS a suboptimal tool of risk stratification in this setting.

Study limitations

This study is limited by its retrospective, single-centre, observational design. Further prospective investigations are needed to confirm our findings and to evaluate and assess how LV GLS can optimise the clinical decision-making in patients with AFMR. LV dilatation or reduced LVEF was an exclusion criterion for the diagnosis of AFMR. However, the chronic volume overload in patients with AFMR may result in LV dilatation and overt systolic dysfunction. Thus, advanced forms of AFMR could be misclassified as VFMR. Moreover, despite LV GLS was calculated by the average of multiple measurements obtained in consecutive cardiac cycles for patients with AF, the variability of the heart rate may have influenced the LV GLS values.

CONCLUSIONS

In patients with significant AFMR, impaired LV GLS was independently associated with an increased risk of all-cause mortality. LV GLS may be a useful tool for the risk stratification of patients with AFMR.

Contributors Concept and design: VD, NAM, JJB and MP. Acquisition, analysis and interpretation of the data: MCM, JS and AT. Drafting of the manuscript: MCM and VD. Critical revision of the manuscript: all the authors. Guarantor: VD.

Funding JS received funding from the European Society of Cardiology (ESC Training Grant App000080404).

Competing interests the Department of Cardiology, Heart Lung Center, Leiden University Medical Center, received research grants from Abbott Vascular, Bayer, Bioentrix, Medtronic, Biotronik, Boston Scientific, GE Healthcare and Edwards Lifesciences. JJB received speaking fees from Abbott Vascular. NAM received speaking fees from Abbott Vascular and GE Healthcare and has been in the Medical Advisory Board of Philips Ultrasound. VD received speaker fees from Abbott Vascular, Medtronic, Edwards Lifesciences, MSD and GE Healthcare. The remaining authors have nothing to disclose.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the institutional review board of the Leiden University Medical Center (P16.003, date of approval 14 June 2021).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines,

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs

Jan Stassen <http://orcid.org/0000-0001-9745-5498>

Anton Tomsic <http://orcid.org/0000-0002-9860-4886>

Meindert Palmen <http://orcid.org/0000-0002-7213-5452>

Victoria Delgado <http://orcid.org/0000-0002-9841-2737>

REFERENCES

- Kagiyama N, Mondillo S, Yoshida K, *et al.* Subtypes of Atrial Functional Mitral Regurgitation: Imaging Insights Into Their Mechanisms and Therapeutic Implications. *JACC Cardiovasc Imaging* 2020;13:820–35.
- Meucci MC, Delgado V. Deep dive into atrial functional mitral regurgitation. *Structural Heart* 2021;5:508–9.
- Kagiyama N, Hayashida A, Toki M, *et al.* Insufficient leaflet remodeling in patients with atrial fibrillation: association with the severity of mitral regurgitation. *Circ Cardiovasc Imaging* 2017;10:e005451.
- Kim D-H, Heo R, Handschumacher MD, *et al.* Mitral Valve Adaptation to Isolated Annular Dilatation: Insights Into the Mechanism of Atrial Functional Mitral Regurgitation. *JACC Cardiovasc Imaging* 2019;12:655–77.
- Ito K, Abe Y, Takahashi Y, *et al.* Mechanism of atrial functional mitral regurgitation in patients with atrial fibrillation: a study using three-dimensional transesophageal echocardiography. *J Cardiol* 2017;70:584–90.
- Takahashi Y, Abe Y, Sasaki Y, *et al.* Mitral valve repair for atrial functional mitral regurgitation in patients with chronic atrial fibrillation. *Interact Cardiovasc Thorac Surg* 2015;21:163–8.
- Machino-Ohtsuka T, Seo Y, Ishizu T, *et al.* Novel Mechanistic Insights Into Atrial Functional Mitral Regurgitation - 3-Dimensional Echocardiographic Study. *Circ J* 2016;80:2240–8.
- Tang Z, Fan Y-T, Wang Y, *et al.* Mitral annular and left ventricular dynamics in atrial functional mitral regurgitation: a three-dimensional and Speckle-Tracking echocardiographic study. *J Am Soc Echocardiogr* 2019;32:503–13.
- Vahanian A, Beyersdorf F, Praz F, *et al.* 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;43:561–632.
- Kim HM, Cho G-Y, Hwang I-C, *et al.* Myocardial Strain in Prediction of Outcomes After Surgery for Severe Mitral Regurgitation. *JACC Cardiovasc Imaging* 2018;11:1235–44.
- Hiemstra YL, Tomsic A, van Wijngaarden SE, *et al.* Prognostic value of global longitudinal strain and etiology after surgery for primary mitral regurgitation. *JACC Cardiovasc Imaging* 2020;13:577–85.
- Namazi F, van der Bijl P, Hirasawa K, *et al.* Prognostic value of left ventricular global longitudinal strain in patients with secondary mitral regurgitation. *J Am Coll Cardiol* 2020;75:750–8.
- 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. *Eur Heart J Cardiovasc Imaging* 2013;14:611–44.
- Lang RM, Bierig M, Devereux RB, *et al.* Recommendations for chamber quantification: a report from the American Society of echocardiography's guidelines and standards Committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European Society of cardiology. *J Am Soc Echocardiogr* 2005;18:1440–63.
- Meucci MC, Stassen J, Marsan NA, *et al.* Prognostic implications of left ventricular global longitudinal strain in patients with atrial functional mitral regurgitation. *J Am Coll Cardiol* 2022;79:1725.
- 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. *Eur Heart J Cardiovasc Imaging* 2016;17:1321–60.
- 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. *J Am Soc Echocardiogr* 2010;23:685–713.
- Meucci MC, Hoogerduijn Strating MM, Butcher SC, *et al.* Left atrial dysfunction is an independent predictor of mortality in patients with cirrhosis treated by transjugular intrahepatic portosystemic shunt. *Hepatology* 2022. doi:10.1002/hep4.2062. [Epub ahead of print: 27 Aug 2022].
- Badano LP, Kolias TJ, Muraru D, *et al.* Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2018;19:591–600.
- Matta M, Ayoub C, Abou Hassan OK, *et al.* Anatomic and functional determinants of atrial functional mitral regurgitation. *Structural Heart* 2021;5:498–507.
- Kim K, Kitai T, Kaji S, *et al.* Outcomes and predictors of cardiac events in medically treated patients with atrial functional mitral regurgitation. *Int J Cardiol* 2020;316:195–202.
- Okamoto C, Okada A, Nishimura K, *et al.* Prognostic comparison of atrial and ventricular functional mitral regurgitation. *Open Heart* 2021;8:e001574.
- Abou R, van der Bijl P, Bax JJ, *et al.* Global longitudinal strain: clinical use and prognostic implications in contemporary practice. *Heart* 2020;106:1438–44.
- Kim M-S, Kim Y-J, Kim H-K, *et al.* Evaluation of left ventricular short- and long-axis function in severe mitral regurgitation using 2-dimensional strain echocardiography. *Am Heart J* 2009;157:345–51.
- Wijesurendra RS, Casadei B. Atrial fibrillation: effects beyond the atrium? *Cardiovasc Res* 2015;105:238–47.
- Morris DA, Boldt L-H, Eichstädt H, *et al.* Myocardial systolic and diastolic performance derived by 2-dimensional speckle tracking echocardiography in heart failure with normal left ventricular ejection fraction. *Circ Heart Fail* 2012;5:610–20.
- Shah AM, Claggett B, Sweitzer NK, *et al.* Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circulation* 2015;132:402–14.
- Abe Y, Akamatsu K, Ito K, *et al.* Prevalence and prognostic significance of functional mitral and tricuspid regurgitation despite preserved left ventricular ejection fraction in atrial fibrillation patients. *Circ J* 2018;82:1451–8.
- Mălăeșcu G-G, Mirea O, Capotă R, *et al.* Left Atrial Strain Determinants During the Cardiac Phases. *JACC Cardiovasc Imaging* 2022;15:381–91.