

Development of a Novel Risk Prediction Model for Sudden Cardiac Death in Childhood Hypertrophic Cardiomyopathy (HCM Risk-Kids)

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IMPORTANCE Sudden cardiac death (SCD) is the most common mode of death in childhood hypertrophic cardiomyopathy (HCM), but there is no validated algorithm to identify those at highest risk.

OBJECTIVE To develop and validate an SCD risk prediction model that provides individualized risk estimates.

DESIGN, SETTING, AND PARTICIPANTS A prognostic model was developed from a retrospective, multicenter, longitudinal cohort study of 1024 consecutively evaluated patients aged 16 years or younger with HCM. The study was conducted from January 1, 1970, to December 31, 2017.

EXPOSURES The model was developed using preselected predictor variables (unexplained syncope, maximal left-ventricular wall thickness, left atrial diameter, left-ventricular outflow tract gradient, and nonsustained ventricular tachycardia) identified from the literature and internally validated using bootstrapping.

MAIN OUTCOMES AND MEASURES A composite outcome of SCD or an equivalent event (aborted cardiac arrest, appropriate implantable cardioverter defibrillator therapy, or sustained ventricular tachycardia associated with hemodynamic compromise).

RESULTS Of the 1024 patients included in the study, 699 were boys (68.3%); mean (interquartile range [IQR]) age was 11 (7-14) years. Over a median follow-up of 5.3 years (IQR, 2.6-8.3; total patient years, 5984), 89 patients (8.7%) died suddenly or had an equivalent event (annual event rate, 1.49; 95% CI, 1.15-1.92). The pediatric model was developed using preselected variables to predict the risk of SCD. The model's ability to predict risk at 5 years was validated; the C statistic was 0.69 (95% CI, 0.66-0.72), and the calibration slope was 0.98 (95% CI, 0.59-1.38). For every 10 implantable cardioverter defibrillators implanted in patients with 6% or more of a 5-year SCD risk, 1 patient may potentially be saved from SCD at 5 years.

CONCLUSIONS AND RELEVANCE This new, validated risk stratification model for SCD in childhood HCM may provide individualized estimates of risk at 5 years using readily obtained clinical risk factors. External validation studies are required to demonstrate the accuracy of this model's predictions in diverse patient populations.

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Sudden cardiac death (SCD) is the most common mode of death outside of infancy in childhood hypertrophic cardiomyopathy (HCM),^{1,2} with higher annual rates compared with those in adults with the disease.³ Current practice guidelines recommend primary prevention implantable cardioverter defibrillators (ICDs) in children based on the presence of clinical risk factors for SCD extrapolated mostly from observational adult studies,^{4,5} but this approach poorly discriminates risk in both adult and pediatric populations.^{6,7} A clinical risk tool (HCM Risk-SCD) that estimates the 5-year risk of SCD was developed⁸ and validated in adults with HCM.⁹⁻¹² The aim of this study was to develop a similar pediatric SCD risk model using a large, international cohort and compare its performance with the adult model.

Methods

Study Population

The study cohort consisted of patients aged 1 to 16 years with HCM who were consecutively evaluated between January 1, 1970, and December 31, 2017, in 39 participating centers located in 17 countries (the International Paediatric Hypertrophic Cardiomyopathy Consortium; eTable 1 in the [Supplement](#)). A diagnosis of HCM was defined as a left-ventricular wall thickness greater than 2 SDs above the body surface area-corrected population mean (z score ≥ 2) that could not be explained solely by abnormal loading conditions or in accordance with published criteria for familial disease.⁵ Patients with prior ventricular fibrillation or sustained ventricular tachycardia (VT), known inborn errors of metabolism or syndromic causes of HCM (eg, RASopathy syndromes, Friedreich ataxia), presentation under 1 year, or less than 1 month of follow-up were excluded (eFigure 1 in the [Supplement](#)). The authors from each participating center guaranteed the integrity of data from their institution and had approval from a local ethics committee with waiver of informed consent.

Patient Assessment and Data Collection

Anonymized, noninvasive clinical data from a baseline evaluation were collected retrospectively, including demographics, cause of the disease, heart failure symptoms (New York Heart Association [NYHA]/Ross functional classification¹³), pedigree analysis, resting and ambulatory 12-lead electrocardiogram, and 2-dimensional Doppler and color transthoracic echocardiogram (from contemporaneously written reports). Patients had planned clinical reviews every 6 to 18 months. Data were collected independently at each participating center.

Clinical Outcomes

The primary study end point was a composite outcome of SCD or an equivalent event (aborted cardiac arrest, appropriate ICD therapy, or sustained VT associated with hemodynamic compromise).^{8,11,14,15} As in previous studies, ICD therapy was considered appropriate if the tachyarrhythmia was ventricular in origin.^{11,16,17} Sudden cardiac death was defined as a witnessed sudden death with or without documented cardiac failure, death within 1 hour of new symptoms, or nocturnal deaths with no

Key Points

Question Can sudden cardiac death risk in children with hypertrophic cardiomyopathy be predicted?

Findings In this cohort study of 1024 consecutively evaluated children (age ≤ 16 years), a prognostic model was developed using preselected predictor variables identified from the literature. The model's ability to predict risk at 5 years was internally validated using bootstrapping.

Meaning This new, validated risk stratification model for sudden cardiac death risk in childhood hypertrophic cardiomyopathy may provide individualized estimates of risk at 5 years using readily obtained data on clinical risk factors; external validation studies are required to demonstrate the accuracy of this model's predictions in diverse patient populations.

antecedent history of worsening symptoms.¹⁸ Outcomes were ascertained by the treating cardiologist at each center.

Selection of Predictor Variables

A systematic review of the literature was performed in December 2015¹⁹ to identify SCD risk factors with sufficient evidence to support their inclusion as predictor variables in the risk model (eTable 2 in the [Supplement](#)). Clinical risk factors were included as predictor variables if they had been examined in more than 2 published studies and independently associated with SCD in 2 or more univariable or multivariable survival analyses. Selection of predictor variables was not limited to studies with multivariable analyses owing to the limited evidence base available in pediatric HCM (all but 1 study included in the meta-analysis was retrospective, the majority had fewer than 150 participants, and most published studies used only univariable analyses).¹⁹ Candidate predictors are defined in [Table 1](#).^{1,8,13-17,20-23} To account for somatic growth, maximal wall thickness and left atrial diameter measurements are expressed as z scores (defined as the number of SDs above or below the body surface area-corrected mean as a given measurement's mean).²⁴ The largest published reference populations for interventricular septal thickness²² and left atrial diameter²³ were chosen following a review of the literature.

Statistical Analysis

Continuous variables are described as mean (SD) or median and interquartile range (IQR) as appropriate. Because the model was developed to predict 5-year SCD risk during childhood (age ≤ 16 years), the follow-up of patients was censored at age 22 years. The follow-up time for all patients was thus calculated from the date of their first evaluation to the date of reaching the study end point, death from another cause, or the date of their most recent evaluation prior to the end of the study period (December 2017 or age 22 years). Kaplan-Meier survival plots were used to describe the failure times.

Handling of Missing Data

Patients with more than 50% of the preselected predictors missing were excluded from model development. Logistic regression was used to identify predictors of missingness. The

Table 1. Candidate Predictor Definitions

Candidate Predictor Variable	Definition	Coding
NYHA/Ross functional class	NYHA functional classification ²⁰ /modified Ross heart failure classification for children ¹³ at baseline evaluation	Binary (NYHA/Ross 1 = 0, NYHA/Ross ≥ 2 = 1)
Unexplained syncope	Defined as a transient loss of consciousness with no identifiable cause at or before first evaluation ^{1,8,14,15}	Binary (no = 0, yes = 1)
Nonsustained ventricular tachycardia	≥3 Consecutive ventricular beats at a rate of ≥120 beats/min lasting <30 s on ambulatory ECG monitoring (minimum duration 24 h) at or before first evaluation ^{16,21}	Binary (no = 0, yes = 1)
Maximal wall thickness z score	Defined as the number of SDs from the population mean ²² ; the 2-D measurement of maximal wall thickness (millimeters) is at baseline evaluation ^a	Continuous (z score)
Left atrial diameter z score	Defined as the number of SDs from the population mean ²³ the 2-D measurement of maximal left-atrial diameter (millimeters) is at baseline evaluation ^b	Continuous (z score)
Maximal LV outflow tract gradient	The maximum LV outflow tract gradient at rest or with Valsalva provocation using continuous wave Doppler from the apical 3- or 5-chamber views ^{17c}	Continuous (mm Hg)

Abbreviations: 2-D, 2 dimensional; ECG, electrocardiogram; LV, left ventricular; NYHA, New York Heart Association.

^a Maximal wall thickness is the greatest thickness as measured by 2-D echocardiography in the parasternal short-axis views of the left ventricle in 4 places at the level of the mitral valve and papillary muscles (anterior and posterior septum, lateral and posterior wall) and in 2 places at the apical level

(anterior and posterior septum).⁵

^b Left atrial diameter is determined by M mode or 2-D echocardiography in the parasternal long-axis plane.

^c Peak outflow tract gradient is determined using the modified Bernoulli equation: gradient = 4V², where V is the peak aortic outflow velocity.

values for the missing predictors were imputed using multiple imputation techniques based on chained equations.²⁵ The imputation model included all predictors of missingness, the outcome, all prespecified predictors of the risk model, and the estimate of the cumulative hazard function.²⁶ A total of 49 imputed data sets were generated, and estimates obtained from the imputed data sets were combined using the Rubin rule.²⁷

Development of the Pediatric Model

A minimum of 10 SCD or equivalent events are required per coefficient in the model to estimate the regression coefficients with adequate precision.²⁸ This means that 50 SCD events would be required to allow estimation of the regression coefficients for the 5 preselected predictors with adequate precision. Additional events would be required for inclusion of nonlinear terms associated with the continuous predictors in the model.

All continuous predictors were centered around their mean values, and univariable Cox proportional hazards regression models were used to test the assumption of linearity with the outcome for each continuous predictor. The final model was developed using a Cox proportional hazards regression model including all 5 preselected predictors and quadratic terms for the continuous predictors where nonlinearity was found in the univariable analysis. The proportional hazards assumption was investigated using Schoenfeld residuals.²⁹ A sensitivity analysis was performed by including the predictors of missingness in the final model. All regression models were fitted using robust SEs to account for clustering by center.³⁰

The probability of SCD at t years for an individual patient can be calculated using the following equation, derived from the Cox proportional hazards regression model:

$$\hat{P}_{SCD \text{ at } t \text{ years}} = 1 - S_0(t)^{\exp(\text{prognostic index})},$$

where $S_0(t)$ is the average survival probability at time t and the prognostic index is the sum of the products of the predictors and their coefficients.

Bootstrapping was used to evaluate the performance of the model since this is the most efficient validation procedure as all aspects of the model development are validated.³¹ For this purpose, 200 bootstrap samples were generated from each imputed data set and estimates were combined. Because the aim of the model is to predict 5-year SCD risk, patients were censored at 5 years from their first evaluation. The calibration slope was used to assess the degree of agreement between the observed and predicted hazards of SCD (a value close to 1 suggests good overall agreement).³² The C index (C-Uno³³) was used to measure how well the model discriminated between high- and low-risk patients.³⁴ A value of 1 indicates perfect discrimination and a value of 0.5 indicates no discrimination. The C index and calibration results presented are an average of the bootstrapped samples. Graphic comparisons of the observed and predicted risk of SCD at 5 years by risk groups (0%–<2%, 2%–<4%, 4%–<6%, and ≥6%) based on an imputed development sample are provided.

The model development process is summarized in eFigure 1 in the [Supplement](#). Statistical analysis was performed using Stata Statistical Software, release 14 (StataCorp LP).

Results

Baseline Clinical Characteristics

The study cohort comprised 1024 patients from 39 centers with a median (IQR) age at baseline evaluation of 11 (7–14) years (eFigure 2A in the [Supplement](#)); 699 patients (68.3%) were boys. A family history of HCM was present in 534 of 1006 patients (53.1%). Baseline clinical characteristics are described in [Table 2](#) and eTable 3 in the [Supplement](#).

Clinical Course and Outcomes During Follow-up

Over a follow-up period of 5984 patient-years (median, 5.3 years; IQR, 2.6–8.3), 77 patients (7.5%) underwent a myectomy, 43 patients (4.2%) required a permanent pacemaker, and 21 patients (2.1%) underwent cardiac transplantation. A total of 267 patients (26.1%) received an ICD for primary (244

[91.4%]) or secondary (23 [8.6%]) prevention of SCD. Fifty-three patients (5.2%) died (SCD, 30 [56.6%]; heart failure, 9 [17.0%], heart failure related, 6 [11.3%]; other cardiovascular related, 3 [5.7%]; non-cardiovascular related, 2 [3.8%]; and unknown cause, 3 [5.7%]), with an annual mortality rate of 0.89 (95% CI, 0.68-1.16). Eighty-nine patients reached the SCD or equivalent end point within 5 years (SCD, 39 [43.8%]; aborted SCD, 16 [18.0%]; appropriate ICD discharge, 24 [27.0%]; and hemodynamically compromising, sustained VT, 10 [11.2%]), with an annual SCD end point rate of 1.49 (95% CI, 1.15-1.92) (eFigure 2B in the [Supplement](#)). Baseline clinical characteristics of patients with and without SCD or SCD equivalent end point and results from univariable regression analyses are reported in **Table 3**. NYHA class 2 or higher, unexplained syncope, nonsustained VT (NSVT), maximal wall thickness (MWT), and left atrium (LA) diameter were associated with SCD at the 5% significance level.

Model Development

The risk model was developed using the entire follow-up data and all events that occurred during the follow-up (ie, 1029 patients with 89 events.) A risk model was developed using the preselected variables (unexplained syncope, NSVT, LA diameter z score, MWT z score, and left-ventricular outflow tract [LVOT] gradient); the estimates of hazard ratios for the resulting model are reported in **Table 4**. Missing data for the preselected variables are summarized in eTable 4 in the [Supplement](#). Complete data were available for 527 patients (51.5%); at least 1 predictor variable was missing in 48.5% of the sample. Including NYHA classification (the only additional predictor of missingness) as a predictor variable had little association with the estimates of the hazard ratios. The risk of SCD at 5 years for an individual patient with HCM can be calculated from the following equation as demonstrated in the HCM Risk-Kids calculator using Excel (Microsoft Corp) (depicted in the eAppendix in the [Supplement](#)).

$$P(\text{SCD at 5 years}) = 1 - 0.949437808^{\exp(\text{prognostic index})},$$

where prognostic index = $0.2171364 \cdot (\text{MWT z score} - 11.09) - 0.0047562 \cdot (\text{MWT z score}^2 - 174.12) + 0.130365 \cdot (\text{LA diameter z score} - 1.92) + 0.429624 \cdot \text{unexplained syncope} + 0.1861694 \cdot \text{NSVT} - 0.0065555 \cdot (\text{maximal LVOT gradient} - 21.8)$.

Validation

The performance of the model for predicting risk at 5 years was assessed using 1029 patients with 58 events. The C index was 0.69 (95% CI, 0.66-0.72) and calibration slope was 0.98 (95% CI, 0.59-1.38). **Figure, B** shows the comparison between the observed and predicted 5-year risk of SCD by clinical risk groups for 1 randomly selected imputed data set.

Clinical Implications

The clinical implications of the model were examined in 527 patients with 34 SCD end points who had complete data to allow calculation of 5-year SCD risk. The SCD end point was reached by 3 patients (1.7%) with a predicted risk lower than 4% (n = 178), 5 patients (5%) with a predicted risk of 4% to less than 6% (n = 100), and 26 patients (10.4%) with a predicted

Table 2. Baseline Clinical Characteristics^a

Baseline Clinical Characteristic	No. (%)
Age, median (IQR), y	11 (7-14)
Male sex	699 (68.3)
Family history	
HCM (n = 1006)	534 (53.1)
SCD (n = 1020)	130 (12.8)
Unexplained syncope (n = 1023)	102 (9.9)
NYHA/Ross classification (n = 1006)	
1	783 (77.8)
2	191 (19)
3	29 (2.9)
4	3 (0.3)
Medical therapy at baseline (n = 1021)	
None	596 (58.4)
β-Blockers	410 (40.2)
Amiodarone	9 (0.9)
Other	6 (0.6)
NSVT on ambulatory ECG (n = 856)	55 (6.4)
MWT, mm	
No.	997
Mean (SD)	17.1 (7.4)
z Score MWT	
No.	906
Mean (SD)	11.1 (7.1)
LA diameter, mm	
No.	712
Mean (SD)	33.4 (8.5)
z Score LA diameter	
No.	675
Mean (SD)	1.9 (2.3)
LVOTg, max	
No.	871
Median (IQR)	9 (6-22)

Abbreviations: ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LA, left atrium; LVOTg max, maximal left-ventricular outflow tract gradient; MWT, maximal wall thickness; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death.

^a Total of 1024 patients unless otherwise indicated.

risk of 6% or greater (n = 249) (**Figure, A**). Using a 5-year SCD risk of 6% or greater to recommend primary prevention with ICD implantation would identify 26 of 34 SCD end points (76.5%), with ICD implantation in 223 of 493 patients (45.2%) not reaching SCD end points within 5 years. Using a 5-year SCD risk of 4% or greater to recommend primary prevention ICD implantation would identify 31 of 34 SCD end points (91.2%), with ICD implantation in 318 of 493 patients (64.5%) not reaching SCD end points within 5 years.

The pediatric model was developed using preselected variables to predict the risk of SCD. The model's ability to predict risk at 5 years was validated; the C statistic was 0.69 (95% CI, 0.66-0.72), and the calibration slope was 0.98 (95% CI, 0.59-1.38). For every 10 ICDs implanted in patients with 6% or more

Table 3. Clinical Characteristics of Patients With and Without Sudden Cardiac Death End Points and Univariable Cox Proportional Hazards Regression Models

Characteristic	No. (%)			Hazard Ratio (95% CI)	P Value
	Whole Cohort (N = 1024)	Patients With SCD End Points (n = 89)	Patients Without SCD End Points (n = 938)		
Age, median (IQR)	11 (7-14)	10 (6-13)	11 (7-14)	1.05 (1.00-1.11)	.06
Male sex	699 (68.3)	65 (73)	634 (67.8)	0.73 (0.50-1.17)	.20
NYHA class >1	223 (22.2)	28 (31.8)	195 (21.2)	1.70 (1.08-2.65)	.02
Family history					
SCD	130 (12.8)	12 (13.5)	118 (12.7)	1.01 (0.55-1.85)	.98
HCM	534 (53.1)	42 (48.3)	492 (53.5)	0.83 (0.55-1.27)	.39
Unexplained syncope	102 (9.9)	16 (18)	86 (9.2)	2.06 (1.20-3.54)	.009
NSVT	55 (6.4)	12 (16.4)	43 (5.5)	1.93 (1.03-3.61)	.04
MWT, mean (SD), mm	17.1 (7.4)	20 (7.5)	16.9 (7.3)	1.05 (1.02-1.07)	<.001
z Score MWT, mean (SD)	11.1 (7.1)	15 (7.5)	10.7 (7)	1.05 (1.02-1.08)	<.001
MWT ≥30 mm	81 (7.9)	25 (31.7)	164 (20.7)	2.35 (1.33-4.18)	.004
LA diameter, mean (SD), mm	33.4 (8.5)	36.5 (9.3)	33 (8.3)	1.05 (1.02-1.08)	.001
z Score LA diameter, mean (SD)	1.9 (2.3)	3.2 (2.6)	1.8 (2.2)	1.19 (1.08-1.30)	<.001
LVOTg max, median (IQR), mm Hg	9 (6-22)	12 (6-36)	9 (6-20)	1.00 (0.99-1.01)	.83
LVOT ≥30 mm Hg	189 (18.4)	25 (31.7)	164 (20.7)	1.48 (0.92-2.38)	.11

Abbreviations: HCM, hypertrophic cardiomyopathy; LA, left atrium; IQR, interquartile range; LVOTg max, maximal left-ventricular outflow tract gradient; MWT, maximal wall thickness; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death.

Table 4. Pediatric Sudden Cardiac Death Risk Prediction Model and Sensitivity Analyses for Predictor of Missingness

Predictor Variable	SCD Risk Prediction Model		Sensitivity Analysis: Model Including Predictors of Missingness	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
NSVT	1.20 (0.53-2.76)	.66	1.16 (0.52-2.61)	.72
LA diameter z score	1.14 (1.03-1.26)	.01	1.13 (1.03-1.25)	.01
MWT				
z Score	1.24 (1.07-1.45)	.005	1.24 (1.07-1.44)	.005
z Score ²	0.995 (0.99-1.00)	.04	0.995 (0.99-1.00)	.04
LVOT gradient	0.99 (0.99-1.00)	.10	0.99 (0.99-1.00)	.11
Unexplained syncope	1.54 (0.79-2.98)	.20	1.52 (0.79-2.92)	.22
NYHA			1.15 (0.62-2.11)	.66
Uno C statistic	0.69 (0.66-0.72)	NA	0.69 (0.66-0.72)	NA
Calibration slope	0.98 (0.59-1.38)	NA	0.96 (0.56-1.36)	NA

Abbreviations: LA, left atrium; LVOT, left ventricular outflow tract; MWT, maximal wall thickness; NA, not applicable; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death.

of a 5-year SCD risk, 1 patient may potentially be saved from SCD at 5 years.

Comparison With Adult Risk Stratification Tool

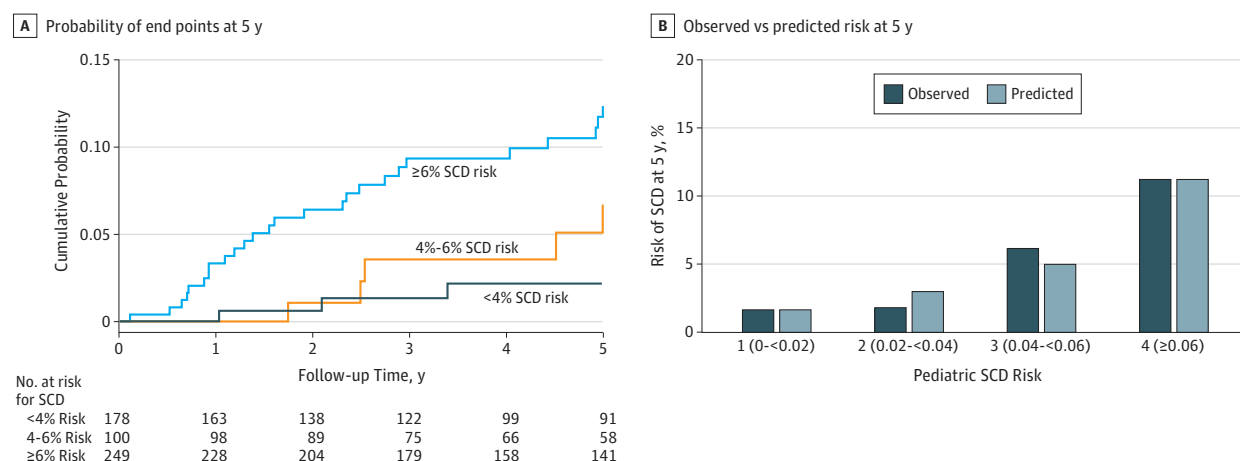
The performance of the pediatric model to predict 5-year risk of SCD was compared with that of the adult risk stratification tool (HCM-Risk SCD). The adult model has modest discriminatory ability (C index, 0.67; 95% CI, 0.65-0.69) but does not predict risk accurately (calibration slope, 0.79; 95% CI, 0.43-1.15) for the pediatric cohort. It seems the risk of SCD is underestimated for all risk groups (eFigure 3 in the [Supplement](#)). Including age and family history of SCD in the pediatric model did not improve its performance (eTable 5 in the [Supplement](#)).

Discussion

To our knowledge, the model presented herein represents the first validated approach to risk stratification in childhood HCM and suggests that systematic risk evaluation can be used to

guide ICD implantation in young patients with the disease. Compared with the prevalence in adults, HCM is a relatively uncommon disease in childhood and has a more diverse cause.^{1,35} Nevertheless, outside of infancy, the disease is caused mostly by mutations in sarcomere protein genes^{36,37} and results in SCD in a significant minority of children.^{3,38} Current approaches to risk stratification in childhood HCM have remained largely unchanged for more than 2 decades, with reliance on the assessment of a small number of clinical features (risk factors) to guide treatment decisions.^{4,5} A recent validation study of this approach to risk stratification has shown it to have limited discriminatory power (C index statistic, 0.62) with a positive predictive value of only 19%.⁶ In adults with HCM, there has been a shift toward quantitative risk prediction based on tools, such as HCM Risk-SCD,⁸ that form the basis of recommendations for ICD therapy based on absolute thresholds of risk. 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

Figure. Performance of the HCM Risk-Kids Model



A, Kaplan-Meier curve showing cumulative probability of sudden cardiac death (SCD) end points within 5 years of baseline evaluation by clinical risk groups calculated by the pediatric SCD risk model. Patients with complete data for the calculation of 5-year SCD risk estimates ($n = 527$) were classified into 3 risk groups (<4%, 4%-6%, and $\geq 6\%$). B, Comparison of observed and predicted

risk by clinical risk group of the pediatric SCD risk model (for 1 imputed data set). Vertical bars represent observed (dark blue) and model-based predicted (light blue) probability of SCD by 5 years. HCM indicates hypertrophic cardiomyopathy.

area, which led us to develop a new, pediatric-specific risk model. This study shows that, if applied to children, the existing adult model may underestimate the incidence of SCD for all risk groups and has a limited discriminatory power.

The new pediatric model that we have developed shows better discrimination between high- and low-risk patients with good calibration between the expected and observed risk. The performance is similar to that reported in adult cohorts for the adult model.¹¹ Predictor variables were included only if previously associated with SCD in published studies with the result that family history of SCD and age at presentation were excluded. The lack of evidence in current literature supporting family history of SCD could be explained by a higher prevalence of de novo mutations in childhood, incomplete reporting of family history, or failure to adjust for family linkage. Although presentation of HCM in young adulthood has been linked with adverse outcomes,³⁹ age was not included as a predictor variable as, outside of infancy,¹ its role in prognosis remains unclear. In keeping with this rationale, including both age and family history of SCD as predictor variables did not improve the model's performance. The effect of age may have been mitigated in the model by the fact that somatic growth in childhood was accounted for by using body surface area-corrected rather than absolute 2-dimensional echocardiographic measurements. Although 2 previous studies reported an increased risk of SCD in the presence of heart failure symptoms,^{40,41} inclusion of this variable did not improve the model's performance.

To our knowledge, this study represents the largest population of childhood HCM with nonsyndromic disease published to date. The baseline demographics were similar to those seen in previous population-based studies^{1,2,35,40} with the exception of familial disease, which was more prevalent than previously reported in registry studies although in keeping with

reports from reference centers.³⁶ This higher prevalence of familial disease may be explained by the exclusion of syndromic disease (eg, RASopathy, inborn errors of metabolism, or Friedreich ataxia) or by family screening as the indication for initial evaluation but could also suggest that familial disease presenting during childhood is more common than usually appreciated. Compared with similar-sized adult cohorts, there was a lower prevalence of traditional risk factors (eg, family history of SCD, NSVT) yet a higher incidence of arrhythmic events (1.49% vs 0.6%¹¹). In addition, risk factors with significant evidence in adult practice, such as family history of SCD and LVOT gradient, were not associated with arrhythmic events on univariable analysis in this cohort. The LVOT gradient appears to be inversely associated with the risk of SCD in this population. The finding that LVOT obstruction may be protective is in agreement with another recent, large pediatric population series but needs further exploration.⁴² Unexplained syncope, degree of hypertrophy, LA diameter, and NSVT showed the strongest association with the study outcome, although this finding was not significant at the 15% level for NSVT. These findings are in agreement with a recent meta-analysis¹⁹ and suggest that risk factors for SCD may differ between adult and pediatric cohorts.

The complete case analysis suggests that the model identifies the majority of patients at risk of an SCD event during the follow-up period. The identification of patients at risk of SCD was at the expense of ICD implantation in 45% of patients not yet reaching the end point during follow-up. However, as previous studies have demonstrated variable latency between ICD implantation and first appropriate therapy,⁴³ these young patients may yet benefit from the decision to implant a device. Further refinement of the model presented could be achieved by exploring the role of novel risk factors for SCD in childhood HCM, including genetic data, late gadolinium

enhancement on cardiac magnetic resonance imaging,⁴⁴ and the resting 12-lead electrocardiogram, which, in a single study,⁴⁵ has been suggested to accurately predict the risk of SCD.

In addition, because childhood is a time of significant somatic growth, the phenotype of a patient may evolve rapidly with a resulting change in the arrhythmic risk profile. Future studies exploring the changing role of individual clinical risk factors during childhood and use of serial clinical investigations in predicting risk would be valuable.

Limitations

Because childhood HCM is a rare disease and SCD is an uncommon event, a multicenter, retrospective, longitudinal design was necessary to develop a pediatric-specific model. This study is therefore limited by inherent problems of retrospective studies, in particular, missing data. The higher proportion of patients with at least 1 missing predictor compared with the adult development cohort (48.5% in the present study vs 21.7%⁸) may be explained by difficulties obtaining certain investigations in young patients (eg, ambulatory electrocardiogram) and the use of contemporaneously written echocardiographic reports.

Because missing data were associated with milder hypertrophy and the absence of heart failure symptoms, the complete case analysis is inherently biased toward those with more severe disease. This bias may explain the predominance of patients with a calculated 5-year risk score of 4% or greater ($n = 349/527$). This bias also suggests that clinicians are more likely to investigate thoroughly in the presence of severe disease.

Because the cohort was recruited longitudinally, the length of follow-up for individual patients varied, with a median length of follow-up of 5.3 years. The longevity of an ICD device is reported to be between 5 and 9 years,^{46,47} although children are known to be at increased risk for lead-related complications necessitating revision.^{14,43} The finite battery life and need for repeated device replacements, along with the lifetime burden of complications, needs to be carefully considered by clinicians when counseling patients and their parents on ICD implantation.

Although this study includes data collected across a wide time period, medical management of children with HCM has not changed significantly over this time, and studies have previously shown no era effect on survival.³ However, patients

presenting in the earliest era (pre-1990) were more likely to be symptomatic for heart failure symptoms and have NSVT detected. Patients presenting in more recent years had lower absolute MWT and corresponding z score, but this difference did not reach statistical significance. The difference in MWT and corresponding z score may be the result of patients being diagnosed at an earlier time point in disease expression, possibly through family screening, although not at a younger age. Inherent to the study design, a survival bias may exist for all eras, as patients not surviving an out-of-hospital arrest are not represented. Future studies comparing those surviving an out-of-hospital arrest with those identified postmortem would be useful but was beyond the scope of this study.

The model should be used only in patients with similar clinical characteristics to the study cohort. In particular, it should not be used in patients presenting in infancy or with syndromic disease, inborn errors of metabolism, or neuromuscular disease.^{3,48} Future studies exploring the risk of SCD in these subgroups are required.

The number of patients undergoing invasive treatment of LVOT obstruction in this cohort was too small to model its association with SCD risk. However, obstructive disease was uncommon in this cohort, with only 18% having a gradient above 30 mm Hg.

Conclusions

We present what we believe to be the first validated risk stratification model for SCD in childhood HCM developed from a large, international cohort using readily collected data on clinical risk factors. The individualized estimates of risk could help clinicians to identify patients at highest risk and balance the risk of an arrhythmic event with prophylactic ICD implantation in conjunction with the patient and their parents or guardians. External validation studies are now required to demonstrate the accuracy of this model's predictions in diverse patient populations. Consensus opinion of experts will be required to determine whether absolute thresholds for ICD recommendations are needed and, if so, where those thresholds should be set. Further refinement of this model could be achieved by including novel clinical risk predictors, such as cardiac magnetic resonance imaging and genetic data.

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Editor's Note

Risk Prediction Model in Children With Hypertrophic Cardiomyopathy A Work in Progress

Robert O. Bonow, MD, MS; Elizabeth M. McNally, MD, PhD

Managing sudden death risk in young patients with hypertrophic cardiomyopathy (HCM) is challenging for its lifetime implications from both action and inaction, and this



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decision often relies on shared decision-making by families and clinicians. Thus, the development of risk

assessment tools to guide parents and health care professionals are welcome additions to the scientific literature. The study by Norrish and coworkers¹ in this issue of *JAMA Cardiology* is an initial step in creating a risk tool, and as a first step, the editors hope this work will stimulate further discussion and investigation to better refine this tool.

The imperfect prediction model proposed by Norrish et al¹ is based on a retrospective sample of 1024 children younger than 16 years with HCM. The international collaboration, involving centers from Europe, Argentina, Australia, and Japan, created a broad cohort from which to draw conclusions. The pediatric HCM risk tool follows methodology similar to the existing European risk tool in adults, which is embedded in the 2014 European Society of Cardiology guidelines with recent external validation.² The European risk tool for adults is more specific, but less sensitive, than the US approach.³

The current score for children proposed by Norrish et al¹ is based on 89 events using 5 preselected risk factors: history of syncope, maximal left ventricular wall thickness, left atrial size, left ventricular outflow tract gradient, and nonsustained ventricular tachycardia. This pediatric risk predictor tool

did not include age, family history, or gene mutation status in its calculation. In adults with HCM, sarcomere gene mutation status identifies patients with HCM at higher risk.⁴ Symptomatic status was evaluated and did not improve the performance of the model.

There are limitations to this childhood risk prediction model worth noting. At best, it had only moderate discrimination (the C statistic is 0.69). There was no external validation. Nearly half of the children from which the model is derived (497 [48.5%]) who experienced nearly two-thirds of the end points (55 [61.8%]) did not have complete data. The median (interquartile) follow-up period was 5.3 (2.6-8.3) years, and this relatively short follow-up interval may be insufficient for the difficult decisions surrounding whether to proceed with the consequences of lifelong implantable cardioverter-defibrillators in children.

However, as with many first-generation risk tools, a less-than-perfect risk score incites future iterations—this is exactly our hope. The importance of a sudden death risk calculator for children with HCM is clear and is of great public health benefit, but this risk score should be viewed as a work in progress. External validation is necessary, and refinement with additional variables such as gene mutation status and magnetic resonance imaging markers will likely enhance the model, as these have been shown to be powerful predictors of outcome. Incorporating these data can be expected to improve performance of the risk tool so that it can be used as a primary driver for device implantation decisions in children.

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