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ORIGINAL RESEARCH

Comprehensive Cardiovascular Magnetic Resonance-Derived Myocardial Strain Analysis Provides Independent Prognostic Value in Acute Myocarditis

Jacqueline L. Vos, MD*; Anne G. Raafs, MD*; Nikki van der Velde, MD; Tjeerd Germans, MD, PhD; Paul Stefan Biesbroek, MD, PhD; Kit Roes, PhD; Alexander Hirsch, MD, PhD; Stephane R. B. Heymans, MD, PhD; Robin Nijveldt, MD, PhD

BACKGROUND: Late gadolinium enhancement and left ventricular (LV) ejection fraction on cardiovascular magnetic resonance (CMR) are prognostic markers, but their predictive value for incident heart failure or life-threatening arrhythmias in acute myocarditis patients is limited. CMR-derived feature tracking provides a more sensitive analysis of myocardial function and may improve risk stratification in myocarditis. In this study, the prognostic value of LV, right ventricular, and left atrial strain in acute myocarditis patients is evaluated.

METHODS AND RESULTS: In this multicenter retrospective study, patients with CMR-proven acute myocarditis were included. The primary end point was occurrence of major adverse cardiovascular events: all-cause mortality, heart transplantation, heart failure hospitalizations, and life threatening arrhythmias. LV global longitudinal strain, global circumferential strain and global radial strain, right ventricular-global longitudinal strain and left atrial strain were measured. Unadjusted and adjusted cox proportional hazard regression analysis were performed. In total, 162 CMR-proven myocarditis patients were included (41 ± 17 years, 75% men). Mean LV ejection fraction was 51 ± 12%, and 144 (89%) patients had presence of late gadolinium enhancement. Major adverse cardiovascular events occurred in 29 (18%) patients during a follow-up of 5.5 (2.2–8.3) years. All LV strain parameters were independent predictors of outcome beyond clinical features, LV ejection fraction and late gadolinium enhancement (LV-global longitudinal strain: hazard ratio [HR] 1.07, *P*=0.02; LV-global circumferential strain: HR 1.15, *P*=0.02; LV-global radial strain: HR 0.98, *P*=0.03), but right ventricular or left atrial strain did not predict outcome.

CONCLUSIONS: CMR-derived LV strain analysis provides independent prognostic value on top of clinical parameters, LV ejection fraction and late gadolinium enhancement in acute myocarditis patients, while left atrial and right ventricular strain seem to be of less importance.

Key Words: acute myocarditis ■ feature tracking ■ myocardial strain ■ prognosis—CMR

Acute myocarditis is an inflammatory disease of the myocardium with a great variation in clinical presentation, ranging from subclinical disease to cardiogenic shock and life-threatening arrhythmias (LTA).[1] Up to 20 percent of patients develop incident heart failure (HF), and/or dilated cardiomyopathy (DCM) with persistent myocardial dysfunction after an acute episode of myocarditis.[1] Currently, cardiovascular magnetic resonance (CMR) plays a major role in both the diagnostic process and prognostic stratification

Correspondence to: Robin Nijveldt, MD, PhD, Department of Cardiology, Radboud University Medical Center Geert Grooteplein 10, 6525 GA, Nijmegen, The Netherlands. Email: robin.nijveldt@radboudumc.nl

*J. L. Vos and A. G. Raafs contributed equally.

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CLINICAL PERSPECTIVE

What is New?

- In this multicenter observational study of 162 acute myocarditis patients, left ventricular strain parameters are independent predictors of major adverse cardiovascular events (longitudinal strain: hazard ratio [HR] 1.07, *P*=0.02; circumferential strain: HR 1.15, *P*=0.02; radial strain: HR 0.98, *P*=0.03); right ventricular and left atrial strain were not.
- Late gadolinium enhancement extent was not associated with event-free survival.

What are the Clinical Implications?

- Cardiovascular magnetic resonance is widely recommended and used in patients with suspected myocarditis, and feature-tracking derived left ventricular strain, which can be easily measured on standard cine images, may improve risk stratification.
- The findings of this study support the incremental prognostic value of feature tracking strain in acute myocarditis patients, stressing the need for future research to improve risk stratification.

Nonstandard Abbreviations and Acronyms

GCS	global circumferential strain
GLS	global longitudinal strain
GRS	global radial strain
LGE	late gadolinium enhancement
LTA	life threatening arrhythmias
MACE	major adverse cardiovascular events

of myocarditis patients. It provides insight in cardiac function and the extent of cardiac inflammation and/or fibrosis.[1–3] The prognostic value of LGE and LVEF is unclear in acute myocarditis. Whereas some studies suggest that these parameters have prognostic value,[4–6] others did not find LGE extent to be associated with outcome in acute myocarditis.[7,8] Consequently, it remains challenging to distinguish patients who are at risk for HF or LTAs, and how to monitor them.[4,5] Since inflammation and scarring, which can lead to HF and LTAs in the future, are often only locally present in the myocardium, global functional parameters such as left- and right-ventricular (RV) volumes and EF are less sensitive to detect these subtle changes. The recently developed post-processing CMR-technique feature tracking measures myocardial deformation also known as strain. Feature tracking strain can detect more subtle and local changes in cardiac function.[9] In substantial proportions of HF patients with recovered LVEF and relatives of patients with dilated cardiomyopathy with normal LVEF, decreased LV strain values have been detected, which are associated with worse outcome.[10,11] The pathophysiological process of acute myocarditis does not only involve the LV but can also cause RV dysfunction.[12–14] Biventricular dysfunction may also predict a worse prognosis,[1] but data about the prognostic value of RV global longitudinal strain (GLS) are lacking. Finally, the prognostic impact of left atrial (LA) functional decline preceding HF remains completely unknown.[15] LA function might be of special interest in acute myocarditis patients, who often do not present with overt HF at initial presentation. LA dysfunction might be a precursor of developing HF in the long term, and as such predict worse outcome. Therefore, the purpose of this study is to perform a comprehensive strain analysis of the heart and to evaluate the prognostic value of CMR-derived LV, RV, and LA strain parameters in acute myocarditis patients.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

Four Dutch clinical centers participated in this retrospective multicenter study: Radboud University Medical Center, Maastricht University Medical Center, Amsterdam University Medical Center, and Erasmus Medical Center. These secondary (or even tertiary) centers are chosen by the study team. All centers are located in urban areas and provide clinical care for both local and referred patients. Suspected acute myocarditis patients who underwent CMR between 2005 and 2019 were identified in local electronic databases by searching for 'myocarditis' in the CMR report field. Patients were included based on the following inclusion criteria: (1) ≥1 clinical symptom and ≥1 diagnostic criterium, or ≥2 diagnostic criteria from different diagnostic categories as stated in the European Society of Cardiology (ESC) position statement;[1] (2) absence or low pretest probability of significant coronary artery disease (stenosis ≥50%) or known pre-existing cardiovascular disease that could explain the syndrome; (3) ≥1 diagnostic CMR myocarditis criterium; (4) a maximum time-frame of 3 months between CMR and hospitalization; and (5) CMR cine images available for offline analysis. Two patients were excluded due to poor quality of the images, 6 patients were lost to follow-up (Figure S1). Data regarding medical history, clinical presentation and electrocardiography were collected using medical records. The study was

performed according to the declaration of Helsinki and was approved by the local institutional medical ethics committees. Written informed consent was either obtained or waived by the local institutional review board.

Follow-Up

The primary predefined end point was the combination of all-cause mortality, heart transplantation, HF hospitalization, and LTAs. Follow-up data were collected using medical records. End of follow-up was June 2020. LTAs were defined as ventricular fibrillation (with or without implantable cardioverter-defibrillator shock), hemodynamic unstable ventricular tachycardia, or sustained ventricular tachycardia with implantable cardioverter-defibrillator shock.

CMR Acquisition and Analysis

CMR imaging was performed on a 1.5T MRI system (Intera, Philips Medical Systems, Best, The Netherlands). Standard cine images were acquired with electrocardiogram gating during repeated end-expiratory breath holds with the patient in supine position. Offline post-processing analyses of all CMR scans were performed on Medis software (Medis Medical Imaging Systems, Leiden, The Netherlands). Consecutive short-axis cine images from base to apex were analyzed to measure LV and RV volumes, LV mass and calculate ventricular EF. Average LA volumes and atrial EF were measured on the 2- and 4-chamber cine images, using the biplane Simpson's area-length method.[16] LGE images, performed 10–15 minutes after administration of an intravenous bolus of a gadolinium-based contrast, were acquired using a two-dimensional, segmented inversion-recovery prepared gradient echo pulse sequence, with similar views as used for the cine-images. The presence of LGE was first assessed visually. If present, LGE extent was quantified in the short-axis images using the full-width at half maximum technique (in grams, and as percentage of total LV mass) and contours where manually adjusted when needed.[17] Nonspecific RV insertion point fibrosis was excluded from the LGE analysis.[18] Presence of edema on the T2-weighted images were analyzed. Normal LVEF or RVEF was defined as ≥50%, as stated in the latest guidelines.[19]

CMR Feature Tracking Analysis

Two trained independent investigators (JV and AR), blinded to outcome and supervised by a level III CMR physician with >15 years of experience (RN), performed offline strain analyses using dedicated software (Qstrain, Medis BV, version 2.0.48.8. Leiden, the Netherlands). LV-GLS (on 2- and 4-chamber cine images), RV-GLS (on 4-chamber cine images), and LV global circumferential and radial strain (GCS and GRS; on mid-ventricular short-axis cine images) were measured. GLS and GCS are both expressed as negative values, and GRS is expressed as a positive value. Endocardial contours were manually drawn in the end-systolic and end-diastolic frame, after which the software automatically tracks endocardial contours in all other consecutive frames. Ventricular contraction time was defined as the time to peak. LV-GCS and LV-GRS were not available in 5 patients due to insufficient quality. LA phasic strain was measured on the 2-, and 4-chamber cine images, and the reservoir (pulmonary venous return during LV systole), conduit (passive filling from the LA to the LV in early and mid-diastole), and booster strain (LA contraction in late diastole) were measured.

To evaluate the inter- and intraobserver variability, a sub analysis of 20 randomly selected CMR scans was performed. Strain analyses of these CMR scans were performed by both investigators and interobserver variability was assessed. In addition, one of the investigators repeated the strain measurements in the same 20 CMR scans, at least 2 weeks after the first measurement, to evaluate intraobserver variability.

Estimation of Strain Reference Values

Current literature does not provide reference values for all strain parameters. JV and AR analyzed CMR-images of 20 healthy volunteers, matched for age and sex, and free of cardiovascular disease. All volunteers were scanned on a GE Sigma Artist 1.5T MR scanner. The protocol was similar as for the acute myocarditis patients. Reference values were calculated based on the standard deviation (SD) of the average value of both analyzers (<2SD). Reference values are summarized in Table S1.

Statistical Analysis

Variables are displayed as numbers (percentage), mean ± SD or median (interquartile range [IQR]). Comparisons between groups were performed using χ^2 tests (or Fisher exact where necessary) for categorical variables, independent samples T-test for normally distributed, or Mann Whitney-U test for not normally distributed, continuous variables. Inter- and intraobserver variability was assessed using intraclass correlation coefficients (ICC). Kaplan–Meier survival curves were estimated for strain parameters using quartiles and differences were assessed by the log-rank test. Unadjusted and adjusted cox proportional hazards regression analyses were performed to determine the hazard ratio (HR) and 95% confidence interval (CI) of all strain parameters (included as continuous parameters). Covariates that are previously suggested to have prognostic value in acute myocarditis (LVEF, RVEF, sex, age, medical history of autoimmune disease, STEMI-like presentation, presence of septal LGE, and LGE extent[5–7]) were univariably tested for their significance in this study population, and, when

Table 1. Clinical Characteristics of Patient Population

	All (n=162)	No MACE (n=133)	MACE (n=29)	*P* value
Demographics (162/162)				
Age (y)	40 [27–54]	35 [25–51]	56 [44–67]	<0.001
Male	121 (75)	104 (78)	17 (59)	0.03
BMI (kg/m^2)	25 ± 4	25 ± 4	26 ± 5	0.57
Medical history (162/162)				
Atrial fibrillation	4 (3)	2 (2)	2 (7)	0.22
Pericarditis	5 (3)	4 (3)	1 (3)	1.00
Myocarditis	9 (6)	8 (6)	1 (3)	1.00
Hypertension	26 (16)	19 (14)	6 (21)	0.41
Hypercholesterolemia	14 (9)	7 (5)	7 (24)	<0.01
Chronic obstructive pulmonary disease	6 (4)	5 (4)	2 (7)	0.61
Diabetes	5 (3)	2 (2)	3 (10)	0.04
Autoinflammatory disease	24 (15)	17 (13)	7 (24)	0.16
Clinical presentation (162/162)				
Chest pain	123 (76)	109 (82)	15 (52)	<0.01
Dyspnea	56 (35)	40 (30)	14 (48)	0.08
Collapse	12 (7)	7 (5)	4 (14)	0.12
Flulike symptoms	98 (61)	86 (65)	12 (41)	0.02
Fever	58 (36)	52 (39)	6 (21)	0.06
Use of toxic substances	9 (6)	5 (4)	3 (10)	0.16
Smoking status				0.12
Never	112 (69)	85 (64)	23 (79)	
Former smoker	20 (12)	16 (12)	5 (17)	
Current smoker	30 (19)	29 (22)	1 (3)	
Heart rate (bpm)	87 ± 27	85 ± 22	99 ± 44	0.02
Systolic blood pressure (mm Hg)	128 ± 24	129 ± 24	122 ± 22	0.22
Diastolic blood pressure (mm Hg)	78 ± 16	79 ± 16	76 ± 17	0.42
Killip class				0.05
Class I	141 (87)	119 (89)	22 (76)	
Class II	15 (9)	9 (7)	4 (14)	
Class III	1 (1)	0	1 (3)	
Class IV	5 (3)	3 (2)	2 (7)	
Laboratory findings				
Creatinine (μmol/L) at admittance (n=159)	77 [68–91]	77 [69–90]	83 [70–104]	0.11
Elevated troponin (%) (n=154)	147 (91)	121 [92]	25 [86]	0.16
Creatine kinase, maximum (U/L) (n=142)	395 [163–836]	482 [218–886]	155 [85–324]	<0.01
NTproBNP, maximum (pmol/L) (n=58)	506 [72–3071]	371 [57–1693]	3600 [335–10473]	0.02
Leucocytes, maximum (10E9/L) (n=156)	10.9 [8.0–14.2]	10.9 [7.9–13.8]	10.4 [7.4–15.4]	0.13
C-reactive protein, maximum (mg/L) (n=156)	45 [15–123]	45 [18–129]	26 [6–113]	0.01
Electrocardiography (162/162)				
Conduction disorders				
High degree AV-block (2nd or 3rd degree)	1 (1)	1 (1)	0	1.00
Left bundle branch block	6 (4)	3 (2)	3 (10)	0.08
Right bundle branch block	6 (4)	5 (4)	1 (3)	1.00
ST-segment elevation	88 (54)	77 (58)	12 (41)	0.14
ST-segment depression	38 (24)	34 (26)	5 (17)	0.47
Genetic testing				
Performed	12 (7)	6 (5)	6 (21)	0.008
Pathogenic or likely pathogenic mutation	2 (1)	1 (1)	1 (3)	

(*Continued*)

Table 1. Continued

	All (n=162)	No MACE (n=133)	MACE (n=29)	*P* value
Admission (162/162)				
Admission duration (days)	7 [4–11]	6 (4–10)	9 (6–16)	0.01
Transfer to intensive care unit	18 (11)	15 (11)	3 (10)	1.00
Start of immunosuppressive therapy	23 (14)	18 (14)	5 (17)	0.57

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).
Abbreviations: BMI indicates body mass index; and MACE, major adverse cardiovascular event.

significant, included in the adjusted models (Table S2). Statistical analysis was performed by JV and AR, supervised by KR, using SPSS 26.0 (IBM Corp., Armon, NY). A *P*-value <0.05 was considered the threshold for significance of an association, without correction for multiplicity in this explorative study. RN had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

RESULTS

Patient Characteristics

A total of 162 patients have been included between 2005 and 2019. Clinical characteristics are summarized in Table 1. Male sex predominated (75%), and the median age was 40 [27–54] years. Patients presented with a ST-elevation myocardial infarction (STEMI)-like presentation in 46% (n=74), with complaints of chest pain and elevated cardiac troponins. Significant coronary artery disease was ruled out in 100 patients (62%) using invasive coronary angiography, in six using coronary computed tomography, and in the remaining patients the clinical pre-test probability for coronary artery disease was too low to perform coronary imaging.

Almost half of the patients had viral myocarditis (49%). Nine percent had an auto-immune disease causing the myocarditis and one-third had an unknown cause. Other less frequent etiologies are summarized in Table S3. EMB was performed in 21 patients (13%) during hospital admission showing signs of active myocarditis. Lymphocytic myocarditis was present in 15 patients (71%). One patient had signs of neutrophilic myocarditis, 2 patients had signs of eosinophilic myocarditis and 2 patients had giant cell myocarditis. The explanted heart of the patient who underwent a heart transplantation showed giant cell myocarditis with progressive myocardial injury.

CMR Parameters and Feature Tracking Parameters

The median time between admission and CMR was 6 (3–9) days. All CMR parameters are described in Table 2. Fifty-four (33%) patients had reduced LVEF (<50%), and 41 (25%) patients had reduced RVEF (<50%). Biventricular dysfunction was present in 28 patients (17%).

LV-GLS was impaired in 45 (28%) patients, LV-GCS was impaired in 28 (18%) patients, and LV-GRS was impaired in 61 (39%) patients. RV-GLS was –26 ± 7 impaired in 20 (13%) patients. In only 15 (10%) patients, both LV and RV-GLS were impaired, based on the predefined reference values.

LA reservoir strain was impaired in 22 (14%) patients. LA conduit and LA booster were impaired in 19 (12%) and 28 (17%) patients, respectively.

T2 weighted imaging was performed in 158 (97%) patients. Myocardial edema was present on the T2 weighted images in 120 (74%) patients. Nonischemic LGE was observed in 144 (89%) patients, predominantly in the septal or lateral LV wall with either a mid-wall or (sub)epicardial pattern. LGE quantification was feasible in 138 (96%) patients with LGE and resulted – together with the patients without LGE – in a median of 5.5% of the LV mass (IQR 2.6–8.9%, Table 2).

Association Between the Individual Strain Parameters, LVEF, and LGE Extent With Occurrence of MACE

In total, 18% (29/162) of the patients reached the primary end point of MACE (all-cause death [n=17], heart transplantation [n=1], LTA [n=11], and HF hospitalization [n=7]) during a median follow-up of 5.5 (2.2–8.3) years (Table S4). Six patients were lost to follow-up, all after at least 1 year of follow-up. Patients with LVEF <50% had a worse prognosis compared to patients with LVEF ≥50% (*P*=0.002, Figure 1A). When we categorized the study population into subgroups of quartile values, all LV strain parameters were associated with prognosis (Log rank for trend: LV-GLS *P*=0.002, LV-GCS *P*=0.002, LV-GRS *P*=0.03, Figure 1B and 1C, Figure S2). Patients with a LV-GLS worse than –18%, had a worse prognosis compared to patients with better LV-GLS. Quartiles of RV-GLS were not differently associated with outcome (*P*=0.20, Figure 1D). Patients with LA conduit strain worse than 11% (lowest quartile) had a worse

Table 2. Cardiac Magnetic Resonance Parameters of Patient Population

	All (n=162)	No MACE (n=133)	MACE (n=29)	*P* value
Functional parameters (162/162)				
Left ventricle				
Ejection fraction (%)	51 ± 12	53 ± 12	46 ± 15	<0.01
End-diastolic volume, indexed (mL/m^2)	96 ± 29	94 ± 28	99 ± 31	0.40
End-systolic volume, indexed (mL/m^2)	49 ± 29	46 ± 27	56 ± 32	0.10
Mass, indexed (g/m^2)	61 ± 15	60 ± 15	60 ± 18	0.95
Cardiac output (L/min)	6.6 ± 1.7	6.7 ± 1.7	6.1 ± 1.8	0.10
Right ventricle				
Ejection fraction (%)	53 ± 9	54 ± 8	51 ± 13	0.17
End-diastolic volume, indexed (mL/m^2)	86 ± 23	86 ± 22	81 ± 28	0.28
End-systolic volume, indexed (mL/m^2)	40 ± 15	40 ± 14	41 ± 21	0.88
Left atrium				
Ejection fraction (%)	57 ± 11	58 ± 10	51 ± 14	<0.01
End-diastolic volume, indexed (mL/m^2)	44 ± 14	19 ± 9	23 ± 12	0.08
End-systolic volume, indexed (mL/m^2)	20 ± 10	44 ± 13	45 ± 17	0.65
Late gadolinium enhancement (162/162)				
Present	145 (90)	121 (91)	24 (83)	0.20
Distribution				
Subendocardial/transmural	4 (3)	4 (3)	0 (0)	1.00
Nonischemic, (sub)epicardial	97 (60)	86 (65)	10 (34)	<0.01
Nonischemic, midmyocardial	107 (66)	89 (67)	18 (62)	0.58
Patchy	16 (10)	14 (11)	2 (7)	0.74
Right ventricular enhancement	6 (4)	4 (3)	2 (7)	0.30
Presence of septal LGE	45 (28)	35 (26)	10 (35)	0.37
Quantification (% of left ventricle)	5.5 [2.6–8.9]	5.5 [2.7–9.0]	4.2 [0.2–8.3]	0.35
T2 weighted imaging				
Performed	158 (97)	127 (95)	29 (100)	0.29
Myocardial edema present	121 (74)	102 (77)	18 (62)	0.27
Insufficient quality	7 (4)	3 (2)	4 (14)	
Pathological pericardial effusion* (162/162)				
Focal	25 (15)	20 (15)	5 (17)	
Global	12 (7)	9 (7)	3 (10)	
Amount (maximum in diastole, cm)	0.76 [0.60–1.09]	0.78 [0.60–1.09]	0.66 [0.60–1.33]	0.77
Strain parameters				
Left ventricle				
Global longitudinal strain (162/162)				
Peak strain (%)	−21 ± 6	−22 ± 5	−17 ± 6	<0.001
Time to peak (% of whole cycle)	43 ± 8	43 ± 7	47 ± 13	<0.004
Global circumferential strain *(157/162)*				
Peak strain (%)	−26 ± 8	−27 ± 8	−22 ± 8	<0.003
Time to peak (% of whole cycle)	42 ± 11	41 ± 9	49 ± 16	<0.001
Global radial strain *(157/162)*				
Peak strain (%)	52 ± 18	55 ± 17	42 ± 20	<0.001
Time to peak (% of whole cycle)	59 ± 39	55 ± 36	75 ± 48	0.02
Right ventricle				
Global longitudinal strain *(162/162)*				
Peak strain (%)	−26 ± 7	−27 ± 7	−25 ± 6	0.20
Time to peak (% of whole cycle)	43 ± 13	42 ± 11	43 ± 11	0.68

(*Continued*)

Table 2. Continued

	All (n=162)	No MACE (n=133)	MACE (n=29)	*P* value
Left atrial phasic strain				
Reservoir (%) *(162/162)*	35 ± 11	36 ± 11	30 ± 12	<0.007
Conduit (%) *(162/162)*	19 ± 9	16.22 ± 5.94	15 ± 7	0.22
Booster (%) *(162/162)*	16 ± 6	20 ± 8	15 ± 8	<0.006
Time between admission and CMR (days) (162/162)	6 [4–10]	6 [4–10]	9 [6–16]	0.009

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).
*Pathological pericardial effusion =>0.5 cm effusion.
CMR indicates cardiovascular magnetic imaging; and MACE, major adverse cardiovascular event.

prognosis compared to patients with better LA conduit strain (Log rank for trend *P*=0.002, Figure 2).

Prognostic Value of Strain Measures to Predict MACE

All LV strain parameters, LA reservoir and LA conduit strain were univariably associated with MACE (included as continuous variables, Table 3). After adjustment for age, sex, and LVEF – which were all univariably associated with outcome - only the LV strain parameters remained significant (LV-GLS: hazard ratio [HR] 1.07, 95% confidence interval [CI] 1.01–1.14, *P*=0.02; LV-GCS: HR 1.15, 95% CI 1.02–1.29, *P*=0.02; LV-GRS: HR 0.98, 95% CI 0.96–0.99, *P*=0.03, Table 4, Table S2), indicating that worse strain values result in higher risk

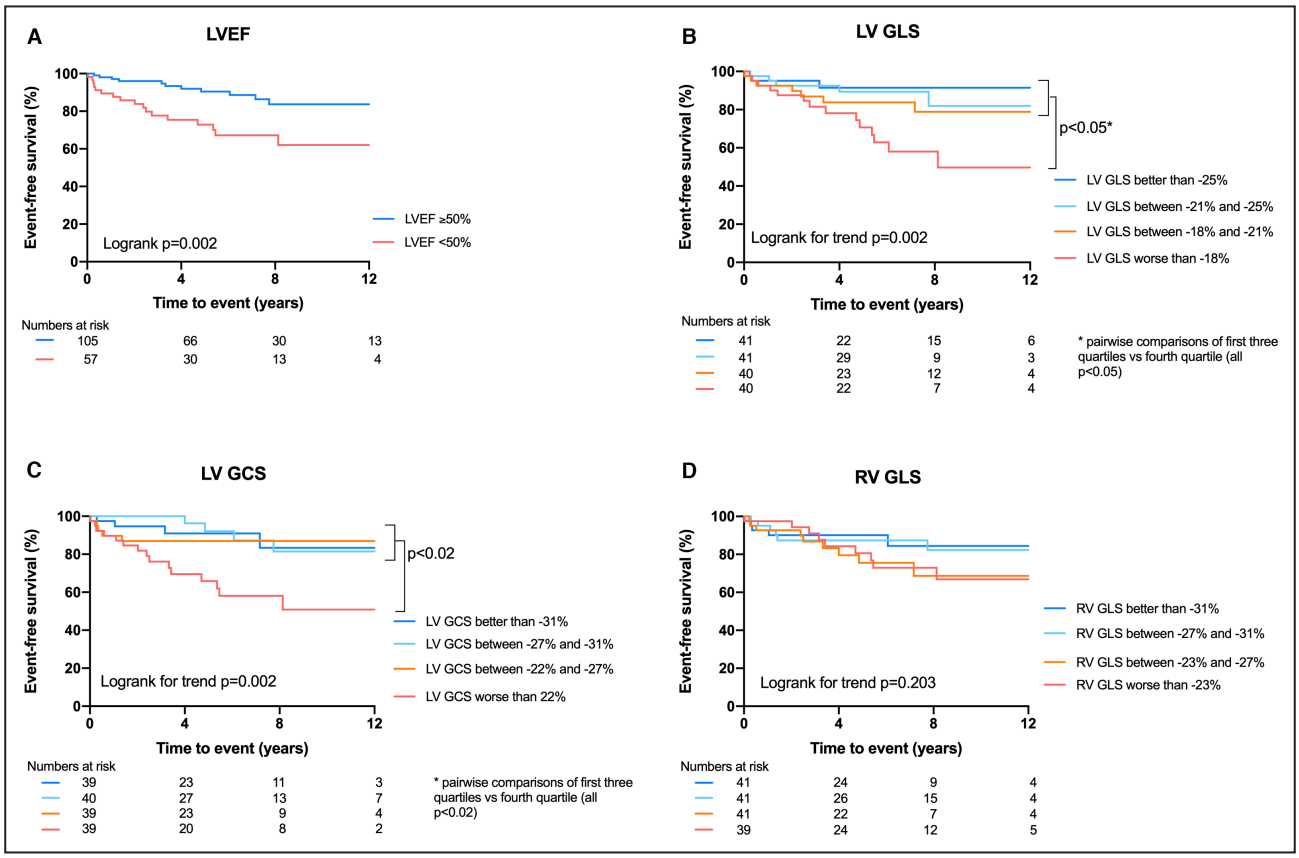

Figure 1. Kaplan–Meier survival analysis of LVEF, LV-GLS, LV-GCS and RV-GLS.
A, Patients with a LVEF <50% have a worse event-free survival compared to patients with a LVEF ≥50%; **B**, Patients with LV GLS worse than –18% have a worse event-free survival compared to patients with better strain values, based on quartiles; **C**, Patients with LV GCS worse than 22% have a worse event-free survival compared to patients with better strain values, based on quartiles; and **D**, RV GLS is not associated with event-free survival. EF indicates ejection fraction; GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricular; and RV, right ventricular.

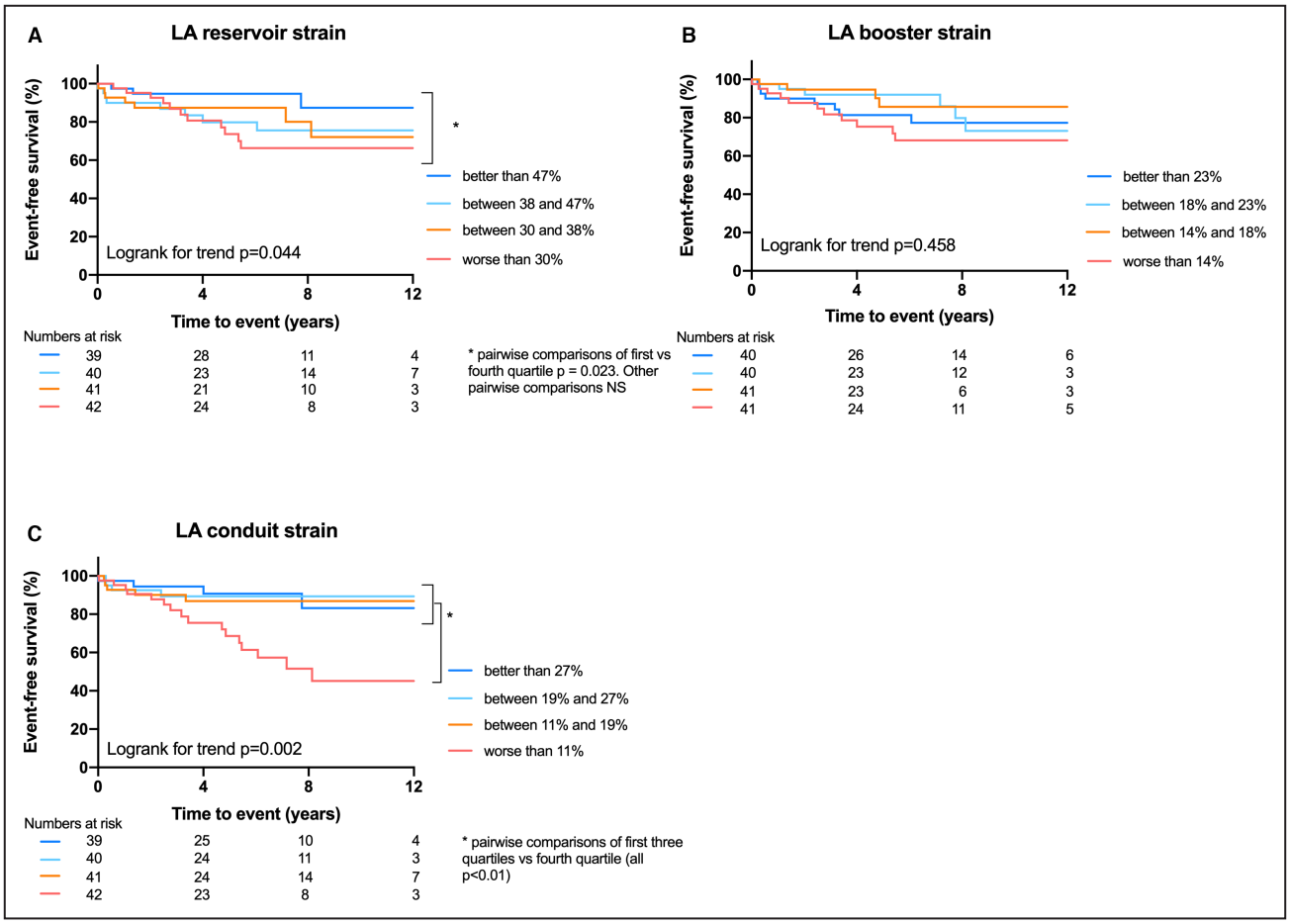

Figure 2. Kaplan–Meier survival analysis of LA strain parameters.
A, LA reservoir strain is associated with event-free survival; **B**, LA booster strain is not associated with event-free survival; **C,** Patients with LA conduit strain worse than 11% have a worse event-free survival compared to patients with better conduit strain values, based on quartiles. LA indicates left atrial.

for the occurrence of MACE. RV-GLS and LA strain parameters were not associated with MACE after adjustment (Table 4). To be noted, LGE presence, extent and septal location were not associated with outcome (Table 3).

Besides strain, age was the only other independent predictor of outcome in this study population in all models (Table S2). Therefore, we stratified patients into 4 equal subgroups, using the median age of 40 years and the median LV-GLS value of –22% as cut-off values (clinical characteristics of the four subgroups are described in Table S5). Patients with older age and worse LV-GLS had a worse outcome as compared to the other groups (Log rank $P<0.001$, Figure 3). Patients younger than 40 years, by contrast, tended to have a good prognosis, irrespective of LV-GLS.

Inter- and Intraobserver Variability

Interobserver variability was good (LV-GCS ICC 0.80–0.90) to excellent (LV-GLS, RV-GLS, LA reservoir, LA conduit ICC, and LA booster, all ICC ≥0.90) for all strain parameters (Table S6). In addition, intraobserver variability analysis was excellent for all (Table S6).

DISCUSSION

This study evaluated the prognostic impact of CMR myocardial strain analysis of both cardiac ventricles and the LA in acute myocarditis patients. LV strain parameters were independent predictors of MACE in acute myocarditis, even beyond clinical and CMR features such as age, sex, STEMI-like presentation, LVEF, and LGE. Right ventricular and left atrial strain were not independent predictors of outcome. Patients older than the age of 40 with impaired LV strain had the worst prognosis.

Endomyocardial biopsy is currently the gold standard to diagnose acute myocarditis.[1] However, endomyocardial biopsies are often only performed in tertiary specialized centers and mainly indicated in recurrent or acute myocarditis with progressive or persistent systolic dysfunction.[20] Also, it is limited by small tissue

Table 3. Univariable Association With MACE

Variables	All patients (n=162)	
	HR (95% CI)	*P* value
Age (y)	1.05 (1.02–1.07)	<0.001
Sex (male)	0.40 (0.19–0.84)	0.015
STEMI-like presentation	1.58 (0.74–3.38)	0.24
Autoinflammatory disease	0.44 (0.19–1.03)	0.06
LVEF (%)	0.97 (0.95–0.99)	0.03
RVEF (%)	0.99 (0.94–1.03)	0.52
LGE presence	2.04 (0.78–5.35)	0.15
LGE quantification (% of LV mass)	1.00 (0.92–1.10)	0.96
Presence of septal LGE	1.29 (0.60–2.79)	0.51
Left ventricular GLS (%)	1.10 (1.05–1.16)	<0.001
Left ventricular GCS (%)	1.07 (1.02–1.11)	0.004
Left ventricular GRS (%)	0.97 (0.95–0.99)	<0.003
Right ventricular GLS (%)	1.03 (0.98–1.10)	0.30
Left atrial reservoir strain (%)	0.96 (0.93–0.99)	<0.005
Left atrial booster strain (%)	0.96 (0.90–1.02)	0.18
Left atrial conduit strain (%)	0.94 (0.89–0.98)	<0.006

GCS indicates global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; RVEF, right ventricular ejection fraction; and STEMI, ST-elevation myocardial infarction.

Table 4. Adjusted Model for the Prediction of MACE (Adjusted for Age, Sex, and LVEF)

Strain parameters	All patients (n=162)	
	HR (95% CI)	*P* value
Left ventricular GLS (%)	1.07 (1.01–1.14)	0.019
Left ventricular GCS (%)	1.17 (1.04–1.32)	0.009
Left ventricular GRS (%)	0.98 (0.96–0.99)	0.028
Left atrial reservoir strain (%)	0.99 (0.96–1.01)	0.73
Left atrial conduit strain (%)	1.01 (0.95–1.08)	0.66

Each strain parameter was adjusted for age, sex, and LVEF.

EF indicates ejection fraction; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LVEF, left ventricular ejection fraction; and MACE, major adverse cardiovascular event.

sizes and sampling error.[20] In recent years, CMR has become an important non-invasive imaging tool for the detection of myocarditis and is described as the non-invasive gold standard in the Lake Louise Criteria.[2,3,21] However, these criteria do not provide information regarding the role of CMR in risk stratification of acute myocarditis patients.

CMR feature tracking is a technique that calculates myocardial deformation and detects more subtle and local myocardial dysfunction, even when global EF is normal.[22] Here, CMR feature tracking appears to be an essential feature for risk stratification in acute myocarditis patients. These findings are in line with a first small pilot study of 37 acute myocarditis patients, revealing that CMR-FT strain parameters are univariable predictors of MACE.[23] The findings from this pilot study were further confirmed by a larger study of 455 myocarditis patients, which showed that LV-GLS is an independent predictor of prognosis over clinical features, LVEF, and LGE in myocarditis patients.[24] Both studies, however, did not address the prognostic value of RV strain and LA function and had no data regarding long-term follow-up. Our data confirm that LV-GLS is an independent and incremental predictor of long-term outcome in patients with acute myocarditis.

Biventricular dysfunction is described as a predictor of MACE in ESC guidelines,[1] but data regarding the prognostic value of RV dysfunction or impaired strain in myocarditis are still scarce. RV-GLS was not associated with outcome in our population, suggesting a limited prognostic role of the RV in acute myocarditis. Interestingly, the prevalence of biventricular dysfunction was relatively low (17%) in this study. Subsequently, most patients had normal RV function and strain. Over the last decade, improvement and increased availability of CMR techniques led to earlier and more frequent diagnosis of acute myocarditis.[3] As a result, less severely ill patients are also being diagnosed with myocarditis, probably explaining the relatively low prevalence of biventricular dysfunction in current myocarditis populations.

Besides ventricular dysfunction, LA-involvement in myocarditis is an underrepresented phenomenon in the current literature. A study including 30 myocarditis patients revealed impaired LA reservoir and conduit function compared to healthy controls, but its prognostic value was not evaluated.[25] Although LA reservoir and conduit strain predicted MACE in our study population in a univariable analysis, it did not when adjusted for age, male sex, and LVEF. Since CMR was performed shortly after initial presentation, we hypothesize that structural and functional atrial remodeling has not yet occurred. The predictive value of LA strain might become more apparent in a later stage of myocarditis, when diastolic dysfunction or dilated cardiomyopathy may develop.

In our study, LGE presence in the acute phase was not associated with the outcome. This may be because non-ischemic LGE is one of the major diagnostic criteria for acute myocarditis. Consequently, its prevalence was extremely high (90%) in our study, in line with previous studies.[8] In both ischemic and nonischemic cardiomyopathies, LGE predicts poor outcome.[26] In the first stage of acute myocarditis, it is hypothesized that LGE also represents patchy distributed cardiac inflammation (edema), which may completely heal over time,[27] besides irreversible fibrosis alone, as is recently pointed out in a meta-analysis.[8] Here, LGE extent was also not associated with worse outcomes in acute

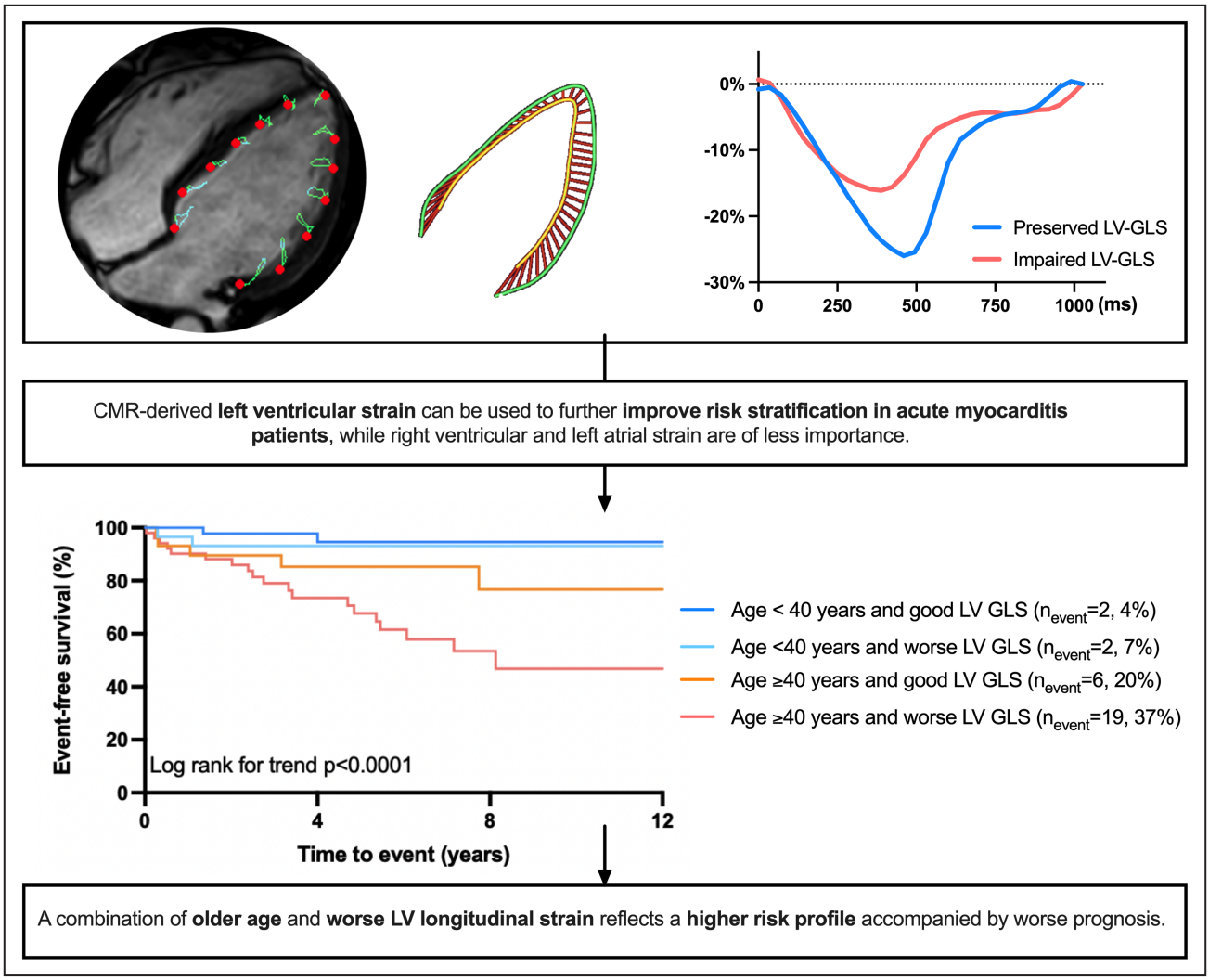

Figure 3. Kaplan–Meier survival analysis of four risk groups combining age and LV-GLS.
Good LV-GLS is defined as LV-GLS better than –22%, worse LV-GLS is defined as worse than –22%. Patients that are 40 years or older and have LV-GLS worse than –22% had a worse outcome as compared to the other groups. Patients younger than 40 years tend to have a good prognosis, irrespective of LV-GLS. GLS indicates global longitudinal strain; and LV, left ventricular.

myocarditis.[8] Thus, LGE in the active acute state of myocarditis might be more indicative for myocardial inflammation than end-stage fibrosis, the latter being associated with worse prognosis.

Clinical Implications

CMR is widely recommended and used in the diagnostic work-up of patients with suspected myocarditis and feature tracking strain can be easily measured on standard cine images.[2,3,21] Also, CMR exceeds in accuracy and reproducibility due to high signal-to-noise ratio and contrast-to-noise ratio compared to echocardiography.[9] In this study, LV strain is a strong predictor of MACE, independent of clinical, and traditional CMR parameters (such as LVEF and LGE presence). Therefore, it is a convenient tool to use in daily clinical practice, and clinicians should consider implementing this in patient management, to better predict which patients develop heart failure or persistent cardiac dysfunction, and to improve patient monitoring. Future studies are needed to validate our findings, to investigate whether the prognostic value of LV-GLS is influenced by other cardiac markers such as NTproBNP, and to provide optimal software-independent prognostic cut-off values.

Study Limitations

Limitations of this study are the lack of availability of EMB and parametric mapping (i.e., T1 or T2 mapping) in most of the patients. However, EMB is not regularly performed in clinical practice and CMR parametric mapping has only been adapted since recent years and therefore long-term outcome is yet unknown. Four Dutch tertiary centers participated in this retrospective study, introducing a selection or representation bias.

However, patients with suspected acute myocarditis are often referred to tertiary, specialized centers for extensive diagnostics and therapy. Moreover, there were no diagnostic codes used to identify patients in the local electronic databases, which might possibly lead to information bias and/or missing data. However, patients were included based on diagnostic criteria from the latest guidelines that are currently applied in clinical practice. Therefore, we believe that this study population represents the general acute myocarditis patient population. We included covariates that are previously described as prognostic markers in acute myocarditis (LVEF, RVEF, sex, age, medical history of autoimmune disease, STEMI-like presentation, presence of septal LGE, and LGE extent[5–7]) in the univariable regression analysis, which might introduce a possible bias. The relatively low event rate, however, limits the ability to perform extensive multivariable analysis and the power to detect (more subtle) differences in LA and RV strain in this cohort. Nonetheless, this study is the first to include LA and RV strain parameters, and provides long-term prognostic information, which is scarce in current literature. To evaluate whether our results are clinically relevant and reproducible besides their statistical significance, external validation in larger, prospective, acute myocarditis studies would be desirable.

CONCLUSIONS

CMR-derived LV strain analysis provides additional prognostic value on top of clinical parameters, LVEF and LGE in acute myocarditis patients, while LA and RV strain do not. A combination of older age and impaired LV longitudinal strain reflects a higher-risk profile accompanied by worse prognosis.

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Affiliations

Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands (J.L.V., R.N.); Department of Cardiology, Cardiovascular Research Institute (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands (A.G.R., S.R.H.); Department of Cardiology, and Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands (N.v.d.V., A.H.); Department of Cardiology, Amsterdam University Medical Center, Amsterdam, The Netherlands (T.G., P.S.B.); and Department of Health Evidence, section Biostatistics, Radboud University Medical Center, Nijmegen, The Netherlands (K.R.).

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Disclosures

None.

Supplemental Material

Tables S1–S6
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Clinical characteristics and strain parameters, with reference value, of healthy controls

	Healthy controls (n=20)	
Demographics		
Age (years)	41 ±12	
Sex	15 (75%)	
BMI (kg/m^2)	25 ±4	
Strain parameter		**Reference value**
LV GLS	-23.43 ± 2.29	-18.85
LV GCS	-27.54 ± 3.25	-20.04
LV GRS	71.19 ± 10.85	49.49
RV GLS	-27.09 ± 4.22	-18.65
LA reservoir	39.70 ± 8.42	22.86
LA booster	16.60 ± 3.81	8.98
LA conduit	23.10 ± 6.64	9.82

Abbreviations: GCS = global circumferential strain, GLS = global longitudinal strain, GRS = global radial strain, LA = left atrial, LV = left ventricular, RV = right ventricular.

Table S2. Common MACE predictors in acute myocarditis patients from literature

N=162	Clinical parameters + LV GLS		Clinical parameters + LV GCS		Clinical parameters + LV GRS		Clinical parameters + LA reservoir strain		Clinical parameters + LA conduit strain	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age	1.05 (1.02-1.07)	**<0.001**	1.05 (1.03-1.08)	**<0.001**	1.05 (1.02-1.07)	**<0.001**	1.05 (1.03-1.08)	**<0.001**	1.05 (1.03-1.08)	**<0.001**
Male sex	0.68 (0.32-1.47)	0.33	0.58 (0.26-1.29)	0.18	0.72 (0.32-1.61)	0.42	0.65 (0.30-1.40)	0.27	0.65 (0.30-1.40)	0.27
LVEF (%)	1.02 (0.98-1.07)	0.36	1.07 (1.01-1.15)	**0.04**	1.01 (0.97-1.05)	0.59	0.98 (0.96-1.00)	0.10	0.98 (0.96-1.00)	0.17
LV GLS (%)	1.07 (1.01-1.14)	**0.02**								
LV GCS (%)			1.17 (1.04-1.32)	**0.01**						
LV GRS (%)					0.98 (0.96-0.99)	**0.03**				
LA reservoir strain (%)							0.99 (0.96-1.03)	0.73		
LA conduit strain (%)									1.01 (0.95-1.08)	0.66

Abbreviations: CI = confidence interval, EF = ejection fraction, GCS = global circumferential strain, GLS = global longitudinal strain, GRS = global radial strain, HR = hazard ratio, LA = left atrial, LV = left ventricular.

Table S3. Overview of (suspected) etiologies of myocarditis

(suspected) Etiology of myocarditis	Frequency, n (%)
Viral	80 (49)
Auto-immune disease	15 (9)
Systemic lupus erythematosus	6 (4)
Systemic sclerosis	7 (4)
Eosinophilic granulomatosis with polyangiitis	1 (0.6)
Miller-Fisher syndrome	1 (0.6)
Giant-cell	1 (0.6)
Eosinophilic	3 (2)
Inflammatory presentation of genetic cardiomyopathy	1 (0.6)
Malaria	1 (0.6)
Polymyositis	1 (0.6)
Toxic after chemotherapy	1 (0.6)
Bacterial	4 (3)
Unknown etiology	55 (34)

Table S4. Overview of causes of death

Cause of death	Frequency, n (%)
Sudden or cardiac death	10 (59)
Cancer	2 (12)
Auto-immune disease	4 (24)
Parkinson	1 (6)

Table S5. Clinical characteristics of four risk groups using age and LV GLS

	Age < 40 years		Age ≥ 40 years		p-value
	Good LV GLS	Worse LV GLS	Good LV GLS	Worse LV GLS	
Demographics					
Age (years)	27 ±7*	26 ±6*	53 ±10†	57 ±10†	*0.59/†0.11
Male	44 (86)	25 (83)	23 (76)	29 (57)	<0.01
BMI (kg/m^2)	25 ±3	26 ±5	25 ±4	25 ±4	NS
Medical history					
Atrial fibrillation	0	0	1 (3)	3 (6)	NS
Pericarditis	2 2 (4)	0	0	3 (6)	NS
Myocarditis	5 (10)	1 (3)	3 (10)	0	NS
Hypertension	2 (4)	3 (10)	5 (16)	16 (31)	0.001
Hypercholesterolemia	3 (6)	0	3 (10)	8 (16)	NS
Chronic obstructive pulmonary disease	1 (2)	0	3 (10)	3 (6)	NS
Diabetes Mellitus	1 (2)	0	1 (3)	4 (8)	NS
Autoinflammatory disease	3 (5)	3 (10)	5 (16)	13 (25)	<0.05
Clinical presentation					
Chest pain	45 (88)	23 (77)	24 (80)	31 (61)	0.01
Dyspnoea	16 (31)	8 (27)	10 (33)	22 (43)	NS
Collapse	4 (8)	1 (3)	0	7 (14)	NS
Flulike symptoms	36 (71)	21 (70)	14 (47)	27 (53)	NS
Fever	26 (51)	12 (40)	10 (33)	10 (20)	<0.01
Smoking status					NS
Never	37 (73)	21 (70)	21 (70)	32 (63)	
Former smoker	4 (8)	0	5 (17)	11 (22)	
Current smoker	10 (20)	8 (27)	4 (13)	8 (16)	
Heart rate (bpm)	80 ±23	98 ±26	80 ±22	92 ±33	<0.01
Systolic blood pressure (mmHg)	125 ±18	122 ±25	132 ±19	132 ±29	NS
Diastolic blood pressure (mmHg)	74 ±12	75 ±18	81 ±11	82 ±19	0.03
Killip class					NS
Class I	49 (96)	26 (87)	27 (90)	39 (76)	
Class II	1 (2)	2 (7)	2 (7)	10 (20)	
Class III	0	0	1 (3)	0	

Class IV	1 (2)	2 (7)	0	2 (4)	
Laboratory findings					
Creatinine (µmol/L) at admittance	77 [69-83]	80 [70-108]	77 [69-91]	81 [67-95]	NS
Elevated troponin (%)	49 (98)	29 (100)	24 (90)	45 (92)	NS
Creatin kinase, maximum (U/L)	529 [363-975]	583 [382-1075]	257 [158-599]	161 [66-485]	NS
NTproBNP, maximum (pmol/L)	167 [36-392]	2226 [537-16650]	199 [5-2650]	1500 [371-4418]	NS
Leucocytes, maximum (10E9/L)	10.6 [8.2-13.2]	11.7 [7.8-14.7]	11.3 [7.5-15.7]	10.6 [8.2-13.8]	NS
C-reactive protein, maximum (mg/L)	31 [16-88]	91 [27-187]	47 [8-126]	43 [9-96]	0.04
Electrocardiography					
Conduction disorders					
High degree AV-block (2^{nd} or 3^{rd} degree)	1 (2)	0	0	1 (2)	NS
Left bundle branch block	0	0	1 (3)	5 (10)	NS
Right bundle branch block	0	2 (7)	2 (7)	2 (4)	NS
ST-segment elevation	38 (76)	21 (75)	15 (50)	14 (24)	<0.001
ST-segment depression	10 (20)	11 (40)	4 (13)	13 (26)	NS
Cardiac MRI					
Left ventricle					
Ejection fraction (%)	58 ±7	46 ±11	59 ±7	43 ±14	<0.001
End-diastolic volume, indexed (mL/m^2)	91 ±16	101 ±24	85 ±21	104 ±42	0.02
End-systolic volume, indexed (mL/m^2)	38 ±9	57 ±25	35 ±13	62 ±41	<0.001
Mass, indexed (g/m^2)	62 ±12	63 ±18	57 ±11	61 ±18	NS
Cardiac output (L/min)	7.1 ±1.7	6.6 ±1.7	6.7 ±1.9	5.8 ±1.5	<0.01
Right ventricle					
Ejection fraction (%)	56 ±5	49 ±9	56 ±4	51 ±13	0.001
End-diastolic volume, indexed (mL/m^2)	93 ±15	86 ±23	89 ±21	76 ±29	<0.01
End-systolic volume, indexed (mL/m^2)	41 ±9	45 ±16	39 ±10	38 ±21	NS
Late gadolinium enhancement					
Present	47 (94)	27 (90)	27 (90)	42 (84)	NS
Quantification (% of LV mass)	6.3 [3.6-8.4]	7.2 [1.8-11.7]	3.6 [2.8-8.7]	3.9 [1.3-7.5]	NS
T2 weighted imaging					
Performed	50 (98)	28 (93)	30 (100)	49 (96)	NS
Myocardial oedema present	47 (94)	23 (82)	17 (57)	33 (49)	**<0.01**
Admission					

Admission duration (days)	5 [4-8]	6 [3-11]	6 [3-12]	9 [6-15]	NS
Transfer to intensive care unit	4 (8)	6 (20)	2 (7)	6 (12)	NS
Start of immunosuppressive therapy	4 (8)	5 (17)	5 (17)	9 (18)	NS
Events					
All-cause death	2	1	3	12	**<0.01**
HF hospitalization	0	1	1	5	NS
Life threatening arrhythmias	1	0	2	8	**0.02**
MACE ‡	3	2	4	20	**<0.01**

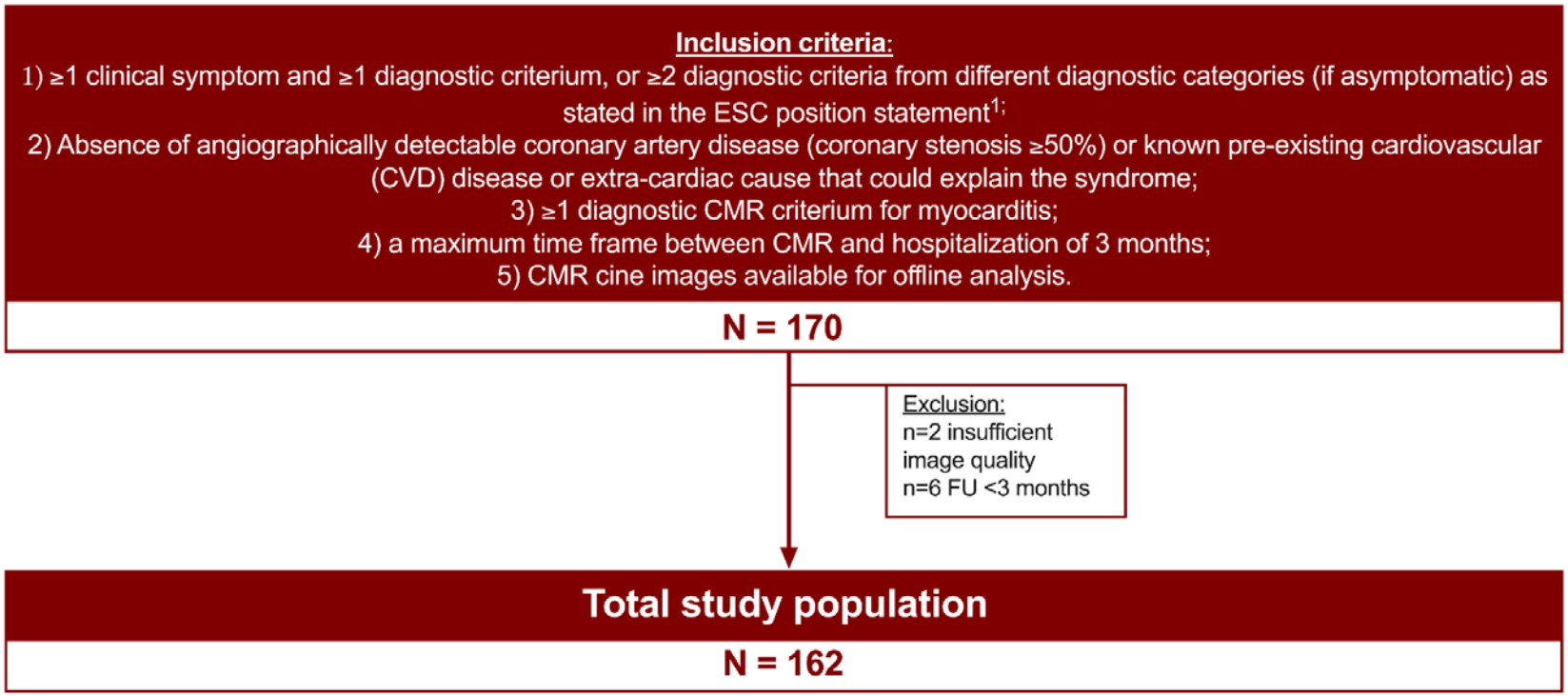
* = good versus low GLS in patients with age <40 years, † = good versus low GLS in patients with age >40 years, ‡ When more than 1 event, the first event was included for the combined endpoint 'MACE'.
NS = not significant.
Data is presented as mean ± standard deviation, median (interquartile range) or number (%).
Abbreviations: BMI = body mass index, MACE = major adverse cardiovascular events.

Table S6. Inter- and intraobserver variability of strain parameters

Strain parameters	Interobserver variability		Intraobserver variability	
	ICC (95% CI)	p-value	ICC (95% CI)	p-value
Left ventricular GLS (%)	0.94 (0.86-0.98)	<0.001	0.92 (0.82-0.97)	<0.001
Left ventricular GCS (%)	0.82 (0.61-0.93)	<0.001	0.91 (0.80-0.97)	<0.001
Left ventricular GRS (%)	0.99 (0.97-1.00)	<0.001	0.91 (0.79-0.97)	<0.001
Right ventricular GLS (%)	0.90 (0.76-0.96)	<0.001	0.95 (0.88-0.98)	<0.001
Left atrial reservoir strain (%)	0.97 (0.92-0.98)	<0.001	0.90 (0.76-0.96)	<0.001
Left atrial conduit strain (%)	0.96 (0.89-0.98)	<0.001	0.96 (0.89-0.98)	<0.001
Left atrial booster strain (%)	0.89 (0.75-0.96)	<0.001	0.88 (0.73-0.95)	<0.001

Abbreviations: GCS = global circumferential strain, GLS = global longitudinal strain, GRS = global radial strain

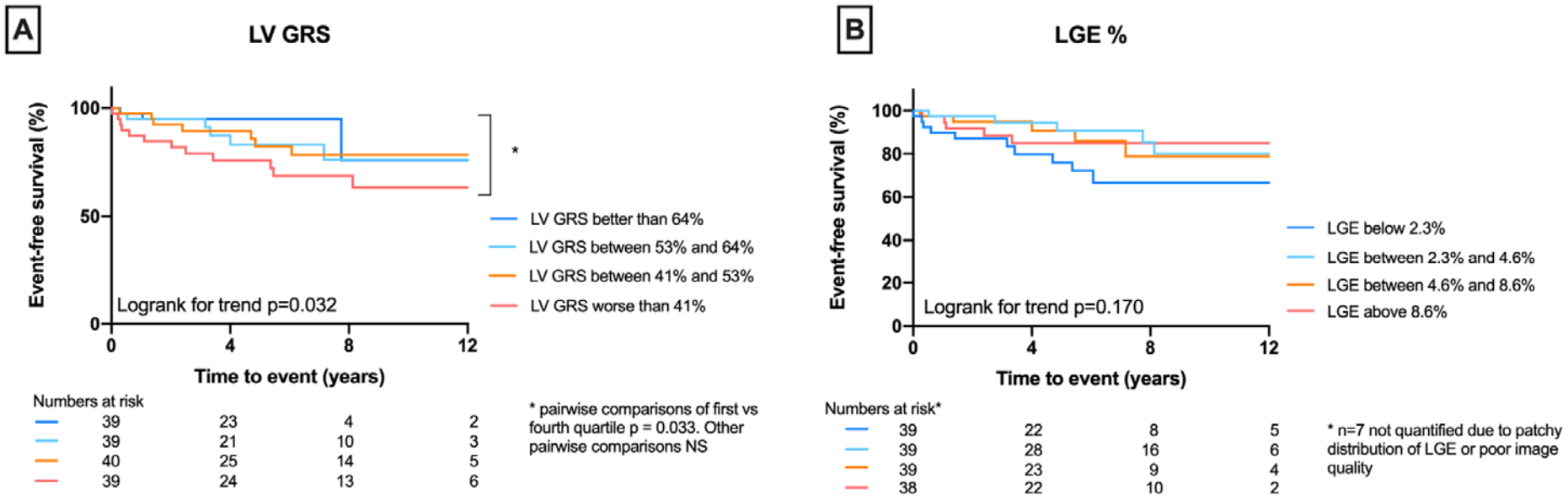
Figure S1. Flowchart of the study population



Suspected acute myocarditis patients who underwent CMR between 2005 and 2019 were retrospectively screened in four Dutch centers. Patients were included when they fulfilled the ESC position statement criteria including a diagnostic CMR criterium and had a maximum timeframe of 3 months between CMR and hospitalization. Patients were excluded if all cine images (short- and both long-axis) were unavailable for offline analysis, of insufficient quality or had no or too short follow-up. A total of 162 patients was included.

Abbreviations: CMR = cardiovascular magnetic resonance, ESC = European Society of Cardiology, FU = follow-up.

Figure S2. Kaplan Meier survival analysis of phasic strain parameters and LGE %



Abbreviations: GRS = global radial strain, LGE = late gadolinium enhancement, LV = left ventricular.

(A) LV-GRS is associated with event-free survival; (B) LGE extent is not associated with event-free survival