Cardiac Magnetic Resonance Imaging in Myocarditis Reveals Persistent Disease Activity Despite Normalization of Cardiac Enzymes and Inflammatory Parameters at 3-Month Follow-Up

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BACKGROUND: There is a major unmet need to identify high-risk patients in myocarditis. Although decreasing cardiac and inflammatory markers are commonly interpreted as resolving myocarditis, this assumption has not been confirmed as of today. We sought to evaluate whether routine laboratory parameters at diagnosis predict dynamic of late gadolinium enhancement (LGE) as persistent LGE has been shown to be a risk marker in myocarditis.

METHODS AND RESULTS: Myocarditis was diagnosed based on clinical presentation, high-sensitivity troponin T, and cardiac magnetic resonance imaging, after exclusion of obstructive coronary artery disease by angiography. Cardiac magnetic resonance imaging was repeated at 3 months. LGE extent was analyzed with the software GT Volume. Change in LGE >20% was considered significant. Investigated cardiac and inflammatory markers included high-sensitivity troponin T, creatine kinase, myoglobin, N-terminal B-type natriuretic peptide, C-reactive protein, and leukocyte count. Twenty-four patients were enrolled. Absolute levels of cardiac enzymes and inflammatory markers at baseline did not predict change in LGE at 3 months. Cardiac and inflammatory markers had normalized in 21 patients (88%). LGE significantly improved in 16 patients (67%); however, it persisted to a lesser degree in 17 of them (71%) and increased in a small percentage (21%) despite normalization of cardiac enzymes.

CONCLUSIONS: This is the first study reporting that cardiac enzymes and inflammatory parameters do not sufficiently reflect LGE in myocarditis. Although a majority of patients with normalizing laboratory markers experienced improved LGE, in a small percentage LGE worsened. These data suggest that cardiac magnetic resonance imaging might add value to currently existing diagnostic tools for risk assessment in myocarditis.

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WHAT IS NEW?

- The majority of participants in this study were found to have persistent late gadolinium enhancement at 3 months despite normalization of cardiac and inflammatory markers.
- Absolute levels of cardiac enzymes and inflammatory markers at baseline did not predict change in late gadolinium enhancement at 3 months.
- Similarly, their relative decrease at 3 months did not correlate with improved late gadolinium enhancement.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Previous research has shown late gadolinium enhancement to be one of the most important predictors of adverse cardiovascular outcomes in myocarditis.
- Although it is common practice to use clinical findings, echo, and biomarkers to monitor clinical course in myocarditis, our findings suggest that such a strategy might not detect all active disease.
- Cardiac magnetic resonance imaging should be considered as an alternative or supplemental strategy for follow-up and risk stratification in patients with myocarditis.

Myocarditis is a common cardiac disease of varying degree of severity.[1–5] Clinical presentation may range from mild symptoms to severe heart failure and ventricular arrhythmias.[6,7] Myocarditis has been reported in up to 25% of young adults presenting with sudden death.[8–12] As of today, there is a major unmet need to accurately diagnose patients with myocarditis and to identify individuals at highest risk for adverse cardiovascular events. One known indicator of poor outcome is persistent late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR).[13,14]

Although cardiac enzymes and inflammatory markers may be elevated in acute myocarditis,[3,7,15,16] their role in predicting disease progression remains unknown. Transcriptomic biomarkers derived from a single endomyocardial biopsy have recently demonstrated promising results as highly accurate diagnostic test for lymphocytic myocarditis.[17,18] However, endomyocardial biopsy is an invasive procedure with the risk of complications and the limitation of sampling error.[19–22] Furthermore, it can only be performed in experienced centers. Therefore, its use is limited to a selected group of patients as outlined by the American Heart Association/American College of Cardiology guidelines.[23,24] These include patients with heart failure requiring inotropic or mechanical circulatory support, Mobitz type 2 second degree or higher heart block, sustained or symptomatic ventricular tachycardia, or failure to respond to guideline-based therapy within 1 to 2 weeks.[23,24] For all other patients with suspected myocarditis, a synopsis of clinical history and noninvasive testing is preferred.[16] Recently, CMR has evolved as the gold standard for noninvasive testing.[25–28] Quantification of LGE can represent a wide variety of tissue processes and has emerged as a diagnostic tool in ischemic heart disease to measure areas of infarction[29] and for risk stratification in ischemic[30,31] and nonischemic heart disease.[32–34]

Although in clinical practice decreasing cardiac enzymes and inflammatory markers are commonly interpreted as being indicative of resolving myocarditis, no cardiac imaging studies have confirmed this assumption as of today. In this study, we sought to evaluate whether absolute serum levels of routine laboratory parameters at the time of diagnosis predict persistence of LGE on CMR at 3 months and whether their decline from baseline to 3-month follow-up correlates with improvement of LGE.

METHODS

Patient Population

All patients who presented to the University Hospital of Zurich between December 2015 and February 2017 with a diagnosis of acute myocarditis were enrolled in this study after written informed consent. The ethics committee of the Kanton of Zurich approved the study protocol. Myocarditis was diagnosed based on clinical criteria, elevated high-sensitivity troponin T, and CMR, after exclusion of obstructive coronary artery disease by coronary angiography or coronary computed tomographic angiography. To create a homogenous cohort that reflects only patients with acute myocarditis, we restricted the analysis to patients with recent symptom onset (≤10 days). Patients with chronic or recurrent myocarditis or symptoms >10 days were excluded from this study.

Laboratory Parameters

The following routine laboratory parameters were measured at baseline and at 3-month follow-up: High-sensitivity troponin T, creatine kinase (CK), myoglobin, NT-proBNP (N-terminal pro-B-type natriuretic peptide), C-reactive protein, and leukocyte count. Chemistry analysis was obtained from heparinized plasma; leukocyte count was calculated from EDTA blood. In addition, blood was screened for the following viruses by polymerase chain reaction: adenovirus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus 1 and 2, human immunodeficiency virus, human herpes virus 6, influenza A, parainfluenza 1 to 4, and parvovirus B19. Furthermore, to screen for an autoimmune pathogenesis, we tested for antinuclear antibodies, antineutrophil cytoplasmic antibody, and rheumatoid factor.

CMR Examination

CMR was performed at diagnosis and at 3-month follow-up on a 1.5- or 3.0-Tesla scanner (SiemensSkyra, Erlangen, Germany

or Philips Achieva, Best, The Netherlands) using an electrocardiography-gated breath-hold protocol. Diagnosis was based on cine-CMR, T2-weighted imaging, and T1-weighted LGE imaging. LGE short-axis images were generated 10 minutes after intravenous administration of a gadolinium-based contrast agent. Routine CMR reporting included evaluation of left ventricular ejection fraction (LVEF) and wall motion abnormalities. Pericardiac involvement was defined as pericardial thickening or effusion on CMR. Two experienced analysts of CMR interpreted all imaging data of this study under the oversight of the director of cardiac imaging of our division. Data analysis was performed in a blinded fashion. Images were post-processed using the software GT Volume from GyroTools LLC (2.1.1) for planimetry. A region of interest was manually drawn around the area with LGE, delineated as bright areas, in each slice in short-axis view. To include only myocardial LGE, endocardium and epicardium were manually delineated (Figure 1). LGE extent was calculated as percentage of left ventricular myocardial volume. A change in LGE extent >20% was considered significant. Intraobserver agreement was tested in a subgroup of 10 patients, and interobserver agreement between the 2 different readers was tested in a subgroup of 5 patients by linear regression and Bland–Altman analysis similar to prior studies.[29,35–37] A $P>0.05$ was considered not significant.

Clinical Follow-Up

All patients presented for 3-month follow-up to our cardiology outpatient clinic at the University Hospital of Zurich. History was obtained to screen for any adverse cardiovascular events, such as arrhythmias, severe chest pain, or dyspnea episodes. During a comprehensive physical examination, routine laboratory parameters were analyzed, including the set of cardiac enzymes and inflammatory parameters obtained at baseline. Furthermore, the patients underwent CMR to measure persistence or progression of LGE. In addition, all patients underwent 12-lead ECG, 48-hour Holter monitoring, and exercise stress testing with a ramp protocol. To evaluate whether persistent LGE at 3 months has any clinical relevance with regards to future adverse cardiovascular events in our cohort, patients were seen again 3 months later for their 6-month follow-up visit.

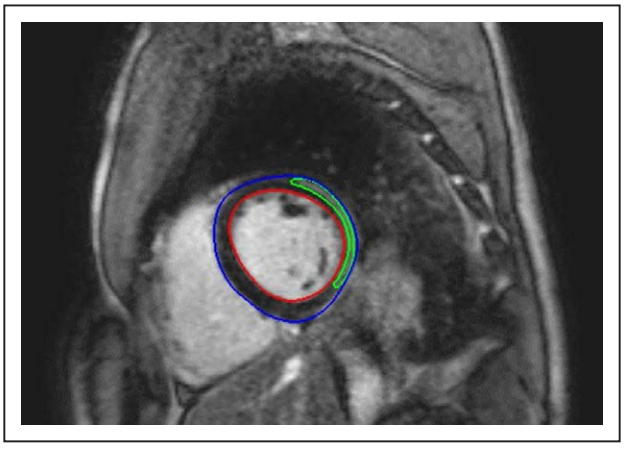

Figure 1. Cardiac magnetic resonance imaging of a patient with acute myocarditis, left ventricular short-axis view: Planimetry measurement in a patient with anterolateral and inferolateral late gadolinium enhancement (LGE).
Epicardium is demarcated in blue and endocardium in red. LGE is delineated in green color on each of a total of 20 slices per patient. All slices are then averaged, and LGE extent is calculated as percent of left ventricular myocardial volume.

Statistical Analysis

Data are reported as mean±SD or median with interquartile range. Correlation between laboratory values and percentage of LGE of left ventricular myocardial volume on magnetic resonance imaging was analyzed using Spearman rank correlation coefficient (r_s). $P<0.05$ was considered statistically significant based on a 2-tailed probability. Analyses were performed with SPSS (version 23 SPSS, Chicago, IL). The first author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

RESULTS

Patient Characteristics

Baseline parameters of patients with decrease in LGE versus those with no change or increase in LGE are illustrated in Table 1. Interestingly, male sex dominated among patients with decrease in LGE. A total of 24 patients were enrolled of which 18 (75%) were men. The mean age was 36±16 years (range: 16–78 years; median: 32 years). Almost half of the patients were smokers (n=10; 42%). There were 3 (13%) patients with concomitant coronary artery disease, 6 (25%) with hypertension, 5 (21%) with dyslipidemia, and 2 (8%) with diabetes mellitus.

At baseline, mean LVEF on CMR was 55±6% and mean LGE measured 14±10% of left ventricular myocardial volume. The interquartile range for LGE was 4.3% to 18.9% with a median of 12.5%. CMR revealed pericardial involvement in 19 patients (79%) and wall motion abnormalities in 6 patients (25%). All patients were monitored with telemetry during the acute phase for a mean of 3±1 days during hospitalization. Four patients (17%) experienced arrhythmias, which included supraventricular tachycardia (n=1), frequent premature ventricular contractions (n=2), and nonsustained ventricular tachycardia (n=1). Viral screening was negative in all tested patients (n=17). Screening for autoimmune disease was only positive in 1 patient who had elevated antinuclear antibodies. This patient was diagnosed with polymyositis with cardiac involvement.

Nonsteroidal anti-inflammatory drugs and colchicine were added in patients with signs and symptoms of pericarditis. β-Blockers and angiotensin-converting enzyme inhibitors were added depending on ejection fraction and blood pressure. Discharge medication included nonsteroidal anti-inflammatory drugs (n=10; 42%), colchicine (n=2; 8%), β-blockers (n=10; 42%), angiotensin-converting enzyme inhibitors (n=11; 46%), angiotensin receptor blockers (n=1; 4%), and diuretics (n=1; 4%).

Table 1. Baseline Conditions of Patients With Decrease in LGE vs Patients With No Change or Increase in LGE

	Patients With Decrease in LGE After 3 mo (n=16)	Patients With No Change or Increase in LGE After 3 mo (n=8)
Mean age (SD)	36 (18)	36 (13)
Male sex, n (%)	14 (88)	4 (50)
Body mass index, mean, kg/m^2 (SD)	26 (4)	28 (6)
Smoker, n (%)	8 (50)	2 (25)
CAD, n (%)	3 (19)	0 (0)
Hypertension, n (%)	5 (31)	1 (12.5)
Dyslipidemia, n (%)	4 (25)	1 (12.5)
Diabetes mellitus, n (%)	2 (12.5)	0 (0)
CMR data, baseline		
Mean LVEF by CMR, % (SD)	55 (6)	55 (7)
LGE % of LV myocardial volume (SD)	15 (9)	11 (10)
Pericardial involvement by CMR, n (%)	13 (81)	6 (75)
Edema by CMR, n (%)	8 (50)	4 (50)
CMR data, 3 mo		
Mean LVEF by CMR, % (SD)	57 (3)	54 (5)
LGE % of LV myocardial volume (SD)	6 (7)	13 (12)
Pericardial involvement by CMR, n (%)	0 (0)	1 (12.5)
Edema by CMR, n (%)	0 (0)	1 (12.5)
Medications on admission n, (%)		
β-Blocker	2 (12.5)	1 (12.5)
ACE inhibitor	2 (12.5)	0 (0)
ARB	1 (6)	0 (0)
MR antagonist	0 (0)	0 (0)
Diuretics	1 (6)	0 (0)
NSAID/colchicine	0 (0)	0 (0)
Medications at discharge, n (%)		
β-Blocker	8 (50)	2 (25)
ACE inhibitor	8 (50)	3 (38)
ARB	1 (6)	0 (0)
MR antagonist	0 (0)	0 (0)
Diuretics	1 (6)	0 (0)
NSAID	7 (44)	3 (38)
Colchicine	2 (12.5)	0 (0)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; and NSAID, nonsteroidal anti-inflammatory drug.

Clinical Visit at 3-Month Follow-Up

Seven patients (29%) continued to report mild symptoms of sharp chest pain, lasting a few seconds. On physical examination, none of the patients showed signs of heart failure. ECGs did not reveal any conduction delays or persistent ST changes. The rate of premature ventricular contractions on 48-hour Holter monitoring was overall low (mean: 0.4±1.2% premature ventricular contractions). Premature ventricular contraction rate did not correlate with LGE extent at baseline (r_s=0.17; P=0.43) or with change in LGE extent after 3 months (r_s=0.08; P=0.72), respectively. Twenty-one patients underwent an additional bicycle stress test. Mean exercise capacity was 179±61 Watts, and mean metabolic equivalents were 9±3. Exercise capacity on stress test did not correlate with LGE peak at baseline (r_s=0.02; P=0.95) or change in LGE extent after follow-up (r_s=0.05; P=0.84).

CMR Data at 3-Month Follow-Up

At 3-month follow-up, LGE resolved entirely in 4 patients (17%), significantly decreased in 12 (50%), and increased in 5 (21%; Figure 2). In 3 patients (12.5%), LGE extent did not change significantly. Neither of the cardiac enzymes or inflammatory parameters (high-sensitivity troponin T, CK, myoglobin, NT-proBNP, C-reactive protein, and leukocyte count) obtained at baseline predicted LGE dynamic sufficiently at 3 months (Table 2). Importantly, decreasing levels of cardiac enzymes and inflammatory parameters from baseline to 3 months did not correlate with resolving LGE (Table 2). Overall, cardiac enzymes and inflammatory parameters had normalized in a majority of patients (n=21; 88%) at 3-month follow-up. Although CMR findings similarly revealed improvement of LGE in most of these patients, LGE continued to persist in a majority (n=17; 71%) of them albeit to a lesser degree. Among the 5 patients, who experienced an increase in LGE at 3-month follow-up, high-sensitivity troponin T levels had normalized in 4 of them (80%), and levels of myoglobin, CK, and NT-proBNP reached normal levels in all of them. There was a negative trend of the relationship between higher levels of CK and myoglobin at baseline and LGE at 3 months (P=0.06), which did not reach statistical significance.

Mean LVEF measured by CMR was 56±4%. In 19 patients (79%), LVEF was normal while in 5 patients (21%), it was mildly impaired. Wall motion abnormalities on CMR were noted in 3 of 24 patients (13%). There was no correlation between LGE extent and LVEF by CMR (r_s=0.11; P=0.62). No correlation was found between LGE and wall motion abnormalities measured by CMR (r_s=0.14; P=0.52).

Reproducibility of CMR Interpretation and Measurements

No major intrareader variability was observed (r^2=0.97 in linear regression; P=0.59 in Bland–Altman). There was strong correlation between the interpretations of the 2

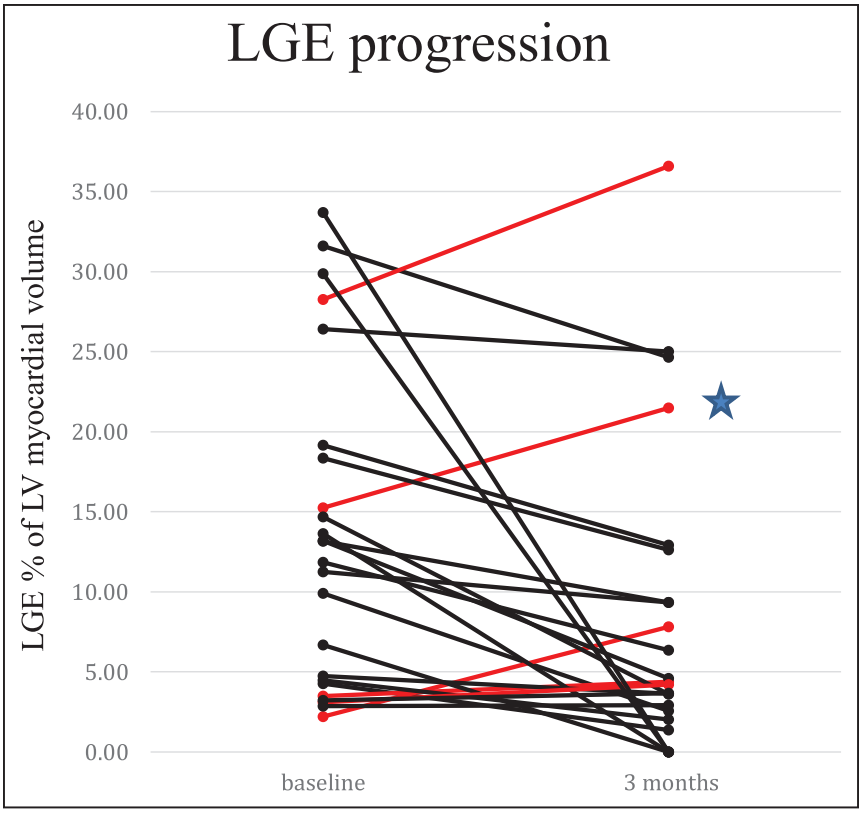

Figure 2. Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging at baseline and 3-mo follow-up. Patients with increase of LGE extent are illustrated in red. Star denotes a patient who experienced an adverse cardiovascular event during 6-mo follow-up. LV indicates left ventricular.

readers of CMR in this study (r^2=0.99). No proportional bias (P=0.82) was observed in the measurements of the 2 different readers obtained from Bland–Altman analysis.

Adverse Cardiovascular Events at 6 Months in Patients With Increase of LGE

In 1 of 5 patients with an increase of LGE extent >20% at 3 months, a major adverse cardiovascular event was reported during the subsequent 3 months. This patient experienced cardiac arrest because of polymorphic ventricular tachycardia requiring resuscitation and implantation of a cardioverter-defibrillator.

DISCUSSION

Here, we report for the first time that routinely used cardiac and inflammatory markers do not sufficiently predict the dynamic of LGE in patients with CMR proven myocarditis. In spite of normalization of such markers and significant LGE improvement in the majority of patients, most of the patients still had LGE on imaging after 3 months. Thus, although it is common practice to use clinical findings, cardiac enzymes, and inflammatory markers to monitor treatment response and clinical course in myocarditis, our findings suggest that such strategy may not be sufficient to risk-stratify patients with myocarditis and that CMR may add value to current diagnostic techniques. The findings of this study have high clinical relevance because LGE has been shown to be one of the most important predictors of adverse cardiovascular outcomes in several cardiac conditions.[13,14]

Previous studies have demonstrated that long-term outcomes in myocarditis, such as normalization of left ventricular function, progression to heart failure, or death, are independent of cardiac enzyme release at the time of diagnosis.[38–40] Although our study consisted of a small number of participants, our data support this observation with novel morphological findings using CMR. Indeed, cardiac enzymes had normalized even in patients of our cohort, who were considered high risk based on the LGE extent at 3-month follow-up. Barone-Rochette et al[14] reported a relationship between LGE extent at 3 months and adverse cardiovascular outcomes, including death of any cause, heart transplant, or recurrence of myocarditis within a year. Whether persistence or increase of LGE at 3-month follow-up reflects active or persistent inflammation or rather scar remains unclear.[16] The largest study on LGE and outcome in myocarditis was conducted by Grün et al[13] in a total of 203 participants with biopsy-proven myocarditis, of which 53% of patients were found to have LGE on baseline CMR. The authors reported LGE to be the best independent predictor of overall and cardiovascular mortality. In the study of Grün et al,[13] none of the patients with absence of LGE experienced sudden cardiac death in a long-term follow-up of 4.7 years while 18 of the 108 patients (17%) with LGE presence experienced sudden cardiac death. In agreement with these findings, an increase of LGE extent was associated with higher risk for

Table 2. Correlation of Laboratory Parameters With LGE Change: Laboratory Parameters at Baseline and Their Decrease From Baseline to 3 Months in Patients With Myocarditis (n=24)

	Reference Range in Laboratory	Median (IQR) Biomarker at Baseline	Correlation With LGE Change at 3 mo	Median (IQR) Biomarker at 3 mo	Correlation With LGE Change at 3 mo	Median (IQR) Biomarker Change After 3 mo	Correlation With LGE Change at 3 mo
Troponin T-hs, ng/L	<14	201 (23 to 683)	r_s=–0.23 (95% CI: –0.65 to 0.26), *P*=0.29	<5 (<5 to 7)	r_s=0.19 (95% CI: –0.29 to 0.6), *P*=0.41	–208 (–719 to –15)	r_s=0.23 (95% CI: –0.23 to 0.6), *P*=0.31
CK, U/L	<190	256 (93 to 449)	r_s=–0.4 (95% CI: –0.73 to 0.05), *P*=0.06	102 (66 to 177)	r_s=–0.36 (95% CI: –0.68 to 0.1), *P*=0.31	–101 (–375 to –9)	r_s=0.21 (95% CI: –0.21 to 0.57), *P*=0.36
Myoglobin, µg/L	28 to 72	39 (23 to 183)	r_s=–0.41 (95% CI: –0.71 to 0.05), *P*=0.06	31 (<21 to 43)	r_s=–0.25 (95% CI: –0.62 to 0.23), *P*=0.28	–21 (–163 to 3)	r_s=0.34 (95% CI: –0.41 to 0.83), *P*=0.14
NT-proBNP, ng/L	<85.8	418 (44 to 699)	r_s=–0.32 (95% CI: –0.66 to 0.14), *P*=0.15	30 (15 to 126)	r_s=0.08 (95% CI: –0.4 to 0.52), *P*=0.72	–259 (–537 to 0)	r_s=0.26 (95% CI: –0.22 to 0.68), *P*=0.28
CRP, mg/L	<5	28 (2 to 52)	r_s=–0.29 (95% CI: –0.67 to 0.17), *P*=0.18	1 (<0.3 to 1.5)	r_s=–0.19 (95% CI: –0.63 to 0.3), *P*=0.41	–16 (–53 to –6)	r_s=0.37 (95% CI: –0.05 to 0.72), *P*=0.09
Leukocyte count, g/L	3 to 9.6	9 (6.7 to 10.6)	r_s=–0.21 (95% CI: –0.58 to 0.28), *P*=0.36	7 (6.0 to 7.3)	r_s=0.01 (95% CI: –0.41 to 0.42), *P*=0.98	–2 (–4.5 to 0.8)	r_s=0.27 (95% CI: –0.23 to 0.59), *P*=0.24

CI indicates confidence interval; CK, creatine kinase; CRP, C-reactive protein; hs, high-sensitivity; IQR, interquartile range; LGE, late gadolinium enhancement; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

major cardiovascular events in our cohort albeit numbers were low. Among the 5 patients with progression of LGE at 3-month follow-up, one developed polymorphic ventricular tachycardia, requiring defibrillation and mechanical resuscitation. In patients without progression of LGE, there were no major adverse cardiovascular events.

In summary, our data show that cardiac enzymes and inflammatory markers do not sufficiently predict LGE findings in myocarditis and that CMR may add value as an additional diagnostic tool for clinical follow-up to detect persistent or worsening LGE at 3 months. Although our study population is small, the data are relevant because of 2 major findings: (1) In the majority of cases, in whom cardiac and inflammatory markers normalized, LGE improved similarly. However, in a considerable percentage of those patients, persistence of LGE was detected albeit to a lesser degree. In some, there was even worsening LGE despite of normalization of laboratory parameters. (2) Our data support findings of other groups describing LGE as risk marker for adverse cardiovascular events in myocarditis.[13,14] Therefore, we suggest that CMR may be considered as an additional tool for improved risk stratification at 3-month follow-up even if serum markers have normalized.

Limitations

The small number of patients in this study likely led to the finding of confidence intervals being large for r_s describing the correlation between biomarkers and LGE (Table 2). There is a possibility that in a larger population, the trend of improving biomarkers in patients with improving LGE could have reached significance, in particular for CK and myoglobin, for which level of significance was closely missed.

A potential limitation is that only patients with visible LGE at baseline were included in our study, whereas patients without LGE, but other signs of myocarditis on CMR, such as myocardial edema (n=1), were not included. Furthermore, patients with recently implanted cardioverter-defibrillator (n=2) could not be included in this study because of magnetic resonance imaging restrictions, which has contributed to a patient cohort with a relatively normal mean LVEF of 55% at baseline and 56% at 3 months. Therefore, proving statistically significant correlations between LVEF and other parameters would be unlikely even if such relationships do in fact exist. Also, correlation to cardiovascular mortality should be interpreted with caution because of limited clinical follow-up data of only 6 months and low patient numbers. Another limitation is that endomyocardial biopsies have not been conducted in our relatively stable patient cohort. In future studies, endomyocardial biopsy might be considered in those patients with persistent or worsening LGE to help identify the underlying cause.

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DISCLOSURES

None.

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FOOTNOTES

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