

Prognostic significance of late gadolinium enhancement quantification in cardiac magnetic resonance imaging of hypertrophic cardiomyopathy with systolic dysfunction

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Abstract Hypertrophic cardiomyopathy (HCM) with systolic dysfunction carries a poor prognosis. Although late gadolinium enhancement (LGE) on cardiac magnetic resonance is associated with adverse cardiac events in HCM and is inversely related to left ventricular ejection fraction (LVEF), it is unknown whether LGE or LVEF more accurately predicts adverse cardiac events in HCM with systolic dysfunction. We retrospectively assessed the extent of LGE with a threshold of 6 standard deviations in 46 consecutive HCM patients with systolic dysfunction defined as LVEF <50 % (average 35 ± 12 %) who underwent cardiac magnetic resonance (35 males, mean age 59 ± 14 years). They were followed up over 1755 ± 594 days. The composite adverse cardiac events end point included cardiovascular death, lethal arrhythmia, cardioembolic stroke, and unplanned heart failure hospitalization. LGE was detected in all patients, and the mean extent was 30 ± 15 %. Twenty-nine patients developed adverse cardiac events. Multivariate Cox proportional hazard analysis revealed the extent of LGE as a good independent predictor of adverse cardiac events. Risk increased with the extent of LGE (hazard ratio = 1.62/10 % increase in LGE,

95 % confidence interval = 1.23–2.15, $p < 0.001$). LVEF was inversely related to the extent of LGE ($r = -0.44$; $p = 0.002$) and was also an independent predictor of adverse cardiac events. Risk decreased with LVEF (hazard ratio = 0.68/10 % increase in LVEF, 95 % confidence interval = 0.51–0.91, $p = 0.010$). The Akaike information criterion evaluating the fit of a model demonstrated that the extent of LGE was a better independent predictor of MACE than LVEF (Akaike information criterion = 172.20 and 178.09, respectively). The extent of LGE was a good independent predictor of adverse cardiac events and reflected mortality and morbidity more precisely than LVEF in HCM with systolic dysfunction.

Keywords Hypertrophic cardiomyopathy · Cardiac magnetic resonance · Late gadolinium enhancement · Prognosis

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease. HCM is widely regarded as being associated predominantly with hyperdynamic left ventricular (LV) systolic function and has a generally benign clinical course, specifically a 1 % annual mortality rate, little or no disability, and normal life expectancy in almost all patients [1–5]. LV myocardial fibrosis, a hallmark of HCM, has been implicated in promoting heart failure (HF) as well as risk of sudden arrhythmic death [6, 7]. Risk stratification in HCM is still largely limited by relatively low positive predictive values of classical clinical risk factors, due in part to low mortality rates, because the clinical markers of myocardial fibrosis have not been defined [8–11]. Recently, late gadolinium enhancement

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(LGE) by cardiac magnetic resonance (CMR) has emerged as the gold standard for imaging of myocardial fibrosis in vivo [12, 13]. Several studies and meta-analyses revealed that LGE has value in predicting adverse cardiac events and is useful in risk stratification in clinical practice, and thus might be a much better predictor than established classical clinical risk factors [10, 11, 14–20]. Although the presence and extent of LGE (% LGE) are clinically relevant, the optimal strategy for quantitating LGE in HCM is not still well defined (i.e., threshold of 2 or 6 standard deviations (SD) and full width at half maximum method) [16, 21]. On the other hand, HCM with overt systolic dysfunction (so-called end-stage phase, defined as LV ejection fraction (LVEF) <50 %) occurs in about 5 % of HCM patients, is a risk factor for adverse cardiac events, and results in an annual mortality rate of over 10 %. One of the cellular mechanisms for HCM with overt systolic dysfunction is marked LV fibrosis, which is detected by LGE [15, 22–26]. % LGE has shown an inverse relationship to LVEF in the general HCM population; however, in HCM patients with LVEF <50 %, the relationship between % LGE and LVEF is unclear because of small sample sizes in previous studies [15, 26]. % LGE in HCM with an LVEF <50 % was found to be distributed over a broad range, while that defined by a threshold of 6SD was reported to constitute a median value of 29 % of the LV volume (interquartile range 16–40 %) [26]. A recent study of a large cohort of 1293 HCM patients demonstrated that % LGE with a threshold of 6SD was a strong predictor of sudden cardiac death even in patients considered to be at lower risk for sudden cardiac death using conventional clinical risk factors. Although this study included 58 (4.5 %) HCM patients with an LVEF <50 %, the prognostic significance of % LGE with a threshold of 6SD in HCM with systolic dysfunction was not investigated [18]. Both systolic dysfunction and % LGE may be novel clinical risk factors useful for risk stratification in HCM; however, it remains unclear whether % LGE or LVEF more precisely predicts mortality and morbidity in HCM with systolic dysfunction [10, 11, 14–18, 23, 27]. Furthermore, the optimal threshold of % LGE for this purpose also remains unresolved.

Therefore, this study aimed to assess the relationship between % LGE and LVEF, as well as the prognostic value of LVEF and % LGE at several thresholds in predicting cardiac events in patients with HCM and systolic dysfunction.

Materials and methods

Patient population

This study was a retrospective analysis of data acquired in patients with HCM who underwent gadolinium-enhanced CMR for further evaluation at the National Cerebral and

Cardiovascular Center between February 2006 and August 2011. Of 114 HCM patients who underwent gadolinium-enhanced CMR, 56 consecutive HCM patients with systolic dysfunction (defined as LVEF <50 %) were identified. Of these, 10 were excluded, for the following reasons: 4 had documented prior myocardial infarction, 2 had a history of post-septal reduction therapy, 1 had a history of LV assist device removal, 1 had a history of mitral annuloplasty, and 2 had incomplete follow-up without sufficient data. The final study group consisted of 46 HCM patients with systolic dysfunction (35 males, mean age 59 ± 14 years). Of these, 40 underwent coronary angiography and were found to have no significant coronary artery disease (defined as >50 % stenosis in 1 major artery). In the 6 patients who did not undergo coronary angiography, we ruled out ischemic heart disease because the distribution of their LGE was not consistent with coronary vascular territories and did not exhibit a subendocardial pattern; 4 of these 6 who underwent stress myocardial scintigraphy showed no stress-induced ischemia. The diagnosis of HCM with systolic dysfunction was based on global LVEF <50 % at CMR acquisition with (1) the presence (or previous documentation) of an unexplained asymmetrical hypertrophied left ventricle on 2-dimensional echocardiography or CMR (maximal wall thickness ≥ 13 mm) in the absence of another disease that could account for the hypertrophy and/or cellular disarray in endomyocardial biopsy, or with (2) proven familial HCM with at least 1 relative who had an unequivocal diagnosis [1, 8, 25, 28]. Patients with coexisting HCM and hypertension were included in the study given the high prevalence of hypertension in a previous HCM cohort [29]. Patients' events were reported by their cardiologists, who reviewed their medical records after hospital stays or attendance at outpatient clinics. Variables included general characteristics and clinical risk factors for sudden cardiac death, such as family history of sudden cardiac death, non-sustained ventricular tachycardia (VT) and syncope, as well as follow-up results. Maximal wall thickness >30 mm was not adopted because of their low prevalence ($n = 1$), and abnormal blood pressure response was not used because 42 of the 46 patients were over 40 years old and the exercise test was performed in very few of them [2, 9]. LV outflow tract obstruction was defined as >30 mmHg, measured by continuous-wave Doppler under resting conditions. The start of follow-up was defined as the date of the initial CMR. Only new events from the time of CMR acquisition were considered as primary or secondary end points. This retrospective study was approved by the Institutional Ethics Committee of the National Cerebral and Cardiovascular Center (M26-07) and conformed to the principles of the Declaration of Helsinki. The institutional review board waived the need of written informed consent from the patients in this study.

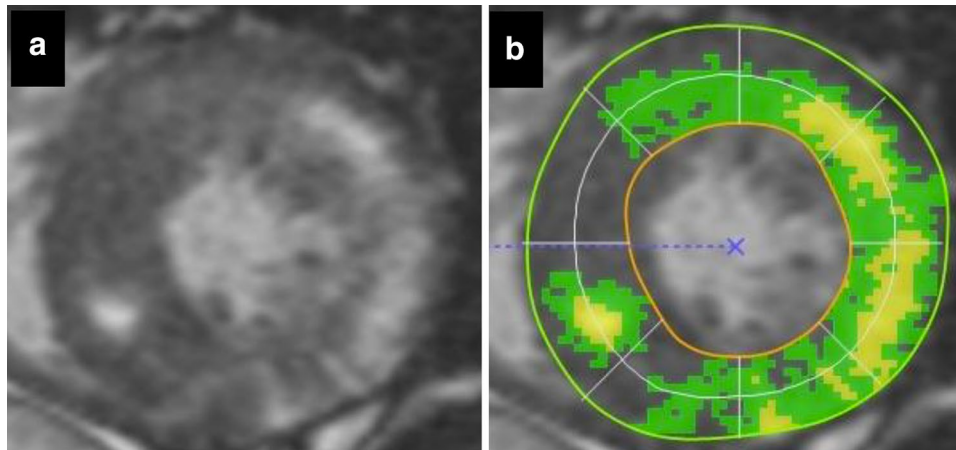


Fig. 1 Quantification of the extent of LGE in CMR. **a** Gray-scale LGE, **b** A region of interest was defined within the remote normal myocardium. The endocardial and epicardial borders were planimtered on the short-axis view. Two gray-scale thresholds of 2SD and 6SD exceeding the mean signal intensity for normal remote myocar-

dium were used to define areas of LGE. LGE volume was derived by summation of discs. Green area indicates LGE with a threshold of $\geq 2SD$ and $< 6SD$, yellow area indicates LGE with a threshold of $\geq 6SD$, and the sum of them indicates LGE with a threshold of $\geq 2SD$. Abbreviations as in Table 1

CMR protocol

CMR imaging was performed using a 1.5-T MR scanner (Magnetom Sonata; Siemens Medical solutions, Erlangen, Germany) with a standardized clinical protocol. All CMR images were electrocardiographically gated and obtained during repeated breath-holds. Cine images were acquired with the true-fast imaging with steady-state free precession (FISP) sequence with the following parameters: repetition time, 3.2 ms; echo time, 1.5 ms; flip angle, 90° ; matrix, 128×128 ; field of view, 200×200 mm; section thickness, 6 mm; and section interval, 10 mm. After localization of the heart, cine images of 9–12 contiguous short-axis sections encompassing the entire LV were collected, along with 2-, 3-, and 4-chamber long-axis projections. Gadopentetate meglumine (0.15 mmol/kg; Magnevist; Schering AG, Berlin, Germany) was then administered at a rate of 3–4 mL/s using a power injector. LGE images were acquired 10 min after the injection with an inversion-recovery prepared true-FISP sequence with inversion time of 300 ms. Among the 9–12 short-axis slices, we excluded both ends of the apex and the base because the scans of these sections did not include the LV muscle or the beveled myocardium, which caused incorrect signal intensities. Then, seven adjacent slices in the middle of the remaining slices were obtained by using localizer of LV long-axis, as previously reported [30, 31]. Other imaging variables consisted of 65 segments, echo time 1.74 ms, flip angle 60° , field of view 340×255 mm, matrix 256×129 , and voxel size $1.3 \times 2.0 \times 8.0$ mm³.

CMR data analysis

Two experienced radiologists used dedicated software to perform cine image analysis (Argus Function; Siemens Medical Solution, Germany) with calculations of LV volume, mass, and function. LGE images were analyzed by one experienced radiologist and one cardiologist on a workstation (Ziostation 2, Ziosoft, Tokyo, Japan). Regions of LGE in 7 short-axis LGE imaging slices were automatically defined as those exhibiting signal intensity above a pre-determined threshold. We defined thresholds of 2SD and 6SD above the mean signal intensity of remote non-damaged myocardium. We used 2SD because it was previously validated in detecting scars in ischemic heart disease and was utilized in several major reports regarding HCM and LGE [6, 11–13]. We used 6SD because semi-automated LGE gray-scale thresholding using 6SD greater than the mean of visually normal remote myocardium was previously shown to provide the best agreement with visual assessment and, therefore, was the most reliable method for assessing % LGE in LV myocardium in HCM [32, 33]. The mass of LGE was calculated using the area of LGE obtained from the 7 LGE imaging slices. % LGE was expressed as a percentage of LV mass according to the following equation: % LGE = [LGE mass (g)]/[LV mass (g)] \times 100. The method used for assessing % LGE and representative image is shown in Fig. 1.

Histopathology

We examined the pathological correlation of LGE with CMR to determine the etiology of LGE with a threshold of

2SD or 6SD in 3 patients with HCM with systolic dysfunction who underwent CMR and heart transplantation.

Statistical analysis

Results were summarized as mean \pm SD or frequency with percentage for continuous and categorical variables, respectively. Continuous variables were compared by the unpaired *t* test or Mann–Whitney *U* test was used, as appropriate. Categorical values were compared by Fisher exact test. The primary composite end point was major adverse cardiac events (MACE), including cardiovascular death, lethal arrhythmia, stroke due to cardiac emboli, and unplanned HF hospitalization. Separate secondary end point was unplanned HF hospitalization alone. Patients were censored at the time of their first event or the time of their last clinical follow-up regarding each end point. Statistical analysis was performed using the number of patients who experienced an index composite outcome and time to the index event. When patients experienced several cardiac events during follow-up, the first cardiac event for each end point was regarded as an index outcome. Demographic, clinical, and CMR scan characteristics were all first tested with univariate Cox proportional hazard analysis for each end point. The presence of LV outflow tract obstruction was excluded from univariate analysis because all 4 patients with this condition underwent de novo septal reduction therapy during the follow-up period without preceding cardiovascular events. For these 4 patients, the end of follow-up was regarded as the time of septal reduction therapy [20]. Multivariate Cox proportional hazards analysis was applied to separately evaluate the influence of LVEF and % LGE with a threshold of 2SD or 6SD on MACE or unplanned HF hospitalization. The covariates included in the multivariate model were selected on the basis of univariate analysis of each end point using a forward stepwise method with entrance and stay criteria of $p < 0.10$; these covariates were limited in number due to the small number of observed events. Because there was strong collinearity (correlation coefficient > 0.6) between LV end-diastolic volume index, end-systolic volume index, and LVEF, only LVEF was included in the multivariate models. History of previous stroke was also excluded from the multivariate analysis for MACE due to low prevalence ($n = 3$). The fits of multivariate models were evaluated by the Akaike information criterion. A p value < 0.05 was considered statistically significant. All analyses were performed with JMP for Windows version 11 (SAS Institute Inc., Cary, NC, USA).

Table 1 Baseline characteristics

	All patients ($n = 46$)
Clinical characteristics	
Age at baseline CMR (years)	58.8 \pm 14.2
Age at diagnosis (years)	48.2 \pm 18.9
Male, n (%)	35 (76)
Family history of HCM, n (%)	10 (22)
Family history of SCD, n (%)	7 (15)
Hypertension, n (%)	14 (30)
AF, n (%)	25 (54)
Non-sustained VT, n (%)	30 (65)
Sustained VT, n (%)	7 (15)
VF, n (%)	4 (9)
Stroke, n (%)	3 (7)
Moderate to severe MR, n (%)	5 (11)
Syncope, n (%)	14 (30)
NYHA class III or IV, n (%)	16 (35)
BNP (pg/ml)	365.2 \pm 277.5
LVOT obstruction, n (%)	4 (9)
Apical hypertrophy, n (%)	6 (13)
Apical aneurysm, n (%)	6 (13)
Baseline CMR parameters	
LVMi (g/m ²)	107.5 \pm 35.0
LVEF (%)	35.3 \pm 12.3
LVEDVi (ml/m ²)	119.9 \pm 77.6
LVESVi (ml/m ²)	84.1 \pm 75.0
% LGE \geq 2SD	53.1 \pm 14.6
% LGE \geq 6SD	30.0 \pm 15.1
Baseline medications	
Beta blocker, n (%)	39 (85)
Ca antagonist, n (%)	6 (13)
ACE inhibitor, n (%)	14 (30)
ARB, n (%)	11 (24)
Diuretics, n (%)	24 (52)
Spironolactone, n (%)	18 (39)
Pimobendan, n (%)	3 (7)
Digitalis, n (%)	6 (13)
Amiodarone, n (%)	16 (35)
Warfarin, n (%)	25 (54)

Values are mean \pm SD or n (%)

ACE angiotensin-converting enzyme, AF atrial fibrillation, ARB angiotensin receptor blocker, BNP B-type natriuretic peptide, CMR cardiac magnetic resonance, HCM hypertrophic cardiomyopathy, LGE late gadolinium enhancement, LVEDVi left ventricular end-diastolic volume index, LVEF left ventricular ejection fraction, LVESVi left ventricular end-systolic volume index, LVMi left ventricular mass index, LVOT left ventricular outflow tract, MR mitral regurgitation, NYHA New York Heart Association, SCD sudden cardiac death, SD standard deviation, VF ventricular fibrillation, VT ventricular tachycardia

Fig. 2 Relationship between LVEF and the extent of LGE. **a** LVEF and % LGE with a threshold of 2SD, **b** LVEF and % LGE with a threshold of 6SD. % LGE with a threshold of 6SD was inversely related to LVEF ($r = -0.44$; $p = 0.002$), but that with a threshold of 2SD was not ($r = -0.28$, $p = 0.060$). Abbreviations as in Table 1

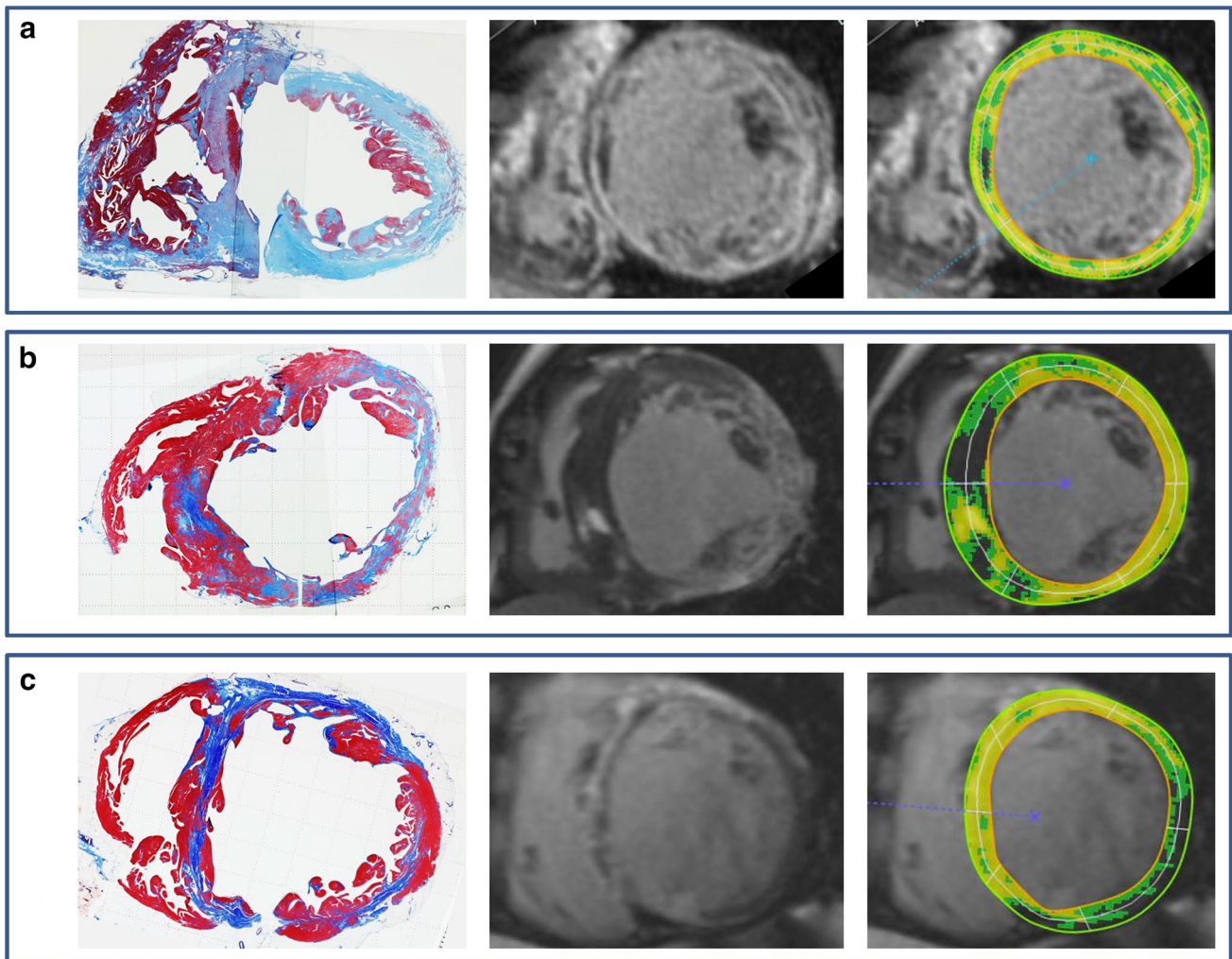
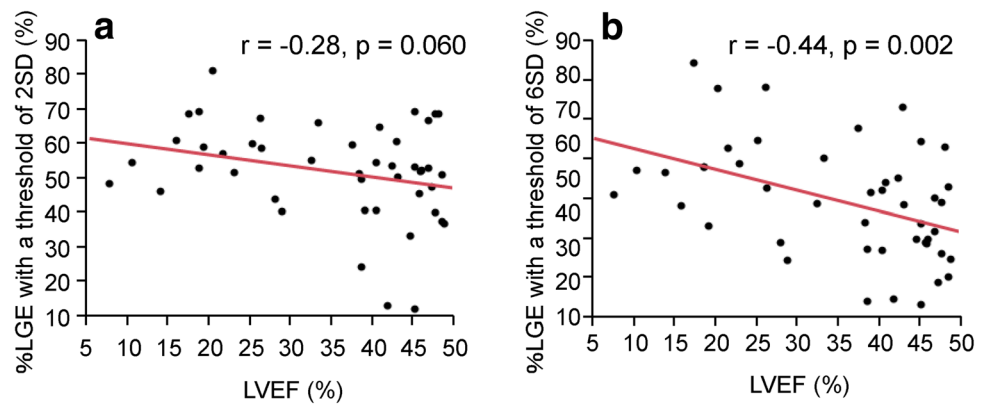


Fig. 3 LGE with histopathological correlation in three patients who underwent CMR and heart transplantation. **a** Histopathological transverse sections of explanted heart from 26-year-old male who underwent CMR 2.6 years before heart transplantation, **b** 28-year-old male,

4.5 years before, **c** 48-year-old male, 6.4 years before. *Right panels* Masson's trichrome staining, *center panels* gray-scale LGE, *left panels* LGE with thresholds of 2SD and 6SD. Abbreviations as in Table 1

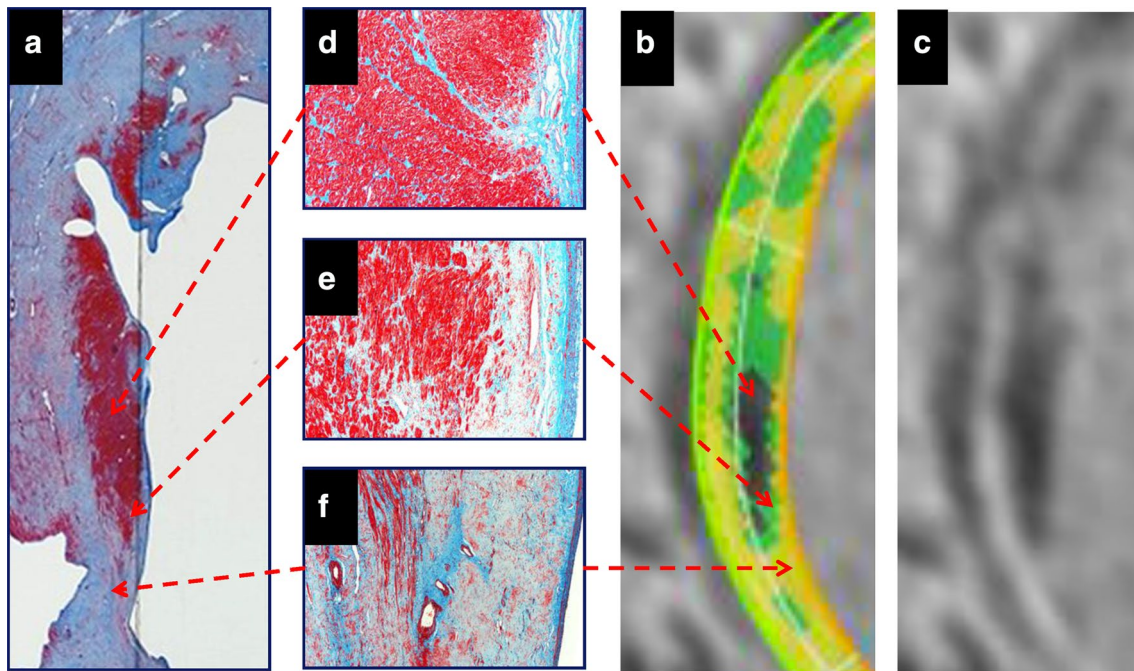


Fig. 4 A representative case of histopathological extent of fibrosis and extent of LGE of CMR. **a** Masson's trichrome stain $\times 2$, **b** LGE with thresholds of 2SD and 6SD, and **c** gray-scale LGE. **d** Histopathological finding of area of no LGE, **e** LGE with a threshold of 2SD, and **f** LGE with a threshold of 6SD. LGE defined using

a threshold of 6SD aligned closely with the distribution of replacement fibrosis, LGE with a threshold of 2SD reflected a mixture of both interstitial and replacement fibrosis, and areas with no LGE also demonstrated diffuse interstitial fibrosis. Abbreviations as in Tables 1 and 2

Table 2 Number of index and cumulative events of MACE

	Number of patients who experienced an index composite MACE outcome <i>n</i> (%)	Cumulative number of events over the follow-up period <i>n</i> (%)
Sudden death	1 (2)	1 (2)
HF death	2 (4)	11 (24)
VF	1 (2)	2 (4)
Sustained VT	2 (4)	5 (11)
Anti-tachycardia pacing	3 (7)	4 (9)
Appropriate ICD discharge	1 (2)	3 (7)
Stroke due to cardiac emboli	1 (2)	3 (7)
LVAD implantation	0 (0)	6 (13)
Heart transplantation	0 (0)	3 (7)
Unplanned HF hospitalization	18 (39)	23 (50)
Total	29 (63)	

HF heart failure, ICD implantable cardioverter-defibrillator, LVAD left ventricular assist device, MACE major adverse cardiac events, other abbreviations as in Table 1

Results

Clinical and CMR characteristics

Forty-six patients were retrospectively followed for 1755 ± 594 days (4.8 ± 1.6 years). Their baseline characteristics are summarized in Table 1. LVEF was

35.3 ± 12.3 %, ranging from 8 to 49 %. LGE was present in all patients; the mean % LGE with thresholds of 2SD and 6SD were 53.1 ± 14.6 and 30.0 ± 15.1 %, respectively. % LGE with a threshold of 6SD was inversely related to LVEF ($r = -0.44$; $p = 0.002$), but that with a threshold of 2SD was not ($r = -0.28$, $p = 0.060$) (Fig. 2).

Histopathological correlation with LGE

We performed histopathological examinations of transverse sections of explanted hearts from 3 patients who underwent heart transplantation. There was excellent agreement between the location and quantity of fibrosis in the explanted hearts and LGE on pre-explant CMR (Fig. 3). Intriguingly, LGE defined using a threshold of 6SD aligned closely with the distribution of replacement fibrosis, LGE with a threshold of 2SD reflected a mixture of both interstitial and replacement fibrosis, and areas with no LGE also demonstrated diffuse interstitial fibrosis (Fig. 4).

Clinical outcomes

During follow-up, percutaneous transluminal septal myocardial ablation was performed in all 4 patients with LV outflow tract obstruction. Implanted cardioverter-defibrillators (ICD) with or without cardiac resynchronization therapy (CRT) were implanted in 11 (24 %) and 10 (22 %) of patients, respectively. In 2 patients receiving ICDs without CRT, the ICDs were upgraded to ICDs with CRT. The reason for ICD implantation in the 21 patients was primary prevention in 15 (71 %) and secondary prevention in 6 (29 %). There were several lethal arrhythmic events and strokes due to cardiac emboli, as listed in Table 2. Overall, 23 of 46 (50 %) patients experienced several instances of unplanned HF hospitalization. Of these, 7 died of HF and 6 received implantable LV assist devices; of those receiving assist devices, 3 underwent heart transplantation and 2 died of HF. On the other hand, in patients without unplanned HF hospitalization, there was 1 sudden cardiac death and 2 HF deaths. Overall, 11 of 46 patients died of HF (Table 2). The number of adverse cardiac events included as index events in primary composite MACE outcome analysis are listed in center column of Table 2. Among the 29 patients with index primary composite MACE events, additional subsequent events were common. The cumulative number of each MACE event over the follow-up period is listed in the right column of Table 2.

MACE

During follow-up, 29 of 46 (63 %) patients met the primary end point of MACE. The breakdown of MACE is shown in Table 2. The univariate Cox proportional hazard analysis comparing different clinical and CMR characteristics is displayed in Table 3. The parameters of hypertension, New York Heart Association class III or IV and plasma B-type natriuretic peptide (BNP) levels reached statistically significant levels. In addition to CMR parameters reflecting LV remodeling, % LGE with threshold of 6SD reached statistically significant levels. Investigation of the

medications being used at the time of CMR revealed that diuretics, spironolactone, and warfarin were administered significantly more frequently among patients with MACE than those without. Significant correlations were observed between LV end-diastolic volume index and end-systolic volume index and between end-systolic volume index and LVEF ($r = 0.99$, $p < 0.0001$ and $r = -0.78$, $p < 0.0001$, respectively). As a result, LV end-diastolic and end-systolic

Table 3 Univariate Cox proportional hazards model for MACE

	HR (95 %CI)	<i>p</i> value
Clinical characteristics		
Age at baseline CMR (years)	0.99 (0.96–1.01)	0.268
Age at diagnosis (years)	0.98 (0.96–1.00)	0.111
Male, <i>n</i> (%)	1.18 (0.51–3.23)	0.710
Family history of HCM, <i>n</i> (%)	0.97 (0.38–2.18)	0.953
Family history of SCD, <i>n</i> (%)	0.98 (0.29–2.53)	0.969
Hypertension, <i>n</i> (%)	0.29 (0.10–0.70)	0.005*
AF, <i>n</i> (%)	1.33 (0.63–2.91)	0.456
Non-sustained VT, <i>n</i> (%)	1.15 (0.53–2.78)	0.729
Sustained VT, <i>n</i> (%)	1.39 (0.51–3.24)	0.488
VF, <i>n</i> (%)	2.42 (0.56–7.19)	0.204
Stroke, <i>n</i> (%)	3.90 (0.89–12.2)	0.068
Moderate to severe MR, <i>n</i> (%)	3.10 (0.89–8.38)	0.072
Syncope, <i>n</i> (%)	1.07 (0.44–2.32)	0.879
NYHA class III or IV, <i>n</i> (%)	3.07 (1.39–6.59)	0.006*
BNP (pg/ml)	1.00 (1.00–1.00)	0.008*
Apical hypertrophy, <i>n</i> (%)	0.43 (0.10–1.24)	0.128
Apical aneurysm, <i>n</i> (%)	0.64 (0.19–1.66)	0.382
Baseline CMR parameters		
LVMi (g/m ²)	1.00 (0.99–1.01)	0.956
LVEF (%)	0.96 (0.93–0.98)	0.003*
LVEDVi (ml/m ²)	1.01 (1.00–1.01)	0.003*
LVESVi (ml/m ²)	1.01 (1.00–1.01)	0.005*
% LGE ≥2SD	1.03 (1.00–1.06)	0.094
% LGE ≥6SD	1.06 (1.03–1.09)	<0.0001*
Baseline medications		
Beta blocker, <i>n</i> (%)	2.27 (0.79–9.61)	0.140
Ca antagonist, <i>n</i> (%)	0.44 (0.07–1.46)	0.201
ACE inhibitor, <i>n</i> (%)	1.78 (0.81–3.75)	0.147
ARB, <i>n</i> (%)	0.57 (0.21–1.31)	0.196
Diuretics, <i>n</i> (%)	4.03 (1.80–9.90)	<0.001*
Spironolactone, <i>n</i> (%)	2.65 (1.25–5.72)	0.011*
Pimobendan, <i>n</i> (%)	2.21 (0.52–6.42)	0.245
Digitalis, <i>n</i> (%)	1.21 (0.35–3.14)	0.730
Amiodarone, <i>n</i> (%)	1.91 (0.90–4.02)	0.092
Warfarin, <i>n</i> (%)	2.27 (1.06–5.25)	0.035*

CI confidence interval, HR hazard ratio; other abbreviations as in Table 1

* $p < 0.05$

Table 4 Multivariate Cox proportional hazards model for risk factors for MACE

	HR (95 %CI)	<i>p</i> value	AIC
Including % LGE with a threshold of 2SD model			
% LGE >2SD (per 10 %)	1.36 (1.00–1.84)	0.049*	178.97
Hypertension, <i>n</i> (%)	0.34 (0.11–0.89)	0.027*	
BNP (per 100 pg/ml)	1.12 (0.98–1.26)	0.095	
Including % LGE with a threshold of 6SD model			
% LGE >6SD (per 10 %)	1.62 (1.23–2.15)	<0.001*	172.20
Hypertension, <i>n</i> (%)	0.43 (0.14–1.12)	0.085	
Including LVEF model			
LVEF (per 10 %)	0.68 (0.51–0.91)	0.010*	178.09
BNP (per 100 pg/ml)	1.17 (1.02–1.31)	0.024*	

AIC Akaike information criterion; other abbreviations as in Tables 1, 2 and 3

* $p < 0.05$

volume indices were omitted while LVEF was selected for multivariate analysis. Multivariable Cox proportional hazard analysis revealed that % LGE with a threshold of 2SD, % LGE with a threshold of 6SD, and LVEF were independent predictors of MACE (hazard ratio = 1.36/10 %, 95 % confidence interval = 1.00–1.84, $p = 0.049$; hazard ratio = 1.62/10 %, 95 % confidence interval = 1.23–2.15, $p < 0.001$; hazard ratio = 0.68/10 %, 95 % confidence interval = 0.51–0.91, $p = 0.010$, respectively). The Akaike information criterion evaluating the fit of a model demonstrated that % LGE with a threshold of 6SD was a better independent predictor of MACE than % LGE with a threshold of 2SD or LVEF (Akaike information criterion = 172.20, 178.97 and 178.09, respectively) (Table 4).

Unplanned HF hospitalization

Overall, 23 of 46 (50 %) patients had unplanned HF hospitalizations (Table 2). Results of the univariate Cox proportional hazard analysis comparing different clinical and CMR characteristics are displayed in Table 5. Age at diagnosis, moderate to severe mitral regurgitation, New York Heart Association class III or IV, and plasma BNP reached statistical significance. In addition to CMR parameters reflecting LV remodeling, % LGE with thresholds of both 2SD and 6SD reached statistical significance. Investigation of the medications being used at the time of CMR revealed that diuretics and spironolactone were administered significantly more frequently among patients with unplanned HF hospitalization than those without. Multivariable Cox proportional hazard analysis revealed that % LGE with a threshold of 2SD and % LGE with a threshold of 6SD were independent predictors of unplanned HF hospitalization (hazard ratio = 1.62/10 %, 95 % confidence

Table 5 Univariate Cox proportional hazards model for unplanned HF hospitalization

	HR (95 %CI)	<i>p</i> value
Clinical characteristics		
Age at baseline CMR (years)	0.98 (0.96–1.01)	0.153
Age at diagnosis (years)	0.98 (0.95–1.00)	0.029*
Male, <i>n</i> (%)	1.22 (0.48–3.72)	0.689
Family history of HCM, <i>n</i> (%)	0.78 (0.26–1.96)	0.618
Family history of SCD, <i>n</i> (%)	1.28 (0.37–3.41)	0.663
Hypertension, <i>n</i> (%)	0.41 (0.13–1.03)	0.059
AF, <i>n</i> (%)	1.25 (0.55–3.00)	0.604
Non-sustained VT, <i>n</i> (%)	1.51 (0.63–4.21)	0.371
Sustained VT, <i>n</i> (%)	0.64 (0.15–1.88)	0.452
VF, <i>n</i> (%)	1.32 (0.21–4.51)	0.719
Stroke, <i>n</i> (%)	1.12 (0.18–3.84)	0.876
Moderate to severe MR, <i>n</i> (%)	4.88 (1.35–14.1)	0.019*
Syncope, <i>n</i> (%)	0.83 (0.30–2.02)	0.697
NYHA class III or IV, <i>n</i> (%)	4.53 (1.89–10.8)	<0.001*
BNP (pg/ml)	1.00 (1.00–1.00)	0.040*
Apical hypertrophy, <i>n</i> (%)	0.43 (0.07–1.46)	0.195
Apical aneurysm, <i>n</i> (%)	0.72 (0.17–2.09)	0.574
Baseline CMR parameters		
LVMi (g/m ²)	1.00 (0.99–1.02)	0.437
LVEF (%)	0.95 (0.91–0.98)	0.001*
LVEDVi (ml/m ²)	1.01 (1.00–1.01)	<0.001*
LVESVi (ml/m ²)	1.01 (1.00–1.01)	<0.001*
% LGE ≥2SD	1.04 (1.01–1.08)	0.013*
% LGE ≥6SD	1.05 (1.03–1.08)	<0.001*
Baseline medications		
Beta blocker, <i>n</i> (%)	2.32 (0.68–14.5)	0.204
Ca antagonist, <i>n</i> (%)	0.32 (0.02–1.50)	0.175
ACE inhibitor, <i>n</i> (%)	2.07 (0.87–4.78)	0.098
ARB, <i>n</i> (%)	0.49 (0.14–1.32)	0.169
Diuretics, <i>n</i> (%)	7.10 (2.61–24.8)	<0.0001*
Spironolactone, <i>n</i> (%)	4.10 (1.74–10.2)	0.001*
Pimobendan, <i>n</i> (%)	3.99 (0.92–12.3)	0.062
Digitalis, <i>n</i> (%)	1.50 (0.43–3.99)	0.484
Amiodarone, <i>n</i> (%)	1.90 (0.81–4.37)	0.139
Warfarin, <i>n</i> (%)	2.01 (0.86–5.23)	0.111

Abbreviations as in Table 1

* $p < 0.05$

interval = 1.19–2.25, $p = 0.002$; hazard ratio = 1.68/10 %, 95 % confidence interval = 1.30–2.16, $p < 0.0001$, respectively); however, LVEF was not an independent predictor (hazard ratio = 0.71/10 %, 95 % confidence interval = 0.47–1.07, $p = 0.098$). The Akaike information criterion evaluating the fit of a model demonstrated that % LGE with a threshold of 6SD was a better independent predictor of unplanned HF hospitalization than % LGE with a

Table 6 Multivariate Cox proportional hazards model for risk factors for unplanned HF hospitalization

	HR (95 %CI)	<i>p</i> value	AIC
Including % LGE with a threshold of 2SD model			
% LGE >2SD (per 10 %)	1.62 (1.19–2.25)	0.002*	142.61
Age at diagnosis (years)	0.96 (0.93–0.99)	0.005*	
Including % LGE with a threshold of 6SD model			
% LGE >6SD (per 10 %)	1.68 (1.30–2.16)	<0.0001*	136.62
Age at diagnosis (years)	0.97 (0.94–0.99)	0.012*	
Including LVEF model			
LVEF (per 10 %)	0.71 (0.47–1.07)	0.098	143.12
NYHA class III or IV	2.74 (0.93–7.88)	0.068	

Abbreviations as in Tables 1, 2, 3 and 4

* $p < 0.05$

threshold of 2SD (Akaike information criterion = 136.62 and 142.61, respectively) (Table 6). Several patients experienced recurrent unplanned HF hospitalization; the number of such hospitalizations per patient was related not to LVEF ($r = -0.06$; $p = 0.798$) nor % LGE with a threshold of 2SD ($r = 0.22$; $p = 0.303$), but to % LGE with a threshold of 6SD ($r = 0.44$; $p = 0.037$) (Fig. 5).

Discussion

The major findings of this study were that % LGE with a threshold of 6SD was a good independent predictor of primary composite MACE and secondary unplanned HF hospitalization end points and reflected both mortality and morbidity more precisely than either % LGE with a threshold of 2SD or LVEF in patients with HCM and systolic dysfunction.

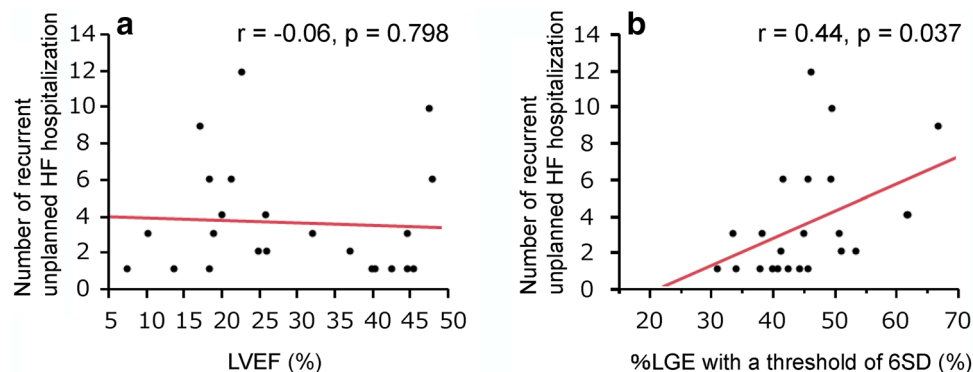


Fig. 5 Relationship between LVEF, the extent of LGE, and number of recurrent unplanned heart failure hospitalizations. **a** LVEF and number of recurrent unplanned HF hospitalizations, **b** % LGE with a threshold of 6SD and number of recurrent unplanned HF hospi-

Although an inverse relationship was observed between LVEF and % LGE with a threshold of 6SD even in HCM with systolic dysfunction (Fig. 2b), the relationship in HCM with systolic dysfunction ($r = -0.44$) was slightly stronger than that in the general HCM population ($r = -0.3$) as shown in a previous report [15]. In the present study, the prognostic value of LVEF was lower than that of % LGE with a threshold of 6SD. This seems to be contradictory, but it is not. In this study population, % LGE with a threshold of 6SD was 30.0 ± 15.1 %, comparable to data from published reports [15, 26]. It was also reported that there was substantial overlap of % LGE with a threshold of 6SD among LVEF subgroups of <50, 50–65, and >65 % [26], and this overlap tendency of % LGE with a threshold of 6SD among LVEF subgroups (i.e., <20, 20–40, and >40 %) was also observed even in HCM with systolic dysfunction as shown in Fig. 2b. Therefore, % LGE with a threshold of 6SD cannot be estimated accurately by the value of LVEF; in other words, the extent of fibrosis implicated in adverse cardiac events cannot be estimated accurately by the value of LVEF. Furthermore, % LGE with a threshold of 6SD is an absolute value that is reflective of myocardial fibrosis, while global LVEF values may vary because of fluctuating heart rate, afterload and/or preload, concomitant conduction disturbance, or mitral regurgitation. These factors suggest that % LGE with a threshold of 6SD is a more accurate predictor than LVEF despite the inverse relationship between % LGE and LVEF. In addition, we investigated only HCM with systolic dysfunction carrying poor prognosis, which may have reduced the prognostic value of LVEF.

Although the risk factors for sudden cardiac death in general HCM patients have been identified, there are limited data for identifying the risk factors for MACE and/or progression of HF in patients with HCM and systolic dysfunction [8, 9]. In fact, we found no significant correlation

talizations. The number of recurrent hospitalizations per patient was related not to LVEF ($r = -0.06$, $p = 0.798$) but to % LGE with a threshold of 6SD ($r = 0.44$; $p = 0.037$). Abbreviations as in Table 1

between any single clinical risk factor and the occurrence of MACE or unplanned HF hospitalization. It is important to identify predictive risk factors for MACE, however, and given that the fibrosis detected by LGE may have prognostic significance in ischemic heart disease and dilated cardiomyopathy [12, 34], it may play a similarly important role in HCM, especially that accompanied by systolic dysfunction. HCM is characterized by diffuse histopathological abnormalities involving the entire LV, including replacement and interstitial fibrosis [21].

Thus, we examined the pathological correlation with CMR and found that LGE defined using a threshold of 6SD aligned closely with the distribution of replacement fibrosis, but LGE with a threshold of 2SD reflected a mixture of both interstitial and replacement fibrosis, as previously reported [21] (Figs. 3, 4). These qualitative differences in fibrosis patterns were considered to result in a gradient of gadolinium deposition and could be distinguished by the LGE threshold used (i.e., 2SD or 6SD). On the other hand, LGE performed using the threshold method cannot visualize diffuse interstitial fibrosis because this type of fibrosis is “nulled” to highlight focal scarring [35]. Indeed, areas with no LGE also had diffuse interstitial fibrosis (Fig. 4). We considered that % LGE with a threshold of 6SD reflects the extent of severe replacement fibrosis in LV masses, providing greater prognostic value than the 2SD threshold. % LGE with a threshold of 6SD was a better independent predictor of MACE and unplanned HF hospitalization and was more significantly associated with recurrent unplanned HF hospitalization than % LGE with a threshold of 2SD. Our data underscore the potential value of assessing the extent and quality of LGE rather than only the presence of LGE for predicting outcomes in HCM with systolic dysfunction.

In this study population, 21 of 46 (46 %) patients underwent implantation of ICDs with or without CRT. These device therapies might have modified clinical outcomes because they can easily detect arrhythmic events, prevent sudden cardiac death due to lethal arrhythmia, and reduce unplanned HF hospitalization. The differences in baseline CMR parameters and cumulative number of cardiac events between patients receiving and not receiving device therapies are shown in Table 7. Patients receiving device therapies not only had significantly younger age, lower LVEF, and larger LV volume index, but also showed a tendency toward larger extent of LGE. Indeed, arrhythmic events were more frequently detected in patients receiving device therapies, while there was 1 sudden cardiac death in device-free patients. The frequencies of HF death, LV assist device implantation, and heart transplantation did not vary according device therapy status; however, the frequencies of both the primary and secondary end points (MACE and unplanned HF hospitalization, respectively)

Table 7 Differences between with or without devices

	With device <i>n</i> = 21	Without device <i>n</i> = 25	<i>p</i> value
Clinical characteristics			
Age at baseline CMR (years)	55.1 ± 11.3	61.9 ± 15.9	0.032*
Male, <i>n</i> (%)	15 (71)	20(80)	0.730
Baseline CMR parameters			
LVMi (g/m ²)	104.6 ± 40.5	109.9 ± 30.4	0.201
LVEF (%)	30.6 ± 12.4	39.3 ± 11.0	0.011*
LVEDVi (ml/m ²)	137.2 ± 89.7	105.4 ± 64.2	0.021*
LVESVi (ml/m ²)	102.2 ± 88.6	68.9 ± 58.9	0.008*
% LGE ≥2SD	55.9 ± 15.0	50.7 ± 14.1	0.193
% LGE ≥6SD	34.1 ± 14.5	26.6 ± 15.0	0.071
Cumulative number of cardiac events			
Sudden death, <i>n</i> (%)	0 (0)	1 (4)	1.000
HF death, <i>n</i> (%)	5 (24)	6 (24)	1.000
VF, <i>n</i> (%)	2 (10)	0 (0)	0.203
Sustained VT, <i>n</i> (%)	5 (24)	0 (0)	0.015*
Anti-tachycardia pacing, <i>n</i> (%)	4 (19)	0 (0)	0.037*
Appropriate ICD discharge, <i>n</i> (%)	3 (14)	0 (0)	0.088
Stroke due to cardiac emboli, <i>n</i> (%)	3 (14)	0 (0)	0.088
LVAD implantation, <i>n</i> (%)	3 (14)	3 (12)	1.000
Heart transplantation, <i>n</i> (%)	2 (10)	1 (4)	0.585
Unplanned HF hospitalization, <i>n</i> (%)	15 (71)	8 (32)	0.017*
MACE, <i>n</i> (%)	18 (86)	11 (44)	0.005*

Values are mean ± SD or *n* (%)

Abbreviations as in Tables 1 and 2

* *p* < 0.05

were significantly higher in patients receiving device therapies. Therefore, patients who were receiving such therapies had a poorer prognosis than patients who were not. This might be influenced by adverse LV remodeling in patients with implantable devices. ICD therapy was confirmed to effectively prevent sudden cardiac death in HCM patients [36, 37]. On the other hand, a previous observational study reported that end-stage HF was the main cause of cardiac death in HCM patients receiving ICD therapy. Furthermore, it was reported that severe HF symptoms and indications for CRT were independent predictors of mortality in HCM patients with ICDs [38]. Both the present study and those mentioned above might demonstrate that the efficacy of ICDs with or without CRT therapy for preventing HF death was limited in HCM patients with systolic dysfunction. Although one study reported that CRT

improved HF symptoms and was associated with reverse remodeling of LV in HCM with systolic dysfunction [39], the advantage of CRT in HCM with systolic dysfunction is still unclear [36, 37].

Limitations

The present study had several limitations. First, it used a retrospective design and relatively small sample size due to the low prevalence of HCM with concomitant systolic dysfunction. Second, this single-center study in a tertiary hospital-based population was probably influenced by referral bias because of this population's high-risk status, presence of serious conditions such as heart transplantation requiring specialized care, and known increased risk of adverse outcomes including mortality and re-hospitalization. Further multicenter collaborative clinical trials are required to identify whether our findings are applicable to a community-based population. Third, in our center, gadolinium-enhanced CMR is performed in patients with HCM based on the judgment of the attending physicians, and not all patients with HCM undergo this procedure. This may result in selection bias. Patients with ICD, pacemakers, or renal insufficiency (estimated glomerular filtration rate <30 ml/min/1.73 m²) were not pre-included in this study population because of contraindications to gadolinium-enhanced CMR, thus reducing the number of subjects prone to cardiovascular events, especially arrhythmic events. Arrhythmic events were more frequently detected in patients who were receiving device therapies than in those who were not, and there was a possibility that arrhythmic events in patients not receiving device therapies were overlooked. This in turn might have modified clinical outcomes. Fourth, we performed endomyocardial biopsy in 35 of 46 patients and excluded metabolic or infiltrative storage disorders characterized by LV hypertrophy, such as amyloidosis and Fabry disease. Regarding the residual 11 patients, we diagnosed them with HCM based on unexplained asymmetrical LV hypertrophy and a family history of HCM. Although this population had no symptoms that suggested a multisystem disorder, it is possible that one or more had a rare storage disease with only cardiac involvement. Fifth, we compared the histopathological findings and LGE results in only 3 patients. Sixth, the diffuse interstitial fibrosis in HCM currently cannot be determined using the threshold method mentioned above. T1 mapping techniques might provide better and more accurate evaluation of diffuse myocardial fibrosis [40, 41]. Finally, we evaluated LGE of only "single shot" CMR; assessing LGE of repeat CMR examinations over time could be useful because HCM-associated fibrosis is usually progressive [42, 43].

Conclusions

% LGE with a threshold of 6SD was a better independent predictor of MACE and unplanned HF hospitalization and reflected mortality and morbidity more precisely than both LVEF and % LGE with a threshold of 2SD in HCM with systolic dysfunction. We suggest that quantification of LGE with a threshold of 6SD is useful for predicting MACE and recurrent unplanned HF hospitalization and can contribute to further risk stratification in patients with HCM and systolic dysfunction.

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Conflict of interest The authors declare that they have no conflict of interest.

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