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Long-term Outcomes of Pediatric-Onset Hypertrophic Cardiomyopathy and Age-Specific Risk Factors for Lethal Arrhythmic Events

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IMPORTANCE Predictors of lethal arrhythmic events (LAEs) after a pediatric diagnosis of hypertrophic cardiomyopathy (HCM) are unresolved. Existing algorithms for risk stratification are limited to patients older than 16 years because of a lack of data on younger individuals.

OBJECTIVE To describe the long-term outcome of pediatric-onset HCM and identify age-specific arrhythmic risk factors.

DESIGN, SETTING, AND PARTICIPANTS This study assessed patients with pediatric-onset hypertrophic cardiomyopathy diagnosed from 1974 to 2016 in 2 national referral centers for cardiomyopathies in Florence, Italy. Patients with metabolic and syndromic disease were excluded.

EXPOSURES Patients were assessed at 1-year intervals, or more often, if their clinical condition required.

MAIN OUTCOMES AND MEASURES Lethal arrhythmic events (LAEs) and death related to heart failure.

RESULTS Of 1644 patients with HCM, 100 (6.1%) were 1 to 16 years old at diagnosis (median [interquartile range], 12.2 [7.3-14.1] years). Of these, 63 (63.0%) were boys. Forty-two of the 100 patients (42.0%) were symptomatic (defined as an New York Heart Association classification higher than 1 or a Ross score greater than 2). The yield of sarcomere gene testing was 55 of 70 patients (79%). During a median of 9.2 years during which a mean of 1229 patients were treated per year, 24 of 100 patients (24.0%) experienced cardiac events (1.9% per year), including 19 LAEs and 5 heart failure–related events (3 deaths and 2 heart transplants). Lethal arrhythmic events occurred at a mean (SD) age of 23.1 (11.5) years. Two survivors of LAEs with symptoms of heart failure experienced recurrent cardiac arrest despite an implantable cardioverter defibrillator. Risk of LAE was associated with symptoms at onset (hazard ratio [HR], 8.2; 95% CI, 1.5-68.4; $P = .02$) and Troponin I or Troponin T gene mutations (HR, 4.1; 95% CI, 0.9-36.5; $P = .06$). Adult HCM risk predictors performed poorly in this population. Data analysis occurred from December 2016 to October 2017.

CONCLUSIONS AND RELEVANCE Pediatric-onset HCM is rare and associated with adverse outcomes driven mainly by arrhythmic events. Risk extends well beyond adolescence, which calls for unchanged clinical surveillance into adulthood. In this study, predictors of adverse outcomes differ from those of adult populations with HCM. In secondary prevention, the implantable cardioverter defibrillator did not confer absolute protection in the presence of limiting symptoms of heart failure.

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Supplemental content

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A diagnosis of hypertrophic cardiomyopathy (HCM) in a child or adolescent is a potential marker of aggressive disease.[1] To date, however, pediatric populations are scarcely represented in the literature on this condition.[2] Prior studies addressing the outcome of pediatric-onset HCM have involved registry populations with heterogeneous causative mechanisms, including nonsarcomeric HCM mimics with diverse pathophysiology and outcomes.[3-6] Alternatively, reports have examined relatively small populations over short follow-up periods[7] or have included young adults with HCM who are aged up to 30 years.[8] Thus, critical issues such as long-term prognosis and predictors of lethal arrhythmic events (LAEs) after a pediatric diagnosis of HCM are unresolved.[1,2] In the present study, based on more than 40 years of observation, we assessed the outcome of patients with HCM who were diagnosed between 1 and 16 years of age, with specific emphasis on age-specific predictors of arrhythmic risk.

Key Points

Question What is the long-term outcome of pediatric-onset hypertrophic cardiomyopathy, and are there age-specific risk factors for lethal arrhythmic events?

Findings In this cohort study, 24 of 100 patients with hypertrophic cardiomyopathy diagnosed between age 1 and 16 years had major events in 9.2 years (mean rate, 1.9% per year), including 19 lethal arrhythmic events (at a mean [SD] age of 23.1 [11.5] years and up to 33 years after diagnosis) and 5 heart failure–related events. Risk was predicted by limiting symptoms at initial evaluation and Troponin I or T gene mutations.

Meaning Pediatric-onset hypertrophic cardiomyopathy is characterized by adverse outcomes driven mainly by arrhythmic events; risk extends well beyond adolescence, requiring unchanged levels of surveillance into adulthood, and predictors of risk in this age group differ from those of adult populations.

Methods

Study Population

We retrospectively reviewed patients diagnosed with HCM between ages 1 and 16 years from 1974 to 2016 at Meyer Children's Hospital and Careggi University Hospital in Florence, Italy.[9] Metabolic and syndromic causes of HCM were excluded (eMethods in the Supplement).[1] Patients were diagnosed after the onset of symptoms, detection of physical or electrocardiographic abnormalities, or in the context of systematic family screenings for HCM, which have been systematically recommended at the study health care centers for the last 3 decades.

The study was approved by Comitato Etico di Area Vasta in Florence. Parental informed consent was acquired at the study enrollment for all patients.

Definitions and Study End Points

Extreme left ventricular hypertrophy (LVH) was defined for patients younger than 12 years as the highest quintile of the cohort's left ventricular maximal wall thickness (ie, more than 18 SD); the adult cutoff value of 30 mm was used for all participants older than 12 years.[9] Limiting symptoms were defined as a Ross score greater than 2 or a New York Heart Association classification higher than level 1, as appropriate[10,11] (eMethods in the Supplement). Lethal arrhythmic events (LAEs) were defined as sudden cardiac death (SCD) or aborted cardiac arrest in patients who were successfully resuscitated or who received appropriate implantable cardioverter-defibrillator (ICD) shocks. Death related to heart failure was regarded as that occurring in the context of cardiac decompensation. Heart transplant was considered as a surrogate for heart failure–related death.

Statistical Analysis

Data analysis occurred from December 2016 to October 2017. Statistical analysis was performed using SPSS, version 21 (IBM Corporation) and R, version 3.3.1 (R Foundation). Data are expressed as percentages, mean and SD, or median with interquartile range (IQR) for skewed distributions. Survival analysis was performed with left truncation method when applicable (eMethods in the Supplement). Prognostic factors for LAE during the follow-up period were assessed by univariable analysis, and characteristics that were significantly ($P < .05$) or nearly significantly ($P < .10$) associated with LAE in the univariable analysis were first entered as candidate variables in a multivariate Cox proportional hazards regression analysis. The final multivariable model was selected using a backward-elimination algorithm (retention threshold $P < .05$) (eMethods in the Supplement).

Results

General Clinical Features

Of 1644 consecutive patients with HCM, 100 (6.1%) were diagnosed between 1 and 16 years of age. Of these, 63 (63.0%) were boys. The median age at diagnosis was 12.2 years (interquartile range [IQR], 7.3 to 14.2 years), and all except 2 were white (**Table 1**). Left ventricular hypertrophy (LVH) was asymmetric in 89 of 100 patients (89.0%), concentric in 7 patients (7.0%), and apical in 4 patients (4.0%). The mean (SD) maximum left ventricle (LV) wall thickness for the pediatric cohort was 21 (6) mm (z score, 12; relative to a base population of the same age, body mass index, and body surface area); this was similar in symptomatic and asymptomatic patients (20 [5] mm vs 21 [6] mm; $P = .43$). Only 32 of 100 patients (32.0%) were diagnosed because of presenting symptoms; another 68 (68.0%) were diagnosed because of abnormalities on screening or a family history of HCM. Genetic testing was available for 70 of 100 patients, with 55 of 70 (79%) carrying a pathogenic or likely pathogenic variant of a thick filament protein (46 of 70 [66%]) or Troponin I or Troponin T genes (9 of 70 [13%]) (Table 1; eTable 1 in the Supplement).

Forty-two patients (42.0%) had limiting symptoms at diagnosis, 7 (7.0%) experienced syncope, and nonsustained ventricular tachycardia occurred in 13 patients (13.0%). During the follow-up period, 17 of 100 patients (17.0%) received an ICD at a median age of 16 years (IQR, 12-33 years), of which 7 ICDs were for primary prevention and 12 for secondary prevention. Eight

Table 1. Characteristics of Patients With Pediatric-Onset Hypertrophic Cardiomyopathy, Grouped by Age at Diagnosis

Baseline Characteristic	No. (%)[a] Whole Cohort (n = 100)	≤12 y At Diagnosis (n = 44)	>12 y At Diagnosis (n = 56)	*P* Value
Demographic characteristics				
Age at diagnosis, y, median (IQR)	12.2 (7.3-14.1)	6.2 (1.1-9.9)	14.0 (13.4-15.5)	.01
Male	63 (63.0)	27 (61)	36 (64)	.83
Family history of HCM	44 (44.0)	25 (57)	19 (34)	.02
Family history of sudden cardiac death	19 (40.0)	10 (23)	9 (16)	.55
Medical history				
NYHA I or Ross score ≤2[a]	58 (58.0)	22 (50)	36 (64)	.04
NYHA II or Ross score 3-6	30 (30.0)	18 (41)	12 (21)	.12
NYHA III or Ross score 7 or 8	12 (12.0)	7 (16)	5 (9)	.31
Left ventricular outflow tract gradient, mm Hg, median (IQR)	8 (5-12)	7 (5-19)	9 (3-11)	.18
Left ventricular outflow tract gradient >30 mm Hg	16 (14.0)	10 (23)	6 (11)	.17
Syncope	7 (7.0)	2 (5)	5 (9)	.44
Angina	13 (13.0)	3 (7)	10 (18)	.14
Late gadolinium enhancement on cardiac magnetic resonance	6/35 (17)	4/12 (33)	2/23 (9)	.06
Nonsustained ventricular tachycardia	13 (13.0)	2 (11)	11 (20)	.01
Pseudo-STEMI electrocardiograph pattern	8 (8.0)	4 (9)	4 (7)	.84
Reason for presentation				
Symptoms	32 (32.0)	12 (27)	20 (37)	.44
Electrocardiograph abnormalities	20 (20.0)	8 (18)	12 (22)	.24
Heart murmur	15 (15.0)	5 (23)	10 (19)	.12
Family history of HCM	22 (22.0)	13 (30)	9 (17)	.31
Family history of sudden cardiac death	11 (11.0)	4 (9)	7 (13)	.18
Drugs				
β-Blockers	87 (87.0)	37 (84)	50 (89)	.65
Verapamil	6 (6.0)	5 (11)	1 (2)	.45
Amiodarone	4 (4.0)	3 (7)	1 (2)	.13
ACE inhibitor	7 (7.0)	2 (5)	5 (9)	.16
Genetic analysis				
Genotype positive	55/70 (79)	27/40 (68)	28/30 (93)	.04
MYH7	19/70 (27)	10/40 (25)	9/30 (30)	.78
MYBPC3	20/70 (29)	8/40 (17)	12/30(40)	.05
TNNT2/TNNI3	9/70 (13)	6/40 (10)	3/30 (10)	.78
MYL2	5/70 (7)	1/40 (3)	4/30 (13)	.12
MYH7 and MYBPC3	2/70 (3)	2/40 (12)	0	.06
Echocardiography				
Left atrial diameter, mm, mean (SD)	35 (7)	37 (7)	33 (8)	.45
Left atrial diameter, *z* score, median (IQR)	3 (2-5)	5 (3-11)	2 (1-3)	.01
LV ejection fraction, %, mean (SD)	65 (5)	65 (9)	68 (8)	.23
LV maximum wall thickness, mm, mean (SD)	21 (6)	20 (5)	22 (7)	.87
LV maximum wall thickness, *z* score, median (IQR)	12 (9-18)	15 (11-20)	11 (7-18)	.01
Extreme left ventricular hypertrophy	19 (19.0)	17 (39)	2 (4)	.01
Restrictive diastolic pattern	11 (11.0)	7 (16)	4 (7)	.45
Characteristics at final evaluation				
Follow-up duration, y, median (IQR)	9.2 (5.3-18.2)	13.4 (7.2-24.9)	7.6 (4.2-13.4)	.04
Age at last follow-up, y, median (IQR)	20.2 (16.4-29.8)	18.1 (14.5-32.6)	21.3 (18.1-27.5)	.01
Symptoms				
NYHA I or Ross score <2[b]	50 (50.0)	21 (47)	29 (52)	.04
NYHA >I or Ross score >2[b]	50 (50.0)	23 (53)	27 (48)	.28

(continued)

Table 1. Characteristics of Patients With Pediatric-Onset Hypertrophic Cardiomyopathy, Grouped by Age at Diagnosis (continued)

Baseline Characteristic	No. (%)[a] Whole Cohort (n = 100)	≤12 y At Diagnosis (n = 44)	>12 y At Diagnosis (n = 56)	*P* Value
Events				
Any cardiovascular event	24 (24.0)	18 (41)	6 (11)	.01
Lethal arrhythmic event	19 (19.0)	14 (32)	5 (9)	.01
Heart failure-related	5 (5.0)	4 (9)	1 (2)	.16
Annual mortality, %	1.9	2.6	1.1	
1 y	1	0	2	
5 y	5	3	8	
10 y	10	13	9	

Abbreviations: ACE, angiotensin converting enzyme; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; NYHA, New York Heart Association; STEMI, ST-elevation myocardial infarction.

[a] Continuous variables are expressed as mean and SD or with median and IQR when appropriate. Multiple measures are corrected by Bonferroni adjustment.

[b] Functional status of children 9 years or younger was evaluated using the Ross score; functional status of children older than 9 years was defined according to NYHA classification.

Table 2. Multivariate Predictors of Lethal Arrhythmic Events

Factor	Univariate Analysis HR (95% CI)	*P* Value	Multivariate Analysis HR (95% CI)	*P* Value
Age at diagnosis, y	2.3 (0.5-16.1)	<.01	1.2 (0.7-7.2)	.21
NYHA >I or Ross score >2[a]	34.1 (4.3-268.6)	<.01	8.2 (1.5-68.4)	.02
Syncope	2.1 (0.2-16.1)	.12	NA[b]	NA[b]
Extreme left ventricular hypertrophy	1.2 (0.4-4.8)	.76	NA[b]	NA[b]
Left ventricular ejection function <50%	5.6 (0.8-68)	.11	NA[b]	NA[b]
Restrictive diastolic filling	5.4 (1.3-21.2)	.02	0.40 (0.3-0.5)	.35
Troponin I or T gene mutation	21.1 (3.8-117.6)	<.01	4.1 (0.9-36.5)	.06
Nonsustained ventricular tachycardia	3.2 (0.9-11.1)	.07	0.6 (0.2-2.4)	.48

Abbreviations: HR, hazard ratio; NA, not applicable; NYHA, New York Heart Association.

[a] Estimates from univariable and multivariable Cox regression models predicting cardiovascular mortality and life-threatening arrhythmic events during the follow-up period in the 100 patients in the cohort.

[b] These data points were excluded from multivariate analysis.

patients (8.0%) underwent myectomy, and 7 (7.0%) developed systolic dysfunction (defined as an LV ejection fraction <50%). Only 1 sarcomere-negative patient (with a rare *JPH2* mutation) developed atrial fibrillation (eTable 1 in the Supplement).

Predictors of Outcome

During a median observation period of 9.2 years (IQR, 5.3 to 18.2 years) and a mean of 1228 patients per year, 24 of 100 patients (12 male and 12 female patients) had cardiovascular events, including 19 LAEs (14 SCD and 5 appropriate ICD shocks) and 5 heart failure-related events (2 heart transplants and 3 deaths). The annual event rate was 0.3% between ages 1 and 10 years, 3.6% between ages 11 and 20 years, and 2.1% between ages 21 and 35 years (eFigure in the Supplement). No events occurred in the 15 patients with negative genetic test results, compared with the 15 events experienced by 55 patients (27%) with genotype-positive test results.

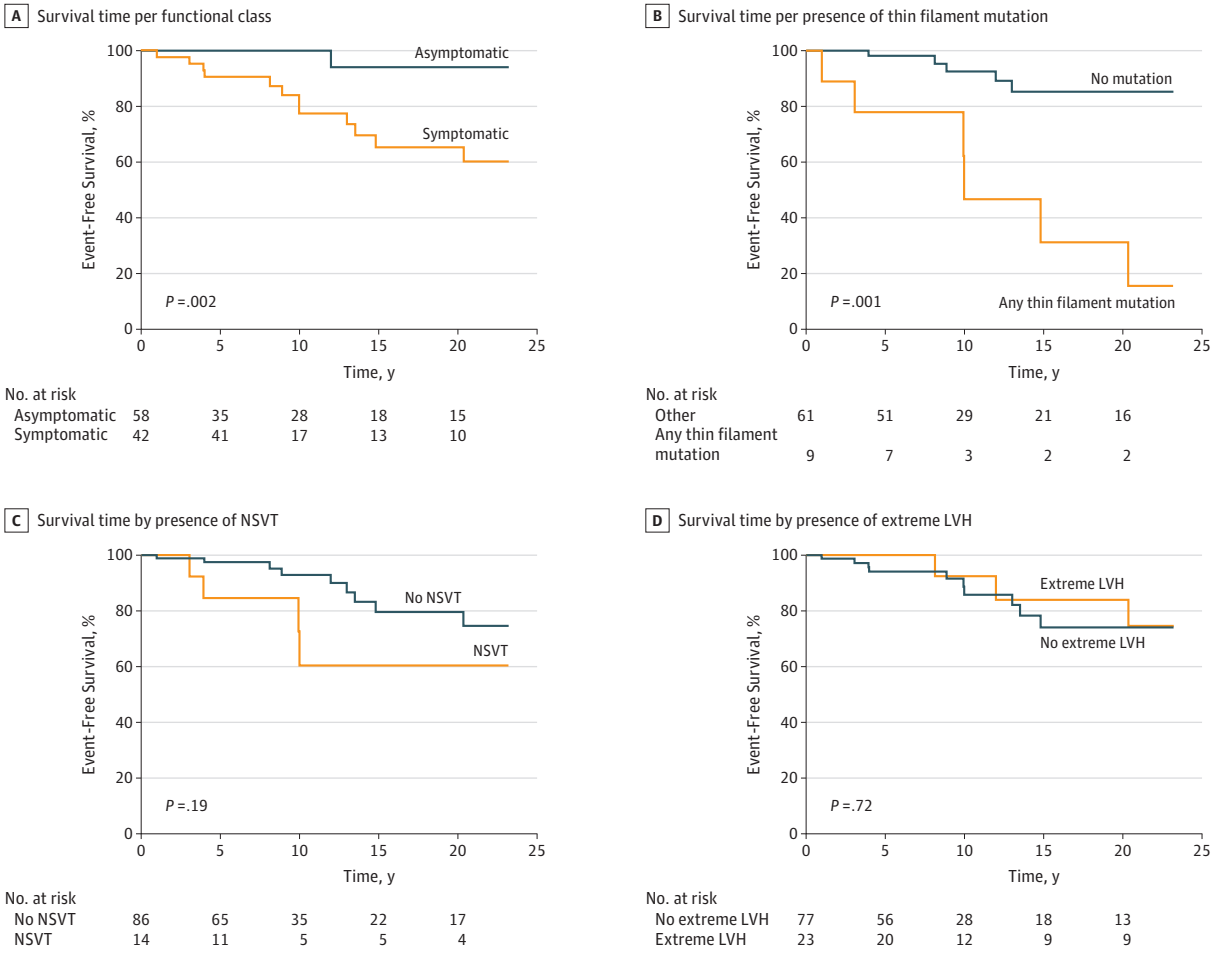
The incidence of LAE during the follow-up period was 1.5 events per 100 person-years. The mean (SD) age at first LAE was 23.1 (11.5) years; 8 of 19 events (42%) occurred at pediatric age (younger than 16 years), 6 of 19 events (32%) between ages 16 and 30 years, and 5 events (26%) after age 30 years (eFigure in the Supplement). Occurrence of LAEs was greater among patients who were diagnosed at or before age 12 years (Table 1), although age at diagnosis did not retain independent predictive value at multivariable analysis (hazard ratio [HR], 1.2; 95% CI, 0.7-7.2; *P* = .21). Only 1 of 58 children (2%) who were asymptomatic at initial clinical evaluation later experienced an LAE (0.27 events per 100 person-years); in comparison, of the 42 patients who were symptomatic at presentation, 18 (43%) later had an LAE (2 events per 100 person-years).

The risk of LAE was predicted by limiting symptoms at diagnosis (HR, 8.2; 95% CI, 1.5-68.4; *P* = .02), and Troponin I or T mutations (HR, 4.1; 95% CI, 0.9-36.5; *P* = .06). Neither extreme LVH nor syncope were associated with impaired survival (**Table 2**; **Figure**). Annual event rates were 0.2% in asymptomatic patients (1 patient experienced an event of 56 of 100 patients who were asymptomatic [56.0%]; 575 person-years), 2.0% in symptomatic patients without *Troponin I* or *T* mutations (35 of 100 [35.0%]; 515 person-years) and 5.0% in symptomatic patients with Troponin I/T mutations (9 of 100 [9.0%]; 138 person-years). Two patients, aged 10 and 11 years, both survivors of LAEs with restrictive evolution of hypertrophic cardiomyopathy and heart failure symptoms, experienced a cardiac arrest despite an ICD because of slow sustained ventricular tachycardia less than the defibrillation threshold (heart rate less than 130 beats per minute). Of these 2 patients, 1 died and the other underwent a successful heart transplant.

Discussion

Over the last 4 decades, a pediatric diagnosis of HCM was uncommon at our institution, accounting for 6% of more than

Figure. Predictors of Lethal Arrhythmic Events in Pediatric-Onset Hypertrophic Cardiomyopathy



Kaplan-Meier estimates of cumulative survival time free from the first lethal arrhythmic event during the follow-up period varied significantly based on the presence of limiting symptoms (New York Heart Association > 1 or Ross score > 2) and thin filament mutations. However, survival was not significantly influenced by nonsustained ventricular tachycardia or extreme left ventricular hypertrophy (maximal wall thickness >30 mm). Parts A, C, and D include all 100 participants; Part B includes the 70 patients who underwent genetic testing. Other indicates patients with any sarcomeric variant not affecting thin filament genes; LVH, left ventricular hypertrophy; NSVT, nonsustained ventricular tachycardia.

1600 patients with HCM, and pediatric onset represented a marker of extended severity. Outcomes were largely driven by LAEs (which accounted for 80.0% of all deaths at 1.5% per 100 person-years). Heart failure–related events were uncommon, consistent with previous studies.[1-7] Notably, only 42.0% of deaths actually occurred while patients were in the pediatric age range, and the event rate remained constantly high during the follow-up period, which ran well into adulthood. In total, about one-quarter of the events occurred when patients were older than 30 years.

Likelihood of arrhythmic events was poorly related to the classic risk factors introduced for adult patients with HCM, including extreme LVH and syncope. This is somewhat expected given that all known risk factors also have low positive predictive accuracy in adults. However, an impressive 79.0% of the patients in this study who experienced an LAE would not have been considered high risk under adult recommendations (eTable 2 in the Supplement).[9] Conversely, we were able to identify both limiting symptoms at diagnosis and disease-causing mutations in Troponin I and T genes as age-specific risk factors, carrying 8-fold and 4-fold increases in the risk of an LAE, respectively. Therefore, risk stratification in patients with pediatric-onset HCM may improve with detailed assessment of functional status as well as genotype.

Only 1 of 58 children (2%) who were asymptomatic at initial clinical evaluation later experienced an LAE (0.27 events per 100 person-years); of the 42 patients symptomatic at presentation, 18 (43%) later had an LAE (2 events per 100 person-years). This difference was likely associated with the severe structural substrate underlying heart failure in pediatric HCM. Despite the unquestionable value of the ICD,[12] we also observed 2 instances in which a device implanted for secondary prevention failed to prevent cardiac arrest in severely symptomatic children.

Our results with regard to Troponin T and I gene mutations are consistent with prior studies highlighting increased arrhythmic risk and likelihood of end stage progression.[13,14]

A recent study failed to show a difference in adverse outcomes in adult patients with HCM with thin vs thick filament gene mutations but identified greater degrees of myocardial fibrosis and diastolic impairment in the former.[15] In the children in this study, a thin filament genotype conveyed a distinctively worse prognosis associated with restrictive phenotypes, marked fibrosis, and severe arrhythmic propensity, possibly mediated by microvascular ischemia. Thus the debate on whether genotyping is clinically useful in HCM seems to be supported by evidence in favor of testing pediatric patients in view of its high yield and predictive value.

Limitations

We acknowledge that the size of the present study is too limited to allow generalization of our findings to the HCM population at large. The novel concept that risk stratification in children may be considerably different from the adult approach is important and warrants further investigation in the field, desirably in dedicated international registries.

Conclusions

Pediatric-onset HCM is rare and associated with adverse outcomes driven mainly by arrhythmic events. Risk extends well beyond adolescence, which calls for unchanged levels of surveillance into adulthood, and predictors differ from those of adult populations with HCM, suggesting an important role for genotype testing and assessing for limiting symptoms. In severely symptomatic children with a prior LAE, the ICD did not confer absolute protection, which warrants early consideration for heart transplant.

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