UNIVERSITÀ DEGLI STUDI DI TRIESTE

Global longitudinal strain by CMR improves prognostic stratification in acute myocarditis presenting with normal LVEF

This is the peer reviewed (post-print) version of the following article:

Original
Global longitudinal strain by CMR improves prognostic stratification in acute myocarditis presenting with normal LVEF / Porcari, A., Merlo, M., Baggio, C., Gagno, G., Cittar, M., Barbati, G., Paldino, A., Castrichini, M., Vitrella, G., Pagnan, L., Cannatà, A., Andreis, A., Cecere, A., Cipriani, A., Raafs, A., Bromage, D.I., Rosmini, S., Scott, P., Sado, D., Di Bella, G., et al.. - In: THE EUROPEAN JOURNAL OF CLINICAL INVESTIGATION. - ISSN 1365-2362. - ELETTRONICO. - 52:10(2022), pp. e13815."-"-e13815."-". [10.1111/eci.13815]

Availability:
This version is available at: 11368/3026904 since: 2022-07-29T05:50:28Z
Publisher:

Published
DOI:10.1111/eci.13815
Terms of use:

Some rights reserved. More details in the PostPrint rights section below.

License:
Digital Rights Management not defined

Publisher copyright

-.-

(Article begins on next page)

22 October 2026

arTs Università degli Studi di Trieste
Archivio della ricerca – postprint

Accepted: 7 May 2022

Global longitudinal strain by CMR improves prognostic stratification in acute myocarditis presenting with normal LVEF

Aldostefano Porcari[1] | Marco Merlo[1] | Chiara Baggio[1] | Giulia Gagno[1] | Marco Cittar[1] | Giulia Barbati[2] | Alessia Paldino[1] | Matteo Castrichini[1] | Giancarlo Vitrella[1] | Lorenzo Pagnan[3] | Antonio Cannatà[1,4,5] | Alessandro Andreis[6] | Annagrazia Cecere[7] | Alberto Cipriani[7] | Anne Raafs[8] | Daniel I. Bromage[4,5] | Stefania Rosmini[5] | Paul Scott[4] | Daniel Sado[4] | Gianluca Di Bella[9] | Gaetano Nucifora[10] | Martina Perazzolo Marra[7] | Stephane Heymans[8] | Massimo Imazio[11] | Gianfranco Sinagra[1]

[1]Centre for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI) and University of Trieste, Trieste, Italy

[2]Department of Medical Sciences, Biostatistics Unit, University of Trieste, Trieste, Italy

[3]Department of Radiology, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), Trieste, Italy

[4]Department of Cardiovascular Sciences - Faculty of Life Sciences & Medicine, King's College London, London, UK

[5]Department of Cardiology, King's College Hospital NHS Foundation Trust, London, UK

[6]University Cardiology A.O.U., Città della Salute e della Scienza di Torino, Turin, Italy

[7]Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy

[8]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, the Netherlands

[9]Department of Cardiology, University of Messina, Messina, Italy

[10]NorthWest Cardiac Imaging Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK

[11]Cardiology, Cardiothoracic Department, University Hospital "Santa Maria della Misericordia", ASUFC, Udine, Italy

Abstract

Background: Prognostic stratification of acute myocarditis (AM) presenting with normal left ventricular ejection fraction (LVEF) relies mostly on late gado-linium enhancement (LGE) characterization. Left ventricular peak global lon-gitudinal strain (LV-GLS) measured by feature tracking analysis might improve prognostication of AM presenting with normal LVEF.

Methods: Data of patients undergoing cardiac magnetic resonance (CMR) for clinically suspected AM in seven European Centres (2013– 2020) were ret-rospectively analysed. Patients with AM confirmed by CMR and LVEF ≥50% were included. LGE was visually characterized: localized versus. non- localized,

subepicardial versus midwall. LV- GLS was measured by dedicated software. The primary outcome was the first occurrence of an adverse cardiovascular event (ACE) including cardiac death, life- threatening arrhythmias, development of
heart failure or of LVEF <50%.

Results: Of 389 screened patients, 256 (66%) fulfilled inclusion criteria: median
age 36 years, 71% males, median LVEF 60%, median LV- GLS - 17.3%. CMR was performed at 4 days from hospitalization. At 27 months, 24 (9%) patients expe-rienced ≥1 ACE (71% developed LVEF <50%). Compared to the others, they
had lower median LV- GLS values (−13.9% vs. −17.5%, $p = .001$). At Kaplan– Meier analysis, impaired LV- GLS (both considered as > −20% or quartiles), non- localized and midwall LGE were associated with ACEs. Patients with LV- GLS≤−20% did not experience ACEs. LV- GLS remained associated with ACEs after adjustment for non-localized and midwall LGE.

Conclusion: In AM presenting with LVEF≥50%, LV- GLS provides independ-ent prognostic value over LGE characterization, improving risk stratification and representing a rationale for further studies of therapy in this cohort.

KEYWORDS

acute myocarditis, cardiac magnetic resonance, global longitudinal strain, normal left ventricular ejection fraction, prognostic stratification

1 | INTRODUCTION

Acute myocarditis (AM) is characterized by a heterogenous clinical presentation and natural history.[1,2] AM patients presenting with normal left ventricular ejection fraction (LVEF) are considered as having benign long-term outcomes[3,4], but the presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging was demonstrated to confer an increased risk of adverse cardiovascular (CV) events (ACEs) and unfavourable evolution[5–7], even in AM with normal LVEF.[7,8] The prognostic role of specific LGE distributions and localizations is still debated.[9,10] Remarkably, up to 25% of unselected patients with AM develops persistent cardiac dysfunction and 12%–25% may acutely deteriorate and either die or progress to end-stage dilated cardiomyopathy (DCM) during follow-up.[11] The incidence and prediction of new-onset systolic dysfunction remains largely unexplored, mostly in low risk myocarditis. Therefore, there is an unmet need for tools able to improve the prediction of LVEF trajectories in the specific AM population presenting with normal LVEF. CMR feature-tracking (FT) strain analysis can reveal subtle systolic dysfunction in ≈20% of AM patients with normal LVEF[12] and reduced CMR-FT global longitudinal peak strain (GLS) was demonstrated to add incremental value for outcome prediction in unselected populations of AM, incremental to LVEF and LGE.[13]

On this basis, we designed a multicentre international study to investigate the prognostic implications of CMR-FT LV-GLS beyond LGE in AM patients presenting with normal LVEF confirmed by CMR Lake Louise Criteria (LLC).[5,6]

2 | METHODS

This was an international, multicentre, retrospective, observational cohort study. Seven tertiary referral centres for cardiomyopathies and myocarditis across Europe (Trieste, Turin, Padua and Messina in Italy, London and Manchester in United Kingdom, Maastricht in The Netherlands) participated in this study (Table S1). Trieste University Hospital (Italy) acted as the coordinating centre. The local Regional Institutional Review Board approved the study (identifier 43_2009), and the participating Centres obtained local institutional review board approvals, where necessary, for the collection of retrospective anonymized data.

2.1 | Study design and inclusion criteria

Data of patients with a diagnosis of suspected AM between 1 January 2013 and 31 August 2020 were collected. The diagnosis of AM was based on current recommendations

of the position statement of the European Society of Cardiology Working Group on myocardial and pericardial diseases.[11] Per protocol, only patients presenting with LVEF ≥50% at first echocardiography and CMR were included.[9] Those presenting with heart failure (HF), major ventricular arrhythmic events (i.e., aborted sudden cardiac death [SCD], sustained or iterative nonsustained ventricular tachycardia [VT]), LVEF <50% or hemodynamic instability were excluded. In detail, AM was suspected in symptomatic patients with chest pain and at least one of the following clinical and imaging diagnostic criteria: new electrocardiographic abnormalities, increased troponin, wall motion abnormalities with normal LVEF at echocardiography and CMR. Then, in all patients, the diagnosis of AM had to be confirmed by the presence of myocardial edema (T2-weighted imaging or regional elevated T2 values) and increased myocardial T1 values or LGE in typical myocarditis patterns.[5,6] CMR exams had to be performed within 14 days from index admission. Endomyocardial biopsy was not performed in this low-risk population according to international statements.[11,14] Patients above 30 years and/or with >1 CV risk factor systematically underwent invasive coronary angiography or computed tomography to rule out coronary artery disease. Thereafter, pre-specified criteria for final inclusion were centrally revised (A.P., M.M., C.B., G.G.). Follow-up was concluded at the end of February 2021.

2.2 | CMR assessment

In all centres, CMR was performed using 1.5 T scanners with dedicated cardiac software, a phased-array surface receiver coil, and vectorcardiogram triggering. CMR images were acquired according to the protocols recommended by the Society for Cardiovascular Magnetic Resonance.[15] In detail, we acquired cine steady-state free precession (cine-SSFP) images during apnea, T2-weighted short-tau inversion recovery (STIR) imaging and/or T2 mapping for myocardial oedema, and LGE in T1-weighted inversion recovery sequences at 5–10 min after gadolinium injection (0.1 mmol/kg) in the short-axis (9–14 images covering the entire LV), two-chamber, three-chamber, and four-chamber planes. The reference CMR criteria for the diagnosis of AM were the traditional LLC[5] in the period 2013–2018 and the updated LLC[6] in the period 2019–2020. Retrospective gating was used as adequate ECG triggering was obtained in the whole cohort. Ventricular volumes and morphology were quantified from the cine images. LGE was visually assessed and further categorized into epicardial, mid-wall or transmural pattern. We used a LGE involving >2 myocardial segments as threshold to define LGE extension[16]: localized LGE (≤2 LV segments) or non-localized LGE (>2 LV segments). Edema was assessed using the signal intensity ratio of the myocardium versus skeletal muscle on T2-weighted images[17] and regional enhancement was evaluated on an 17-segment model of the LV. Cardiac deformation imaging was performed using dedicated cardiac software (CVI42®, Circle Cardiovascular Imaging). Biventricular endocardial- and epicardial borders were manually traced in long-axis two-chamber, three-chamber and four-chamber sequences at end-diastole in electrocardiography-gated cine-SSFP sequences using a point-and-click approach. Subsequently, the software's automatic border tracking algorithm was applied. Accurate tracking was assured by visual review of all borders. In case of poor tracking, the border was readjusted manually until adequate tracking was achieved. Scans that did not allow for a reliable tracking were excluded from the analysis ($n = 26$). SSFP-cine images of AM patients were centrally revised and CMR-FT analysis was performed at Trieste with the only exception of AM patients from London and Padua. The presence and extent of LGE as well as myocardial edema were assessed at the center where the CMR was performed. All participating centers have recognized experience in the diagnosis and management of patients with myocarditis. Variability analyses were performed (see "Statistical Analysis"). All CMR parameters, including CMR-FT features, were analysed by operators blinded to patients' baseline characteristics and outcome.

2.3 | Outcome measures

The primary outcome was an unfavourable evolution defined as the first occurrence of an ACE, which included cardiac death, development of clinically symptomatic HF requiring administration of diuretics, life-threatening arrhythmias or permanent LVEF <50% with ≥5% drop in LVEF (measured by echocardiography). Additional analysis was performed using the development of LVEF<50% on echocardiography during follow-up. In each study site, patients underwent annual cardiological evaluation, ECG recording and echocardiography with measurement of LVEF according to Simpson's biplane method. The events were collected from the electronical database of each hospital and, if needed and according to local protocols, from patients' general practitioners and/or telephone contacts with patients and their relatives.

2.4 | Statistical analysis

Descriptive statistics between the study groups were calculated. Continuous variables were expressed as median

with interquartile range (IQR) [25°; 75°], according to the distribution shape. Differences between groups were evaluated using Mann–Whitney U test for continuous variables and the Chi-square (χ^2) or Fisher's exact test for dichotomous variables, as appropriate. To explore the effect of LV-GLS on the risk of ACEs, a non-parametric smoothed regression approach was used to interpolate the relationship.[18] In addition, LV-GLS values were grouped into quartiles to investigate the relationship with the risk of ACEs. The Kaplan–Meier method was used to estimate the global survival and the composite end point curve, and the log rank test was used to compare the curves. In the case of secondary end points, to account for the presence of competing risks, cumulative incidence curves were estimated and compared using appropriate methods.[19] To evaluate the incremental prognostic role of CMR-FT LV-GLS over standard of care, three predictive nested models were compared in an exploratory analysis: the "clinical model" (including age, dyspnoea and chest pain at presentation), the "clinical-LGE model" (including "clinical model" risk score plus LGE distribution and localization) and the "clinical-LGE-GLS" model (including the "clinical-LGE model" risk score plus LV-GLS, considered as continuous variable). The goodness of fit (chi-square test) and c-statistics for each multivariable model for the prediction of ACEs were reported. The predictive accuracy of risk scores obtained from the multivariable models was evaluated by means of time-dependent area under the curve (AUC) of the corresponding ROC curves.[20] Data on variability analyses is available in Supplementary Materials.

We defined a p-value < .05 as statistically significant. Statistical analyses were performed using IBM SPSS Statistics 24.0 package (New York, NY) statistical software version 20 and the software R (R Foundation for Statistical Computing; https://www.r-project.org), packages "rms", "cmprsk" and "timeROC".

3 | RESULTS

3.1 | Study population

From the initial cohort of 389 consecutive patients referred to CMR for suspected myocarditis, 133 (34%) were excluded: 86 (22%) not fulfilling the inclusion criteria of the study, 26 (7%) without suitable images for CMR-FT analysis and 22 (6%) without follow-up information (Figure S1).

The final study cohort consisted of 256 patients. Table 1 summarizes the main baseline characteristics of the study population. Median age was 36 years, 71% were males. Baseline median LVEF measured by CMR was 60% (IQR 56–63), while the median LV-GLS was −17.3% (IQR −19.5 to −15.4). The median time between hospital admission and CMR imaging was 4 [IQR 2–12] days.

3.2 | Outcomes

During a median follow-up of 27 months [IQR 13–58], a total of 30 ACEs occurred. In detail, 6 patients experienced more than one CV event. Twenty-four patients (9% of the study population) experienced at least one ACE and were considered in the outcome analyses (see Table 2 for the incidence rate of each specific event). Only two patients (0.8%) experienced non-cardiac death during follow-up. The development of LVEF <50% was the predominant ACE, occurring as first ACE in 17 out of the 24 patients (71%) at a median time of 14.5 months. In two out of 17 (11.7%) cases, the development of LVEF<50% was concomitant or preceded by recurrent myocarditis.

3.2.1 | LGE and CV events

Compared to the others, patients experiencing ACEs presented more frequently mid-wall LGE (29% vs. 10% in patients with and without ACEs, respectively, $p = .001$) and diffuse LGE (83% vs. 54% in patients with and without ACEs, respectively, $p = .006$). At survival analysis, non-localized LGE and mid-wall LGE were associated with higher rates of ACEs compared to localized LGE and subepicardial LGE ($p = .001$ and $p = .005$, respectively) **(Figure 1)**. The presence of anteroseptal (AS) LGE was not associated with an increased risk of ACEs ($p = .794$). Of note, all patients experiencing ACEs presented with infero-lateral (IL) LGE (Figure S2).

3.2.2 | CMR-FT LV-GLS and ACEs

Median CMR-FT LV-GLS values were more impaired in patients experiencing ACEs compared to the others (−13.9% [−15.6 to −9.7] vs. −17.5% [−19.7 to −15.7] in patients with and without ACEs respectively, $p = .001$) **(Table 1)**. Moreover, a linear effect of LV-GLS on the risk of ACEs was observed until −20%, with a subsequent plateau **(Figure 2)**. This effect was modelled in the multivariable regression models.

A full list of parameters tested at univariable analysis is showed in Table S3. LV-GLS was associated with ACEs (HR for each unit increase 1.375 [1.210–1.552], $p < .001$). CMR-FT LV-GLS remained always associated to ACEs after extensive bivariable analyses, in particular after adjustment for LGE distribution or localization **(Table 3)**.

TABLE 1 Baseline characteristics of the study population

Parameters	Available	All ($n = 256$)	No ACEs ($n = 232$)	≥1 ACEs ($n = 24$)	p Value
Age	256 (100%)	36 [25–50]	35 [25–48]	49 [22–65]	.07
Male sex	256 (100%)	182 (71%)	165 (71%)	17 (71%)	.97
BMI	256 (100%)	24 [23–28]	24 [23–28]	26 [21–31]	.49
Flu-like Syndrome	246 (96%)	107 (44%)	98 (44%)	9 (41%)	0.79
Chest Pain	**254 (99%)**	**213 (84%)**	**197 (86%)**	**16 (67%)**	**.01**
Palpitations	207 (81%)	14 (7%)	10 (6%)	4 (17%)	.09 (F)
Dyspnea	**217 (85%)**	**37 (17%)**	**30 (15%)**	**7 (37%)**	**.01**
Hypertension	203 (79%)	35 (17%)	29 (16%)	6 (30%)	.11
Dyslipidemia	**199 (78%)**	**21 (11%)**	**16 (9%)**	**5 (28%)**	**.01**
Diabetes	**200 (78%)**	**8 (4%)**	**4 (2%)**	**4 (21%)**	**.003 (F)**
CKD (<60 ml/min)	255 (99%)	5 (2%)	3 (1%)	2 (8%)	.07 (F)
Previous MI	216 (85%)	5 (2%)	4 (2%)	1 (4%)	.44 (F)
ST Elevation	190 (74%)	69 (36%)	62 (36%)	7 (41%)	.66
Negative T waves	196 (77%)	55 (28%)	49 (28%)	6 (33%)	.60
QRS >120 ms	195 (77%)	14 (7%)	11 (6%)	3 (20%)	.08 (F)
Aspirin	**156 (61%)**	**83 (53%)**	**80 (57%)**	**3 (19%)**	**.006 (F)**
Beta Blockers	156 (61%)	87 (56%)	79 (56%)	8 (50%)	.62
ACE-i	156 (61%)	53 (34%)	48 (34%)	5 (31%)	.80
CMR LVEF	256 (100%)	60% [56–63]	60% [56–63]	60% [56–63]	.66
CMR LVEF ≥55%	256 (100%)	214 (84%)	195 (84%)	19 (79%)	0.66
LGE Pattern	256 (100%)				
Subepicardial LGE	**256 (100%)**	**187 (73%)**	**177 (76%)**	**10 (42%)**	**.001**
Mid-wall LGE	**256 (100%)**	**30 (12%)**	**23 (10%)**	**7 (29%)**	**.001**
Subepicardial + Mid-wall	**256 (100%)**	**39 (15%)**	**32 (14%)**	**7 (29%)**	**.001**
Non-localized LGE	**256 (100%)**	**146 (57%)**	**126 (54%)**	**20 (83%)**	**.006**
LGE distribution	256 (100%)				
AS LGE	256 (100%)	36 (14,1%)	32 (14%)	4 (17%)	0.70
IL LGE	**256 (100%)**	**215 (84%)**	**191 (82%)**	**24 (100%)**	**.02**
CMR-FT analysis					
LV-GLS > −20%	**256 (100%)**	**209 (81.6%)**	**185 (80%)**	**24 (100%)**	**.01**
Median LV-GLS	256 (100%)	**-17.3 [−19.5 to −15.4]**	**−17.5 [−19.7 to −15.7]**	**−13.9 [−15.6 to −9.7]**	**<.001**

Bold identifies parameters with statistically significant p values.

Abbreviations: %, percentage; ACE-I, angiotensin-converting enzyme inhibitors; ACEs; adverse cardiovascular events; AS, anteroseptal; BMI, body mass index; CKD, chronic kidney disease; CMR-FT, cardiac magnetic resonance feature tracking; F; fischer test; IL, infero-lateral; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LV-GLS, left ventricular- global longitudinal strain; MI, myocardial infarction.

At Kaplan–Meier survival analysis, at a median follow-up of 27 months, reduced LV-GLS (both > −20% or stratified using quartiles of the study population) was associated with an increased risk of ACEs ($p = .01$ and $p < .001$, respectively) **(**Figure 3**)**. The prognostic value of reduced LV-GLS was confirmed also in AM patients presenting with LVEF ≥55% ($p = .01$) (Figure S3). Finally, no ACE was experienced when LV-GLS at presentation was <−20%.

3.2.3 | CMR-FT LV-GLS for the prediction of LV systolic dysfunction

A full list of parameters tested at univariable analysis for development of LVEF <50% is showed in Table S3. At bivariable analysis, LV-GLS remained associated to development of LV dysfunction after adjustment for clinical and LGE parameters that were significant following univariable analysis (Table S4). The prognostic value of

	ACEs[a]	
	Events ($n = 24$)	IR (100 p/years)
SCD	1	0.12
Aborted SCD due to VF	1	0.12
Appropriate ICD interventions[b]	0	-
SVT	4	0.50
Development of HF	1	0.12
Development of LVEF<50%	17	2.21

Abbreviations: ACEs, adverse cardiovascular events; HF, heart failure; ICD, implantable cardioverter defibrillator; IR, incidence rate; LVEF, left ventricular ejection fraction; p/yrs, patients/years; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation.

[a]The first ACE has been taken into account.

[b]ATP + shocks on SVT.

TABLE 2 Incidence of ACEs in the study population

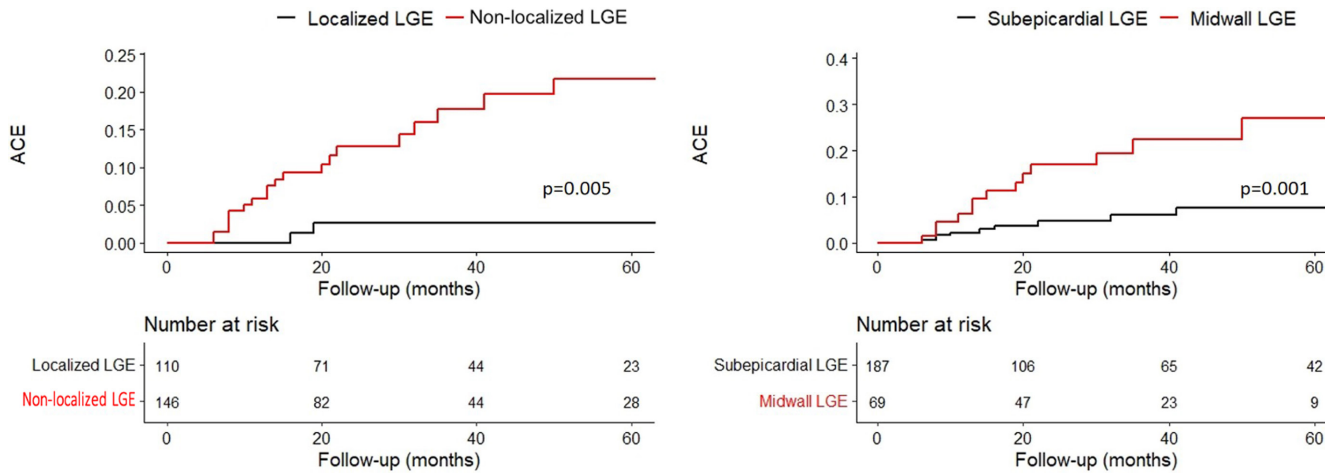

FIGURE 1 Kaplan Meier curves: The prognostic role of non-localized (left panel) and mid-wall (right panel) LGE in predicting ACEs. ACEs, adverse cardiovascular events; LGE, late gadolinium enhancement

CMR-FT LV-GLS, LGE distribution and localization for the development of LVEF <50% was further confirmed in a dedicated competing risk analysis (Figure S4).

3.3 | Incremental value of CMR-FT analysis in predictive models

Three predictive nested models were built and compared in an exploratory analysis (see "Statistical Analysis" section): the "clinical-LGE-GLS model" resulted in a further incremental prognostic accuracy for ACEs with respect to the "clinical-LGE model", in a time-dependent ROC analysis (AUC from 0.756 to 0.847; $p < .001$) (Figure S5).

3.4 | Intra- and inter-centre variability

Table S5 shows intra- and inter-centre variability of CMR-FT LV-GLS strain values. Overall, CMR-FT values showed a satisfactory level of reproducibility, with an estimated 95% CI of ICC value containing 0.90 for LV-GLS.

4 | DISCUSSION

In the present study, a total of 256 patients were analysed from seven international centres. To the best of our knowledge, this is the largest analysis investigating the prognostic role of CMR-FT LV-GLS in AMs confirmed by CMR, presenting with normal LVEF and low-risk syndrome. The main findings here reported can be summarized as follows: (1) CMR-FT LV-GLS is globally reduced (median −17.3%, IQR −19.5 to −15.4) in patients with AM confirmed by CMR with normal LVEF, compared to available reference values[21,22]; (2) during a median follow-up of 2 years, a unfavourable natural history identified by the occurrence of ACEs was found in 9% of cases (development of LVEF <50% in 71% of cases); 3) LV-GLS > −20% at baseline CMR-FT analysis is linearly associated with a higher risk

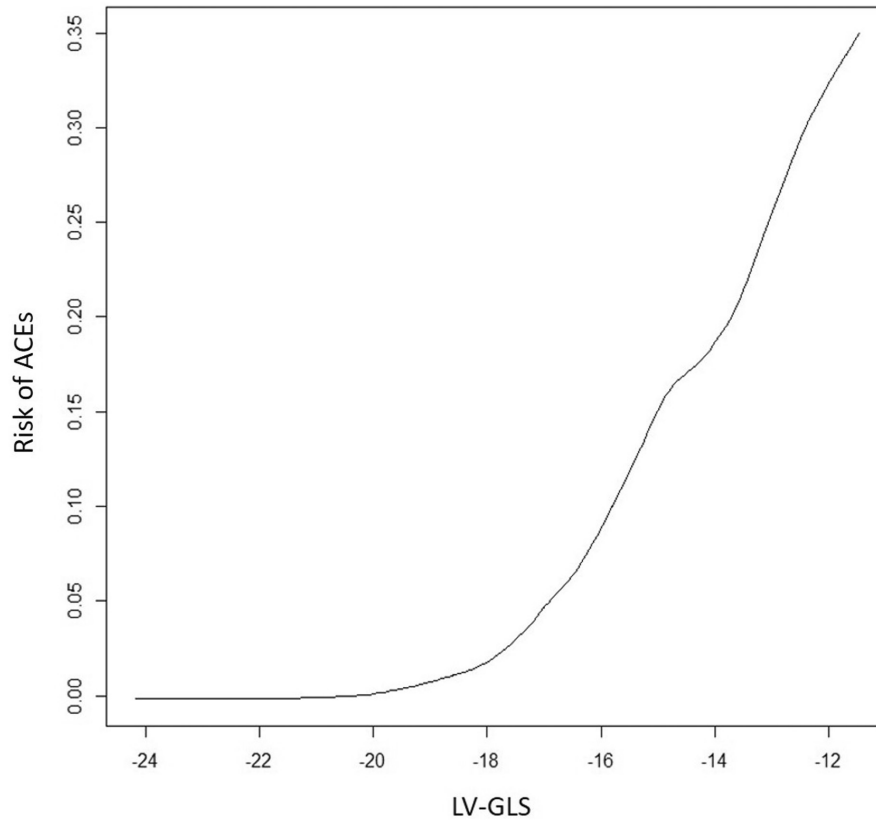

FIGURE 2 Relationship between LV-GLS and the risk of ACEs. No effect of LV-GLS in predicting ACEs was seen until −20% and then a linear increasing effect was observed. ACEs, adverse cardiovascular events; LV-GLS: left ventricular global longitudinal strain

TABLE 3 Bivariable analysis for ACEs

	HR (95% CI) for ACEs (%)	
Covariates	**Unadjusted HR**	***p* Value**
LV-GLS	**1.371 (1.213–1.550)**	**<.001**
Age	**1.021 (1.000–1.042)**	**.04**
LV-GLS	**1.368 (1.187–1.576)**	**<.001**
Dyslipidemia	2.124 (0.746–6.047)	.15
LV-GLS	**1.395 (1.204–1.617)**	**<.001**
Diabetes	**4.821 (1.571–14.796)**	**.006**
LV-GLS	**1.375 (1.192–1.586)**	**<.001**
Dyspnea	1.996 (0.767–5.197)	.06
LV-GLS	**1.379 (1.186–1.604)**	**<.001**
Aspirin/NSAIDs	**0.233 (0.066–0.830)**	**.02**
LV-GLS	**1.381 (1.213–1.571)**	**<.001**
Subepicardial LGE	**0.325 (0.144–0.734)**	**.007**
LV-GLS	**1.367 (1.200–1.558)**	**<.001**
Non-localized LGE	2.909 (0.991–8.540)	.05

Bold identifies parameters with statistically significant *p* values.

Abbreviations: %, percentage; ACEs, adverse cardiovascular events; AS, anteroseptal; CI, confidence interval; HR, hazard ratio; LGE, late gadolinium enhancement; LV-GLS, left ventricular- global longitudinal strain; NSAID, non-steroidal anti-inflammatory drugs.

of ACEs (even considering particularly the development of LVEF <50%), independently of LGE characterization. Conversely, values of CMR-FT LV-GLS < −20% were associated with a favourable natural history.

These results have major implications for clinical practice. Collecting large populations of patients with confirmed and well-characterized AM has been a hard task to pursue over the years and many studies included heterogeneous populations with "clinically suspected" AM without CMR-LLC. Conversely, we applied stringent inclusion criteria in order to identify a homogenous population of patients with a clinical and CMR diagnosis of myocarditis, preserved LV systolic function and no high risk features at presentation; and performed deep phenotypic cardiac characterization to identify prognostic parameters within our cohort. AM with normal LVEF has been traditionally reported has having a benign outcome. However, in the present study, a non-negligible incidence of ACEs is observed in the ~2 years following AM. This suggests that our current understanding of natural history in this AM subgroup should be re-evaluated. In our cohort, CMR-FT LV-GLS emerged as a novel and independent tool for the identification of patients at increased risk of adverse evolution, particularly of developing LV systolic dysfunction. This event commonly proceeds the onset of HF and potentially DCM during follow-up. This novel finding was endorsed by the observation that routine measurement of CMR-FT LV-GLS in combination with LGE characterization resulted in a significantly improved reclassification of patients' risk (Figure S5). This information provides a rationale for further studies of therapy in this cohort and patient-tailored follow-up.

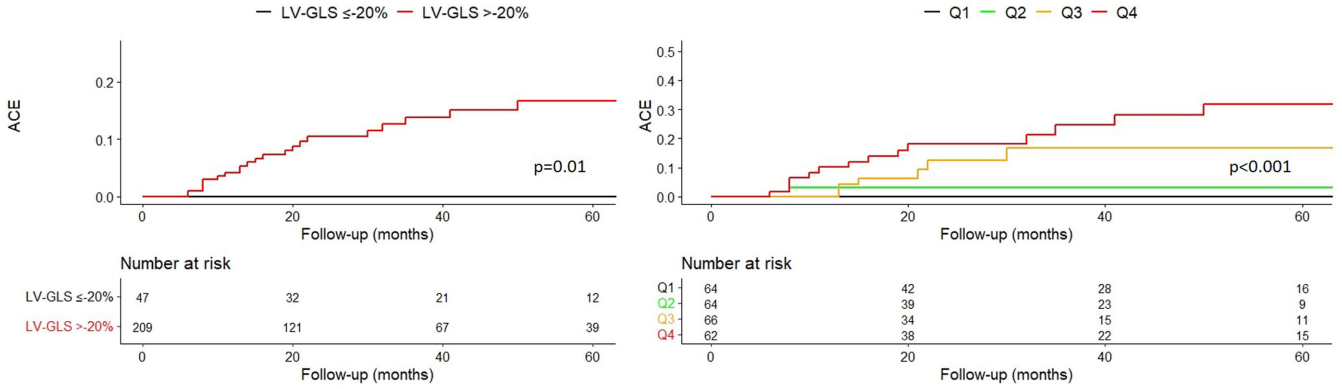

FIGURE 3 Kaplan Meier curves: The prognostic role of CMR-FT reduced LV-GLS (Left panel) and LV-GLS stratified in quartiles (right panel) in predicting ACEs. LV-GLS, left ventricular global longitudinal strain; ACEs, major adverse cardiovascular events; Q, Quartile. LV-GLS values were divided in quartiles, as following: Q1 (≤ −19.59%), Q2 (−19.51% to −17.21%), Q3 (−17.20% to −15.32%) and Q4 (≥ −15.31%)

4.1 | The prognostic role of LGE characterization

Prognostic stratification in AM patients presenting with normal LVEF remains challenging and currently relies on clinical characteristics and LGE.[1,3,4] Our findings strongly support accurate LGE characterization (Figure 1), as non-localized and mid-wall distribution patterns were associated with unfavourable natural history (even considering only the development of LVEF <50%). Although the prognostic value of LGE is widely recognized[17,23,24], its reliability in AM patients with normal LVEF and low-risk clinical presentations remains controversial. The present study expands the existing evidence supporting the prognostic role of LGE characterization in this population.[9] However, AS LGE did not confer a higher risk of ACEs in our cohort compared to the ITAMY study, despite a similar event rate (9% vs. 7.7%, respectively). A number of reasons might explain these discrepancies, including different CV events in the primary end point (the development of LVEF<50% was not included in the ITAMY study) and a longer median follow-up in the ITAMY study compared to our analysis (52 vs. 27 months, respectively). Of note, in our cohort, AS LGE coexisted with IL LGE in all patients experiencing CV events, leading to a diffuse LGE pattern. Further research is required to define the role of AS LGE in this AM population.

4.2 | The prognostic role of CMR-FT LV-GLS

CMR-FT LV-GLS might represent a novel parameter for the identification of patients with AM presenting with LVEF ≥50% and "low-risk" clinical syndromes who are at particularly higher risk of adverse cardiac remodelling. The rationale supporting this finding relies on the ability of CMR-FT imaging to detect subtle systolic dysfunction, as previously reported.[12,25,26] Our results suggest that LV-GLS should be considered as a continuous rather than binary (normal vs. reduced) parameter. This concept clearly emerged when using strain quartiles (Figure 3) and, mostly, from the correlation analysis between LV-GLS and ACEs that was higher as LV-GLS value decreased below −20%, in an almost linear fashion (Figure 2). Remarkably, no AM patient with LV-GLS ≤ −20% experienced ACEs during follow-up. This value supports, in the specific scenario of AM presenting with normal LVEF, the recently published reference values for CMR-FT from the Society for Cardiovascular Magnetic Resonance.[27] From a clinical perspective, LV-GLS could hypothetically be used to identify patients without residual risk of CV events at discharge. Although intriguing, further studies on larger validation cohorts are required.

Interestingly, the prognostic impact of CMR-FT LV-GLS in AM has been recently reported by Fischer et al.[13] That study enrolled only 152 out of 453 (33%) patients fulfilling CMR-LLC for the diagnosis of AM, regardless of LVEF at presentation. Furthermore, "preserved LVEF" was defined as LVEF ≥40%. Therefore, results from the subgroup with "preserved LVEF" might not be fully representative of the value of CMR-FT LV-CMR in AM with LVEF ≥50%. While the study by Fischer et al.[13] paved the way for the transition of CMR-FT imaging from research to clinical practice in unselected AM, our results highlight the independent role of CMR-FT LV-GLS in the challenging subgroup of AM patients presenting with normal LVEF, which lacks reliable prognostic markers to date. In a sensitivity analysis, this finding was further confirmed in the subgroup presenting with LVEF ≥55% (Figure S3). CMR-FT is a contrast-free, widely feasible technique using cine-SSFP sequences routinely acquired in all CMR laboratories.[26] Measurements are highly reproducible between operators[12,28] with similar accuracy irrespective of field strengths (1.5 and 3 Tesla)[29], making this a promising technique in the near future.

4.3 | The quest for novel prognostic tools in AM with normal LVEF

The predictive models in our exploratory analysis suggest that CMR-FT LV-GLS might provide an advantage over LGE patterns and extent for prognostication of AM patients presenting with normal LVEF. Therefore, the routine measurement of LV-GLS at first CMR might provide a closer insight into the real CV risk of AM patients with normal LVEF and represents the rationale for further studies of therapy in this cohort. If our hypothesis is confirmed by future studies, LV-GLS could become a robust parameter for routine measurement in everyday clinical activity for the early identification of AM patients at increased risk among those presenting with LVEF ≥50%. Furthermore, LGE persistence, extent, pattern and localization might be evaluated after the acute phase of AM for risk prediction.[30]

4.4 | Limitations

The strength of the present analysis lies in the stringent inclusion criteria adopted that, unlike other studies, offered the unique opportunity to collect and investigate a homogeneous population of patients with CMR-proven AM presenting with LVEF ≥50% and low risk features, although at the cost of an absolute small number of events. This study has intrinsic limitations derived from the retrospective design and the possibility of varying treatment based on empirical decisions by treating clinicians. Among patients who developed LVEF<50% during follow-up, 35% ($n = 6/17$ patients) were taking beta blockers and 12% ($n = 2/17$ patients) were taking ACE inhibitors. Therefore, it is unclear how therapies such as beta-blockers and angiotensin-converting enzyme inhibitors have influenced ACEs in our cohort. Although previous myocardial infarction might increase the risk of ACEs, only one out of five patients with a minor myocardial infarction and no subendocardial LGE on CMR images experienced an ACE (i.e., development of HF). Troponin and natriuretic peptides values were not comparable among centres due to different assay sensitivity and change in the assay in use over time in the same institutions. T1 and T2 values were available only in CMR exams performed between 2019 and 2020 following the publication of the updated LLC for the diagnosis of AM.[6] The presence of LGE was a primary inclusion criterion in our study, thus potentially explaining its lower prognostic value compared to previous studies. Characterization of LGE extent was not performed, but it suffers from low reproducibility among different operators. Myocardial edema was variably defined by T2-weighted imaging or T2 parametric mapping, according to local protocols. The correlation between LV-GLS measured by CMR-FT and echocardiography could not be explored in the present analysis and requires further dedicated research. The development of LVEF <50% does not represent a traditional "major" ACE; however, it is a clinically relevant event in a population traditionally considered at "low-risk" and allowed us to provide novel findings in the clinical management of those specific AM patients. We performed extensive bivariable analyses to confirm the independent value of LV-GLS compared to other parameters due to a low absolute number of events, which was directly related to the low CV risk of the study population. To partially overcome this limitation, we performed a sensitivity analysis adopting the "nested-models" strategy to evaluate the independent value of LV-GLS taking into account the other relevant clinical variables. Further studies are required to confirm the results of our hypothesis generating research in a full multivariable model. Finally, CMR-FT can suffer from inter-vendor variability.

5 | CONCLUSIONS

In a large cohort of AM patients presenting with normal LVEF, CMR-FT LV-GLS provided independent prognostic value over clinical features and LGE patterns. A LV-GLS ≤ −20% might aid in the identification of patients without residual CV risk and favourable natural history. CMR-FT LV-GLS measured at the first CMR is a possible tool to improve risk stratification and to guide decision-making in routine clinical practice.

ACKNOWLEDGEMENT

We would like to thank Fondazione CRTrieste, Fondazione CariGO, Fincantieri and all the healthcare professionals for the continuous support to the clinical management of patients affected by cardiomyopathies, followed in Heart Failure Outpatient Clinic of Trieste, and their families.

CONFLICT OF INTEREST

The authors report no conflict of interest related to the present study.

ORCID

Aldostefano Porcari https://orcid.org/0000-0003-3307-0825
Antonio Cannatà https://orcid.org/0000-0001-7609-6297
Alberto Cipriani https://orcid.org/0000-0001-7842-6202

REFERENCES

1. Sinagra G, Anzini M, Pereira NL, et al. Myocarditis in clinical practice. *Mayo Clin Proc*. 2016;91(9):1256-1266.

2. Pollack A, Kontorovich AR, Fuster V, Dec GW. Viral myocarditis—diagnosis, treatment options, and current controversies. *Nat Rev Cardiol*. 2015;12(11):670-680.
3. Anzini M, Merlo M, Sabbadini G, et al. Long-term evolution and prognostic stratification of biopsy-proven active myocarditis. *Circulation*. 2013;128(22):2384-2394.
4. Ammirati E, Cipriani M, Moro C, et al. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis. *Circulation*. 2018;138(11):1088-1099.
5. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White paper. *J Am Coll Cardiol*. 2009;53(17):1475-1487.
6. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;72(24):3158-3176.
7. Porcari A, De Luca A, Grigoratos C, et al. Arrhythmic risk stratification by cardiac magnetic resonance tissue characterization: disclosing the arrhythmic substrate within the heart muscle. *Heart Fail Rev*. 2020;27(1):49-69.
8. Georgiopoulos G, Figliozzi S, Sanguineti F, et al. Prognostic impact of late gadolinium enhancement by cardiovascular magnetic resonance in myocarditis. *Circ Cardiovasc Imaging*. 2021;14(1):e011492.
9. Aquaro GD, Perfetti M, Camastra G, et al. Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY study. *J Am Coll Cardiol*. 2017;70(16):1977-1987.
10. Imazio M, Angelico G, Andriani M, et al. Prevalence and prognostic impact of septal late gadolinium enhancement in acute myocarditis with or without preserved left ventricular function. *Am J Cardiol*. 2018;122(11):1955-1958.
11. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on myocardial and pericardial diseases. *Eur Heart J* 2013;34(33):2636–2648, 2648a-2648d.
12. Porcari A, Merlo M, Crosera L, et al. Strain analysis reveals subtle systolic dysfunction in confirmed and suspected myocarditis with normal LVEF. A cardiac magnetic resonance study. *Clin Res Cardiol*. 2020;109(7):869-880.
13. Fischer K, Obrist SJ, Erne SA, et al. Feature tracking myocardial strain incrementally improves prognostication in myocarditis beyond traditional CMR imaging features. *JACC Cardiovasc Imaging*. 2020;13(9):1891-1901.
14. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-e239.
15. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized Cardiovascular Magnetic Resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson*. 2020;22(1):17.
16. Gentile P, Merlo M, Peretto G, et al. Post-discharge arrhythmic risk stratification of patients with acute myocarditis and life-threatening ventricular tachyarrhythmias. *Eur J Heart Fail*. 2021;23(12):2045-2054.
17. Grani C, Eichhorn C, Biere L, et al. Prognostic value of cardiac magnetic resonance tissue characterization in risk stratifying patients with suspected myocarditis. *J Am Coll Cardiol*. 2017;70(16):1964-1976.
18. Harrell F. *Regression Modeling Strategies: with Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. 2nd ed. Springer; 2015. doi:10.1007/978-3-319-19425-7.15
19. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16(3):1141-1154.
20. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: current methods and applications. *BMC Med Res Methodol*. 2017;17(1):53.
21. Vo HQ, Marwick TH, Negishi K. MRI-derived myocardial strain measures in Normal subjects. *JACC Cardiovasc Imaging*. 2018;11(2 Pt 1):196-205.
22. Taylor RJ, Moody WE, Umar F, et al. Myocardial strain measurement with feature-tracking cardiovascular magnetic resonance: normal values. *Eur Heart J Cardiovasc Imaging*. 2015;16(8):871-881.
23. Mahrholdt H, Wagner A, Deluigi CC, et al. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. *Circulation*. 2006;114(15):1581-1590.
24. Grun S, Schumm J, Greulich S, et al. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol*. 2012;59(18):1604-1615.
25. Luetkens JA, Schlesinger-Irsch U, Kuetting DL, et al. Feature-tracking myocardial strain analysis in acute myocarditis: diagnostic value and association with myocardial oedema. *Eur Radiol*. 2017;27(11):4661-4671.
26. Amzulescu MS, De Craene M, Langet H, et al. Myocardial strain imaging: review of general principles, validation, and sources of discrepancies. *Eur Heart J Cardiovasc Imaging*. 2019;20(6):605-619.
27. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, et al. Reference ranges ("normal values") for Cardiovascular Magnetic Resonance (CMR) in adults and children: 2020 update. *J Cardiovasc Magn Reson off J Soc Cardiovasc Magn Reson*. 2020;22(1):87.
28. Schmidt B, Dick A, Treutlein M, et al. Intra- and inter-observer reproducibility of global and regional magnetic resonance feature tracking derived strain parameters of the left and right ventricle. *Eur J Radiol*. 2017;89:97-105.
29. Schuster A, Morton G, Hussain ST, et al. The intra-observer reproducibility of cardiovascular magnetic resonance myocardial feature tracking strain assessment is independent of field strength. *Eur J Radiol*. 2013;82(2):296-301.
30. Aquaro GD, Ghebru Habtemicael Y, Camastra G, et al. Prognostic value of repeating cardiac magnetic resonance in patients with acute myocarditis. *J Am Coll Cardiol*. 2019;74(20):2439-2448.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Porcari A, Merlo M, Baggio C, et al.. Global longitudinal strain by CMR improves prognostic stratification in acute myocarditis presenting with normal LVEF. *Eur J Clin Invest*. 2022;52:e13815. doi: 10.1111/eci.13815