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ORIGINAL RESEARCH

The Prognostic Value of Left Ventricular Entropy From T1 Mapping in Patients With Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND The prognostic value of left ventricular (LV) entropy in hypertrophic cardiomyopathy (HCM) is unclear.

OBJECTIVES This study aimed to assess the prognostic value of LV entropy from T1 mapping in HCM.

METHODS A total of 748 participants with HCM, who underwent cardiovascular magnetic resonance (CMR), were consecutively enrolled. LV entropy was quantified by native T1 mapping. A competing risk analysis and a Cox proportional hazards regression analysis were performed to identify potential associations of LV entropy with sudden cardiac death (SCD) and cardiovascular death (CVD), respectively.

RESULTS A total of 40 patients with HCM experienced SCD, and 65 experienced CVD during a median follow-up of 43 months. Participants with increased LV entropy (≥4.06) were more likely to experience SCD and CVD (all $P < 0.05$) in the entire study cohort or the subgroup with low late gadolinium enhancement (LGE) extent (<15%). After adjustment for the European Society of Cardiology predictors and the presence of high LGE extent (≥15%), LV mean entropy was an independent predictor for SCD (HR: 1.03; all $P < 0.05$) by the multivariable competing risk analysis and CVD (HR: 1.06; 95% CI: 1.03-1.09; $P < 0.001$) by multivariable Cox regression analysis.

CONCLUSIONS LV mean entropy derived from native T1 mapping, reflecting myocardial tissue heterogeneity, was an independent predictor of SCD and CVD in participants with HCM. (Cardiac Magnetic Resonance Imaging Clinical Application Registration Study; ChiCTR1900024094) (JACC: Asia 2024;■:■–■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CVD = cardiovascular death

ECV = extracellular volume fraction

ESC = European Society of Cardiology

HCM = hypertrophic cardiomyopathy

LGE = late gadolinium enhancement

LV = left ventricular

SCD = sudden cardiac death

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disease with a prevalence of 1:200 to 1:500 in the general adult population.[1] In addition to myocardial hypertrophy, HCM is characterized by myocardial fiber disarray and increased extracellular matrix with an accumulation of interstitial fibrosis. Late gadolinium enhancement imaging (LGE) allows for the identification of areas of focal fibrosis, the presence and extent of which is associated with disease progression and adverse outcomes in HCM.[2] In addition, left ventricular (LV) native T1 and extracellular volume fraction (ECV) can detect diffuse fibrosis,[3] associated with cardiovascular death (CVD), sudden cardiac death (SCD), and unplanned rehospitalization for heart failure in HCM.[4] However, the measurements of native T1 and ECV have been based on a threshold of signal intensity rather than the voxel values of the entire ventricular myocardium.

Entropy is a typical measure of the complexity of an image and could quantify tissue heterogeneity by calculating all signal intensity values within the images. Previous studies reported that LV entropy, derived from LGE-CMR, was associated with arrhythmia events and mortality in patients with dilated cardiomyopathy and after myocardial infarction, respectively.[5,6] Gould et al[7] also reported that LV mean entropy was a robust prognosticator for appropriate implantable cardioverter defibrillator therapy in a mixed cardiomyopathy cohort and patients with ischemic cardiomyopathy. Moreover, LV entropy from the LGE images was shown to be associated with ventricular arrhythmia in a small sample cohort with HCM[8] and could help risk stratification.[9] However, the prognostic value of LV entropy derived from T1 mapping was not well explored.

Wu et al[10] reported LV entropy was better correlated with LV wall thickness, myocardial LGE, and strain parameters than mean T1 times in patients with HCM, which indicated that entropy from native T1 mapping may provide more information than mean T1 times. We hypothesized that LV entropy generated from the native T1 mapping presented tissue heterogeneity and may help improve risk classification in HCM. Accordingly, the study aimed to explore the relationship of LV entropy from native T1 images to sudden cardiac death (SCD) and cardiovascular death (CVD).

METHODS

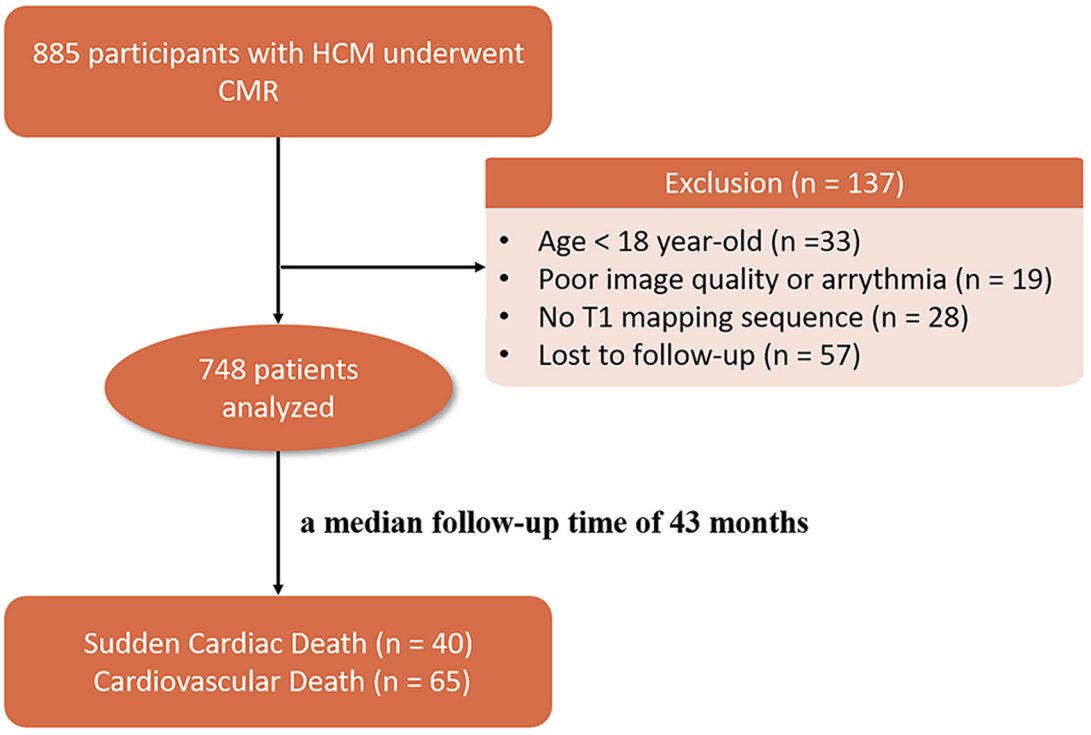
STUDY PARTICIPANTS. We prospectively recruited consecutive adult participants with HCM who underwent 3.0-T CMR from September 2013 to December 2021 in the West China Hospital of Sichuan University. This prospective cohort study was previously registered in the Chinese Clinical Trial Registry (ChiCTR1900024094) and approved by the Institutional Ethics Committee of West China Hospital, Sichuan University. Informed consent was obtained from each participant. The patients received their diagnoses by the following criteria: 1) LV maximal wall thickness ≥15 mm within at least 1 myocardial segment (or ≥13 mm in the first-degree relative of an index patient with confirmed HCM); and 2) assessed by echocardiography and CMR in the absence of secondary causes (cardiac, systemic, or metabolic disease) of myocardial hypertrophy.[1] The exclusion criteria are depicted in Figure 1. Demographic data, medical history, CMR parameters, and prognostic data for each patient were collected for each study participant. Of the 748 participants with HCM, 256 were previously reported in a different analysis based on LV trabecular complexity on cine imaging.[11]

CARDIOVASCULAR MR. CMR with ECG gating was performed on a 3.0-T scanner (Magnetom Tim Trio or Skyra, Siemens Healthineers) with a 32-channel cardiac phased-array receiver coil or a 30-channel body coil. Steady-state free precession cine images of the entire LV, from the base to the apex, were acquired in sequential short-axis views during breath-holds. More details are provided in the Supplemental Methods.

Native T1 mapping at the basal, mid, and apical levels with ECG gating was acquired before the injection of gadolinium using motion-corrected modified Look-Locker inversion recovery sequence (MOLLI) (Siemens works-in-progress 448, protocol: 5[3]3). Parameters for MOLLI were as follows: temporal resolution 740 ms, TE 1.06 ms, flip angle 35°, bandwidth 930 Hz/pixel, initial T1 100 ms with 80s increments, parallel imaging factor 2, matrix size 256 × 144, in-plane spatial resolution 2.4 × 1.8 mm, total acquisition time 11 heartbeats.[11-13]

CMR ANALYSES. The LV function and the quantitation of LV LGE were calculated on commercially available software (Medis Suite 3.2, Medis Medical Imaging Systems) by experienced operators (YWX, with 5 years of experience, and JW, with 8 years of

FIGURE 1 Study Flowchart



Seven hundred forty-eight adult participants with hypertrophic cardiomyopathy (HCM) were included for analysis. During a median follow-up duration of 43 months, 40 patients experienced sudden cardiac death–related events, and 65 participants reached the cardiovascular death endpoint. CMR = cardiovascular magnetic resonance.

experience). The approaches to calculating ventricular function and mass were in accordance with the Society for Cardiovascular Magnetic Resonance recommendations.[14] Detailed information is provided in the Supplemental Methods.

ENTROPY ANALYSIS. The LV entropy analysis for native T1 mapping was performed using MATLAB 2014 (Mathworks) as reported in previous studies.[15] The endocardium and epicardium were manually delineated for the 3 short-axis native T1 slices (YWX, with 5 years of experience, and JW, with 8 years of experience) to ensure that the endocardium did not include blood pool and the epicardium did not include epicardial fat. We excluded the apical slice for the analysis if there was an LV apical aneurysm. Then LV entropy representing the heterogeneity of the heart was calculated as follows:

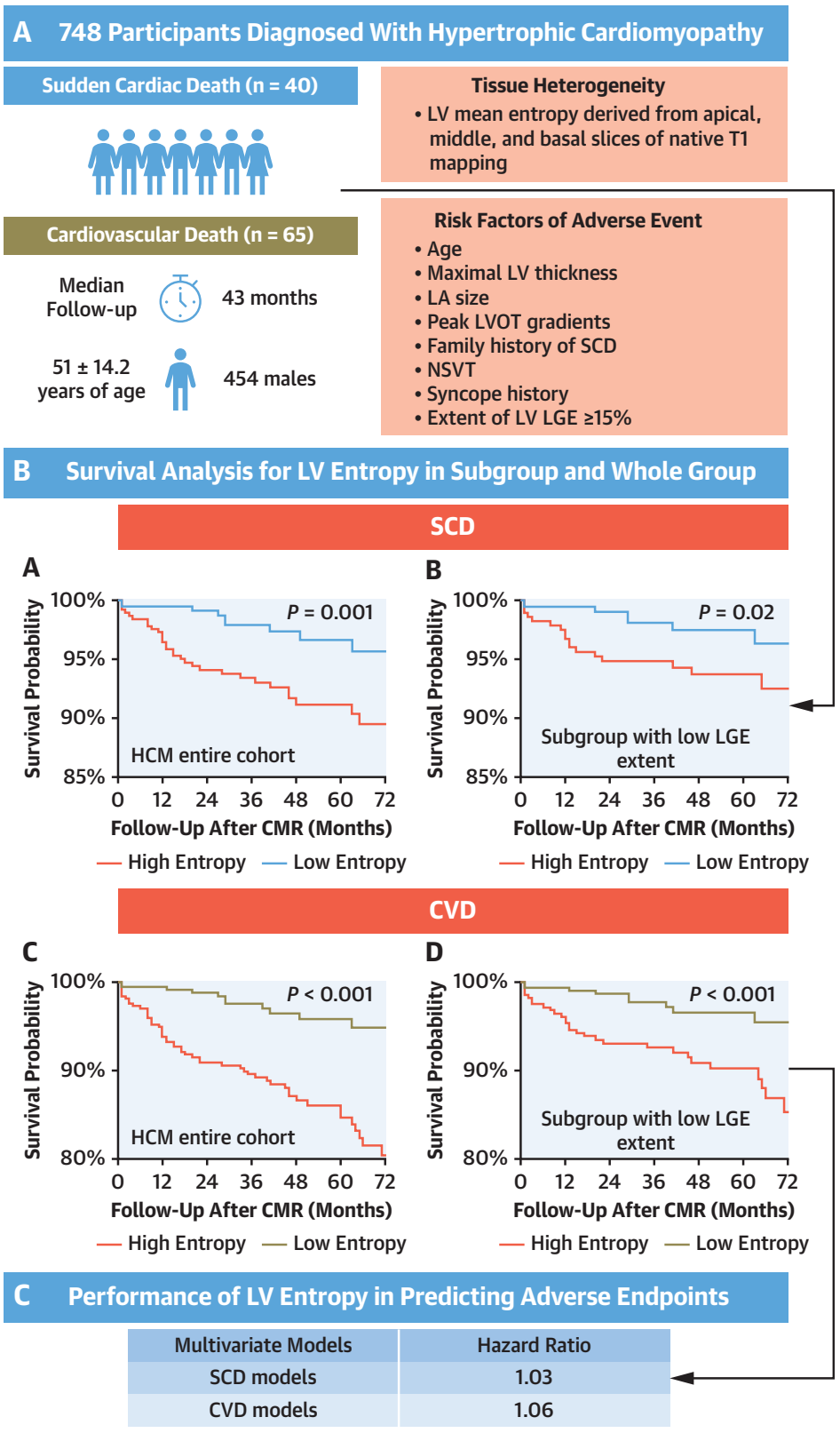
$$Entropy = -10\sum_{i=1}^{n} P(x_i)log_b P(x_i)$$

$P(x_i)$ represents the probability distribution of the signal intensity, x refers to the signal intensity, and b is an arbitrarily chosen base number (2).[5]

PARTICIPANT FOLLOW-UP. Follow-up duration was defined as the time from the initial CMR date until September 2022 or the endpoint if occurred earlier. SCD-related endpoints were defined as SCD, resuscitated cardiac arrest event, and appropriate ICD discharge event. Additionally, CVD contained cardiac or stroke-related deaths and SCD. All patients were regularly followed up on an annual basis. All follow-up data were collected through telephone interviews or medical records from the hospital information system.

STATISTICAL ANALYSES. Statistical analyses were performed using the survival analysis packages based on R version 4.1.0 (RStudio: Integrated Development for R) and SPSS version 24.0 (IBM Corporation). The competing risk analysis was performed to determine the association between variables and SCD, and the Cox proportional hazard regression was performed to

CENTRAL ILLUSTRATION Prognostic Value of LV Entropy in Patients With HCM



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determine the association between variables and CVD. To avoid model overfitting resulting from the low incidence of events, we limited each model to 3 variables (respecting the 1:10 rule) for SCD prediction. The median of LV mean entropy was used to split the high and low mean entropy subgroups. Survival curves for the study endpoints were fitted through the Kaplan-Meier method, and the group was classified by the median of LV mean entropy with comparison using the log-rank test. The intraclass correlation coefficient (ICC) was performed for the reproducibility analysis of LV entropy from native T1 mapping. A P value <0.05 was considered a statistically significant difference. More details are provided in the Supplemental Methods.

RESULTS

PARTICIPANT CHARACTERISTICS. We recruited 885 consecutive patients with HCM who underwent CMR. A total of 137 patients were excluded (**Figure 1**), and the data from 748 adult participants with HCM (mean age 51.0 ± 14.2 years, 454 male, mean BMI 24.2 ± 3.5 kg/m^2, and mean BSA 1.7 ± 0.2 m^2) (**Central Illustration**) were analyzed. The baseline characteristics are presented in **Table 1**. The mean LVEF was 61.0% ± 10.3% and the mean RVEF was 58.9% ± 9.5%. LGE was present in 534 (72%), and the median LGE extent was 3.9% (IQR: 0%-9.6%). There were a total of 343 participants (45.9%) with Stage C-D based on the American College of Cardiology (ACC)/American Heart Association (AHA) heart failure category.

COMPARISONS BETWEEN PARTICIPANTS WITH LOW AND HIGH MEAN ENTROPY. We divided the participants with HCM through the median value of LV mean entropy (4.06) into subgroups with low and high mean entropy (**Table 1**). The group with increased LV mean entropy (≥4.06) had a reduced LV systolic function (LVEF, 59.8% ± 11.2% vs 62.3% ± 9.2%; $P = 0.001$), an increased maximum LV thickness (22.0 ± 5.1 mm vs 21.1 ± 5.3 mm; $P = 0.03$), and a higher LGE extent (6.0%, IQR: 2.0%-14.8% vs 2.1%, IQR: 0%-6.1%; $P < 0.001$) and a lower proportion of patients with low LGE extent (<15%) (76.2% vs 91.9%; $P < 0.001$), a higher native T1 (1,364.4 ± 73.9 ms vs 1,301.0 ± 53.8 ms; $P < 0.001$), and ECV (30.8% ± 4.9% vs 28.1% ± 4.1%; $P < 0.001$) when compared with the low LV mean entropy group (<4.06).

CORRELATION BETWEEN LV ENTROPY AND CARDIAC STRUCTURE. All LV entropy variables were weakly associated with LVEF, maximal LV wall thickness, LGE extent, and high LGE extent (Supplemental Table 1) (all $P < 0.03$). Furthermore, LV mean and apical entropy had a weak correlation with reduced RV dilation (RV end-diastolic volume index and end-systolic volume index; $r = -0.1$ to -0.08; $P \leq 0.03$).

FOLLOW-UP AND OUTCOMES. During a median follow-up duration of 43 months (IQR: 22-65 months), 40 of 748 patients (5.3%) experienced SCD-related events, including SCD in 19 (3%), resuscitation after cardiac arrest event in 12 (2%), and appropriate ICD discharge in 9 (1%). A total of 65 (8.7%) participants reached the CVD endpoint, including 18 cardiovascular deaths due to heart failure, 7 stroke-related mortalities, and 40 SCD-related endpoints.

SURVIVAL ANALYSIS. Kaplan-Meier curve analyses revealed that participants with high LV entropy (≥4.06) were more likely to experience SCD-related events ($P = 0.001$) (**Figure 2A**, **Central Illustration**) and CVD ($P < 0.001$) (**Figure 2C**, **Central Illustration**) by the log-rank test. In addition, in the subgroup with low LGE extent (<15%), participants with HCM with an increased mean entropy (≥4.06) exhibited a higher rate of reaching SCD ($P = 0.02$) (**Figure 2B**, **Central Illustration**) and CVD ($P < 0.001$) (**Figure 2D**, **Central Illustration**).

The univariable Cox regression analysis is demonstrated in **Table 2**. Age (HR: 1.03, 95% CI: 1.01-1.06; $P = 0.01$), atrial fibrillation (AF) (HR: 5.51, 95% CI: 2.16-14.08; $P < 0.001$), nonsustained ventricular tachycardia (NSVT) (HR: 4.37, 95% CI: 2.22-8.59; $P < 0.001$), LVEF (HR: 0.96, 95% CI: 0.93-0.98; $P = 0.001$), an LV apical aneurysm (HR: 3.61, 95% CI:

CENTRAL ILLUSTRATION Continued

(A) A total of 748 patients with hypertrophic cardiomyopathy (HCM) were included in the study. (B) Increased left ventricular (LV) mean entropy (≥4.06) was associated with a significantly increased incidence of sudden cardiac death (SCD) and cardiovascular death (CVD) endpoint events in the total study group (A to C) and patients with low LGE extent (<15%) (B to D). (C) In multivariable analysis, following adjustment for the European Society of Cardiology predictors and the presence of high LGE extent (≥15%), LV mean entropy was an independent predictor of SCD and CVD. CMR = cardiac magnetic resonance; LGE = late gadolineum enhancement; LVOT = left ventricular outflow tract; NSVT = nonsustained ventricular tachycardia.

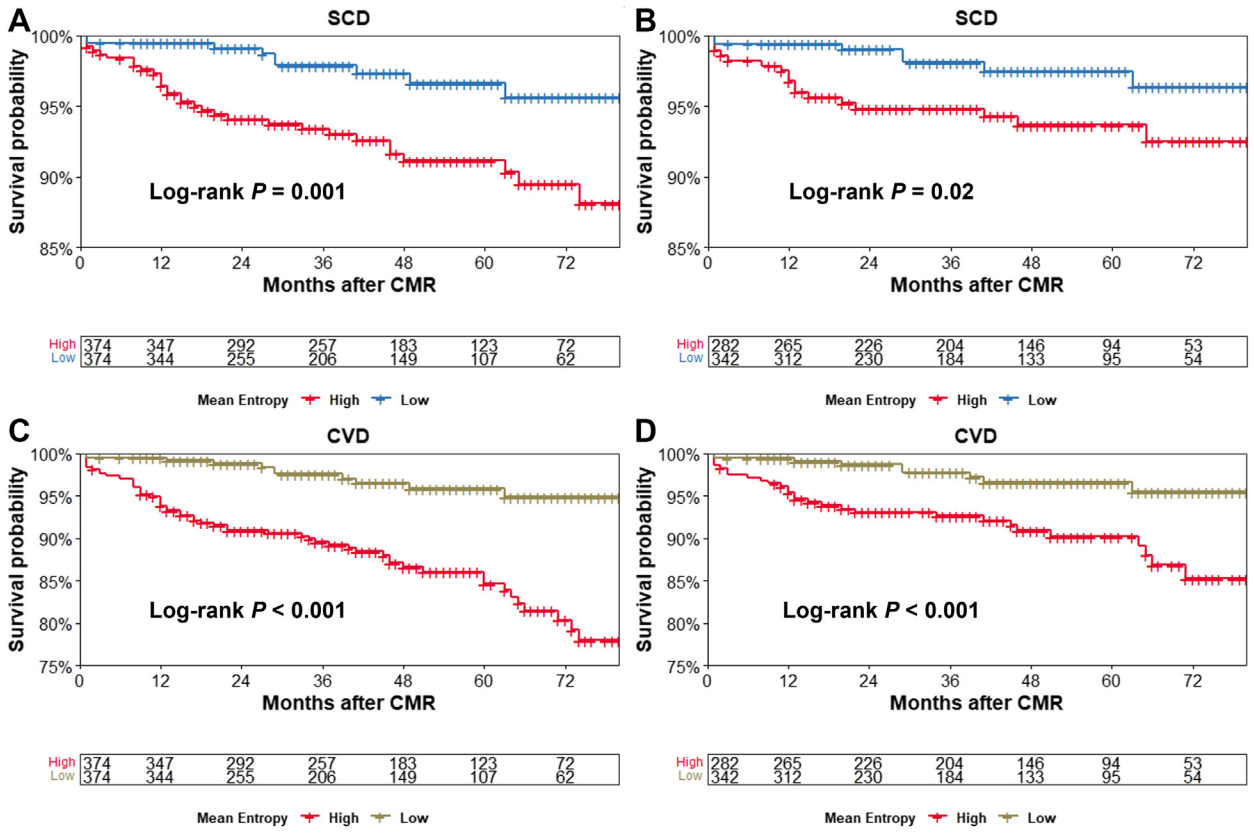
TABLE 1 Demographic, Clinical, and CMR Phenotypic Characteristics in Participants with HCM

	Patients With HCM (n = 748)	HCM With Low Mean Entropy (n = 374)	HCM With High Mean Entropy (n = 374)	*P* Value
Age (y)	51.0 ± 14.2	50.4 ± 13.7	51.7 ± 14.7	0.23
Male	454 (60.7)	282 (75.4)	172 (46.0)	**<0.001**
Height (cm)	163.0 ± 8.4	164.7 ± 8.2	161.3 ± 8.2	**<0.001**
Weight (kg)	64.6 ± 11.8	68.1 ± 11.3	61.2 ± 11.4	**<0.001**
BMI (kg/m^2)	24.2 ± 3.5	25.0 ± 3.1	23.5 ± 3.6	**<0.001**
BSA (m^2)	1.7 ± 0.2	1.7 ± 0.2	1.6 ± 0.2	**<0.001**
SBP (mm Hg)	126.9 ± 19.1	129.2 ± 19.4	124.7 ± 18.6	**0.002**
DBP (mm Hg)	77.8 ± 12.4	79.0 ± 12.6	76.6 ± 12.1	**0.008**
HR (beats/min)	74.4 ± 13.7	74.8 ± 13.2	74.1 ± 14.1	0.45
Diabetes mellitus	64 (8.6)	34 (9.1)	30 (8.0)	0.60
Hypertension	241 (32.2)	133 (35.6)	108 (28.9)	0.05
CAD	69 (9.2)	36 (9.6)	33 (8.8)	0.71
Atrial fibrillation	18 (2.4)	4 (1.1)	14 (3.7)	0.02
NT-proBNP (pg/mL)	1,057.5 (432.8-2,107.3)	1,222.5 (482.5-2,440.0)	950.5 (408.3-1,850.5)	0.14
Serum creatinine (μmol/L)	78.2 ± 21.3	79.1 ± 23.6	77.3 ± 19.2	0.42
Obstructive HCM	308 (41.2)	161 (43)	147 (39.3)	0.30
NYHA functional class				0.13
I/II	665 (88.9)	339 (90.6)	326 (87.2)	
III/IV	83 (11.1)	35 (9.4)	48 (12.8)	
Peak LVOT gradients (mm Hg)	6 (5-49)	14 (5-56)	5 (5-44)	0.11
Family history of SCD	68 (9.1)	29 (7.8)	39 (10.4)	0.20
History of syncope	83 (11.1)	34 (9.1)	49 (13.1)	0.08
NSVT	68 (9.1)	23 (6.1)	45 (12.0)	0.01
ESC risk score	2.7 ± 1.9	2.5 ± 1.5	2.9 ± 2.2	**0.007**
Beta-blocker	465 (62.2)	235 (62.8)	230 (61.5)	0.71
ACEI inhibitors or ARB	81 (10.8)	41 (11)	40 (10.7)	0.91
Spironolactone	50 (6.7)	17 (4.5)	33 (8.8)	**0.02**
Diuretics	70 (9.4)	22 (5.9)	48 (12.8)	**0.001**
Antiplatelet drug	3 (0.4)	2 (0.5)	1 (0.3)	1.00
Coumadin	35 (4.7)	9 (2.4)	26 (7.0)	**0.003**
CMR parameters				
LVEF (%)	61.0 ± 10.3	62.3 ± 9.2	59.8 ± 11.2	**0.001**
LVEDVi (mL/m^2)	81.9 ± 20.9	80.5 ± 15.6	83.3 ± 25.1	0.09
LVESVi (mL/m^2)	33.2 ± 20.0	31.2 ± 13.8	35.3 ± 24.7	**0.01**
RVEF (%)	58.9 ± 9.5	58.9 ± 8.5	58.9 ± 10.4	0.93
RVEDVi (mL/m^2)	62.0 ± 14.9	63.1 ± 14.0	60.9 ± 15.7	0.05
RVESVi (mL/m^2)	36.4 ± 10.0	37.2 ± 9.2	35.6 ± 10.7	**0.03**
LV mass index (g/m^2)	97.4 ± 34.9	99.4 ± 32.2	95.4 ± 37.5	0.13
Max LVT (mm)	21.6 ± 5.2	21.1 ± 5.3	22.0 ± 5.1	0.03
LA size (mm)	40.4 ± 6.8	40.2 ± 6.4	40.5 ± 7.2	0.56
LV LGE extent (%)	3.9 (0-9.6)	2.1 (0-6.1)	6.0 (2.0-14.8)	**<0.001**
LV LGE presence	534 (72)	239 (64.2)	295 (79.7)	**<0.001**
Low LGE extent (</15%)	624 (84.1)	342 (91.9)	282 (76.2)	**<0.001**
Native T1 (ms)	1332.9 ± 72.0	1301.0± 53.8	1364.37 ± 73.85	**<0.001**
ECV (%)	29.5 ± 4.7	28.1 ± 4.1	30.78 ± 4.92	**<0.001**
LV entropy				
LGE mean entropy	5.83 ± 0.78	5.82 ± 0.66	5.84 ± 0.89	0.69
Mean entropy	4.06 (1.48-8.83)	1.49 (0.71-2.58)	8.83 (5.83-14.42)	**<0.001**
Basal entropy	3.18 (1.23-8.20)	1.37 (0.46-2.61)	8.02 (4.12-13.13)	**<0.001**
Middle entropy	2.14 (0.62-6.13)	0.70 (0.16-1.57)	5.93 (2.87-10.46)	**<0.001**
Apical entropy	4.23 (1.06-11.53)	1.47 (0.34-3.34)	11.67 (6.1-22.59)	**<0.001**

Values are mean ± SD, n (%), or median (IQR). The **bold** type of the *P* values showed a value of less than 0.5.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; BSA = body surface area; CAD = coronary artery disease; CVD = cardiovascular death; DBP = diastolic blood pressure; ECV = extracellular volume; ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; HR = heart rate; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular; LVEDVi = LV end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; LVOT = left ventricular outflow tract; Max LVT = left ventricular maximal wall thickness; NSVT = nonsustained ventricular tachycardia; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVESVi = right ventricular end-systolic volume index; SBP = systolic blood pressure; SCD = sudden cardiac death.

FIGURE 2 **Kaplan-Meier Analyses for Study Endpoints for Left Ventricular Entropy**



Patients were stratified by left ventricular mean entropy cutoff value (4.06). In the (A to C) total study group and (B to D) patients with low late gadolinium enhancement extent (<15%), Kaplan-Meier curve analyses revealed that participants with high left ventricular entropy were more likely to experience sudden cardiac death–related events (A to B) and cardiovascular death endpoint (C to D). CMR = cardiovascular magnetic resonance.

1.11-11.72; $P = 0.03$), high LGE (≥15%) extent (HR: 3.51; 95% CI: 1.86-6.60; $P < 0.001$), LV LGE extent (HR: 1.05; 9% CI: 1.03-1.07; $P < 0.001$), all LV mean entropy (HR: 1.05; 95% CI: 1.02-1.09; $P = 0.001$) were significant predictors of SCD (Table 2). Age (HR: 1.04; 95% CI: 1.02-1.06; $P < 0.001$), AF (HR: 4.01; 95% CI: 1.73-9.29; $P = 0.001$), left atrial size (HR: 1.05; 95% CI: 1.02-1.09; $P = 0.002$), NSVT (HR: 3.82; 95% CI: 2.22-6.59; $P < 0.001$), history of syncope (HR: 2.20; 95% CI: 1.22-3.97; $P = 0.009$), LVEF (HR: 0.95; 95% CI: 0.93-0.97; $P < 0.001$), RVEF (HR: 0.96; 95% CI: 0.94-0.98; $P < 0.001$), an LV apical aneurysm (HR: 3.02; 95% CI: 1.10-8.32; $P = 0.03$), high LGE (≥15%) extent (HR: 3.96; 95% CI: 2.42-6.47; $P < 0.001$), extent of LV LGE (HR: 1.05; 95% CI: 1.04-1.07; $P < 0.001$), and all LV entropy parameters (LV mean entropy, HR: 1.07; 95% CI: 1.05-1.10; all $P < 0.001$) were independently associated with CVD (Table 2). However, there was no independent prognostic value of LV LGE entropy on SCD and CVD (all $P > 0.05$).

Inasmuch as there was collinearity between LV mean entropy and LV LGE extent, LV LGE extent was converted to a discrete variable denoted by a cutoff value of 15% for the multivariable Cox model when the model included LV entropy and LGE. The cutoff value of LGE was based on previous studies demonstrating that a threshold for LGE (≥15%) of the LV represents a significant (>2-fold) increase in all-cause mortality, cardiovascular mortality, SCD, and heart failure risk.[2,16] In a multivariable competing risk analysis, LV mean entropy was a significant predictor for SCD (HR: 1.03; 95% CI: 1.00-1.06; $P = 0.01$-0.03), after adjustment for age, maximal LV thickness, LA size, peak left ventricular outflow tract resting gradients, family history of SCD or history of syncope, and presence of high LV LGE extent (≥15%) (Table 3).

TABLE 2 Univariate Cox Analysis for SCD and CVD Endpoint by Baseline CMR Indexes

	SCD		CVD	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (y)	1.03 (1.01-1.06)	**0.01**	1.04 (1.02-1.06)	**<0.001**
Male	1.10 (0.58-2.08)	0.77	0.64 (0.4-1.05)	0.08
Diabetes mellitus	1.18 (0.42-3.31)	0.76	1.50 (0.72-3.14)	0.28
Hypertension	1.07 (0.55-2.07)	0.85	0.92 (0.54-1.57)	0.76
CAD	0.75 (0.23-2.44)	0.63	0.93 (0.40-2.15)	0.86
Atrial fibrillation	5.51 (2.16-14.08)	**<0.001**	4.01 (1.73-9.29)	**0.001**
Apical aneurysm	3.61 (1.11-11.72)	**0.030**	3.02 (1.10-8.32)	**0.030**
NT-proBNP (pg/mL)	1.00 (1.00-1.00)	0.15	1.00 (1.00-1.00)	0.13
Obstructive HCM	0.98 (0.52-1.85)	0.96	1.05 (0.64-1.72)	0.85
Peak LVOT gradients (mm Hg)	1.00 (0.99-1.01)	0.54	1.00 (0.99-1.01)	0.90
Family history of SCD	1.43 (0.56-3.66)	0.45	1.37 (0.66-2.88)	0.40
History of syncope	1.99 (0.92-4.32)	0.08	2.20 (1.22-3.97)	**0.009**
NSVT	4.37 (2.22-8.59)	**<0.001**	3.82 (2.22-6.59)	**<0.001**
ESC risk score	1.11 (0.99-1.24)	**0.080**	1.13 (1.04-1.23)	**0.003**
CMR parameters				
LVEF (%)	0.96 (0.93-0.98)	**0.001**	0.95 (0.93-0.97)	**<0.001**
RVEF (%)	0.98 (0.95-1.01)	0.27	0.96 (0.94-0.98)	**<0.001**
LV mass index (g/m^2)	1.00 (1.00-1.01)	0.36	1.01 (1.00-1.01)	0.11
Max LVT (mm)	1.01 (0.96-1.07)	0.61	1.01 (0.96-1.05)	0.72
Max LVT >30 mm	0.32 (0.04-2.35)	0.27	0.61 (0.19-1.94)	0.40
LA size (mm)	1.04 (1-1.09)	0.07	1.05 (1.02-1.09)	**0.002**
LV LGE extent (%)	1.05 (1.03-1.07)	**<0.001**	1.05 (1.04-1.07)	**<0.001**
LV LGE presence	4.09 (1.26-13.33)	**0.020**	2.23 (1.06-4.7)	**0.030**
High LGE extent (≥15%)	3.51 (1.86-6.6)	**<0.001**	3.96 (2.42-6.47)	**<0.001**
Native T1 (ms)	1.00 (1.00-1.01)	0.06	1.01 (1.00-1.01)	**<0.001**
ECV (%)	1.05 (0.99-1.12)	0.11	1.10 (1.05-1.15)	**<0.001**
LV entropy				
LGE mean entropy	1.25 (0.39-4.01)	0.70	1.17 (0.48-2.89)	0.73
Mean entropy	1.05 (1.02-1.09)	**0.001**	1.07 (1.05-1.1)	**<0.001**
Basal entropy	1.03 (1.00-1.06)	**0.048**	1.05 (1.03-1.07)	**<0.001**
Middle entropy	1.04 (1.01-1.07)	**0.003**	1.05 (1.03-1.07)	**<0.001**
Apical entropy	1.03 (1.01-1.05)	**0.002**	1.04 (1.03-1.05)	**<0.001**

The **bold** type of the *P* values showed a value of less than 0.5.
Abbreviations as in Table 1.

In addition, multivariable Cox regression analyses showed that LV mean entropy also remained a strong independent predictor for CVD (HR: 1.06; 95% CI: 1.03-1.09; $P < 0.001$) after the presence of high LV LGE extent was included in the model (Table 3).

REPRODUCIBILITY. We found excellent intra- and interobserver reproducibility for LV entropy analysis (inter-ICC, range, 0.82-0.94, and intra-ICC, range, 0.96-1.00) (Supplemental Table 2).

DISCUSSION

In this study, we assessed the prognostic value of LV entropy measured by native T1 in participants with HCM. First, increased LV entropy was associated with SCD or CVD in participants with HCM, and the relationship was maintained even in individuals with low LGE extent (<15%). Second, in a multivariable Cox analysis, LV mean entropy remained an independent predictor of SCD and CVD after adjustment of ESC individual predictors and the presence of high LGE extent (≥15%).

Ye et al[8] found that scar heterogeneity quantified by the entropy within the scar was strongly associated with ventricular arrhythmia in HCM even after adjustment for LVEF, %LGE, LV maximal wall thickness, and left atrial diameter (HR: 2.682; 95% CI: 1.022-7.037; $P = 0.039$) in a small cohort of individuals with HCM, and Amano et al[17] reported that entropy of LGE was significantly higher in patients with HCM with a history of ventricular tachyarrhythmia than in those without (AUC = 0.72). In addition, Zhao et al[9] reported that LV LGE entropy was a robust prognosticator in predicting SCD, hospital readmission because of heart failure, and ICD implantation for ventricular arrhythmias in 109 patients with HCM

TABLE 3 Multivariable Competing Risk Analysis for SCD and Cox Regression Analysis for CVD

	SCD			CVD	
Multivariable Competing Risk	HR (95% CI)	*P* Value	Multivariable Cox Regression	HR (95% CI)	*P* Value
Model 1			Model 1		
Age (per 1-y increase)	1.03 (1.00-1.05)	**0.020**	Age (per 1-y increase)	1.03 (1.02-1.06)	**<0.001**
High LGE extent (≥15%)	2.68 (1.38-5.19)	**0.004**	LA size (per 1 mm increase)	1.03 (0.997-1.07)	0.07
LV mean entropy (per 1 increase)	1.03 (1.01-1.06)	**0.020**	NSVT	2.50 (1.38-4.52)	**0.002**
Model 2			History of syncope	1.67 (0.89-3.13)	0.11
Max LVT (per 1 mm increase)	1.00 (0.95-1.05)	0.99	High LGE extent (≥15%)	3.17 (1.90-5.29)	**<0.001**
High LGE extent (≥15%)	2.73 (1.40-5.34)	**0.003**			
LV mean entropy (per 1 increase)	1.03 (1.01-1.06)	**0.010**			
Model 3					
LA size (per 1 mm increase)	1.02 (0.98-1.07)	0.31	Model 2		
High LGE extent (≥15%)	2.59 (1.34-5.04)	**0.005**	Age (per 1 year increase)	1.03 (1.02-1.05)	**<0.001**
LV mean entropy (per 1 increase)	1.03 (1.01-1.06)	**0.020**	LA size (per 1 mm increase)	1.04 (0.999-1.07)	0.06
Model 4			NSVT	2.45 (1.36-4.42)	**0.003**
Peak LVOT gradients (per 1 mm Hg increase)	1.00 (0.99-1.01)	0.9	History of syncope	1.40 (0.74-2.66)	0.30
High LGE extent (≥15%)	2.74 (1.44-5.21)	**0.002**	LV mean entropy (per 1 increase)	1.07 (1.05-1.10)	**<0.001**
LV mean entropy (per 1 increase)	1.03 (1.01-1.06)	**0.020**			
Model 5					
Family history of SCD	1.56 (0.59-4.18)	0.37			
High LGE extent (≥15%)	2.80 (1.44-5.47)	**0.003**	Model 3		
LV mean entropy (per 1 increase)	1.03 (1.01-1.06)	**0.020**	Age (per 1 year increase)	1.03 (1.01-1.05)	**<0.001**
Model 6			LA size (per 1 mm increase)	1.03 (0.99-1.07)	0.13
NSVT	3.30 (1.59-6.83)	**0.001**	NSVT	2.15 (1.16-3.97)	**0.010**
High LGE extent (≥15%)	2.39 (1.23-4.66)	**0.010**	History of syncope	1.33 (0.69-2.56)	0.40
LV mean entropy (per 1 increase)	1.03 (0.997-1.06)	0.08	High LGE extent (≥15%)	2.22 (1.28-3.84)	**0.004**
Model 7			LV mean entropy (per 1 increase)	1.06 (1.03-1.09)	**<0.001**
History of syncope	1.83 (0.81-4.14)	**0.150**			
High LGE extent (≥15%)	2.77 (1.45-5.31)	**0.002**			
LV mean entropy (per 1 increase)	1.03 (1.00-1.06)	**0.030**			

The **bold** type of the *P* values showed a value of less than 0.5.
Abbreviations as in Table 1.

(AUC: 0.893; 95% CI: 0.794-0.993; $P < 0.001$), whereas the 2020 AHA/ACC guideline for risk stratification specified AUC 0.716 (95% CI: 0.617-0.815; $P = 0.002$). We did not find LGE entropy to be of independent prognostic value for SCD and CVD in our cohort. Our study results may differ from those of the Zhao et al[9] study as a result of patient selection. The Zhao et al[9] study had 21 patients (19.2%) reaching endpoints in 109 patients during a mean follow-up duration of 23 ± 7 months. Our study was conducted in a relatively low-risk HCM cohort with a lower LV LGE extent.

Furthermore, LGE reflects only focal scarring, and some participants without LGE also experienced arrhythmia events and SCD in HCM.[18] The T1 mapping technique can detect and quantify diffuse fibrosis and has good correlation with the histological collagen volume fraction in HCM.[3] Native T1 and ECV by CMR can characterize diffuse changes in the myocardium, and native T1 has been shown to be elevated in HCM compared with individuals with hypertension and healthy control subjects.[19] The increase could also be detected in sarcomere-gene mutation carriers with negative cardiac phenotype.[20] In addition, previous studies revealed that native T1 was associated with adverse cardiovascular events in HCM.[4,21] However, the prognostic value of LV entropy derived from T1 mapping in HCM has not been previously studied.

Wu et al[10] included 93 patients with HCM and reported that LV entropy generated from native T1 mapping was related to LV maximal wall thickness, myocardial fibrosis, and strain parameters in patients with HCM and that LV entropy showed better performance in differentiating LGE+ from LGE- segments than did mean T1 times. This difference may be caused by variations in hypertrophy and fibrosis resulting in variations in T1 elevation across different regions of the myocardium. Thus, entropy could reflect myocardial heterogeneity better than the native T1 value. In addition, Neisius et al[22] revealed that fibrosis patterns from native T1 mapping can

better differentiate between hypertensive heart disease and HCM than can global native T1. These studies indicated that LV tissue heterogeneity from native T1 images may provide more information than mean T1 times alone in HCM.

In addition, Nakamori et al[23] revealed that tissue heterogeneity, derived from native T1 mapping, was an important predictor of ventricular tachycardia and ventricular fibrillation in 115 patients with nonischemic dilated cardiomyopathy. We further demonstrated that LV tissue heterogeneity quantified by native T1 images was highly associated with SCD and CVD in HCM. Therefore, our study highlights the importance of detecting LV tissue heterogeneity in HCM, and LV T1 entropy may help to identify patients at higher risk, especially for patients with HCM with a low amount of LGE.

STUDY LIMITATIONS. Our study had limitations. This was a single-center study, and the results need to be verified in a larger multicenter cohort of participants with HCM. Second, the LV entropy was calculated by only 3 representative slices of LV, including basal, middle, and apical slices. Third, our study was conducted in a relatively low-risk HCM cohort because no patient had ICD at baseline for the CMR study. However, our study found the robust prognostic value of LV entropy in predicting adverse events in a low-risk cohort, which will help to improve risk stratification in low-risk HCM with HCM.

CONCLUSIONS

Myocardial tissue heterogeneity measured by entropy derived from native T1 mapping by CMR was an independent predictor of SCD and CVD in HCM. Risk stratification based on LV entropy from native T1 images may help with further risk stratification of HCM.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Left ventricular entropy derived from native T1 mapping, reflecting myocardial tissue heterogeneity, has excellent prognostic value for the identification of high-risk patients with HCM in a low-risk cohort. Adding this marker may improve risk stratification in patients with HCM.

TRANSLATIONAL OUTLOOK: Myocardial tissue heterogeneity may be a valuable clinical prognosticator in HCM, and the potential relationship between LV entropy and histopathological changes needs to be further explored. Future multicenter studies are warranted to validate these findings.

REFERENCES

1. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice Guidelines. *J Am Coll Cardiol*. 2020;76(25):e159–e240. https://doi.org/10.1016/j.jacc.2020.08.045

2. Weng Z, Yao J, Chan RH, et al. Prognostic value of LGE-CMR in HCM: a meta-analysis. *J Am Coll Cardiol Img*. 2016;9(12):1392–1402. https://doi.org/10.1016/j.jcmg.2016.02.031

3. Iles LM, Ellims AH, Llewellyn H, et al. Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. *Eur Heart J Cardiovasc Imaging*. 2015;16(1):14–22. https://doi.org/10.1093/ehjci/jeu182

4. Li Y, Liu X, Yang F, et al. Prognostic value of myocardial extracellular volume fraction evaluation based on cardiac magnetic resonance T1 mapping with T1 long and short in hypertrophic cardiomyopathy. *Eur Radiol*. 2021;31(7):4557–4567. https://doi.org/10.1007/s00330-020-07650-7

5. Muthalaly RG, Kwong RY, John RM, et al. Left ventricular entropy is a novel predictor of arrhythmic events in patients with dilated cardiomyopathy receiving defibrillators for primary prevention. *J Am Coll Cardiol Img*. 2019;12(7 Pt 1):1177–1184. https://doi.org/10.1016/j.jcmg.2018.07.003

6. Androulakis AFA, Zeppenfeld K, Paiman EHM, et al. Entropy as a novel measure of myocardial tissue heterogeneity for prediction of ventricular arrhythmias and mortality in post-infarct patients. *J Am Coll Cardiol EP*. 2019;5(4):480–489. https://doi.org/10.1016/j.jacep.2018.12.005

7. Gould J, Porter B, Claridge S, et al. Mean entropy predicts implantable cardioverter-defibrillator therapy using cardiac magnetic resonance texture analysis of scar heterogeneity. *Heart Rhythm*. 2019;16(8):1242–1250. https://doi.org/10.1016/j.hrthm.2019.03.001

8. Ye Y, Ji Z, Zhou W, et al. Mean scar entropy by late gadolinium enhancement cardiac magnetic resonance is associated with ventricular arrhythmias events in hypertrophic cardiomyopathy. *Front Cardiovasc Med*. 2021;8:758635. https://doi.org/10.3389/fcvm.2021.758635

9. Zhao X, Jin F, Wang J, Zhao X, Wang L, Wei H. Entropy of left ventricular late gadolinium enhancement and its prognostic value in

hypertrophic cardiomyopathy a new CMR assessment method. *Int J Cardiol*. 2023;373:141. https://doi.org/10.1016/j.ijcard.2022.11.017

10. Wu CW, Wu R, Shi RY, et al. Histogram analysis of native T1 mapping and its relationship to left ventricular late gadolinium enhancement, hypertrophy, and segmental myocardial mechanics in patients with hypertrophic cardiomyopathy. *J Magn Reson Imaging*. 2019;49(3):668–677. https://doi.org/10.1002/jmri.26272

11. Wang J, Li Y, Yang F, et al. Fractal analysis: prognostic value of left ventricular trabecular complexity cardiovascular MRI in participants with hypertrophic cardiomyopathy. *Radiology*. 2021;298(1):71–79. https://doi.org/10.1148/radiol.2020202261

12. Wan K, Sun J, Yang D, et al. Left ventricular myocardial deformation on cine MR images: relationship to severity of disease and prognosis in light-chain amyloidosis. *Radiology*. 2018;288(1):73–80. https://doi.org/10.1148/radiol.2018172435

13. Wang J, Bravo L, Zhang J, et al. Radiomics analysis derived from LGE-MRI predict sudden cardiac death in participants with hypertrophic cardiomyopathy. *Front Cardiovasc Med*. 2021;8:766287. https://doi.org/10.3389/fcvm.2021.766287

14. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): board of trustees task force on standardized post-processing. *J Cardiovasc Magn Reson*. 2020;22(1):19. https://doi.org/10.1186/s12968-020-00610-6

15. Wang J, Yang F, Liu W, et al. Radiomic analysis of native T1 mapping images discriminates between MYH7 and MYBPC3-related hypertrophic cardiomyopathy. *J Magn Reson Imaging*. 2020;52(6):1714–1721. https://doi.org/10.1002/jmri.27209

16. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130(5):484–495. https://doi.org/10.1161/CIRCULATIONAHA.113.007094

17. Amano Y, Suzuki Y, Yanagisawa F, Omori Y, Matsumoto N. Relationship between extension or texture features of late gadolinium enhancement and ventricular tachyarrhythmias in hypertrophic cardiomyopathy. *Biomed Res Int*. 2018;2028:4092469. https://doi.org/10.1155/2018/4092469

18. Ho CY, Lopez B, Coelho-Filho OR, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. *N Engl J Med*. 2010;363(6):552–563. https://doi.org/10.1056/NEJMoa1002659

19. Xu J, Zhuang B, Sirajuddin A, et al. MRI T1 mapping in hypertrophic cardiomyopathy: evaluation in patients without late gadolinium enhancement and hemodynamic obstruction. *Radiology*. 2020;294(2):275–286. https://doi.org/10.1148/radiol.2019190651

20. Hinojar R, Varma N, Child N, et al. T1 Mapping in discrimination of hypertrophic phenotypes: hypertensive heart disease and hypertrophic cardiomyopathy: findings from the International T1 multicenter cardiovascular magnetic resonance study. *Circ Cardiovasc Imaging*. 2015;8(12):e003285. https://doi.org/10.1161/CIRCIMAGING.115.003285

21. Qin L, Min J, Chen C, et al. Incremental values of T1 mapping in the prediction of sudden cardiac death risk in hypertrophic cardiomyopathy: a comparison with two guidelines. *Front Cardiovasc Med*. 2021;(8):661673. https://doi.org/10.3389/fcvm.2021.661673

22. Neisius U, El-Rewaidy H, Nakamori S, Rodriguez J, Manning WJ, Nezafat R. Radiomic analysis of myocardial native T(1) imaging discriminates between hypertensive heart disease and hypertrophic cardiomyopathy. *J Am Coll Cardiol Img*. 2019;12(10):1946–1954. https://doi.org/10.1016/j.jcmg.2018.11.024

23. Nakamori S, Ngo LH, Rodriguez J, Neisius U, Manning WJ, Nezafat R. T1 Mapping tissue heterogeneity provides improved risk stratification for ICDs without needing gadolinium in patients with dilated cardiomyopathy. *J Am Coll Cardiol Img*. 2020;13(9):1917–1930. https://doi.org/10.1016/j.jcmg.2020.03.014

KEY WORDS cardiac magnetic resonance, entropy, hypertrophic cardiomyopathy, sudden cardiac death, T1 mapping

APPENDIX For supplemental methods, references, and tables, please see the online version of this paper.