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Prognostic Value of Cardiac Magnetic Resonance Tissue Characterization in Risk Stratifying Patients With Suspected Myocarditis

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ABSTRACT

BACKGROUND Diagnosing myocarditis is challenged by nonspecific clinical signs and symptoms and low accuracy of endomyocardial biopsy. Cardiac magnetic resonance imaging (CMR) provides both cardiac anatomy and tissue characterization in this setting, but the prognostic value of this method as a primary assessment tool in patients with suspected myocarditis remains limited.

OBJECTIVES This study sought to determine cardiac event-free survival of a consecutive cohort with suspected myocarditis with regard to CMR findings.

METHODS Six hundred seventy patients with suspected myocarditis underwent CMR including late gadolinium enhancement (LGE) parameters between 2002 and 2015 and were included and followed. We performed multivariable model for major adverse cardiovascular events (MACE) and determined the continuous net reclassification improvement by LGE markers.

RESULTS At a median follow-up of 4.7 years (interquartile range [IQR]: 2.3 to 7.3 years), 98 patients experienced a MACE. Two hundred ninety-four (44%) patients showed LGE presence, which was associated with a more than doubling risk of MACE (hazard ratio [HR]: 2.22; 95% confidence interval [CI]: 1.47 to 3.35; $p < 0.001$). Annualized MACE rates were 4.8% and 2.1% corresponding to LGE presence and absence, respectively ($p < 0.001$). In the multivariable model, LGE presence maintained significant association with MACE (HR: 1.72; 95% CI: 1.08 to 2.76; $p = 0.023$). The computed continuous net reclassification improvement was 0.39 (95% CI: 0.10 to 0.67) when LGE presence was added to the multivariable model for MACE. Regarding location and pattern, septal and midwall LGE showed strongest associations with MACE (HR: 2.55; 95% CI: 1.77 to 3.83 and HR: 2.39; 95% CI: 1.54 to 3.69, respectively; both $p < 0.001$). A patchy distribution portended to a near 3-fold increased hazard to MACE (HR: 2.93; 95% CI: 1.79 to 4.80; $p < 0.001$). LGE extent (per 10% increase) corresponded to a 79% increase in risk of MACE (HR: 1.79; 95% CI: 1.25 to 2.57; $p = 0.002$). A normal CMR study corresponded to low annual MACE and death rates of 0.8% and 0.3%, respectively.

CONCLUSIONS CMR tissue characterization provides effective risk stratification in patients with suspected myocarditis. (J Am Coll Cardiol 2017;70:1964–76) © 2017 by the American College of Cardiology Foundation.

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Myocarditis remains a leading cause of sudden cardiac death in athletes (1) and in dilated cardiomyopathy (2). Diagnosis of this condition is challenging given its nonspecific signs and symptoms (3), a lack of diagnostic reference standard, and low accuracies of electrocardiogram (ECG), echocardiography, biomarkers, and even invasive endomyocardial biopsy (EMB) (4,5). With its technical benefits of localizing regional dysfunction and matching tissue characterization, cardiac magnetic resonance imaging (CMR) has become the primary imaging tool in many centers characterizing disease severity and planning of patient management (6). The Lake Louise criteria had established the current recommended diagnostic criteria incorporating early gadolinium enhancement, late gadolinium enhancement (LGE), and T2-weighted imaging for edema detection (6). However, prognostic evidence using CMR for patients with suspected myocarditis currently remains limited. The present study aimed to evaluate the prognostic value of tissue characterization by CMR in risk stratification of patients presenting with suspected myocarditis.

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METHODS

STUDY POPULATION. The study included consecutive patients referred by their treating physician to undergo CMR for "suspected myocarditis" as the primary clinical question between December 2002 and December 2015 at our center. We included patients with presenting signs/symptoms of any 1 of these 3 groups: 1) acute chest pain syndromes with symptom onset <2 weeks before CMR; 2) subacute (onset ≥2 weeks) of dyspnea or signs of left ventricular (LV) dysfunction; and 3) subacute (onset ≥2 weeks) presentation of ventricular arrhythmias syncopal spells or abnormal ECG.

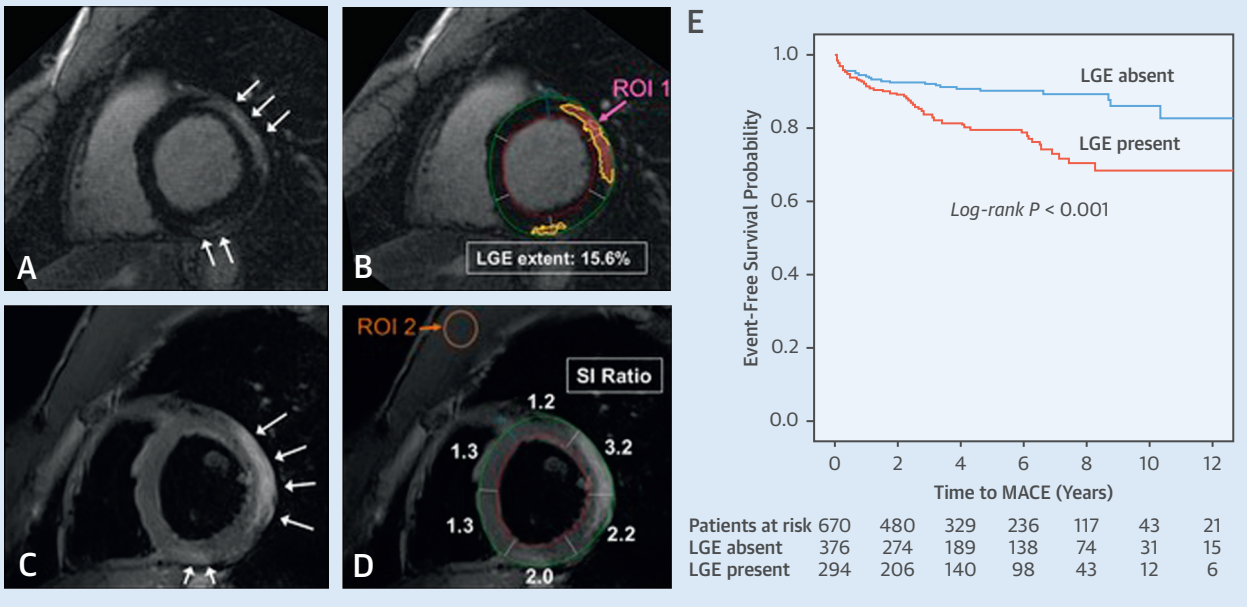
Exclusion criteria included: 1) any evidence of coronary artery disease (CAD) by either previous documented medical history, any imaging findings of CAD, or significant epicardial coronary stenosis by invasive coronary angiography; 2) any evidence of hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, cardiac sarcoidosis, or cardiac amyloidosis; and 3) any evidence of Takotsubo cardiomyopathy, constrictive pericarditis, Loeffler endocarditis, ventricular noncompaction, cardiac tumor, pulmonary embolism, or severe valve disease. Clinical data, cardiac biomarkers, and ECG at the time of the CMR were analyzed. ECGs were analyzed according to the following ECG criteria: low QRS voltage was defined by ≤5 mm in limb leads or ≤10 mm in all precordial leads (7), QTc prolongation >450 ms for males and >470 ms for females (8), and ST-depression as ≥0.1 mV at 80 ms from the J point, asymmetrical T-wave inversion ≥0.1 mV deep in 2 or more leads except aVR (9), and Q-wave as >0.3 mV in depth and/or >40 ms in duration in at least 2 contiguous leads except aVR (10). T-wave inversion was defined by negative amplitude ≥1 mm in at least 2 contiguous leads (11) and ST-segment elevation after the J point in 2 contiguous leads with the cutoff points of ≥0.2 mV in men and ≥0.15 mV in women in leads V_2-V_3, and/or ≥0.1 mV in other leads (12).

CMR IMAGING PROTOCOL AND IMAGE POST-PROCESSING. Patient scanning was performed with a 3.0-T or a 1.5-T system (Tim Trio and Aera, Siemens, Erlangen, Germany). A standardized CMR consisting of cine steady-state free precession imaging (repetition time [TR], 3.4 ms; echo time [TE], 1.2 ms; in-plane spatial resolution, 1.6 × 2 mm) for LV function and LV mass was used. Cine imaging was obtained in 8 to 14 matching short-axis (8-mm thick with no gap) and 3 radial long-axis planes. All patients underwent a fast-gradient echo technique LGE imaging protocol (TR, 4.8 ms; TE, 1.3 ms; inversion time, 200 to 300 ms) to detect fibrosis, using a segmented inversion-recovery pulse sequence starting 10 to 15 min after a weight-based injection (cumulative dose 0.15 mmol/kg) of gadolinium diethylenetriamine penta-acetic acid (Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, New Jersey) or gadobenate dimeglumine (Multihance, Bracco Diagnostic, Princeton, New Jersey). In patients with estimated glomerular filtration rate <60 ml/min/1.73 m^2, contrast dose was restricted to 0.1 mmol/kg or 20 ml, depending on which was lower in volume based on our institutional policy (13). T1 measurements were acquired using a validated cine Look-Locker sequence (14), with a non-slice-selective adiabatic inversion pulse, followed by segmented gradient-echo acquisition for 17 cardiac phases/times after inversion (TE = 2.5 ms; TR = 5.5 ms; flip angle = 10°; 192 × 128 matrix; 6-mm slice), spread over 2 cardiac cycles (inversion time increments for T1 measurements of 100 ms pre-contrast, and 55 ms post-contrast, slice thickness 8 mm, TR >RR intervals pre-contrast and 3 RR intervals post-contrast). The Look-Locker sequence was performed in short-axis slices at basal, mid, and apical LV levels. T1 mapping images were acquired in the same LV

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging
CI = confidence interval
ECG = electrocardiogram
ECV = extracellular volume
EMB = endomyocardial biopsy
HR = hazard ratio
ICC = intraclass correlation coefficient
IQR = interquartile range
LGE = late gadolinium enhancement
LV = left ventricular
LVEF = left ventricular ejection fraction
MACE = major adverse cardiovascular event(s)
TE = echo time
TR = repetition time
WMA = wall motion abnormality

CENTRAL ILLUSTRATION **Patient With Suspected Myocarditis Who Was Referred for CMR Evaluation and Event-Free Survival Probability Curve**



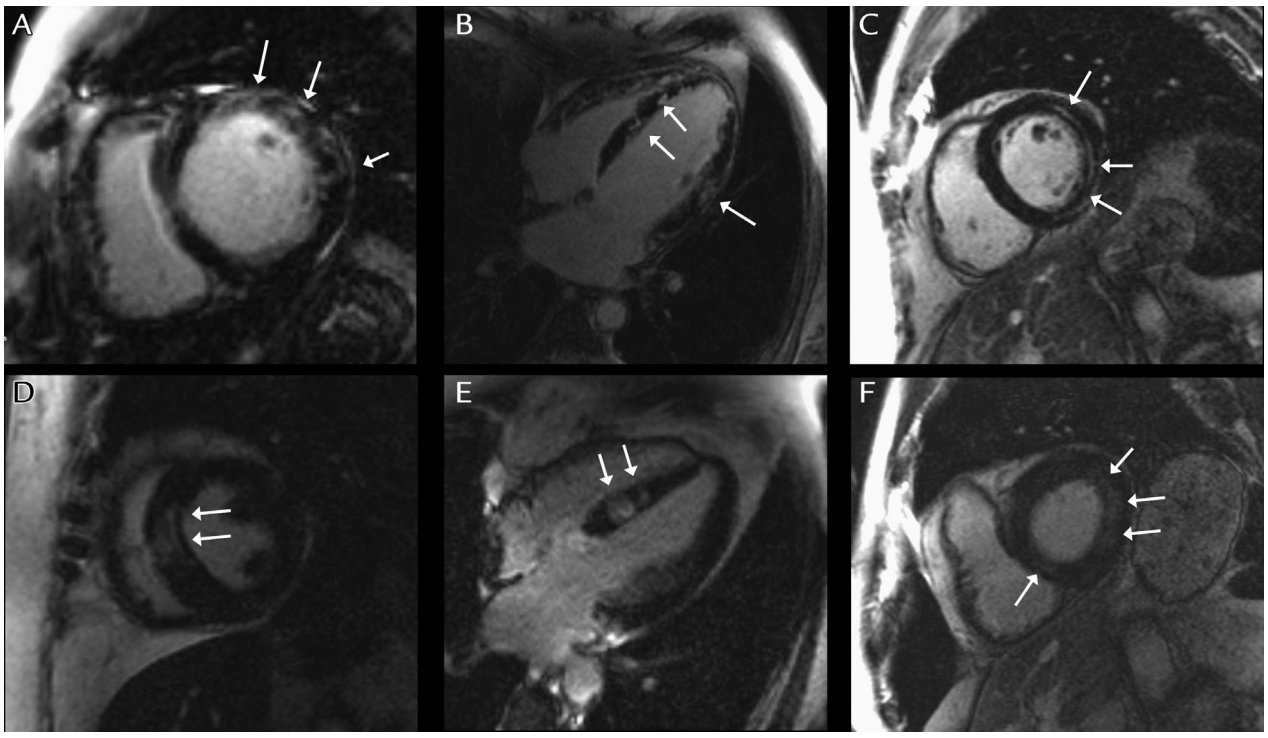
Gräni, C. et al. J Am Coll Cardiol. 2017;70(16):1964–76.

This is a case of a 20-year-old male without prior cardiac history who was referred for CMR with suspected myocarditis. The patient presented with chest pain, electrocardiogram changes with inferior ST-segment elevations, elevated troponin, and no angiographically significant coronary artery disease. No recent viral or other illness was known and the patient did not take any medication nor was there illegal substance abuse. EMB was not performed. CMR showed linear, epicardial LGE **(A)** in the anterior, anterolateral, and inferior/inferolateral segments **(white arrows)**. LGE extent was measured using the FWHM quantification method with an ROI 1 placed in the identified affected myocardium **(pink arrow/pink contour).** LGE extent presented to be 15.6% **(B).** On T2-weighted imaging there is increased signal in the same segments where LGE was present **(C, white arrows).** Signal intensity (SI) ratio of myocardium/skeletal muscle **(D,** ROI 2 with **brown arrow/brown contour)** indicates edema in the affected segments with SI ratio being ≥2.0. **(E)** The event-free (MACE) survival probability curve of patients with suspected myocarditis showed that patients with LGE presence had a significantly worse outcome compared to those without LGE. CMR = cardiac magnetic resonance imaging; EMB = endomyocardial biopsy; FWHM = full width half maximum; LGE = late gadolinium enhancement; MACE = major adverse cardiovascular event; ROI = region of interest.

short-axis slices, once before and up to 3 times after the injection of gadolinium spanning across a post-contrast period of approximately 30 min. Commercially available software (MASS v15, 2008, Medis, Leiden, the Netherlands) was used to post-process and quantify all CMR images. CMR variables were calculated. Further wall motion abnormalities (WMA), and pleural and pericardial effusion were visually assessed. Epicardial and endocardial contours were placed manually on all LGE images, then LGE mass was quantified by using the full width half maximum signal intensity threshold cutoff technique above the mean intensity of remote myocardium in the same slice (15) (**Central Illustration**), and calculation of LGE percentage according to the LV mass was performed. LGE was further assessed by its localization (anterior, inferior, septal, lateral), its distribution (linear, patchy, or diffuse), and its pattern (epicardial, midwall) (**Figure 1**).

EXTRACELLULAR VOLUME MEASUREMENTS AND T2-WEIGHTED IMAGING. Since 2009, T1 mapping and extracellular volume (ECV) calculation was incorporated in our protocol and was performed as clinically possible in all referred patients (available in 179; 27% of our patients). For each Look-Locker T1-mapping sequence the endo- and epicardial borders of the LV were traced. Using commercially available software (QMASS MR, Medis Medical Imaging Systems, Leiden, the Netherlands), signal intensity versus time curves were generated from regions of interest in the LV and blood pool. The signal intensity versus time curves for each segment and the blood pool were fitted to an analytical expression for the inversion recovery to obtain T1*, and corrected for the effects of radiofrequency pulse during inversion recovery to calculate T1. The reciprocal of T1 ($R1 = 1/T1$) was used to plot the myocardial R1 against the R1 in the blood pool. Subsequently, the slope of

FIGURE 1 Examples of Different LGE Distributions and Patterns Seen in the Cohort



(A) Patient #1. A short-axis view is displayed with a patchy LGE distribution and an epicardial and midwall pattern, which can also be depicted in the same patient in a 4-chamber view **(B). (C)** Patient #2. The short-axis image showing LGE presence in anterolateral, inferolateral, and inferior locations, in a linear distribution and a mostly midwall pattern. **(D, E)** Patient #3. A patchy distribution with midwall pattern located in the septum is shown in a short-axis view, which was confirmed by a 4-chamber view **(E). (F)** Patient #4. A diffuse LGE distribution, mainly in the midwall. **White arrows** describe LGE. LGE = late gadolinium enhancement.

least-squares regression line for R1 in tissue versus R1 in blood (limited data points with R1 in blood $<3.5\ s^{-1}$) was used to estimate the partition coefficient for gadolinium (λ_{Gd}). This represents an extension of the formula: $\lambda Gd = (1/T1_{Myo\ Post} - T1_{Myo\ Pre})/(1/T1_{Blood\ Post} - 1/T1_{Blood\ Pre})$. λGd was then multiplied by blood plasma fraction (1 minus the hematocrit expressed as a value between 0 and 1), to obtain segmental myocardial ECV. The global myocardial ECV for an individual was calculated by averaging the myocardial segmental ECV values from all the short-axis slices. Hematocrit was derived from routine blood laboratory testing nearest to the CMR examination. An abnormal elevation of ECV was defined by a 2 SD cutoff of ≥35% (16). T2-weighted inversion recovery prepared fast-spin echo sequence was performed using 3 short-axis slices of 12-mm thickness at the base, mid, and apex and a single long-axis slice in a 4-chamber view were performed in 467 (70%) cases (203 missing). Myocardial edema was evaluated by assessing the ratio of the signal intensity in the different myocardial segments compared to the skeletal muscle (musculus pectoralis major or minor) in each segment as described previously (**Central Illustration**). A ratio of ≥2 was considered abnormal (6).

FOLLOW-UP OF CLINICAL ENDPOINTS. All subjects were assessed by an interrogation of Social Security Death Index of the United States and a detailed review of all available electronic medical records. When electronic medical records were insufficient, subjects were evaluated by a standardized checklist-based patient questionnaire by mail and/or followed up by conducting a scripted telephone interview based on the same standardized checklist. The retrospective screening and the follow-up was performed between June 2016 and April 2017. A priori-defined primary major adverse cardiac events (MACE) included: 1) all-cause death; 2) heart failure decompensation requiring hospital admission (17); 3) heart transplantation; 4) documented sustained ventricular arrhythmia (>30 s); and 5) recurrent acute myocarditis

TABLE 1 Baseline Characteristics

	All Patients (N = 670)	LGE Present (n = 294)	LGE Absent (n = 376)	p Value
Baseline				
Age, yrs	47.8 ± 16.0	49.2 ± 16.4	46.8 ± 15.5	0.052
Female	278 (41)	90 (31)	188 (50)	<0.001
Body mass index, kg/m^2	27.8 ± 6.3	27.7 ± 5.9	27.8 ± 6.7	0.893
Acuteness of presentation				
Acute chest pain syndromes (<2 weeks)	350 (52)	169 (57)	181 (48)	<0.001
Subacute presentation (≥2 weeks) with dyspnea or left ventricular dysfunction	201 (30)	91 (31)	110 (29)	
Subacute presentation (≥2 weeks) with ventricular arrhythmias, syncopal spells, or abnormal ECG	119 (18)	34 (12)	85 (23)	
Cardiovascular history				
Hypertension	181 (27)	78 (27)	103 (27)	0.953
Tobacco	76 (11)	38 (13)	38 (10)	0.304
Diabetes	60 (9)	22 (8)	38 (10)	0.495
Dyslipidemia	138 (21)	65 (22)	73 (19)	0.636
Medications				
Aspirin	186 (28)	94 (33)	92 (25)	0.035
ACE inhibitors	229 (35)	114 (40)	115 (31)	0.019
Beta-blockers	266 (40)	142 (49)	124 (33)	<0.001
Diuretics	135 (21)	78 (27)	57 (16)	<0.001
Statins	142 (22)	74 (26)	68 (18)	0.020
Insulin	23 (4)	7 (2)	16 (4)	0.032
ECG				
Left bundle branch block	57 (9)	27 (9)	30 (8)	0.579
Right bundle branch block	43 (6)	20 (7)	23 (6)	0.719
PR duration, ms	156 (141–176)	158 (144–178)	154 (140–174)	0.087
PR prolongation (≥200 ms)	36 (5)	17 (6)	19 (5)	0.684
QRS duration, ms	99.7 ± 23.3	100.1 ± 23.9	99.3 ± 22.9	0.670
QRS prolongation (≥120 ms)	89 (13)	40 (14)	49 (13)	0.901
QTc duration, ms	444.5 ± 40.8	449.5 ± 42.3	440.5 ± 39.2	0.008
QTc prolongation (>470 ms female, >450 ms male)	241 (36)	116 (39)	125 (33)	0.206
Significant Q-wave	74 (11)	38 (13)	36 (10)	0.248
ST-segment elevation	32 (5)	19 (6)	13 (4)	0.087
ST-depression	26 (4)	13 (4)	13 (4)	0.576
T-wave inversion	170 (25)	83 (28)	87 (23)	0.198
Low voltage	46 (7)	30 (10)	16 (4)	0.003
Abnormal ECG	278 (42)	130 (44)	148 (39)	0.206
Laboratory testing				
Troponin abnormal	170 (63)	104 (73)	66 (52)	<0.001
Troponin peak, ng/ml	0.08 (0.0–0.46)	0.14 (0.0–0.6)	0.02 (0.0–0.3)	0.002
Creatine kinase abnormal	70 (40)	40 (42)	30 (38)	0.580
Creatine kinase peak, U/l	0.99 ± 0.33	1.07 ± 0.36	0.91 ± 0.27	<0.001
White blood cell count abnormal	105 (35)	61 (39)	44 (30)	0.121
White blood cell count (10^9/l)	8.3 (6.6–11.4)	8.7 (6.7–11.4)	7.9 (6.4–12.0)	0.317

Values are mean ± SD, n (%), or median (interquartile range). The following numbers were available for the laboratory testing: troponin n = 268 (402 missing), creatine kinase n = 170 (500 missing), white blood cell count n = 302 (368 missing). Frequency data were represented as number of cases (percentage of corresponding group, excluding missing data).

ACE = angiotensin-converting enzyme; ECG = electrocardiogram; LGE = late gadolinium enhancement.

based on elevated myocardial biomarkers (troponin or creatine kinase), absence of CAD during hospitalization and presence of CMR criteria for myocarditis such as T2-weighted imaging of the myocardium to skeletal muscle ratio ≥2 and LGE in epicardial and or mid-myocardium in nonischemic distribution (6). When more than 1 event occurred in a patient subject, the first event was used. Secondary event included all-cause mortality. All study procedures were approved by our Institutional Review Board in accordance with our institutional guidelines. Informed consent was waived by our Institutional Review Board but all

patients had the option of refusing follow-up contact by returning a study letter.

STATISTICAL ANALYSIS. Categorical variables were presented as percentages of the entire cohort or as a percentage of the corresponding group if relevant data were missing. Continuous variables were expressed as mean ± SD or as median values with interquartile range (IQR) depending on normality of distributions. Categorical variables were compared using the Fisher exact test, whereas comparisons for continuous data were performed using a 2-sample Student *t* test or Wilcoxon rank-sum test, when appropriate. A 2-sided p value of <0.05 was deemed significant. Time to event was measured from the date of CMR study. Univariable and multivariable associations of risk covariates with clinical events were determined by Cox proportional hazards regression. Survival hazard function curves were displayed using Kaplan-Meier. Interobserver and intraobserver variabilities of CMR parameters were performed using intraclass correlation coefficient (ICC). We performed a clinical multivariable analysis including key clinical features. In addition, we built a multivariable model for MACE that contained a parsimonious set of strongest predictive variables using a backward elimination strategy with a level of stay criteria of $p < 0.01$. All variables in Tables 1 to 4, except laboratory tests and LGE parameters, were considered. Of note, presence of WMAs, not sublocations, was considered for this model. LGE presence was then added to the multivariable model to assess the prognostic value of LGE, incremental to the variables in the multivariable model. Given that treatment-related clinical risk categories have not been defined in patients with suspected myocarditis, we performed computed continuous net reclassification index (NRI) to determine the incremental value of LGE presence above a set of known clinical risk markers (18). The validity of the proportional-hazards assumption was tested by adding a time-dependent interaction variable for each of the covariates in the model. SAS was used for all statistical analysis version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS. A total of 744 patients were identified. As shown in Figure 2, 59 (7.9%) were excluded based on CMR findings consistent with myocardial infarction (n = 35), cardiac amyloidosis (n = 6), ventricular noncompaction (n = 3), Takotsubo cardiomyopathy (n = 4), constrictive pericarditis (n = 2), cardiac sarcoidosis (n = 2), and Loeffler endocarditis (n = 2), and 1 each for arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, pulmonary embolism, cardiac tumor, and severe valve disease. The remaining 670 formed the study cohort and atherosclerotic coronary disease was considered unlikely to be the etiology of the patients' symptoms based on the initial cardiac work-up, including an

TABLE 2 CMR Baseline Characteristics

	All Patients (N = 670)	LGE Present (n = 294)	LGE Absent (n = 376)	p Value
LVEF, %	49.6 ± 15.0	44.7 ± 15.7	53.4 ± 13.2	<0.001
LVEF <40%	200 (29.9)	113 (38.4)	87 (23.1)	<0.001
LVEDVi, ml/m^2	97.6 ± 33.1	105.3 ± 37.9	91.4 ± 27.4	<0.001
LVEDV, ml	189.1 ± 70.0	206.6 ± 81.8	175.1 ± 55.2	<0.001
LVESVi, ml/m^2	52.8 ± 34.4	62.6 ± 39.8	44.9 ± 27.0	<0.001
LVESV, ml	102.2 ± 68.6	122.6 ± 81.8	85.9 ± 50.3	<0.001
LV mass index, g/m^2	60.6 ± 16.8	65.0 ± 18.0	56.7 ± 14.8	<0.001
LV mass, g	118.1 ± 38.6	129.3 ± 40.8	109 ± 34.4	<0.001
RVEF, %	48.8 ± 11.1	45.8 ± 12.9	51.4 ± 8.6	<0.001
RVEDVi, ml/m^2	79.9 ± 21.3	82.0 ± 21.8	78.1 ± 20.7	0.027
RVEDV, ml	155.6 ± 50.6	162.1 ± 53.3	150.0 ± 47.6	0.004
RVESVi, ml/m^2	41.7 ± 17.4	45.7 ± 20.3	38.3 ± 13.8	<0.001
RVESV, ml	81.4 ± 38.1	90.4 ± 44.5	73.9 ± 29.8	<0.001
Pericardial effusion	169 (25)	96 (33)	73 (19)	<0.001
Pleural effusion	83 (12)	48 (16)	35 (9)	0.006
Wall motion abnormalities location				
Wall motion abnormalities at rest	280 (42)	181 (62)	99 (26)	<0.001
Wall motion abnormalities anterior	203 (30)	128 (44)	75 (20)	<0.001
Wall motion abnormalities lateral	203 (30)	132 (45)	71 (19)	<0.001
Wall motion abnormalities inferior	213 (32)	135 (46)	78 (21)	<0.001
Wall motion abnormalities septal	235 (35)	145 (49)	90 (24)	<0.001
LGE location				
LGE anterior	70 (10)	70 (24)	–	–
LGE lateral	177 (26)	177 (60)	–	–
LGE inferior	137 (20)	137 (47)	–	–
LGE septal	171 (26)	171 (58)	–	–
LGE mass, g	2.6 ± 5.4	6.2 ± 6.8	–	–
LGE mass, %	2.2 ± 4.4	5.1 ± 5.4	–	–
LGE distribution				
Linear	166 (25)	166 (57)	–	–
Patchy	117 (18)	117 (40)	–	–
Diffuse	11 (2)	11 (4)	–	–
LGE pattern				
Epicardial	168 (25)	168 (57)	–	–
Midwall	115 (17)	115 (39)	–	–
Transmural (diffuse distribution)	11 (2)	11 (4)	–	–
T2-weighted ratio mean	1.80 ± 0.79	1.80 ± 0.75	1.81 ± 0.82	0.857
T2-weighted ratio abnormal (≥2.0)	125 (27)	63 (29)	62 (25)	0.230
ECV mean (per 10% increase)	3.2 ± 0.60	3.3 ± 0.60	3.1 ± 0.60	0.004
ECV mean ≥35%	50 (27)	28 (35)	22 (22)	0.066

Values are mean ± SD or n (%). The following data for T2-weighted imaging and ECV were available: T2-weighted n = 467 (203 missing), ECV n = 191 (479 missing). Frequency data were represented as number of cases (percentage of corresponding group, excluding missing data).

CMR = cardiac magnetic resonance; ECV = extracellular volume; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end diastolic volume; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVi = left ventricular end-systolic volume index; RVEDV = right ventricular end-diastolic volume; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVESVi = right ventricular end-systolic volume index.

TABLE 3 Univariable Association for MACE and Death: Clinical Variables

Potential Predictors	MACE		Death	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Baseline				
Age, yrs	1.03 (1.01–1.04)	<0.001	1.06 (1.04–1.08)	<0.001
Female	1.60 (1.07–2.38)	0.021	1.75 (0.94–3.27)	0.077
Body mass index, kg/m^2	1.05 (1.02–1.08)	0.001	1.00 (0.95–1.05)	0.991
Referral reasons				
Acute (<2 weeks) vs. subacute presentation (≥2 weeks)	1.87 (1.22–2.86)	0.003	1.39 (0.73–2.64)	0.315
History				
Hypertension	1.72 (1.14–2.61)	0.011	2.04 (1.05–4.24)	0.035
Tobacco	1.59 (0.99–2.58)	0.057	2.11 (0.96–2.00)	0.079
Diabetes	2.51 (1.49–4.22)	0.001	1.26 (0.47–3.39)	0.651
Dyslipidemia	1.46 (0.93–2.28)	0.101	1.82 (0.94–3.54)	0.076
Medications				
Aspirin	1.47 (1.19–1.82)	<0.001	1.35 (1.07–1.72)	0.012
ACE inhibitors	1.80 (1.21–2.68)	0.004	1.42 (0.76–2.65)	0.268
Beta-blockers	2.34 (1.55–3.51)	<0.001	3.70 (1.88–7.28)	<0.001
Diuretics	3.03 (2.01–4.56)	<0.001	3.34 (1.79–6.26)	<0.001
Statins	1.50 (0.95–2.35)	0.080	1.29 (0.63–2.64)	0.485
Insulin	3.62 (1.82–7.21)	<0.001	2.5 (0.77–8.12)	0.128
ECG				
Left bundle branch block	0.81 (0.37–1.74)	0.585	0.27 (0.04–1.96)	0.196
Right bundle branch block	1.04 (0.48–2.25)	0.917	1.90 (0.74–4.86)	0.180
PR duration, ms	1.00 (0.99–1.00)	0.758	0.99 (0.98–1.00)	0.207
PR prolongation (≥200 ms)	1.47 (0.68–3.20)	0.332	1.61 (0.49–5.32)	0.435
QRS duration, ms	1.00 (0.99–1.01)	0.758	1.00 (0.98–1.01)	0.649
QRS prolongation (≥120 ms)	0.90 (0.49–1.66)	0.746	0.76 (0.27–2.16)	0.609
QTc duration, ms	1.01 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	<0.001
QTc prolongation (>470 ms female, >450 ms male)	2.25 (1.47–3.45)	<0.001	2.77 (1.39–5.52)	0.004
Significant Q-wave	1.40 (0.81–2.44)	0.230	1.66 (0.73–3.78)	0.229
ST-segment elevation	0.47 (0.15–1.48)	0.195	0.39 (0.05–2.83)	0.350
ST-depression	0.61 (0.19–1.94)	0.404	1.04 (0.25–4.35)	0.953
T-wave inversion	1.26 (0.82–1.94)	0.295	0.82 (0.40–1.70)	0.594
Low voltage	1.92 (1.05–3.52)	0.034	1.39 (0.49–3.91)	0.532
Abnormal ECG	1.16 (0.78–1.74)	0.455	0.93 (0.50–1.75)	0.824
Laboratory tests				
Troponin abnormal	1.01 (0.57–1.79)	0.968	1.54 (0.50–4.79)	0.454
Troponin peak, ng/ml	1.07 (0.90–1.27)	0.467	0.93 (0.56–1.53)	0.774
Creatine kinase abnormal	1.19 (0.62–2.29)	0.596	2.30 (0.66–7.99)	0.188
Creatine kinase peak, U/l	1.00 (1.00–1.00)	0.594	1.00 (1.00–1.00)	0.819
White blood cell count abnormal	1.79 (1.09–2.92)	0.021	1.11 (0.49–2.50)	0.810
White blood cell count peak, 10^9/l	1.02 (0.98–1.06)	0.406	0.98 (0.89–1.07)	0.636

The following numbers were available for the laboratory testing: troponin n = 268 (402 missing), creatine kinase n = 170 (500 missing), white blood cell count n = 302 (368 missing).

CI = confidence intervals; HR = hazard ratio; MACE = major adverse cardiovascular event; other abbreviations as in Table 1.

absence of significant stenosis on invasive coronary angiography (n = 213, 32%), a negative stress ECG or nuclear/echocardiographic imaging (n = 192, 29%), a negative coronary computed tomographic angiography (n = 4, 0.6%), and a low CAD likelihood by clinical assessment alone (n = 261, 39%). At a median of 4.7 (IQR: 2.3 to 7.3) years, 2 (0.3%) patients were lost to follow-up. Mean age was 48 ± 16 years and 392 (59%) were male. Two hundred sixty (38.8%) were admitted as inpatients. CMR studies were performed using a 3.0-T scanner in 535 (79.9%) and the remaining using a 1.5-T scanner. Overall baseline characteristics and CMR characteristics including LGE parameters are depicted in Tables 1 and 2. The study cohort consisted of 52% who presented with acute chest pain syndromes, 30% with subacute dyspnea and/or LV dysfunction, and 18% with subacute and atypical signs/symptoms. In this cohort, 376 (56%) of the cohort had LGE negative on CMR but 291 of these 376 (77%) presented with either an acute chest pain syndrome (n = 181, 48%) or subacute dyspnea or LV dysfunction (n = 110, 29%). A minority of patients underwent EMB (n = 57, 9%), and their results were in most cases unspecific, which is consistent with other studies (4-6). Of 479 patients who underwent T2-weighted imaging, 125 (27%) had an abnormal T2-weighted ratio (≥2), with 77 (62%) having no matching abnormal LGE. The median number of days of symptoms before CMR was 7 (IQR: 3 to 14 days). In total, 155 (23%) had a recent infection in the past 3 weeks, and it was more prevalent in patients with the LGE presence (n = 83, 28%) compared to those without LGE (n = 72, 19%, p = 0.007). The median delay between ECG and CMR study was 1 day (IQR 0 to 6 days). Regarding ECG findings, LGE presence was not associated with ST-segment abnormalities, left bundle branch block, or presence of Q-waves (p = 0.680, p = 0.580, and p = 0.260, respectively). However, presence of LGE septal pattern was associated with presence of Q-waves (18% vs. 11%; p = 0.030). The other LGE patterns did not show significant association with any ECG findings (19).

The interobserver ICCs were 0.88, 0.93, 0.75, and 0.93 for LGE, LV ejection fraction (LVEF), T2-weighted ratio, and ECV, respectively. The intraobserver ICCs were 0.89, 0.96, 0.82, and 0.94 for LGE, LVEF, T2-weighted ratio, and ECV, respectively.

UNIVARIABLE AND MULTIVARIABLE ASSOCIATIONS WITH MACE, DEATH, AND EVENT-FREE SURVIVAL. MACE occurred in 98 (15%) patients including 29 deaths (4%), 38 (6%) heart failure hospitalizations, 22 (3%) cases of sustained ventricular arrhythmia, 7 (1%) recurrent myocarditis, and 2 (0.3%) heart transplantations. In 294 (44%) patients, LGE was present on CMR. The event-free probability curves in the Central Illustration show that patients with LGE presence were associated with significant increased hazards to MACE (p < 0.001) and death (p = 0.034). Annualized event rates dichotomized by LGE presence were 2.1% and 4.8%, respectively (p < 0.001) for MACE and 0.9% and 1.7% (p = 0.027), respectively, for death (Figure 3). In the event-free MACE

probability curve (Figure 4) of patients with LVEF ≥40%, LGE presence maintains its prognostic association with MACE (p = 0.004). However, patients with LVEF <40% had worse outcome compared to patients with LVEF ≥40% (p = 0.008), and the addition of LGE presence did not provide additional prognostic association with MACE in the subgroup of LVEF <40% (Figure 4). Figure 5 shows the annualized event rates stratified by LGE presence and LVEF dichotomized by a 40% cutoff. Subjects with LVEF <40% and LGE presence experienced markedly higher cardiac events. In subjects with LVEF ≥40%, annualized event rates increased from 1.1% in LGE absence to 2.6% in patients with LGE presence (p = 0.004). In subjects with LGE presence, the annualized event rates escalated from 2.6% to 6.4% (p = 0.002) with LVEF ≥40% and LVEF <40%, respectively. Univariable association of clinical and CMR variables are shown in Tables 3 and 4. In Table 5, univariable association of LGE parameters for MACE based on acuteness of presentation (acute vs. subacute) is presented. With regard to myocardial pattern of LGE, midwall and patchy involvement showed a more than 2-fold increased hazards to MACE. Septal LGE location showed strong association with MACE, whereas lateral location did not show significant association with MACE. When all LGE locations (anterior, inferior, septal, and lateral) were entered into a Cox regression model using a stepwise forward selection strategy using p < 0.05 as criteria for model entry, only septal location of LGE was selected. When all LGE distributions (linear, patchy, and diffuse) and all LGE patterns (epicardial, midwall, and transmural) were entered into a Cox regression model using a stepwise forward selection strategy using p < 0.05 as criteria for model entry, only mid-wall fibrosis was selected. In the multivariable clinical model including age, sex, body mass index (kg/m^2), dyspnea, diuretics, LVEF 40%, WMA, QTc, and LGE presence, LGE presence maintained significant association with MACE, with an adjusted hazard ratio (HR) of 1.72 (95% confidence interval [CI]: 1.08 to 2.76; p = 0.023). LGE extent per 10% increase was associated with a 79% increase in risk of MACE. Mean T2-weighted ratio was not associated with MACE or death (HR: 1.12; 95% CI: 0.84 to 1.48; p = 0.436 and HR: 1.08; 95% CI: 0.70 to 1.67; p = 0.737, respectively). However, an abnormal T2-weighted ratio (≥2.0) was significantly associated with outcome (MACE HR: 2.14; 95% CI: 1.30 to 3.52; p = 0.003 and death HR: 2.82; 95% CI: 1.35 to 5.92; p = 0.006). ECV calculation using T1 mapping was performed in a subset of 189 subjects (28%), of which 10 were excluded due to low image quality. ECV mean (per 10% increase) was associated with a >2-fold and near 4-fold increased MACE and death, respectively. A "normal" CMR, defined by a LVEF ≥55%, no WMA, and no LGE, portends to a very low annual event rates of MACE and death, compared to subjects with an "abnormal" CMR (0.9% vs. 4.7%, and 0.4% vs. 1.7% for MACE and death, respectively).

One hundred nineteen patients (18%) were considered low risk given their subacute and atypical

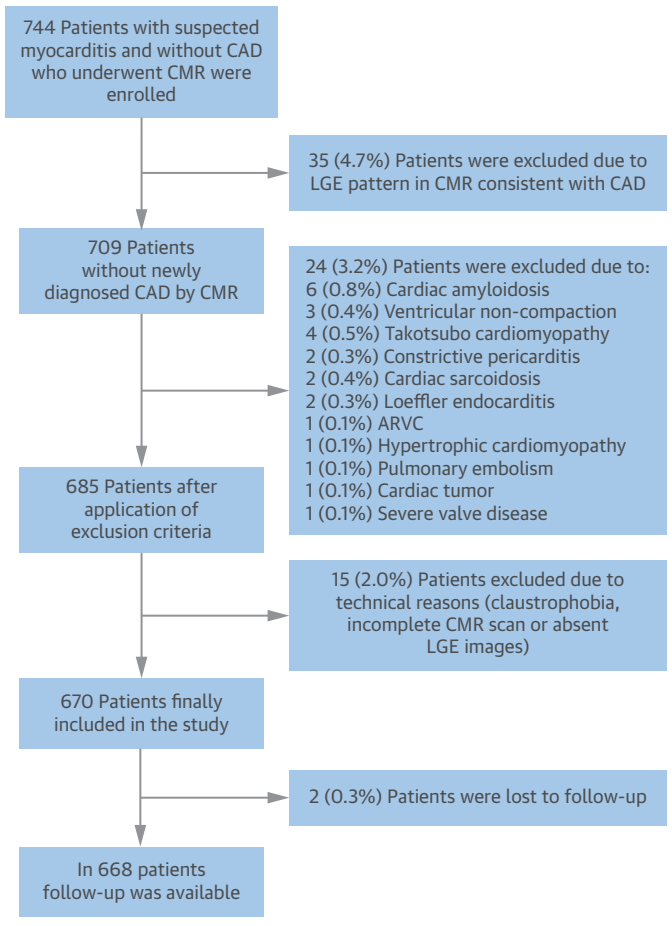
TABLE 4 Univariable Association for MACE and Death: CMR Variables

CMR Potential Predictors	MACE		Death	
	HR (95% CI)	p Value	HR (95% CI)	p Value
LVEF, %	0.95 (0.94–0.97)	<0.001	0.96 (0.94–0.98)	<0.001
LVEF <40%	3.91 (2.07–7.38)	<0.001	4.0 (2.95–5.44)	<0.001
LVEDVi, ml/m^2	1.01 (1.00–1.02)	<0.001	1.00 (0.99–1.01)	0.396
LVEDV, ml	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.01)	0.629
LVESVi, ml/m^2	1.01 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.015
LVESV, ml	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.02)	0.028
LV mass index, g/m^2	1.01 (1.00–1.03)	0.021	1.01 (0.99–1.03)	0.178
LV mass, g	1.01 (1.00–1.01)	0.010	1.00 (0.99–1.01)	0.520
RVEF, %	0.95 (0.93–0.96)	<0.001	0.95 (0.93–0.98)	<0.001
RVEDVi, ml/m^2	1.00 (0.99–1.01)	0.570	1.01 (0.99–1.02)	0.447
RVEDV, ml	1.00 (1.00–1.01)	0.199	1.01 (0.99–1.01)	0.805
RVESVi, ml/m^2	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.04)	0.003
RVESV, ml	1.01 (1.01–1.01)	<0.001	1.01 (1.00–1.02)	0.014
Pericardial effusion	2.31 (1.54–3.45)	<0.001	3.36 (1.81–6.26)	<0.001
Pleural effusion	4.19 (2.71–6.47)	<0.001	5.06 (2.65–9.67)	<0.001
Wall motion abnormalities location				
Wall motion abnormalities at rest	3.50 (2.26–5.40)	<0.001	4.26 (2.08–8.72)	<0.001
Wall motion abnormalities anterior	4.09 (2.72–6.14)	<0.001	4.26 (2.24–8.08)	<0.001
Wall motion abnormalities lateral	3.69 (2.46–5.52)	<0.001	3.41 (1.82–6.39)	<0.001
Wall motion abnormalities inferior	4.35 (2.87–6.58)	<0.001	4.73 (2.44–9.16)	<0.001
Wall motion abnormalities septal	4.03 (2.65–6.12)	<0.001	3.79 (1.98–7.27)	<0.001
LGE presence	2.22 (1.47–3.35)	<0.001	1.99 (1.05–3.75)	0.034
LGE location				
LGE anterior	1.76 (1.03–3.00)	0.040	2.57 (1.22–5.40)	0.013
LGE lateral	1.37 (0.90–2.09)	0.145	1.07 (0.53–2.15)	0.847
LGE inferior	1.82 (1.18–2.80)	0.006	1.50 (0.75–3.00)	0.225
LGE septal	2.55 (1.77–3.83)	<0.001	1.78 (0.92–3.41)	0.084
LGE mass, g	1.04 (1.02–1.06)	0.001	1.01 (0.96–1.07)	0.578
LGE percentage, %	1.05 (1.02–1.09)	0.002	1.03 (0.98–1.09)	0.262
LGE extent (per 10% increase)	1.79 (1.25–2.57)	0.002	1.11 (0.52–2.38)	0.262
LGE distribution				
Linear	1.30 (0.85–2.00)	0.240	1.08 (0.54–2.17)	0.821
Patchy	2.93 (1.79–4.80)	<0.001	2.73 (1.29–5.80)	0.009
Diffuse	1.86 (0.45–7.71)	0.394	2.28 (0.30–17.30)	0.424
LGE pattern				
Epicardial	1.26 (0.82–1.95)	0.291	1.6 (0.84–3.07)	0.156
Midwall	2.39 (1.54–3.69)	<0.001	1.99 (0.99–4.00)	0.052
T2-weighted ratio mean	1.12 (0.84–1.48)	0.436	1.08 (0.70–1.67)	0.737
T2-weighted ratio abnormal (≥2.0)	2.14 (1.30–3.52)	0.003	2.82 (1.35–5.92)	0.006
ECV mean (per 10% increase)	2.09 (1.07–4.08)	0.031	3.93 (1.11–13.86)	0.034
ECV mean ≥35%	3.38 (1.43–7.97)	0.005	5.51 (1.01–30.14)	0.049

The following data for T2-weighted imaging and ECV were available: T2-weighted n = 467 (203 missing), ECV n = 179 (490 missing).

Abbreviations as in Tables 2 and 3.

FIGURE 2 Consort Diagram of Patient Enrollment



ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement.

symptoms and normal LV function. When these 119 patients were excluded, the robust associations of LGE presence and LGE extent (per 10%) with MACE persisted, and they corresponded to a 2-fold (HR: 2.02; p = 0.001) and a 69% (HR: 1.69; p = 0.005) increase in MACE, respectively. A septal location and a midwall pattern remained the features of highest risks (HR: 2.30 and 2.35; both p = 0.0001).

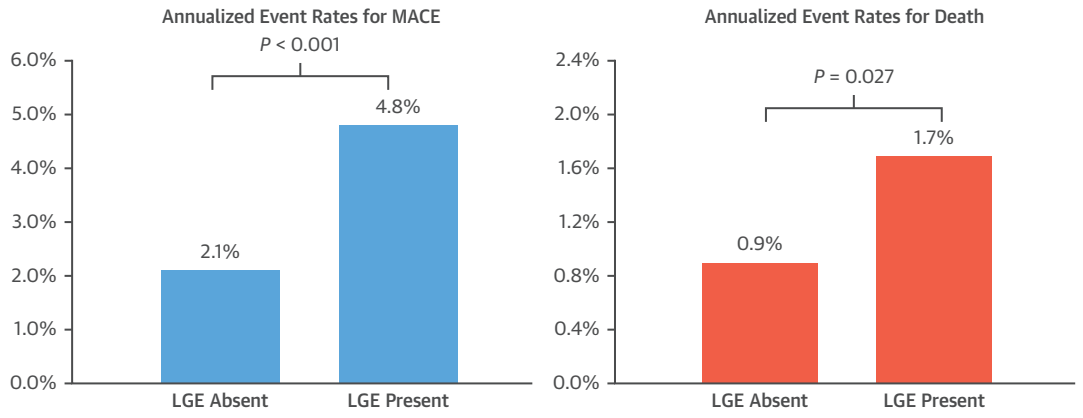
RISK RECLASSIFICATION AND NET RECLASSIFICATION IMPROVEMENT. Using a backward elimination regression strategy, a parsimonious set of multivariable predictors formed a clinical model that included patient age in years, body mass index (kg/m^2), right ventricular ejection fraction (RVEF) (%), and LVEF <40%. When LGE presence was added, the continuous NRI was 0.39 (95% CI: 0.10 to 0.67) with the proportion of events and nonevents correctly reclassified in 22.8% and 16.6% of the cases, respectively. The validity of the proportional-hazards assumption was tested valid for all variables in this model.

DISCUSSION

Diagnosis of acute myocarditis remains challenging due to a lack of clinical reference standard and the nonspecificities of presenting signs and symptoms and ECG findings. In experienced centers, CMR has become a routine clinical investigation; however, the current prognostic evidence of this approach is limited. Our consecutive cohort represents the largest effort to-date when patients were referred to undergo CMR for suspected myocarditis as the primary concern. We showed that key CMR variables of tissue characterization provide strong prognostic values in risk stratifying patients in this heterogeneous clinical setting.

Other studies had reported prognostic association of LGE but in more narrowed clinical settings. Grün et al. (3) studied 222 pre-selected endomyocardial biopsy-proven myocarditis patients with CMR and they observed that LGE was the strongest independent predictor of all-cause mortality in this high-risk cohort with moderate LV dysfunction. In another study of 58 pediatric patients with myocarditis, LVEF and LGE both showed independent association with outcome (20). However, the pediatric cohort generally has a more fulminant course of myocarditis (21) and such results might not extrapolate to an adult population. Other studies used CMR criteria for myocarditis for study inclusion and thus could not fully represent the diverse setting when CMR was the key noninvasive modality called upon to diagnose and prognosticate patient risk. Chopra et al. (22) assessed 112 patients with a CMR-based diagnosis of myocarditis, and reported that an infarct-like LGE pattern were more likely to show larger LGE extent, lower LVEF, lower RVEF, and a greater risk of MACE at a short-term follow-up of 16 months. Similarly, the study by Sanguineti et al. (23) included 203 patients with myocarditis based on CMR criteria and it showed that LVEF was a predictor for MACE in adjusted analysis, whereas LGE-based variables were not. Our study design targeted the more common practice setting when consecutive patients with suspected myocarditis were referred to CMR for diagnosis and risk stratification, regardless of any decision to perform EMB. In fact, EMB is no longer routinely performed in patients with suspected myocarditis in most centers given its high false negative rate in this clinical setting (4,5).

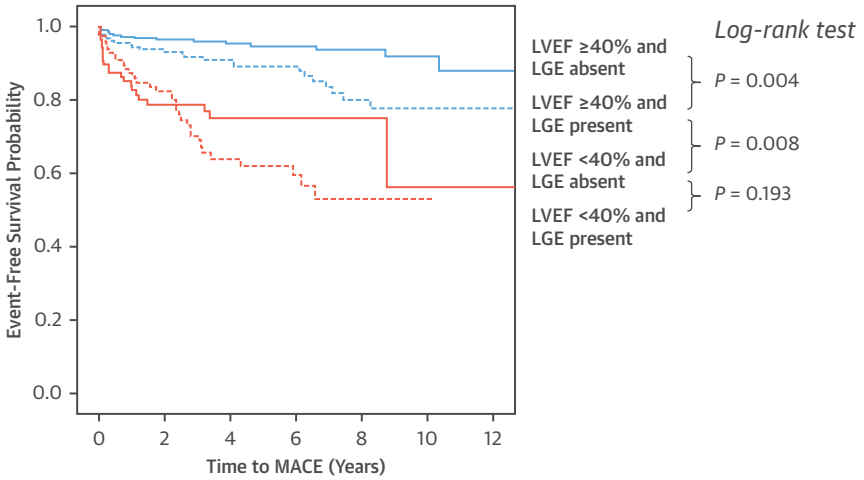
FIGURE 3 Annualized Event Rates Between LGE Presence and LGE Absence in Patients With Suspected Myocarditis



There are significant differences between the annualized event rates for MACE and death between patients with suspected myocarditis and LGE presence versus those without LGE. LGE = late gadolinium enhancement; MACE = major adverse cardiac event(s).

A typical epicardial or midwall LGE pattern has been associated with the diagnosis of myocarditis (24), but prognosis implications of myocardial patterns have not been reported. We showed that patients having midwall and septal LGE involvement showed a higher risk for MACE. This finding is consistent with the prior report from Mahrholdt et al. (25) who showed that LGE involvement of the septal

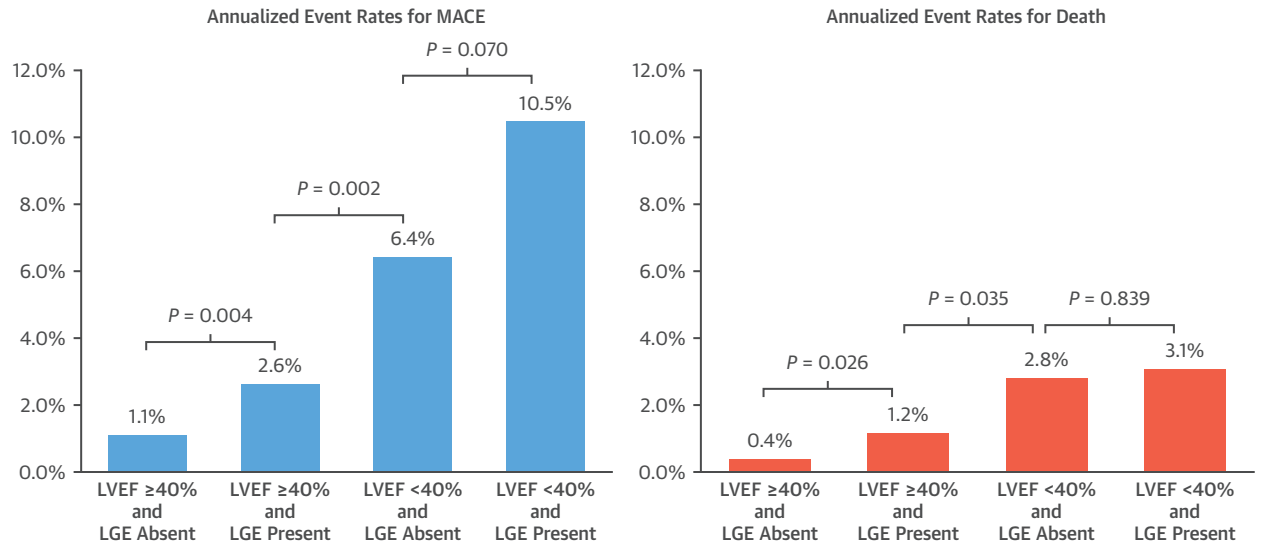
FIGURE 4 The Event-Free (MACE) Survival Probability Curve of Patients With Suspected Myocarditis and Combination of LGE Presence and LVEF Are Displayed



Patients at risk	670	480	329	236	117	43	21
LVEF ≥40% and LGE absent	289	223	155	111	64	28	14
LVEF ≥40% and LGE present	181	137	104	75	39	11	6
LVEF <40% and LGE absent	87	51	34	27	10	3	1
LVEF <40% and LGE present	113	69	36	23	4	1	0

Patients with LVEF ≥40% and LGE absence have a significantly better prognosis compared to those with LVEF ≥40% and LGE presence. However, patients with LVEF <40% and LGE absence or presence have the worst outcome compared to those with LVEF ≥40%. LVEF = left ventricular ejection fraction; other abbreviations as in Figures 1 and 3.

FIGURE 5 Annualized Event Rates Between LGE Presence and LGE Absence and LVEF in Patients With Suspected Myocarditis



There are significant differences between the annualized event rates for MACE and death between patients with suspected myocarditis and LVEF ≥40% with LGE presence versus those without LGE. In patients with suspected myocarditis and LVEF <40%, annualized event rates for MACE and death were not significantly different between patients with LGE present versus patients without LGE. Abbreviations as in Figures 1, 3, and 4.

wall was associated with infection from the more serious human herpesvirus 6 and persistent LV dysfunction, whereas LGE involvement of the lateral wall was associated with the more benign parvovirus B19 and better healing at follow-up. Schumm et al. (26) studied 405 patients with clinically suspected myocarditis and reported favorable prognosis in patients who had a normal CMR. The study by Schumm et al. (26) included patients with infiltrative diseases which take on a different natural history than patients with myocarditis. In comparison to their study, we confirmed the favorable outcomes of a normal CMR study in our larger study cohort of patients with a primary suspicion of myocarditis, but also observed robust prognostic value of LGE incremental to LVEF. We performed LGE quantification and observed that there is a role for quantitative analysis of LGE imaging in patients with suspected myocarditis. Finally, pericardial and pleural effusion detected by CMR, previously discussed as additional diagnostic criteria for myocarditis (27), are significant risk markers probably representing a more serious concurrent serositis.

T2-weighted imaging, a pulse sequence sensitive to regional or global increases of myocardial water (interstitial edema) that are known to be an integral part of the inflammatory response, is part of the Lake Louise criteria and is considered to help establish the diagnosis of myocarditis (6). We observed in our subgroup analysis that there is also an association of abnormal T2-weighted imaging with outcome. Because myocarditis is considered to be a diffuse disease with inflammation of the myocardium, recent

TABLE 5 Univariable Association of LGE Parameters for MACE Based on Acuteness of Presentation

	Acute Presentation (n = 350)		Subacute Presentation (n = 320)	
CMR Potential Predictors	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
LGE presence	1.97 (1.20–3.25)	0.008	2.43 (1.18–5.00)	0.016
LGE percentage	1.74 (1.18–2.58)	0.005	1.26 (0.45–3.53)	0.664
LGE location				
LGE anterior	1.42 (0.76–2.66)	0.275	2.09 (0.73–5.99)	0.169
LGE lateral	1.38 (0.83–2.28)	0.212	1.11 (0.50–2.49)	0.798
LGE inferior	1.80 (1.08–3.01)	0.024	1.59 (0.71–3.56)	0.258
LGE septal	2.49 (1.53–4.07)	<0.001	2.40 (1.16–4.95)	0.017
LGE distribution				
Linear	1.50 (0.90–2.49)	0.119	0.83 (0.36–1.94)	0.670
Patchy	1.77 (1.01–3.07)	0.044	3.86 (1.83–8.14)	<0.001
Diffuse	0.63 (0.09–4.58)	0.651	3.84 (0.52–28.25)	0.187
LGE pattern				
Epicardial	1.23 (0.74–2.06)	0.426	1.07 (0.46–2.48)	0.877
Midwall	2.15 (1.24–3.70)	0.006	2.88 (1.38–6.01)	0.005
Transmural	2.83 (0.69–11.61)	0.149	–	–

Abbreviations as in Tables 2 and 3.

trials using the newer approaches of native T1 mapping and ECV were shown to improve the diagnostic accuracy of myocarditis compared to the standard Lake Louise criteria (28). In other patient cohorts, such as sarcoid patients or systemic inflammatory disease patients (e.g., systemic lupus erythematosus) recent studies showed that mapping techniques and ECV were superior to other CMR features in detecting diseased patients (29,30). However, a challenge for the CMR community is to decipher whether such findings in myocarditis or other inflammatory diseases represent active inflammation or chronic fibrosis, or indeed both. In our subset analysis, ECV showed a significant association with MACE and death and might be of additional value for outcome prediction in patients with suspected myocarditis. However, to make definite conclusions, larger studies are needed to support these findings.

STUDY LIMITATIONS. First, our study has the limitations from a retrospective design without a strategic randomization to any specific therapy. Consequently, potential biases introduced by CMR findings to patient outcomes due to medical or procedural therapies exist. Second, assessing the clinical causes of patient deaths retrospectively is imprecise, so our study was not powered to inform regarding the association of CMR findings with cardiac or arrhythmic deaths. Third, early gadolinium enhancement (EGE) has inconsistent image quality and reproducibility is challenging for technical reasons (timing of image acquisition); therefore, EGE is not routinely used in many centers (31). Furthermore, EGE has lower accuracy than LGE and T2-weighted imaging in diagnosing myocarditis (31). Although EGE is described in the Lake Louise criteria (6), our CMR protocol did not include EGE imaging. Last, T2-weighted images are often affected by artifacts which may introduce inaccuracies to T2-weighted ratio. Further technical development of T2 mapping may be promising in scaling the severity of myocardial edema. Lastly, risk characteristics of our cohort were influenced by local use of CMR imaging in this clinical setting and this may constitute a source of referral bias.

CONCLUSIONS

CMR tissue characterization provides effective risk stratification in patients with suspected myocarditis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with suspected myocarditis, tissue characterization by CMR provides effective risk stratification incremental to key clinical markers including LV function. Patients with suspected myocarditis and a normal CMR study have a favorable outcome.

TRANSLATIONAL OUTLOOK: Future studies may identify genetic markers that predict the course of patients with suspected myocarditis and may help to develop new therapeutic strategies to treat the disease.

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