





External validation of the HCM Risk-Kids model for predicting sudden cardiac death in childhood hypertrophic cardiomyopathy

Gabrielle Norrish ^{1,2}, Chen Qu³, Ella Field^{1,2}, Elena Cervi¹, Diala Khraiche⁴, Sabine Klaassen^{5,6,7}, Tiina H. Ojala ⁸, Gianfranco Sinagra⁹, Hirokuni Yamazawa¹⁰, Chiara Marrone¹¹, Anca Popoiu¹², Fernando Centeno¹³, Sylvie Schouvey¹⁴, Iacopo Olivetto ¹⁵, Sharlene M. Day¹⁶, Steve Colan¹⁷, Joseph Rossano¹⁸, Samuel G. Wittekind¹⁹, Sara Saberi²⁰, Mark Russell²⁰, Adam Helms²⁰, Jodie Ingles ²¹, Christopher Semsarian²², Perry M. Elliott^{2,23}, Carolyn Y. Ho²⁴, Rumana Z. Omar³, and Juan P. Kaski^{1,2*}

¹Centre for Inherited Cardiovascular Diseases, Great Ormond Street Hospital, London WC1N 3JH, UK; ²Institute of Cardiovascular Sciences, University College London, London, UK; ³Department of Statistical Science, University College London, London, UK; ⁴Necker – Enfants Malades hospital, Paris, France; ⁵Department of Paediatric Cardiology, Charité – Universitätsmedizin Berlin, Berlin, Germany; ⁶Experimental and Clinical Research Centre (ECRC), a joint cooperation between the Charité Medical Faculty and the Max-Delbrück-Centre for Molecular Medicine (MDC), Charité – Universitätsmedizin Berlin, Berlin, Germany; ⁷DZHK (German Centre for Cardiovascular Research), partner site Berlin, Berlin, Germany; ⁸Department of Paediatric Cardiology, New Children's Hospital, University of Helsinki, Helsinki, Finland; ⁹Heart Muscle Disease Registry Trieste, University of Trieste, Trieste, Italy; ¹⁰Department of Paediatrics, Faculty of Medicine and Graduate school of Medicine, Hokkaido University Hospital, Sapporo, Japan; ¹¹Fondazione Toscana G Monasterio, Massa-Pisa, Italy; ¹²Department of Paediatrics, Children's Hospital 'Louis Turcanu', University of Medicine and Pharmacy "Victor Babes" Timisoara, Timisoara, Romania; ¹³Rio Hortega University Hospital, Valladolid, Spain; ¹⁴Hospital Saint Joseph, Marseille, France; ¹⁵Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy; ¹⁶Department of Internal Medicine, University of Pennsylvania, Philadelphia, PA, USA; ¹⁷Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; ¹⁸Children's Hospital of Philadelphia, Philadelphia, PA, USA; ¹⁹Cincinnati Children's Hospital Medical Center, Heart Institute, Cincinnati, OH, USA; ²⁰Department of Internal Medicine-Cardiology, University of Michigan, Ann Arbor, MI, USA; ²¹Cardio Genomics Program at Centenary Institute, The University of Sydney, Sydney, Australia; ²²Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, The University of Sydney, Sydney, Australia; ²³St Bartholomew's Centre for Inherited Cardiovascular Diseases, St Bartholomew's Hospital, West Smithfield, London, UK; and ²⁴Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

Received 6 August 2021; revised 22 September 2021; editorial decision 13 October 2021; online publish-ahead-of-print 31 October 2021

Aims

Sudden cardiac death (SCD) is the most common mode of death in childhood hypertrophic cardiomyopathy (HCM). The newly developed HCM Risk-Kids model provides clinicians with individualized estimates of risk. The aim of this study was to externally validate the model in a large independent, multi-centre patient cohort.

Methods and results

A retrospective, longitudinal cohort of 421 patients diagnosed with HCM aged 1–16 years independent of the HCM Risk-Kids development and internal validation cohort was studied. Data on HCM Risk-Kids predictor variables (unexplained syncope, non-sustained ventricular tachycardia, maximal left ventricular wall thickness, left atrial diameter, and left ventricular outflow tract gradient) were collected from the time of baseline clinical evaluation. The performance of the HCM Risk-Kids model in predicting risk at 5 years was assessed. Twenty-three patients (5.4%) met the SCD end-point within 5 years, with an overall incidence rate of 2.03 per 100 patient-years [95% confidence interval (CI) 1.48–2.78]. Model validation showed a Harrell's C-index of 0.745 (95% CI 0.52–0.97) and Uno's C-index 0.714 (95% 0.58–0.85) with a calibration slope of 1.15 (95% 0.51–1.80). A 5-year predicted risk threshold of $\geq 6\%$ identified 17 (73.9%) SCD events with a corresponding C-statistic of 0.702 (95% CI 0.60–0.81).

* Corresponding author. Tel: +44 20 7829 8839, Fax: +44 20 7762 6727, Email: j.kaski@ucl.ac.uk

Members of ERN GUARD-HEART (European Reference Network for Rare and Complex Diseases of the Heart; <http://guardheart.ern-net.eu>).

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Conclusions

This study reports the first external validation of the HCM Risk-Kids model in a large and geographically diverse patient population. A 5-year predicted risk of $\geq 6\%$ identified over 70% of events, confirming that HCM Risk-Kids provides a method for individualized risk predictions and shared decision-making in children with HCM.

Keywords

Sudden death • Paediatric • Hypertrophic cardiomyopathy • Risk stratification

What's new?

- In a large and geographically diverse patient population, a 5-year hypertrophic cardiomyopathy (HCM) Risk-Kids predicted sudden cardiac death risk of $\geq 6\%$ identified over 70% of events.
- This study confirmed that HCM Risk-Kids provides a validated individualized tool for shared decision-making to guide implantable defibrillator implantation in children with HCM.

Introduction

Sudden cardiac death (SCD) is the most common mode of death in childhood hypertrophic cardiomyopathy (HCM) outside of infancy and occurs more frequently than in adult patients.^{1–3} Despite this, identification of patients who might benefit from primary prevention implantable defibrillator (ICD) implantation remains challenging, as current risk tools have been shown to have a limited ability to discriminate between those at high and low risk.⁴ In 2019, we developed a risk prediction model for SCD in childhood HCM (HCM Risk-Kids), using data from 1024 patients.⁵ This model, which uses readily available non-invasive clinical variables, had superior discriminatory ability on internal validation analysis than the currently recommended approaches to risk stratification^{6,7} but has not yet been externally validated in an independent population. The aim of this study was to validate the HCM Risk-Kids model in an independent, diverse, multi-centre patient population.

Methods

Patients

The study cohort comprised consecutively evaluated patients aged 1–16 years meeting diagnostic criteria for HCM from nine participating centres in the International Paediatric Hypertrophic Cardiomyopathy Consortium and the Sarcomeric Human Cardiomyopathy Registry (SHaRe) (Supplementary material online, Table S1). SHaRe centres that had contributed data to the HCM Risk-Kids development cohort were excluded. Included patients were evaluated between 1995 and 2019. Hypertrophic cardiomyopathy was defined as a maximal left ventricular wall thickness (MLVWT) of more than two standard deviations (SDs) above the body surface area (BSA)-corrected mean in the absence of abnormal loading conditions that could account for the abnormality.⁶ Patients were excluded if they had a prior history of ventricular fibrillation or sustained ventricular tachycardia (VT), known inborn errors of metabolism or syndromic disease (e.g. Friedreich's ataxia, RASopathy syndrome), <1-month follow-up, or missing data for more than 50% of HCM Risk-Kids model predictor variables (Supplementary material online, Figure S1).

Patient assessment and data collection

Anonymized clinical data from baseline evaluation were collected retrospectively, including demographics, heart failure symptoms [New York

Heart Association (NYHA) or Ross functional classification], pedigree analysis, resting and ambulatory 12-lead electrocardiogram (ECG), and two-dimensional (2D) Doppler and colour transthoracic echocardiogram. Hypertrophic cardiomyopathy Risk-Kids⁵ predictor variables were recorded at the time of, or prior to baseline evaluation: specifically, unexplained syncope (defined as a transient loss of consciousness with no identifiable cause), non-sustained ventricular tachycardia (NSVT) (defined as ≥ 3 consecutive ventricular beats at a rate of ≥ 120 beats per minute lasting ≤ 30 s on ambulatory ECG monitoring), MLVWT Z score,⁸ left atrial (LA) diameter Z score (defined as the number of SDs away from population mean the 2D measurement of LA diameter),⁹ and maximal left ventricular outflow tract (LVOT) gradient (defined as the maximal LVOT gradient at rest or with Valsalva provocation using continuous wave Doppler from apical three- or five-chamber views). Family history of SCD was defined as the sudden death of one or more first-degree relatives <40 years, or sudden death in a first-degree relative with a diagnosis of HCM at any age.⁶ Data were collected independently at participating centres and data integrity is guaranteed by each participating author.

Clinical outcomes

The primary study end-point was SCD or an equivalent event (aborted cardiac arrest, appropriate ICD therapy for a ventricular tachyarrhythmia, or sustained VT associated with haemodynamic compromise⁵). SCD was defined as a witnessed sudden death with or without documented cardiac failure, death within 1 h of new symptoms, or nocturnal deaths with no history of worsening symptoms.⁶ Outcomes were determined by the treating cardiologist at each centre without knowledge of the HCM Risk-Kids estimates.

Statistical methods

Statistical analysis was performed using Stata statistical software (Version 14) and R studio (Version 1.7). Variables are described as mean \pm SD, median [interquartile range (IQR)], and counts or percentages as appropriate. Group comparisons were performed using the Student's *t*-test, Mann–Whitney, or χ^2 test as appropriate. Follow-up time was calculated from the time of baseline evaluation to the date of reaching the study end-point, death from another cause, or date of most recent evaluation. The Kaplan–Meier method was used to estimate the incidence of reaching the study end-point. Univariable Cox regression models were used to investigate the association of clinical variables with the study end-point.

Missing data

Patients with more than three HCM Risk-Kids predictor variables missing were excluded from the validation cohort. Data were assumed to be missing at random and missing predictors were imputed using multiple imputations techniques based on chained equations.¹⁰ The imputation model included potential predictors of missingness, the outcome, HCM Risk-Kids predictor variables, and the estimate of the Nelson Aalen cumulative hazard function. A total of 75 imputed datasets were created. Estimates from imputed datasets were combined using Rubin's rule.¹¹

Hypertrophic cardiomyopathy Risk-Kids model validation

Follow-up was censored at 5 years and the estimated 5-year risk of SCD was calculated for each individual patient using the HCM Risk-Kids model:⁵

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

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

The C-index (Uno and Harrell's) was used to measure how well the model discriminated between high- and low-risk patients (a value of 1 indicates perfect discrimination, while a value of 0.5 indicates no discrimination).^{12–14} Bootstrapping was used to calculate the confidence intervals (CIs) for Uno's C-index. Harrell's C-index is subject to bias if the amount of censoring is high¹³ but is presented to enable comparison with alternative paediatric risk models. The calibration slope was used to assess the degree of agreement between the observed and predicted risk of SCD (a value close to 1 suggests good overall agreement).¹⁵ Model calibration was described graphically by stratifying patients into three risk groups based on tertiles of model predicted 5-year risk of SCD event from one imputed dataset.

The positive predictive value (PPV) of using different thresholds of HCM Risk-Kids estimated risk at 5 years in one imputed dataset was calculated by dividing (sensitivity \times prevalence) by [(sensitivity \times prevalence) + (1 – specificity) \times (1 – prevalence)] and expressed as a percentage. The negative predictive value (NPV) was calculated by dividing [specificity \times (1 – prevalence)] by [(1 – sensitivity) \times prevalence) + (specificity) \times (1 – prevalence)] and expressed as a percentage.

Validation of hypertrophic cardiomyopathy Risk-Kids threshold ($\geq 6\%$)

Current European Society of Cardiology (ESC) guidelines in adult patients recommend ICD implantation in the presence of an estimated 5-year risk of SCD $\geq 6\%$.⁶ The discriminatory ability of using an estimated 5-year HCM Risk-Kids SCD risk threshold of $\geq 6\%$ was assessed and the C-statistic was calculated.

Ethics

This study complies with the Declaration of Helsinki. Local ethical approval was given for each collaborating centre with waiver of informed consent for retrospective, anonymized data.

Results

Baseline clinical characteristics

The study cohort consisted of 421 patients (males $n = 258$, 64%) evaluated over a 30-year period [1990–1999 $n = 11$ (2.6%); 2000–2009 $n = 89$ (21.1%); 2010–2020 $n = 321$ (76.3%)] with a median age at

baseline evaluation of 12.3 years (7.3, 14.4) (Figure 1A). Two hundred and fifty (59.4%) of these were recruited from the SHaRe registry (Supplementary material online, Table S1). Baseline clinical characteristics are summarized in Table 1. Compared to the HCM Risk-Kids development and internal validation population, this cohort of patients was slightly older at baseline evaluation [median age 12.3 (7.3–14.4) vs. 11 (7–14) years, $P = 0.0001$] and had a shorter follow-up time [median follow-up 3.5 (1.8–6.6) vs. 5.3 (2.6–8.3) years, $P = 0.0001$]. Differences in baseline clinical characteristics are summarized in Table 1.

Clinical outcomes and sudden cardiac death end-points

The validation study cohort had a median total follow-up of 3.48 years (IQR 1.83–6.62; range 1 month–20.7 years). Fourteen patients (3.3%) died and 10 (2.4%) underwent cardiac transplantation. Cause of death was SCD ($n = 10$), heart failure related ($n = 1$), other cardiovascular (CV) ($n = 1$), non-CV ($n = 1$), and unknown ($n = 1$). Annual and 5-year cumulative mortality or transplant incidence rates were 1.24% (95% CI 0.52–2.96) and 5.21% (95% CI 0.31–8.70), respectively. Four patients (1.0%) were lost to follow-up. Thirty-nine patients (9.3%) experienced an SCD or equivalent event (SCD $n = 10$; resuscitated cardiac arrest $n = 11$; appropriate ICD therapy for ventricular tachyarrhythmia $n = 16$; sustained VT with haemodynamic compromise $n = 2$), with an overall incidence of 2.03 per 100 patient-years (95% CI 1.48–2.78) (Figure 2A). Annual and 5-year cumulative incidence of an SCD or equivalent event was 1.49% (95% CI 0.67–3.29) and 8.6% (95% CI 6.67–13.0), respectively. Analyses were focused on the 23 patients who had SCD or equivalent events within 5 years of follow-up (Figure 1B). Baseline characteristics in those with and without an SCD or equivalent event at 5 years are shown in Table 2.

Missing data

Missing data were seen in 1, 2, or 3 predictor variables in 122 (29.0%), 89 (21.1%), and 87 (20.7%) patients, respectively. There were missing data for four of five HCM Risk-Kids predictor variables (Table 1). A comparison of the distribution of predictors before and after imputation is shown in Supplementary material online, Table S2. The proportion of missing data for HCM Risk-Kids predictor variables by SCD outcome is shown in Supplementary material online, Table S3.

Hypertrophic cardiomyopathy Risk-Kids Model validation

The performance of the HCM Risk-Kids model in predicting risk at 5 years was assessed in 421 patients with 23 events. Harrell's C-index was 0.745 (95% CI 0.52–0.97) and Uno's C-index 0.714 (95% CI 0.58–0.85). The calibration slope was 1.15 (95% CI 0.51–1.80). Table 3 and Figure 3A describe the agreement between predicted and observed 5-year cumulative proportion of SCD or equivalent events for each tertile of predicted risk in one imputed dataset.

Validation of using a predicted risk of $\geq 6\%$

In a single imputed dataset, 125 (29.7%) patients had a predicted 5-year risk of $\geq 6\%$. Sudden cardiac death events occurred in

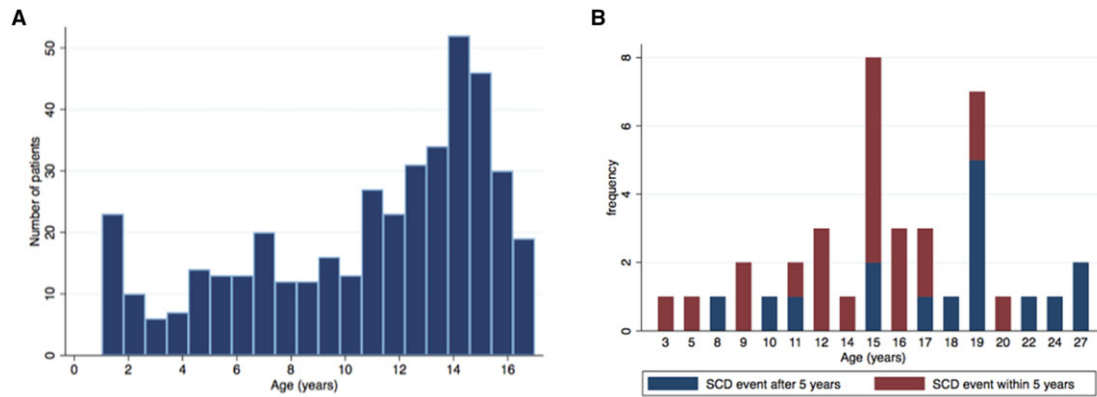


Figure 1 Bar chart showing (A) age at presentation and (B) age at sudden cardiac death event by timing after baseline clinical follow-up.

Table 1 Baseline clinical characteristics

Clinical characteristic	Validation cohort (n = 421)	HCM Risk-Kids development cohort (n = 1024)	P-value
Male gender (n = 403)	258 (64.0%)	699 (68.3%)	0.125
Age, median (Q1–Q3)	12.3 (7.3–14.4)	11 (7–14)	0.0001
NYHA/Ross (n = 154)			
1	110 (71.4%)	783 (77.8%)	0.079
≥2	44 (28.6%)	223 (22.2%)	
Family history HCM	198 (47.0%)	534 (53.1%)	0.037
Family history SCD	47 (11.2%)	130 (12.8%)	0.406
Unexplained syncope	15 (3.6%)	102 (9.9%)	<0.0001
NSVT (n = 246)	8 (3.3%)	55 (6.4%)	0.059
MWT (mm) (n = 408), mean ± SD	16.5 ± 7.8	17.1 ± 7.4	0.1207
MWT z score (n = 354)			
Median (Q1–Q3)	7.6 (4.7–13.6)	8.9 (5.8–14.9)	<0.0001
Mean ± SD	9.8 ± 7.3	11.1 ± 7.1	0.0025
LA diameter (mm) (n = 292), mean ± SD	30.8 ± 9.0	33.4 ± 8.5	<0.0001
LA diameter z score (n = 264), mean ± SD	1.3 ± 2.4	1.9 ± 2.3	0.0003
LVOT gradient (n = 205), median (Q1–Q3)	9 (5–24)	9 (6–22)	0.0469
LVOT obstruction (≥30 mmHg) (n = 234)	45 (22.0%)	189 (18.4%)	0.2448

Comparisons are made using χ^2 test for categorical variables and unpaired t-test or Mann–Whitney for continuous variables. For clinical characteristics N = 421 unless otherwise indicated.

HCM, hypertrophic cardiomyopathy; LA, left atrium; LVOT, left ventricular outflow tract obstruction; MWT, maximal wall thickness; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death; SD, standard deviation.

6 patients (2.0%) with a predicted risk <6% and 17 (13.6%) with a predicted risk ≥6. The clinical characteristics of those patients experiencing an SCD event with a predicted risk <6% is described in [Supplementary material online, Table 4](#). Five-year survival free from SCD or an equivalent event was 96.5% (95% CI 92.2–98.5) and 81.3% (95% CI 71.1–88.2), respectively, with a corresponding hazard ratio of 6.16 (95% CI 2.43–15.65, $P < 0.001$) ([Figure 2B](#)). The

combined C-statistic for all imputed datasets for using a 5-year predicted risk threshold of ≥6% was 0.702 (95% CI 0.60–0.81). [Figure 3B](#) describes the agreement between predicted and observed 5-year cumulative proportion of SCD events using a threshold of ≥6%. The positive and negative predictive value of using different thresholds of HCM Risk-Kids estimated risk (≥5, ≥6, ≥7, ≥8) to guide ICD implantation decisions are shown in [Supplementary material online, Table S5](#).

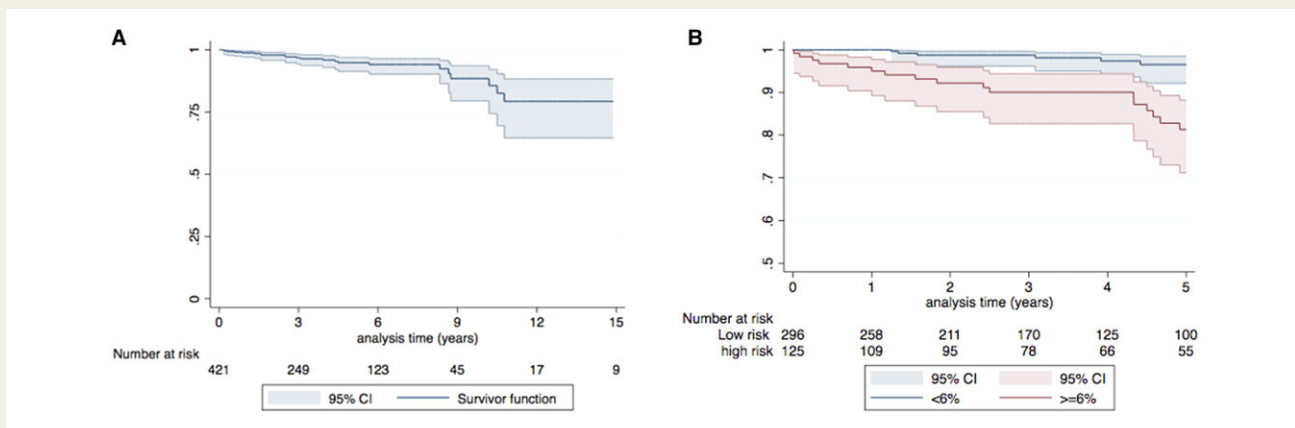


Figure 2 Kaplan–Meier curves showing event-free survival (A) for whole cohort (B) by risk category ‘high risk’ (hypertrophic cardiomyopathy Risk-Kids estimated 5-year risk $\geq 6\%$) and ‘low risk’ (hypertrophic cardiomyopathy Risk-Kids estimated 5-year risk $< 6\%$) [hazard ratio of 6.16 (95% confidence interval 2.43–15.65), $P < 0.001$]. CI, confidence interval.

Table 2 Baseline clinical characteristics of patients with and without sudden cardiac death end-points at 5 years

Clinical characteristic	SCD end-point (n = 23)	No SCD end-point (n = 398)	Hazard ratio (95% CI)	P-value
Male gender (n = 403)	15 (65.2%)	243 (64.0%)	1.00 (0.43–2.37)	0.993
Age (years), median (Q1–Q3)	12.6 (10.6–14.8)	12.2 (7.1–14.4)	1.06 (0.96–1.18)	0.242
NYHA/Ross 2+	5 (26.3%)	39 (28.9%)	0.94 (0.34–2.26)	0.911
Family history HCM	15 (62.2%)	183 (46.0%)	1.84 (0.78–4.33)	0.166
Family history SCD	4 (17.4%)	43 (10.8%)	1.38 (0.47–4.06)	0.562
Unexplained syncope	4 (17.4%)	11 (2.8%)	6.76 (2.29–19.94)	0.001
NSVT (n = 246)	1 (5.6%)	7 (3.1%)	1.19 (0.16–9.00)	0.868
MWT z score (n = 354), median (Q1–Q3)	14.7 (9.0–18.3)	7.4 (4.6–13.1)	1.06 (1.01–1.11)	0.013
LA diameter z score (n = 264), mean \pm SD	1.2 \pm 2.4	2.0 \pm 2.5	1.14 (0.97–1.35)	0.121
LVOT gradient (n = 205), median (Q1–Q3)	5.8 (5–9)	9 (4.8–25)	0.99 (0.97–1.01)	0.406
LVOT obstruction (≥ 30 mmHg) (n = 234)	41 (22.3%)	41 (19.1%)	0.95 (0.32–2.83)	0.928

CI, confidence interval; HCM, hypertrophic cardiomyopathy, LA, left atrial, LVOT, left ventricular outflow tract, MWT, maximal wall thickness, NYHA, New York Heart Association, NSVT, non-sustained ventricular tachycardia, SCD, sudden cardiac death; SD, standard deviation.

Table 3 Observed vs. hypertrophic cardiomyopathy Risk-Kids model predicted 5-year freedom from sudden cardiac death

Risk group category	Risk tertile (%)	Average predicted risk (%)	Observed risk (95% CI)
Low risk	< 2.60	1.66	2.49% (0.59–10.21)
Medium risk	2.61–5.50	3.78	3.95% (1.23–12.28)
High risk	> 5.50	9.58	17.42% (11.14–26.67)

CI, confidence interval, Calculated from one imputed dataset.

Discussion

This study reports the first external validation of the HCM Risk-Kids model in a large, independent, and geographically diverse patient population. A 5-year predicted risk of $\geq 6\%$ identified over 70% of events, confirming that HCM Risk-Kids provides a validated individualized tool for shared decision-making to guide ICD implantation in children with HCM.

External validation of the hypertrophic cardiomyopathy Risk-Kids model

In 2019, the first validated risk prediction model for SCD in childhood HCM (HCM Risk-Kids⁵) which uses readily available non-invasive

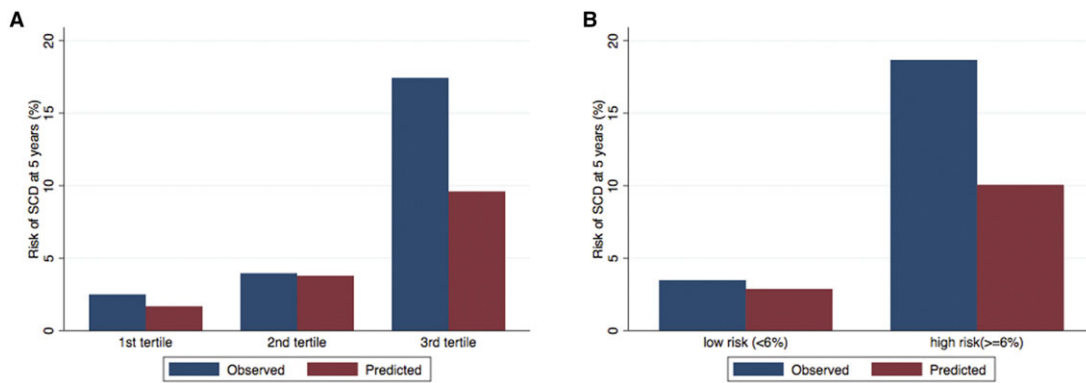


Figure 3 Comparison of observed and predicted risk in one imputed dataset by (A) predicted risk tertile (B) risk category 'high risk' (hypertrophic cardiomyopathy Risk-Kids estimated 5-year risk $\geq 6\%$) and 'low risk' (hypertrophic cardiomyopathy Risk-Kids estimated 5-year risk $< 6\%$). Vertical bars represent observed (dark blue) and hypertrophic cardiomyopathy Risk-Kids model predicted (red) probability of sudden cardiac death event by 5 years follow-up. SCD, sudden cardiac death.

clinical variables to estimate the risk of an SCD event occurring within 5 years was published. Internal validation of this model in the development cohort showed it to have superior performance for predicting SCD risk in children with HCM compared to a previously published external validation of current paediatric European⁶ and North American guidelines⁷ (*C*-index 0.69 vs. *C*-statistic 0.62⁴). This finding has been corroborated in the only small external validation study of the HCM Risk-Kids model to date, which reported a *C*-statistic of 0.771 and 0.677 for a HCM Risk-Kids 5-year estimated risk threshold of $\geq 4\%$ and $\geq 6\%$, respectively.¹⁶ In the present study, we provide the first large-scale external validation of this model, confirming its superior ability to identify patients at high risk of SCD events (Harrell's *C*-index 0.75 and Uno's *C*-index 0.71). Compared to the development cohort, the external validation cohort was older at baseline and had a lower prevalence of traditional clinical risk factors for SCD, which could suggest that they had phenotypically milder disease. The proportion of patients with unexplained syncope, for example, was lower than in the development cohort (3.6% vs. 9.9%), but comparable to estimates from previously published population studies (3–18%).^{2,3,17} This likely represents variability in the phenotype of childhood HCM but could also be explained by under-reporting of symptoms in retrospective population studies. Although the validation cohort had markers of phenotypically milder disease, the incidence of SCD event rates was not different between the two populations. The finding that the HCM Risk-Kids model has good discriminatory ability despite the differences in baseline clinical phenotype could strengthen its clinical utility. However, it is possible that the demographics and phenotype of the cohort could have resulted in higher estimates of performance than would be seen in real-world practice. The accuracy of risk estimates was better for those at lower risk of events and, in common with adult risk stratification models, appeared to be under-estimated for those at highest risk. Although this is unlikely to affect a clinicians' decision to implant an ICD in an individual patient, prospective studies are required to investigate how the risk model performs in clinical practice.

Clinical application of the hypertrophic cardiomyopathy Risk-Kids model

There is currently no consensus on the absolute SCD risk that justifies ICD implantation during childhood and potential benefits must be balanced with the increased risk of device-related complications seen in young patients.¹⁸ The 2014 adult ESC guidelines recommend using a 5-year estimated risk threshold of $\geq 6\%$, calculated using the HCM Risk-SCD model,¹⁹ to guide ICD implantation but recognize that an ICD may also be appropriate in intermediate risk patients (4–6% risk at 5 years).⁶ By way of comparison, we explored the clinical impact of using a threshold of $\geq 6\%$ in childhood HCM. One-third of patients had a 5-year HCM Risk-Kids estimated SCD risk of $\geq 6\%$ and using this threshold to guide ICD implantation identified 74% (17/23) of SCD events. A previous validation study of the current paediatric guidelines reported that 3% (14/411) and 31% (127/411) met ICD recommendation thresholds identifying 7% (23/43) and 51% (22/43) SCD events for the European and North American guidelines, respectively. The discriminatory ability of a HCM Risk-Kids estimated SCD risk of $\geq 6\%$ for identifying those at risk of SCD events is therefore substantially higher than current European and North American guidelines (*C*-statistic 0.70 vs. 0.62)⁴, and comparable to the performance of the adult HCM Risk-SCD model.^{19,20} Of those patients experiencing an SCD event with a low HCM Risk-Kids predicted risk of SCD, all but one had clinical features of mild disease and would also not have been recommended for ICD implantation using the current European or North American guidelines. This demonstrates a problem common to all risk models and reinforces the central role that clinical decision-making should play in risk stratification decisions. Seven in eight patients who had an ICD implanted for a risk of $\geq 6\%$ did not experience an appropriate ICD therapy within 5 years, with the accompanying burden of ICD-related complications, which are recognized to be higher in a paediatric population. However, as the risk of an arrhythmic event persists throughout childhood into adolescence and adulthood,²¹ a subset of these patients may yet benefit

from ICD implantation. Additionally, subcutaneous ICD devices offer the hope that the future burden of ICD-related complications will be lower for younger patients receiving primary prevention devices.

Adopting a threshold for HCM Risk-Kids estimated risk could be a useful adjunct to facilitate shared decision-making between patients, families, and clinicians around ICD implantation in childhood HCM. Yet, given the low incidence of mortality secondary to competing causes, a threshold of 6% may be inappropriate for childhood disease and expert consensus opinion would be required to determine an appropriate risk threshold. The HCM Risk-Kids model was developed to predict 5-year SCD risk at first evaluation and validated in patients up to the age of, and including, 16 years of age. The ESC guideline-adopted validated adult HCM Risk-SCD model should be used for patients beyond that age.^{6,19} Importantly, although HCM Risk-Kids has superior discriminatory ability compared to current guidelines, in real work clinical practice it remains imperfect with patients at risk of events unprotected and a high number of patients without an event exposed to the risk of device-related complications. Future iterations of HCM Risk-Kids using serial clinical data to enable reassessment of risk during follow-up and identification of other novel risk factors are needed to improve outcomes.

Comparison with other paediatric risk models

Since the publication of HCM Risk-Kids, a separate paediatric-specific model was developed in a North American multi-centre retrospective cohort (PRIMaCY) of 572 patients up to 18 years of age.³ Both models use readily available clinical predictors, chosen based on either three decades of published literature (HCM Risk-Kids)⁵ or an association with the end-point of an arrhythmic event in a development cohort (PRIMaCY).³ Despite the different approaches to predictor selection, the variables included in the two models are almost identical, reflecting clinical markers of disease severity. Important differences include the measure of left ventricular hypertrophy (MLVWT vs. interventricular septal and posterior wall thickness) and use of age at diagnosis as a predictor variable in the PRIMaCY model. Age is not included in HCM Risk-Kids as, with the exception of infant-onset disease, there is limited evidence that it is important for risk stratification^{1,22–24} and including it as a predictor during model development did not improve model performance.⁵ However, the effect of age is likely to have been partially accounted for by the use of BSA-corrected echocardiographic measurements. A subset of the SHaRe cohort also served as the validation cohort for the PRIMaCY model and model performance and discriminatory ability was higher for HCM Risk-Kids (Harrell's C-index 0.75 vs. 0.71). Although CIs for the performance estimates were not reported for the PRIMaCY model, given that both the development and internal validation and the external validation cohorts for the HCM Risk-Kids model are nearly twice as large as PRIMaCY, they would be expected to be at least as wide as in our own external validation cohort, reflecting uncertainty in the estimates due to small patient numbers and missing data. The estimate of Harrell's C-index may be subject to bias in the presence of moderate to high levels of censoring and Uno's C-index has been recommended for use in these situations.¹³ Further independent prospective external validation studies of these two models are needed to compare performance in clinical practice, but the results

of this study suggest that HCM Risk-Kids outperforms current European and North American guidelines and has a similar discriminatory performance to the adult HCM Risk-SCD model.^{6,7,20}

Future directions

In order to facilitate ongoing reassessment of HCM Risk-Kids in temporally and geographically diverse populations, we have made the model widely available (www.hcmriskkids.org) to improve accessibility for clinicians. Incorporation of the model into clinical practice will provide contemporary data for prospective validation studies. Childhood HCM is characterized by significant heterogeneity and phenotype, and therefore risk profile may change before transition to adult care, representing a challenge for risk prediction strategies.² Hypertrophic cardiomyopathy Risk-Kids was designed to be used at baseline clinical assessment, regardless of proband status, to predict the risk of an SCD event occurring within 5 years of follow-up. However, in clinical practice, reassessment of a patient's risk during follow-up taking into account the changing cardiac phenotype would be of clinical benefit. Future studies exploring the changing role of individual clinical risk factors during childhood and the use of serial clinical data to predict time-dependent risk are required. This could be particularly important for patients presenting through family screening, who may have milder disease at baseline compared to childhood family probands. The role of genotype in risk prediction for children and adults with HCM remains unclear.^{21,25} Although a disease-causing sarcomeric variant was associated with an SCD event in the PRIMaCY cohort, including it in the risk prediction model did not significantly improve model accuracy.³ Previous studies have been limited by their retrospective, longitudinal design meaning genetic testing was not systematically performed in all patients. Data on genetic testing were not systematically collected in this cohort but future large-scale prospective multi-centre registries are needed to explore the genotype–phenotype correlations in childhood HCM. Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging has been shown to be an independent risk factor for SCD or equivalent events in adult HCM populations²⁶ and recent studies have shown that the presence of LGE could improve risk stratification, particularly for patients with an intermediary 5-year ESC SCD risk score.^{27,28} Paediatric studies to date have been underpowered to detect a difference in SCD risk²⁹ but, the presence of, or degree of LGE has been reported to improve the discriminatory ability of HCM Risk-Kids model in a small single-centre study.¹⁷ Future studies to confirm the role of LGE in risk stratification for childhood HCM and its inclusion in future iterations of HCM Risk-Kids model should be explored. This study did not aim to validate the use of HCM Risk-Kids in patients with infant-onset or syndromic causes of left ventricular hypertrophy (LVH) (e.g. inborn errors of metabolism, RASopathy syndrome, or neuromuscular disorders) and indeed the model is not currently validated for use in these patient groups, as they were excluded from the model development cohort. These groups of patients are recognized to have a worse overall prognosis, with death most commonly attributed to heart failure or non-cardiac causes. Future studies to explore the risk of SCD and impact that competing causes of mortality have on risk stratification for these patient groups are needed.

Limitations

This study is limited by its retrospective longitudinal design, as necessitated for a rare condition with low event rates. The most significant limitations, in common with other paediatric and adult HCM cohort studies, are missing data and the relatively low number of events. The proportion of missing data was higher than in the HCM Risk-Kids development cohort but similar to the PRIMaCY validation cohort. This may partly be explained by the use of contemporaneously written echocardiographic reports, different local echocardiographic scanning protocols, and difficulty in obtaining some investigations in younger patients (e.g. ambulatory ECGs). To ensure our imputation of missing data was robust, we incorporated all predictors in the imputation model that we considered to be important to explain missingness. A comparison of the distribution of predictors before and after imputation confirmed that the distributions were similar and had not been distorted. As the external validation cohort was smaller, despite having a similar overall annual SCD event rate, there was a low number of events ($n = 23$) within 5 years, resulting in wide CIs for the estimated annual incidence rate. The true incidence of SCD events occurring in childhood HCM is unknown, but large population studies have reported an annual incidence rate of 1–2%^{1–3} suggesting that the outcomes of this study population are representative of the wider childhood HCM. The small population sample and low event rate resulted in wide CIs for the C-index and the calibration slope values, which represents uncertainty in the estimates. The median length of follow-up for the validation cohort was shorter than the development cohort and only two-fifths of patients had a follow-up of 5 years or longer. The HCM Risk-Kids model predicts the risk of an SCD event occurring within 5 years of follow-up meaning that patients with shorter follow-up times could still reach the SCD end-point within 5 years. This could affect the estimates of predictive accuracy (negative and positive predictive value) for the model. The limitations of the study design could be addressed with future prospective, large multi-centre studies assessing the performance of risk prediction models in childhood HCM.

Finally, the number of patients who underwent surgical gradient reduction (myectomy) was small; our current understanding of the impact surgical gradient reduction has on risk is limited and the model should therefore be used cautiously in this patient group.

Conclusions

This study shows that the HCM Risk-Kids model has superior ability to identify childhood patients at high risk for SCD over 5 years compared to current risk stratification guidelines and alternative paediatric risk models with over 70% of events predicted by an estimated risk of $\geq 6\%$. The model provides a validated individualized tool for shared decision-making to improve risk stratification and guide ICD implantation in children with HCM. Incorporation of the model into routine clinical care will enable independent prospective model validation and assessment of the effect of its use in clinical practice.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Acknowledgements

Dr Jaana Pihkala (Department of Paediatric Cardiology, New Children's Hospital, University of Helsinki, Finland); Dr Anita Hiippala (Department of Paediatric Cardiology, New Children's Hospital, University of Helsinki, Finland); Dr Giulia Grilli (Heart Muscle Disease Registry Trieste, University of Trieste, Italy); Dr Pierluigi Lesizza (Heart Muscle Disease Registry Trieste, University of Trieste, Italy); Dr Alessandro Pierri (Heart Muscle Disease Registry Trieste, University of Trieste, Italy); Simon Theisen (Charite – Universitätsmedizin Berlin, Germany); and Nadya Al-Wakeel (Charite – Universitätsmedizin Berlin, Germany).

Funding

This work was supported by the British Heart Foundation (FS/16/72/32270 to G.N. and J.P.K.). E.F. and J.P.K. are supported by Max's Foundation and Great Ormond Street Hospital Children's Charity. J.P.K. is supported by a Medical Research Council Clinical (MRC)-National Institute for Health Research (NIHR) Clinical Academic Research Partnership (CARP) award. This work is (partly) funded by the NIHR GOSH BRC. R.Z.O. and C.Q. work at University College London Hospitals/University College London who received a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. C.Y.H. receives funding from the National Institutes of Health and consulting honoraria from Myokardia, Inc./Bristol Myers Squibb. This work was financially supported by the Foundation for Paediatric Research, Finland (T.H.O.). C.S. is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (#1154992). J.I. is supported by a National Health and Medical Research Council (NHMRC) Career Development Fellowship (#1162929). J.I. receives research grant support from Myokardia, Inc.

Conflict of interest: none declared.

Data availability

The data underlying this article cannot be shared publicly as consent for dissemination of patient data was not obtained. G.N., J.P.K., C.Q., and R.Z.O. had access to all data and final responsibility for submission of the manuscript.

References

- Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *Circulation* 2007;**115**:773–781.
- Norrish G, Field E, McLeod K, Iliina M, Stuart G, Bhole V, Uzun O, Brown E, Daubeney PEF, Lota A, Linter K, Mathur S, Bharucha T, Kok KL, Adwani S, Jones CB, Reinhardt Z, Kaski JP. Clinical presentation and survival of childhood hypertrophic cardiomyopathy: a retrospective study in United Kingdom. *Eur Heart J* 2019;**40**:986–993.
- Miron A, Lafreniere-Roula M, Fan CS, Armstrong KR, Dragulescu A, Papaz T, Manliot C, Kaufman B, Butts RJ, Gardin L, Stephenson EA, Howard TS, Aziz PF, Balaji S, Beauséjour Ladouceur V, Benson LN, Colan SD, Godown J, Henderson HT, Ingles J, Jeewa A, Jefferies JL, Lal AK, Mathew J, Jean-St-Michel E, Michels M, Nakano SJ, Olivetto I, Parent JJ, Pereira AC, Semsarian C, Whitehill RD, Wittekind SG, Russell MW, Conway J, Richmond ME, Villa C, Weintraub RG, Rossano JW, Kantor PF, Ho CY, Mital S. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. *Circulation* 2020; **142**:217–229.

4. Norrish G, Ding T, Field E, McLeod K, Iliina M, Stuart G, Bhole V, Uzun O, Brown E, Daubeney PEF, Lota A, Linter K, Mathur S, Bharucha T, Kok KL, Adwani S, Jones CB, Reinhardt Z, Omar RZ, Kaski JP. A validation study of the European Society of Cardiology guidelines for risk stratification of sudden cardiac death in childhood hypertrophic cardiomyopathy. *Europace* 2019;**21**:1559–1565.
5. Norrish G, Ding T, Field E, Ziolkowska L, Olivotto I, Limongelli G, Anastasakis A, Weintraub R, Biagini E, Ragni L, Prendiville T, Duignan S, McLeod K, Iliina M, Fernández A, Bökenkamp R, Baban A, Kubuš P, Daubeney PEF, Sarquella-Brugada G, Cesar S, Marrone C, Bhole V, Medrano C, Uzun O, Brown E, Gran F, Castro FJ, Stuart G, Vignati G, Barriaes-Villa R, Guereta LG, Adwani S, Linter K, Bharucha T, Garcia-Pavia P, Rasmussen TB, Calcagnino MM, Jones CB, De Wilde H, Toru-Kubo J, Felice T, Mogensen J, Mathur S, Reinhardt Z, O'Mahony C, Elliott PM, Omar RZ, Kaski JP. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM Risk-Kids). *JAMA Cardiol* 2019;**4**:918–927.
6. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.
7. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evannovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Sorajja P. 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**:e533–e557.
8. Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, Pearson G, Camarda J, Cnota J, Cohen M, Dragulescu A, Frommelt M, Garuba O, Johnson T, Lai W, Mahgerefteh J, Pignatelli R, Prakash A, Sachdeva R, Soriano B, Soslow J, Spurney C, Srivastava S, Taylor C, Thankavel P, van der Velde M, Minich L. Relationship of echocardiographic Z scores adjusted for body surface area to age, sex, race, and ethnicity: the pediatric heart network normal echocardiogram database. *Circ Cardiovasc Imaging* 2017;**10**:e006979.
9. Neilan TG, Pradhan AD, King ME, Weyman AE. Derivation of a size-independent variable for scaling of cardiac dimensions in a normal paediatric population. *Eur J Echocardiogr* 2009;**10**:50–55.
10. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999;**18**:681–694.
11. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, United States: Wiley Classics Library; 2004.
12. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. *Stat Med* 2011;**30**:1105–1117.
13. Rahman MS, Ambler G, Choodari-Oskooei B, Omar RZ. Review and evaluation of performance measures for survival prediction models in external validation settings. *BMC Med Res Methodol* 2017;**17**:60.
14. Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA* 1982;**247**:2543–2546.
15. Steyerberg EV. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. New York, United States: Springer; 2009.
16. Petryka-Mazurkiewicz J, Ziolkowska L, Kowalczyk-Domagala M, Mazurkiewicz L, Boruc A, Spiewak M, Misko J, Bieganowska K, Marczak M, Brzezinska-Rajszyz G. LGE for risk stratification in primary prevention in children with HCM. *JACC Cardiovasc Imaging* 2020;**13**:2684–2686.
17. Ziolkowska L, Turska-Kmieć A, Petryka J, Kawalec W. Predictors of long-term outcome in children with hypertrophic cardiomyopathy. *Pediatr Cardiol* 2016;**37**:448–458.
18. Kaski JP, Tome Esteban MT, Lowe M, Sporton S, Rees P, Deanfield JE, McKenna WJ, Elliott PM. Outcomes after implantable cardioverter-defibrillator treatment in children with hypertrophic cardiomyopathy. *Heart* 2007;**93**:372–374.
19. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; 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**:2010–2020.
20. O'Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, Cecchi F, Olivotto I, Kitaoka H, Gotsman I, Carr-White G, Mogensen J, Antoniadis L, Mohiddin SA, Maurer MS, Tang HC, Geske JB, Siontis KC, Mahmoud KD, Vermeer A, Wilde A, Favalli V, Guttmann OP, Gallego-Delgado M, Dominguez F, Tanini I, Kubo T, Keren A, Bueser T, Waters S, Issa IF, Malcolmson J, Burns T, Sekhri N, Hoeger CW, Omar RZ, Elliott PM. An international external validation study of the 2014 European Society of Cardiology guideline on sudden cardiac death prevention in hypertrophic cardiomyopathy (evidence from HCM). *Circulation* 2018;**137**:1015–1023.
21. Maurizi N, Passantino S, Spaziani G, Girolami F, Arretini A, Targetti M, Pollini I, Tomberli A, Pradella S, Calabri GB, Vinattieri V, Bertaccini B, Leone O, De Simone L, Rapezzi C, Marchionni N, Cecchi F, Favilli S, Olivotto I. Long-term outcomes of pediatric-onset hypertrophic cardiomyopathy and age-specific risk factors for lethal arrhythmic events. *JAMA Cardiol* 2018;**3**:520–525.
22. Alexander PMA, Nugent AVW, Daubeney PEF, Lee KJ, Sleeper LA, Schuster T, Turner C, Davis AM, Semsarian C, Colan SD, Robertson T, Ramsay J, Justo R, Sholler GF, King I, Weintraub RG; On behalf of the National Australian Childhood Cardiomyopathy Study. Long-term outcomes of hypertrophic cardiomyopathy diagnosed during childhood: results from a national population-based study. *Circulation* 2018;**138**:29–36.
23. Ostman-Smith I, Wettrell G, Keeton B, Holmgren D, Ergander U, Gould S, Bowker C, Verdicchio M. Age- and gender-specific mortality rates in childhood hypertrophic cardiomyopathy. *Eur Heart J* 2008;**29**:1160–1167.
24. Maron BJ, Tajik AJ, Ruttenberg HD, Graham TP, Atwood GF, Victorica BE, Lie JT, Roberts WC. Hypertrophic cardiomyopathy in infants: clinical features and natural history. *Circulation* 1982;**65**:7–17.
25. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA, Helms AS, Colan SD, Girolami F, Cecchi F, Seidman CE, Sajeev G, Signorovitch J, Green EM, Olivotto I; For the SHaRe Investigators. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation* 2018;**138**:1387–1398.
26. Weng Z, Yao J, Chan RH, He J, Yang X, Zhou Y, He Y. Prognostic value of LGE-CMR in HCM: a meta-analysis. *JACC Cardiovasc Imaging* 2016;**9**:1392–1402.
27. Todiere G, Nugara C, Gentile G, Negri F, Bianco F, Falletta C, Novo G, Di Bella G, De Caterina R, Zachara E, Re F, Clemenza F, Sinagra G, Emdin M, Aquaro GD. Prognostic role of late gadolinium enhancement in patients with hypertrophic cardiomyopathy and low-to-intermediate sudden cardiac death risk score. *Am J Cardiol* 2019;**124**:1286–1292.
28. Freitas P, Ferreira AM, Arteaga-Fernández E, de Oliveira Antunes M, Mesquita J, Abecasis J, Marques H, Saraiva C, Matos DN, Rodrigues R, Cardim N, Mady C, Rochitte CE. The amount of late gadolinium enhancement outperforms current guideline-recommended criteria in the identification of patients with hypertrophic cardiomyopathy at risk of sudden cardiac death. *J Cardiovasc Magn Reson* 2019;**21**:50.
29. Axelsson Raja A, Farhad H, Valente AM, Couce JP, Jefferies JL, Bundgaard H, Zahka K, Lever H, Murphy AM, Ashley E, Day SM, Sherrid MV, Shi L, Bluemke DA, Canter CE, Colan SD, Ho CY. Prevalence and progression of late gadolinium enhancement in children and adolescents with hypertrophic cardiomyopathy. *Circulation* 2018;**138**:782–792.