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ORIGINAL RESEARCH

Prognostic Cardiac Magnetic Resonance Markers of Left Ventricular Involvement in Arrhythmogenic Cardiomyopathy for Predicting Heart Failure Outcomes

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BACKGROUND: Left ventricular (LV) involvement is frequently observed in arrhythmogenic cardiomyopathy (ACM). We investigated the association of LV myocardial assessment using cardiac magnetic resonance (CMR) with clinical outcomes including heart failure (HF)-related events in ACM.

METHODS AND RESULTS: We retrospectively analyzed 60 patients with ACM between 2005 and 2020 according to the 2010 Task Force Criteria and assessed HF-related events (HF hospitalization, heart transplantation, and cardiac death) and ventricular tachycardia events. We analyzed CMR findings including late gadolinium enhancement (LGE) in all subjects and obtained mapping values (native T1, extracellular volume, and T2) on 30 (50%) patients out of them. Among the study population (mean age 49 years, 77% male), 41 (68%) patients had LV LGE. During a median follow-up of 34 months, there were 13 (22%) HF-related events, and 20 (30%) ventricular tachycardia events. Kaplan-Meier survival analysis revealed that HF-related events occurred only in patients with LV LGE (+) (versus LV LGE (-), log-rank P=0.006), and the events were not significantly different regarding right ventricular LGE (log-rank P>0.999). When categorized by median value for each mapping parameter, HF-related events occurred more in patients with higher native T1 (versus lower native T1, log-rank P=0.002), and higher T2 (versus lower T2, log-rank P=0.002), higher extracellular volume (versus lower extracellular volume, log-rank P=0.002). However, regarding ventricular tachycardia events, there were no significant differences according to these CMR markers.

CONCLUSIONS: LV myocardial assessment using CMR with LGE imaging and native T1, T2, and extracellular volume markers were significantly associated with HF-related event risk in patients with ACM.

Key Words: arrhythmogenic right ventricular cardiomyopathy ■ cardiac magnetic resonance ■ heart failure ■ late gadolinium enhancement ■ left ventricular involvement

Arrhythmogenic cardiomyopathy (ACM) is a genetic heart disease characterized by progressive fibro-fatty replacement of myocardium and arrhythmogenic features.[1] The Task Force Criteria revised in 2010 has been used to diagnose ACM, focusing primarily on right ventricular (RV) structural alterations and arrhythmogenic features.[2] However, there has been a growing body of evidence for left-sided involvement in ACM.[3] A recent report about autopsy findings in sudden cardiac death subjects revealed that 12% of these sudden

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CLINICAL PERSPECTIVE

What Is New?

- Left ventricular (LV) involvement is frequently seen in patients with arrhythmogenic cardiomyopathy (ACM) when analyzing cardiac magnetic resonance (CMR) images.
- The patients with ACM who experienced heart failure (HF)-related events (eg, HF hospitalization, heart transplantation, and cardiac death due to HF) tended to have more abnormalities in the LV on CMR images.
- The CMR features were the presence of late gadolinium enhancement, higher values of tissue mapping parameters such as native T1, extracellular volume) fraction, and T2; these parameters were analyzed in LV myocardium, and they were significantly correlated with more HF events in patients with ACM.

What Are the Clinical Implications?

- Advanced fibro-fatty replacement of LV myocardium accounts for more late gadolinium enhancement on CMR in ACM, but it was not associated with ventricular arrhythmia outcomes.
- Unlike ventricular arrhythmia events, the HF-related events occurred more in patients with ACM with LV late gadolinium enhancement and higher native T1, extracellular volume, and T2 values.
- CMR features including late gadolinium enhancement and mapping parameters for LV myocardium can be used in prediction for HF events in patients with ACM.

Nonstandard Abbreviations and Acronyms

ACM	arrhythmogenic cardiomyopathy
ECV	extracellular volume
ICD	implantable cardioverter-defibrillator
LGE	late gadolinium enhancement

cardiac death cases were diagnosed with ACM, 87% of them had histopathologic left ventricular (LV) involvement, and 17% were isolated LV disease.[4] Thus, the recent international expert report emphasized that the current classification of ACM includes the "biventricular disease phenotype" and the "left-dominant phenotype,"[5] and they proposed "Padua criteria" to upgrade the criteria for the entire spectrum of ACM.[6] In this context, there have been several reports which investigated the cardiovascular magnetic resonance (CMR) imaging features of the LV phenotype in ACM and the association with clinical outcomes.[7–9] However, most of these reports focused on arrhythmia-related outcomes and did not pay attention to heart failure (HF) outcomes. Recently, Zghaib et al showed that LV abnormalities on CMR were not associated with arrhythmic outcomes in patients with ACM.[10] Although LV involvement is known to be a poor prognostic factor in ACM,[11,12] there have been little data about HF outcomes assessed by CMR in these subjects. Moreover, there are limited data on the assessment of ACM using T1 and T2 mapping techniques, which are used widely for myocardial characterization in various cardiomyopathies. The present study aimed to assess LV involvement using CMR including mapping techniques and its clinical impact on adverse cardiovascular outcomes, especially on HF-related outcomes in patients presenting with ACM.

METHODS

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

Study Population and Clinical Diagnosis

We retrospectively investigated the patients with clinically diagnosed ACM who underwent CMR between March 2005 and June 2020 at a single tertiary university hospital. The ACM diagnosis was established as definite, borderline, or possible diagnosis according to the 2010 modified Task Force Criteria which were based on both imaging and non-imaging criteria.[2] In addition, we classified them in type "dominant-right/biventricular/ or dominant-left" according to the "Padua criteria" as previously reported.[6] The clinical data including patient information and outcomes were collected by electronic medical record. Even though the clinical characteristics met the Task Force Criteria for ACM, the subject was excluded when the CMR findings strongly suggested other pathology (eg, cardiac sarcoidosis). Finally, 60 patients with ACM were analyzed. Coronary angiography or coronary CT angiography was performed in 53 (88%) subjects and treadmill test was done in 5 (8%) subjects for evaluation of ischemic heart disease. All data were analyzed by 2 independent expert cardiologists (K.H.C., J.O.). The present study (CArdiovascular Mri Union in Severance, CAMUS-001) was approved by the Institutional Review Board of the Yonsei University Health System (4-2019-0764). Given the retrospective nature of this study, written informed consent was waived per recommendation of our institution's institutional review board for this study.

Electrocardiographic and Transthoracic Echocardiographic Data

All subjects underwent an ECG and we analyzed the baseline echocardiography to investigate the features

suggestive of classic ACM and distinctive features LV involvement, as previously described.[2,12–14] In addition to the analysis of conventional ECG parameters, the following ECG features were investigated: separated duration of the QRS complex in right precordial leads (V$_{1-3}$) and left precordial leads (V$_{4-6}$); T-wave inversion in right precordial leads (V$_{1-3}$), left precordial leads (V$_{4-6}$); epsilon waves in right precordial leads (V$_{1-3}$), defined as reproducible low amplitude signals between the end of the QRS complex and the onset of the T wave; terminal activation duration (TAD) of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V$_1$, V$_2$, or V$_3$, in the absence of complete right bundle-branch block (RBBB); and RBBB. All these parameters were analyzed by the two expert cardiologists and were investigated for clinical diagnosis of ACM and study analysis.

All subjects underwent transthoracic echocardiography (Vivid 7, GE Medical Systems, Milwaukee, WI, USA). Regional wall motion abnormalities of the RV (akinesia, dyskinesia, or aneurysm) were documented, and chamber sizes, ejection fraction of LV, fractional area change of RV, and E velocity over mitral tissue Doppler velocity (e') ratio (E/e') were measured.

CMR Protocol and Image Analysis
CMR was performed using a 3-T MR scanner (Magnetom Trio Tim, Siemens Healthcare, Erlangen, Germany) with a six-channel anterior body matrix coil and a spine matrix coil array. Cine images were acquired in the short-axis (SA) plane orientation covering both ventricles by using a retrospectively ECG-gated balanced steady-state free precession (TrueFISP) sequence. Cardiac localization was achieved using a steady-state free-precession sequence under ECG gating.

Native T1 mapping images were acquired in three SA planes (basal, mid, and apical LV) by using a modified look-locker inversion-recovery (MOLLI) sequence at the end-expiratory phase with "5(3)3" scheme. A nonselective inversion pulse, a TrueFISP single-shot readout sequence in the mid-diastolic phase, was employed. Fully automated, non-rigid motion correction was applied to register individual T1 images before inline T1 fitting was performed using a mono-exponential three-parameter fit.

After T1 mapping, T2 mapping images were acquired before contrast injection using a T2-prepared single-shot TrueFISP sequence, along the same planes as those used for T1 mapping. T2 pixel maps were generated by fitting pixel intensities onto a two-parameter mono-exponential signal model after automatic in-plane non-rigid motion correction.

Post-contrast T1 mapping images were acquired at least 15 minutes after injection along the same

three SA planes as those used for pre-T1 mapping. The "4(1)3(1)2" scheme using 3 inversion pulses were used for post-contrast T1 mapping. Hematocrit values were acquired on the same day before CMR imaging. Native and post T1 values of the LV blood pool were measured using a circular region of interest larger than 10 mm^2, avoiding the papillary muscle.

Extracellular volume (ECV) fraction was calculated using the native and post-contrast T1 values of the LV myocardium and blood pool with the following equation:

$$ECV(\%) = [(\Delta R1 \text{ of myocardium}/\Delta R1 \text{ of LV blood pool})] \times (1 - \text{Hematocrit}) \times 100$$

$$R1 = 1/T1, \ \Delta R1 = (\text{Post} - \text{contrast R1} - \text{Pre} - \text{contrast R1})$$

The global T1, T2, and ECV were measured using the mean values of 16 segments of LV for the analysis. The edges of the myocardium were excluded by applying a 10% offset to minimize the partial volume artifact.

Late gadolinium enhancement (LGE) magnetic resonance images were acquired 10 minutes after contrast injection of a 0.2-mmol/kg intravenous dose of a gadolinium contrast agent (Dotarem, Guerbet, France) using a magnitude- and phase-sensitive inversion-recovery-prepared TrueFISP sequence, with the inversion time adjusted to null, thus representing the normal myocardium. These LGE images were obtained along the same axis plane covering the whole LV. The appropriate inversion time before LGE MR imaging was determined using the fast low-angle shot sequence with varying inversion times (from 150 to 650 ms to null). The quantification of LGE was determined using a signal threshold versus reference mean method with a signal intensity threshold of 5 standard deviations (SD) above that of a normal-appearing myocardium. For the measurement of native T1 values LGE (-) area, T1 values were measured manually in a well-defined region of interest in the mid-ventricle, avoiding the LGE (+) area. T1 dispersion was calculated as the SD of native T1 in all segments as previously described.[15] Our previous study showed the normal reference value measured by the same MRI protocol for native T1, T2, and ECV as 1205.4±37.4 ms, 48.6±5.6 ms, and 25.7%±2.4%, respectively.[16] The native T1, T2, and ECV measurements were done only in a subpopulation 30/60 (50%) subjects because these methods were not available before 2011 in our institution.

LV fat infiltration was identified by a high signal intensity with india-ink etching artifact cine image,[17,18] and LGE on both ventricles were visually identified by two radiologists.

For functional analysis, SA cine images were transferred to the software (Circle Cardiovascular Imaging

Inc., Calgary, Alberta, Canada). Endocardial borders of the RV and endocardial and epicardial borders of the LV wall on end-diastolic and end-systolic images were delineated automatically. Some correction was done if needed. Both ventricular volume and systolic functions were calculated.

All patients with sub-endocardial or transmural involvement patterns of LV LGE on CMR and patients with a history of percutaneous coronary artery intervention were examined again to exclude ischemic cardiomyopathy. The reference values of each mapping parameter in healthy subjects using this protocol were described previously.[16] CMR images were analyzed by two expert radiologists (Y.J.H. and Y.J.K.) who were blinded to baseline patient information and clinical outcomes. When diagnosing ACM using CMR with imaging criteria of Task Force Criteria, the diagnosis was based on analyzing the regional wall motion abnormality on the cine image, RV volume, and ejection fraction, not LGE or mapping data.

Definitions of Clinical Manifestations and Events During Follow-Up

Patients with a final diagnosis of ACM underwent follow-up for HF-related events (a composite of HF hospitalization, heart transplantation, and cardiac death due to pump failure), and ventricular tachycardia (VT) events.

HF, which is one of the initial manifestation types, was defined as the presence of symptoms or signs (dyspnea, fatigue, peripheral edema, or pulmonary edema on chest x-ray) suggestive of volume overload with identified structural/functional cardiac abnormalities, as the ACC/AHA guideline suggested.[19] HF hospitalization event was defined as an unexpected admission for worsening symptoms or signs of HF which needed treatment with intravenous diuretics, vasodilators, or inotropic agents after diagnosis of ACM. Heart transplantation was regarded as a HF-related event if the transplantation was performed because of the patient's end-stage HF status. Cardiac death due to pump failure was defined as death occurring with worsening symptoms of HF lasting at least 24 hours without other evidence of identified life-threatening arrhythmia or acute myocardial infarction.

VT event during follow-up is a composite of documented sustained VT and VT requiring appropriate therapy from an implantable cardioverter-defibrillator (ICD). Sustained VT was defined as sustained ventricular beats with >100 bpm for >30 seconds documented by holter monitoring, unexpected hospital visit, or regular ICD interrogation data. Appropriate ICD therapy (anti-tachycardia pacing or shock) was also regarded as VT event during follow-up and was identified from ICD interrogation data. Sudden cardiac death, one of

the initial manifestations, was defined as resuscitated unexpected cardiac arrest with witnessed prodromal symptoms lasting <24 hours.

Endomyocardial Biopsy and Genetic Analysis

Among the study population, we performed endomyocardial biopsies in 23 (38%) subjects. In addition, the study population was tested using a next-generation sequencing panel from 12 (20%) subjects to determine whether they had genetic mutations related to ACM. The determination of pathogenicity (pathogenic or likely-pathogenic) for the variants was based on the American College of Medical Genetics and Genomics guideline.[20]

Statistical Analysis

Continuous variables were presented as mean±SD or median (interquartile range [IQR]) and categorical variables were expressed as a percentage of the group total. Because we analyzed a small sample of patients, comparisons between groups were made using the permutation test versions of the t-test for continuous variables and Fisher's exact test for categorical variables. Variables that were not normally distributed were log-transformed for analysis if needed (eg, N-terminal prohormone brain natriuretic peptide). Survival rates were estimated using the Kaplan-Meier survival method, and differences were analyzed using a log-rank test. Mapping values (native T1, T2, ECV) of the variables in the Kaplan-Meier analysis were divided based on the median value of each variable (higher group versus lower group). All statistical tests were two-tailed, and 95% CI were calculated. All statistical analyses were performed using R software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria) with "survminer" and "coin" packages.

RESULTS

Baseline Clinical Characteristics

The baseline characteristics of study patients are summarized in Table 1. Of the 60 patients who were finally analyzed, 33 (55%) patients were categorized as definite ACM, eight (13%) as borderline ACM, and 19 (32%) as possible ACM. The mean age at diagnosis was 49±18 years and 46 (77%) were male. Five patients (8%) presented with sudden cardiac death, 24 (40%) patients presented with VT, and 17 (28%) patients had symptoms or signs of HF at the time of diagnosis. Twenty-three (38%) patients underwent ICD implantation, and the purpose of ICD implantation was mostly for secondary prevention (91%). To characterize

Table 1.   Baseline Characteristics in the Total Patient Group Regarding HF Events

	Total (n=60)	HF event (-) (n=47)	HF event (+) (n=13)	P value
Clinical demographics				
Age at diagnosis, y	49±18	47±17	49±18	0.185
Male sex, n (%)	46 (77)	36 (77)	10 (77)	>0.999
Body surface area, m²	1.8±0.2	1.8±0.2	1.7±0.2	0.193
Hypertension, n (%)	16 (27)	12 (26)	2 (15)	0.731
Diabetes, n (%)	7 (12)	5 (11)	2 (15)	0.639
CAD, n (%)	4 (7)	3 (6)	1 (8)	>0.999
Atrial fibrillation, n (%)	13 (22)	9 (19)	3 (31)	0.450
Initial manifestation, n (%)				
Sudden cardiac death	5 (8)	5 (11)	0 (0)	0.575
VT	24 (40)	21 (45)	3 (23)	0.210
HF	17 (28)	9 (19)	8 (62)	0.005
Task Force criteria, n (%)				
Definite	33 (55)	24 (51)	9 (69)	0.062
Borderline	8 (13)	5 (11)	3 (23)	
Possible	19 (32)	18 (38)	1 (8)	
Medications, n (%)				
Beta-blockers	35 (58)	29 (62)	6 (46)	0.354
Anti-arrhythmics	15 (25)	12 (26)	3 (23)	>0.999
ACEi/ARBs	33 (55)	23 (49)	10 (77)	0.115
MRAs	21 (35)	14 (30)	7 (54)	0.187
Loop diuretics	24 (40)	12 (26)	12 (92)	<0.001
VT management, n (%)				
ICD	23 (38)	18 (38)	5 (39)	>0.999
RFA	6 (10)	5 (11)	1 (8)	>0.999

Data are presented as mean±standard deviation or number (percentage). HF event is defined as a composite of HF hospitalization, heart transplantation, and cardiac death during follow-up period. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CAD, coronary artery disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; RFA, radiofrequency ablation, and VT, ventricular tachycardia.

the clinical profile of patients with and without HF-related events, we divided the study population into two groups based on the occurrence of HF-related events during the follow-up (Table 1). Notably, in terms of medication, patients who had HF-related events were more likely to be treated with loop diuretics (92% versus 26%, P<0.001).

Baseline Laboratory Data, ECG, and Echocardiographic Findings

Baseline laboratory, ECG, and echocardiographic data are shown in Table 2. Patients with HF-related events had significantly lower hemoglobin and serum sodium levels, and significantly higher N-terminal prohormone brain natriuretic peptide levels. We analyzed baseline ECGs as previously described, but we found no statistically different ECG findings between the two groups. Patients with HF-related events had significantly lower left ventricular ejection fraction (LVEF) as assessed by echocardiography, compared with patients without HF-related events (39%±15% versus 50%±14%, P=0.017).

CMR Imaging Findings

Table 3 shows the functional, structural, and qualitative/quantitative tissue characteristics examined by CMR. Patients who had HF-related events had lower LVEF, as assessed by CMR compared with patients without HF-related events (35%±17% versus 48%±13%, P=0.009), and right ventricular ejection fraction (RVEF) was not significantly different (32%±13% versus 40%±13%, P=0.077). Forty-one patients (68%) had LV LGE and 36 (60%) patients had RV LGE. There was no significant difference in the presence of RV LGE in the two groups, but LV LGE was more common in patients with HF-related events than patients without HF-related events (100% versus 60%, P=0.005). The presence of LV fatty infiltration was not significantly different between the two groups (62% versus 53%, P=0.755). Based on these CMR markers and other clinical findings, we classified these subjects according to the "Padua criteria." Notably, there was no subject with dominant-right type among patients who had HF-related events. We also measured quantitative mapping parameters, including native T1, ECV, and T2 values in available patients (n=30, Table 3). In this analysis, patients with HF-related events had higher native T1, LGE-free native T1, ECV, and T2 values. According to the presence of LV LGE (Table 4 and 5), the patients with LV LGE had lower LVEF than those without LGE, which was in line with the recent observations that LV LGE is related to LV systolic dysfunction.[5,7] In addition, native T1 values, dispersion of native T1, ECV fraction, and T2 values were significantly increased in patients with LV LGE compared with patients without LV LGE (Table 5).

Genetic Analysis, ACM Phenotype, and Mapping Values: Supplemental Analysis

Genetic analysis revealed that 4 out of 12 patients had pathogenic or likely pathogenic ACM-related variants. Table S1 shows these subjects with ACM-related genetic mutations, their phenotypes, and mapping values. The results cannot show statistical significance due to the small number of samples, but we observed that the native T1, ECV, and T2 values were higher in patients with DSP/TMEM43 mutation (biventricular type) than those with PKP2 mutation (dominant-right type).

Table 2. Laboratory, ECG, and Echocardiographic Findings According to HF Events

	HF event (-) (n=47)	HF event (+) (n=13)	P value
Laboratory data			
Hematocrit, %	43.6±5.1	39.4±5.5	0.015
BUN, mg/dL	15.7±7.6	17.5±7.5	0.470
eGFR, mL/min per 1.73 m^2	83±13	81±15	0.730
Serum sodium, mEq/L	141±2	137±5	<0.001
NT-proBNP, pg/mL [IQR]	151 [83; 1047]	1150 [951; 4090]	<0.001
Log (NT-proBNP)	2.3±0.8	3.2±0.5	<0.001
ECG			
RBBB, n (%)	14 (30)	4 (31)	>0.999
QTc interval, ms	454±34	468±35	0.200
TWI (V$_{1-3}$), n (%)	27 (57)	5 (39)	0.347
TWI (V$_{4-6}$), n (%)	19 (40)	7 (54)	0.529
Epsilon wave (V$_{1-3}$), n (%)	6 (13)	4 (31)	0.201
TAD (V$_{1-3}$), n (%)	13 (28)	7 (54)	0.101
Echocardiogram			
RV regional dyskinesia/ aneurysm, n (%)	34 (72)	8 (62)	0.504
RV FAC, %	34±12	76±9	0.088
RV FAC ≤35%, n (%)	25 (53)	11 (85)	0.056
LVEF, %	50±14	39±15	0.017
LVEF ≤40%, n (%)	12 (26)	7 (54)	0.089
LAVI, mL/m^2	28±17	38±19	0.049
E/e'	11±7	18±8	0.009

BUN indicates blood urea nitrogen; E/e', early diastolic mitral inflow/early diastolic mitral annular tissue velocity; eGFR, estimated glomerular filtration rate; IQR, interquartile range; HF, heart failure; LAVI, left atrium volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RBBB, right bundle-branch block; RV, right ventricular; RV FAC, right ventricular fractional area change; TAD, terminal activation delay; and TWI, T-wave inversion.

Table 3. Cardiac Magnetic Resonance Findings According to HF Events

	HF Event (-) (n=47)	HF Event (+) (n=13)	P value
Functional and structural assessment			
LVEF, %	48±13	35±17	0.009
LVEF ≤40%, n (%)	13 (28)	7 (70)	0.025
LVEDVi, mL/m^2	96±32	106±17	0.294
RVEF, %	40±13	32±13	0.077
RVEF ≤35%, n (%)	16 (35)	5 (50)	0.476
RVEDVi, mL/m^2	130±49	166±62	0.046
Tissue characterization			
RV LGE, n (%)	28 (60)	8 (62)	>0.999
LV LGE, n (%)	28 (60)	13 (100)	0.005
LV LGE amount, % [IQR] (n=36)	16 [8; 31]	21 [13; 40]	0.055
RV fatty infiltration, n (%)	9 (19)	2 (15)	>0.999
LV fatty infiltration, n (%)	25 (53)	8 (62)	0.755
Padua criteria, n (%)			
Dominant-right	12 (26)	0 (0)	0.074
Biventricular	34 (72)	12 (92)	
Dominant-left (possible)	1 (2)	1 (8)	
Quantitative parameters (n=30)			
Native T1 value, ms	1291±68	1433±69	<0.001
T1 dispersion, ms	133±49	135±32	0.910
LGE-free T1 value, ms	1274±57	1382±75	<0.001
ECV fraction, %	29.6±4.7	40.9±6.4	<0.001
T2 value, ms	50.7±3.7	58.2±3.7	<0.001

ECV indicates extracellular volume, HF, heart failure; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVi, indexed LV end-diastolic volume; LVEF, left ventricular ejection fraction; RV, right ventricular; RVEDVi, indexed RV end-diastolic volume; and RVEF, RV ejection fraction.

Clinical Outcomes

During the median follow-up period of 34 months (IQR, 15–63 months), there was a total of 13 (22%) HF-related events and a total of 20 (33%) VT events (Table 5). All heart transplantations (7%) were performed in patients with end-stage HF, and one cardiac death (2%) event was also related to HF. Among 13 HF-related events, 9 (69%) were re-hospitalization for HF, while the other 4 (31%) were the first HF-related events for each. All HF-related events occurred in patients with LV LGE (Figure 1A) (log-rank P=0.0055). Furthermore, there was no significant difference in the rate of HF-related events in patients with and without RV LGE (Figure 1B) (log-rank P>0.999). According to the measurable CMR parameters for the systolic function of each ventricle, HF-related events more occurred in patients with reduced LVEF (Figure 1C, log-rank P=0.0014), but the events were not different regarding RVEF (Figure 1D).

We also analyzed the clinical outcomes using mapping parameters in the measurable subgroup. Since the mapping value of the subjects in this study was higher than the normal reference value (Native T1: 1205.4±37.4 ms, ECV: 25.7±2.4%, T2: 48.6±5.6 ms) measured by the same MRI protocol as our study,[16] the values of the variables in the Kaplan-Meier survival analysis for relative comparative analysis were divided based on the median value of each variable. At first, we divided the patients into two groups according to the median value of each native T1 (1308ms), ECV fraction (30.2%), and T2 value (52.5ms) (higher group versus lower group) for analysis. Interestingly, HF-related events occurred more in subjects with higher native T1, T2, and ECV groups (Figure 2). In addition, similar trends were observed when analyzing HF-related events with LGE or mapping parameters including T1, T2, and ECV and LV dysfunction according to LVEF measured by CMR (Figure S1).

Table 4. Clinical Characteristics According to LV LGE

Clinical variable	LV LGE (-) (n=19)	LV LGE (+) (n=41)	P value
Clinical demographics			
Age at diagnosis, y	46±16	50±19	0.486
Male sex, n (%)	15 (79)	31 (74)	>0.999
Body surface area, m²	1.8±0.2	1.8±0.2	0.885
Hypertension, n (%)	3 (16)	13 (32)	0.229
Diabetes, n (%)	1 (5)	6 (15)	0.414
CAD, n (%)	1 (5)	3 78)	>0.999
Atrial fibrillation, n (%)	4 (21)	9 (22)	>0.999
Initial manifestation, n (%)			
Sudden cardiac death	4 (21)	1 (2)	0.031
VT	9 (47)	15 (37)	0.572
HF	2 (11)	15 (37)	0.063
Others	4 (21)	10 (24)	

CAD indicates coronary artery disease; HF, heart failure; LV LGE, left ventricular late gadolinium enhancement; and VT, ventricular tachycardia.

Figure 3 shows representative cases of ACM with and without LV involvement as assessed by CMR. However, regarding VT events, there were no significant differences according to LGE in both ventricles, native T1, or T2 values (Figure S2).

DISCUSSION

The principal findings of the current study were as follows: (1) patients with LV LGE had more HF-related events and (2) higher native T1, T2, and ECV values could predict a higher risk of HF-related events in patients with ACM.

Clinical Outcomes According to CMR Features in ACM

Although the LGE degree varies between studies, there are LV scars with LGE in a majority (60%–70%) of patients with ACM.[7] Abnormal CMR findings, including LGE in the LV and/or RV, have been reported to be associated with ventricular arrhythmic events.[9,21] However, the most recent study showed that typically manifested LV abnormalities on CMR were not associated with arrhythmic outcomes in patients with ACM,[10] which is a consistent finding of our results. Our finding could be supported by a recent study of DSP cardiomyopathy (one subtype of ACM) that showed the LV involvement including LV LGE was also not related to VT events.[22] Considering the nature of ACM, a heterogeneous disease, it is thought that the genetic backgrounds and clinical courses of each study may be different. Nevertheless, it is meaningful that we showed that CMR markers (LGE, native T1, ECV, and T2 mapping) were associated with HF-related outcomes in patients with ACM.

Table 5. Cardiac Magnetic Resonance Findings According to LV LGE

	LV LGE (-) (n=19)	LV LGE (+) (n=41)	P value
Functional and structural assessment			
LVEF, %	51±9	43±16	0.032
LVEF ≤ 40%, n (%)	2 (11)	96 (49)	0.007
RVEF, %	42±13	36±13	0.094
RVEF ≤ 35%, n (%)	4 (21)	17 (46)	0.086
LVEDVi, mL/m²	84±22	105±31	0.013
RVEDVi, mL/m²	127±55	142±52	0.440
Quantitative parameters (n=30)			
Native T1 value, ms	1276±65	1352±92	0.023
T1 dispersion, ms	96±30	153±39	<0.001
LGE-free T1 value, ms	1276±65	1307±81	0.279
ECV fraction, %	27.5±3.1	35.0±7.1	0.002
T2 value, ms	49.7±2.9	54.0±5.1	0.016
LV LGE pattern, n (%)			
Subendocardial	…	8 (20)	…
Midmural	…	7 (17)	…
Subepicardial	…	32 (76)	…
Transmural	…	15 (37)	…
Clinical events, n (%)			
Cardiac death	0 (0)	1 (2)	>0.999
Heart transplant	0 (0)	4 (10)	0.297
Heart failure hospitalization	0 (0)	13 (32)	0.005
Ventricular arrhythmia events	8 (42)	12 (29)	0.384
Sudden cardiac death	0 (0)	0 (0)	>0.999
Sustained VT	3 (16)	11 (39)	0.414
Appropriate ICD therapy	7 (37)	6 (15)	0.089
All adverse cardiovascular events	8 (42)	21 (51)	0.585

ECV indicates extracellular volume, ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVi, indexed LV end-diastolic volume; LVEF, left ventricular ejection fraction; RV, right ventricular; RVEDVi, indexed RV end-diastolic volume; RVEF, RV ejection fraction; and VT, ventricular tachycardia.

CMR Mapping Techniques and Tissue Characterization in ACM

We analyzed by using mapping techniques on CMR in available patients. Native T1 mapping is a promising technique for detection of earlier stages of cardiomyopathy and quantitative measurement of myocardial change.[23] A recent brief report showed that native T1 values were higher in patients with ACM than control subjects, but it did not show any relationship with clinical outcomes.[15]

Together with native T1, ECV also represents diffuse myocardial fibrosis.[24] In ACM, ECV expansion occurs
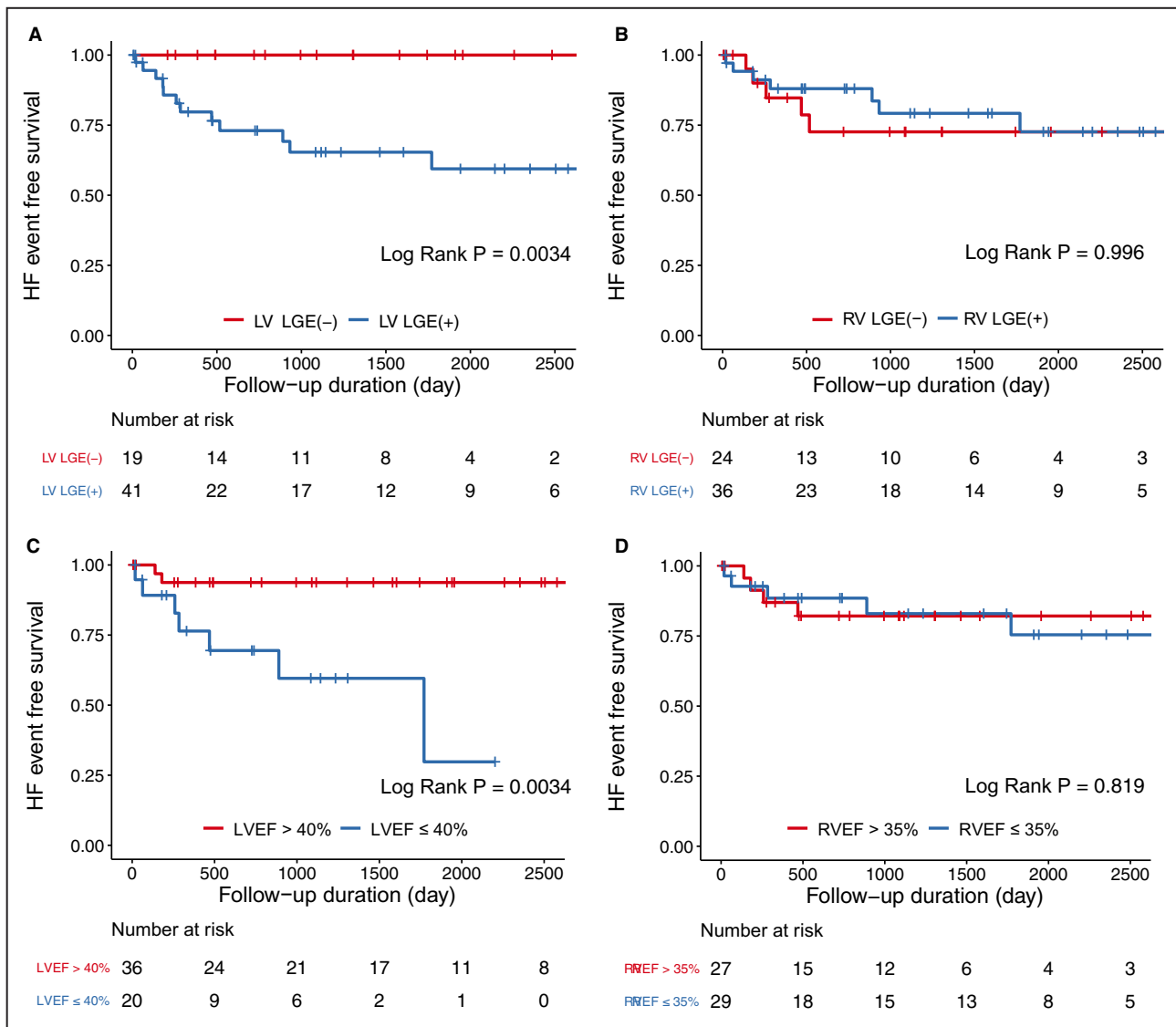
Figure 1. Survival curves categorized by LGE and ejection fraction for each ventricle.
Kaplan-Meier survival curves for heart failure-related events according to the presence of late gadolinium enhancement (LGE) in the LV (**A**), and in the RV (**B**), and ejection fraction of the LV (**C**), and the RV (**D**). EF indicates ejection fraction HF, heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; RV, right ventricle; RVEF, right ventricular ejection fraction.

because fibro-fatty tissue deposits in the extracellular interstitium. Our results showed that CMR-derived ECV, as well as native T1, value could have a prognostic value for the prediction of clinical outcomes in patients with ACM.

However, native T1 and ECV have some limitations in ACM. The lowering of T1 by fat components can underestimate myocardial fibrosis in the fibro-fatty area of the myocardium. For this reason, the previous study focused on the diagnostic value of the dispersion of native T1 in ACM.[15] Fat itself also can underestimate CMR-derived ECV because fat had less gadolinium enhancement than fibrosis.[25] Nevertheless, we showed that ECV and T1 measured in the LV myocardium were related to clinical outcomes in patients with ACM.

In the group with HF-related events, the T2 value was higher than that in the no-event group. An elevated T2 value is a well-known marker of myocardial edema and inflammation.[26–28] Along with T1 and ECV, our results indicated that high T2 value could also be associated with HF-related events in patients with ACM. We thought that the elevated T2 value in patients who experienced the HF-related events was attributed to the inflammation as many studies have reported inflammatory infiltration in ACM.[29]

The recent studies have shown that ACM with DSP mutations is more associated with LV involvement than traditional ACM (particularly with PKP2 mutations),[30] and PKP2 genotype carriers are more arrhythmic than DSC2/DSG2/DSP or gene-negative carrier status,
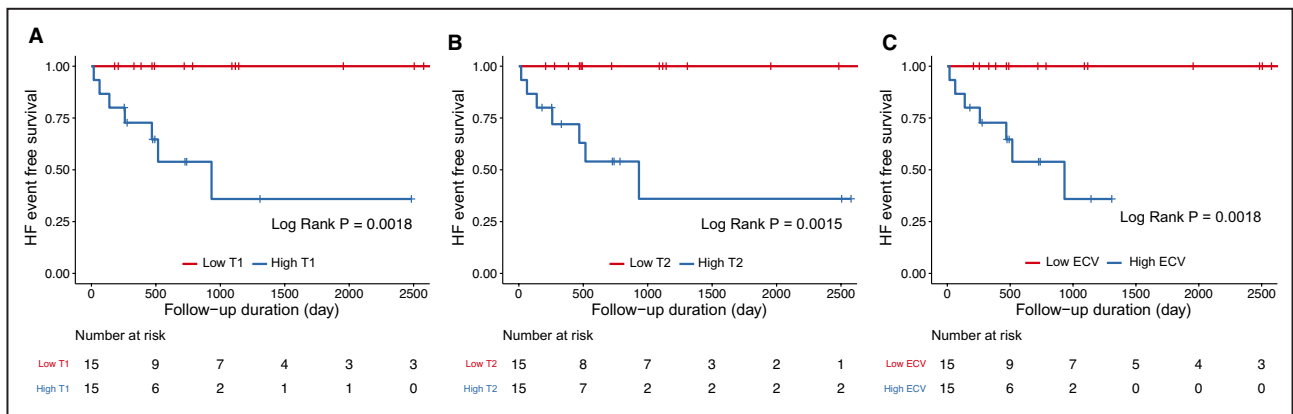
Figure 2. Survival curves categorized by T1, T2, and ECV.
The survival curves the events according to native T1 mapping value (**A**) (high vs low, cut-off value: 1308 ms, as a median value), T2 mapping values (**B**) (high vs low, cut-off value: 52.5 ms, as a median value), and extracellular volume (ECV) fraction (**C**) (high vs low, cut-off value: 30.2%, as a median value). HF indicates heart failure.

whereas reduced LVEF was mostly seen among DSC2/DSG2/DSP carriers.[31] But these studies did not show any comparisons in CMR mapping values between DSP versus PKP2 ACM. For the first time, we found a patient with DSP mutation had high mapping values than those with PKP2 mutation as far as we know, and it can trigger further studies in the future.

From the present results, we showed that LGE, native T1, ECV, and T2 values measured by CMR were associated with HF-related events in patients with ACM. ACM had long been recognized as a disease of the right side of the heart. It is not completely possible to distinguish whether the hospitalization for HF is due to RV or LV abnormality, but given
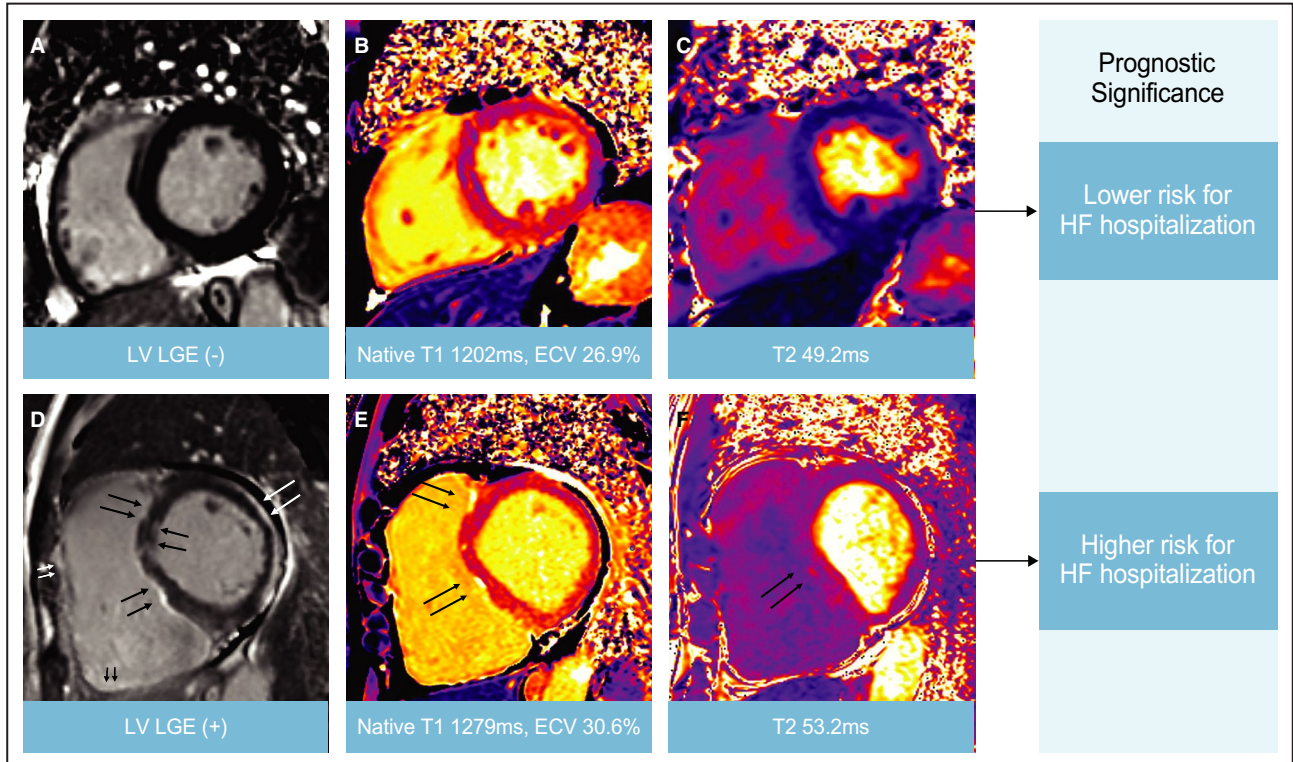

Figure 3. LV LGE and tissue characteristics on CMR in patients with ACM.
The prognostic significance of LV late gadolinium enhancement (LGE) and mapping parameters on cardiac magnetic resonance (CMR) in patients with arrhythmogenic cardiomyopathy (ACM). A 66-year-old male presented with ventricular tachycardia (**A** through **C**), and a 54-year-old male presented with heart failure (**D** through **F**). Arrows (black, white) indicate focal LGEs. HF indicates heart failure; LV, left ventricular.

that ACM is a biventricular disease, it is expected that the importance of understanding the characteristics of the LV myocardium will be increasingly emphasized.

Study Limitations

The main limitation of this study was the small study population. Especially, mapping values were obtained in half of the study population (50%). Due to the variability of CMR protocol in each participant, some portions of CMR data were impossible to analyze including the mapping parameters. In fact, the novel mapping techniques were not available for routine use before 2011 in our institution. Since the study was conducted in such a small number of patients, the results based on the analysis with mapping parameters are not conclusive; however, we suggest that they can be hypothesis-generating. Also, the lack of genetic testing results is another important limitation of our research. We could obtain a better understanding of ACM by combining CMR data if we performed genetic tests for all subjects. For this reason, subjects classified by the Padua criteria as dominant-left (possible) in the present results lack the genetic basis to be classified as definite dominant-left subtype. However, we found an interesting signal for the association of the mapping parameters with different genetic mutations in ACM. Finally, we did not confirm ACM by cardiac biopsy in all subjects. We performed endomyocardial biopsies in just 23 patients. However, in clinical practice, performing a biopsy in ACM is challenging considering the low yield of positive pathologic results. Because of these limitations, findings of LV LGE and elevated T1, T2 values in LV myocardium certainly raise significant concern for the presence of myocarditis and/or cardiac sarcoidosis in the study population. Nevertheless, the present study investigated the clinical significance of CMR findings in patients with ACM satisfying the current diagnostic criteria, so it has significant implications in this population.

CONCLUSIONS

The assessment of LV involvement using CMR with LGE imaging is now crucial in patients with clinically diagnosed ACM according to the 2010 Task Force Criteria. From the results of our study, we have shown that the presence of LGE in LV myocardium and higher native T1, ECV, and T2 values measured by CMR were associated with more HF-related events in patients with ACM. Further research is needed to confirm that these LV myocardial characteristics from CMR are associated with the clinical outcomes in this patient population.

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SUPPLEMENTAL MATERIAL

Table S1. Gene analysis, ACMG classification and mapping values of genetic ACM patients.

Age/sex	Variant	Padua criteria	LGE RV/LV	Native T1 (ms)	T2 (ms)	ECV (%)
29/ Male	PKP2 (P)	RV	-/-	1216.9	24.5	50.6
30/ Male	PKP2 (LP), BAG3 (LP)	RV	+/-	1342	30.3	49.7
72/ Male	DSP (P)	Biventricular	+/+	1435.6	42.1	57.9
52/ Male	TMEM43 (LP)	Biventricular	+/+	1357	38.9	52.8

ACM, arrhythmogenic cardiomyopathy; ACMG, American College of Medical Genetics and Genomics guideline; BAG3, Bcl2-associated athanogene 3; DSP, desmoplakin; ECV, extracellular volume fraction; LGE, late gadolinium enhancement; LP, likely pathogenic; LV, left ventricle; P, pathogenic; PKP2, plakophilin-2; RV, right ventricle; TMEM43, transmembrane Protein 43.

Figure S1. Survival Curves for heart failure-related events categorized by LGE, native T1, T2, and ECV in addition to CMR LVEF.
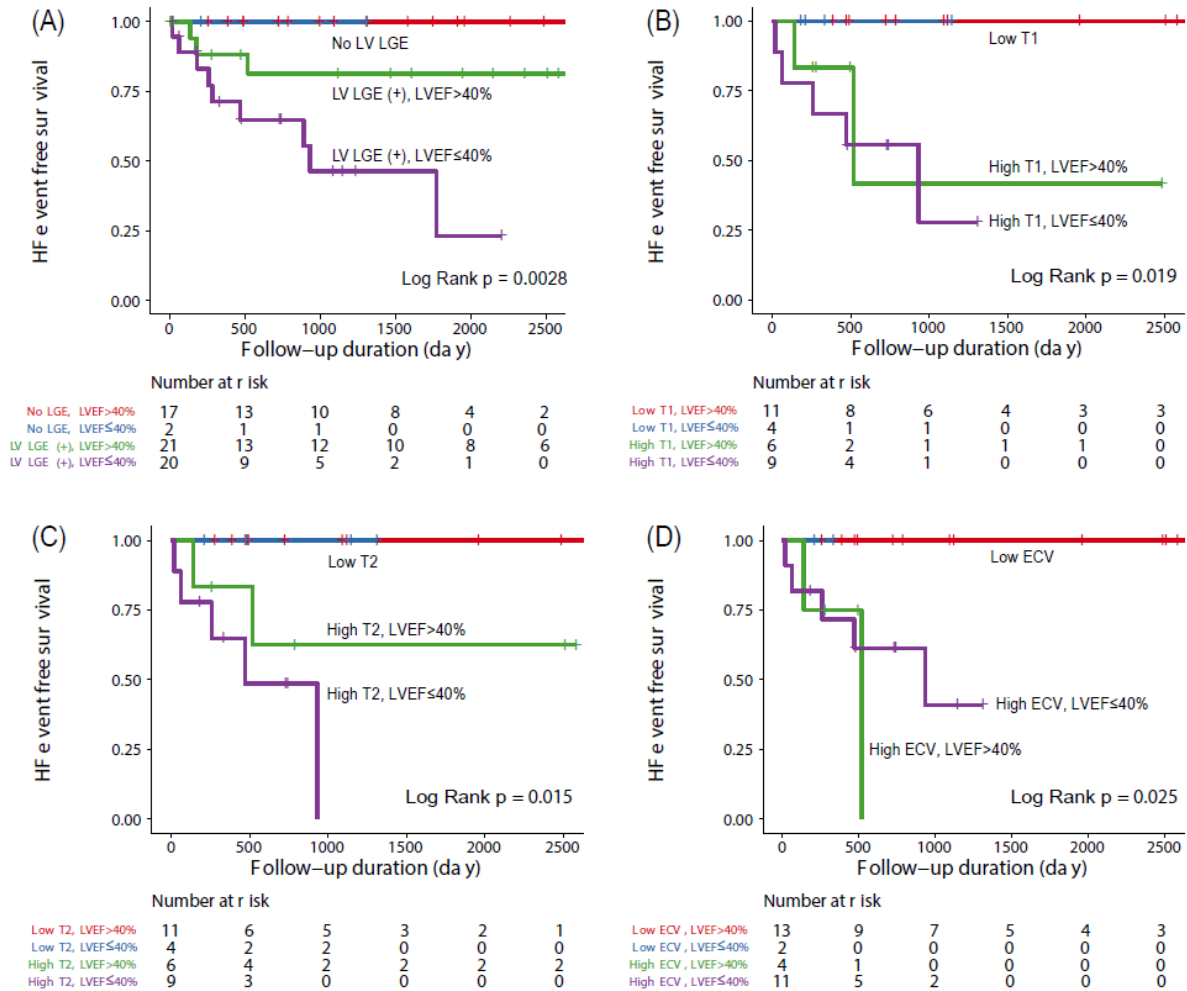
Kaplan-Meier survival curves for heart failure-related events according to LV late gadolinium enhancement (LGE) (A), native T1 (B), T2 (C), and ECV (D) in addition to CMR LVEF (>40 or ≤40%).

ECV, extracellular volume; CMR, cardiac magnetic resonance; LV, left ventricle; EF, ejection fraction.

Figure S2. Survival Curves for VT Categorized by LGE, native T1, and T2.
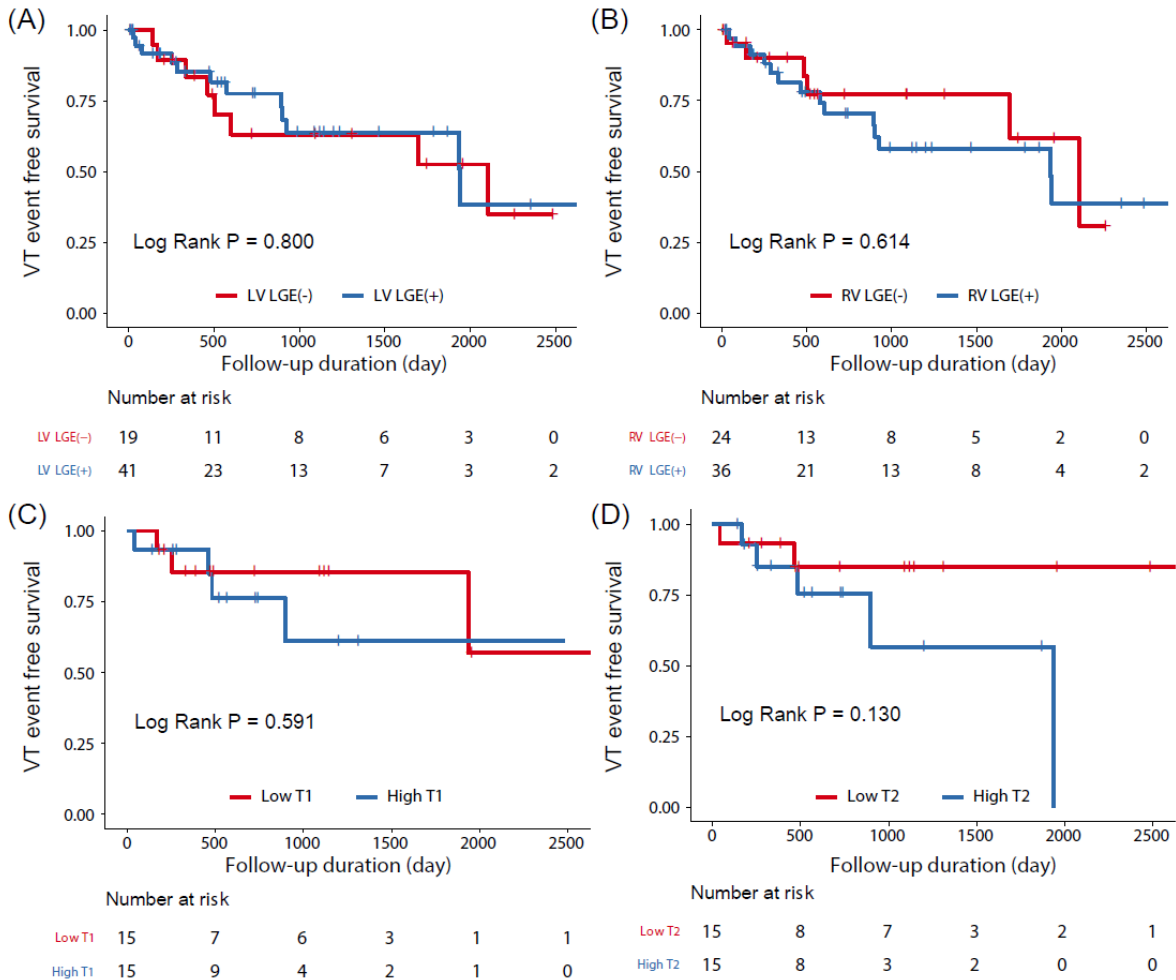
Kaplan-Meier survival curves for ventricular arrhythmic events according to LV late gadolinium enhancement (LGE) (A), RV LGE (B), native T1 (C), and T2 (D).

LV, left ventricle; RV, right ventricle; VT, ventricular tachycardia.