Circulation

ORIGINAL RESEARCH ARTICLE

A Validated Model for Sudden Cardiac Death Risk Prediction in Pediatric Hypertrophic Cardiomyopathy

BACKGROUND: Hypertrophic cardiomyopathy is the leading cause of sudden cardiac death (SCD) in children and young adults. Our objective was to develop and validate a SCD risk prediction model in pediatric hypertrophic cardiomyopathy to guide SCD prevention strategies.

METHODS: In an international multicenter observational cohort study, phenotype-positive patients with isolated hypertrophic cardiomyopathy <18 years of age at diagnosis were eligible. The primary outcome variable was the time from diagnosis to a composite of SCD events at 5-year follow-up: SCD, resuscitated sudden cardiac arrest, and aborted SCD, that is, appropriate shock following primary prevention implantable cardioverter defibrillators. Competing risk models with cause-specific hazard regression were used to identify and quantify clinical and genetic factors associated with SCD. The cause-specific regression model was implemented using boosting, and tuned with 10 repeated 4-fold cross-validations. The final model was fitted using all data with the tuned hyperparameter value that maximizes the c-statistic, and its performance was characterized by using the c-statistic for competing risk models. The final model was validated in an independent external cohort (SHaRe [Sarcomeric Human Cardiomyopathy Registry], n=285).

RESULTS: Overall, 572 patients met eligibility criteria with 2855 patient-years of follow-up. The 5-year cumulative proportion of SCD events was 9.1% (14 SCD, 25 resuscitated sudden cardiac arrests, and 14 aborted SCD). Risk predictors included age at diagnosis, documented nonsustained ventricular tachycardia, unexplained syncope, septal diameter *z*-score, left ventricular posterior wall diameter *z* score, left atrial diameter *z* score, peak left ventricular outflow tract gradient, and presence of a pathogenic variant. Unlike in adults, left ventricular outflow tract gradient had an inverse association, and family history of SCD had no association with SCD. Clinical and clinical/genetic models were developed to predict 5-year freedom from SCD. Both models adequately discriminated between patients with and without SCD events with a c-statistic of 0.75 and 0.76, respectively, and demonstrated good agreement between predicted and observed events in the primary and validation cohorts (validation c-statistic 0.71 and 0.72, respectively).

CONCLUSION: Our study provides a validated SCD risk prediction model with >70% prediction accuracy and incorporates risk factors that are unique to pediatric hypertrophic cardiomyopathy. An individualized risk prediction model has the potential to improve the application of clinical practice guidelines and shared decision making for implantable cardioverter defibrillator insertion.

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Clinical Perspective

What Is New?

- Patients with pediatric hypertrophic cardiomyopathy had a high 5-year cumulative sudden cardiac death risk of 9.1%.
- A large international cohort analysis identified a positive association of unexplained syncope and nonsustained ventricular tachycardia, a nonlinear association of age, septal and left ventricular posterior wall thickness and left atrial diameter, and no association of left ventricular outflow tract gradient with sudden cardiac death risk (inverse association with a gradient ≥100 mm Hg).
- An integrated model that incorporated all age-appropriate risk factors provided individualized scores for 5-year sudden cardiac death risk and is the first prediction model to be externally validated in an independent cohort with high performance accuracy.

What Are the Clinical Implications?

- The decision for primary prevention implantable cardioverter defibrillators in patients with pediatric hypertrophic cardiomyopathy should not be based on a single risk factor, but should incorporate all age-appropriate, evidence-based risk factors.
- The PRIMACY (Precision Medicine for Cardiomyopathy) sudden cardiac death risk prediction model can be implemented within hospital electronic health systems as a point-of-care tool to help guide physicians in shared decision making with patients with childhood-onset hypertrophic cardiomyopathy and families regarding primary prevention implantable cardioverter defibrillator.

Hypertrophic cardiomyopathy (HCM) is the most common form of cardiomyopathy affecting at least 1 in 500 individuals and is a leading cause of sudden cardiac death (SCD) in adolescents and young adults.[1–3] SCD is related primarily to the occurrence of significant arrhythmias including ventricular fibrillation or sustained ventricular tachycardia (VT).[4,5] Implantable cardioverter defibrillators (ICDs) can prevent SCD by detecting and terminating sustained VT or ventricular fibrillation. They are offered to patients who have survived documented near-death events, known as secondary prevention ICD, or prophylactically to those who have not yet experienced an event but who are deemed at high risk for an event, known as primary prevention ICD. Despite the availability of this life-saving intervention, the lack of precision in predicting SCD risk hampers timely ICDs in at-risk individuals, resulting in tragic but preventable deaths. Risk is often overestimated in lower-risk patients, resulting in potentially unwarranted ICD implantation.[6–10] This can have negative medical, psychological, and financial consequences, because ICD therapy is associated with a 20% complication rate, and an 11% inappropriate shock rate in children (higher with epicardial ICD placement).[8,11–14]

Published clinical practice guidelines define high risk for SCD by the presence of ≥1 clinical risk factors.[4,15,16] However, clinical practice recommendations are inconsistently and variably applied in practice likely because ICD decision making is driven by a subjective perception of risk with considerable variability in risk tolerance among practitioners and patients, and a more conservative uptake because of a higher complication rate of ICDs in pediatric than in adult patients.[8,16,17] In recent years, the European Society of Cardiology developed and validated a web-based tool that incorporates evidence-based clinical risk factors into an algorithm to predict 5-year sudden death risk in adult patients >16 years of age, but does not apply to children.[18–22] This model did not include other potential risk factors like the genetic etiology of HCM that can influence the risk of SCD.[15,23,24] In addition, studies have shown that the European Society of Cardiology 2014 risk prediction model had a lower sensitivity in high-risk populations. As a result, the European Society of Cardiology 2014 model frequently misidentified patients who experienced a SCD event as low risk.[20,25–27] A recent study from the United Kingdom reported on the performance of a SCD risk prediction model for pediatric HCM developed using 5 preselected clinical variables with a c-statistic of 0.69, but this model has not been externally validated.[28] The lack of evidence-based decision support for SCD risk prediction in childhood HCM has been identified as an important practice gap.

The purpose of our study was to develop and validate a risk prediction model for SCD in pediatric HCM using evidence-based risk factors to assist physicians and patients in shared decision making for primary prevention ICD implantation.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Cohort and Participating Centers

This was a multicenter retrospective observational cohort study of pediatric patients with clinically diagnosed childhood-onset HCM. Eligibility criteria included clinical diagnosis of HCM, LV posterior wall or septal thickness *z* score ≥2,[29,30] age <18 years at the time of diagnosis, absence of a SCD event before diagnosis, and at least 1 follow-up assessment after diagnosis. Genotype-positive subjects who did not have echocardiographic evidence of LV hypertrophy and patients with known or suspected secondary causes of HCM, ie, clinical syndromes like RASopathies (Noonan syndrome, Noonan syndrome with multiple lentigines, Costello syndrome, Cardiofaciocutaneous syndrome, and Neurofibromatosis type 1), endocrine, metabolic, mitochondrial, or neuromuscular disorders, hypertension, and

structural heart defects were excluded. Age at diagnosis was defined as the age at echocardiogram at which the diagnosis of HCM was made. All centers used the same echocardiographic criteria for the diagnosis of hypertrophy.

The primary cohort included patients from 11 sites participating in the PRIMaCY study (Precision Medicine for Cardiomyopathy), an international registry of patients with pediatric HCM launched in 2017. These included 4 Canadian, 6 US, and 1 Australian site. For model validation in an independent cohort, we used data from patients with childhood-onset HCM from SHARE (the Sarcomeric Human Cardiomyopathy Registry), a registry of 15 international centers capturing longitudinal clinical data on deidentified patients with HCM.[23] For the 4 sites that contributed data to both registries, any overlapping patients were excluded from the validation cohort. Clinical, genetic, and outcomes data were collected from the medical records in all eligible patients from the time of diagnosis to last follow-up. Echocardiographic data were collected at initial diagnosis and at last follow-up. For patients with major cardiac events (death, transplant, SCD), data were captured before the event. Echocardiographic data were collected from clinical reports, and, where feasible, missing data were collected through a re-review of the echocardiograms at local sites by the research team. SCD events were reviewed by site investigators to confirm the cause of death. The research protocol was approved by the institutional research ethics boards at all sites and waiver of consent was obtained for this retrospective study. All patient data were deidentified for data sharing and analyses. The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Selection of Predictor Variables

To generate a risk prediction model, candidate risk factors based on the American College of Cardiology Foundation/American Heart Association published clinical practice guidelines were assessed.[4] Echocardiographic measurements of wall thickness and chamber sizes were converted to *z* scores using the Boston *z* score calculator.[29,30] The risk factors included age at diagnosis, family history of SCD, history of recent unexplained syncope within 6 months before the diagnosis, documented nonsustained VT (defined as ≥3 beats at ≥120 bpm on ambulatory ECG), interventricular septal diameter (IVSD) *z* score, LV posterior wall diameter (LVPWD) *z* score, left atrial (LA) diameter *z* score, and peak resting LV outflow tract (LVOT) gradient on echocardiography. Genetic results from clinical testing were captured from medical records and, through research sequencing, in a subset of patients. Data included affected gene and variant pathogenicity, that is, pathogenic/likely pathogenic, variant of uncertain significance or benign.[31] Variant classification was reconfirmed using American College of Medical Genetics criteria at the core site. Patients harboring pathogenic/likely pathogenic variants in cardiomyopathy genes were considered genotype positive (Table I in the Data Supplement). Ethnicity information was only available in 102 patients and therefore was not included in the analysis.

Statistical Analysis

All statistical analyses were performed using R version 3.4.1 with survival, multiple imputation by chained equations, mboost, riskRegression, and mlr packages. Clinical characteristics were summarized using descriptive statistics. Continuous variables were summarized using median and interquartile range, whereas categorical variables were summarized using frequencies and proportions. The primary outcome was time to an SCD event during 5-year follow-up defined as a composite outcome of SCD, resuscitated sudden cardiac arrest (including sustained VT/ventricular fibrillation), and aborted SCD events, that is, appropriate shock in a patient with a primary prevention ICD. Event-free survival was estimated by using the Kaplan-Meier method as was the cumulative proportion of SCD events over time.

Model Development and Performance Assessment

General Modeling Approach

To generate a risk prediction model, the relative contribution of the clinical and genetic predictors was quantified by using a competing risk model for SCD events with non-SCD death as the competing risk. This analysis was implemented by using cause-specific regression. To ensure that the quantification was pertinent to the clinical context, patients were administratively censored at 5 years from first evaluation. Two models were considered: a clinical-only model and a clinical/genetic model that included genotype status of the patient. Patients harboring a pathogenic/likely pathogenic causal variant on genetic testing, that is, genotype-positive patients, were compared with patients without a causal variant on testing. We applied a model-boosting algorithm to the cause-specific hazard regression to identify and quantify the association between the candidate risk factors and the composite outcome. For continuous risk factors, the associations were modeled without the assumption of linearity using penalized *b*-splines. The estimated nonlinear associations were summarized graphically. On the fitting of the 2 boosted models, we then obtained the linear predictors and baseline hazard for the SCD events. This cause-specific hazard regression implementation for competing risk data has been previously described.[32]

Model Tuning

To tune the boosting model, we applied 10 repeated 4-fold cross-validations to determine the hyperparameter of the boosting model. In this exercise, we considered a small learning rate (step size) of 0.01 and a large number of steps. Within each cross-validation iteration, we imputed the missing values by using multiple imputation by chained equations before training the model. This scheme of nested imputations was demonstrated in a similar prognostic study setting.[33,34] The plausibility of missing at random assumed in the imputation depends on the candidate risk factors. As long as the candidate risk factors considered in the study are comprehensive, as in our study, this assumption is reasonable. Next, we applied the trained model and calculated the c-statistic on the cross-validation data for each step. The optimal number of steps (ie, the value of the boosting model hyperparameter) was the one that maximized the c-statistic averaged over all cross-validation iterations. The final model was then fitted using all data with the optimal hyperparameter value estimated in the model-tuning exercise. Given the competing risk data, separate cause-specific hazard regression models were

fitted and tuned: 1 for SCD events and the other for non-SCD deaths. Because of a small number of patients with non-SCD deaths, we only applied 3-fold cross-validation to identify and quantify the risk factors associated with non-SCD deaths.

Model Performance

On model fitting, both prognostic index and the 5-year cumulative proportion of SCD events were quantified for each patient. The discriminatory power of the final model was quantified using the c-statistic for competing risk models.[35] Model calibration was assessed by stratifying patients into 3 risk groups based on tertiles of the predicted 5-year probability of a SCD event and by creating a calibration curve to show the relationship between the observed and predicted 5-year probability of events.

Model Validation

The final model was externally validated using an independent replication cohort consisting of 285 eligible patients from SHaRe after excluding 321 patients that overlapped with the discovery cohort. The Harrell c-statistic was calculated, and calibration curves were constructed using quantiles of predicted risk as described above.

RESULTS

The final derivation cohort consisted of 572 eligible patients with phenotype-positive HCM diagnosed between 1987 and 2018. This included 535 unrelated probands and 37 affected siblings of the probands. The distribution of cases by center and by age at diagnosis is shown in Figure I in the Data Supplement. Baseline clinical and echocardiographic characteristics at diagnosis for the primary and validation cohorts are displayed in Table 1. A total of 368 (64%) patients had asymmetrical septal hypertrophy. There were no cases of apical hypertrophy. The median age at diagnosis was 9.8 years (interquartile range, 2.1–13.9). The median follow-up duration was 3.9 (1.5–6.7) years (duration to either death or the last known date alive). Of 565 patients, 336 (59%) received β-blockers during follow-up; medication data were not available in 7 patients. Of the 311 (54%) subjects who had genetic testing reported, 160 (28%) were identified as carrying at least 1 causal pathogenic/likely pathogenic variant. The affected genes in the primary and validation cohorts are shown in Table I in the Data Supplement.

Time to SCD Events

Over the 2855 total patient-years of follow-up, 53 patients experienced a SCD event, including 14 sudden deaths, 25 resuscitated sudden cardiac arrests, and 14 appropriate shocks in patients with primary prevention ICDs. No patients in the cohort were phenotype negative at the time of a SCD event. Of the 102 patients who received an ICD for primary prevention, 14 (13.7%) experienced an appropriate shock; 88 did not experience an appropriate shock; of 23 patients with >5 years of follow-up after ICD, 3 (13%) experienced an appropriate shock. Overall, 7 experienced an inappropriate shock. Inappropriate shock information was unavailable in 19 patients (Figure II in the Data Supplement). Figure III in the Data Supplement shows the indications for primary prevention ICD implantation with 63% patients receiving an ICD for a single indication. The median time to a SCD event from diagnosis was 2.2 years (interquartile range, 0.9–5.2), and median age at an SCD event was 14.5 years (interquartile range, 12.4–17.1). The cumulative proportion of SCD events at 1-year follow-up was 2.8% (95% CI, 1.4%–4.2%), and at 5 years was 9.1% (6.3%–11.9%) (Figure 1A).

Clinical Predictors of Time to SCD Events

The final clinical model included age at diagnosis, IVSD *z* score, LVPWD *z* score, LA diameter *z* score, peak LVOT gradient, nonsustained VT, and history of syncope. LA diameter *z* score was imputed in 21% patients in the overall cohort, and LVOT gradient was imputed in 29% patients in the overall cohort. Of the 53 patients who experienced a SCD event, LA diameter was imputed in 13%, and LVOT gradient was imputed in 17% patients. Our analysis suggested that a history of nonsustained VT increased the likelihood of experiencing SCD events by 2.8-fold (hazard ratio [HR], 2.87 [95% CI, 1.00–6.57]), and a history of syncope increased the likelihood of experiencing SCD events by 7.4-fold (HR, 7.40 [95% CI, 1.21–32.81]) (Table 2). A family history of SCD was not considered an important predictor either in the overall cohort or in the subset with familial HCM. Figure 2 shows the regression-adjusted association of the continuous risk factors with the composite outcome. Each panel summarizes the nonlinear association between a predictor and the SCD event. SCD risk increased with increased age at diagnosis, IVSD *z* score, LVPWD *z* score, and LA diameter *z* score. However, this positive correlation between IVSD and LVPWD *z* scores plateaued at a *z* score >20. In contrast, the risk associated with peak resting LVOT gradient remained flat when the gradient was ≤100 mm Hg and showed an inverse association with SCD risk as the gradient increased further. For example, an increase in peak LVOT gradient from 100 to 120 mm Hg reduced the SCD risk by ≈10%. There was no difference in the cumulative proportion of SCD events in patients with and without β-blocker use during follow-up (*P*=0.138) (data not shown). To further clarify the association with age, we compared outcomes in patients diagnosed before 5 years of age versus later (Table II in the Data Supplement). One-third of patients were diagnosed before 5 years of age. They had a higher frequency of non-SCD deaths and transplant than those diagnosed later, and these non-SCD events occurred at a median age of <1

Table 1. Clinical Characteristics of the PRIMaCY and SHaRe Cohorts

Clinical Characteristics	Number Ascertained	Variable* (PRIMaCY)	Number Ascertained	Variable* (SHaRe)	*P* Value
Age at first evaluation, y	572	9.8 (2.1–13.9)	285	13.8 (8.3–16.2)	<0.001
Male sex	572	394 (68.9)	285	199 (69.8)	0.81
Genetic testing done	572	311 (54.4)	285	166 (58.2)	0.315
Genetic testing results	311		166		0.024
Positive		160 (51.4)		108 (65.0)	
Inconclusive		66 (21.2)		27 (16.3)	
Negative		85 (27.3)		31 (18.7)	
Family history of hypertrophic cardiomyopathy	550	264 (48.0)	285	102 (35.8)	<0.001
Family history of SCD	572	105 (18.4)	206	29 (14.1)	0.196
Documented nonsustained ventricular tachycardia	572	18 (3.1)	88	7 (8)	0.037
History of unexplained syncope	572	17 (3.0)	285	6 (2.1)	0.51
Received β-blocker	565	336 (59.1)	284	127 (44.7)	<0.001
Echocardiographic features at diagnosis, *z* score					
Interventricular septal diameter	572	9.5 (5.0–16.8)	283	9.4 (4.7–16.7)	0.66
Left ventricular posterior wall diameter	566	2.4 (0.3–5.0)	269	2.4 (0.6–4.9)	0.43
Left atrial diameter	453	1.1 (0.1–2.1)	190	1.4 (0.3–2.5)	0.035
Peak resting left ventricular outflow tract gradient, mm Hg	401	13 (0.0–46.0)	90	10 (7–18)	0.81
Left ventricular outflow tract obstructed (qualitative)	121	19 (16)	175	40 (23)	0.141
Survival outcomes					
SCD events	572	53 (9.3)	285	22 (7.7)	<0.001
SCD	572	14 (2.4)	285	8 (2.8)	
Resuscitated sudden cardiac arrest	572	25 (4.4)	285	9 (3.2)	
Appropriate shock with prophylactic implantable cardioverter-defibrillator	572	14* (2.4)	285	5 (1.8)	
Incidence rate†					
Years from diagnosis	572	3.9 (1.5–6.7)	285	3.9 (1.6–7.4)	
Patient-years of follow-up	572	2855	285	1400	
Outcomes					
Event free	572	17.9	285	18.3	
SCD event	572	1.9	285	1.6	
Non-SCD death	572	3.2	285	0.5	

Numbers in parentheses indicate percent, unless otherwise indicated. PRIMaCY indicates Precision Medicine for Cardiomyopathy; SCD, sudden cardiac death; and SHaRe, Sarcomeric Human Cardiomyopathy Registry.

*Continuous variables were summarized using median and interquartile range; categorical variables were summarized using frequencies and proportions (%).

†Incidence rate refers to events per 100 patient-years of follow-up.

year. In contrast, early-onset HCM cases had an overall lower frequency of SCD events than those diagnosed later, but the median age at SCD events was not different, suggesting that the penetrance of SCD remains highest in adolescent and teenage years regardless of age at diagnosis. The overall lower frequency of SCD in early-onset cases may also be related, in part, to the higher non-SCD mortality and transplant in early life. There were no sex-related differences in the risk for SCD events.

Performance of the Clinical Prediction Model

The final clinical model was applied to the full cohort. The c-statistic was 0.75, indicating a good discriminatory power. Subjects were stratified by tertile of predicted risk, and the cumulative proportion of SCD events over time was plotted for each tertile (Figure 2F). The difference in the cumulative proportion of SCD events across strata of predicted risk was significant ($P<0.001$). Calibration (the agreement between

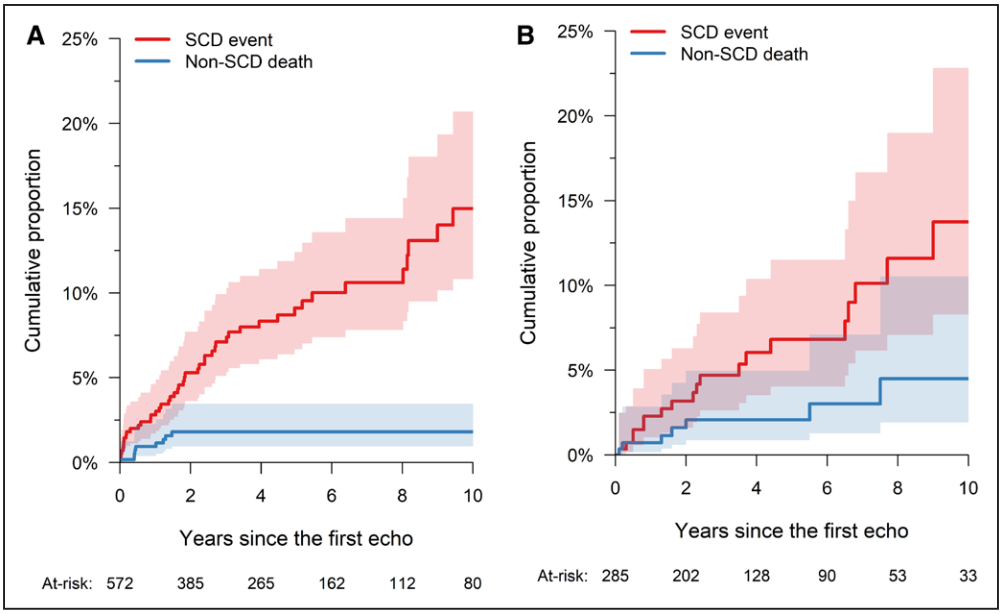

Figure 1. Cumulative proportion of SCD events estimated using competing risk models in PRIMaCY and SHaRe cohorts.
A, PRIMaCY cohort (n=572): The cumulative proportion of SCD events in patients with pediatric HCM at 1-year follow-up was 2.8% (95% CI, 1.4%–4.2%), at 5 years was 9.1% (95% CI, 6.3%–11.9%), and at 10 years was 15.0% (95% CI, 10.0%–19.7%). The cumulative proportion of death from other causes at 1-year follow-up was 0.9% (95% CI, 0.1%–1.8%), at 5 years was 1.8% (95% CI, 0.6%–3.0%), and at 10 years was 1.8% (95% CI, 0.6%–3.0%). **B**, SHaRe cohort (n=285): The cumulative proportion of SCD events at 1-year follow-up was 2.3% (95% CI, 0.5%–4.1%), at 5 years was 6.8% (95% CI, 3.2%–10.3%), and at 10 years was 13.7% (95% CI, 6.5%–20.4%). The cumulative proportion of death from other causes at 1-year follow-up was 0.7% (95% CI, 0.0%–1.7%), at 5 years was 2.1% (95% CI, 0.2%–3.9%), and at 10 years was 4.5% (95% CI, 0.6%–8.2%). Echo indicates echocardiogram; HCM, hypertrophic cardiomyopathy; PRIMaCY, Precision Medicine for Cardiomyopathy Study; SCD, sudden cardiac death; and SHaRe, Sarcomeric Human Cardiomyopathy Registry.

the magnitude of predicted risk versus observed risk) was assessed by stratifying predicted risk into tertiles and plotting the observed cumulative proportion of SCD events over time against the mean predicted risk for that tertile. This showed that subjects with predicted risk in the highest tertile had the highest observed cumulative proportion of SCD events and subjects in the lowest tertile of model-predicted risk had the lowest observed cumulative proportion of SCD events. The calibration curve in Figure 2G shows good agreement between predicted and observed 5-year cumulative proportion of SCD events for each tertile of predicted risk (Table 3).

Clinical and Genetic Predictors of Time to SCD Events

The first clinical/genetic model was generated using all clinical predictors discussed earlier along with a genotype-positive status. Similar to the clinical model, SCD risk was higher with a history of nonsustained VT (HR, 2.58 [95% CI, 1.00–6.17]), and a history of syncope (HR, 7.23 [95% CI, 1.09–33.57]). In addition, the presence of a pathogenic/likely pathogenic variant (ie, being genotype positive) elevated the likelihood of experiencing SCD events (HR, 1.32 [95% CI, 1.00–2.12]) in comparison with the confirmed absence of a pathogenic variant on genetic testing (Table 2). For continuous risk factors, Figure 3 shows the regression-adjusted effects of the predictors on the primary outcome with a relationship similar to the clinical model.

Performance of the Combined Clinical/Genetic Model

The final clinical/genetic model was applied to the full cohort to generate a cumulative proportion curve for 5-year incidence of SCD events. This showed the ability of the risk prediction model to discriminate between 3 tertiles of SCD risk similar to the clinical model ($P<0.001$) (Figure 3F). Figure 3G shows the calibration curve for the 3 risk tertiles with good agreement between predicted and observed SCD event–free survival with an overall c-statistic of 0.762, which was similar to the clinical model (Table 3).

Other Models Considered

Because the genes involved can influence the risk of SCD, we also explored the association of a pathogenic/likely pathogenic variant in *MYH7*, *MYBPC3*, or other HCM-associated genes, that is, gene-specific associations versus confirmed absence of a variant. The presence of a pathogenic/likely pathogenic variant in *MYBPC3* was associated with a higher risk of SCD events but the increase in risk was modest, with a HR, 1.022 (95%, 1.00–1.78). The c-statistic of this model was 0.726, which was lower than that of the

Table 2. Categorical Predictors of 5-Year Sudden Cardiac Death Risk

Model	Hazard Ratios (95% CI)
Clinical	
Prior history of nonsustained ventricular tachycardia	2.87 (1.00–6.57)
Prior history of syncope	7.40 (1.21–32.81)
Clinical/genetic	
Prior history of nonsustained ventricular tachycardia	2.58 (1.00–6.17)
Prior history of syncope	7.23 (1.09–33.57)
Pathogenic variant in any gene (reference: confirmed absence of variant)	1.32 (1.00–2.12)

first genetic model. Therefore, this model was not considered for further validation. The study was not powered to examine the effect of variant burden on SCD risk because only 2.8% patients harbored multiple pathogenic variants.

External Validation

For independent validation of the risk prediction models, we analyzed 285 phenotype-positive patients with childhood-onset HCM from SHaRe. There were minor differences in clinical characteristics between the SHaRe and the primary cohorts. The SHaRe patients were older at diagnosis, and the racial distribution was 89.6% White, 4.5% Asian, and 5.2% Black (Table 1). A higher proportion was genotype positive, a lower proportion was familial, and a higher proportion had nonsustained VT and higher LA diameter *z* scores at baseline. The type of SCD events are shown in Figure IV in the Data Supplement. The cumulative proportion of SCD events at 1-year follow-up was 2.3% (0.5%–4.1%), and at 5 years was 6.8% (3.2%–10.3%) with a total of 22 SCD events over a median follow-up of 3.3 (1.3–7.0) years (Figure 1B). The incidence of SCD events was not significantly different from the discovery cohort (*P*=0.57). Patients in the replication cohort were scored using both risk prediction models, and the performance of each model in the validation cohort was assessed. The c-statistic was 0.707 for the clinical model and 0.724 for the clinical/genetic model with acceptable agreement between the predicted and observed 5-year cumulative proportion of SCD events for both models.

DISCUSSION

The incidence of sudden cardiac death in pediatric HCM is significantly higher than in adults.[28] The 5-year risk of a SCD event in our study was 9.1%. However, only 25% received an ICD that was able to abort the event. The remaining patients either died without an ICD or received an ICD only after experiencing the event. In addition, of the 102 patients in the cohort who received a primary prevention ICD, 86% did not receive an appropriate shock including many who had a 5-year follow-up. This is comparable to adult studies and highlights a major gap in knowledge on how to risk stratify for sudden death in the pediatric population.[14,36,37] The practice guidelines to date have relied on adult markers for risk stratifying children and adolescents.[4] Using data from a multicenter consortium of pediatric HCM centers, we found important differences in risk factors between children and adults. Using age-specific risk factors, we developed and validated a pediatric SCD risk prediction model that can bridge this gap in knowledge and provide the evidence needed by clinicians to assist in decision making for SCD prevention. At present, only 1 in 9 prophylactic ICDs are appropriate implantations.[38] The use of a prediction tool has the potential to increase appropriate ICD implantation while reducing unwanted ICD implantation in a vulnerable population that is at higher risk of ICD complications because of their small size and physiological differences from adults.

To develop this model, we used an evidence-based approach to determine whether the conventional risk factors for SCD identified mostly through adult studies apply to children. Our analysis confirmed the positive association of age, history of syncope, nonsustained VT, LV wall thickness, and LA diameter with SCD risk, but also revealed some important differences between pediatric and adult risk factors. For example, although there was a linear relationship between septal thickness and SCD risk, the risk plateaued with massive septal hypertrophy suggesting that, unlike in adults, there was no clear septal *z* score threshold that conferred an independent risk of SCD. Also, there was no significant association between peak resting LVOT gradient with SCD, and there was an inverse association with SCD at very high gradients. This was likely not related to medication use because SCD event frequency was not different by β-blocker use. It is not clear if this could be related to a possible protective effect of septal myectomy in patients with high gradients.[9,39] The finding of a positive association of age with SCD risk is consistent with the known higher penetrance of SCD in adolescents and teenagers.[7] The overall lower frequency of SCD in early-onset cases may also be related in part to a lower survival into teenage years because of a higher non-SCD mortality and transplant in early life. The difference in outcomes is unlikely to be related to the presence of nonsarcomeric gene variants in younger patients (all of whom had isolated HCM at the time of diagnosis and follow-up) because nonsarcomeric gene variants accounted for <3% of early-onset cases. Our previous work has shown that the sarcomeric genotype itself can influence disease onset and severity with the affected sarcomeric gene, variant burden, and de novo status associated with earlier-onset HCM and lower

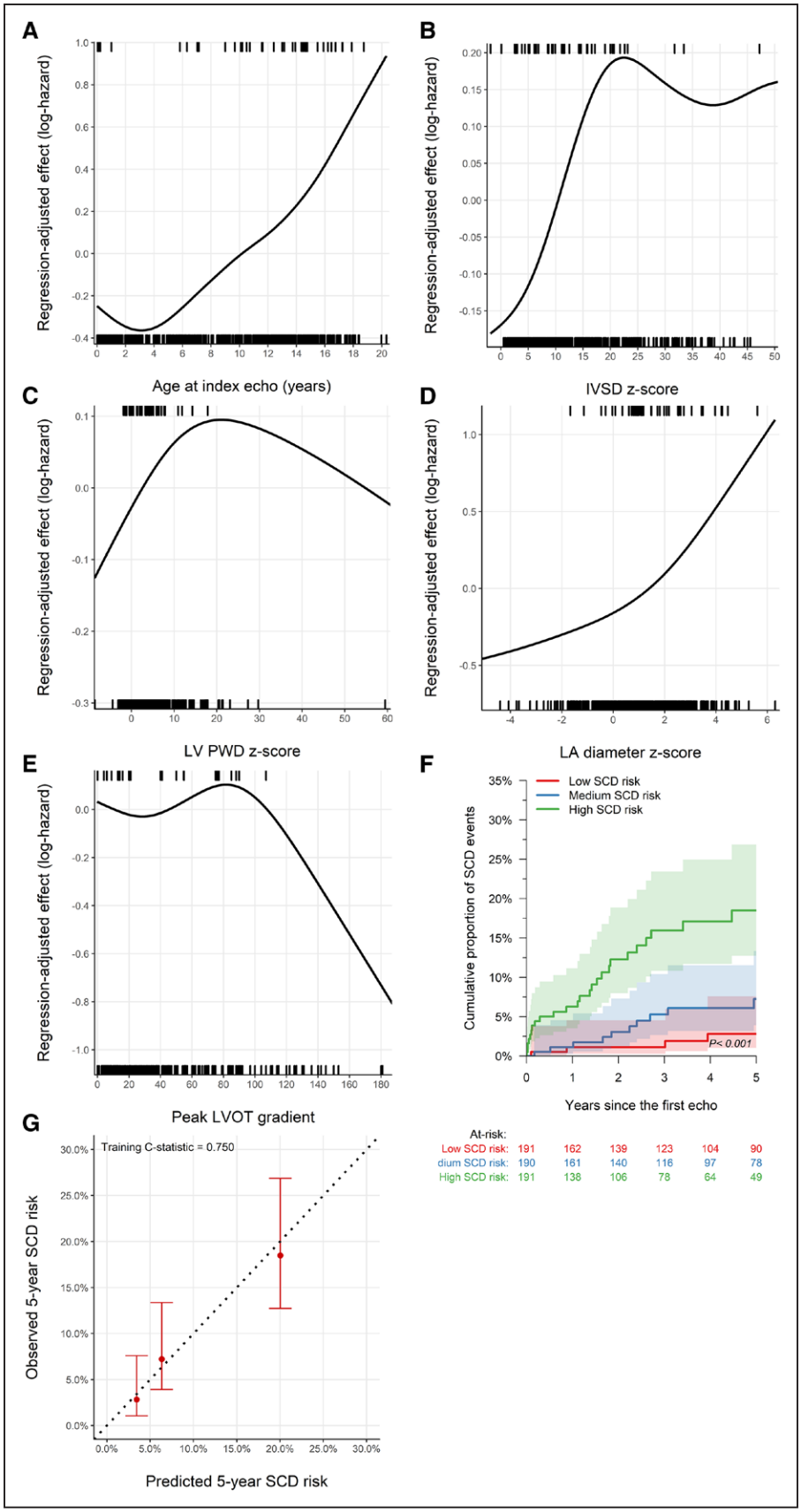

Figure 2. Regression-adjusted effects of continuous covariates and clinical SCD risk prediction model performance (n=572).
A through **E**, The top of each figure shows the observed values of the continuous risk predictor among patients with pediatric HCM in the training cohort who experienced the composite SCD outcome; the bottom shows the observed values of the predictor among those who did not experience (*Continued*)

Figure 2 Continued. the composite SCD outcome. SCD risk increased with age at diagnosis (**A**); increase in IVSD *z* score (**B**); LVPWD *z* score (**C**); and LA diameter *z* score (**D**). **E**, The risk associated with peak resting LVOT gradient remained flat when the gradient was ≤100 mm Hg and decreased as the gradient increased to >100 mm Hg. **F**, The cumulative proportion of SCD events stratified by tertiles of risk predicted by the clinical-only model, that is, predicted risk <4.7%, 4.7% to 8.3%, and >8.3%. **G**, The calibration curve for the clinical model applied to the training cohort shows the predicted versus the observed 5-year risk of the composite SCD outcome. The prediction accuracy, that is, c-statistic of the model, was 0.75. The dashed line, the 45° line through 0, represents a perfectly calibrated model between the observed and the predicted 5-year survival probabilities. Echo indicates echocardiogram; HCM, hypertrophic cardiomyopathy; IVSD, interventricular septal diameter; LA, left atrium; LVOT, left ventricular outflow tract; LVPWD, left ventricular posterior wall diameter; and SCD, sudden cardiac death.

freedom from not just SCD, but also the need for myectomy, transplant, or death.[40]

We noted that a family history of SCD did not emerge as a significant risk factor, which may be so for several reasons, including the often sporadic occurrence of childhood HCM, a higher likelihood that SCD events may not have manifested yet in young adult relatives of child probands, and the limitation in tracking all family SCD events in a retrospective study design. Furthermore, family history may be protective because it prompts screening, early diagnosis, and timely follow-up and interventions in family members. The lack of statistically significant associations between family history of SCD and LVOT gradient with SCD risk in childhood HCM is consistent with other recently published reports.[7,41–43]

Prior studies have reported that patients carrying at least 1 pathogenic/likely pathogenic variant were more likely to experience earlier disease onset and worse patient outcomes.[10,23,24,40,44,45] This aligns with our finding that genotype-positive individuals had a 1.3-fold higher risk of experiencing a SCD event than individuals who were genotype negative on genetic testing after accounting for all clinical risk factors. In a first attempt to incorporate genetic risk into the prediction model, we observed only a modest difference in prediction accuracy between the clinical and combined models. The failure to see a larger difference may be related to the limited uptake of genetic testing whereby only 54% patients had undergone genetic testing with less than one-third being genotype positive. We also explored the effect of incorporating affected gene and variant burden into the model but were likely underpowered to identify meaningful genotype-specific differences in SCD risk. Larger studies are needed to analyze and incorporate genotype-specific differences in risk predictions.

Last, our model provided a good prediction accuracy with a c-statistic of 0.75 in comparison with a recent study in a UK cohort where the c-statistic was 0.69 in the training set with no external validation.[28] The UK study included 5 preselected risk factors that were not reevaluated before inclusion in the model. Their model did not include age at diagnosis, and did not differentiate between IVSD and LVPWD *z* scores as independent predictors of SCD risk, but instead used maximal LV wall thickness in any segment. We reevaluated all potential risk factors to ensure that all evidence-based risk factors were included and the nonlinear relationship of the risk factors with SCD risk was incorporated into the model to improve its accuracy. We were able to externally validate the clinical and clinical/genetic models, as well, using an independent cohort. The predictive accuracy of both models remained >0.7, which is comparable in performance to the adult SCD risk calculator in clinical use.[18] The decrease in c-statistic in the validation cohort may have been related to a nonsignificantly lower SCD event rate attributable to a potential survivor bias, because the SHaRe validation cohort was composed predominantly of adult-age survivors of childhood-onset HCM.

Clinical Significance

There is an important potential for our findings to assist in clinical decision making to prevent one of the most tragic outcomes of pediatric HCM. Our study reports the only independently validated model for SCD risk prediction in pediatric HCM, and the only study that provides evidence from a large ethnically and geographically relevant North American pediatric cohort. Our findings reinforce that most SCD risk factors are not binary and that, in children, the decision for ICD

Table 3. Observed Versus Model-Predicted 5-Year Freedom From Sudden Cardiac Death (n=572)

Risk Group Categories	Risk Tertile, %	Average Predicted Risk, %	Observed Risk, %(95% CI)	C-Statistic
Clinical model				
Low risk	<4.7	3.4	2.8 (1.1–7.6)	0.750
Medium risk	4.7–8.3	6.3	7.2 (3.9–13.4)	
High risk	>8.3	20.0	18.5 (12.7–26.9)	
Clinical/genetic model				
Low risk	<4.7	3.3	1.9 (0.6–5.9)	0.762
Medium risk	4.7–8.3	6.2	7.6 (4.1–14.1)	
High risk	>8.3	20.0	18.8 (13.1–27.1)	

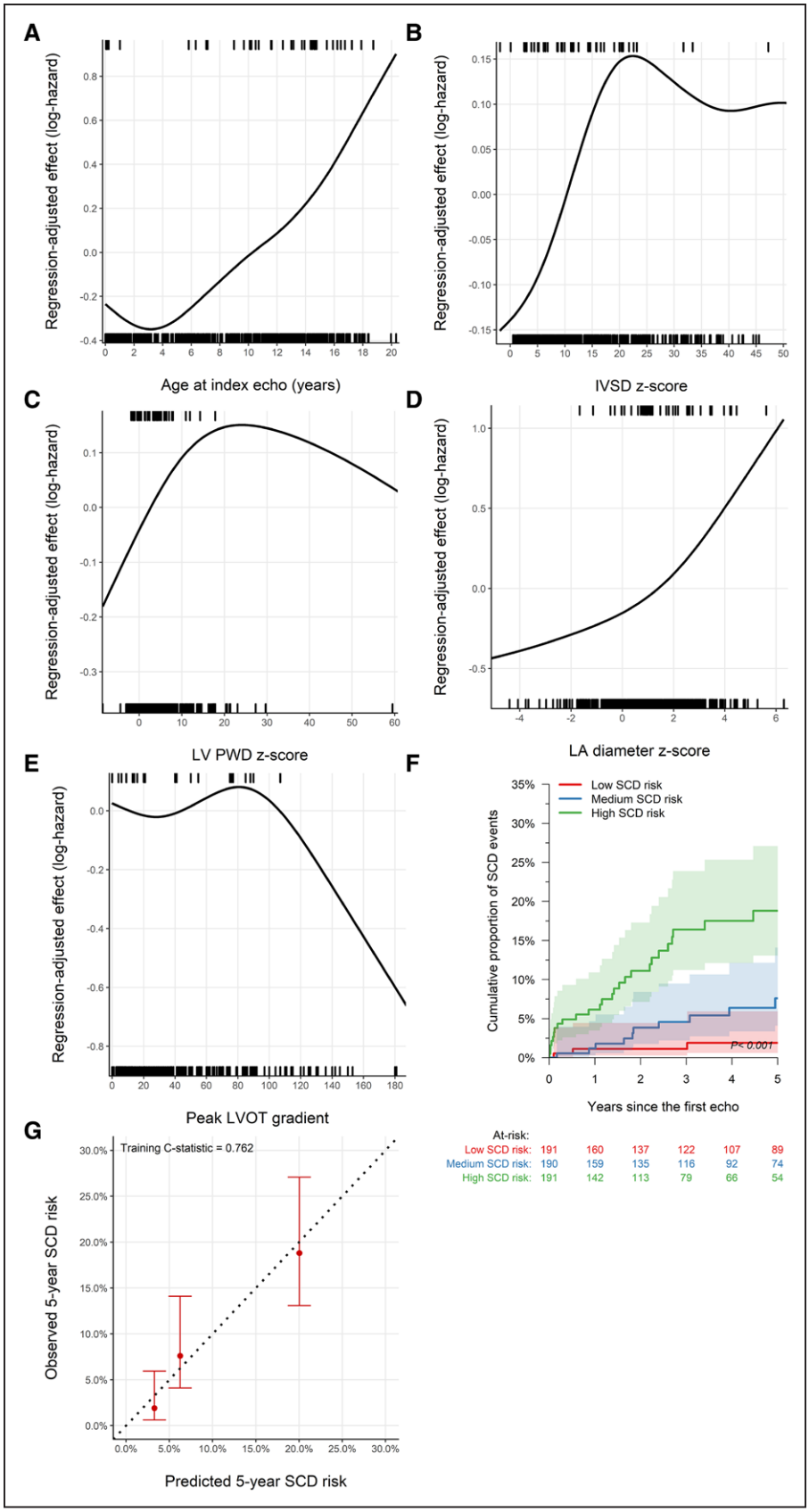

Figure 3. Regression-adjusted effects of continuous covariates and clinical/genetic SCD risk prediction model performance (n=572).
A through **E**, The top of each figure shows the observed values of the continuous risk predictor among patients with pediatric HCM in the training cohort who experienced the composite SCD outcome; the bottom shows the observed values of the predictor among those who did not experience the composite SCD outcome. SCD risk increased with age at first evaluation (**A**); increase in IVSD *z* score (**B**); LVPWD *z* score (**C**); and LA diameter *z* score (**D**). (*Continued*)

Figure 3 Continued. **E**, The risk associated with peak resting LVOT gradient remained flat when the gradient was ≤100 mm Hg and decreased as the gradient increased above 100 mm Hg. **F**, Cumulative proportion of SCD events stratified by tertiles of risk predicted by the clinical/genetic model, that is, predicted risk <4.7%, 4.7% to 8.3%, and >8.3%. **G**, The calibration curve for the clinical/genetic model applied to the training cohort shows the predicted versus the observed 5-year risk of the composite SCD outcome. The prediction accuracy, that is, c-statistic of the model, was 0.762. The dashed line, the 45° line through 0, represents a perfectly calibrated model between the observed and the predicted 5-year survival probabilities. Echo indicates echocardiogram; HCM, hypertrophic cardiomyopathy; IVSD, interventricular septal diameter; LA, left atrium; LVOT, left ventricular outflow tract; LVPWD, left ventricular posterior wall diameter; and SCD, sudden cardiac death.

should not be made on the basis of a single risk factor, especially given the higher ICD complication rates in this age group. The model ensures that all validated risk factors are considered in the decision-making process by using an unbiased approach.[46] The algorithm we have developed not only encapsulates practice recommendations but also provides an individualized estimate of 5-year sudden death risk that can be used in ICD shared decision making between patient and provider as opposed to a binary classification of high versus low risk. The American College of Cardiology/American Heart Association guidelines include the following class I recommendation, highlighting the emphasis on shared decision making for ICD between patients and providers: "The decision to place an ICD in patients with HCM should include application of individual clinical judgment, as well as a thorough discussion of the strength of evidence, benefits and risks to allow the informed patient's active participation in decision making."[4] Ultimately, this model has the potential for use as a decision support tool to facilitate ICD shared decision making through individualized risk prediction, and improve clinical outcomes through appropriate ICD use in high-risk patients.

Limitations

The study has limitations inherent to any retrospective analysis, that includes missing data, survivor bias, and lower uptake of genetic testing in the earlier era. Missing echocardiographic data were addressed through a re-review of echocardiograms where available and through imputation where this was not possible. We deliberately did not perform an echocardiographic core laboratory analysis because a real-world, point-of-care tool has to rely on locally acquired data. We did however standardize the calculations for *z* score measurements. Our study did not include emerging risk factors like late gadolinium enhancement on cardiac magnetic resonance imaging because of challenges related to the low yield of late gadolinium enhancement in children, lack of a clear definition for an abnormal cutoff especially in children, variability in cardiac magnetic resonance imaging use across centers, and the inability to perform this test in younger children without sedation that limits universal clinical use at this time. Atypical ventricular phenotypes such as apical aneurysm formation, which are rare in pediatric HCM, were also not included as risk factors. Although some patients harbored variants in nonsarcomeric genes like RASopathy-associated genes, we confirmed that patients were nonsyndromic at the time of clinical ascertainment and did not have a phenotype consistent with a syndromic, metabolic, or neuromuscular phenotype. We recognize that some appropriate ICD discharges may have been for self-terminating VT/ventricular fibrillation which can overestimate SCD. Antitachycardia pacing events were also not captured. Despite an acceptable predictive accuracy of our model at present, we recognize that childhood and adolescence are times of significant dynamic change in cardiac growth and phenotypic expression. Future iterations of the model will need to be dynamic and incorporate the trajectory of phenotypic change in HCM with time to further improve prediction accuracy.

CONCLUSIONS

The independently validated PRIMaCY model has >70% accuracy for SCD risk prediction in pediatric HCM. We anticipate that clinical uptake of this model of risk prediction will improve the application of clinical practice guidelines, facilitate shared decision making around ICD implantation through individualized risk prediction, and improve clinical outcomes through appropriate ICD use in high-risk pediatric patients while avoiding ICDs in low-risk patients. An important future goal will be to incorporate this model into hospital electronic health systems as a point-of-care tool for physicians and to assess the implementation effectiveness of this approach in the application of clinical practice guidelines.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Figures I–IV
Data Supplement Tables I–II

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