Radiology

ORIGINAL RESEARCH • CARDIAC IMAGING

Cardiac MRI to Predict Sudden Cardiac Death Risk in Dilated Cardiomyopathy

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Conflicts of interest are listed at the end of this article.

See also the editorial by Sakuma in this issue.

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Background: Sudden cardiac death (SCD) is one of the leading causes of death in individuals with nonischemic dilated cardiomyopathy (DCM). However, the risk stratification of SCD events remains challenging in clinical practice.

Purpose: To determine whether myocardial tissue characterization with cardiac MRI could be used to predict SCD events and to explore a SCD stratification algorithm in nonischemic DCM.

Materials and Methods: In this prospective single-center study, adults with nonischemic DCM who underwent cardiac MRI between June 2012 and August 2020 were enrolled. SCD-related events included SCD, appropriate implantable cardioverter-defibrillator shock, and resuscitation after cardiac arrest. Competing risk regression analysis and Kaplan-Meier analysis were performed to identify the association of myocardial tissue characterization with outcomes.

Results: Among the 858 participants (mean age, 48 years; age range, 18–83 years; 603 men), 70 (8%) participants experienced SCD-related events during a median follow-up of 33.0 months. In multivariable competing risk analysis, late gadolinium enhancement (LGE) (hazard ratio [HR], 1.87; 95% CI: 1.07, 3.27; $P = .03$), native T1 (per 10-msec increase: HR, 1.07; 95% CI: 1.04, 1.11; $P < .001$), and extracellular volume fraction (per 3% increase: HR, 1.26; 95% CI: 1.11, 1.44; $P < .001$) were independent predictors of SCD-related events after adjustment of systolic blood pressure, atrial fibrillation, and left ventricular ejection fraction. An SCD risk stratification category was developed with a combination of native T1 and LGE. Participants with a native T1 value 4 or more SDs above the mean (1382 msec) had the highest annual SCD-related events rate of 9.3%, and participants with a native T1 value 2 SDs below the mean (1292 msec) and negative LGE had the lowest rate of 0.6%. This category showed good prediction ability (C statistic = 0.74) and could be used to discriminate SCD risk and competing heart failure risk.

Conclusion: Myocardial tissue characteristics derived from cardiac MRI were independent predictors of sudden cardiac death (SCD)–related events in individuals with nonischemic dilated cardiomyopathy and could be used to stratify participants according to different SCD risk categories.

Clinical trial registration no. ChiCTR1800017058

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Supplemental material is available for this article.

Dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement and dysfunction in the absence of coronary artery disease or volume overloading (1). Despite advances in DCM management, such as medication, device therapy, and heart transplant, there is still substantial mortality in affected individuals, principally driven by heart failure (HF) and sudden cardiac death (SCD) (2,3). SCD accounts for approximately 30% of all deaths in individuals with DCM. Recognition of individuals who are at high risk of SCD is challenging.

Current guidelines recommend that individuals with a left ventricular ejection fraction (LVEF) of less than 35% and New York Heart Association (NYHA) class II or III receive an implantable cardioverter-defibrillator (ICD) for the primary prevention of SCD (4). However, this criterion does not consider that although individuals with an LVEF of less than 35% have a high risk of SCD, they also have a high competing risk of HF death (5). Serial studies, such as the Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality, or DANISH, trial, showed that the all-cause mortality of individuals receiving an ICD was not significantly reduced compared with that of a control group (6–9). In consideration of the limited resources in developing regions and the potential complications of ICD therapy, more precise methods are warranted to identify individuals with DCM with a high risk of SCD but not HF.

Previous studies have found that myocardial tissue characteristics, such as myocardial scarring and fibrosis, are ideal substrates for ventricular arrythmia and SCD events

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Abbreviations

DCM = dilated cardiomyopathy, ECV = extracellular volume fraction, HF = heart failure, HR = hazard ratio, ICD = implantable cardioverter-defibrillator, LGE = late gadolinium enhancement, LVEF = left ventricular ejection fraction, SCD = sudden cardiac death

Summary

Myocardial tissue characterization with cardiac MRI showed sudden cardiac death (SCD) event prediction ability and could discriminate SCD risk from competing heart failure event risk in individuals with nonischemic dilated cardiomyopathy.

Key Results

- In a prospective study of 858 participants with nonischemic dilated cardiomyopathy who underwent cardiac MRI, late gadolinium enhancement (LGE) (hazard ratio [HR], 1.87; $P = .03$), native T1 (HR per 10-msec increase, 1.07; $P < .001$), and extracellular volume fraction (HR per 3% increase, 1.26; $P < .001$) were independent predictors of sudden cardiac death (SCD)–related events.
- A risk category based on LGE and native T1 could stratify participants with different risks of SCD-related events (C statistic = 0.74) and was superior to LGE and 35% left ventricular ejection fraction in recognizing SCD-related events (C statistic = 0.66, $P < .001$).

(10–12). Myocardial fibrosis is an important pathophysiologic feature in the process of DCM development (13), and myocardial histologic analysis has confirmed that there are two types of fibrosis—focal fibrosis and diffuse fibrosis—that can be detected with cardiac MRI (14). Focal fibrosis, mainly manifesting as late gadolinium enhancement (LGE) on cardiac MRI scans, has been widely shown to be associated with SCD events (15–17). Diffuse myocardial fibrosis quantified by T1 mapping and extracellular volume fraction (ECV) has shown potential ability to predict a poor prognosis (18,19). However, the role of myocardial fibrosis in recognizing and distinguishing different clinical outcomes remains unclear.

Thus, in our study, we aimed to determine whether myocardial tissue characterization with cardiac MRI could predict SCD events and propose a SCD stratification algorithm in nonischemic DCM.

Materials and Methods

Study Participants

Our study complied with the principal of the Declaration of Helsinki, was approved by the institutional ethics committee of West China Hospital of Sichuan University, and was registered with the Chinese Clinical Trial Registry (ChiCTR1800017058). Written informed consent was obtained from all enrolled participants. In this single-center study, adults with nonischemic DCM who underwent cardiac MRI between June 2012 and August 2020 in the West China Hospital of Sichuan University were prospectively and consecutively enrolled. The diagnosis of DCM was made according to the classification of cardiomyopathies from the European Society of Cardiology Working Group (20). The inclusion criteria were based on the reduced LVEF (<50%) and elevated left ventricular end-diastolic dimension (>55 mm). Information on physical examination findings, laboratory results, and medication use was collected at enrollment. The exclusion criteria are listed in Appendix S1. The data from 497 of the 858 participants were previously reported in another study (21). The previous study explored the prognostic value of left atrial strain in participants with DCM, while our study focused on the myocardial tissue characteristics and SCD end point, enrolled more participants, and included different survival analyses.

Participant Follow-up and Outcomes

Follow-up was performed through a review of medical records and telephone interviews at 12-month intervals until November 2021 by two cardiologists (Y.X. and K.W., with 7 and 10 years of experience, respectively). The cause of death was carefully analyzed through communication with participants' physicians and a review of hospitalization records. The primary end point was SCD-related end points, including SCD, appropriate ICD shock, and resuscitation after cardiac arrest. The secondary end points were HF-related end points, including HF death and heart transplant, and composite end points, including cardio-

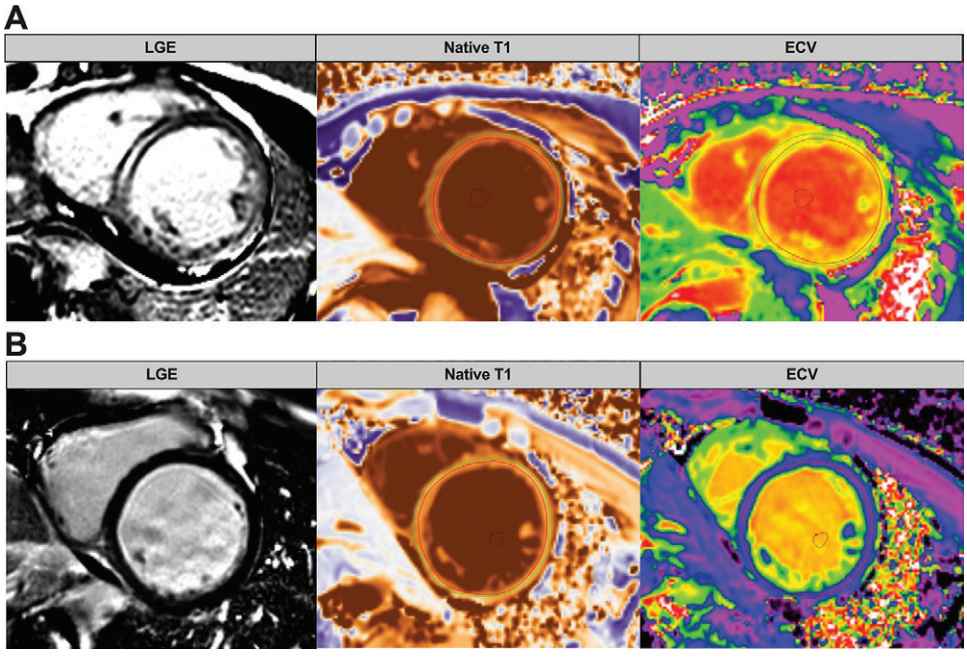


Figure 1: Examples of patients with different cardiac MRI risk profiles. **(A)** Cardiac MRI scans in a 47-year-old woman with dilated cardiomyopathy and left ventricular ejection fraction (LVEF) of 35% show midwall fibrosis on late gadolinium enhancement (LGE) image and elevated native T1 (1474 msec, greater than the mean reference value + 4 SDs) and extracellular volume fraction (ECV) (40.5%, greater than the mean reference value + 4 SDs) values. She experienced sudden cardiac death 15 months later. **(B)** Cardiac MRI scans in a 39-year-old man with dilated cardiomyopathy and LVEF of 24% show the negative LGE and normal native T1 (1240 msec, less than the mean reference value + 2 SDs) and ECV (24.6%, less than the mean reference value + 2 SDs) value. He was still alive after 90 months.

vascular death, heart transplant, appropriate ICD shock, and resuscitation after cardiac arrest.

MRI Acquisition

All studies were performed with a 3.0-T MRI scanner (MAGNETOM Trio or Skyra; Siemens Healthcare) with a 32-channel cardiac coil or a 30-channel body coil. Steady-state free precession cine images were acquired in standard two-, three-, and four-chamber long-axis and short-axis cine stacks covering the ventricles. T1 mapping using a modified Look-Locker inversion-recovery sequence (MOLLI) was performed in the midventricular short-axis plane. LGE images were acquired in the long-axis plane and consecutive short-axis plane using an inversion-recovery gradient-echo sequence. Typical parameters are presented in Appendix S1 (online).

MRI Postprocessing and Analysis

MRI scans were analyzed by experienced operators (Y.L. and W.L., with 5 and 7 years of experience, respectively) who were blinded to the clinical information using Medis Suite (version 3.2; Medis Medical Imaging Systems). The results were reviewed by a radiologist (J.S., with >15 years of experience). The biventricular volume, ejection fraction, and left ventricular mass were calculated using consecutive short-axis images according to the recommended standard protocol of the Society for Cardiovascular Magnetic Resonance (22). The ventricular volume and mass were indexed to the body surface area. LGE was deemed present when the area of enhancement could be seen in two phase-encoding directions and two orthogonal views. The presence of LGE was evaluated by two independent readers blinded to the participants' clinical data (Y.X., W.L.). A third expert (Y.C., with >10 years of experience) adjudicated the results in cases of disagreement. The LGE pattern was categorized as linear midwall, subepicardial, focal, and multiple patterns. Native T1 values were acquired by manually tracing the endo- and epicardial borders on the midventricular short-axis image with careful avoidance of the blood pool, papillary muscle, and epicardial fat. The ECV was calculated with the following formula: (1 – hematocrit level) × ([1/T1 myocardium$_{post}$ – 1/T1 myocardium$_{pre}$]/[1/T1 blood$_{post}$ – 1/T1 blood$_{pre}$]), where myocardium$_{post}$ and myocardium$_{pre}$ are postcontrast and native T1 values of myocardium, respectively, and T1 blood$_{post}$ and T1 blood$_{pre}$ are postcontrast and native T1 values of blood, respectively (Fig 1). Reproducibility analysis and results are presented in Appendix S1.

Statistical Analyses

Continuous variables are presented as the means ± SD or medians. Categorical variables are expressed as counts and percentages. Comparisons between groups were performed with independent *t* tests for continuous parameters and χ^2 tests for categorical parameters. Cox regression analysis was performed to determine the association between variables and composite end points. We incorporated variables with $P < .05$ in the univariable analysis into the multivariable analysis. Variance inflation factor was calculated to avoid collinearity, and parameters with variance inflation factor greater than 3 were excluded from the multivariable analysis. We performed competing risk regression analysis as described by Fine and Gray for the specific end point (23). Parameters demonstrating a significant univariable association ($P < .05$) were included in the multivariable competing risk analysis accounting for other events as competing risks. Two separate multivariable models were established for the analysis of native T1 (model 1) and ECV (model 2). Hazard ratios (HRs) and corresponding 95% CIs were calculated. The survival curves were performed with Kaplan-Meier analysis and were compared with the log-rank test.

According to the competing risk regression analysis results, we built an SCD risk stratification category combining LGE presence and native T1 and ECV values. The native T1 and ECV values were transformed into category variables according to the mean reference value and SD of native T1 (mean, 1202 msec ± 45 [SD]) and ECV (mean, 27% ± 3) in our center (24). First, we divided participants into six groups by LGE and native T1 values. Group 1 comprised patients with a native T1 value less than 2 SDs greater than the reference value (1292 msec) and negative for LGE. Group 2 comprised participants with a native T1 value between 2 SDs and less than 4 SDs greater than the reference value (1382 msec) and negative for LGE. Group 3 comprised participants with a native T1 value less than 2 SDs greater than the reference value and positive for LGE. Group 4 comprised participants with native T1 between 2 SDs and less than 4 SDs greater than the reference value and positive for LGE. Group 5 comprised participants with native T1 4 SDs or higher than the reference value and negative for LGE. Group 6 comprised participants with native T1 4 SDs or greater

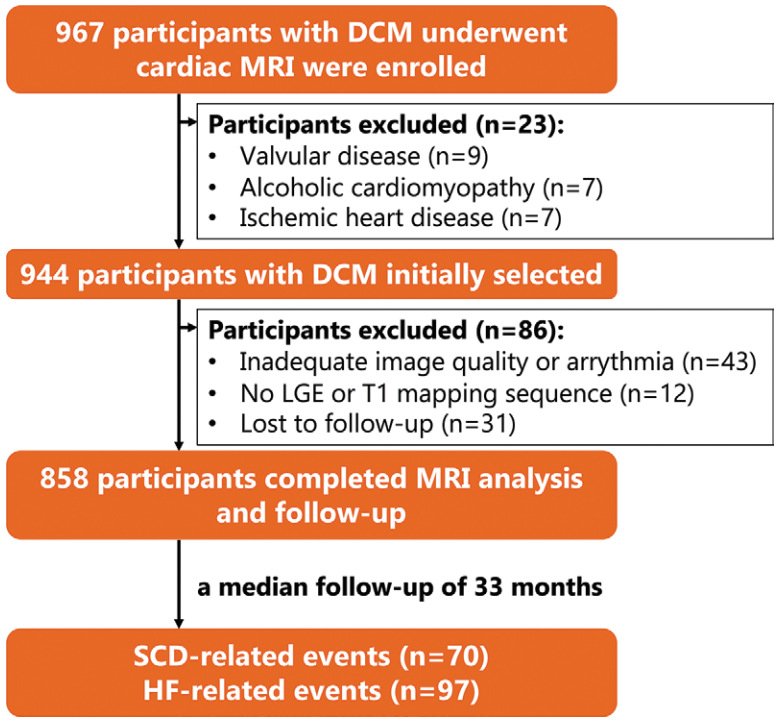


Figure 2: Study flowchart. DCM =dilated cardiomyopathy, HF = heart failure, LGE = late gadolinium enhancement, SCD = sudden cardiac death.

Table 1: Baseline Characteristics of Participants with Dilated Cardiomyopathy, SCD-related Events, and HF-related Events

Characteristic	All Participants (n = 858)	SCD-related Events (n = 70)	HF-related Events (n = 97)	P Value
Age (y)*	48 ± 15	51 ± 16	49 ± 15	.30
Age range (y)	18–83	18–79	19–78	
Male	603 (70)	46 (66)	66 (68)	.75
Female	255 (30)	24 (34)	31 (32)	.75
Systolic BP (mm Hg)*	116 ± 18	111 ± 17	108 ± 16	.21
Diastolic BP (mm Hg)*	76 ± 13	72 ± 12	71 ± 12	.62
BMI (kg/m^2)*	24 ± 4	23 ± 3	23 ± 5	.79
NYHA class				.002
I	81 (9)	2 (3)	1 (1)	…
II	318 (37)	22 (31)	18 (19)	…
III	339 (40)	36 (51)	44 (45)	…
IV	120 (14)	10 (14)	34 (35)	…
Hypertension	195 (23)	11 (16)	14 (14)	.82
Diabetes	113 (13)	10 (14)	22 (23)	.18
LBBB	108 (13)	9 (13)	21 (22)	.14
Atrial fibrillation	157 (18)	21 (30)	25 (26)	.55
Smoking	372 (43)	30 (43)	44 (45)	.75
Alcohol use	236 (28)	18 (26)	23 (24)	.77
Medication use				
ARNI/ACEI/ARB	698 (81)	53 (76)	76 (78)	.69
β-blockers	719 (83)	58 (83)	72 (74)	.19
MRA	640 (75)	55 (79)	79 (81)	.65
Diuretic	604 (70)	52 (74)	89 (92)	.002
Digoxin	208 (24)	25 (36)	49 (51)	.06
Warfarin	119 (14)	16 (23)	21 (22)	.85
LVEF*	25.9 ± 12.0	21.8 ± 9.0	18.6 ± 7.8	.02
LVEDVi (mL/m^2)*	175.8 ± 58.4	198.2 ± 55.7	226.4 ± 71.4	.007
LVESVi (mL/m^2)*	134.6 ± 59.1	158.8 ± 55.8	186.7 ± 68.3	.005
LVMi (g/m^2)*	86.5 ± 27.5	85.1 ± 25.4	92.1 ± 29.9	.13
RVEF (%)*	37.6 ± 14.8	35.1 ± 13.7	29.5 ± 13.4	.01
LGE present	372 (44)	45 (64)	57 (59)	.47
LGE pattern				.23
Linear midwall	185 (22)	20 (29)	26 (27)	…
Subepicardial	24 (3)	8 (11)	3 (3)	…
Focal	50 (6)	1 (1)	3 (3)	…
Multiple	113 (13)	16 (23)	25 (26)	…
Native T1 (msec)*	1307 ± 75	1356 ± 77	1334 ± 83	.08
ECV (%)*	31.6 ± 5.6	34.9 ± 5.1	34.6 ± 5.1	.84

Note.—Unless otherwise indicated, data are numbers of participants, with percentages in parentheses. P value indicates comparison between SCD-related events and HF-related events. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ARNI = angiotensin receptor neprilysin inhibitor, BMI = body mass index, BP = blood pressure, ECV = extracellular volume fraction, HF = heart failure, LBBB = left bundle branch block, LGE = late gadolinium enhancement, LVEDVi = left ventricular end-diastolic volume index, LVEF = left ventricular ejection fraction, LVESVi = left ventricular end-systolic volume index, LVMi = left ventricular mass index, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association, RVEF = right ventricular ejection fraction, SCD = sudden cardiac death.

* Data are means ± SDs.

than the reference value and positive for LGE. Then, we incorporated the groups with similar annual event rates and constructed four different risk categories. The same method was applied for the LGE and ECV values. The subdistributional HR of the risk stratification was calculated with multivariable competing risk analysis adjusted for systolic blood pressure, New York Heart Association class, diabetes, left bundle branch block, atrial fibrillation, and LVEF. The category discrimination was assessed using C statistics. The ability of the category to reclassify SCD risk was determined through calculation of the net reclassification improvement and integrated discrimination improvement. Reproducibility analysis was evaluated by calculating the intraclass correlation coefficient. Statistical analyses were performed with SPSS (version 25; IBM) and R (version 4.0.4; The R Foundation for Statistical Computing) statistical software. Two-tailed $P < .05$ indicated a statistically significant difference.

Results

Participant Characteristics

Of 967 participants screened in our center between June 2012 and August 2020, 109 were excluded due to valvular disease (n = 9), alcoholic cardiomyopathy (n = 7), ischemic heart disease (n = 7), inadequate image quality or arrhythmia (n = 43), no LGE or T1 mapping sequence (n = 12), and loss to follow-up (n = 31). A total of 858 participants (mean age, 48 years ± 15; 603 [70%] male) were included in the final analysis (Fig 2). The baseline clinical and cardiac MRI characteristics are presented in Table 1. The mean LVEF was 25.9% ± 12.0, LGE was present in 372 of 858 (43%) participants, the mean native T1 was 1307 msec ± 75, and the mean ECV was 31.6% ± 5.6. LGE was seen in the linear midwall in 185 (22%) participants, was subepicardial in 24 (3%) and focal in 50 (6%), and had multiple patterns in 113 (13%).

Follow-up and Outcomes

During a median follow-up of 33.0 months (IQR, 20.4–51.6), SCD-related events occurred in 70 participants; these included 52 SCDs, 14 appropriate ICD shocks, and four resuscitations after cardiac arrest. Ninety-seven participants experienced HF-related events, including 81 deaths due to HF and 16 heart transplants. In total, 167 participants reached the composite end point. The cumulative incidence of the composite end point and different outcomes are shown in Figure 3. When compared with participants who experienced an HF-related event, participants who experienced an SCD-related event had a lower NYHA class (P = .002), higher LVEF (P = .02) and right ventricular ejection fraction (P = .001), and lower left ventricular end-diastolic volume index (P = .007) and left ventricular end-systolic volume index (P = .005). The LGE prevalence (45 SCD-related events [64%], 57 HF-related events [59%]; P = .47), native T1 (SCD-related events, 1356 msec ± 77; HF-related events, 1334 msec ± 83; P = .08), and ECV (SCD-related events, 34.9% ± 5.1; HF-related events, 34.6% ± 5.1; P = .84) were not significantly different between the patients with SCD- or HF-related events (Table 1).

Survival Analysis

Results for uni- and multivariable competing risk regression analyses for SCD-related events are shown in Table 2. In the multivariable competing risk regression model, when HF-related events were counted as competing risks, native T1 (per 10-msec increase: HR, 1.07; 95% CI: 1.04, 1.11; P < .001) and LGE (HR, 1.87; 95% CI: 1.07, 3.27; P = .03) in model 1 and only ECV (per 3% increase: HR, 1.26; 95% CI: 1.11, 1.44; P < .001) in model 2 were independent predictors of SCD-related events. Kaplan-Meier curve analysis showed that participants with LGE were

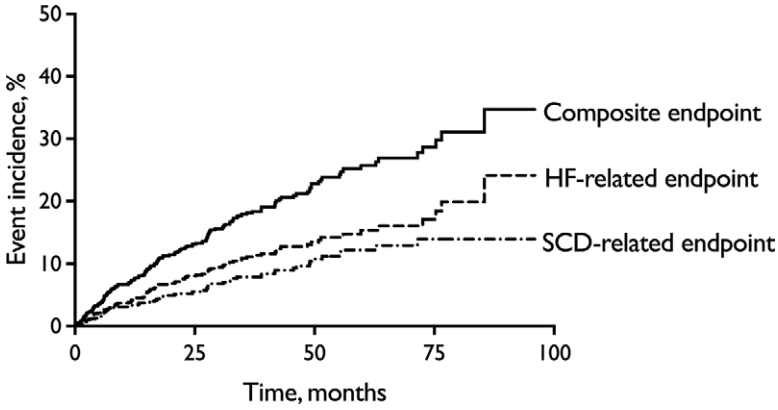


Figure 3: Cumulative incidence rates of composite end point, heart failure (HF)–related events, and sudden cardiac death (SCD)–related events.

Table 2: Uni- and Multivariable Competing Risk Regression Analyses for Sudden Cardiac Death–related Events

Risk Regression Analysis	Hazard Ratio	P Value
Univariable		
Age	1.02 (1.00, 1.04)	.06
Male sex	0.77 (0.47, 1.25)	.29
Systolic BP	0.98 (0.97, 1.00)	.017
NYHA class	1.26 (0.98, 1.62)	.07
Hypertension	0.60 (0.31, 1.14)	.12
Diabetes	1.14 (0.58, 2.24)	.71
LBBB	0.95 (0.48, 1.90)	.89
Atrial fibrillation	1.88 (1.11, 3.21)	.02
LVEDVi	1.01 (1.01, 1.01)	.01
LVEF	0.97 (0.95, 0.99)	.004
RVEF	0.99 (0.97, 1.00)	.15
LGE presence	2.86 (1.73, 4.73)	<.001
Native T1 (per 10-msec increase)	1.09 (1.07, 1.12)	<.001
ECV (per 3% increase)	1.38 (1.24, 1.52)	<.001
Multivariable		
Model 1		
Systolic BP	1.00 (0.98, 1.01)	.79
Atrial fibrillation	1.56 (0.86, 2.83)	.14
LVEF	0.99 (0.96, 1.01)	.35
LGE present	1.87 (1.07, 3.27)	.03
Native T1 (per 10-msec increase)	1.07 (1.04, 1.11)	<.001
Model 2		
Systolic BP	1.00 (0.98, 1.01)	.75
Atrial fibrillation	1.58 (0.87, 2.85)	.13
LVEF	0.99 (0.96, 1.01)	.30
LGE present	1.74 (0.97, 3.12)	.06
ECV (per 3% increase)	1.26 (1.11, 1.44)	<.001

Note.—Data in parentheses are 95% CIs. BP = blood pressure, ECV = extracellular volume fraction, LBBB = left bundle branch block, LGE = late gadolinium enhancement, LVEDVi = left ventricular end-diastolic volume index, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, RVEF = right ventricular ejection fraction.

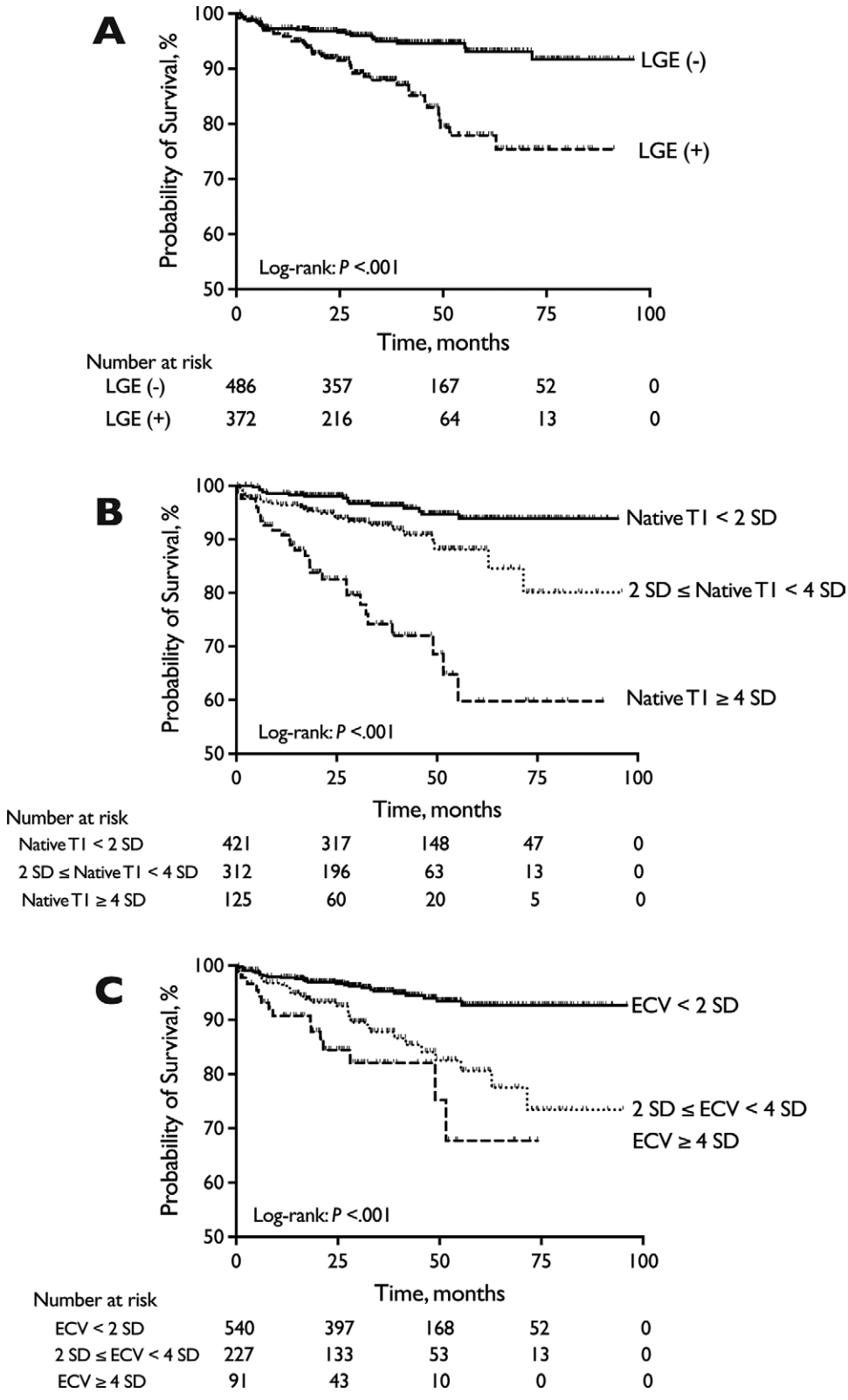


Figure 4: Kaplan-Meier curve of sudden cardiac death (SCD)–related events according to **(A)** late gadolinium enhancement (LGE), **(B)** native T1, and **(C)** extracellular volume fraction (ECV) values. Native T1 and ECV were transformed into categories according to the mean of the normal reference value and 2 and 4 SDs.

more likely to experience SCD-related events ($P < .001$). Participants with native T1 or ECV greater than or equal to the mean plus 4 SDs had a higher risk of SCD-related events, while participants with native T1 or ECV less than the mean plus 2 SDs were associated with a lower event rate ($P < .001$) (Fig 4).

In the analysis of HF-related events, LGE (HR, 1.61; 95% CI: 1.02, 2.53; $P = .04$) in model 1 and ECV (per 3% increase: HR, 1.16; 95% CI: 1.04, 1.29; $P < .001$) in model 2 still showed independent predictive value, while native T1 did not show evidence of an independent association with HF events ($P = .15$). LVEF was independently associated with HF-related events but not SCD-related events (Table S1). Table S2 shows the results of Cox regression analyses for the composite end point. Systolic blood pressure, New York Heart Association class, LVEF, LGE, native T1, and ECV were independent predictors of the composite end point ($P < .05$).

SCD Risk Stratification Category

Among the six groups based on native T1 and LGE, the annual SCD-related event rate increased from group 1 to group 6. Participants with native T1 less than the mean plus 2 SDs and negative LGE (group 1) had the lowest annual event rate of 0.6%, while participants with native T1 greater than or equal to the mean plus 4 SDs and positive LGE (group 6) had the highest annual event rate of 10.2%. According to the event rate among different groups (Fig 5A), we further classified participants into four risk groups (Fig 5B): the high-risk group (groups 5 and 6, $n = 125$ [15%]), defined as a native T1 value at least 4 SDs greater than the reference value, had an annual event rate of 9.3%; the moderate-to-high risk group (group 4, $n = 154$ [18%]), defined as a native T1 value between 2 SDs and less than 4 SDs greater than the reference value and positive for LGE, had an annual event rate of 3.9%; the low-to-moderate risk

group (groups 2 and 3, n = 288 [34%]), defined as 2 SDs and less than 4 SDs greater than the reference value and negative for LGE (group 2) and as a native T1 value less than 2 SDs greater than the reference value and positive for LGE (group 3), had an annual event rate of 2.2%; and the low-risk group (group 1, n = 291 [34%]), defined as native T1 value less than 2 SDs greater than the reference value and negative for LGE, had an annual event rate of 0.6%. Kaplan-Meier curve analysis showed different survival probabilities across the defined risk strata (P < .001) (Fig 6).

Then, similar methods were applied to classify participants according to LGE and ECV. We divided participants into three risk groups: the groups with high risk had an annual event rate of 3.9%, the groups with moderate risk had an annual event rate of 2.8%, and the group with low risk had an annual event rate of 1.0% (Fig S1). Significantly different survival probability (P < .001) among groups is shown in Figure S2.

The C statistic for the combination of LGE and native T1 to predict SCD-related events was 0.74, which was significantly higher than that for the combination of LGE and ECV (C statistic = 0.70, P < .001) and the combination of LGE and 35% LVEF (C statistic = 0.66, P < .001). Adding LGE and native T1 to LVEF also incrementally improved the reclassification indexes (net reclassification improvement = 0.28, P < .001) and discrimination indexes (integrated discrimination improvement, 0.11; P < .001). Adding native T1 to LGE and LVEF significantly improved the net reclassification improvement (net reclassification improvement = 0.16, P = .04), not integrated discrimination improvement (integrated discrimination improvement = 0.04, P = .30). Figure 7 shows the association of the SCD risk stratification category based on LGE and native T1 with different end points. The relative HR increased from participants with low risk to those with high risk according to our risk stratification category for SCD-related events. However, for HF-related events, the relative HR did not demonstrate a significant difference among the low-risk group, low-to-moderate–risk group (HR, 1.38; 95% CI: 0.76, 2.51), and high-to-moderate–risk group (HR, 1.40; 95% CI: 0.82, 2.36). Although the high-risk group also showed an increased risk of experiencing HF-related events (HR, 3.09; 95% CI: 1.57, 6.10), participants in this group had a much higher risk of experiencing an SCD-related event (HR, 9.71; 95% CI:

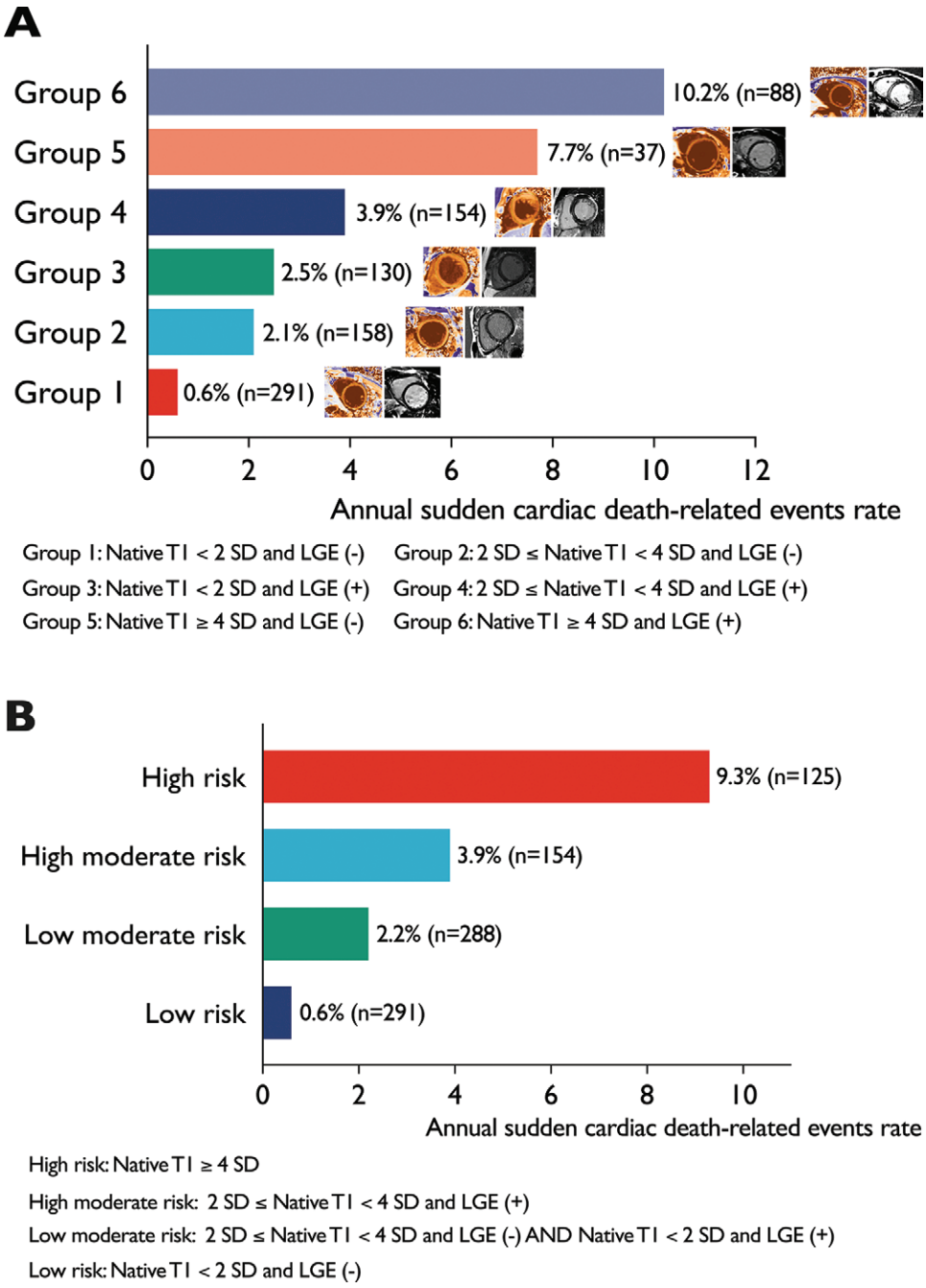
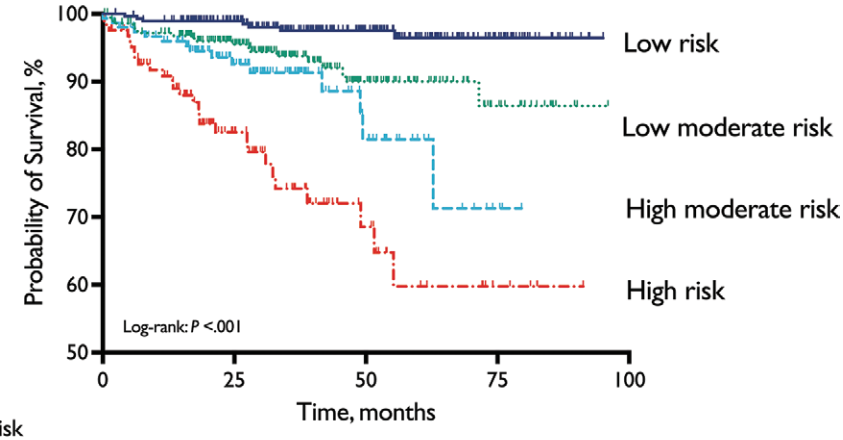


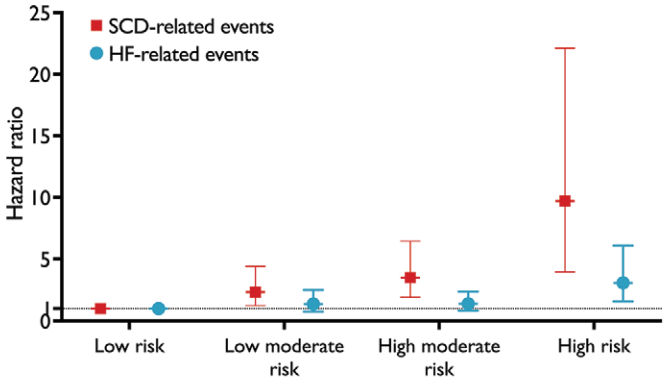
Figure 5: Annual sudden cardiac death (SCD)–related event risk in different groups classified by native T1 and late gadolinium enhancement (LGE) values. **(A)** Annual SCD-related event rate among different groups according to native T1 and LGE. **(B)** Annual rate in our proposed SCD risk stratification categories. Native T1 was transformed into categories according to the mean of the normal reference value and 2 and 4 SDs.



Number at risk

Low risk	291	229	116	38	0
Low moderate risk	288	197	73	19	0
High moderate risk	154	87	22	3	0
High risk	125	60	20	5	0

Figure 6: Kaplan-Meier curve of sudden cardiac death (SCD)–related events according to the SCD risk stratification categories.



SCD-related events HR (95% CI)	As reference	2.34 (1.25, 4.42)	3.51 (1.91, 6.45)	9.71 (3.98, 22.12)
HF-related events HR (95% CI)	As reference	1.38 (0.76, 2.51)	1.40 (0.82, 2.36)	3.09 (1.57, 6.10)

Figure 7: Subdistributional hazard ratios (HRs) of the proposed risk stratification categories in different outcomes. Multivariable competing regression analysis was performed to identify the association of proposed categories with sudden cardiac death (SCD)– or heart failure (HF)–related events. Multivariable analysis was adjusted for systolic blood pressure, New York Heart Association class, diabetes, left bundle branch block, atrial fibrillation, and left ventricular ejection fraction.

3.98, 22.12). For the risk stratification category based on LGE and ECV, the moderate- and high-risk groups showed significant increases of HR for both SCD and HF events ($P < .05$) (Fig S3). Thus, the risk stratification model based on LGE and native T1 was better at recognizing SCD-related events and distinguishing SCD-related events from competing HF-related events.

Discussion

In our study, we explored the association between myocardial tissue characterization with cardiac MRI and sudden cardiac death (SCD)–related events in nonischemic dilated cardiomyopathy and developed a model for SCD risk stratification based on myocardial fibrosis characteristics. The main findings were as follows: First, late gadolinium enhancement (LGE) (hazard ratio [HR], 1.87; $P = .03$), native T1 (HR per 10-msec increase, 1.07; $P < .001$), and the extracellular volume fraction (ECV) (HR per 3% increase, 1.26; $P < .001$) were independent predictors of SCD-related events, including SCD, appropriate implantable cardioverter-defibrillator shocks, and resuscitation after cardiac arrest in multivariable competing risk regression analysis. The ECV, but not the native T1 value, was also associated with heart failure (HF)–related events. Second, a risk category based on LGE and native T1 could be used to stratify participants with different risks of experiencing SCD-related events (C statistic = 0.74) and was superior to the LGE and left ventricular ejection fraction (C statistic = 0.66) in recognizing SCD-related events. Third, our risk stratification category could discriminate between the risk of SCD- and HF-related events.

Previous studies have shown the relationship between focal replacement fibrosis detected by means of LGE and SCD outcomes. A meta-analysis including seven studies and 1827 participants with nonischemic DCM showed that participants with left ventricular midwall fibrosis had a significantly higher risk of experiencing SCD or aborted SCD events (25). A study of individuals with DCM and an LVEF of 40% or higher and no indication for ICD implantation found that LGE independently predicted SCD and aborted SCD events, and the competing risk of nonsudden death was low in these individuals (17). Another meta-analysis including 29 studies across a wide spectrum of individuals with DCM showed that the association of LGE and arrhythmia was present in individuals with an LVEF less than 35% but was even stronger when the LVEF was 35% or higher (26). Thus, LGE may serve as a more appropriate risk adjudicator than the LVEF in individuals undergoing ICD therapy. In accordance with these studies, our results also showed that LGE presence was associated with a significantly higher risk of SCD events.

However, LGE reflects only focal fibrosis, and some participants without LGE also experienced arrhythmia events and SCD. Diffuse interstitial fibrosis is common in the remodeling process of DCM and is associated with the generation of reentry circuits and focal tachycardia (27,28). The T1 mapping technique can be used to detect and quantify diffuse fibrosis and has good correlations with the histologic collagen volume

fraction in DCM (29). A large cohort study showed that native T1 was an independent predictor of all-cause mortality in individuals with nonischemic cardiomyopathy (18). Another study found that the ECV was more strongly associated with major adverse cardiac events than native T1 in individuals with DCM (30). However, the study of T1 mapping separately on arrhythmia events is limited in DCM. Nakamori et al (19) showed that T1 mapping tissue heterogeneity was an important predictor of ventricular tachycardia and ventricular fibrillation in 115 individuals with DCM. Our results further showed that ECV was associated with both SCD- and HF-related events, and native T1 was an independent predictor of only SCD-related events. The ability to predict different outcomes helps to distinguish confusing but pivotal clinical events. In our cohort, native T1 was more appropriate in distinguishing SCD- and HF-related events than the ECV, and a combination of replacement fibrosis and diffuse fibrosis based on LGE and native T1 was much stronger in predicting SCD-related events than HF-related events.

Our study had several limitations. First, this was a single-center study without an external and independent validation cohort. Second, the number of SCD-related events was relatively low in this study, which carries the risk of model overfitting in the regression analysis and overestimation of the performance of our proposed categories. Third, the proportion of participants undergoing ICD therapy was low in our cohort; therefore, arrhythmic events may be underestimated. However, our results could reflect the real-world clinical practice and SCD incidence rate without much device interference. In addition, different scanners and techniques can result in different native T1 and ECV values, and our reference value may not be applicable to the reference value at other centers. Last, genetic information is associated with SCD in DCM; however, not all participants in this study underwent genetic testing. Combining genetic data and MRI results may further improve the predictive ability of our proposed categories, which could be explored in the future.

In conclusion, myocardial tissue characterization with cardiac MRI, including late gadolinium enhancement (LGE), native T1 value, and extracellular volume fraction, were independent predictors of sudden cardiac death (SCD)–related events in nonischemic dilated cardiomyopathy. The risk category based on LGE and native T1 could be used to stratify participants with different SCD risks and discriminate non-SCD events. The application of myocardial tissue characterization in the identification of participants who might benefit from primary prevention implantable cardioverter-defibrillator therapy warrants further study.

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Data sharing: Data generated or analyzed during the study are available from the corresponding author by request.

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