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Prognostic factors in hypertrophic cardiomyopathy in children: An MRI based study

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ABSTRACT

Background: Clinical and prognostic role of cardiac magnetic resonance (CMR) in adult population with hypertrophic cardiomyopathy (HCM) have been largely assessed.
We sought to investigate the role of CMR for predicting cardiovascular events in children with HCM.
Methods: CMR was performed in 116 patients with HCM (37 sarcomeric mutations, 31 other mutations, mean age 10.4 ± 4.3 yrs). CMR protocol included cine imaging for evaluation of morphology and function and late gadolinium enhancement (LGE). Hard cardiac events (sustained VT, resuscitated cardiac arrest, sudden cardiac death, end-stage heart failure, heart transplant and appropriate ICD intervention) were recorded through a median follow-up of 4 (1–7) years.
Results: During follow-up 21 heart cardiac events occurred. At maximal-rank statistic the optimal cut-point for LGE extent for predicting events was ≥2%. Syncope, non-sustained ventricular tachycardia (NSVT) and LGE extent ≥2% were independent predictors of events. At Harrel's C statistic combination of LGE extent ≥2% and syncope was the strongest model for predicting events. HR of patients with LGE extent ≥2% and no history of syncope was 3.6 (1.1–12.2) that increased to 37.6 (5.4–161) in those with LGE extent ≥2% and syncope. The median time dependent AUC of LGE extent (0.88, 95% CI 0.86–0.89) was significantly higher than that of syncope (0.63, 95% CI 0.61–0.66, $p < 0.0001$) and NSVT (0.52, 95% CI 0.50–0.53, $p < 0.0001$).
Conclusions: In children with HCM, LGE and syncope were independent predictors of hard cardiac events at follow-up.

Abbreviations: HCM, Hypertrophic cardiomyopathy; SCD, sudden cardiac death; CHF, congestive heart failure; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement technique; LV, left ventricle; BSA, body surface área; LVOT, left ventricular outflow tract; ICD, implantable cardioverter defibrillator; AUC, area under the curve; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVH, left ventricular hypertrophy.

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[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[3] Equally contribution as last author.

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1. Introduction

Hypertrophic cardiomyopathy (HCM) in children represents a very heterogeneous group of inherited heart muscle diseases, being the most common genetic cardiomyopathy, with an incidence of ≈0.47 per 100,000 in children [1,2]. Several forms of HCM exist, including those confined to the heart as well as those associated to complex syndromes (inborn errors of metabolism, neuromuscular disease, chromosomal abnormalities). Sudden cardiac death (SCD) and progression to end-stage congestive heart failure (CHF) are the main causes of death in children with HCM, with an overall mortality rate of 1–2.5% [1,3–8].

Risk stratification in pediatric HCM population is challenging and basically hampered by the lack of data. Indeed, american and european guidelines recommend different risk factors [9,10]; moreover, a growing number of recent publications suggest new risk factors and clinical risk scores, clearly underlying the need for further investigation [11–16].

In adult patients, cardiac magnetic resonance (CMR) is gradually becoming the new gold standard for diagnosis of HCM, providing data on cardiac morphology, function and tissue characterization, and also improving prognostic stratification through evaluation and quantification of fibrosis by late gadolinium enhancement (LGE) technique [17–22]. In pediatric patients, presence and progression over time of LGE on CMR have been reported [23,24], although its prognostic significance needs to be further evaluated to better understand its clinical implication in this specific subset of patients.

In this study, we sought to investigate the role of CMR, and particularly of LGE, in predicting cardiovascular events in a cohort of children with HCM.

2. Methods

2.1. Patients

All consecutive patients aged <18 years undergoing CMR for HCM in 2 different institutions (Hopital Necker, Paris, France and Fondazione Toscana G. Monasterio, Pisa, Italy) were retrospectively reviewed from March 2007 to February 2021. Exclusion criteria were: *Z*-score wall thickness at CMR <2; secondary forms of left ventricular hypertrophy (as aortic stenosis, aortic coarctation, systemic hypertension).

A complete diagnostic evaluation was performed in all patients. All included patients underwent clinical, electrocardiographic and echocardiographic evaluation at the time of CMR.

The study complied with European GRPD law on retrospective studies (MR004 conformity, registration n° 20,210,702,142,351).

2.2. CMR imaging

Cardiac magnetic resonance was performed using a 1.5 Tesla magnet (MR450 GE Medical systems, Milwaukee, USA). Images were acquired with a 32-channel phased-array cardiac coil and a vector electrocardiogram for R wave triggering using a standard CMR imaging protocol. 4-chamber, 2-chamber and short-axis cine images from the mitral plane valve to the apex of the left ventricle (LV) were acquired using a steady-state free precession FIESTA (fast imaging employing steady-state acquisition) pulse sequence with the following parameters: 30 phases, slice thickness 6–8 mm, no gap, views per segment according to heart rate, number of excitation 1–4, field of view according to bost size 45° flip angle, repetition time/echo time equal to 3.5/1.5. LGE images were acquired in short-axis views 5–10 min after the administration of gadolinium chelate (Dotarem Guerbet 0.2 mmol/kg). An inversion recovery T1-weighted gradient echo sequence was used with the following parameters: field of view according to patient size, slice thickness 6–8 mm, no gap between each slice, repetition time 4.6 ms, echo time 1.3, 20° flip angle, number of excitation 1–2. The appropriate inversion time was set to null normal myocardium. All exams were performed in free-breathing using sedation in children under 25 kg. Analysis of CMR images was performed using a commercially available research software package (Mass 6.1, Leiden, the Netherlands). Left ventricular mass was measured by the analysis of the cine short-axis images. The endocardial and epicardial contours of LV myocardium were manually traced in the end-diastolic and the end-systolic phases. End-diastolic volume index, end-systolic volume index, mass and mass index were measured as previously described [22,25–27]; LV end-diastolic wall thickness was measured as previously described [27].

The phenotype of the LV hypertrophy was described according to the distribution of hypertrophic segments, as previously reported [22]. Briefly, 5 patterns of hypertrophy were described: 1) hypertrophy of the inter-ventricular septum and/or the anterior free wall; 2) hypertrophy of the ventricular apex; 3) hypertrophy of the inferior and/or inferolateral wall; 4) apical-septal hypertrophy; 5) diffuse hypertrophy. The number of hypertrophic segments was also reported: 1) <3 segments involved; 2) ≥3 and < 8; 3) ≥8 [28].

The extent of LGE was measured using a previously validated method [29]. Briefly, endocardial and epicardial contours in each image were manually traced to identify LV myocardium.. The mean signal intensity and standard deviation were measured in a region of interest with non-enhanced myocardium. Myocardial voxels with signal intensity higher than the average signal intensity of the region of interest plus 6 standard deviations were considered enhanced [22,29]. The percentage of enhanced voxels in the entire LV myocardium was measured. Extent of LGE was expressed in grams and percentage of LV mass. The left atrial area was also measured in systole from the 4 chamber view and indexed by body surface area (BSA). Presence of myocardial recess (crypts), myocardial coronary bridges, mitral papillary valve anomalies were also reported. Assessment of left ventricular outflow tract (LVOT) obstruction was based on previously reported echocardiographic criteria [30].

2.3. Follow-up and outcomes

Follow-up was performed according to regional policies, involving regular clinical and echocardiographic examinations. Hard cardiac events included: resuscitated cardiac arrest, SCD, end-stage heart failure, heart transplant and appropriate implantable cardioverter defibrillator (ICD) intervention.

Other adverse events experienced during the follow-up, such as ICD primary prevention implant, unexplained syncope and LVOT surgery were also recorded.

2.4. Statistical analysis

All the results were expressed as the mean ± SD or as the median (25th–75th) for variables with normal and non-normal distributions, respectively. Continuous variables were compared by the ANOVA test with Bonferroni correction for normally distributed variables or by the Wilcoxon nonparametric test or Kruskal Wallis when appropriate. Categorical variables were analysed by a Fisher exact test. Inter-rater agreement kappa was calculated to assess reproducibility between 2 independent investigators to detect LGE extent >2% of LV mass. A maximally selected rank statistical analysis was performed to define the optimal cut-off of the LGE for survival analysis using the maxstat package of R software. The Kaplan-Meier analysis were used to compare longitudinal curve of survival-free from events among groups. Univariate and multivariate Cox regression analysis were used to explore the impact of each significant variable in the analysis to predict the occurrence of a combined endpoint (cardiac death, appropriate ICD intervention, resuscitated cardiac arrest). For multivariate analysis we included all variables with a significant p value in the univariate. The risk of multicollinearity among the covariates was evaluated by the variance inflation factor (VIF). VIF values <10 indicated a low risk of multicollinearity. Harrel's C statistic and the McFadden R^2 were used to compare different models of multivariate analysis.

3. Results

A total of 116 patients (70% males) were included. Age ranged from 1 to 16 years (mean 10 ± 4 years). Demographic and clinical data from patients are summarized in Table 1. Family history of HCM or SCD was reported in 33 (28%) patients and 12 (10%) respectively. Genetic evaluation was completed in 87 (75%) patients: in 37/86 (43%) patients a sarcomeric mutation was identified; 13/87 (15%) had a neuromuscular disease (Friedreich ataxia in 8/13); 8/87 (9%) had Noonan syndrome; 2/87 (2%) a mitochondrial syndrome; 3/87 (3%) a glycogenosis; 5/87 (6%) had other syndromes (Pierre Robin in 1; Trisomy 21 in 1; Mowat-Wilson in 1; trisomy 4 in 1; cardio-facial syndrome in 1); 19 /87 (22%) had a negative genetic result and were considered idiopathic forms (Supplementaryfigure 1).

In 20 patients (17%) presence of LVOT obstruction at rest was detected by echocardiography and confirmed by CMR. Ten patients had history of unexplained syncope before CMR study and in 3 cases non sustained ventricular tachicardia (NSVT) at 24-h Holter monitoring was detected. Overall, 56 (48%) patients were receiving betablockers therapy at the time of CMR.

3.1. Cardiac magnetic resonance

CMR data are summarized in Table 1. The mean maximal end-diastolic wall thickness was 15 ± 6 mm, Zscore 8.8 (5.1–13.4). Hypertrophy involved <3 segments in 29% of patients, ≥3 and < 8 segments in 47% and ≥ 8 segments in 24%. Specifically, hypertrophy involved the inter-ventricular septum and/or the anterior free wall in 56 (48.3%) patients; it was confined to the ventricular apex in 1 patient and to the inferior and/or inferolateral wall in 12 patients (10,2%). Finally, it was apical-septal in 15 (13%) and diffuse in 32 patients (27.5%). LGE was positive in 46% of patients. The median of LGE extent was 1.6 g (25th–75th 0–4.4), corresponding to 0.6% (25th–75th 0–3) of LV mass. A very good reproducibility for detect LGE extent >2% of LV mass was found (inter-rater agreement kappa = 0.82).

3.2. Sarcomeric vs non sarcomeric vs gene-negative HCM

Comparing HCM patients groups according to the type of mutation present, we found that patients with sarcomeric mutation were more likely to have a positive family history of HCM and higher maximal wall thickness and LGE extent. On the other hand, patients with non-sarcomeric or unidentified mutations have a more diffuse pattern of the hypertrophy (Table and Fig. 1).

3.3. Clinical follow-up

Median follow-up was 4 years (25th–75th 1–7 years). 21 patients (18%) experienced hard cardiac events, specifically 5 of them had SCD, 1 end-stage heart failure, 5 indications to heart trasplant, 1 sustained ventricular tachycardia, and 9 resuscitated cardiac arrest). During follow-up, 7 patients underwent surgical myectomy for LVOT obstruction. ICD was implanted in 11 patients in primary prevention. Patients with hard cardiac events at follow-up experienced more often a syncope before CMR (p = 0.01), had a lower LVEF % (p < 0.001) at CMR and higher LGE extent (p = 0.01) (Table 2). Moreover, the presence of myocardial crypts was associated with hard cardiac events (p = 0.016). At maximal rank statistic (MaxStat, Fig. 1), an LGE extent of ≥2% was chosen as the best threshold to predict the occurrence of hard cardiac events in this population. Univariate Cox regression analysis (Supplementary Table 1) identified history of unexplained syncope, previous NSVT and LGE extent ≥2% of LV mass as predictors of hard cardiac events. In Fig. 2, three models of multivariate Cox regression analysis combining these three predictors are showed. Compared to other models, the one including LGE extent ≥2% of LV mass and previous unexplained syncope was the most effective to predict the endpoint, having the highest Harrel's C (0.75 (0.62–0.89) and the lowest McFadden R^2 (0.14).

The analysis of Kaplan-Meier survival curves showed that patients with LGE extent ≥2% had worse prognosis than those with lower extent (p < 0.0001; Fig. 1). Similarly, patients with syncope had worse

Table 1
Clinical and CMR characteristics of the whole population and according to genetic profile.

	Whole population	Sarcomeric	Non Sarcomeric	Negative	P value
	n = 116	n = 37	n = 31	n = 19	
Clinical features					
Gender male, n (%)	81 (70)	25 (67.8)	21 (68)	15 (83)	0.5
Age (mean, SD, years)	10.4 ± 4.3	11 (8;14.5)	9 (6.2;12.7)	12 (5.7;15.5)	0.4
Previous unexplained syncope, n (%)	10 (8.6)	0	4 (10.8)	1 (3.2)	0.5
Family history of HCM, n (%)	33 (28.5)	20 (54)	6 (33)	2 (6.5)	**0.01**
Family history of SCD, n (%)	12 (10)	7 (19)	1 (3.2)	3 (17)	0.08
Betablockers therapy, n (%)	56 (48)	17 (47)	12 (39)	12 (75)	0.05
LVOT obstruction	20 (17)	9 (24)	5 (16)	5 (28)	0.16
Genetic evaluation	86 (74)				
CMR data					
LVEF (%)	63.5 ± 8.8	61 (55;67)	63 (59;67)	68.5 (58;73)	0.05
LVEDVi (ml/m^2)	78 ± 13.5	80 (70;87)	75 (68;85)	75 (68;87)	0.45
LVESVi (ml/m^2)	29 ± 10	29 (26;37)	26 (22.5;34)	23 (20;30)	0.02
LV mass index (g/m^2)	85 ± 27	77 (64;98)	79 (64;109)	84 (71;92)	0.79
Max Wall thickness (mm)	15.3 ± 5	16 (14;20.5)	12 (10;15)	14 (10;18.5)	0.01
LA area index (cm^2/m^2)	12.4 (9;15.3)	12.6 (8.9;15.3)	12 (10.7;16.7)	12.5 (10;15.3)	0.7
N. of hypertrophic segments					0.001
<3	33(29)	9 (24.5)	8 (26)	6 (33)	
≥3 and < 8	55(47)	26 (70)	7 (23)	10 (56)	
≥ 8	28(24)	2 (5.5)	16 (52)	2 (11)	
LGE extent (gr)	1.6 (0; 4.4)	2.4 (0.4;5.1)	0 (0;1.2)	1.3 (0.42;5.7)	0.03
LGE extent/LV mass (%)	0.56 (0; 3)	1.85 (0;4.1)	0 (0;0.62)	1.7 (0.25;5)	0.008
LGE extent/LV mass (%) ≥2%,	26 (23)	13 (43)	3 (11)	5 (31)	0.01
Crypts, n (%)	39(33)	21 (57)	7 (23)	12 (67)	0.1
Mitral valve anomalies, n (%)	66(57)	26 (72)	12 (48)	9 (50)	0.1

Legend: HCM: hypertrophic cardiomyopathy, LA: left atrium, LGE: Late Gadolinium Enhancement, LV: Left Ventricle; LVEF: Left Ventricle Ejection Fraction, LVEDVi: Left Ventricle End-Diastolic Volume indexed by body surface area; LVESVi: Left Ventricle End-Systolic Volume indexed by body surface area; LVH: Left Ventricle Hypertrophy, SCD: sudden Cardiac Death.

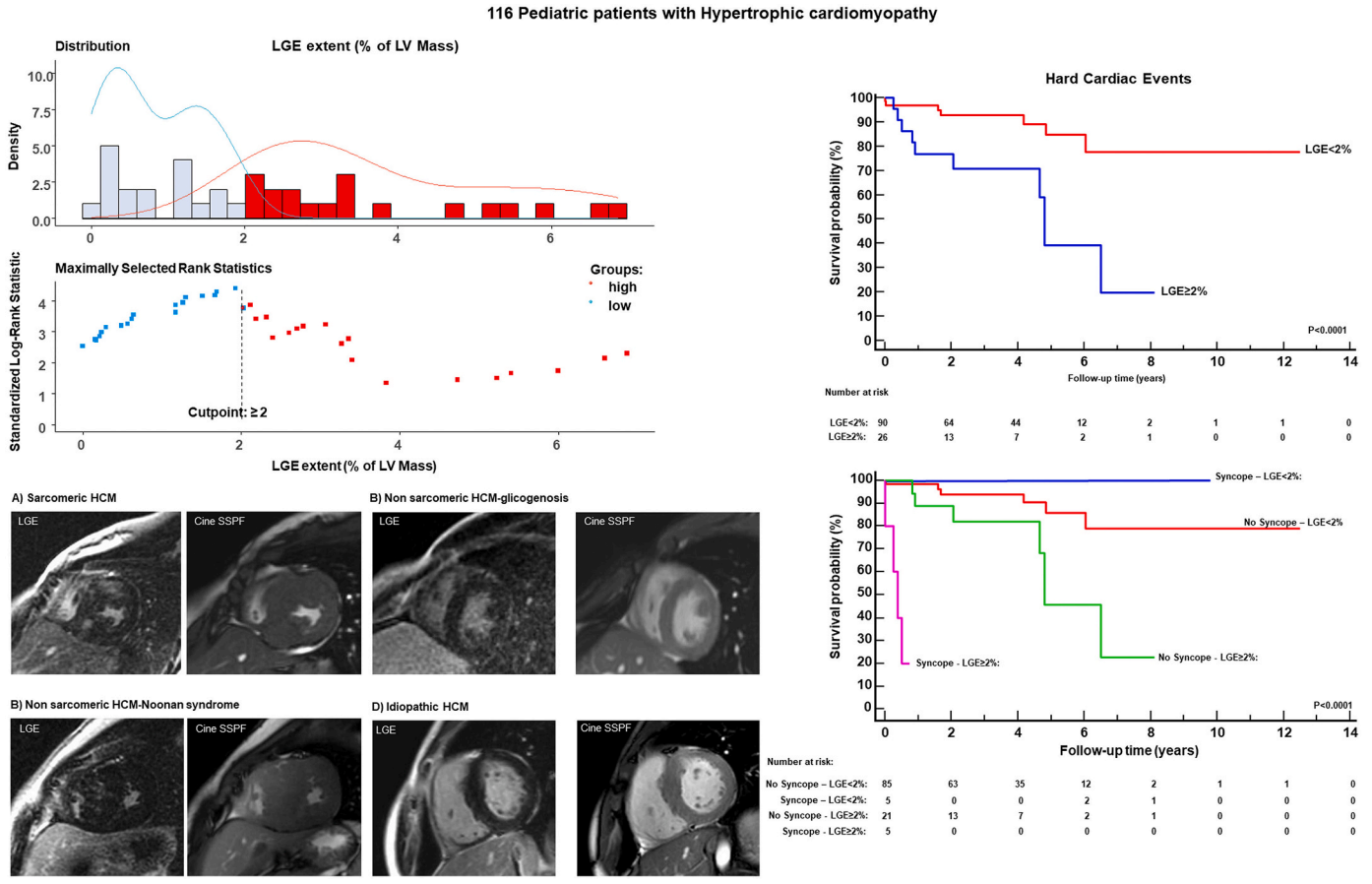

Fig. 1. Main results of the study. In the upper left panel, the maximal rank statistic analysis is shown: as evident in the maximal rank statistic plot, a late gadolinium enhancement (LGE) extent of ≥2% was the optimal cut-point to predict the occurrence of hard cardiac events during the follow-up time. In the left lower panel, morphological features of different HCM phenotypes are shown: visualization of cine short-axis image and late gadolinium enhancement (LGE) in 4 HCM pediatric patients: A) Sarcomeric HCM; B) Non sarcomeric HCM-glicogenosis; C) Non sarcomeric HCM-Noonan syndrome; D) Idiopathic HCM. At Kaplan-Meier analysis (right panels), the survival-free from hard cardiac events was worse in patients with LGE extent ≥2% than in other patients (upper panel). As evident in the second Kaplan-Meier analysis (lower panel), the survival-free from events was worse in patients with LGE extent ≥2% and Syncope than in other patients. The HR of patients with LGE extent ≥2% and no history of syncope was 3.6 (1.1–12.2) that increased to 37.6 (5.4–161) in those LGE extent ≥2% and syncope.

survival-free from hard cardiac events (p = 0.0001; supplementary Fig. 2). However, the combination of syncope and LGE extent ≥2% had the worse survival of all groups (Fig. 1). The HR of patients with LGE extent ≥2% and no history of syncope was 3.6 (1.1–12.2) that increased to 37.6 (5.4–161) in those with LGE extent ≥2% and syncope.

The time-dependent area under the curve (AUC) of LGE extent, previous unexplained syncope and NSVT are imaged in supplementary Fig. 3. The AUC of LGE extent increased with the follow-up, whereas the AUC of syncope and NSVT decreased over time. Particularly, the AUC of NSVT decreased under the 0.5 level after 4 years of follow-up. The median time dependent AUC of LGE extent (0.88, 95% CI 0.86–0.89) was significant higher than that of syncope (0.63, 95% CI 0.61–0.66, p < 0.0001) and NSVT (0.52, 95% CI 0.50–0.53, p < 0.0001).

4. Discussion

We reported here the results of one of the largest pediatric HCM cohorts published to date analyzing comprehensive CMR and clinical parameters and for a very reasonable follow up period at a median of 4 years. We aimed to characterize pediatric HCM phenotypes, trying to assess the prognostic significance of LGE imaging during follow up including different genetic subtypes of HCM.

According to the clinical classification described by Colan et al. in PCMR registry [2], our population consisted mostly of non-infantile forms of HCM: 76% of our cohort had genetic test, resulting in 43% of sarcomeric HCM and 36% non sarcomeric HCM (including neuromuscular diseases), whereas in the remaining 22% of patients no specific genetic anomaly was found (idiopathic forms).

Sarcomeric HCM had the highest wall thickness at CMR and the highest LGE extent; whereas, in non-sarcomeric HCM the pattern of hypertrophy was mostly diffuse, with a lower wall thickness and LGE extent.

Moreover, LGE was observed in 45% of patients, with a mean LGE extent of 0,6% of total LV mass. Comparing these data with those reported by Raja et al. in 195 pediatric patients with diagnosis of overt sarcomeric HCM [23], we observed that LGE prevalence is consistent in the 2 cohorts (45% vs 46%); whereas, LGE extent is lower in the whole population (0.6% vs 2.9%), but quite similar if we consider only sarcomeric forms (1.85%). Furthermore, comparing our LGE data with those reported in adult population by Todiere et al., we observed that LGE prevalence is lower (45% vs 81% respectively), such as the LGE extent (1,85% in sarcomeric-HCM vs 4% of LV mass). These data of prevalence and LGE extent, measured with the 6-standard deviation method (6 SD), are consistent with the well-established concept that fibrosis is a progressive phenomenon, both in adults and children [19–23].

In our cohort 21 patients had hard cardiac events (18%), mostly in sarcomeric HCM (69%). This rate is similar to that reported by Marston et al. in a childhood HCM population (20%), although they considered an overall composite endpoint encompassing heart failure, ventricular

Table 2
Characteristics of the population with and without hard cardiac events at follow-up.

	Hard cardiac event	No event	P
Clinical features			
n (%)	21 (18)	93 (80)	
Gender male, n (%)	68 (73)	11 (51)	0.07
Age (years)	10.6 (8;14)	10.6 (7;14)	0.95
Obesity	4(18)	10(11)	0.37
Previous unexplained syncope, n (%)	5 (24)	5 (5,4)	0.01
Familiar History of HCM, n (%)	6 (29)	27 (29)	1
Familiar history of SCD, n (%)	2 (10)	10 (11)	0.3
Betablockers therapy, n (%)	7 (12.5)	4 (7.5)	0.5
Genetic profile (n 87)			0.1
• Sarcomeric mutation, n (%)	9 (69.2)	28 (38.4)	
• Non sarcomeric, n (%)	3 (23)	28 (38.4)	
• Negative, n (%)	1 (7.7)	17 (23)	
CMR data			
LVEF (%)	56 (52;59)	65.5 (60;70)	<0.001
LVEDVi (ml/m^2)	78 (66;83)	78 (69;87)	0.25
LVESVi (ml/m^2)	33.5 (28;36.5)	27 (21;34)	0.002
LV mass index (g/m^2)	69 (59;97)	80.5 (67;105)	0.2
Max Wall thickness (mm)	15 (13;18)	14 (11;20)	0.34
LA area index (mm^2/m^2)	13.3 (12;21)	12.5 (10.5;15.4)	0.1
Number of hypertrophic segments			0.3
<3, n (%)	5 (24)	26 (28)	
≥3 and < 8, n (%)	13 (62)	41 (45)	
≥8, n (%)	3 (14)	25 (27)	
LGE extent (gr)	4.7 (1.9;8)	0.97 (0;3.4)	0.01
LGE extent (% of LV mass)	3.6 (2.6;10)	0.24 (0;2.3)	0.01
LGE extent ≥ 2%, n (%)	13 (43)	3 (11)	0.01
Crypts, n (%)	10 (53)	26 (28)	0.03
LVOT obstruction, n (%)	1 (5)	19 (20)	0.1

Legend: HCM: hypertrophic cardiomiopathy; LA: Left Atrium; LGE: Late Gadolinium Enhancement; LV: Left Ventricle; LVEF: Left Ventricle Ejection Fraction; LVEDVi: Left Ventricle End-Diastolic Volume indexed by body surface area; LVESVi: Left Ventricle End-Systolic Volume indexed by body surface area; LVH: Left Ventricle Hypertrophy; SCD: Sudden Cardiac Death; LVOT: left ventricle outflow tract.

arrhythmias, atrial fibrillation, stroke, and all-cause death [31]. In contrast, Lafreniere-Roula et al. reported a lower rate of hard events (3.2%) in children screened for HCM [32], 41% of which occurring before 10 years of age. The different rates of hard events found between studies may reflect the different characteristics of the population included and also the definitions of hard cardiac event. Moreover, although CMR is acquiring a growing diagnostic role in the field of pediatric cardiomyopathies, it doesn't represent a routine diagnostic tool in all centers yet and its use is conditioned by local policies and expertises, thus our population may have a selection bias and be considered a 'high risk population'.

Unexplained syncope, previous NSVT and LGE extent ≥2% of LV mass were predictors of hard cardiac events in univariate analysis. Of note, at maximal-rank statistic the optimal cut-point for LGE extent for predicting events was ≥2%, which is lower than the reported adult cut point at 15%. Having 2% of LGE is quite assimilable to the concept of its presence or absence, especially in consideration of technical challenge in children to have a good quality signal in late enhancement sequences. This data suggests that the real unfavorable factor in our cohort is just the presence of LGE, not the amount of it, probably because presence of LGE, even in small quantity, means that the process towards adverse remodeling is started and it will lead to a worse prognosis over time. Corroborating the hypothesis of a dynamic irreversible remodeling once the fibrotic process has started is the fact that the AUC of LGE extent increased during follow-up, whereas the AUC of syncope and NSVT decreased over time. The median time dependent AUC of LGE extent was significant higher than that of syncope and NSVT, underlying the importance of LGE alone as expression of the progression of the disease. The strenght of the statistical model of LGE alone suggest that this parameter should be interpretated as an expression of the severity of the disease, especially in pediatric population where clinical signs are often controversial and left ventricular dysfunction is rare. We have also explored with several statistical methods the role of LGE associated to clinical variables on major adverse events during follow up: the model including LGE extent ≥2% of LV mass and previous unexplained syncope had the highest Harrel's C (0.75 (0.62–0.89) and lowest McFadden R^2 (0.14).

This is the first reported finding in pediatric HCM demonstrating a prognostic role of LGE alone and also associated to clinical variables.

Raja AA et al. [23] did not find any correlations between the extent of LGE and adverse events at follow up, having the same percentage of adverse events in the cohort and the same method of quantification.

As underlined by Norrish G et al. [16], approaches to risk stratification in childhood HCM have remained largely unchanged for >2 decades [33,34], with reliance on the assessment of a small number of clinical characteristics (risk factors) to guide treatment decisions. A recent study about this approach has shown it to have limited discriminatory power (Cindex statistic, 0.62) with a positive predictive value of only 19% [8]. In adults a HCM Risk-SCD has been proposed by O'Mahony et al. [35]. However, the HCM Risk-SCD tool is not recommended for use in childhood as patients younger than 16 years were specifically excluded in its development and echocardiographic variables were not corrected for body surface.

Challenge in this specific topic is also demonstrated by differences between european and american guidelines [33,34]. While european guidelines recommend the use of four major risk factors (maximum LV wall thickness > 30 or z-score > 6, unexplained syncope, NSVT and family history of SCD) and indicate implantable cardioverter defibrillator (ICD) implant whenever 2 or more clinical risk factors are present [34], american guidelines suggest the same risk stratification scheme for children and adults affected by HCM. Specifically, in presence of one of the three major risk factors (family history of sudden cardiac death, extreme LVH, unexplained syncope] an ICD is recommended with a class IIa indication [33].

Recently, Norrish G et al. [20] proposed a risk model based on clinical and echocardiographic preselected variables (unexplained syncope, NSVT, LA diameter z score, MWT z score, and left-ventricular outflow tract gradient) but without inlcuding any CMR parameter. Another model was proposed by Miron et al. in 2020 [36] with pretty similar risk factors with the novelty of considering pathogenic variants but still without considering CMR data. No risk model including CMR variables has been evaluated thus far. Our data suggest that integration of clinical variables (syncope) to CMR features (LGE) could provide a strong prediction model of cardiac adverse events. Moreover, presence of LGE, detected at the beginning of the process, seems to be a sign of severity of the disease in terms of adverse and progressive remodeling.

Longitudinal studies in bigger cohorts are needed to better understand the progression rate of fibrotic process and its prognostic implication with the objective to provide a comprehensive score including clinical and imaging variables in children with HCM.

4.1. Study limitations

This is an observational retrospective study with all limits intrinsic to its own nature. Sarcomeric form was the most prevalent HCM in our cohort with small samples of other forms, thus comparison between groups with detailed statistical analysis was not possible. At the time of CMR acquisition, parametric mapping techniques were not available, thus mapping analysis was not performed.

Moreover, although CMR is acquiring a growing diagnostic role in the field of pediatric cardiomyopathies, it doesn't represent a routine diagnostic tool in all centers yet and its use is conditioned by local policies and experties, thus our population may have a selection bias and

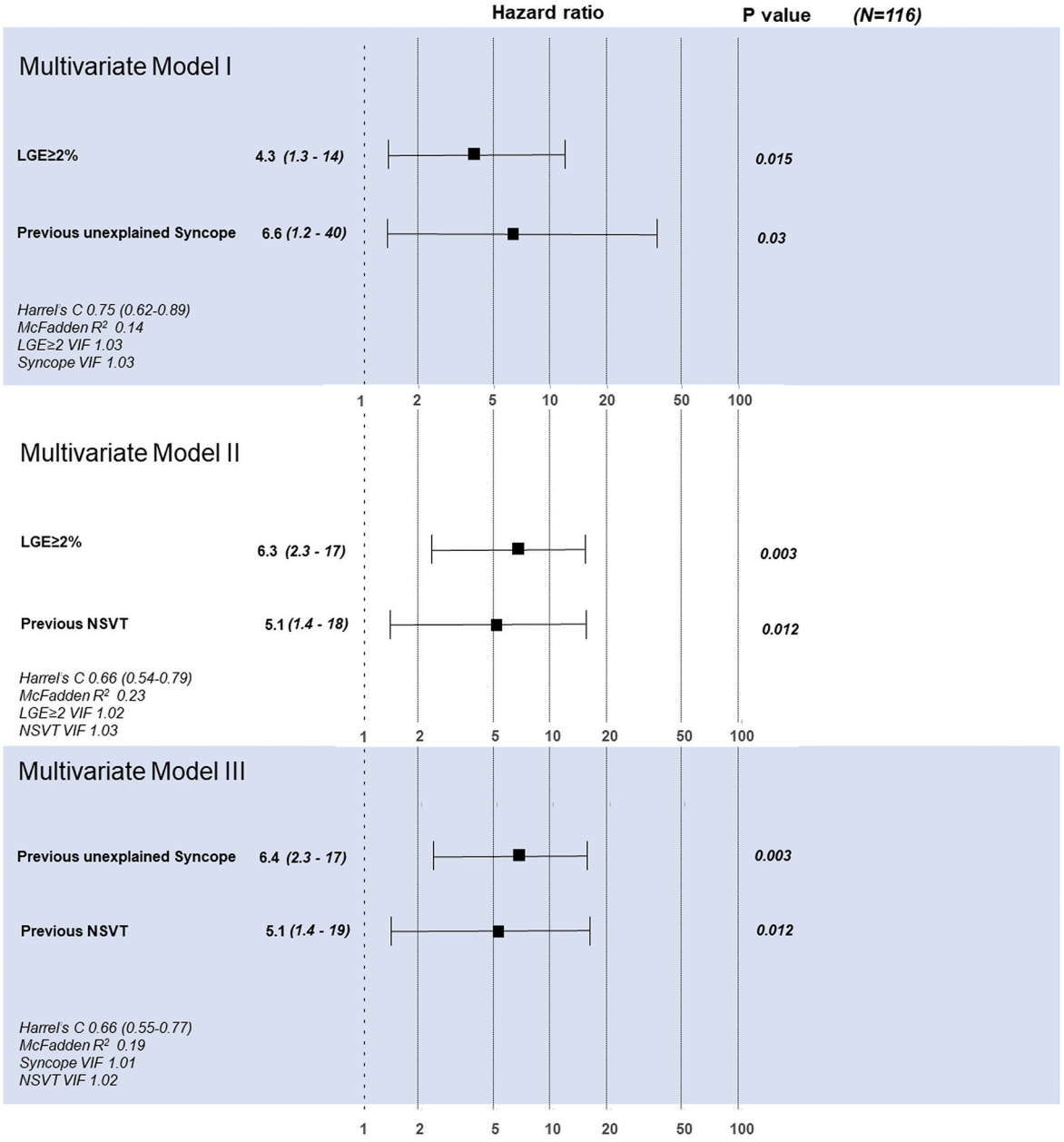

Fig. 2. Models of multivariate Cox regression: LGE extent ≥2%, previous unexplained syncope and NSVT were independent predictors of hard cardiac events in all the 3 models.

be considered a 'high risk population'.

5. Conclusions

In children and adolescents with HCM, LGE was present in 45% of patients. Patients with unexplained previous syncope and LGE extent ≥2% had the worse survival in terms of hard cardiac events. Moreover, prognostic significance of LGE extent increased with the follow-up, whereas that of syncope and NSVT decreased over time.

More longitudinal studies are needed to confirm the prognostic role of LGE in children with CMH and to eventual add it in a multi parametric risk score including clinical and imaging factors.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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