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Predictive Value of Cardiac Magnetic Resonance Imaging-Derived Myocardial Strain for Poor Outcomes in Patients with Acute Myocarditis

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Objective: To evaluate the utility of cardiovascular magnetic resonance (CMR)-derived myocardial strain measurement for the prediction of poor outcomes in patients with acute myocarditis.

Materials and Methods: We retrospectively analyzed data from 37 patients with acute myocarditis who underwent CMR. Left ventricular (LV) size, LV mass index, ejection fraction and presence of myocardial late gadolinium enhancement (LGE) were analyzed. LV circumferential strain (Ecc_{SAX}), radial strain (Err_{SAX}) from mid-ventricular level short-axis cine views and LV longitudinal strain (Ell_{LV}), radial strain (Err_{Lax}) measurements from 2-chamber long-axis views were obtained. In total, 31 of 37 patients (83.8%) underwent follow-up echocardiography. The primary outcome was major adverse cardiovascular event (MACE). Incomplete LV functional recovery was a secondary outcome.

Results: During an average follow-up of 41 months, 11 of 37 patients (29.7%) experienced MACE. Multivariable Cox proportional hazard regression analysis, which included LV mass index, LV ejection fraction, the presence of LGE, Ecc_{SAX}, Err_{SAX}, Ell_{LV}, and Err_{Lax} values, indicated that the presence of LGE (hazard ratio, 42.88; $p = 0.014$), together with ErrLax (hazard ratio, 0.77 per 1%, $p = 0.004$), was a significant predictor of MACE. Kaplan-Meier analysis demonstrated worse outcomes in patient with LGE and an Err_{Lax} value ≤ 9.48%. Multivariable backward regression analysis revealed that Err_{Lax} values were the only significant predictors of LV functional recovery (hazard ratio, 0.54 per 1%; $p = 0.042$).

Conclusion: CMR-derived Err_{Lax} values can predict poor outcomes, both MACE and incomplete LV functional recovery, in patients with acute myocarditis, while LGE is only a predictor of MACE.

Keywords: *Myocarditis; Magnetic resonance imaging; Major adverse cardiovascular events; Ventricular dysfunction; Left ventricle; Strain*

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INTRODUCTION

Myocarditis is an acute or chronic inflammatory disease of the myocardium that can be caused by infectious pathogens such as viruses, bacteria, toxic fungi and Chlamydia, as well as by toxic and hypersensitivity reactions (1). The short-term prognosis for acute myocarditis is typically good, but dilated cardiomyopathy or sudden cardiac death can also occur (1-3). Several parameters, including clinical symptoms such as advanced New York Heart Association (NYHA) functional classes, certain viruses or immunohistologic

signs of inflammation identified by endomyocardial biopsy (EMB), left ventricle (LV) function, and late gadolinium enhancement (LGE), are predictors of poor outcomes (4-6). Because EMB is invasive, has a complication rate of 6% and is not appropriate for all patients (7), cardiovascular magnetic resonance (CMR) can be an alternative tool for the prediction of poor outcomes. CMR is non-invasive and can assess LV size, function and LGE simultaneously.

Left ventricular myocardial systolic strain and deformation parameters are altered during early-stage pathogenesis, and can be measured with CMR (8-10). Tagged-CMR, in which magnetization saturation bands arranged in a grid format are placed onto the myocardium, is an established method for the assessment of regional LV function. However, myocardial tagging has not been widely adopted due to the necessity for additional scans and complex, time-consuming post-processing of images (11, 12). Recently developed feature tracking software enables the measurement of myocardial strain using CMR cine images. The software tracks endocardial and epicardial borders across frames to quantify the LV wall motion during the cardiac cycle. CMR-derived feature tracking methods are vendor-independent and thus do not require additional sequences (13). Furthermore, feature tracking-derived measurements of circumference have acceptable inter-observer reproducibility, and feature tracking-derived myocardial strain can predict acute myocarditis with high sensitivity and specificity (9, 14). However, there have been no reports on the prognostic value of CMR-derived myocardial strain measurements in acute myocarditis patients.

Therefore, the primary objective of this study was to evaluate the utility of CMR-derived myocardial strain measurements for the prediction of poor outcomes, defined as major adverse cardiac events (MACE) or incomplete LV functional recovery, in patients with acute myocarditis.

MATERIALS AND METHODS

Study Population

This retrospective study was approved by the Institutional Review Board of our hospitals. This study reviewed the database of 42 patients with suspected myocarditis who underwent CMR between August 2004 and March 2014 in Pusan National University Hospital or Pusan National University Yangsan Hospital. Based on previous descriptions of myocarditis (10, 15-19), acute myocarditis patients were included who presented with the following: 1) symptoms and signs suggestive of acute myocarditis, such as fever, viral prodrome, chest pain, dyspnea, palpitation, effort intolerance or presyncope, or syncope within 6 weeks of admission; 2) evidence of structural or functional abnormalities on echocardiography or CMR, or of myocardial injury indicated by elevated biomarkers (troponin I level > 0.1 ng/mL or creatine kinase MB [CK-MB] fraction > 6.2 ng/mL); and 3) no evidence of coronary artery disease observed on coronary angiography in patients older than 35 years. Patients with coronary artery disease (n = 3), chronic myocarditis (n = 1), and a patient who did not undergo coronary angiography (n = 1) were excluded. A total of 37 patients comprised the study population. Medical records were reviewed for clinical symptoms, demographic factors (age, sex, weight, and height), past history (hypertension, hypercholesterolemia, diabetes, smoking), electrocardiogram (ECG) findings, initial troponin I, brain natriuretic peptide and CK-MB levels, pathologic EMB results, CMR findings and beta-blocker medication status. Control study subjects were 10 normal individuals (mean age, 36.2 ± 10 years; 5 females) with no history of cardiovascular disease, unremarkable findings on physical examination, and a low probability of heart disease.

Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance was performed using 1.5T (Magnetom Sonata, Siemens Healthcare, Berlin, Germany [12 patients]; Magnetom Avanto, Siemens Healthcare, Erlangen, Germany [16 patients]), and 3T (Achieva, Philips Healthcare, Best, the Netherlands [7 patients and 10 normal subjects]; Magnetom Skyra, Siemens Healthcare, Erlangen, Germany [2 patients]) CMR imaging scanners. All cine images were acquired using a balanced, steady-state, free precession sequence during a gentle expiratory breath-hold. Short-axis cine images from cardiac base to apex, and long-axis cine images in 2- and 4-chamber views were obtained using the following scan parameters: echo time (TE)/repetition time (TR)/flip-angle = 1.1 ms/54.8 ms/50°, slice thickness = 8 mm, gap = 2 mm, matrix = 192 x 119 (Magnetom Sonata); TE/TR/flip-angle = 1.2 ms/60.1 ms/79°, slice thickness = 8 mm, gap = 2 mm, matrix = 192 x 109 (Magnetom Avanto); TE/TR/flip-angle = 1.5 ms/2.9 ms/40°, slice thickness = 10 mm, no gap, matrix = 176 x 168 (Achieva); TE/TR/flip-angle = 1.1 ms/57.9 ms/79°, slice thickness = 8 mm, gap = 2 mm, matrix = 192 x 109 (Magnetom Skyra). LGE imaging was performed with whole-heart coverage of the short-

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axis following administration of 0.2 mmol/kg gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany), using a T1-weighted mid-diastolic inversion recovery sequence and a patient-adapted prepulse delay (TE/TR/flip-angle = 4.3 ms/750 ms/30°, slice thickness = 8 mm, gap = 2 mm, matrix = 256 x 148 [Magnetom Sonata]; TE/TR/flip-angle = 5.6 ms/488 ms/25°, slice thickness = 8 mm, gap = 2 mm, matrix = 256 x 134 [Magnetom Avanto]; TE/TR/flip-angle = 3 ms/6.1 ms/25°, slice thickness 10 mm, no gap, matrix = 224 x 166 [Achieva]; TE/TR/flip-angle = 3.2 ms/751 ms/25°, slice thickness = 8 mm, gap = 2 mm, matrix = 256 × 156 [Magnetom Skyra]). Images were analyzed by a blinded radiologist with 7 years' experience with cardiac imaging. All routine CMR analyses, except strain and strain rate, were performed using commercially available software (IntelliSpace Portal, Philips Healthcare, Cleveland, OH, USA). LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), LV myocardial mass index (LVMI), LV ejection fraction (EF) and right ventricle EF (RVEF) were derived from short axis-segmentation of CMR. All strain parameters were measured using dedicated software (CVI42, Circle Cardiovascular Imaging Inc., Calgary, Canada) (Fig. 1). LV circumferential strain (Ecc_{SAX}) and radial strain (Err_{SAX}) measurements were obtained using mid-ventricular level short-axis cine views. LV longitudinal strain (Ell_{LV}) and radial strain (Err_{Lax}) measurements were obtained from a 2-chamber long-axis view. All strain values were calculated by averaging the peak segmental values of radial, circumferential, and longitudinal strain for each strain direction. To assess intra-observer agreement, all measurements were repeated after 1 month in 20 randomly selected subjects. To assess inter-observer agreement for myocardial strain, all myocardial strains were measured in those subjects by another radiologist with 5 years' experience with cardiac imaging. Patterns and presence of myocardial LGE were assessed visually. Patterns of LGE were classified as subendocardial, subepicardial, mid-wall or transmural enhancement.

We performed a subgroup analysis between myocarditis patients with a preserved LVEF (≥ 55%, n = 16), myocarditis patients with impaired LVEF (< 55%, n = 21), and normal subjects (n = 10).

Clinical Outcomes

Outcomes were assessed by chart review or telephone interview. As a primary outcome, all patients were followed up to assess the incidence rate of MACE, defined in terms of cardiac death, heart transplantation, implanted cardioverter defibrillator or pacemaker, rehospitalization following a cardiac event, or embolic stroke. Time to MACE is provided in days. Incomplete LV functional recovery was a secondary outcome in the patient group (n = 31) who underwent follow-up echocardiography after 1 year. Incomplete LV functional recovery was defined as an LVEF value < 60% (5). Two-dimensional transthoracic echocardiography was performed by a diagnostic cardiac sonographer using commercial echocardiographic systems (iE33, Philips Electronics, Amsterdam, the Netherlands; Vivid-Q, GE

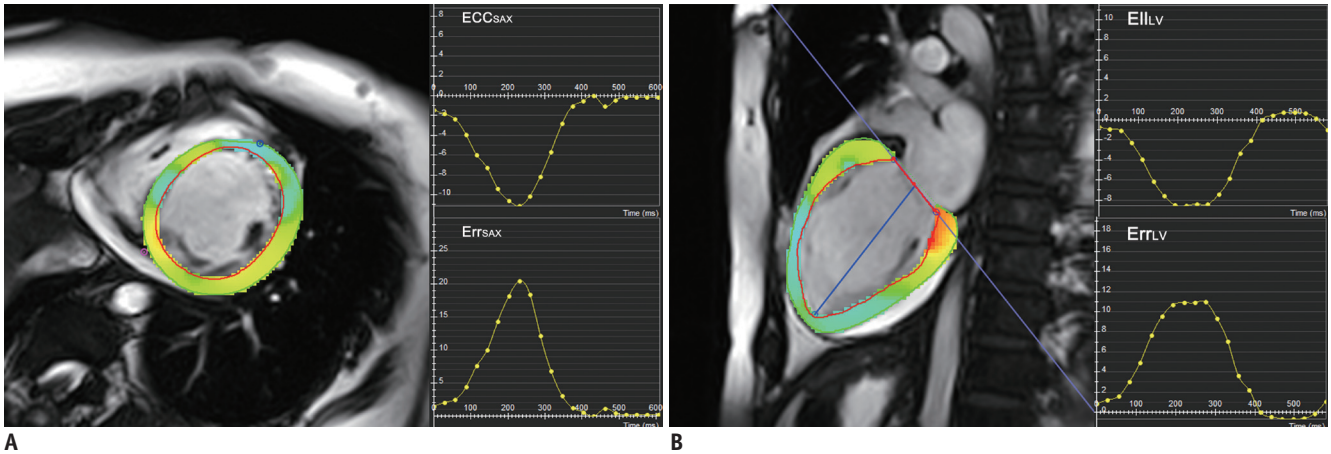

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Fig. 1. Myocardial strain measurement by feature tracking method in 43-year-old female patient with acute myocarditis.
After endocardial and epicardial borders of LV were traced semi-automatically, software (CVI42) automatically tracked endocardial and epicardial borders across frames during cardiac cycle. Ecc_{SAX} and Err_{SAX} measurements **(A)** were obtained using mid-ventricular level short-axis cine views. Ell_{LV} and Err_{Lax} measurements **(B)** were obtained from 2-chamber long-axis view. Ecc_{SAX} = LV circumferential strain measured from short-axis cine views, Ell_{LV} = LV longitudinal strain measured from long-axis cine views, Err_{Lax} = LV radial strain measured from long-axis cine views, Err_{SAX} = LV radial strain measured from short-axis cine views, LV = left ventricular

Medical Systems Israel Ltd., Tirat Carmel, Israel; Sequoia, Siemens AG, Munich, Germany) according to a standardized protocol in the cardiac laboratories of Pusan National University Hospital and Pusan National University Yangsan Hospital. The LVEF was measured using the modified Simpson's method as recommended by the American Society of Echocardiography (20).

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc (ver. 14.10.2, MedCalc Software, Mariakerke, Belgium) software packages. Categorical group data, presented as percentages, were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables are presented as means ± SDs and were compared using the Student's *t* test for normally distributed data or the Mann-Whitney U-test for non-normally distributed data. Normality was tested with the Kolmogorov-Smirnov test. Subgroup analysis between normal subjects, myocarditis patients with impaired EF, and myocarditis patients with preserved EF was performed with a one-way analysis of variance with Bonferroni's correction for normally distributed data, and the Kruskal-Wallis test with a Mann-Whitney U test for ordinary data or non-normally distributed data. Univariate and backward multivariate Cox proportional hazards models were used to assess independent associations with MACE. After setting the cut-off value using receiver-operating characteristics (ROC) curve analysis, Kaplan-Meier curves were calculated to visualize and compare (log-rank test) patients' MACE-free survival curves. Variables that differed significantly between groups, with or without incomplete LV functional recovery on univariate analysis, were analyzed using backward logistic regression analysis to identify independent predictors of incomplete LV functional recovery. ROC analysis was performed to assess the ability of selected variables to predict incomplete LV functional recovery. After setting the cut-off value, the sensitivity and specificity values for incomplete LV recovery were calculated. Finally, intra- and inter-observer reproducibility was calculated using the intra-class correlation coefficient (ICC), where an ICC value < 0.4 represented poor reproducibility, ICC scores between 0.4 and 0.75 indicated fair-to-good reproducibility, and ICC scores > 0.75 indicated excellent reproducibility. A p value < 0.05 was taken to indicate statistical significance.

RESULTS

Study Population

Table 1 summarizes the characteristics of the study cohort. The mean age of the patients was 41.5 ± 17.5 years

Table 1. Baseline Characteristics of Patients

	Patients with Follow-Up (n = 37)
Age, years	41.5 ± 17.5
Female	15 (40.5)
BMI, kg/m^2	22.5 ± 2.8
Past history	
Hypertension	3 (8.1)
Hypercholesterolemia	0 (0)
Diabetes	2 (5.4)
Smoking	7 (18.9)
Duration between symptom onset and CMR examination, days	11.6 ± 8.5
Clinical presentation	
Respiratory symptoms	16 (43.2)
Chest pain	22 (59.5)
Palpitation	2 (5.4)
Dyspnea	22 (59.5)
Presyncope or syncope	12 (32.4)
Fever	10 (27.0)
ECG alteration	31 (83.8)
ST elevation	15 (40.5)
ST depression	9 (24.3)
Negative T	7 (18.9)
Pathologic Q	4 (10.8)
AV block	4 (10.8)
LBBB or RBBB	4 (10.8)
Ventricular tarchycardia	1 (2.7)
Initial NYHA functional class	
I/II	15 (40.5)
III/IV	22 (59.5)
Initial blood testing	
Troponin I, ng/mL	9.5 ± 13.0
BNP, pg/mL	1168.7 ± 1229.3
CK-MB, ug/L	39.0 ± 36.5
Patients who underwent endomyocardial biopsy	7 (18.9)
Beta-blocker medication	20 (54.1)
MACE	11 (29.7)

Data are provided as n (%) or mean ± SD. AV = atrioventricular, BMI = body mass index, BNP = brain natriuretic peptide, CK-MB = creatine kinase MB, CMR = cardiovascular magnetic resonance, ECG = electrocardiography, LBBB = left bundle branch block, MACE = major adverse cardiovascular events, NYHA = New York Heart Association, RBBB = right bundle branch block

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Table 2. CMR Findings of Patients with Acute Myocarditis and Normal Subjects

	Myocarditis Patients (n = 37)	Normal Subjects (n = 10)	*P*
Age, years	41.5 ± 17.5	36.2 ± 10.0	0.274
Female	15 (40.5)	5 (50.0)	0.723
BMI, kg/m^2	22.5 ± 2.8	22.0 ± 3.2	0.640
CMR imaging parameter			
LVEDVI, mL/m^2	81.4 ± 39.4	67.2 ± 10.1	0.310
LVESVI, mL/m^2	48.9 ± 41.3	26.6 ± 5.3	0.003
LVMI, g/m^2	67.7 ± 23.5	46.4 ± 11.2	0.008
RVEF, %	50.8 ± 14.2	59.1 ± 5.3	0.075
LVEF, %	45.8 ± 17.1	60.7 ± 3.0	0.001
Presence of LGE	23 (62.2)	NA	NA
Ecc_{SAX}, %	-9.53 ± 4.87	-14.76 ± 2.03	< 0.001
Err_{SAX}, %	14.81 ± 7.77	23.46 ± 5.20	0.002
Ell_{LV}, %	-10.58 ± 4.76	-17.52 ± 4.45	< 0.001
Err_{Lax}, %	19.13 ± 8.88	36.25 ± 15.15	< 0.001

Values are n (%) or means ± SD. BMI = body mass index, CMR = cardiovascular magnetic resonance, Ecc_{SAX} = LV circumferential strain measured from short-axis cine views, Ell_{LV} = LV longitudinal strain measured from long-axis cine views, Err_{Lax} = LV radial strain measured from long-axis cine views, Err_{SAX} = LV radial strain measured from short-axis cine views, LGE = late gadolinium enhancement, LV = left ventricle, LVEDVI = left ventricular end-diastolic volume index, LVEF = left ventricular ejection fraction, LVESVI = left ventricular end-systolic volume index, LVMI = left ventricular mass index, NA = not applicable, RVEF = right ventricular ejection fraction

Table 3. Comparison of Myocardial Stain Parameters between Myocarditis Patients without and with Preserved EF and Normal Subjects

	Patients with Impaired EF (n =21)	Patients with Preserved EF (n =16)	Normal Subjects (n = 10)	*P*
Age, years	36.1 ± 17.8	48.5 ± 14.8	36.2 ± 10.0	0.051
Female	9 (42.9)	6 (37.5)	5 (50.0)	0.824
BMI, kg/m^2	22.0 ± 3.0	23.1 ± 2.5	22.0 ± 3.2	0.463
Strain parameters				
Ecc_{SAX}, %	-8.90 ± 5.57†	-10.36 ± 3.76*	-14.76 ± 2.03*†	0.002
Err_{SAX}, %	13.50 ± 7.40†	16.54 ± 8.12	23.46 ± 5.20†	0.004
Ell_{LV}, %	-9.89 ± 4.92†	-11.48 ± 4.53*	-17.52 ± 4.45*†	< 0.001
Err_{Lax}, %	18.78 ± 9.50†	19.60 ± 8.29*	36.25 ± 15.15*†	< 0.001

Values are n (%) or means ± SD. *Significantly different between myocarditis patients with preserved EF and normal subjects, †Significantly different between myocarditis patients with impaired EF and normal subjects. BMI = body mass index, Ecc_{SAX} = LV circumferential strain measured from short-axis cine views, EF = ejection fraction, Ell_{LV} = LV longitudinal strain measured from long-axis cine views, Err_{Lax} = LV radial strain measured from long-axis cine views, Err_{SAX} = LV radial strain measured from short-axis cine views, LV = left ventricle

Table 4. Intra-Observer and Inter-Observer Reproducibility According to Intra-Class Correlation for Strain Quantification on CMR

	Intra-Observer ICC (95% CI)	Inter-Observer ICC (95% CI)
Ecc_{SAX}	0.92 (0.80–0.97)	0.93 (0.83–0.97)
Err_{SAX}	0.98 (0.96–0.99)	0.92 (0.82–0.97)
Ell_{LV}	0.97 (0.92–0.99)	0.94 (0.86–0.98)
Err_{Lax}	0.87 (0.71–0.95)	0.90 (0.76–0.96)

CI = confidence interval, CMR = cardiovascular magnetic resonance, Ecc_{SAX} = LV circumferential strain measured from short-axis cine views, Ell_{LV} = LV longitudinal strain measured from long-axis cine views, Err_{Lax} = LV radial strain measured from long-axis cine views, Err_{SAX} = LV radial strain measured from short-axis cine views, ICC = intra-class correlation coefficient, LV = left ventricle

and 15 (40.5%) patients were female. The most common symptoms were dyspnea and chest pain, followed by respiratory symptoms, and presyncope or syncope. When patients were stratified by the initial clinical manifestation of the disease, 17 patients (45.9%) had infarct-like onsets. Also, 9 patients (24.3%) had arrhythmia such as atrioventricular block (n = 4, 10.8%), left or right bundle branch block (n = 4, 10.8%), and ventricular tachycardia (n = 1, 2.7%). The majority of patients had an abnormal ECG upon admission (n = 31, 83.8%), with ST elevation as the most common finding (n = 15, 40.5%), followed by ST depression (n = 9, 24.3%). EMB was performed in seven patients (18.9%), of whom six were diagnosed with

myocarditis using the Dallas criteria. A single patient had a sample insufficient for diagnosis. Beta blockers were used in 20 patients (54.1%).

CMR Findings

Cardiovascular magnetic resonance was performed within 11.6 ± 8.5 days (range: 0–31 days) of symptom onset in the myocarditis patients. The mean LVEF value was 45.8%, and the mean LVEDVI was 81.4 mL/m^2 (Table 2). LGE, which was present in 23 of 37 patients (62.2%), was typically located in mid-wall (6/23, 26.1%) or subepicardial areas (17/23, 73.9%) of the LV wall. There were significant differences between patient and control groups in terms of LVESVI, LVMI, and LVEF. LVEDVI tended to be higher in patients with acute myocarditis. Furthermore, all myocardial strain parameters, including Ecc_{SAX}, Err_{SAX}, Ell_{LV}, and Err_{Lax},

Table 5. Univariate Cox Regression Analysis: MACE

	MACE (n = 11)	No MACE (n = 25)	HR (95% CI)	*P*
Age, years	45.0 ± 15.0	40.0 ± 18.5	1.01 (0.97–1.05)	0.624
Female	5 (45.5)	10 (40.0)	1.32 (0.39–4.41)	0.655
BMI, kg/m^2	22.5 ± 1.1	22.5 ± 3.3	1.02 (0.82–1.27)	0.874
Past history				
Hypertension	0 (0)	3 (12.0)	0.04 (0.0–262.62)	0.477
Hypercholesterolemia	0 (0)	0 (0)	NA	NA
Diabetes	1 (9.9)	1 (4.0)	3.10 (0.38–25.41)	0.293
Smoking	3 (27.3)	4 (16.0)	1.43 (0.52–3.93)	0.490
ECG alteration				
ST elevation	2 (18.2)	13 (52.0)	0.29 (0.06–1.34)	0.112
ST depression	1 (9.9)	8 (32.0)	0.33 (0.04–2.60)	0.290
Negative T	3 (27.3)	4 (16.0)	1.32 (0.33–5.25)	0.689
Pathologic Q	1 (9.9)	3 (12.0)	0.82 (0.10–6.41)	0.848
AV block	2 (18.2)	2 (8.0)	0.61 (0.13–2.88)	0.530
LBBB or RBBB	1 (9.1)	3 (12.0)	1.22 (0.15–9.79)	0.852
Ventricular tachycardia	0 (0)	1 (4.0)	0.47 (0–458654.76)	0.710
Initial NYHA functional class				
III/IV	8 (72.7)	14 (56.0)	2.14 (0.57–8.12)	0.263
Initial blood testing				
Troponin I, ng/mL	10.3 ± 12.2	17.9 ± 24.9	0.98 (0.94–1.02)	0.289
BNP, pg/mL	1125.5 ± 91.02	748.4 ± 761.5	1.00 (1.00–1.00)	0.126
CK-MB, ug/L	17.8 ± 27.3	57.7 ± 60.1	0.98 (0.96–1.00)	0.103
Beta-blocker medication	6 (54.5)	14 (56.0)	0.89 (0.27–2.90)	0.836
CMR imaging parameter				
LVEDVI, mL/m^2	102.7 ± 59.4	72.4 ± 23.3	1.01 (1.00–1.02)	0.119
LVESVI, mL/m^2	75.7 ± 62.2	37.6 ± 21.4	1.01 (1.00–1.02)	0.073
LVMI, g/m^2	81.4 ± 33.3	61.9 ± 15.4	1.02 (1.00–1.05)	0.039
RVEF, %	42.9 ± 17.1	54.1 ± 11.6	0.97 (0.93–1.00)	0.068
LVEF, %	33.4 ± 17.8	61.2 ± 10.0	0.96 (0.93–0.99)	0.007
Presence of LGE	10 (90.9)	13 (50.0)	9.93 (1.25–79.0)	0.030
Ecc_{SAX}, %	-6.2 ± 6.0	-10.9 ± 3.6	1.20 (1.07–1.35)	0.003
Err_{SAX}, %	9.5 ± 6.2	17.0 ± 7.4	0.87 (0.79–0.96)	0.005
Ell_{LV}, %	-7.0 ± 3.8	-12.2 ± 4.2	1.33 (1.11–1.61)	0.003
Err_{Lax}, %	12.2 ± 8.0	22.1 ± 7.6	0.87 (0.80–0.95)	0.002

Values are n (%) or mean ± SD. AV = atrioventricular, BMI = body mass index, BNP = brain natriuretic peptide, CI = confidence interval, CK-MB = creatine kinase MB, CMR = cardiovascular magnetic resonance, Ecc_{SAX} = LV circumferential strain measured from short-axis cine views, ECG = electrocardiography, Ell_{LV} = LV longitudinal strain measured from long-axis cine views, Err_{Lax} = LV radial strain measured from long-axis cine views, Err_{SAX} = LV radial strain measured from short-axis cine views, HR = hazard ratio, LBBB = left bundle branch block, LGE = late gadolinium enhancement, LV = left ventricle, LVEDVI = LV end-diastolic volume index, LVEF = LV ejection fraction, LVESVI = LV end-systolic volume index, LVMI = LV mass index, MACE = major adverse cardiovascular events, NA = not applicable, NYHA = New York Heart Association, RBBB = right bundle branch block, RVEF = right ventricular ejection fraction

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were significantly lower in patients with myocarditis. Three subgroups showed no significant differences in age (p = 0.051), sex (p = 0.824), and body mass index (p = 0.463) (Table 3). All myocardial strain parameters of myocarditis patients with impaired LV function were significantly reduced compared to normal subjects. Also, Ecc_{SAX} (-10.36 ± 3.76 vs. -14.76 ± 2.03, p = 0.001), Ell_{LV} (-11.48 ± 4.53 vs. -17.52 ± 4.45, p = 0.008), and Err_{Lax} (19.60 ± 8.29 vs. 36.25 ± 15.15, p = 0.001) showed significant differences between patients with preserved EF and normal subjects. However, there were no significant differences in all strain parameters between myocarditis patients with impaired EF and patients with preserved EF. There was excellent intra-observer reproducibility between the first and second evaluations for all strain parameters (ICC = 0.87–0.98) (Table 4). There was also excellent inter-observer reproducibility between two observers for all strain parameters (ICC = 0.90–0.94). There was excellent intra-observer reproducibility (ICC = 0.84–0.97) for LVEDVI, LVESVI, LVMI, and LVEF measurements. Fair-to-good intra-observer reproducibility (ICC = 0.68) was determined for RVEF measurements.

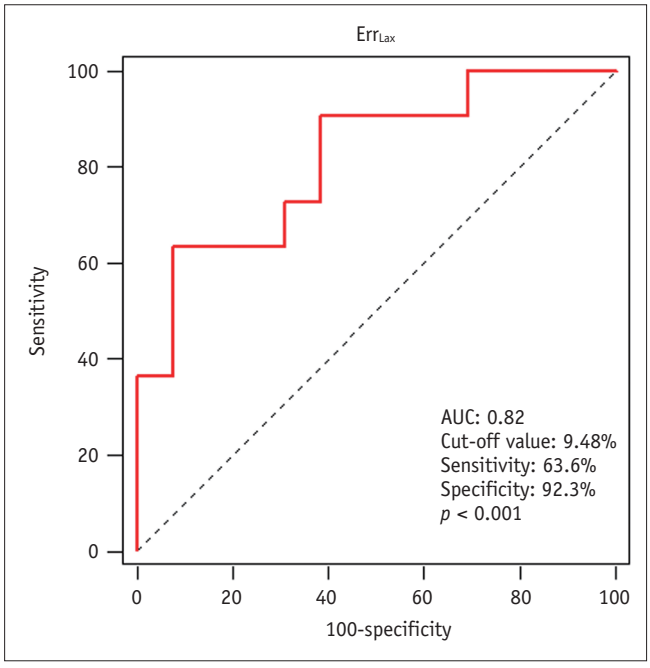

Fig. 2. Receiver operating characteristic curve for prediction of MACE. MACE was defined in terms of cardiac death, heart transplantation, implantable cardioverter defibrillator or pacemaker, rehospitalization following cardiac event, or embolic stroke. AUC = area under the curve, Err_{Lax} = LV radial strain measured from long-axis cine views, LV = left ventricle, MACE = major adverse cardiovascular events

Clinical Outcomes: MACE

All 37 patients were available for clinical follow-up for at least one year. During an average follow-up of 41 ± 34 months (range: 0–112 months), 11 of 37 patients (29.7%) suffered a MACE, including cardiac death (n = 2), heart transplantation (n = 1), cardiac pacemaker (n = 1), rehospitalization due to cardiac events (n = 4), or embolic stroke (n = 3). All cardiac deaths occurred within 1 month of CMR acquisition.

Table 5 displays the results of the univariate Cox regression analysis used to evaluate the predictors of MACE. The analysis revealed that LVMI, LVEF, the presence of LGE, and Ecc_{SAX}, Err_{SAX}, Ell_{LV}, and Err_{Lax}, values were significant unadjusted predictors of MACE. Multivariable Cox proportional hazard regression analysis, which included LVMI, LVEF, the presence of LGE and Ecc_{SAX}, Err_{SAX}, Ell_{LV}, and Err_{Lax} values, indicated that the presence of LGE (hazard ratio, 42.88; 95% confidence interval [CI]: 2.15–855.0, p = 0.014) and Err_{Lax} (hazard ratio, 0.77 per 1%; 95% CI: 0.64–0.92, p = 0.004) were significant predictors of MACE.

Receiver-operating characteristic curves for Err_{Lax} to obtain optimal cut-off values for predicting MACE during follow-up showed an area under the curve (AUC) of 0.82 (95% CI: 0.657–0.925). The cut-off value with the best combination of sensitivity and specificity for Err_{Lax} was ≤ 9.48% (sensitivity, 63.6%; specificity, 92.3%) (Fig. 2). Kaplan-Meier survival curves for MACE are displayed in Figure 3. Kaplan-Meier analysis demonstrated that the worst outcomes occurred in patients with LGE and an Err_{Lax} value ≤ 9.48%. Only 1 of 14 patients without LGE (7.1%) experienced MACE, whereas 10 of 23 patients with LGE (43.5%) experienced MACE. Figure 3C shows that outcomes in patients with LGE and an Err_{Lax} value ≤ 9.48% were significantly worse than in patients with LGE and an Err_{Lax} > 9.48%. All patients with LGE and an Err_{Lax} value ≤ 9.48% experienced MACE.

Clinical Outcomes: Functional Improvement

A total of 31 of 37 patients (83.8%) underwent follow-up echocardiography after 1 year. Six patients were excluded because of death during the follow-up period (2/31, 6.5%) or absence of follow-up echocardiography (4/31, 12.9%). Of the 31 patients, 71% (22/31) had normal LVEF on follow-up echocardiography, and 16% (5/31) had normal LVEF on initial echocardiography. Table 6 lists the results of univariate analysis by logistic regression. A multivariable backward stepwise regression analysis, that included

LVEDVI, LVESVI, LVEF, Ecc_{SAX}, Err_{SAX}, Ell_{LV}, and Err_{Lax} values, demonstrated that Err_{Lax} was the only significant predictor of incomplete LV functional recovery (hazard ratio, 0.54 per 1%; 95% CI: 0.29–0.976; $p = 0.042$). ROC curves for Err_{Lax} to obtain optimal cut-off values for the prediction of incomplete LV functional recovery during follow-up showed an AUC value of 0.96 (95% CI: 0.82–1.0) (Fig. 4). The cut-off value with the best combination of sensitivity and specificity for Err_{Lax} was 14.9% (sensitivity, 88.9%; specificity, 95.5%).

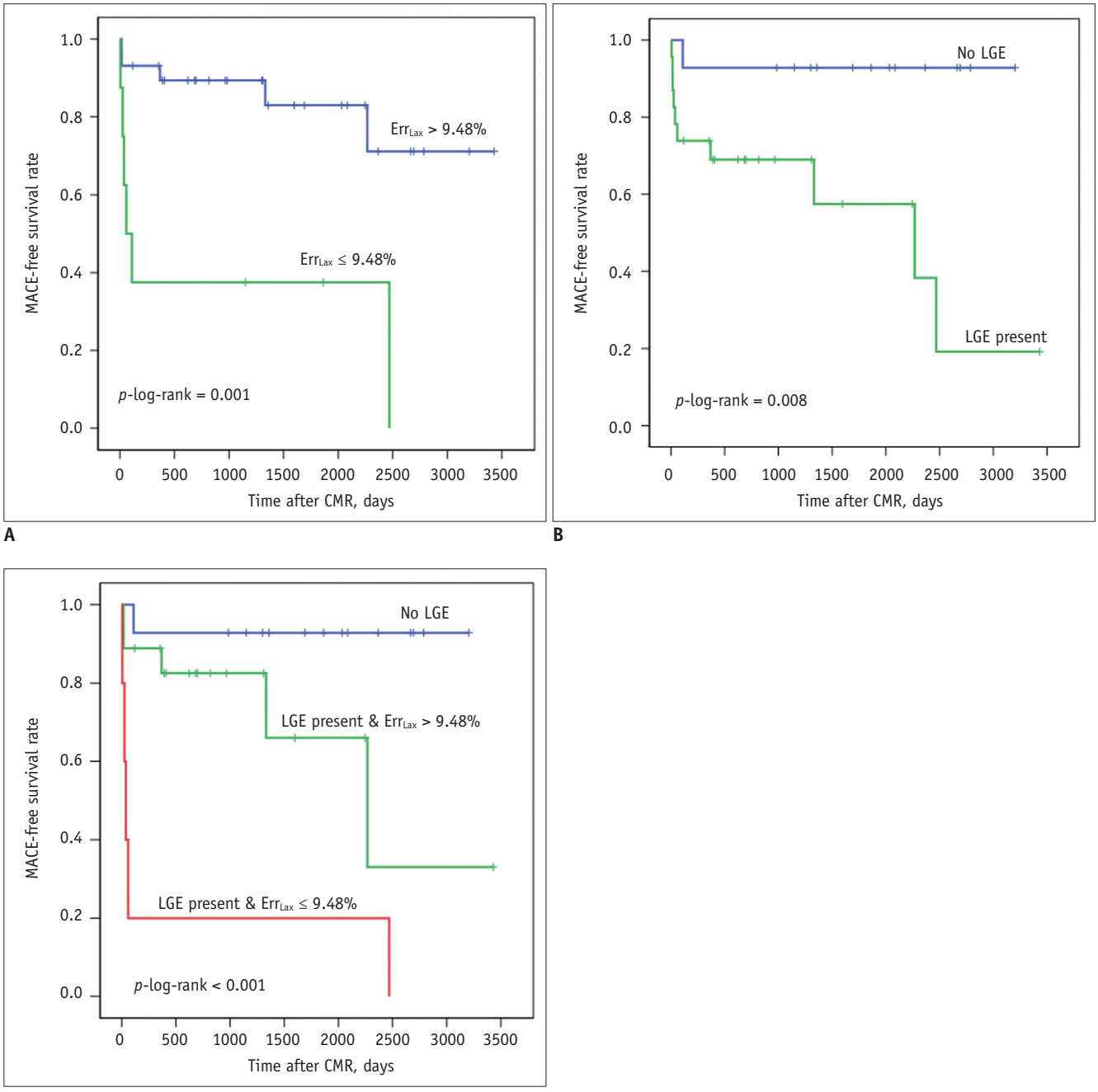

Fig. 3. MACE according to Err_{Lax} or presence of LGE.
A. Survivial in patients with $Err_{Lax} \leq 9.48\%$ vs. those with $Err_{Lax} > 9.48\%$. Note that only one patient without LGE experienced MACE dring follow-up. **B.** Survivial in patients with LGE vs. those without LGE. **C.** Survivial in patients with $Err_{Lax} \leq 9.48\%$ and presence of LGE vs. those with $Err_{Lax} \leq 9.48\%$ and presence of LGE vs. those without LGE. Patients with LGE and decreased Err_{Lax} ($\leq 9.48\%$) had worse outcome, compared to patients with LGE only. CMR = cardiovascular magnetic resonance, Err_{Lax} = LV radial strain measured from long-axis cine views, LGE = late gadolinium enhancement, LV = left ventricle, MACE = major adverse cardiovascular events

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DISCUSSION

This retrospective study presented the following results: 1) all myocardial strain parameters were significantly impaired in patients with acute myocarditis, 2) even patients with a preserved EF showed significantly reduced Ecc_{SAX}, Ell_{LV}, and Err_{Lax}, 3) Err_{Lax} measured on CMR independently predicted MACE or normalized LVEF values in patients with acute myocarditis, 4) all patients with LGE and low Err_{Lax} values experienced MACE.

In contrast to previous studies (5, 21), we included CMR-derived myocardial strain as a possible predictor

Table 6. Univariate Analysis: Incomplete Left Ventricular Functional Recovery

	Total (n = 31)	Incomplete LV Functional Recovery (n = 9)	Complete LV Functional Recovery (n = 22)	Odds Ratio (95% CI)	*P*
Age, years	42.4 ± 17.1	51.8 ± 14.9	38.5 ± 16.7	1.06 (1.0–1.12)	0.063
Female	12 (38.7)	4 (30.8)	9 (69.2)	1.16 (0.24–5.53)	0.856
BMI, kg/m^2	22.4 ± 2.8	22.8 ± 2.8	22.2 ± 2.9	1.08 (0.81–1.43)	0.617
Past history					
Hypertension	3 (9.7)	2 (66.7)	1 (33.3)	6.0 (0.47–76.71)	0.168
Diabetes	2 (6.5)	2 (100.0)	0 (0)	NA	0.999
Smoking habit	5 (16.1)	1 (1.1)	4 (18.2)	0.56 (0.05–5.86)	0.630
ECG alteration					
ST elevation	12 (38.7)	1 (8.3)	11 (91.7)	0.13 (0.13–1.18)	0.069
ST depression	9 (29.0)	3 (33.3)	6 (66.7)	1.33 (0.25–7.11)	0.736
Negative T	5 (16.1)	1 (20.0)	4 (80.0)	0.56 (0.05–5.86)	0.630
Pathologic Q	3 (9.7)	0 (0)	3 (100.0)	NA	0.999
AV block	3 (9.7)	1 (11.1)	2 (9.1)	6.0 (0.47–76.7)	0.168
LBBB or RBBB	4 (1.3)	1 (11.1)	3 (13.6)	7.92 (0.07–8.81)	0.849
Ventricular tarchycardia	1 (3.2)	0 (0)	1 (4.5)	NA	NA
Initial NYHA functional class					
III/IV	21 (67.7)	7 (77.8)	14 (63.6)	2.0 (0.33–12.05)	0.449
Initial blood testing					
Troponin I, ng/mL	15.3 (21.9)	79.3 (34.4)	13.6 (14.6)	1.01 (0.98–1.05)	0.515
BNP, pg/mL	917 (882.9)	1010.6 (1068.4)	876 (825.1)	1.00 (1.00–1.00)	0.732
CK-MB, ug/L	47.2 (53.1)	44 (48.5)	48.5 (46.6)	1.00 (0.98–1.02)	0.834
Beta-blocker medication	17 (45.2)	4 (44.4)	13 (59.1)	0.55 (0.12–2.65)	0.459
CMR imaging parameter					
LVEDVI, mL/m^2	79.2 ± 37.8	112.9 ± 54.6	65.5 ± 14.8	1.08 (1.01–1.45)	0.019
LVESVI, mL/m^2	46.6 ± 40.5	84.7 ± 58.3	31.1 ± 13.2	1.10 (1.0–1.18)	0.011
LVMI, g/m^2	114.0 ± 45.3	79.5 ± 33.7	63.2 ± 19.1	1.03 (0.99–1.06)	0.109
RVEF, %	91.1 ± 28.2	43.5 ± 18.7	54.7 ± 10.4	0.94 (0.89–1.00)	0.059
LVEF, %	46.8 ± 16.9	29.1 ± 13.4	54.0 ± 12.4	0.89 (0.82–0.96)	0.003
Presence of LGE	20 (64.5)	7 (77.8)	13 (59.1)	1.39 (0.27–7.04)	0.698
Ecc_{SAX}, %	-10.1 ± 4.2	-6.2 ± 4.6	-11.7 ± 2.9	1.47 (1.13–1.91)	0.005
Err_{SAX}, %	15.5 ± 7.7	7.4 ± 3.9	18.8 ± 6.3	0.69 (0.54–0.89)	0.004
Ell_{LV}, %	-11.2 ± 4.6	-7.3 ± 3.1	-12.8 ± 4.1	1.46 (1.10–1.95)	0.009
Err_{Lax}, %	20.3 ± 8.8	10.5 ± 5.3	24.2 ± 6.3	0.70 (0.55–0.90)	0.005

Values are n (%) or means ± SD. AV = atrioventricular, BMI = body mass index, BNP = brain natriuretic peptide, CK-MB = creatine kinase MB, CMR = cardiovascular magnetic resonance, Ecc_{SAX} = LV circumferential strain measured from short-axis cine views, ECG = electrocardiography, Ell_{LV} = LV longitudinal strain measured from long-axis cine views, Err_{Lax} = LV radial strain measured from long-axis cine views, Err_{SAX} = LV radial strain measured from short-axis cine views, LBBB = left bundle branch block, LGE = late gadolinium enhancement, LV = left ventricle, LVEDVI = LV end-diastolic volume index, LVEF = LV ejection fraction, LVESVI = LV end-systolic volume index, LVMI = LV mass index, MACE = major adverse cardiovascular events, NA = not applicable, NYHA = New York Heart Association, RBBB = right bundle branch block, RVEF = right ventricular ejection fraction

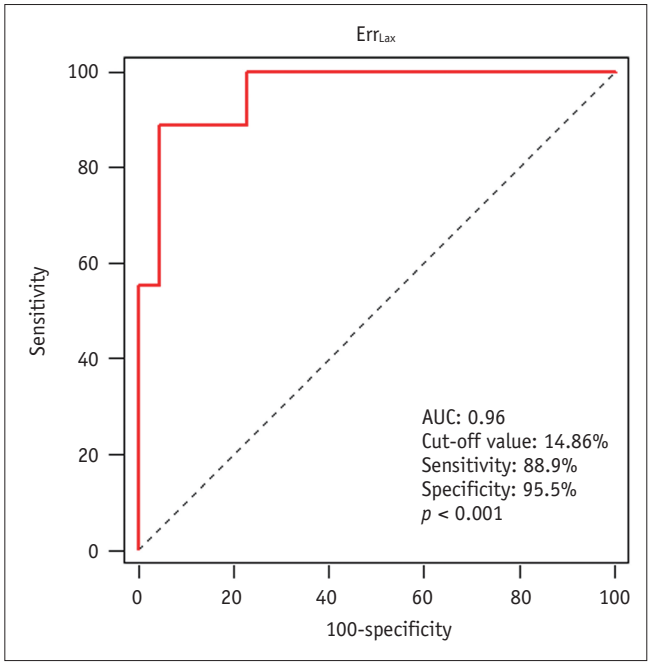

Fig. 4. Receiver operating characteristic curve for prediction of incomplete left ventricular functional recovery. AUC = area under the curve, Err_{Lax} = LV radial strain measured from long-axis cine views, LV = left ventricle

of MACE or incomplete LV functional recovery in acute myocarditis. Few previous studies have evaluated LV strain in echocardiography of patients with acute myocarditis, or its prognostic values (10). Hsiao et al. (10) reported that longitudinal and circumferential strain measured with echocardiography were significant predictors of major clinical events in 45 acute myocarditis patients. However, their study employed a relatively short follow-up period (mean = 19.8 months), and did not adjust for potential confounding factors through the use of multivariate analysis. Furthermore, echocardiography is inherently limited in patients with poor echogenic windows, and echocardiographic strain parameters may depend on insonation angle (22).

Cardiovascular magnetic resonance-derived feature tracking using steady-statefree precession CMR images is analogous to echocardiographic speckle tracking, but uses a higher spatial resolution and reproducible wall motion tracking (23). One recent study reported that CMR-derived myocardial strain measured with the feature tracking method can predict preserved residual EF in ST elevation myocardial infarction (22). CMR-derived myocardial strain can predict acute myocarditis with high sensitivity and specificity, and significantly reduced cardiac strain is shown even in patients with a preserved EF (9, 14, 24). However, there are no prior studies on the predictive value of CMR-derived myocardial strain measurements in acute myocarditis patients.

In this study, all strain parameters, including Ecc_{SAX}, Err_{SAX}, Ell_{LV}, and Err_{Lax} values, were characterized by excellent intra- and inter-observer reproducibility. This result agrees with those of previous studies of CMR feature tracking methods in which considerable intra-observer reproducibility in global myocardial strain measurements was demonstrated (25). In the present study, intra-observer reproducibility was lower for Ecc_{SAX} than for Err_{SAX} and Ell_{LV} in contrast to previous reports in which Ecc_{SAX} was the most reproducible strain parameter (25, 26). This discrepancy may be due to differences in the software used to obtain myocardial strain measurements. Schuster et al. (27), compared the reproducibility of CMR feature-tracking softwares, and found that Circle had better reproducibility for Err_{SAX} than TomTec (Diogenes or 2D Cardiac Performance Analysis-MR, TomTec GmbH, Unterschleissheim, Germany). In that study, Err_{SAX} was more reproducible than Ecc_{SAX} using Circle, which is similar to the result of the present study. Therefore, further studies are required to assess intra- and inter-observer reproducibility of Ell_{LV} and Err_{Lax} with respect to the type of feature tracking software used.

Myocardial LGE is a marker of irreversible myocardial injury, e.g., necrosis and fibrosis (16). The presence of LGE is reportedly an independent predictor of a poor outcome, defined as heart transplantation, the requirement for extracorporeal membrane oxygenation or a ventricular assist device, and/or death (5, 21), is in agreement with the present results. Moreover, a recent study of the long-term outcome of patients after acute myocarditis found that NYHA functional class > II and larger LGE mass were independent predictors for the occurrence of long-term MACE (24). LGE was detected in 62.2% of patients in this study, which is a relatively high proportion compared with the 53.2% detected in a previous report (53.2%) (5). This discrepancy may be due to differences in the interval between clinical onset of the disease and CMR examination (mean duration = 11.6 days vs. < 5 days), as well as the characteristics of the study populations. CMR studies conducted during the first day of myocarditis may be less sensitive than those conducted after 7 days because of the focal nature of the early stages of the disease (16). The prominence of LGE may vary accordingly.

The present analysis of the subgroup of patients who underwent follow-up echocardiography revealed that

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Err_{Lax} values ≤ 14.9% independently predicted incomplete functional recovery (p = 0.042). Although a similar result was obtained previously for myocardial infarction (22), this study assessed, for the first time, the relationship between Err_{Lax} values and myocardial strain. This relationship was based on an analysis of cine images using a feature tracking method during incomplete LV functional recovery in myocarditis. Unexpectedly, LGE did not appear to play a prominent role in this subgroup, contrary to data from a previous myocarditis study (4). This discrepancy may have been due to death during follow-up or absence of follow-up echocardiography in a subgroup of patients. Either of these might introduce a selection bias that could affect the reliability of the data and result in an underestimation of the role of LGE.

This study had several limitations. Its retrospective design and relatively small sample size could be improved in the future by the use of prospective designs and larger cohorts. It included clinically validated suspected acute myocarditis patients only. EMB was not used as a reference standard because of its limited sensitivity (28), and it is not routinely performed in clinical practice. Several previous studies (10, 29, 30) also relied on a combination of clinical, laboratory, ECG and angiographic findings to identify myocarditis. Furthermore, we could not use Lake Louise Criteria for diagnosis of acute myocarditis, because a T2-weighted sequence or an early gadolinium enhancement sequence was not performed in most cases. Therefore, we included patients with clinically suspected myocarditis according to a combination of clinical, laboratory, ECG and angiographic findings. CMR scanners with different field strengths (i.e., 1.5T and 3T scanners) were used in the present study, which may have affected the imaging analyses. However, previous studies indicated no significant differences in global strain parameters, volumes or EF were found with different field strengths (25).

In conclusion, CMR-derived LV radial strain (Err_{Lax}) values can predict MACE or normalized LVEF in patients with acute myocarditis. The presence of scars, indicated by LGE, is also a good independent predictor of MACE. These results indicate that large, longitudinal follow-up studies are required to further establish LGE and CMR-derived myocardial strain as independent predictors of MACE in acute myocarditis.

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