Diagn Interv Radiol 2023; DOI: 10.4274/dir.2023.221859

CARDIOVASCULAR IMAGING

ORIGINAL ARTICLE

Can left ventricular entropy by cardiac magnetic resonance late gadolinium enhancement be a prognostic predictor in patients with left ventricular non-compaction?

Yun-Ting Ma#
Lu-Jing Wang#
Xiao-Ying Zhao
Yue Zheng
Li-Hui Sha
Xin-Xiang Zhao

#Co-first author Yun-Ting Ma and Lu-Jing Wang contributed to this work equally.

PURPOSE

Left ventricular non-compaction (LVNC) is considered rare; however, the use of cardiac magnetic resonance (CMR) has shown that its incidence is not uncommon, and its clinical presentation remains variable, with an uncertain prognosis. Risk stratification of major adverse cardiac events (MACE) in patients with LVNC remains complex. Therefore, this study aims to determine whether tissue heterogeneity from late gadolinium enhancement-derived entropy is associated with MACE in patients with LVNC.

METHODS

This study was registered in the Clinical Trial Registry (CTR2200062045). Consecutive patients who underwent CMR imaging and were diagnosed with LVNC were followed up for MACE, which was defined by heart failure, arrhythmias, systemic embolism, and cardiac death. The patients were divided into MACE and non-MACE groups. The CMR parameters included left ventricular (LV) entropy, LV ejection fraction (LVEF), LV end-diastolic volume, LV end-systolic volume (LVESV), and LV mass (LVM).

RESULTS

Eighty-six patients (age: 45.48 ± 16.64 years; female: 62.7%; LVEF: 42.58 ± 17.20%) were followed up for a median of 18 months and experienced 30 MACE events (34.9%). The MACE group showed higher LV entropy, LVESV, and LVM and lower LVEF than the non-MACE group. LV entropy [hazard ratio (HR): 1.710, 95% confidence interval (CI): 1.078–2.714, $P = 0.023$] and LVEF (HR: 0.961, 95% CI: 0.936–0.988, $P = 0.004$) were independent predictors of MACE ($P < 0.050$) according to the Cox regression analysis. Receiver operating characteristic curve analysis revealed that the area under the curve of LV entropy was 0.789 (95% CI: 0.687–0.869, $P < 0.001$), LVEF was 0.804 (95% CI: 0.699–0.878, $P < 0.001$), and the combined model of LV entropy and LVEF was 0.845 (95% CI: 0.751–0.914, $P < 0.050$).

CONCLUSION

LGE-derived LV entropy and LVEF are independent risk indicators of MACE in patients with LVNC. The combination of the two factors was more conducive to improving the prediction of MACE.

KEYWORDS

Left ventricular non-compaction, cardiac magnetic resonance, entropy, major adverse cardiovascular events, prognosis

From the Department of Radiology (Y-T.M., X-Y.Z., Y.Z., L-H.S., X-X.Z. ✉ zhaoxinxiang2918@outlook.com), The Second Affiliated Hospital of Kunming Medical University, Kunming, China; Department of Radiology (L-J.W), West China Hospital of Sichuan University, Chengdu, China.

Received 30 August 2022; revision requested 19 September 2022; last revision received 06 January 2023; accepted 31 January 2023.

Epub: 20.03.2023

Publication date: xx.xx.2023

DOI: 10.4274/dir.2023.221859

You may cite this article as: Ma YT, Wang LJ, Zhao XY, Zheng Y, Sha LH, Zhao XX. Can left ventricular entropy by cardiac magnetic resonance late gadolinium enhancement be a prognostic predictor in patients with left ventricular non-compaction? . *Diagn Interv Radiol.* 20 March 2023 DOI: 10.4274/dir.2023.221859 [Epub Ahead of Print].

Left ventricular non-compaction (LVNC) is a heterogeneous disease that leads to changes in cardiac function and structure. In 2007, the European Society of Cardiology classified LVNC as unclassified cardiomyopathy, affecting mainly the apical, anterior, and lateral walls of the left ventricle (LV).[1] Typical histologic manifestations of LVNC include abnormally thickened trabeculae, deep intertrabecular depression, disordered arrangement of the myofilament bundles, intermyofilament fibrosis, and microcirculatory ischemia.[2] The disease may be asymptomatic at the beginning; however, major adverse cardiovascular events (MACE), such as heart failure (HF), arrhythmias, systemic emboli, and cardiac death, often occur at the end stage. The incidence of MACE in patients with LVNC has been reported to be approximately 38%.[3] Therefore, the long-term prognosis of patients with LVNC is poor, necessitating the search for effective indicators that would aid in assessing the risk of MACE in patients with LVNC, which is crucial for early clinical treatment and intervention.

As the gold standard for the non-invasive assessment of cardiac structure and function,[4] cardiac magnetic resonance (CMR) enables the direct observation of the anatomy of LVNC and provides insight into myocardial perfusion imaging, the visualization of non-compacted myocardium, detection of myocardial fibrosis, and identification of intracavitary thrombi. Therefore, CMR plays a crucial role in the diagnosis, risk stratification, and treatment of patients with LVNC.[5,6] Positive late gadolinium enhancement (LGE) and LV systolic dysfunction [left ventricular ejection fraction (LVEF) <50%] have been used to determine the prognosis of patients with LVNC.[3] However, some investigations have discovered that even individuals with negative LGE and normal LVEF can develop MACE.[7] Therefore, it is necessary to explore improved measures for assessing the prognosis of patients with LVNC. Entropy, a parameter based on the texture analysis of LGE, reflects the heterogeneity of the myocardium by evaluating the complexity of the image signal.[8] The calculation of entropy is based on the distribution of the signal intensity (SI) of the LV myocardium on the LGE images, which elucidates the characteristics of the myocardial tissue. There is no study that investigated the prognostic value of LV entropy in LVNC. Therefore, this study aims to explore the predictive value of LV entropy derived from LGE for MACE in patients with LVNC.

Main points

- Left ventricular (LV) entropy obtained based on cardiac magnetic resonance late gadolinium enhancement was an effective predictor of major adverse cardiac events in patients with LV non-compaction.
- The prognostic value of LV entropy combined with LV ejection fraction was higher than individual indicators.
- The optimal cut-off value for LV entropy was 5.09.

Methods

Study population

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (no: PJ2022105, date of the approval: March 18th, 2022), and the requirement for written informed consent was waived. This study was registered in the Clinical Trial Registry (number: CTR2200062045). Patients diagnosed with LVNC using 3.0T CMR between January 2015 and October 2020 were included in this study. The diagnostic criteria followed the Petersen criteria of 2005:[9] 1) a typical bilayered myocardial structure with a thin, compacted epicardial layer and a thick, non-compacted endocardial layer; and 2) the end-diastolic non-compacted/compacted myocardium ratio (NC/C) was >2.3 in any long-axis LV CMR image (Figure 1). The exclusion criteria for the study were as follows (Figure 2): 1) other diseases causing elevated troponin levels (such as pulmonary embolism and aortic dissection); 2) other cardiac diseases (such as myocardial infarction, hypertrophic cardiomyopathy, valvular cardiomyopathy, and congenital heart disease); 3) other severe diseases (such as malignant tumors, chronic kidney disease, liver disease, and severe infectious disease); 4) insufficient imaging quality; and 5) patients lost to follow-up. All patients were followed up by telephone, and the electronic medical records from the last visit were reviewed, with MACE as the endpoint. MACE included 1) HF: hospitalization for HF, cardiac resynchronization therapy implantation, or heart transplantation; 2) arrhythmia: malignant ventricular arrhythmia (ventricular fibrillation, sustained or non-sustained ventricular tachycardia, and implantable cardioverter-defibrillator) and atrial fibrillation; 3) systemic embolism, stroke, myocardial infarction, or peripheral arterial embolism; and 4) cardiac death. The patients were divided into MACE and non-MACE groups based on the presence or absence of MACE during the follow-up period. Elevated values for B-type natriuretic peptide (BNP) (pg/mL) were defined as ≥35 pg/mL and >125 pg/mL for N-terminal pro-BNP (NT-proBNP).

Cardiac magnetic resonance scanning

CMR imaging was performed using a 3.0-T scanner (Philips Achieva, Best, The Netherlands) and an 8-channel phased-array cardi-

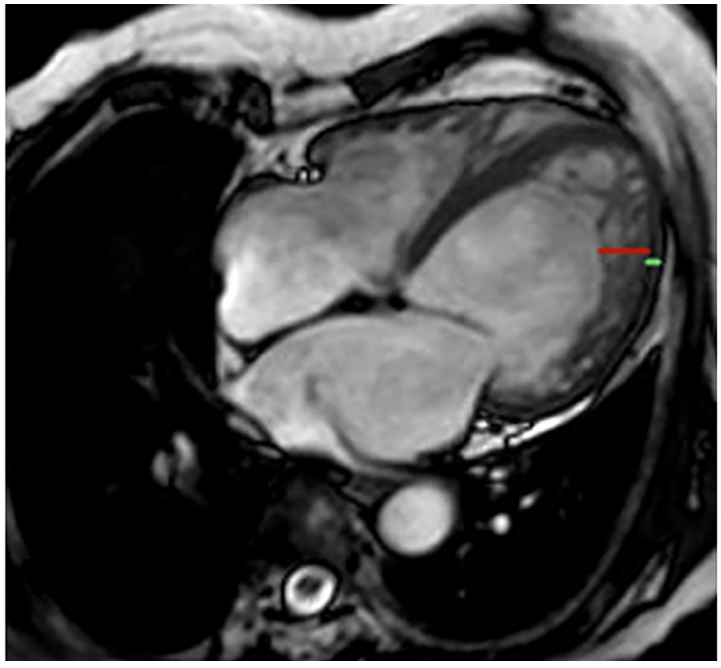

Figure 1. Cardiac magnetic resonance measurements in patients with left ventricular non-compaction. On the four-chamber cine image at the end-diastole, the non-compacted myocardium (red line)/compacted myocardium (green line) was 3.7.

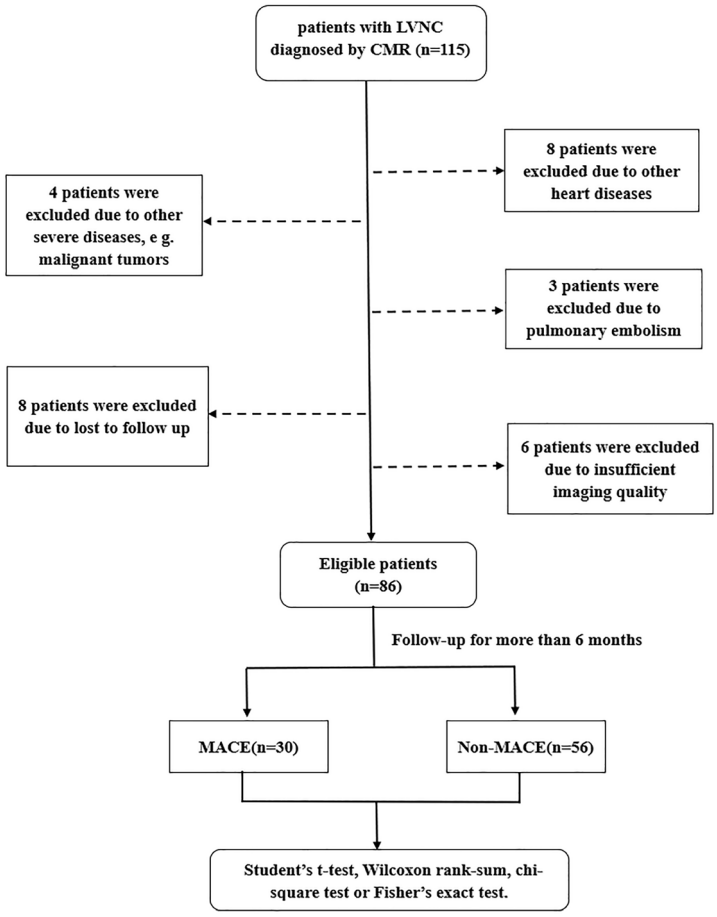

Figure 2. Patient inclusion study flow chart. LVNC, left ventricular non-compaction; CMR, cardiac magnetic resonance; MACE, major adverse cardiovascular events.

ac coil using magnetic resonance imaging (MRI)-compatible chest electrocardiogram gating technology. The true fast imaging with steady-state precession sequence was used for the positioning scan. The scanning parameters were as follows: repetition time (TR), 400 ms; echo time (TE), 1.08 ms; slice thickness, 6 mm; and field of view, 311 mm × 340 mm. Cardiac cine images of the short and long axis (LV of two, three, and four chambers) were obtained using a fast steady-state free precession sequence. The scanning parameters were as follows: TE, 1.52 ms; TR, 3.0 ms; flip angle, 45°; matrix, 178 × 181; and FOV, 350 × 350 mm. In each acquisition, 30 cardiac cycles were collected in each slice, with a slice thickness of 8 mm and a slice interval of 0 mm. The LGE images were acquired in the long-axis (two and four chambers) and short-axis planes 15 minutes after the intravenous administration of 0.2 mmol/kg of gadolinium-based contrast. The scanning parameters were as follows: TE, 2.4 ms; TR, 5.0 ms; flip angle, 25°; FOV, 320 mm × 320 mm; matrix, 168 × 153; slice thickness, 10 mm; and slice spacing, 0 mm.

Cardiac magnetic resonance image analysis

Measurements of the ventricles and atrium were acquired on steady-state free precession sine images according to the protocol used by Kawel-Boehm et al.[10] and Gürdoğan et al.[11] The anteroposterior diameter of the left atrial diameter was measured in the three-chamber cine images parallel to the mitral valve. The LV end-diastolic diameter was obtained at the level of the basal papillary muscles on the short-axis view. The diameter of the right atrium was measured during atrial diastole (maximal size of the left atrium) in the four-chamber cine images. The right ventricular end-diastolic diameter was measured on the four-chamber cine images parallel to the tricuspid valve and 1 cm distal. An analysis of the CMR images was performed using CVI 42 post-processing software (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). The endocardial and epicardial contours of the LV were automatically outlined on the short-axis cine sequence to obtain the CMR parameters, including LVEF, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV mass (LVM). The LV endocardial and epicardial contours were semi-automatically outlined on the LGE short-axis images (LV contouring was performed independently for all patients by two cardiac MRI physicians blinded to the study results; one patient underwent remeasurements at one-month intervals, and the inter- and intra-observer agreements were analyzed). Regions without over-enhancement on the LGE short-axis images were considered normal myocardial regions and were automatically selected as regions of interest (ROI). After the endocardial and epicardial contours were outlined and the ROI were set, the software automatically generated the myocardial enhancement volume percentage (LGE%). LGE was defined as myocardium six standard deviations above the mean SI. The images were subsequently imported into Python 3.8 (MathWorks, Natick, MA) software for the analysis of LV entropy. To compute the probability distribution, $P(x)$, of the SI values in the LV, the SI value of each pixel point was rated from 0 to 255. The $P(x)$ of each SI value was then calculated by counting the frequency of each SI value within the range. The entropy was calculated using the following formula:[12]

$$H(\mathbf{X}) = \mathrm{E}_{x\sim P}[I(x)] = -\mathrm{E}_{x\sim P}[\log P(x)] = \sum_{x} P(x)\log P(x)$$

where x represents the SI of each pixel point and $P(x)$ represents the probability distribution of the SI in the LV. The LV entropy was obtained subsequently (Figure 3a, b). The tissue composition was homogenous (one SI value) when the entropy was zero, whereas an entropy of 10 indicated the most robust heterogeneity.

Statistical analysis

Statistical analysis was performed using SPSS (version 26.0; IBM, Armonk, New York) and MedCalc v 15.8 (MedCalc Software, Ostend, Belgium). The mean ± standard deviation was used for normally distributed variables, whereas the M (P25, P75) was used for non-normally distributed data. The categorical variables were described as frequencies and percentages. The Student's t-test and Wilcoxon rank-sum test were used to compare the continuous variables between the two groups. The categorical variables were compared using the chi-squared test or Fisher's exact test. To assess effective risk variables, those with $P < 0.050$ among the univariable Cox proportional Hazard model were included in the multivariable Cox regression analysis. The hazard ratio (HR) and 95% con-

fidence intervals (CI) for each risk factor were also obtained. The diagnostic performance of various models was evaluated using the receiver operating characteristic (ROC) curve analysis, and the cut-off values of LV entropy were determined. The DeLong test was used to compare the area under the curve (AUC) of different predictive models. Survival analysis of patients with LVNC was performed using the Kaplan–Meier method, and the log-rank test was used to assess differences between the survival curves. Furthermore, $P < 0.050$ was considered statistically significant. The intra- and inter-observer consistency of LV entropy was analyzed using the intraclass correlation coefficient (ICC), and ICC >0.75 indicated good consistency.

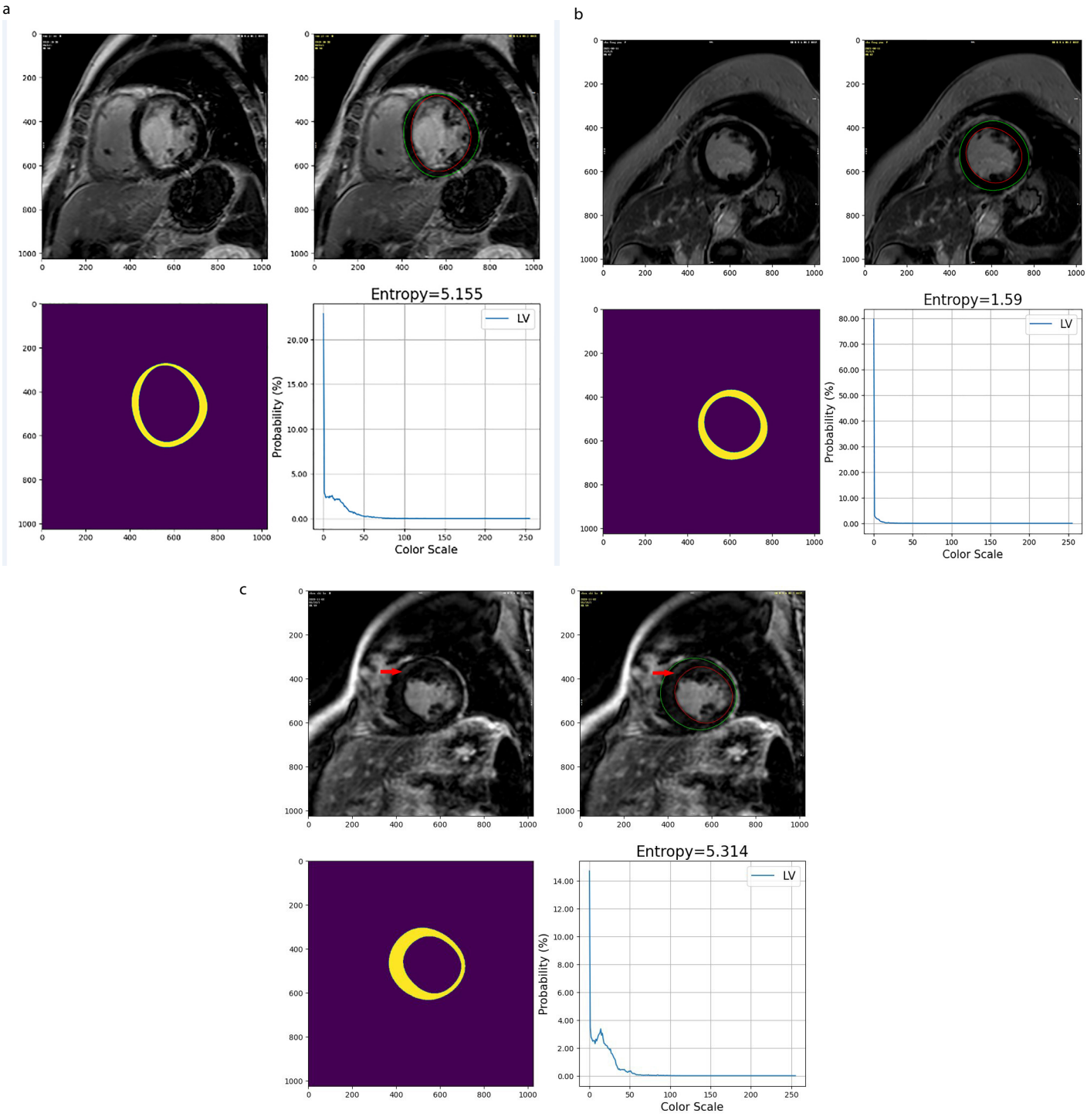

Figure 3. Three patients with left ventricular non-compaction. **(a)** A 46-year-old male patient with LVNC [NC (red line)/C (green line): 2.5], with preserved LVEF (55.46%) and high LV entropy (5.155), had a stroke after 23 months of follow-up. **(b)** A 46-year-old female patient with LVNC [NC (red line)/C (green line): 3.0], with low LVEF (32.47%) and low LV entropy (1.59), had non-MACE during the 10-month follow-up period. **(c)** A 63-year-old male patient with LVNC [NC (red line)/C (green line): 2.4], had non-MACE during the 11-month follow-up period, with preserved LVEF (50.07%) and high LV entropy (5.314). The red arrow showed the LGE. LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; NC, non-compacted; C, compacted; LGE, late gadolinium enhancement.

Results

Baseline characteristics of patients

A total of 115 patients were diagnosed with LVNC using CMR imaging. After excluding 29 cases, 86 patients with LVNC (45.48 ± 16.64 years, 54% men) were enrolled in this trial, including 56 patients without MACE and 30 patients with MACE (including 16 cases of HF, nine cases of arrhythmia, two cases of stroke, two cases of myocardial infarction, and one case of cardiac death). The baseline characteristics of the patients are shown in Table 1. There were 54 (62%) men in this cohort: 23 (76.7%) were in the MACE group, and 31 (55.4%) were in the non-MACE group. The average age of the study cohort patients was 45.48 ± 16.64 years, and the age of the patients in the MACE group was significantly higher than that of the patients in the non-MACE group (52.90 ± 15.66 years vs. 41.50 ± 15.90 years, $P < 0.050$). The differences between the two groups were not statistically significant ($P > 0.050$) for sex, height, weight, body mass index, hypertension, diabetes mellitus, alcohol consumption, smoking, lipid levels, alanine aminotransferase, aspartate aminotransferase, creatinine, uric acid, elevated BNP or NT-proBNP levels, and the New York Heart Association classification.

Cardiac magnetic resonance parameters of the patients

The CMR parameters of the patients with LVNC are shown in Table 2. Compared with the non-MACE group, the LVEF of the MACE group was lower (49.14 ± 13.75% vs. 30.35 ± 16.47%). The MACE group showed higher LV entropy, LVESV, left atrial diameter, LV diameter, and LVM when compared with the non-MACE group (5.08 ± 1.09 vs. 3.72 ± 1.34; 120.27 ± 51.32 mL vs. 94.37 ± 59.55 mL; 39.05 ± 7.57 mm vs. 35.55 ± 7.65 mm; 60.13 ± 11.5 mm vs. 55.45 ± 9.67 mm; 124.97 ± 38.86 g vs. 99.02 ± 35.91 g; $P < 0.050$). There were no significant differences between the two groups in terms of LVEDV, right atrial diameter, right ventricular diameter, NC/C ratio, and LGE% ($P > 0.050$).

Risk factors for major adverse cardiovascular events

The results of univariate and multivariate Cox regression analysis are listed in Table 3. Univariate analysis showed that age, LVEF, LVM, and LV entropy were effective predictors of MACE ($P < 0.050$). After adjusting for age and CMR parameters (LVESV, LA diameter, LV diameter, and LVM), further multivariate analysis revealed that LVEF and LV entropy remained significant predictors of MACE ($P < 0.050$). A negative correlation was found between the risk of MACE and LVEF (HR: 0.961, 95% CI: 0.936–0.988, $P = 0.004$), whereas the risk of MACE was positively associated with LV entropy (HR: 1.710, 95% CI, 1.078–2.714; $P = 0.023$).

Predictive values of indicators

The predictive values of LV entropy, LVEF, and the combined model of the two indicators for MACE in patients with LVNC are shown in Figure 4. The ROC curve analysis revealed that the predictive efficacy of the combined model of LV entropy and LVEF was the highest (AUC: 0.845, 95% CI: 0.751–0.914, $P < 0.050$), followed by LVEF (AUC: 0.804, 95% CI: 0.699–0.878, $P < 0.001$) and LV entropy (AUC: 0.789, 95% CI: 0.687–0.869, $P < 0.001$). The cut-off value of LV entropy was 5.09, with a sensitivity of 63% and a specificity of 86%. The Kaplan–Meier analysis showed that the MACE-free survival of patients with LV entropy <5.09 was significantly higher than that of patients with LV entropy ≥5.09 ($P < 0.001$) (Figure 5a, b). Moreover, the cut-off value of LVEF was 34.22%, with a sensitivity of 70% and a specificity of 84%. However, DeLong's test showed no statistically significant differences in the AUC among the three models ($P > 0.050$).

Intra- and inter-observer variability of LV entropy

The results of the ICC consistency test are presented in Table 4. LV entropy showed good intra- and inter-observer agreements (ICC >0.75).

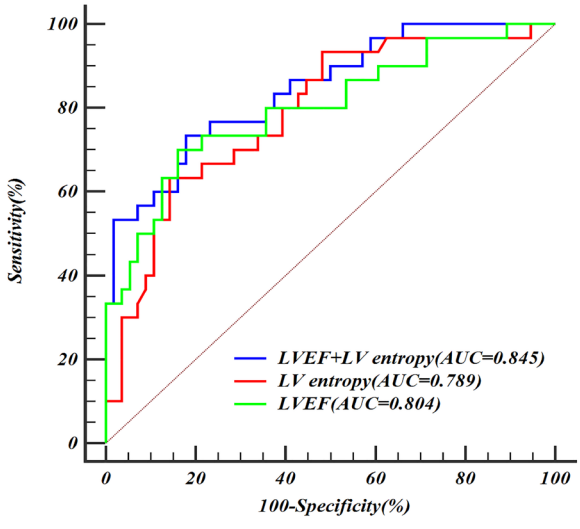

Figure 4. Receiver operating characteristic analysis. The ROC analysis of LV entropy (AUC: 0.789, 95% CI: 0.687–0.869, $P < 0.001$), LVEF (AUC: 0.804, 95% CI: 0.699–0.878, $P < 0.001$), and the combined model of LVEF and LV entropy (AUC: 0.845, 95% CI: 0.751–0.914, $P < 0.050$) for predicting MACE of LVNC. ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; LVEF, left ventricular ejection fraction; LV, left ventricular.

Discussion

The LV entropy obtained based on CMR-LGE was used for the first time in this study to predict the risk of MACE in patients with LVNC. It was demonstrated that LV entropy was a reliable indicator of prognosis in patients with LVNC and that the risk of MACE increased as LV entropy increased. Further, LV entropy could effectively predict the risk of MACE in patients with LVNC when used alone. The cut-off value for LV entropy was 5.09, and LV entropy as a novel predictor of MACE in patients with LVNC could provide valid information for clinical treatment and intervention, which could help improve the prognosis of patients with LVNC. The diagnostic rate of LVNC is rising as imaging technology and knowledge of LVNC advance, and most of the patients are relatively young.[13] Compared with sex–age-matched healthy volunteers, patients with LVNC have a much higher risk of developing MACE,[14] and HF occurs more commonly than other cardiac diseases, including dilated cardiomyopathy.[15,16] In this study, the incidence of MACE in patients with LVNC was 34.9%, with HF occurring most frequently, which was consistent with previous reports.[17-19] Therefore, investigating the prognosis of patients with LVNC has significant clinical implications.

Many studies have been conducted to predict the risk of MACE in patients with LVNC using the thickness of non-compacted myocardium and LV trabeculated mass, atrial size, LVEF, LGE, brain natriuretic peptide, and genes[3,7,19-23] with LVEF and LGE being the most commonly used predictors.[3,24] However, Yu et al.[25] found that even patients with LVEF-preserved LVNC could have impaired LV systolic function and were at risk for MACE. Additionally, although LGE could reflect a certain degree of pathological changes, such as myocardial fibrosis, it relies on a subjective visual evaluation by radiologists and might be erroneous when the degree of myocardial fibrosis is modest or when the myocardium is diffusely fibrotic.[26]

A novel texture analysis method based on CMR-LGE images was developed to quantify the degree of cardiac tissue heterogeneity of the myocardial tissue and entropy.[8]

Table 1. Baseline characteristics of patients with left ventricular non-compaction

	Total (n = 86)	MACE (n = 30)	Non-MACE (n = 56)	χ2/t/Z value	*P* value
Age (years)	45.48 ± 16.64	52.90 ± 15.66	41.50 ± 15.90	3.186	0.002*
Male [n (%)]	54	23 (76.7)	31 (55.4)	3.797	0.063
Height (m²)	1.66 ± 7.55	1.67 ± 6.99	1.65 ± 7.84	0.785	0.435
Weight (kg)	64.80 ± 13.36	65.20 ± 15.56	65.59 ± 12.17	0.201	0.419
BMI (kg/m²)	22.62 [20.74, 25.74]	21.74 [19.69, 26.02]	21.06 [21.06, 25.57]	-1.047	0.295
Hypertension [n (%)]	25	10 (33.3)	15 (26.8)	0.406	0.620
Diabetes [n (%)]	8	3 (10.0)	5 (8.9)	0.000	1.000
Drinking [n (%)]	26	13 (43.3)	13 (23.2)	3.749	0.083
Smoking [n (%)]	27	13 (43.3)	14 (25.0)	3.048	0.093
TC (mmol/L)	4.0 7 ± 1.04	4.11 ± 1.17	4.05 ± 0.97	0.273	0.786
TG (mmol/L)	1.16 [0.95, 1.61]	1.21 [0.93, 1.58]	1.15 [0.96, 1.83]	-0.217	0.828
HDL (mmol/L)	1.08 [0.92, 1.26]	1.01 [0.87, 1.28]	1.10 [0.98, 1.29]	-1.011	0.312
LDL (mmol/L)	2.53 ± 0.77	2.52 ± 0.93	2.53 ± 0.69	-0.070	0.944
ALT	28.00 [19.00, 43.25]	28.50 [22.75, 43.50]	26.50 [18.25, 43.75]	-0.594	0.553
AST	24.50 [18.00, 31.00]	26.00 [19.75, 32.50]	23.50 [18.00, 30.75]	-1.175	0.240
Cr (umoL/L)	80.29 ± 19.20	85.70 ± 15.80	77.39 ± 20.33	1.943	0.055
UA (umoL/L)	427.66 ± 137.90	417.86 ± 123.73	432.91 ± 145.72	-0.480	0.632
NYHA classification	-	-	-	-1.784	0.074
NYHA I, n (%)	42 (48.8)	11 (36.7)	31 (55.4)	-	-
NYHA II, n (%)	34 (39.5)	14 (46.7)	20 (35.7)	-	-
NYHA III, n (%)	9 (10.5)	5 (16.7)	4 (7.1)	-	-
NYHA IV, n (%)	1 (1.2)	0 (0.0)	1 (1.8)	-	-
Elevated BNP or NT-proBNP	35 (40.7)	12 (40.0)	23 (41.1)	0.009	0.923

*Statistically significant. BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; UA, uric acid; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; MACE, major adverse cardiovascular events; LVNC, left ventricular nonc-ompaction.

Table 2. Cardiac magnetic resonance parameters of patients with left ventricular non-compaction

	Total (n = 86)	MACE (n = 30)	Non-MACE (n = 56)	χ2/t/Z value	*P* value
LVEF (%)	42.58 ± 17.20	30.35 ± 16.47	49.14 ± 13.75	-5.632	<0.001
LVEDV (mL)	179.04 ± 64.06	194.06 ± 53.65	170.99 ± 68.08	1.607	0.089
LVESV (mL)	103.40 ± 57.86	120.27 ± 51.32	94.37 ± 59.55	2.014	0.047*
LA diameter (mm)	36.77 ± 7.76	39.05 ± 7.57	35.55 ± 7.65	2.032	0.047*
LV diameter (mm)	57.09 ± 10.52	60.13 ± 11.5	55.45 ± 9.67	1.998	0.049*
RA diameter (mm)	42.92 ± 7.65	44.80 ± 8.66	41.91 ± 6.92	1.683	0.096
RV diameter (mm)	36.45 ± 11.58	36.85 ± 13.91	36.23 ± 10.26	0.233	0.816
LVM (g)	108.07 ± 38.79	124.97 ± 38.86	99.02 ± 35.91	3.103	0.003*
LV entropy	4.19 ± 1.41	5.08 ± 1.09	3.72 ± 1.34	4.775	<0.001*
NC/C ratio	2.7 [2.4, 3.2]	2.7 [2.4, 3.6]	2.7 [2.4, 3.0]	-1.240	0.215
LGE%	4.69 [2.48, 8.45]	5.31 [3.36, 10.21]	4.21 [2.11, 7.90]	-1.404	0.160

*Statistically significant. LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LA, left atrial; LV, left ventricle; RA, right atrium; RV, right ventricular; LVM, left ventricular mass; NC, non-compacted; C, compacted; LGE: late gadolinium enhancement; MACE, major adverse cardiovascular events.

Entropy represents the homogeneity of an image. The entropy of an image with perfectly homogeneous pixels is zero, indicating a homogeneous, single-tissue component. The more different the tissue components of the myocardium, the more heterogeneous the LGE image signal and the higher the entropy value. Therefore, entropy can be used to evaluate the heterogeneity of the myocardial tissue and provide prognostic information objectively and quantitatively. Entropy has also been applied to other cardiac diseases. Androulakis et al.[8] demonstrated that LV entropy is correlated with the prognosis of patients with myocardial infarction. A previous study also confirmed that entropy was a valid predictor of MACE in patients with myocardial infarction.[27] Muthalaly et al.[28] used LV entropy to predict the risk of ventricular arrhythmias in patients with dilated cardiomyopathy and found that LV entropy combined with LGE significantly improved risk prediction. Therefore, the ability of LV entropy to assess the risk of ischemic and non-ischemic heart disease has been validated.

Although the typical pathology of patients with LVNC is characterized by multiple thick myotubular trabeculae,[2,29,30] it has also been suggested that hyper tubularity may only be a physiological alteration.[20,31] Further research has confirmed that the degree of myocardial fibrosis is directly connected to the long-term prognosis of patients with LVNC[32-34] and that the hyper trabeculation of LVNC is not an essential factor affecting prognosis.[15,20] Myocardial histological alterations in patients with LVNC are the pathological basis for the development of MACE. Therefore, LV entropy can quantitatively assess the degree of myocardial fibrosis in patients with LVNC and reflect the prognosis.

In this study, LV entropy was significantly higher in the MACE group than in the non-MACE group, suggesting that the patients in the MACE group had more severe and heterogeneous LV myocardial fibrosis. Further

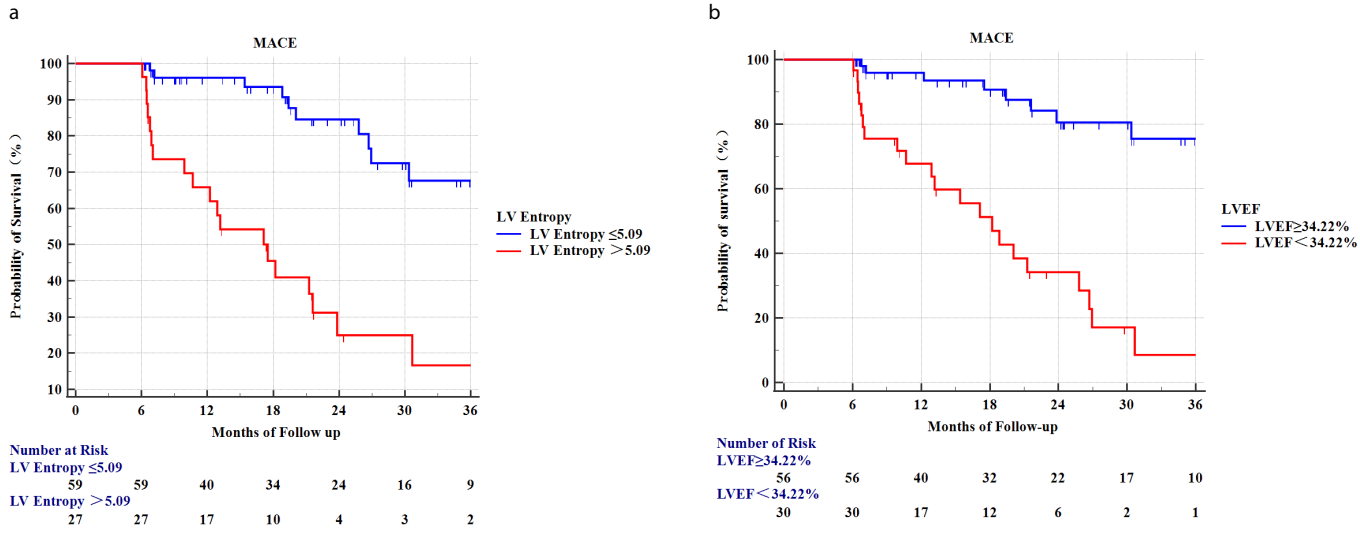

Figure 5. Prognostic value of left ventricle entropy and left ventricular ejection fraction in patients with left ventricular non-compaction. Kaplan–Meier curves showed the difference in non-MACE survival when the patients were stratified according to LV entropy **(a)** and LVEF **(b)**. LV, left ventricular; MACE, major adverse cardiovascular events; LVNC, left ventricular non-compaction.

Table 3. Risk factors for major adverse cardiovascular events in patients with left ventricular non-compaction

	Univariate analysis		Univariate analysis	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.028 (1.007–1.050)	0.008*	1.015 (0.988–1.043)	0.275
LVESV (mL)	1.005 (0.999–1.011)	0.077		
LVEF (%)	0.942 (0.920–0.965)	<0.001*	0.961 (0.936–0.988)	0.004*
LA diameter (mm)	1.033 (0.989–1.080)	0.143		
LV diameter (mm)	1.029 (0.996–1.063)	0.086		
LVM (g)	1.010 (1.002–1.018)	0.013*	1.005 (0.995–1.015)	0.310
LV entropy	2.058 (1.426–2.971)	<0.001*	1.710 (1.078–2.714)	0.023*

*Statistically significant. LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LA, left atrial; LV, left ventricular; LVM, left ventricular mass; HR, hazard ratio; CI, confidence interval.

Table 4. Intra- and inter-observer variability of left ventricle entropy

Parameters	Inter-observer		Intra-observer	
	ICC	95% CI	ICC	95% CI
LV entropy	0.978	0.967–0.986	0.984	0.976–0.990

LV, left ventricular; ICC, intraclass correlation coefficient; CI, confidence interval.

Cox regression analysis showed that LV entropy was a valid predictor of MACE, with a HR >1, indicating that LV entropy was a risk factor for MACE. The risk of MACE in patients with LVNC rises with increasing LV entropy. This study showed that age, LVESV, left atrial diameter, LV diameter, LVEF, LVM, and LV entropy differed significantly between the MACE and non-MACE groups. However, the univariable Cox proportional hazard model indicated that age, LVESV, left atrial diameter, and LV diameter were not predictors of MACE. Although Ramchand et al.[19] suggested that patients with LVNC had a higher risk for the occurrence of MACE, owing to elevated LVESV and LV dilatation, some researchers hypothesized that this mainly responded to myocardial remodeling in the advanced disease stage and was poorly associated with the risk of MACE in patients at the early stage.[35] A further multivariable Cox regression analysis showed that age and LVM were not valid predictors of MACE in patients with LVNC after excluding the effect of confounding factors, while LVEF and LV entropy remained effective predictors of MACE. Previous studies have shown that young age (<18 years) is a risk factor for MACE in patients with LVNC.[24] However, 97% of this study's participants were adults, which may be the reason why age was not a valid predictor of MACE in this study. Additionally, although myocardial remodeling in patients with LVNC could lead to an increase in LVM, it was confirmed that multiple myocardial trabeculae in patients with LVNC could affect the calculation of LVM. Therefore, the assessment of the prognosis may not be accurate.[31] The results of the ROC curve analysis demonstrated that LV entropy and LVEF had good predictive values for MACE in patients with LVNC. The predictive efficacy improved when LV entropy was combined with LVEF. However, DeLong's test revealed no statistically significant difference between the AUC of LV entropy, LVEF, and the combined models of LV entropy and LVEF. This showed that LV entropy as a single prediction model was powerful in predicting MACE in patients with LVNC, which may help simplify the prediction model. The cut-off value for LV entropy was 5.09, indicating that MACE may be more likely to occur in patients with LVNC and LV entropy >5.09. Therefore, more attention should be paid to patients with LVNC and high LV entropy in clinical practice. This study initially verified that LV entropy could be used to predict the risk of MACE in patients with LVNC. However, this study had several limitations. 1) This was a single-center study, and the CMR images of all study populations were obtained using the same device. Whether the difference in the device and field strength could affect the measurement of entropy or not requires further exploration. 2) Among the participants in this trial, 97% were adults. More pediatric patients must be included in follow-up studies. 3) This study did not perform T1 mapping and extracellular volume fraction. Future studies with T1 mapping and extracellular volume fractions are required to validate the findings of this study. 4) Although it was found that LV entropy is a novel parameter that could predict the prognosis of patients with LVNC, the relatively small number of events was a fundamental limitation. Multivariate analysis was considered an exploratory study. Therefore, future prospective studies with larger sample sizes are required to validate these findings.

In conclusion, the LV entropy obtained from CMR-LGE is an effective predictor of MACE in patients with LVNC. The risk of MACE increases with increasing entropy, which could provide a more comprehensive risk stratification for patients with LVNC.

Conflict of interest disclosure

The authors declared no conflicts of interest.

Funding

This research was supported by Major Special Projects in Yunnan Province (202203AC100007), the National Natural Science Foundation of China (82160332), the Kunming Medical University Joint Special Project: Key Project (202201AY070001-097), and the In-Hospital Clinical Research Program of the Second Affiliated Hospital of Kunming Medical University (ynllT2021010).

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