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LGE-CMR-derived texture features reflect poor prognosis in hypertrophic cardiomyopathy patients with systolic dysfunction: preliminary results

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Abstract

Objectives To evaluate the prognostic value of texture features based on late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) images in hypertrophic cardiomyopathy (HCM) patients with systolic dysfunction.

Methods 67 HCM patients with systolic dysfunction (41 male and 26 female, mean age ± standard deviation, 46.20 years ± 13.38) were enrolled. All patients underwent 1.5 T CMR cine and LGE imaging. Texture features were extracted from LGE images. Cox proportional hazard analysis and Kaplan-Meier analysis were used to determine the association of texture features and traditional parameters with event free survival.

Results Family history (hazard ratio [HR]=2.558, 95 % confidence interval [CI]=1.060–6.180), NYHA III-IV (HR=5.627, CI=1.652–19.173), left ventricular ejection fraction (HR=0.945, CI=0.902–0.991), left ventricular end-diastolic volume index (HR=1.006, CI=1.000–1.012), LGE extent (HR=1.911, CI=1.348–2.709) and three texture parameters [X0_H_skewness (HR=0.783, CI=0.691–0.889), X0_GLCM_cluster_tendency (HR=0.735, CI=0.616–0.877) and X0_GLRLM_energy (HR=1.344, CI=1.173–1.540)] were significantly associated with event free survival in univariate analysis ($p<0.05$). The HR of LGE extent (HR=1.548 [CI=1.046–2.293], 1.650 [CI=1.122–2.428] and 1.586 [CI=1.044–2.409] per 10 % increase, $p<0.05$) remained significant when adjusted by one of the three texture features.

Conclusion Increased LGE heterogeneity (higher X0_GLRLM_energy, lower X0_H_skewness and lower X0_GLCM_cluster_tendency) was associated with adverse events in HCM patients with systolic dysfunction.

Key Points

- *Textural analysis from CMR can be applied in HCM.*
- *Texture features derived from LGE images can capture fibrosis heterogeneity.*
- *CMR texture analysis provides prognostic information in HCM patients.*

Sainan Cheng and Mengjie Fang contributed equally to this work. Di Dong and Shihua Zhao contributed equally as the corresponding authors.

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Keywords Hypertrophic cardiomyopathy · Cardiac magnetic resonance · Late gadolinium enhancement · Texture features · Event-free survival

Abbreviations and acronyms

CMR	Cardiac magnetic resonance
CRTD	Cardiac resynchronization therapy defibrillator
GLCM	Grey-level co-occurrence matrix
GLRLM	Grey-level run-length matrix
HCM	Hypertrophic cardiomyopathy
ICC	Intra-/inter-class correlation coefficient
ICD	Implantable cardioverter defibrillator
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
ROC	Receiver operating characteristic
ROI	Region of interest
SCD	Sudden cardiac death
SD	Standard deviation

Introduction

Hypertrophic cardiomyopathy (HCM) is a common genetic heart muscle disease characterized by increased left ventricular (LV) wall thickness. The prevalence of HCM in general population is more than 1 to 500 [1]. The clinical profiles and outcomes proved to be heterogeneous. Most patients with HCM have an excellent prognosis, but a small number experience sudden cardiac death (SCD) or heart failure [2]. A key mechanism for adverse events is considered to be myocardial fibrosis, which is a hallmark of HCM.

Cardiac magnetic resonance (CMR) is an accurate and highly reproducible measurement for patients with myocardial hypertrophy or cardiac dysfunction [3]. Since the first report in 2002 [4], late gadolinium enhancement (LGE) derived from CMR has gained wide interest to assess fibrosis in HCM. Several studies of large cohorts indicated that LGE presence and extent vary among HCM patients, and they both are possibly associated with worse prognosis. [5–8]. But patients with the same amount of LGE may experience different outcomes. There remains a clinical need to identify novel LGE markers to help in risk stratification.

Medical image texture analysis is in contrast to the traditional practice of treating medical images as pictures intended solely for visual interpretation. Texture contains important information about the structural arrangement of surfaces and their relationship to the surrounding environment which are often invisible to the naked eye. It can provide further insights into the heterogeneity of lesions by using a range of parameters, including energy, entropy, skewness, uniformity, cluster tendency, etc. Recently, the prognostic value of texture analysis based on MR imaging have been validated in oncology studies, including breast cancer [9, 10], glioblastoma [11], lung cancer [12] and colorectal cancer [13]. For patients with invasive breast cancer, higher T2 uniformity and lower T2 entropy exhibited better recurrence-free survival [9]. For patients with primary colorectal cancer [13], five texture features (lower entropy, kurtosis and standard deviation of pixel distribution; higher uniformity and skewness) were associated with a poorer 5-year overall survival rate. But texture analysis is potentially applicable to all diseases [14].

We hypothesize that texture analysis will find some characteristics of LGE to predict patients' outcome. We focus on HCM patients with systolic dysfunction, which can potentially work as a good and easy platform to assess LGE texture features and correlate them to patients' outcome. Thus, the purpose of this preliminary study was to evaluate texture features of LGE-CMR images in HCM patients with systolic dysfunction to assess its prognostic potential and to add information to further stratify this subgroup of patients.

Materials and methods

Patient cohort

Institutional review board approval was obtained for this study, and the need for informed patient consent was waived owing to its retrospective nature. We collected 67 HCM patients with advanced systolic dysfunction from January 2011 to January 2016 in Fuwai Hospital (National Center for Cardiovascular Diseases of China). All patients underwent systematic clinical evaluation and CMR examinations. HCM was defined by a wall thickness ≥15 mm or ≥13 mm in adult relatives of HCM patients that is not explained solely by loading conditions [15]. Systolic dysfunction was defined by LV ejection fraction (LVEF) <45 % at CMR [16], reflecting global systolic dysfunction; in addition, for patients with atrial fibrillation (AF), LVEF <50 % at echocardiography by averaging a minimum of five beats was also necessary [17]. Subjects were excluded if they were known to have significant coronary artery disease (defined as the presence of 50 % luminal stenosis), aortic stenosis, amyloidosis, hypertension without good control, congenital heart disease or contraindications to CMR. Syncope, New York Heart Association (NYHA) class and family history were recorded.

CMR imaging protocol

CMR examinations were performed on a 1.5-T scanner (Magneton Avanto, Siemens Medical Systems, Erlangen, Germany) with 12-channel surface phased array coils. A three-lead vector cardiogram was used for cardiac synchronization. The study consisted of: (1) scout imaging; (2) LV structure and function imaging (cine imaging); (3) first-pass perfusion imaging; and (4) LGE imaging. Total acquisition time averaged 45 min. All images were acquired with breath holding. Cine images were acquired in three long-axis views (LV two-chamber, four-chamber and LV outflow tract) and series of short-axis planes encompassing the entire LV using balanced steady state free precession sequence (field of view, 370×320mm; matrix, 192×162; slice thickness, 8mm; slice gap, 2mm). Ten to 15 min after a total dose of 0.2 mmol/kg intravenous gadopentate dimeglumine (Magnevist, Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA), LGE images were obtained at the same position as cine images using a segmented phase-sensitive inversion recovery Turbo Fast Low Angle Shot sequence (field of view, 370×320mm; matrix, 256×168; slice thickness, 8mm; slice gap, 2mm) (see Online Supplementary Material).

Conventional CMR image quantitative analysis

All images were analysed offline using a workstation with commercially available software (Intellispace portal, Philips) according to standardized CMR post-processing [18]. Conventional CMR parameters including structural and functional parameters (maximum LV wall thickness, LV mass, left atrial volume index, LV end-diastolic volume index, LV end-systolic volume index, LVEF, stroke volume index, cardiac output index) and LGE extent (LGE%) [18].

Structural and functional parameters were analysed based on cine images (see Online Supplementary Material). Left atrial volume was calculated using a biplane area-length method. Epicardial and endocardial borders of LV myocardium were manually traced in short-axis LGE images. User-defined referral regions were drawn in normal myocardium and regions of LGE were defined when the signal intensity exceeded 5 standard deviations (SD) of referral regions [19]. The regions of LGE were fine-tuned by the operator to reduce false positives when necessary. LGE imaging was quantitatively analysed using the American Heart Association 17-segment model [18]. Quantitative assessment was performed independently by a radiologist (G.Y. with 9 years of CMR experience) blinded to clinical information.

LGE semantic features

LGE can be described by radiologist-defined qualitative semantic features and computer-derived quantitative texture features. LGE semantic features, also known as LGE patterns, include mid-wall striae or patches, right ventricular side of septum, transmural, subendocardial and subepicardial [20].

LGE semantic features were interpreted by two radiologists (X.C. with 6 years of CMR experience and S.C. with 3 years of CMR experience) in consensus. Any discrepancies between the two readers were adjudicated by a senior observer (S.Z. with >10 years of CMR experience). Visual examples of LGE with different semantic features are shown in the Online Supplementary Material, Table 1.

LGE image segmentation and quantitative texture feature extraction

LGE image segmentation: LGE images were retrieved from the picture archiving and communication system and loaded into ITK-SNAP 2.2.0 software for further segmentation. Eight slices of short axial LGE images were obtained in each patient. Segmentation was done on the total volume of LGE by a radiologist (G.Y., a radiologist with 9 years of experience with CMR) blinded to the clinical profiles. The regions of interest (ROIs) were drawn as large as possible around the entire visible fibrosis, but not including edge voxels to avoid partial volume effect. ROIs that were too small (<50 mm^2) to interpret were excluded.

Texture feature extraction: An image low-pass filtering process was performed to implement image smoothing and de-noising. Separable filtering was used to avoid the multi-dimensional convolution. The convolution was performed with a low-pass "Coiflet 1" wavelet filter along x-direction and y-direction separately. A total of 90 quantitative features were extracted from the original image and its corresponding smoothed image, including the features from the categories of histogram, shape, grey-level co-occurrence matrix (GLCM) and grey-level run-length matrix (GLRLM) (see Online Supplementary Material). The process of image filtering and feature extraction was performed using in-house software with algorithms implemented in MATLAB 2014a (Mathworks, Natick, MA, USA). This was performed by an observer (M.F.) who was blinded to clinical outcome. (Fig. 1)

Intra-/inter-reader agreement analysis: Three months later, 30 patients were selected randomly and segmented again by the same radiologist (G.Y.) and by another radiologist (C.C. with 4 years of CMR experience) to assess intra-/inter-reader agreement of the feature analysis.

Follow-up

All patients were followed-up via clinic visit or telephone interview every 6 months after CMR examination. The endpoint was the composite of cardiovascular death (cardiac death due to progression of heart failure or SCD), aborted SCD, heart transplantation and unscheduled heart failure

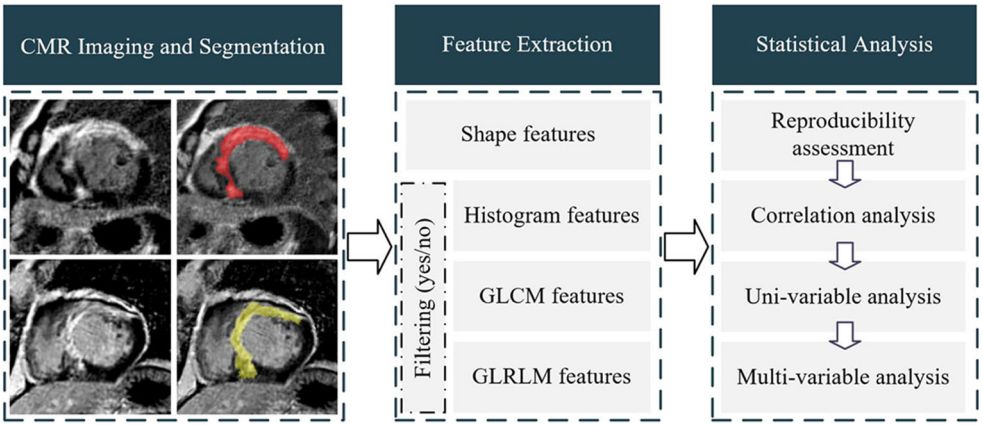

Fig. 1 Imaging segmentation and quantitative texture feature analysis flow chart

hospitalization. SCD was defined as witnessed sudden death with or without documented ventricular fibrillation or death within 1 h of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms [21]. Unscheduled heart failure hospitalization was defined as unscheduled admission for heart failure associated with the need for either increased therapy or new therapy for heart failure, and the length of stay was at least 24 h [22]. Aborted SCD was diagnosed in patients who received an appropriate implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRTD) discharge for ventricular arrhythmia or had a non-fatal episode of ventricular fibrillation or spontaneous sustained ventricular tachycardia (>30 s in duration) causing hemodynamic compromise and/or requiring cardioversion [23]. The duration of follow-up was determined from the CMR study date to the occurrence of an endpoint or the date of the last clinical follow-up.

Statistical analysis

Continuous variables are given as mean ± SD and categorical variables are described with frequencies and percentages. Based on different groups of the independent segmentations of 30 patients, the intra-/inter-class correlation coefficient (ICC) was used to estimate the robustness of the texture features extracted. An ICC greater than 0.75 was regarded as being in good agreement. In order to evaluate the relationships between different texture features, the Spearman correlation coefficients (hereafter denoted r) between each pair of features were computed. We divided all the features into different groups to ensure all pairs of features in each group had a |r| greater than 0.6. To identify texture features as the non-redundancy prognostic indicators, multivariate Cox proportional hazard regression analysis with backward stepwise selection was performed twice. In detail, this feature selection method was firstly implemented on each feature group to find their representative features and to reduce the number of candidate features, and then it was implemented on the all candidate features to determine a non-redundant and highly informative set of texture features. Backward stepwise selection was applied by using the likelihood-ratio test with Akaike's information criterion as the stopping rule [24, 25].

Kaplan-Meier curves and log rank test were used to explore the association of the LGE extent and texture features with survival. LGE extent and each texture feature were dichotomized according to the receiver operating characteristic (ROC) optimum point to split the survival curves [26]. Univariate and multivariate proportional hazard analysis was used to estimate the predictors of end point events. In addition, the prognostic abilities of the predictors were assessed by calculating the concordance probability (C index). p values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using R software (version 3.2.5; http://www.Rproject.org).

Results

Clinical characteristics and survival outcomes

A total of 67 patients were included (Fig. 2). Table 1 summarizes the baseline characteristics of the study population (more detail are shown in the Online Supplementary Material, Table 1). The average follow-up time was 20.62±12.70 months. There were seven cardiovascular deaths, including six deaths due to progression of heart failure and one SCD. Nine patients underwent heart transplantations. Eight patients underwent ICD or CRTD implantation after CMR scans and two of them experienced adequate discharge during the follow-up (see Online Supplementary Material, Table 2 for details). Two patients were unexpectedly admitted to hospital for worsening heart failure. One patient presented with sustained ventricular tachycardia. Overall, 21 patients reached the end-point. No patients died of noncardiac causes during the follow-up period.

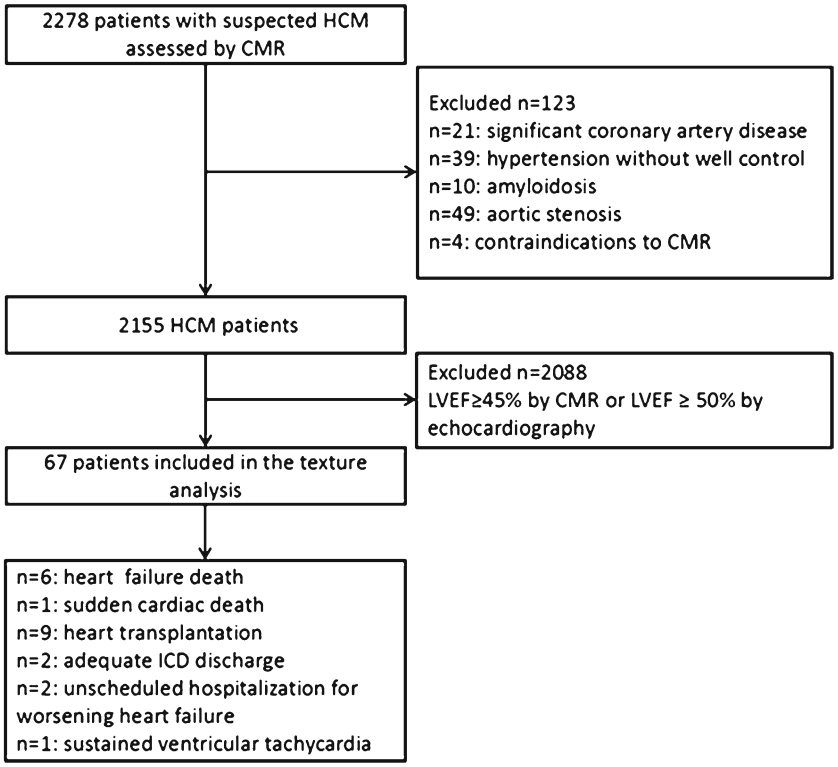

Fig. 2 Recruitment pathway for patients in this study

CMR parameters and texture features

Conventional CMR quantitative parameters are summarized in Table 1. LGE semantic features analysis showed that a transmural pattern was the most common LGE pattern in HCM with systolic dysfunction (Table 2). After assessing the reproducibility, we obtained 84 robust texture features in which ICCs were higher than 0.75. Then, 11 different groups of correlative features were recognized. Backward stepwise selection was implemented on each feature group and a total of 19 features remained. Beginning with these candidate features, a further feature selection was performed. Finally, three quantitative features (X0_H_skewness, X0_GLCM_cluster tendency and X0_GLRLM_energy) were identified as non-redundancy prognostic indicators and all of them had significant prognostic ability (Table 3).

Table 1 Clinical characteristics and conventional cardiac magnetic resonance (CMR) parameters of the patient cohort

Clinical parameters	
Age, years†	46.20±13.38
Male sex, n*	41 (61.19 %)
Family history of HCM or SCD, n*	29 (43.28 %)
Syncope, n*	6 (8.96 %)
NYHA functional class III-IV, n*	39 (58.21 %)
Conventional CMR parameters	
Maximum LV wall thickness, mm†	18.67±4.14
LV end-diastolic volume index, ml/m^{2}†	102.48±55.57
LV end-systolic volume index, ml/m^{2}†	72.85±47.34
LV ejection fraction, %†	32.23±9.34
Stroke volume index, ml/m^{2}†	30.14±12.75
Cardiac output index, L/m^{2}†	2.37±0.97
Left atrial volume index, ml/m^{2}†	91.43±44.85
LV mass index, g/m^{2}†	76.13±36.68
LGE extent, %†	31.79±13.81

* Data in parentheses are percentages

† Data are given as means ± standard deviations

SCD sudden cardiac death, *NYHA* New York Heart Association, *LV* left ventricular, *LGE* late gadolinium enhancement

Table 2 LGE semantic features of the patient cohort

LGE semantic features	Number	Percentage
Transmural	25	37.31
Non-transmural		
Only mid-myocardial striae or patches	18	26.86
Only right ventricular side of septum	7	10.45
Only subendocardial	2	2.99
Only subepicardial	3	4.48
≥ 2 non-transmural patterns	12	17.91

LGE late gadolinium enhancement

Table 3 Quantitative texture features employed in this study and intuitive description

Quantitative texture features	Category	Low-pass filtering	Mean±SD	Intuitive description
X0_H_skewness	Histogram	No	(0.75±4.25) ×10^-1	It computes the asymmetry of the first-order histogram and tends to emphasize the intensity mean being skewed to the low value
X0_GLCM_cluster_tendency	GLCM	No	(9.29±4.17) ×10^0	It measures the degree of cluster of the co-occurrence matrix and tends to emphasize the regions without any regular intensity patterns
X0_GLRLM_energy	GLRLM	No	(1.21±2.29) ×10^5	It squares each run length and tends to emphasize the unified textures

X0 features were extracted from the original image without low-pass filtering, *X1* features were extracted from its corresponding smoothed image with low-pass filtering, *H* histogram, *GLCM* grey-level co-occurrence matrix, *GLRLM* grey-level run-length matrix

Survival analysis

Among the clinical variables, family history of HCM or SCD (hazard ratio (HR)=2.558, 95 % confidence interval [CI]=1.060–6.180, p=0.037) and NYHA III-IV (HR=5.627, CI=1.652–19.173, p=0.006) were associated with adverse outcome. Regarding conventional CMR parameters, lower LVEF (HR=0.945, CI=0.902–0.991, p=0.019), higher LV

Table 4 Univariate Cox proportional hazard analyses of variables associated with event-free survival

Variable	Hazard ratio (95% CI)	C index (95 % CI)	p value
Clinical parameters			
Male sex	2.290 (0.838–6.259)	0.669 (0.440–0.898)	0.106
Family history of HCM or SCD	2.558 (1.060–6.180)	0.779 (0.621–0.938)	0.037
Syncope	2.402 (0.695–8.300)	0.682 (0.437–0.926)	0.166
NYHA functional class III-IV	5.627 (1.652–19.173)	0.879 (0.750–1.000)	0.006
Conventional CMR parameters			
Maximum LV wall thickness	0.918 (0.800–1.053)	0.375 (0.219–0.532)	0.220
LV end-diastolic volume index	1.006 (1.000–1.012)	0.626 (0.490–0.761)	0.040
LV ejection fraction	0.945 (0.902–0.991)	0.308 (0.214–0.401)	0.019
Stroke volume index	1.003 (0.973–1.034)	0.501 (0.368–0.634)	0.862
Cardiac output index	1.052 (0.694–1.593)	0.492 (0.369–0.616)	0.812
Left atrial volume index	1.007 (1.000–1.014)	0.616 (0.519–0.713)	0.064
LV mass index	0.998 (0.986–1.011)	0.431 (0.287–0.575)	0.766
LGE extent	1.911 (1.348–2.709)*	0.717 (0.600–0.833)	<0.0001
LGE semantic features			
Transmural	2.029 (0.861–4.783)	0.660 (0.466–0.853)	0.106
Only mid-myocardial striae or patches	3.913 (0.911–16.808)	0.768 (0.509–1.000)	0.067
Only right ventricular side of septum	3.221 (0.430–24.109)	0.869 (0.642–1.000)	0.255
Only subendocardial†	–	–	-
Only subepicardial	3.019 (0.699–13.044)	0.782 (0.505–1.000)	0.139
≥ 2 non-transmural patterns	1.841 (0.672–5.045)	0.644 (0.399–0.888)	0.235
Quantitative texture features			
X0_H_skewness	0.783 (0.691–0.889)*	0.276 (0.160–0.391)	<0.0001
X0_GLCM_cluster tendency	0.735 (0.616–0.877)*	0.259 (0.153–0.365)	<0.0001
X0_GLRLM_energy	1.344 (1.173–1.540)*	0.711 (0.606–0.817)	<0.0001

* HRs were calculated per 0.1, 0.1, 1 and 10^6 increase of the features value (LGE volume fraction, X0_H_skewness, X0_GLCM_cluster_tendency and X0_GLRLM_energy) respectively

† The sample size was too small to calculate HR and ICC

SCD sudden cardiac death, *NYHA* New York Heart Association, *LV* left ventricular, *LGE* late gadolinium enhancement, *GLCM* grey-level co-occurrence matrix, *GLRLM* grey-level run-length matrix

end-diastolic volume index (HR=1.006, CI=1.000–1.012, p=0.040) and LGE extent (HR=1.911 per 10 % increase, CI=1.348–2.709, p<0.001) exhibited worse event free survival outcome. Regarding texture features, X0_H_skewness (HR=0.783 per 0.1 increase, CI=0.691–0.889), X0_GLCM_cluster_tendency (HR=0.735 per 1 increase, CI=0.616–0.877) and X0_GLRLM_energy (HR=1.344 per 106 increase, CI=1.173–1.540) showed a prognostic value of event-free survival outcome (p<0.001) (Table 4).

Concerning the limited number of observed events, multivariable Cox proportional hazard analysis only included LGE extent and one texture feature. When LGE extent and one of the texture features [X0_H_skewness (HR=0.835, CI=0.723–0.965, p=0.015), X0_GLCM_cluster_tendency (HR=0.762, CI=0.629–0.924, p=0.006) and X0_GLRLM_energy (HR=1.344, CI=0.985–1.415, p=0.072) were included in the multivariable analysis, LGE extent (HR=1.548 [CI=1.046–2.293], 1.650 [CI=1.122–2.428] and 1.586 [CI=1.044–2.409] per 10 % increase respectively, p<0.05) remained a good independent predictor of event-free survival outcome, whereas X0_GLRLM_energy did not reach statistical significance.

The optimum points of LGE, X0_H_skewness, X0_GLCM_cluster tendency and X0_GLRLM_energy selected by ROC were 37 %, -0.286, 8.017 and 5.052×10^4, respectively. Kaplan-Meier curves divided by optimum point were significantly different for all variables. Higher LGE extent, higher X0_GLRLM_energy, lower X0_H_skewness and lower X0_GLCM_cluster tendency were associated with adverse events. (Figs. 3 and 4)

Discussion

The preliminary study evaluated the prognostic value of LGE extent and LGE texture features in HCM patients with systolic dysfunction (end-stage HCM patients). The main findings are that some texture features linked to LGE heterogeneity are strongly associated with adverse events in HCM patients with systolic dysfunction. To our knowledge, this is the first research concerning the prognostic value of texture analysis based on LGE images in HCM. Similar to previous studies, we also found that the LGE extent had a prognostic value in

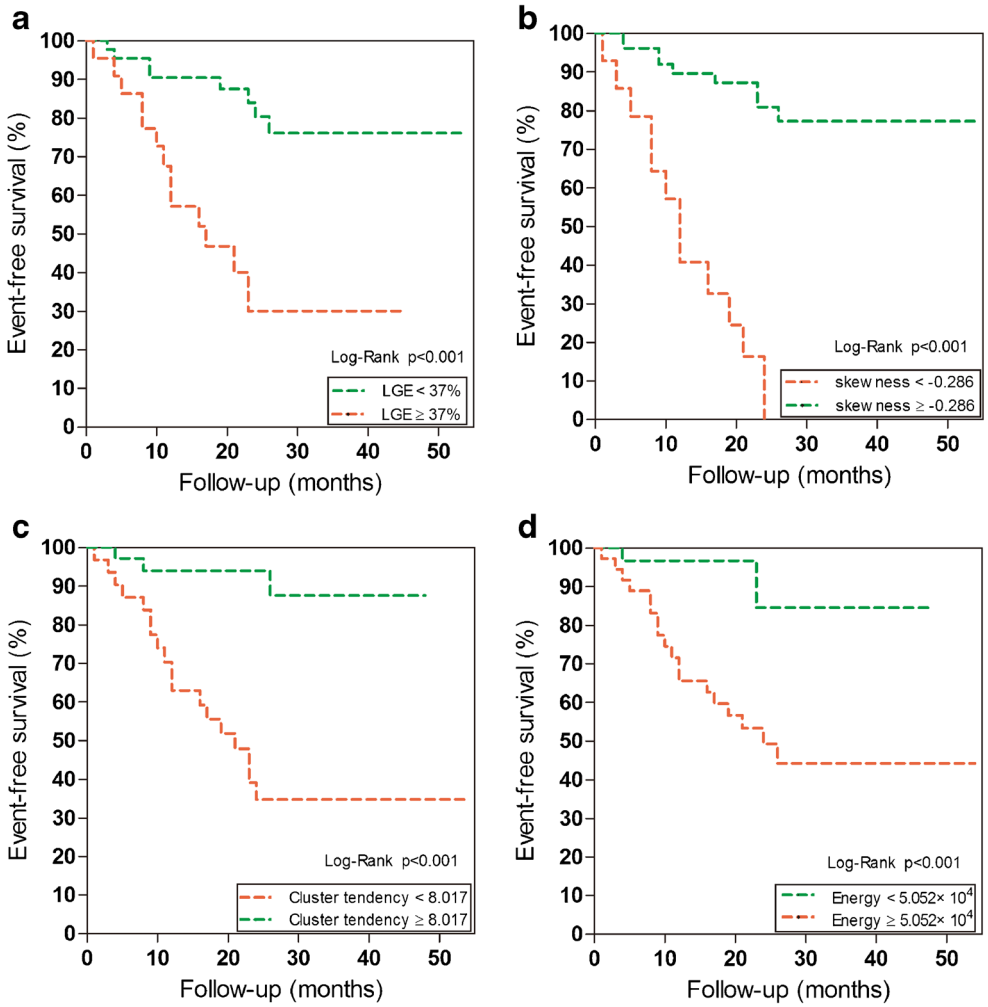

Fig. 3 Kaplan–Meier curves for LGE extent, X0_H_skewness, X0_GLCM_cluster tendency and X0_GLRLM_energy. For each parameter, the ROC optimum point was chosen to divide the entire cohort into two parts. Statistical significance between curves was determined using the log-rank test

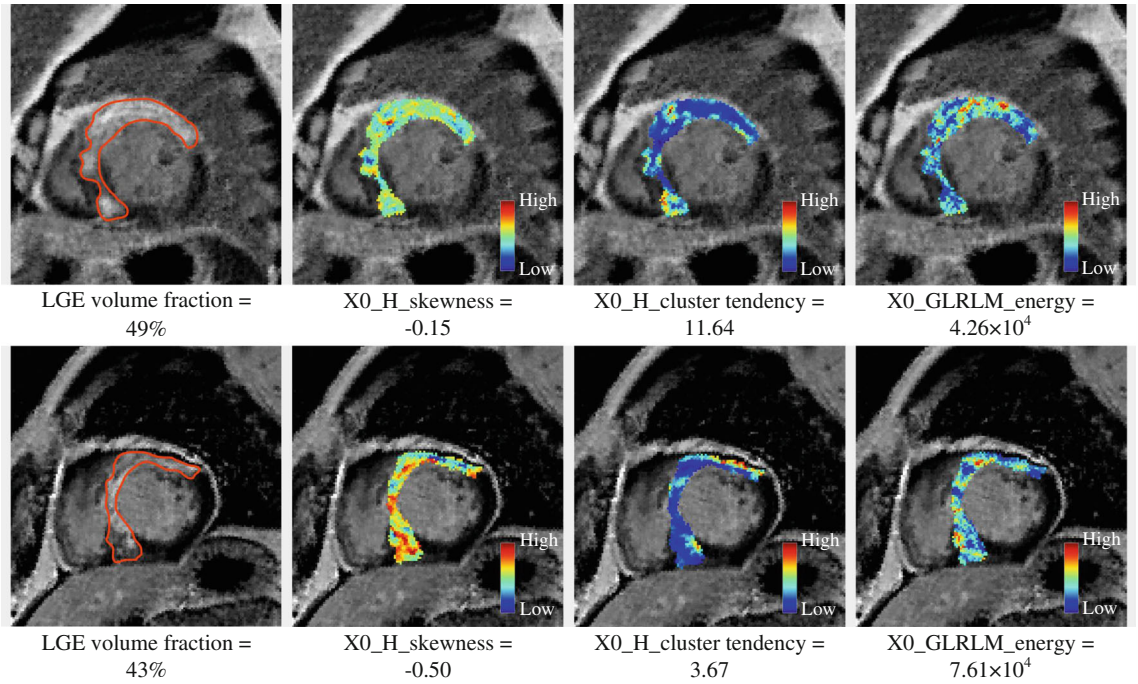

Fig. 4 Feature maps of two HCM patients with systolic dysfunction. From left to right: Short-axis LGE images, feature maps of X0_H_skewness, X0_H_cluster tendency and X0_GLRLM_energy. The texture features were computed per voxel by using a 5×5 patch centered at each voxel. Top row: Images in a 58-year-old man who was classified as low risk according to feature analysis. He underwent ICD implant 7 days after CMR scan and no adverse events occurred during 26 months of follow-up. Bottom row: Images in a 47-year-old man who was classified as high risk according to feature analysis. He underwent ICD implant 6 days after CMR scan and experienced adequate ICD discharge 12 months after ICD implant

predicting adverse cardiovascular events among HCM patients with systolic dysfunction.

Myocardial fibrosis, which can be detected in vivo by CMR-LGE, is an important cause of arrhythmia and progressive heart failure in HCM patients. The histological basis of LGE in HCM represented regions of increased myocardial collagen [4]. The expansion of extra-cellular space caused by myocardial collagen replacement leads to increased gadolinium concentration and slow-down of the contrast agent wash-out, which may explain the signal enhancement. We found an association between LGE extent and adverse outcome in HCM patients, as already shown in literature [27], which is of importance for risk stratification and further clinical decision making (such as cardiac transplantation and ICD therapy) [28, 29].

Nevertheless, LGE extent cannot assess the risk accurately due to the variable phenotype of HCM, and the adverse outcomes may be over-predicted especially in patients with large amount of LGE. In our study, some patients with similar LGE extent experienced different survival outcomes. This may be partially explained by the LGE (fibrosis) heterogeneity. The LGE heterogeneity may be caused by different fibrosis type and the mix between fibrosis and viable myocytes. There are at least three qualitative types of fibrosis in HCM with systolic dysfunction, that is, prevalently replacement (or scar-like), prevalently interstitial-perimyocyte and mixed fibrosis type according to a histological study of 30 transplanted HCM hearts with systolic dysfunction [30]. The heterogeneously distributed fibrosis not only forms electric conduction barriers but also facilitates the formation of critical isthmuses of viable myocytes that support re-entrant circuits, which is especially arrhythmogenic [31]. Novel markers to assess LGE heterogeneity is needed to improve characterization and stratification of LGE in end-stage HCM.

Therefore, our preliminary findings might have an important role in characterizing myocardial fibrosis heterogeneity, thus possibly adding information related to outcome and prognosis of HCM patients with systolic function. Specifically, we found that higher X0_GLRLM_energy, lower X0_H_skewness and lower X0_GLCM_cluster_tendency were all associated with adverse outcomes. The expansion of extra-cellular space varying degrees caused by different types of fibrosis could lead to lower symmetric myocardial intensity and consequently lower X0_GLCM_cluster_tendency, which tends to emphasize the regions without any regular intensity patterns. The disordered myocytes architecture and mix between fibrosis and viable myocytes may cause the increase of X0_GLRLM_energy, which tends to emphasize the unified textures. Dense tissue, such as myocardial scarring, may lead to a decrease of X0_H_skewness, the value of which could be suppressed by the right-skewed distribution of the CMR intensity histogram.

It is worth noting that we focused on the HCM with systolic dysfunction, which represented a very specific subgroup of HCM. The prevalence is 3.5 % (44/1259) in HCM patients according to Harris's study [32]. It is associated with high rates of heart failure death and sudden death. The overall annual mortality rate is approximately 11 % [32]. If we could distinguish patients with poor prognosis, they will benefit from more effective management strategies directed toward appropriate pharmacological treatment of pump failure and atrial fibrillation, defibrillator implantation and timely evaluation for heart transplantation. This distinctive terminal phase of HCM patients usually presents with a relatively large amount of fibrosis (occupying almost over a third of the LV) [30]. The outstanding and relatively extensive LGE can enhance texture features stability and potentially work as a good and easy platform to assess LGE texture features and correlate them to patients' outcome. Therefore, our study was only focused on HCM patients with advanced systolic dysfunction. In the study, only 21 patients reached the endpoint. Despite the limited study collective, the preliminary result demonstrated that LGE texture features may be potential predictors for prognostic assessment. The findings can be the base of further studies of general HCM.

There are several limitations to this preliminary study. First, the number of study subjects was limited and the follow-up period was short, which make it difficult to observe a robust survival outcome. Despite the limited study collective, our findings concerning LGE images should be taken as a preliminary indicator that texture analysis can be used to characterize the myocardial fibrosis spatial heterogeneity. In addition, in the multivariable analysis, the covariates are limited in number due to the number of observed events. Therefore, the predictive value of CMR parameters might be slightly lower than the current estimates from the multivariable analysis, due to over-fitting when applying the method to future cases. Furthermore, we only evaluated typical LGE areas, but the normal appearing myocardium may also contain atypical diffuse fibrosis or subtle myocardial abnormalities that were not detected by LGE.

Conclusion

In conclusion, our study showed that increased fibrosis heterogeneity (higher X0_GLRLM_energy, lower X0_H_skewness and lower X0_GLCM_cluster_tendency) was associated with adverse events in HCM patients with systolic dysfunction. Texture features could take advantage of conventional LGE-CMR images. This is a preliminary study due to the limited sample size, and further work should be conducted with a large cohort of general HCM patients and novel techniques, for example radiomics, to validate our findings.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Shihua Zhao.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry Di Dong and Mengjie Fang have significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board because of the retrospective nature.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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