JAMA Cardiology | Original Investigation

Myocardial Scarring and Sudden Cardiac Death in Young Patients With Hypertrophic Cardiomyopathy
A Multicenter Cohort Study

Raymond H. Chan, MD, MPH; Laurine van der Wal, MD; Gabriela Liberato, MD; Ethan Rowin, MD; Jonathan Soslow, MD; Shiraz Maskatia, MD; Sherwin Chan, MD; Amee Shah, MD; Mark Fogel, MD; Lazaro Hernandez, MD; Shafkat Anwar, MD; Inga Voges, MD; Marcus Carlsson, MD, PhD; Sujatha Buddhe, MD; Kai Thorsten Laser, MD; Gerald Greil, MD; Emanuela Valsangiacomo-Buechel, MD; Iacopo Olivotto, MD; Derek Wong, MD; Cordula Wolf, MD; Heynric Grotenhuis, MD, PhD; Carsten Rickers, MD; Kan Hor, MD; Tobias Rutz, MD; Shelby Kutty, MD, PhD; Margaret Samyn, MD; Tiffanie Johnson, MD; Keren Hasbani, MD; Jeremy P. Moore, MD; Ludger Sieverding, MD; Jon Detterich, MD; Rodrigo Parra, MD; Paweena Chungsomprasong, MD; Olga Toro-Salazar, MD; Arno A. W. Roest, MD, PhD; Sven Dittrich, MD; Henrik Brun, MD; Joseph Spinner, MD; Wyman Lai, MD; Adrian Dyer, MD; Robert Jablonowsk, MD, PhD; Christian Meierhofer, MD; Dominik Gabbert, PhD; Milan Prsa, MD; Jyoti Kandlikar Patel, MD; Andreas Hornung, MD; Simone Goa Diab, MD; Aswathy Vaikom House, MD; Harry Rakowski, MD; Lee Benson, MD; Martin S. Maron, MD; Lars Grosse-Wortmann, MD

IMPORTANCE The ability to predict sudden cardiac death (SCD) in children and adolescents with hypertrophic cardiomyopathy (HCM) is currently inadequate. Late gadolinium enhancement (LGE) by cardiovascular magnetic resonance (CMR) imaging is associated with SCD events in adults with HCM.

OBJECTIVE To examine the prognostic significance of LGE in patients with HCM who are younger than 21 years.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, retrospective cohort study was conducted from April 8, 2015, to September 12, 2022, in patients with HCM who were younger than 21 years and had undergone CMR imaging across multiple sites in the US, Europe, and South America. Observers of CMR studies were masked toward outcomes and demographic characteristics.

EXPOSURE Natural history of HCM.

MAIN OUTCOME AND MEASURES The primary outcome was SCD and surrogate events, including resuscitated cardiac arrest and appropriate discharges from an implantable defibrillator. Continuous and categorical data are expressed as mean (SD), median (IQR), or number (percentage), respectively. Survivor curves comparing patients with and without LGE were constructed by the Kaplan-Meier method, and likelihood of subsequent clinical events was further evaluated using univariate and multivariable Cox proportional hazards models.

RESULTS Among 700 patients from 37 international centers, median (IQR) age was 14.8 (11.9-17.4) years, and 518 participants (74.0%) were male. During a median (IQR) [range] follow-up period of 1.9 (0.5-4.1) [0.1-14.8] years, 35 patients (5.0%) experienced SCD or equivalent events. LGE was present in 230 patients (32.9%), which constituted an mean (SD) burden of 5.9% (7.3%) of left ventricular myocardium. The LGE amount was higher in older patients and those with greater left ventricular mass and maximal wall thickness; patients with LGE had lower left ventricular ejection fractions and larger left atrial diameters. The presence and burden of LGE was associated with SCD, even after correcting for existing risk stratification tools. Patients with 10% or more LGE, relative to total myocardium, had a higher risk of SCD (unadjusted hazard ratio [HR], 2.19; 95% CI, 1.59-3.02; $P < .001$). Furthermore, the addition of LGE burden improved the performance of the HCM Risk-Kids score (before LGE addition: 0.66; 95% CI, 0.58-0.75; after LGE addition: 0.73; 95% CI, 0.66-0.81) and Precision Medicine in Cardiomyopathy score (before LGE addition: 0.68; 95% CI, 0.49-0.77; after LGE addition: 0.73; 95% CI, 0.64-0.82) SCD predictive models.

CONCLUSIONS AND RELEVANCE In this retrospective cohort study, quantitative LGE was a risk factor for SCD in patients younger than 21 years with HCM and improved risk stratification.

JAMA Cardiol. 2024;9(11):1001-1008. doi:10.1001/jamacardio.2024.2824
Published online September 25, 2024.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Lars Grosse-Wortmann, MD, Department of Pediatrics, Doernbecher Children's Hospital, Oregon Health and Science University, 707 SW Gaines St, Portland, OR 97239 (grossewo@ohsu.edu).

Hypertrophic cardiomyopathy (HCM) is the most common genetically determined cardiomyopathy[1] and is a leading cause of sudden cardiac death (SCD) in children and adolescents.[2] Implantable cardiac defibrillators (ICDs) are the only effective treatment of life-threatening arrhythmias. However, the advantages of ICDs are offset by substantial morbidity related to their use, particularly for young patients. Inappropriate ICD shocks occur in up to 6.5% of children annually, among other complications.[3] The overall goal must be to implant ICDs only in patients at the highest risk for SCD. Despite available prognostication tools,[4-7] the ability to identify these patients, while avoiding ICD implants in patients unlikely to experience SCD, remains insufficient.

Myocardial fibrosis, detected by cardiac magnetic resonance (CMR) imaging late gadolinium enhancement (LGE), has been linked to SCD in adults with HCM.[8] The association of LGE with SCD in pediatric patients with HCM has not been unequivocally established.[9-11] None of the currently available pediatric risk stratification models, and only 1 of the adult models,[12] include LGE as a variable. The objectives of this study were to examine the association between LGE and SCD in a pediatric HCM population and to investigate the ability of LGE to improve the performance of existing risk assessment tools for SCD in pediatric patients with HCM.

Key Points

Question Is late gadolinium enhancement (LGE) associated with sudden cardiac death (SCD) risk in patients aged 21 years and younger with hypertrophic cardiomyopathy (HCM)?

Findings In this cohort study of 700 patients younger than 21 years with HCM, LGE was independently associated with SCD, and a greater amount of enhancement was linked to an increase in SCD risk. The addition of LGE burden improved the performance of current risk stratification tools.

Meaning LGE was associated with enhanced classification of sudden cardiac risk in children, adolescents, and young adults with hypertrophic cardiomyopathy and should be considered in clinical evaluation of these patients.

Methods

Study Design

In this retrospective, multicenter cohort study, patients from 37 international sites were enrolled. The institutional review boards at each of the participating sites waived the requirements for informed consent due to the retrospective nature of the study. This study followed the Enhancing the Quality and Transparency of Health Research (EQUATOR) reporting guidelines. This study was conducted from April 8, 2015, to September 12, 2022.

Participants

Patients younger than 21 years with phenotypic HCM who underwent CMR were eligible for inclusion. Patients with other types of HCM (eg, syndromic or associated with metabolic, neuromuscular, or storage diseases) and those with conditions placing an abnormal afterload on the left ventricle (LV) (eg, hypertension and aortic stenosis) were excluded.

Data Collection

Demographic, electrocardiographic, echocardiographic, clinical, and genetic information was collected from patients' medical records. The maximal LV outflow tract (LVOT) gradients from the echocardiogram with the shortest time interval to CMR study were collected. LVOT obstruction was defined as a gradient of 30 mm Hg or greater.

CMR imaging on a 1.5-T or 3-T scanner included steady-state free-precession cine acquisitions in 3 long-axis planes and sequential short-axis slices, as well as LGE images, acquired 10 to 20 minutes after intravenous administration of gadolinium in identical planes as cine images. Images from all centers were transferred to a core laboratory at the Hospital for Sick Children (Toronto, Ontario, Canada) for analysis. LV and right ventricular (RV) volumes, masses and ejection fractions (EFs) were quantified from short-axis cine stacks by a single reader (L.v.d.W.) in the routine clinical fashion using commercially available software (QMass version 8.0 [Medis Medical Imaging Systems]). Maximal LV wall thickness was defined as the greatest dimension at any site within the myocardium. Left atrial (LA) diameter was measured on 3-chamber cine images during atrial diastole by a single observer (R.H.C). Biometric measurements scores were converted into *z* scores using published formulae.[13] The presence and extent of LGE were assessed by a single observer (R.H.C.). Quantification of LGE was performed using manual segmentation, along with the 4 and 6 SD method, as described elsewhere.[8] The total volume of LGE was expressed as a proportion of total LV mass (%LGE). All image analyses occurred masked to the patients' clinical information and outcomes. For intraobserver agreement, 50 randomly selected studies were reanalyzed after 12 months by the same observer, who was masked to the initial results. To test interobserver agreement, LGE was quantified by Drs Chan and Grosse-Wortmann on 50 randomly selected studies.

Primary End Point

The primary study outcome was SCD, defined as an otherwise unexpected death within 1 hour from the onset of symptoms in patients with previously stable or uneventful clinical course. Potentially lethal cardiovascular events in which patients were successfully resuscitated from cardiac arrest with documented ventricular fibrillation or appropriate shocks from an ICD were regarded as equivalent to SCD.[4,14]

Statistical Analysis

Continuous and categorical data were expressed as means (SDs), for normally distributed continuous data; medians (IQRs), for non-normally distributed continuous data; or as frequencies, respectively. Comparisons of characteristics between groups were made with unpaired *t* test, χ^2 test, or Fisher exact test where appropriate.

Kaplan-Meier survivor curves comparing patients with and without LGE were constructed, and differences between groups were examined using log-rank tests for equality of survivor

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	No. (%)			*P* value
	All patients (N = 700)	With LGE (n = 230)	Without LGE (n = 470)	
Demographics				
Sex				
Female	182 (26.0)	59 (25.7)	123 (26.2)	.55
Male	518 (74.0)	171 (74.3)	347 (73.8)	
Age at diagnosis, median (IQR), y	12.0 (7.0-15.0)	13.0 (9.0-16.0)	12.0 (7.0-15.0)	.01
Age at CMR, median (IQR), y	14.8 (11.9-17.4)	15.7 (13.2-18.0)	14.2 (11.2-17)	<.001
Follow-up duration, median (IQR), y	1.9 (0.5-4.1)	2.1 (0.6-4.2)	1.8 (0.5-4.1)	.002
Initial referral reason[a]				
Dyspnea or murmur	282 (40.3)	101 (43.9)	181 (38.5)	.17
Family history or screening	229 (32.7)	71 (30.9)	158 (33.6)	.47
Chest pain	81 (11.6)	31 (13.5)	50 (10.6)	.27
Palpitations	46 (6.6)	20 (8.7)	26 (5.5)	.11
Syncope	50 (7.1)	19 (8.3)	31 (6.6)	.42
Clinical status				
NYHA/Ross class, mean (SD)	1.2 (0.5)	1.3 (0.6)	1.2 (0.5)	.02
History of syncope	80 (11.4)	35 (15.2)	45 (9.6)	.02
Documented NSVT	44 (6.3)	20 (8.7)	24 (5.1)	.09
Echocardiography				
LVOT obstruction (gradient >30 mm Hg)	170 (24.3)	59 (25.7)	111 (23.6)	.43
CMR, mean (SD)				
LVEF, %	59 (9)	57 (10)	59 (9)	.20
LV mass *z* score	3.8 (3.7)	5.5 (3.7)	3.4 (3.5)	<.001
LV mass or volume ratio	1.01 (0.58)	1.21 (0.78)	0.92 (0.39)	<.001
Septal thickness, mm	15.8 (6.4)	19.7 (6.5)	13.8 (5.2)	<.001
Posterior wall thickness, mm	10.8 (3.6)	11.1 (4.2)	10.6 (3.3)	.08
Maximal wall thickness, mm	19.7 (6.6)	24.0 (6.6)	17.5 (5.5)	<.001
Maximal wall thickness *z* score	11.8 (6.1)	15.8 (5.8)	10.8 (5.7)	<.001
LA diameter *z* score	0.9 (1.7)	1.4 (1.8)	0.8 (1.7)	<.001
RVEF, %	71 (9)	74 (8)	70 (9)	<.001
Presence of LGE, No. (%)	230 (32.9)	NA	NA	NA
LGE, g	NA	12.5 (19.7)	NA	NA
LGE, g/m^2	NA	7.6 (12.4)	NA	NA
LGE, percentage of total myocardium	NA	5.9 (7.3)	NA	NA

Abbreviations: CMR, cardiac magnetic resonance; EF, ejection fraction; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NA, not applicable; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; RV, right ventricle; RVEF, right ventricular ejection fraction.

[a] May have more than 1 response.

functions. Relationships between LGE as both a binary variable (present vs absent) and as a continuous variable (expressed as %LGE), along with other clinical and imaging variables and the likelihood of subsequent SCD events, were assessed through univariate and multivariable Cox proportional hazards models. Proportional hazards assumptions were tested graphically and with time-dependent covariates before proceeding.

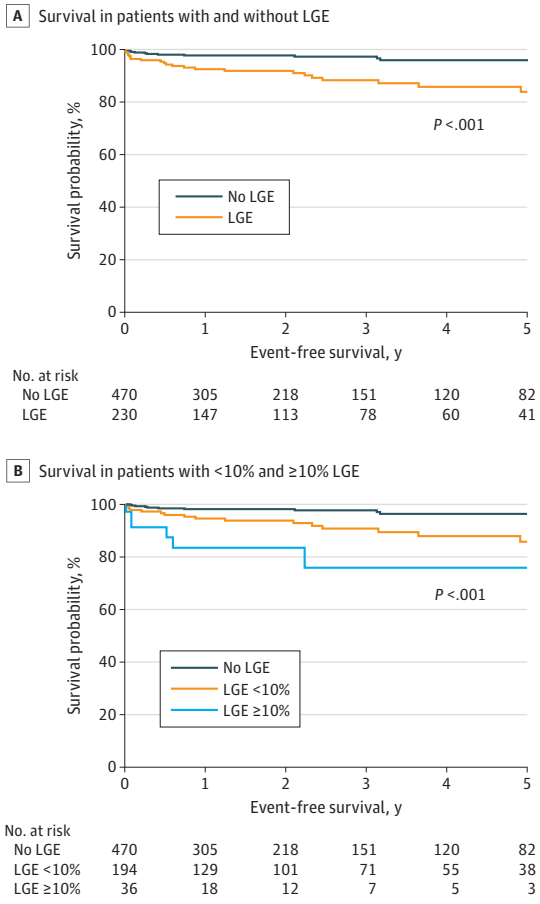
Furthermore, the incremental value of LGE when added to pediatric risk models was evaluated, including the HCM Risk-Kids score[6] and the Precision Medicine in Cardiomyopathy (PRIMaCY) tool.[7] This was assessed using 3 separate methods: (1) likelihood ratio tests; (2) Akaike information criterion; and (3) C statistics. In addition, 2 adult risk scores often applied to children were also included as methods: (1) the American Heart Association (AHA)/American College of Cardiology (ACC) criteria[12] and (2) the European Society of Cardiology (ESC) risk calculator.[4] A sensitivity analysis was undertaken in which these scores were applied to the current population, and the performance of presence and extent of LGE when added to them was tested. Two-tailed $P<.05$ was regarded as statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute) and R version 3.6.2 (The R Foundation).

Results

Study Patients

A total of 700 patients were included. Clinical and demographic characteristics, as well as CMR and echocardiography findings, are presented in **Table 1.** At the time of CMR, the median (IQR) patient age was 14.8 (11.9-17.4) years. Of 700 patients, 518 (74.0%) were male. Median (IQR) [range] fol-

Figure. Kaplan-Meier Curves



Kaplan-Meier curves comparing the sudden cardiac death–free survival between patients with and without late gadolinium enhancement (LGE) (A) and between patients without vs with <10% and ≥10% LGE, respectively (B), relative to total left ventricular myocardium.

low-up time from study entry to most recent evaluation or death was 1.9 (0.5-4.1) [0.1-14.8] years. The median (IQR) interval between echocardiogram and CMR was 44 (12-134) days. Of 700 total patients, 170 patients (24.3%) had LVOT obstruction. Biventricular systolic function was preserved in all patients. On average, LA size was normal. There were no patients with apical aneurysms.

LGE

Of 700 patients, 233 patients (33.3%) had LGE, which constituted a mean (SD) burden of 5.9% (7.3%) of LV myocardium. Patients with LGE were older, and the amount of LGE was significantly correlated with age (0.15% increase in %LGE per year; $P < .001$), higher LV mass (0.15% LGE per 10 g LV mass or 0.28% LGE per 10 g/m^2 LV mass; $P < .001$), maximal wall thickness (0.23% LGE per mm or 0.24 LGE per z score point), and a larger LA diameter (0.12% LGE per mm or 0.45% per z score point; $P < .001$). Patients with greater LGE burden also had significantly lower LVEF (−0.54% per 1% LGE; $P < .001$) (Table 1). The visual grayscale thresholding method demonstrated high reproducibility via intraobserver variability (correlation coefficient [k] = 0.78; $P < .001$), with a mean (SD) difference of −1.3 (5.9) g, and interobserver variability (k = 0.83; $P < .001$), with a mean (SD) difference of 0.3 (5.9) g.

Outcomes

Thirty-five patients (5.0%) experienced SCD or an equivalent event at a mean (SD) [range] age of 14.8 (3.9) [6.3-27.0] years. This included 3 patients with SCD, 20 patients with resuscitated arrest, 14 patients with appropriate ICD shock, and 3 patients with more than 1 event. For further detail, see eTable 1 in Supplement 1. The characteristics of each of these patients, along with their 5-year SCD predictions by the HCM Risk-Kids and PRIMaCY tools, are summarized in eTable 2 in Supplement 1. One female patient aged 7 months, with no LGE and an LVEF of 45%, died of heart failure 4.5 months after the CMR. Patients who experienced SCD had a slightly worse New York Heart Association/Ross status and were older than their non-SCD counterparts (eTable 1 in Supplement 1). They were more likely to have sustained a prior syncopal event (23% vs 11%; $P = .05$) and to have experienced nonsustained ventricular tachycardia in the past (26% vs 5.3%; $P < .001$). Patients who experienced SCD had thicker interventricular septae (mean [SD], 19.9 [6.7] mm vs 14.8 [5.9] mm; $P < .03$) and larger LA diameters (mean [SD] z score, 1.36 [1.8] vs 0.8 [1.7]; $P < .03$) and were more likely to have LGE (68.6% vs 31.0%; $P < .001$; Table 1). Patients who were free from SCD experienced LVOT obstruction more often than patients who experienced SCD (25% vs 5.7%; $P = .009$). Of patients with LGE, 17 of 230 patients (7.4%) experienced SCD compared with 10 of 470 patients without LGE (2.1%) ($P < .001$). Univariate Cox analysis showed that the presence of LGE was associated with an increased SCD risk (hazard ratio [HR], 4.46; 95% CI, 2.16-9.20; $P < .001$). LGE confined to the RV insertion points in the interventricular septum was not associated with increased SCD risk. Five-year event rates were 3.6% in 230 LGE-negative patients and 15.7% in 470 LGE-positive patients (log-rank $P < .001$; **Figure**, A). Patients with 10% more LGE relative to total myocardium had a 2-fold or greater SCD risk (unadjusted HR, 2.19 per 10% increase in LGE; 95% CI, 1.59-3.02; $P < .001$) (Figure, B). Patients with 0.1% to 9.9% LGE and 10% or more LGE had 5-year event rates of 14.2% and 24.1%, respectively (log-rank $P < .001$). When LGE was adjusted for the HCM Risk-Kids and PRIMaCY tools (**Table 2**) or for the AHA/ACC or ESC tools (eTable 3 in Supplement 1), LGE remained independently associated with SCD. The Risk-Kids and PRIMaCY scores are intended for use in patients younger than 16 and 18 years, respectively. Thus, in addition to the entire cohort, sensitivity analyses for patients younger than 16 and 18 years were performed, whereby LGE remained independently associated with SCD, with slightly different effect estimates (eTable 4 in Supplement 1). Estimating SCD risk, we did not observe an interaction between age and LGE burden, and LGE remained associated with SCD in all 3 age tertiles within the cohort (eTable 5 in Supplement 1). To further explore the utility of LGE across baseline risk profiles, we performed a subgroup analysis of patients with HCM Risk-Kids scores within the median 2 quartiles of the population to ex-

Table 2. Performance of Late Gadolinium Enhancement (LGE) When Adjusted for HCM Risk-Kids and PRIMaCY Existing Risk Assessment Tools

Model	HR (95% CI)		
	Association with SCD, univariate	Bivariate adjusted by adding HCM Risk-Kids	Bivariate adjusted by adding PRIMaCY score[a]
Presence of LGE	Unadjusted = 4.46 (2.16-9.20)	Adjusted = 3.45 (1.58-7.53)	Adjusted = 3.69 (1.78-6.68)
P value	<.001	.002	.001
%LGE	Unadjusted/10% LGE = 2.19 (1.59-3.02)	Adjusted/10% LGE = 1.90 (1.33-2.72)	Adjusted/10% LGE = 1.96 (1.39-2.76)
P value	<.001	<.001	<.001

Abbreviations: %LGE, proportion of total left ventricle mass; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; PRIMaCY, Precision Medicine in Cardiomyopathy; SCD, sudden cardiac death.

[a] The formula for the PRIMaCY score is unpublished; however, an online calculator is available (https://primacycalculator.com) and was used to compute the 5-year risk.

Table 3. Previously Identified Variables Associated With Sudden Cardiac Death (SCD) Included in Commonly Used Risk Stratification Tools

Variable	Univariate hazard ratio (95% CI)	*P* value	Included in	
			HCM Risk-Kids score	PRIMaCY score
Age	1.00 (0.93-1.06)	.88	Yes	Yes
Prior history of NSVT	4.11 (1.78-9.52)	<.001	Yes	Yes
Prior history of syncope	2.00 (0.87-4.61)	.10	Yes	Yes
Maximal wall thickness >30 mm	2.12 (0.98-4.56)	.06	No	No
Maximal wall thickness *z* score >11[a]	1.38 (0.76-2.96)	.24	Yes[b]	No
Interventricular septal thickness *z* score	1.06 (0.96-1.18)	.25	No	Yes
Posterior wall thickness *z* score	0.92 (0.71-1.19)	.53	No	Yes
LA diameter *z* score	1.18 (0.97-1.45)	.11	Yes	Yes
LVOT gradient ≥30 mm Hg[c]	0.37 (0.09-1.57)	.009	Yes[d]	Yes[d]
Extensive LGE[e]	10.7 (4.3-26.1)	<.001	No	No
LVEF <50%	2.76 (1.29-5.92)	.009	No	No
Family history of SCD	1.31 (0.56-3.04)	.54	No	No
Pathogenic mutation	2.10 (0.81-5.42)	.13	No	Yes

Abbreviations: HCM, hypertrophic cardiomyopathy; LA, left atrium; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; PRIMaCY, Precision medicine in cardiomyopathy.

[a] Corresponds to a wall thickness of 30 mm in an adult male with 1.73 m^2 body surface area.

[b] As a continuous variable.

[c] LVOT obstruction conveyed a protective effect in the Risk-Kids and PRIMaCY scores.

[d] Included not as *z* score in this tool.

[e] Extensive LGE defined as >15% LGE.

amine the intermediate risk subgroup without setting arbitrary demarcation points of the scores. In these 350 patients, whose median HCM Risk-Kids estimate was 5.6% per 5 years, there were 19 events. After adjusting for the HCM Risk-Kids score, LGE continued to be independently associated with SCD risk (adjusted HR per 10% LGE, 1.77; *P* = .05). Similarly, in 351 patients whose median 5-year PRIMaCY estimate was 10.3%, there were 13 patients with SCD events. LGE was also independently associated with SCD risk (adjusted HR per 10% LGE, 3.11; *P* = .02). RVEF was associated with SCD in univariate analysis (HR per 10% drop in RVEF, 1.51; 95% CI, 1.06-2.17; *P* = .02) but was not significant in multivariable analysis.

Genetics

Of 700 total patients, 357 patients (51.0%) had genetic test results available. In 170 of these patients (47.6%), 1 or more pathogenic variants for sarcomeric HCM were identified. There were no known pathogenic variants in 147 patients (41.2%). A variant of unknown significance was detected in 41 patients (11.5%). The 3 most common variants were in the *MYH7* gene in 70 patients (39% of gene-positive patients), in the *MYBPC3* gene in 66 patients (35%), and in cardiac troponin genes in 7 patients (4%). Patients who experienced SCD or a surrogate event were more likely to harbor a pathogenic variant for sarcomeric HCM (68% vs 47%; *P* = .04), and pathogenic variants were more common in LGE-positive patients (55% vs 44%; *P* = .06). There was a trend toward increased SCD risk in Cox survival analysis (**Table 3**). There was no statistically significant difference regarding family history of SCD between patients with or without LGE and with or without SCD.

Performance of the HCM Risk-Kids and PRIMaCY Risk Stratification Tools

The univariate hazard ratios of HCM Risk-Kids and PRIMaCY are summarized in Table 3. The addition of LGE improved the performance of both risk scores, as demonstrated by improved C statistics (**Table 4**), as well as for the AHA/ACC and ESC tools (eTable 6 in Supplement 1). Other metrics, including the likelihood ratio and Akaike information criterion, also demonstrated significant improvements with the addition of LGE. To estimate the degree of optimism for the C statistic estimate, internal validation using 1000 bootstrap samples was used. This provided an empirical estimation of the performance metrics, without an external cohort, by training the model on each resample and aggregating the results. The degree of optimism observed for the C statistic estimates was found to be limited (<0.01 optimism of C statistic for all; Table 4), suggesting that the risk of overfitting the dataset was low. (For example, the optimism-corrected C statistic for the model with HCM Risk-Kids plus LGE was calculated to be: 0.73 minus 0.007, equaling 0.723.) We found no evidence of interaction of LGE with risk severity as determined by the HCM Risk-

Table 4. HCM Risk-Kids and PRIMaCY Model Improvement by Addition of Quantitative LGE

Model	LR χ^2 value	AIC	C statistic (95% CI)	Bootstrap internal validation optimism for C statistic
HCM Risk-Kids score	9.81	405	0.66 (0.58-0.75)	0.001
HCM Risk-Kids score + LGE	18.9	398	0.73 (0.66-0.81)	0.007
PRIMaCY score	9.69	405	0.68 (0.49-0.77)	0.001
PRIMaCY score + LGE	20.9	396	0.73 (0.64-0.82)	0.005

Abbreviations: AIC, Akaike information criterion; C, concordance; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LR, likelihood ratio; PRIMaCY, Precision Medicine in Cardiomyopathy.

Kids or PRIMaCY tools, including those considered to be in the intermediate-risk subgroups.

Discussion

Accurate identification of patients with HCM who are at risk of SCD is paramount in pediatric patients, who are more prone to device-related complications than adults and have a longer exposure to lifetime risks.[3] It is estimated that, using current calculators, 10 ICDs are placed for each child saved, while simultaneously missing some children who die from SCD.[6,7,14] The current study is among the largest in childhood HCM.[15-17] Our results indicate the potential importance of LGE when making decisions about ICD implantation in children and adolescents with HCM. Specifically, we discovered the following important findings. First, the presence of LGE is a risk factor for SCD, independent of other pediatric and adult decision aids for ICD placement. Second, the risk of SCD increases with a greater extent of LGE. Third, to our knowledge, this is the first ever head-to-head comparison of the most commonly used SCD risk stratification tools using an independent cohort, all of which performed comparably. Fourth, the addition of LGE improves the performance of the aforementioned HCM SCD risk stratification tools.

The reported prevalence of LGE in children with HCM ranges widely from 18% to 73%.[11,18,19] In the previously largest series, which included 155 patients, LGE was detected in 46% of patients.[20] The current study, with more than 4-fold the number of patients, found a prevalence of 33%. The observation of a lower LGE prevalence in children and adolescents, compared to the reported prevalence of approximately 60% in adults,[21] supports the paradigm that LGE develops and progresses gradually over time.[20,22] Indeed, in the current study, patients who presented with LGE were older, and the burden of LGE was correlated with age. Patients with LGE had greater LV wall thickness and total myocardial mass, lower LVEF, and larger LA size, indicating an association of myocardial scarring with both systolic and diastolic dysfunction.

While LGE has been demonstrated to be an independent marker of SCD risk in adults,[21] its utility in risk stratification in children and adolescents has not been previously established. In the largest prior study, which involved a mixed cohort of 116 children with both sarcomeric and other types of HCM, LGE was associated with a combined end point of sustained ventricular tachycardia, resuscitated cardiac arrest, SCD, end-stage heart failure, appropriate ICD intervention, or heart transplant.[10] However, data on the role of LGE in the cohort of sarcomeric HCM, or regarding SCD risk specifically, were not presented. The current results demonstrate an independent association between LGE and SCD; patients with LGE were 4-fold more likely to experience SCD than patients without LGE. The SCD risk was higher with greater amounts of LGE. The utility of LGE to help with risk assessment appears to apply similarly to a broad range of baseline risk profiles, as assessed using PRIMaCY and HCM Risk-Kids scores. Of note, patients who exhibited LGE were not only more likely to experience SCD, but were also older, with greater LV wall thickness, LV mass, and an LV mass-to-volume ratio. In addition to LGE, other parameters that feature in contemporary SCD risk stratification tools demonstrated differences between patients with and without SCD events. These included LA diameter and LV thickness. In this cohort, both lower LVEF and lower RVEF were seen in patients who experienced SCD.

To our knowledge, the current study is the first to compare the 2 pediatric SCD risk stratification scores with the 2 adult risk tools (which have been applied to children and adolescents in the past) in a head-to-head comparison using a large, independent cohort. Reassuringly, the performance of all of these tools was within a close range of one another in identifying patients at risk of SCD. This is not surprising, as the parameters that are included in each, including the 2 tools primarily designed for adult patients, overlap, and candidate variables in newer scores were chosen based on previous literature. However, our study also demonstrates that these strategies need improvement to make ICD decisions with greater confidence in the pediatric population. HCM Risk-Kids and PRIMaCY metrics identify high-risk patients, but their results may suggest ICD placement in some patients who do not end up experiencing an SCD event. In fact, a recent validation of the PRIMaCY tool in an independent cohort suggested an overestimation of SCD risk.[23] Our results suggest that LGE adds independent prognostic information for identifying patients with HCM who are at higher SCD risk. In our cohort, LGE remained associated with SCD, even after adjusting for the prognostic information from the HCM Risk-Kids and PRIMaCY scores. Conversely, the addition of LGE improved the performance of each of these tools, indicated by an increase in C statistics and other metrics. Furthermore, our results indicate that the burden of LGE, in addition to its presence, contains useful information. However, even relatively small amounts of LGE, unless confined to the RV insertion points, had prognostic significance, in line with a 2022 study by Ali et al,[10] which found that LGE involving as little as 2% of the myocardium was associated with the composite adverse outcome in their mixed HCM cohort. Despite the independent association of LGE with SCD, it should be emphasized that the use of LGE in risk stratification needs to be considered in conjunction with other, previously proven

clinical risk factors, as no single marker in isolation can accurately predict SCD risk in all patients. The absence of LGE was not absolutely protective against SCD risk in this cohort, suggesting that susceptibility to potentially lethal ventricular tachyarrhythmias in HCM can be influenced by factors other than myocardial fibrosis, identified by CMR. However, the adjusted HRs provided in Table 2 can be useful in estimating SCD risk, taking into account a patient's LGE burden integrated into existing risk stratification and scoring systems.

We found a greater prevalence of pathogenic variants in patients with SCD events, but no association with SCD risk in univariate regression. Compared with other factors, the association of genetic information in the PRIMaCY tool with outcome appears to be modest. Further study, which will likely take into account specific variants, rather than grouping all pathogenic changes into 1 parameter, may yield additional prognostic benefit.

Limitations

The current study has the limitations of a retrospective study. Although the cohort size was respectable and the largest thus far with CMR information, the modest number of SCD events posed a limitation in our multivariate analysis. Thus, even though patients with large amounts of LGE are at higher risk of SCD, independent of other risk scores, the small number of SCD events in this study does not yet permit the conclusion that use of LGE will improve risk stratification in an individual patient. The follow-up duration was variable and in the order of months for some patients; a longer follow-up duration may have yielded a greater number of events and is the subject of an ongoing study. This cohort is likely not entirely representative of the entire pediatric HCM population, as patients with more severe phenotypes or malignant family histories may be more likely to be referred to CMR. Independent validation of the risk models with external cohorts, ideally prospectively, would be invaluable to assess the validity of this study's findings.

Conclusions

LGE is associated with SCD in pediatric patients with HCM. These results, which need to be confirmed in independent cohorts, suggest that quantitative measure of LGE can become part of a comprehensive approach to identify patients at highest risk of SCD. Future work is needed to demonstrate how to use LGE in a risk score that includes other risk factors.

ARTICLE INFORMATION

Accepted for Publication: July 15, 2024.

Published Online: September 25, 2024. doi:10.1001/jamacardio.2024.2824

Author Affiliations: Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada (R. H. Chan, Rakowski); Department of Primary and Long-term Care, University of Groningen, Groningen, the Netherlands (van der Wal); Heart Institute, University of São Paulo Medical School, São Paulo, Brazil (Liberato); Hypertrophic Cardiomyopathy Center, Lahey Hospital and Medical Center, Burlington, Massachusetts (Rowin, Maron); Vanderbilt University Medical Center, Nashville, Tennessee (Soslow); Lucile Packard Children's Hospital, Stanford University, Palo Alto, California (Maskatia); Texas Children's Hospital, Baylor College of Medicine, Houston (Maskatia, Spinner); Children's Mercy Hospital, Kansas City, Missouri (S. Chan); Columbia University Irving Medical Center, New York, New York (Shah); Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania (Fogel); Joe DiMaggio Children's Hospital, Hollywood, Florida (Hernandez); University of California, San Francisco, School of Medicine (Anwar); Benioff Children's Hospital, University of California, San Francisco (Anwar); Department of Congenital Heart Disease and Pediatric Cardiology, University of Schleswig-Holstein, Kiel, Germany (Voges, Gabbert); Pediatric Heart Centre, University Children's Hospital, Giessen, Germany (Voges); Centre for Mathematical Sciences, Lund University, Lund, Sweden (Carlsson); Seattle Children's Hospital, University of Washington, Seattle (Buddhe); Heart and Diabetes Center, Ruhr University Bochum, Bad Oeynhausen, Germany (Laser); University of Texas Southwestern Medical Center, Dallas (Greil, Dyer); University Children's Hospital, Zurich, Switzerland (Valsangiacomo-Buechel); Careggi University Hospital, Florence, Italy (Olivotto); Meyer Children's Hospital IRCCS, Florence, Italy (Olivotto); Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada (Wong); German Heart Center Munich, Department of Congenital Heart Defects and Pediatric Cardiology, Technical University of Munich, Munich, Germany (Wolf, Meierhofer); Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands (Grotenhuis); University Heart Center, Hamburg, Germany (Rickers); Nationwide Children's Hospital, Columbus, Ohio (Hor); Service of Cardiology, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland (Rutz, Prsa); Division of Cardiology, Department of Pediatrics, Children's Hospital and Medical Center, University of Nebraska Medical Center, Omaha (Kutty); Taussig Heart Center, Department of Pediatrics, Johns Hopkins Hospital, Baltimore, Maryland (Kutty); Herma Heart Institute, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee (Samyn); Indiana University School of Medicine, Indianapolis (Johnson, Patel); Texas Center for Pediatric and Congenital Heart Disease, Dell Children's Medical Center, University of Texas at Austin, Austin (Hasbani); Division of Cardiology, Department of Pediatrics, University of California, Los Angeles, Medical Center (Moore); University Children's Hospital Tuebingen, Tuebingen, Germany (Sieverding, Hornung); Keck School of Medicine, University of Southern California, Los Angeles (Detterich); Heart Institute, Children's Hospital Los Angeles, Los Angeles, California (Detterich); Pontificia Universidad Católica de Chile, Santiago, Chile (Parra); Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand (Chungsomprasong); Connecticut Children's Medical Center, Hartford (Toro-Salazar); Department of Pediatrics, Leiden University Medical Center, Leiden, the Netherlands (Roest); Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany (Dittrich); Department of Pediatric Cardiology, Oslo University Hospital, Oslo, Norway (Brun, Diab); Children's Hospital of Orange County, Orange, California (Lai); Cook Children's Medical Center, Fort Worth, Texas (Dyer); Clinical Physiology, Department of Clinical Sciences Lund, Skåne University Hospital, Lund University, Lund, Sweden (Jablonowsk); University of Oklahoma Health Sciences Center, Oklahoma City (House); Department of Paediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada (Benson); Department of Pediatrics, Doernbecher Children's Hospital, Oregon Health and Science University, Portland (Grosse-Wortmann).

Author Contributions: Drs R. Chan and Grosse-Wortmann had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: R. Chan, van der Wal, Rowin, Carlsson, Greil, Wong, Grotenhuis, Hor, Kutty, Lai, Rakowski, Benson, Maron, Grosse-Wortmann.
Acquisition, analysis, or interpretation of data: R. Chan, van der Wal, Liberato, Rowin, Soslow, Maskatia, S. Chan, Shah, Fogel, Hernandez, Anwar, Voges, Carlsson, Buddhe, Thorsten Laser, Greil, Valsangiacomo Buechel, Olivotto, Wong, Wolf, Grotenhuis, Rickers, Hor, Rutz, Samyn, Johnson, Hasbani, Moore, Sieverding, Detterich, Parra, Chungsomprasong, Toro-Salazar, Roest, Dittrich, Brun, Spinner, Lai, Dyer, Jablonowsk, Meierhofer, Gabbert, Prsa, Kandlikar Patel, Hornung, Goa Diab, Vaikom House, Grosse-Wortmann.
Drafting of the manuscript: R. Chan, van der Wal, Greil, Gabbert, Grosse-Wortmann.
Critical review of the manuscript for important intellectual content: R. Chan, van der Wal, Liberato, Rowin, Soslow, Maskatia, S. Chan, Shah, Fogel, Hernandez, Anwar, Voges, Carlsson, Buddhe, Thorsten Laser, Greil, Valsangiacomo Buechel, Olivotto, Wong, Wolf, Grotenhuis, Rickers, Hor, Rutz, Kutty, Samyn, Johnson, Hasbani, Moore,

Sieverding, Detterich, Parra, Chungsomprasong, Toro-Salazar, Roest, Dittrich, Brun, Spinner, Lai, Dyer, Jablonowsk, Meierhofer, Prsa, Kandlikar Patel, Hornung, Goa Diab, Vaikom House, Rakowski, Benson, Maron, Grosse-Wortmann.
Statistical analysis: R. Chan, Grosse-Wortmann.
Obtained funding: Carlsson, Rakowski, Grosse-Wortmann.
Administrative, technical, or material support: R. Chan, van der Wal, Liberato, Fogel, Anwar, Voges, Buddhe, Thorsten Laser, Greil, Valsangiacomo Buechel, Wong, Grotenhuis, Samyn, Sieverding, Detterich, Parra, Chungsomprasong, Toro-Salazar, Roest, Dittrich, Brun, Meierhofer, Prsa, Hornung, Goa Diab, Vaikom House, Grosse-Wortmann.
Supervision: R. Chan, Maskatia, Fogel, Carlsson, Greil, Olivotto, Grotenhuis, Rickers, Kutty, Hasbani, Toro-Salazar, Spinner, Rakowski, Maron, Grosse-Wortmann.

Conflict of Interest Disclosures: Dr S. Chan reported grants from Jazz Pharmaceuticals and Hyperfine Inc and personal fees from GE Healthcare and Deepsight Technologies outside the submitted work. Dr Rowin reported research funding from Pfizer and iRhythm. Dr Fogel reported a US National Institutes of Health (NIH) grant in myocardial scarring. Dr Carlsson reported grants from the Swedish Heart and Lung Foundation and from the Agreement on Medical Education and Research Skane during the conduct of the study; grants from the Swedish research council outside the submitted work; and personal fees from serving as a contractor for the NIH outside the submitted work. Dr Olivotto reported personal fees from Bristol Myers Squibb, Cytokinetics, Rocket Pharma, and Tenaya; grants from Amicus, Menarini International, and Chiesi outside the submitted work; and serving on the advisory board of and receiving research grants from Bristol Myers Squibb-Myokardia, Cytokinetics, Sanofi Genzyme, Shire Takeda, Amicus, Menarini International, Tenaya, Lexeo, Edgewise, Lexicon, and Rocket Pharma. Dr Wolf reported a small fee per patient entered in eCRF from Oregon Health and Science University during the conduct of the study. Dr Hor reported consultancy or advisory roles with Bayer AG, Bristol Myers Squibb, Capricor Therapeutics, Daiichi Sankyo, PTC Therapeutics, Revidia Therapeutics, Sarepta Therapeutics, Stealth Biotherapeutics, Vertex Pharmaceuticals, Wave Life Science, Blade Therapeutics, FibroGen, and Foresee Pharmaceuticals; research funding from Sarepta Therapeutics; and speakers' bureau activity for NS Pharma and PTC Therapeutics. Dr Sieverding reported grants from Stiftung zur Förderung der Erforschung von Zivilisationserkarnkungen both during the conduct of the study and outside the submitted work. Dr Hornung reported grants from Stiftung zur Förderung der Erforschung von Zivilisationserkrankungen both during the conduct of the study and outside the submitted work. Dr Grosse-Wortmann reported grants from the Children's Cardiomyopathy Foundation during the conduct of the study and personal fees from Siemens Healthineers outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by the Children's Cardiomyopathy Foundation.

Role of the Funder/Sponsor: The Children's Cardiomyopathy Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank Mrs Rita Nobile and Mr Dariusz Mroczek from the Hospital for Sick Children (Toronto, Ontario, Canada) for coordinating this study and for their information technology support, respectively.

REFERENCES

1. Colan SD, Lipshultz SE, Lowe AM, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *Circulation*. 2007;115(6):773-781. doi:10.1161/CIRCULATIONAHA.106.621185

2. Gajewski KK, Saul JP. Sudden cardiac death in children and adolescents (excluding Sudden Infant Death Syndrome). *Ann Pediatr Cardiol*. 2010;3(2):107-112. doi:10.4103/0974-2069.74035

3. Maron BJ, Spirito P, Ackerman MJ, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2013;61(14):1527-1535. doi:10.1016/j.jacc.2013.01.037

4. O'Mahony C, Jichi F, Pavlou M, et al; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35(30):2010-2020. doi:10.1093/eurheartj/eht439

5. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2020;76(25):3022-3055. doi:10.1016/j.jacc.2020.08.044

6. Norrish G, Ding T, Field E, et al. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM Risk-Kids). *JAMA Cardiol*. 2019;4(9):918-927. doi:10.1001/jamacardio.2019.2861

7. Miron A, Lafreniere-Roula M, Steve Fan CP, et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. *Circulation*. 2020;142(3):217-229. doi:10.1161/CIRCULATIONAHA.120.047235

8. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130(6):484-495. doi:10.1161/CIRCULATIONAHA.113.007094

9. Spinner JA, Noel CV, Denfield SW, et al. Association of late gadolinium enhancement and degree of left ventricular hypertrophy assessed on cardiac magnetic resonance imaging with ventricular tachycardia in children with hypertrophic cardiomyopathy. *Am J Cardiol*. 2016;117(8):1342-1348. doi:10.1016/j.amjcard.2016.01.032

10. Ali LA, Marrone C, Martins DS, et al. Prognostic factors in hypertrophic cardiomyopathy in children: an MRI based study. *Int J Cardiol*. 2022;364:141-147. doi:10.1016/j.ijcard.2022.06.043

11. Chaowu Y, Shihua Z, Jian L, Li L, Wei F. Cardiovascular magnetic resonance characteristics in children with hypertrophic cardiomyopathy. *Circ Heart Fail*. 2013;6(5):1013-1020. doi:10.1161/CIRCHEARTFAILURE.113.000414

12. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary: a Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2020;142(25):e533-e557.

13. Buechel EV, Kaiser T, Jackson C, Schmitz A, Kellenberger CJ. Normal right- and left ventricular volumes and myocardial mass in children measured by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2009;11(1):19. doi:10.1186/1532-429X-11-19

14. Maron BJ, Mackey-Bojack S, Facile E, Duncanson E, Rowin EJ, Maron MS. Hypertrophic cardiomyopathy and sudden death initially identified at autopsy. *Am J Cardiol*. 2020;127:139-141. doi:10.1016/j.amjcard.2020.04.021

15. Norrish G, Cleary A, Field E, et al. Clinical features and natural history of preadolescent nonsyndromic hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2022;79(20):1986-1997. doi:10.1016/j.jacc.2022.03.347

16. Wilkinson JD, Lowe AM, Salbert BA, et al. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. *Am Heart J*. 2012;164(3):442-448. doi:10.1016/j.ahj.2012.04.018

17. Ho CY, Day SM, Ashley EA, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation*. 2018;138(14):1387-1398. doi:10.1161/CIRCULATIONAHA.117.033200

18. Windram JD, Benson LN, Dragelescu A, et al. Distribution of hypertrophy and late gadolinium enhancement in children and adolescents with hypertrophic cardiomyopathy. *Congenit Heart Dis*. 2015;10(6):E258-E267. doi:10.1111/chd.12286

19. Smith BM, Dorfman AL, Yu S, et al. Clinical significance of late gadolinium enhancement in patients<20 years of age with hypertrophic cardiomyopathy. *Am J Cardiol*. 2014;113(7):1234-1239. doi:10.1016/j.amjcard.2013.12.034

20. Axelsson Raja A, Farhad H, Valente AM, et al. Prevalence and progression of late gadolinium enhancement in children and adolescents with hypertrophic cardiomyopathy. *Circulation*. 2018;138(8):782-792. doi:10.1161/CIRCULATIONAHA.117.032966

21. Weng Z, Yao J, Chan RH, et al. Prognostic value of LGE-CMR in HCM: a meta-analysis. *JACC Cardiovasc Imaging*. 2016;9(12):1392-1402. doi:10.1016/j.jcmg.2016.02.031

22. Habib M, Adler A, Fardfini K, et al. Progression of myocardial fibrosis in hypertrophic cardiomyopathy: a cardiac magnetic resonance study. *JACC Cardiovasc Imaging*. 2021;14(5):947-958. doi:10.1016/j.jcmg.2020.09.037

23. Norrish G, Protonotarios A, Stec M, et al. Performance of the PRIMaCY sudden death risk prediction model for childhood hypertrophic cardiomyopathy: implications for implantable cardioverter-defibrillator decision-making. *Europace*. 2023;25(11):5-8. doi:10.1093/europace/euad330