Characteristics and Longer-Term Outcomes of Contemporary Patients <18 Years of Age With Hypertrophic Cardiomyopathy

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We describe characteristics and outcomes of contemporary pediatric hypertrophic cardiomyopathy (PHC) patients. We studied 398 consecutive pediatric HC patients (<18 years, median 14 years, 65% boys) seen at our center between 2002 and 2018. Baseline clinical and pediatric echocardiographic data was collected. Left ventricular outflow tract gradient (LVOTG), LV fractional shortening and Z-score for left ventricular (LV) wall thickness were calculated. Sudden cardiac death (SCD), appropriate internal defibrillator discharge (ICD), myectomy, and orthotopic heart transplant (OHT) were composite primary endpoint. A total of 133 (33%) had symptoms (71 [18%] dyspnea, 77 [19%] angina, and 19 [5%] syncope), 109 (27%) were on beta-blockers; 179 (45%) had family history of HC. A total of 146 (37%) underwent genetic testing (of which 91 (62%) were HC-gene positive). Basal septal LV thickness, septal LV z-score and fractional shortening were 1.2 ± 0.6 cm, 4.8 ± 5.6, and 42% ± 8, whereas 23% had extreme LV hypertrophy (z-score > 6) and 8% had LVOTG >30 mm Hg (range 0 to 139 mm Hg). At a median of 5.9 years (interquartile range 2.4, 9), there were 23 (6%) ICD's placed, and 47 (12%) primary composite events (9 [2%] deaths, 3 [1%] appropriate ICD discharge, 29 [7%] myectomy, and 8 [2%] OHT). There were no in hospital deaths following myectomy/OHT. Presence of symptoms (Hazard ratio or HR 2.45), ventricular tachycardia (HR 1.52), and higher basal septal LV z-score (HR 1.10) were independently associated with primary composite outcomes. LV septal z-score >4 was independently associated with events on spline analysis. Rate of SCD/appropriate ICD discharge was 0.5%/year. In conclusion, contemporary PHC patients seen at an experienced center have excellent outcomes with presence of symptoms and higher LV septal thickness associated with primary composite events. **(Am J Cardiol 2021;140:110−117)**

Hypertrophic cardiomyopathy (HC) is a commonly inherited cardiomyopathy with a varied phenotypic expression ranging from asymptomatic to congestive heart-failure (CHF) to sudden cardiac death (SCD).[1,2] Children with HC are considered in the highest risk spectrum, especially for SCD, with previous reports suggesting an annualized mortality reaching up to 6%/year.[3−10] The last decade has seen a major evolution in HC management, including improved diagnosis and risk stratification tools, increased primary prevention ICDs, improved postcardiac arrest revival strategies, improved surgical techniques to relieve LVOT obstruction, and post-transplantation survival. This has resulted in significant reduction in HC-related adverse events reaching as low as 0.5%/year.[12] However, these observations were made in adult HC patients, and the data suggesting improved survival in children is less clear.[3−7] A previous report has suggested that with modern management, the event rate in younger HC patients is very low.[13] However, that study included young adults up to 30 years of age, with only a small proportion of truly pediatric patients (16%). In the current study, we sought to study characteristics and outcomes of pediatric HC patients, evaluated and managed at our referral center.

Methods

The study sample consisted of 398 consecutive HC patients (<18 years) evaluated at our tertiary care center, between 2002 and 2018. These patients are part of an institutional review board approved observational registry. Because of different pathophysiology, patients with metabolic and syndromic profiles were not included. Patients were diagnosed by experienced pediatric cardiologists based on symptoms, detection of physical or electrocardiographic abnormalities, or in the context of systematic family screenings for HC. The diagnosis of HC was made based on typical features, with ventricular myocardial hypertrophy in a nondilated LV, occurring in absence of any other disease responsible for hypertrophy.[1,2]

Baseline clinical data (including genetic testing, where available) were manually extracted from electronic medical records. New York Heart Association class was recorded. Follow-up information was collected by manual extraction from electronic medical records. Presence of atrial

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fibrillation (AF) was recorded, based on history, electrocardiograms, and Holter data. Nonsustained ventricular tachycardia (VT), wide complex tachycardia at ≥120 beats per minute, lasting >3 beats but <30 seconds or sustained VT, lasting >30 seconds were recorded, based on history and Holter data. Adult American College of Cardiology/American Heart Association (ACC/AHA) SCD risk factors were also recorded.[1]

Patients underwent surgical relief of LVOT obstruction for intractable symptoms (New York Heart Association class III-IV, angina, syncope) associated with severe LVOT obstruction despite maximal medical therapy. Patients with advanced symptoms (not related to LVOT obstruction), and intractable to maximal medical therapy underwent orthotopic heart transplantation. Final decision regarding surgical approaches was made after a consensus between experienced pediatric cardiologists and cardiothoracic surgeons. Date of surgery was recorded. Details of surgical techniques by our group have been described previously.[14−17] The basic technique of myectomy involved muscle resection below the membranous septum, removing muscle over both papillary muscles, and often extending to both trigones.

All patients underwent comprehensive pediatric echocardiograms using commercially available instruments (Philips, WA, General Electric, WI and Siemens, PA). All echocardiograms were interpreted by experienced pediatric cardiologists. Maximal end-diastolic LV wall thickness, LV dimensions, and left atrial area were measured according to guidelines.[18] Using previously published data, relevant z-scores were calculated for LV wall thickness and dimensions.[19] Extreme LVH was defined as any LV wall thickness z-score >6 and/or maximal LV wall thickness >3 cm.[1,2,8] Resting LVOT peak velocity was measured by continuous-wave Doppler echocardio graphy, and pressure gradient was estimated by using simplified Bernoulli equation. Care was taken to avoid contamination of LVOT waveform by MR. In patients with resting LVOT gradients <30 mm Hg, provocative maneuvers, including Valsalva and amyl nitrite were used. Maximal LVOT gradient was recorded, and defined as the highest recorded gradient (either resting or provoked) in a patient.[20] A subgroup of patients underwent a standard contrast enhanced cardiac magnetic resonance (CMR) examinations, as described previously, and presence or absence of late gadolinium enhancement (LGE) was ascertained.[21]

The duration of follow-up ranged between initial evaluations at our center to event/last follow-up. Death notification was confirmed by observation of death certificate or verified with a family member. In addition to clinical follow-up, we queried individual state and nationally available databases. The last query was performed in December 2018. Sudden death was defined as unexpected sudden collapse occurring <1 hour from symptom onset in otherwise stable patients.[22] In addition, we recorded successful resuscitation from cardiac arrest (aborted sudden deaths) or appropriate implantable cardioverter defibrillator (ICD) shocks (with electrogram reviews at our institution by pediatric electrophysiologists). Heart transplant was considered as a surrogate for heart failure−related death. Primary composite endpoint included death, aborted death, appropriate ICD discharge, heart transplant, and need for surgical myectomy. Death, heart transplantation, aborted death/appropriate ICD discharge were secondary (hard) endpoints.

Continuous variables are expressed as mean ± standard deviation and/or median (with interquartile range [IQR]) and compared using analysis of variance (normal distribution) or Mann-Whitney test (non-normal distribution), as appropriate. Categorical data are expressed as percentage and compared using chi-square. To assess for the association of various predictors with longer-term events, multivariable Cox proportional hazards analysis was utilized. Hazard ratios (HR) with 95% confidence interval (CI) were calculated. For univariable analysis, variables known to be associated with outcomes in HC patients were studied. Variables that had a significant ($p < 0.05$) association with primary events on univariable analysis were subsequently considered for the multivariable model. Also, the functional relationship between LV septal z-score and risk of events was assessed using penalized splines to estimate hazards in a Cox Proportional Hazards model. Relationship between exposure and response were described with the fitted splines and standard error bars with HR on the Y-axis and exposure in the X-axis. A rug plot is also displayed along the X-axis representing distribution of the underlying data. Using the splines, we estimated the appropriate cutoff of LV septal z-score associated with increased mortality (where the HR of 1 was crossed). Additionally, Kaplan-Meier curves were generated to determine the cumulative proportion of patients with events as a function over time, and compared using log-rank or Generalized Wilcoxon statistic, as appropriate. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, Illinois) and R 3.4.3 (R foundation for Statistical Computing, Vienna, Austria). A p-value of <0.05 was considered significant.

Results

The median age of the study sample was 14 years (IQR 10, 16 years), with 65% boys (32 [8%] patients <1 year in age). The clinical data as a whole, as well as separated on basis of median age, are shown in Tables 1and 2. Of the 146 patients who underwent genetic testing, 91 (62%) were HC gene positive and 36 (25%) had variance of unknown significance. The breakdown of different HC-related mutations was as follows: MYBPC3 (n = 50, 55%), MYH7 (n = 33, 36%), TNNT (n = 8, 9%). Older children had more symptoms, a higher proportion of medical therapy, greater LV dimensions and higher septal thickness. However, only 8% patients had a maximal LVOT gradient ≥30 mm Hg, with no differences between the 2 subgroups. Similarly, in the subgroup that underwent CMR, 46% had presence of LGE, with no significant differences within the 2 subgroups.

The median follow-up was 5.9 years (interquartile range 2, 9 years). In this time frame 29 (7%) patients underwent surgical myectomy to relieve severe LVOT obstruction which was intractable to maximally tolerated medical therapy (12 [7%] in those <14 years of age and 17 [8%] in those ≥14 years of age, p = 0.42). In addition, 8 (2%) patients underwent heart transplantation due to heart failure, without

Table 1
Baseline characteristics of study sample

Variable	Total (N = 398)	Age (years)		p-value
		<14 (n = 179)	≥ 14 (n = 219)	
Age (years)	12±6 (median 14, IQR 10,16)	7.4±5	16.2±2	<0.001
Men	257 (65%)	107 (60%)	150 (69%)	0.04
White	312 (78%)	146 (82%)	165 (76%)	0.18
Black	44 (11%)	15 (8%)	29 (13%)	
Other	42 (11%)	18 (10%)	24 (11%)	
Body surface area (m^2)	1.48±0.6	1.02±0.5	1.9±0.4	<0.001
Probands	222 (56%)	72 (32%)	150 (68%)	<0.001
Referred for family screening	176 (44%)	107 (61%)	69 (39%)	
Family history of HC	179 (45%)	88 (49%)	91 (42%)	0.10
Family history of SCD	43 (11%)	20 (11%)	23 (11%)	0.48
History SCD	10 (2%)	4 (2%)	6 (3%)	0.75
History of NSVT	17 (5%)	4 (6%)	3 (4%)	0.52
History of genetic testing performed	146 (37%)	73 (41%)	73 (33%)	0.08
HC gene positive (out of 146 gene testing performed)	91 (62% of those tested)	45/73 (62% of those tested)	46/73 (62% of those tested)	0.86
Beta-blockers	109 (27%)	35 (20%)	74 (34%)	<0.01
Calcium channel blocker	14 (4%)	4 (2%)	10 (5%)	0.16
ACE-I/ARB	17 (4%)	9 (5%)	8 (4%)	0.33
Angina pectoris	77 (19%)	27 (15%)	50 (23%)	0.03
Palpitations	42 (11%)	7 (4%)	35 (16%)	<0.001
Syncope	19 (5%)	3 (2%)	16 (7%)	0.007
NYHA Class				
I	327 (82%)	158 (88%)	169 (86%)	<0.01
II	34 (9%)	5 (3%)	29 (13%)	
III/IV	37 (9%)	16 (9%)	21 (10%)	
Symptomatic (dyspnea, syncope and/or angina)*	133 (33%)	28 (16%)	105 (48%)	<0.001
Adult ACC/AHA risk factors for SCD				
0	321 (81%)	151 (84%)	170 (78%)	0.18
1	72 (18%)	27 (15%)	45 (21%)	
2	5 (1%)	1 (0.3%)	4 (1%)	

* 76 patients had multiple presenting symptoms.

HC = hypertrophic cardiomyopathy; SCD = sudden cardiac death; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; ACC/AHA = American College of Cardiology and American Heart Association; ACE-I/ARB = Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker.

Table 2
Imaging parameters of study sample

Variable	Total (N = 398)	Age <14 years (n = 179)	Age ≥ 14 years (n = 219)	p-value
LV ejection fraction (%)	68±11	67±11	69±10	0.18
LV fractional shortening	42±8	43±8	42±8	0.29
LV end-diastolic dimension (cm)	4.26±1.0	3.6±1.	4.6±0.7	<0.001
LV end- diastolic dimension z-score	-0.97±0.1	-0.68±0.2	-1.21±0.2	0.002
Maximal basal septal LV thickness (cm)	1.15±0.6	0.98±0.5	1.30±0.6	<0.001
VS LV z-score	4.8±3	4.7±3	5.0±4	<0.001
Maximal posterior wall thickness (cm)	0.87±0.4	0.70±0.3	1.02±0.3	<0.001
Posterior wall z-score	2.1±1	2.0±0.9	2.1±1	0.12
Extreme LV hypertrophy (Any LV wall thickness z-score > 6)	91 (23%)	43 (24%)	48 (22%)	0.62
Maximal LV hypertrophy > 3 cm	10 (3%)	2 (1%)	8 (4%)	0.10
Systolic anterior motion of mitral valve	126 (32%)	43 (24%)	83 (38%)	<0.01
Resting LVOT gradient (mm Hg)	Median 7 (range 0-128 mm)	Median 6 (range 0-57 mm)	Median 7 (range 0-128 mm)	0.71
Maximal LVOT gradient (mm Hg)*	Median 11(range 0-139 mm Hg)	Median 7 (range 0-79 mm)	Median 13 (range 0-139 mm)	<01
Maximal LVOT gradient ≥ 30 mm Hg	31 (8%)	14 (8%)	17 (8%)	0.99
LGE present on CMR (out of 133 CMR's performed)	61/133 (46%)	19/61 (42%)	42/72 (48%)	0.55

LV = left ventricle; LVOT = left ventricular outflow tract; VS = ventricular septal; LGE = late gadolinium enhancement.

significant LVOT obstruction, intractable to maximal medical therapy (4 each in those <14 and ≥14 years of age, p = 0.52). There were no in-hospital deaths following either surgery. There were 23 (6%) transvenous ICD's placed for primary prevention (no epicardial), slightly lower proportion in those <14 years versus those ≥14 years of age (6 [3%] vs 17 [8%], p = 0.05). There were no complications recorded with ICD implantation. There were 9 (2%) deaths and 3 (1%) aborted sudden deaths with appropriate ICD discharges during longer-term follow-up. As a result, there were 47 (12%) primary and 19 (5%) secondary composite events.

The data on univariable and multivariable Cox Proportional Hazard analysis demonstrating data on association of various relevant predictors with primary composite events are shown in Table 3. Presence of symptoms, NSVT and a higher septal z-score were independently associated with primary composite events. A significantly higher proportion of symptomatic patients had primary composite events versus those who were asymptomatic (28/47 [60%] vs 105/35 [30%], log-rank p-value <0.01, Figure 1a).

Presence of symptoms (HR 3.49 [95% CI 1.04, 7.98], p = 0.04) and higher LV septal Z-score (HR 1.08 [95% CI 1.02 to 1.15], p = 0.03) were also independently associated with secondary composite endpoints on multivariable Cox Proportional Hazard analysis. Of note, adult ACC/AHA SCD risk factors (none vs ≥1) were not associated with secondary composite outcomes (HR 1.69 [95% CI 0.21 to 3.94], p = 0.58). Also, a significantly higher proportion of symptomatic patients had secondary composite events versus those who were asymptomatic (11/19 [58%] vs 122/379 [32%], log-rank p-value <0.01, Figure 1b). In the subgroup of patients who underwent a CMR (n = 133), presence of LGE was associated with higher proportion of secondary composite events (n = 7) on univariable Cox Proportional Hazard analysis (HR 1.89 [95% CI 1.02, 6.84], p = 0.04). However, in the subgroup of patients who underwent genetic testing (n = 146), gene-positive status was not associated with secondary composite events on univariable Cox Proportional Hazard analysis (HR 1.88 [95% CI 0.42, 8.50], p = 0.52).

Subsequently, to test the functional relationship between LV septal thickness-score and risk of events (and establish clinically applicable cut-off), we performed spline analysis. We demonstrate that the risk of both primary (Figure 2a) and secondary (Figure 2b) composite events increased significantly beyond an LV septal thickness z-score of 4. A significantly higher proportion of patients with an LV-septal thickness z-score ≥4 had primary composite events versus those who with z-score <4 (41/47 [87%] vs 152/351 [43%], log-rank p-value <0.01, Figure 3a). Similarly, a significantly higher proportion of patients with LV-septal thickness z-score ≥4 had secondary composite events versus those who were asymptomatic (14/19 [74%] vs 79/379 [47%], log-rank p-value <0.01, Figure 3b).

Of note, on univariable Cox Proportional Hazard analysis, LV septal z-score (HR 1.05 [95% CI 1.01 to 1.17], p = 0.04) and age <1 year at diagnosis (HR 1.07 [95% CI 1.02 to 1.16], p = 0.03) were significantly associated with a composite endpoint of sudden death (including aborted sudden death) or appropriate ICD discharge (number of events 12).

Discussion

In the current study of a large group of HC patients ≤18 years of age, we demonstrate that only 33% patients were symptomatic (a higher proportion in the subgroup older than the median age of 14 years of age) and a similar proportion were on appropriate medical therapy. During follow-up, 6% had a primary prevention ICD, whereas 7% and 2% had surgical myectomy and cardiac transplantation, respectively. There were no in-hospital procedural/surgical deaths and a total of 3% hard events (death ± appropriate ICD discharge) during follow-up (approximately 0.5%/year). As would be expected, only 1 in 5 patients had at least 1 major adult ACC/AHA SCD risk factor. However, standard ACC/AHA SCD risk factors were not significantly associated with primary or secondary events.

In adults, if evaluated diligently using various provocative maneuvers, an elevated LVOT gradient is observed in ~70% HC patients,[23] providing incremental prognostic value[24,25] and an improved survival in patients with NYHA

Table 3
Univariable and multivariable Cox Proportional Hazard Analysis in the study sample (n = 398) for longer-term primary composite endpoints (n = 47)

Variable	Univariable		Multivariable	
	Hazard ratio	p-value	Hazard ratio	p-value
Age	1.01 [0.96-1.07]	0.60		
Age <1 year vs. older	1.26 [0.38-4.14]	0.70		
Male	1.07 [0.58-1.99]	0.83		
Proband vs. referred for family screening	1.63 [0.81-2.97]	0.18		
Family history of HC	1.77 [0.88-3.56]	0.12		
Family history of sudden death	1.16 [0.41-3.29]	0.78		
Symptoms of dyspnea/angina/syncope	3.13 [1.73-5.66]	<0.001	2.45 [1.40-4.30]	<0.001
History of NSVT	1.30 [1.07-1.57]	0.008	1.52 [1.22-1.89]	<0.01
Adult ACC/AHA SCD risk factors	1.50 [0.83-2.23]	0.17		
LV fractional shortening	1.03 [0.97-1.09]	0.24		
LV septal thickness z-score	1.12 [1.07-1.16]	<0.001	1.10 [1.02-1.18]	0.006

HCM = hypertrophic cardiomyopathy; SCD = sudden cardiac death; NSVT = nonsustained ventricular tachycardia; ACC/AHA = American College of Cardiology and American Heart Association; LV = left ventricle.

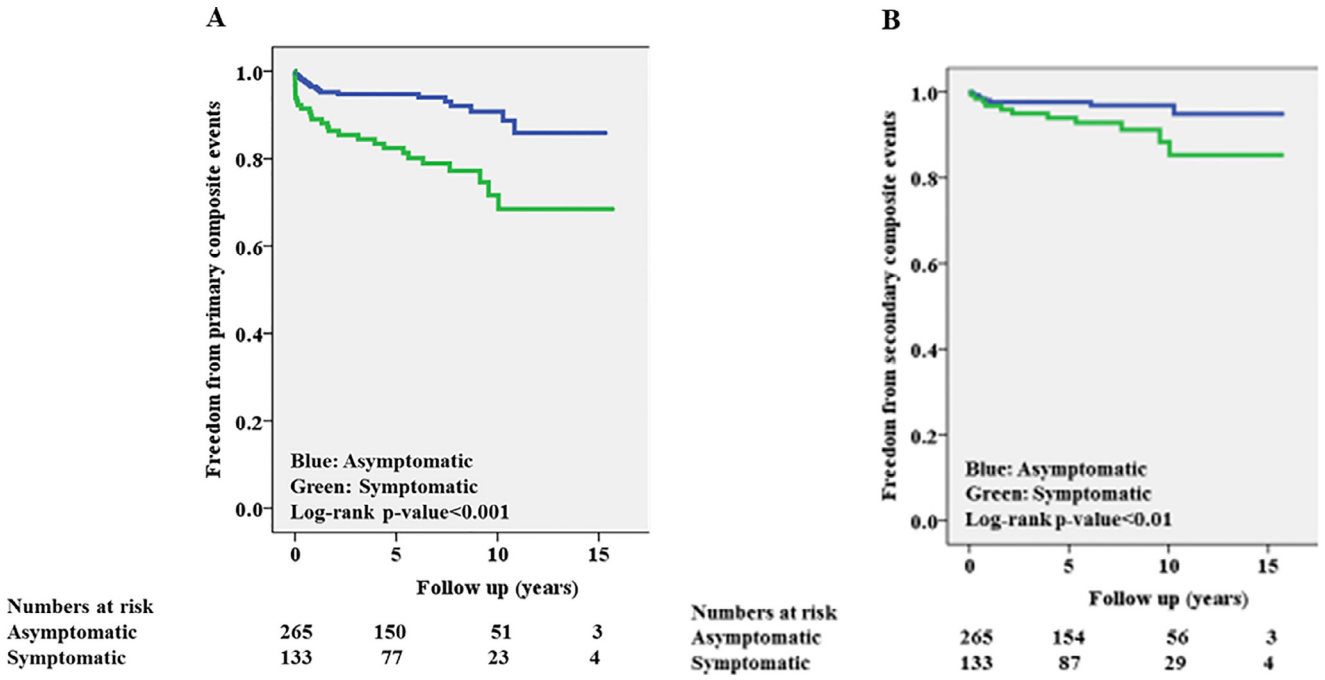

Figure 1. Kaplan-Meier survival curves demonstrating long term primary (a) and secondary (b) outcomes of the entire study sample (n = 398), separated on basis of presence or absence of symptoms at presentation.

Class I versus those with Class II and III/IV.[25] Whereas not uniformly performed in the pediatric population, provokable maneuvers to elicit LVOT gradients appear safe (at least in our experience) and should be considered in during echocardiography, especially in those with basal septal hypertrophy. Indeed, in our study sample, 7% patients had surgical myectomy to relieve severe symptomatic LVOT obstruction with excellent results.

From the perspective of future risk, the current study demonstrates that simple extrapolation of risk factors derived from adults (like the ACC/AHA risk factors) may not be appropriate in children; and we would have to develop tailored risk stratification tools. Indeed, an important adult risk factor of massive LVH (>3 cm) was only observed in a small proportion of patients. However, based on spline analysis, we demonstrate that an LV septal z-score >4 (which would fall below the "massive LVH" threshold of a z-score>6 in vast majority of children) was independently associated with primary and secondary events. In addition, LGE might potentially have a role in

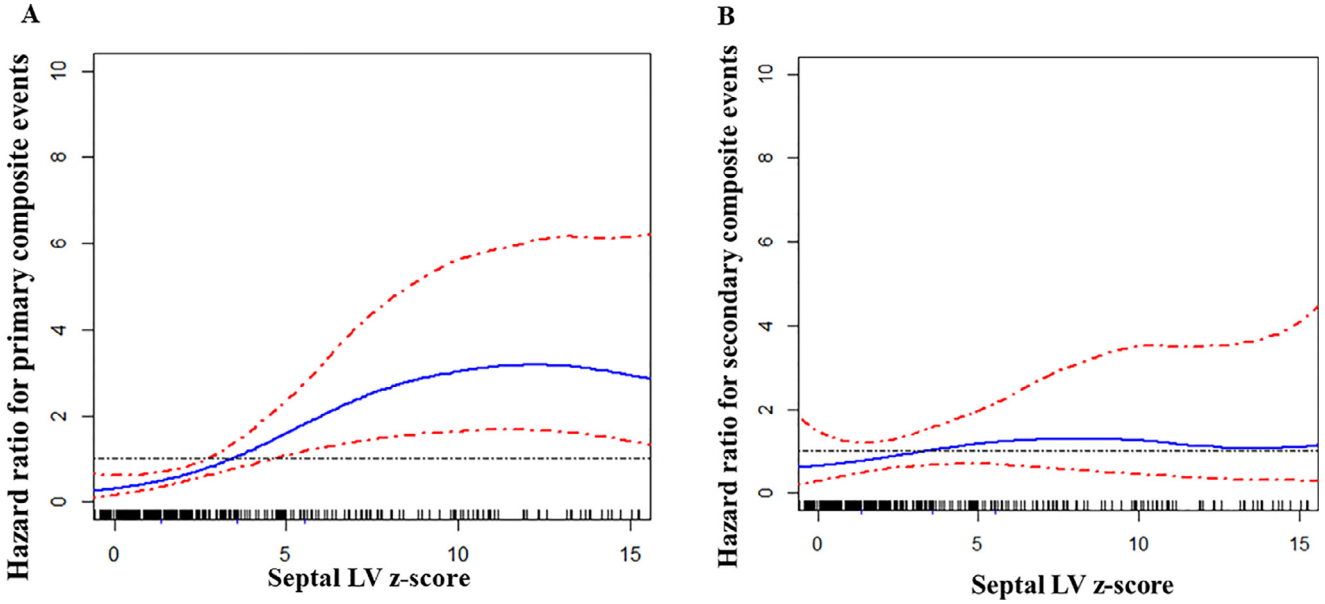

Figure 2. Penalized spline analysis testing the functional relationship between primary (a) and secondary (b) composite events and LV septal z-score. Abnormal cutoff is assumed where the hazard ratio of 1 is crossed. Please see text for details. In the current sample, an LV septal z-score ≥4 was associated with increased longer-term risk of primary or secondary composite events.

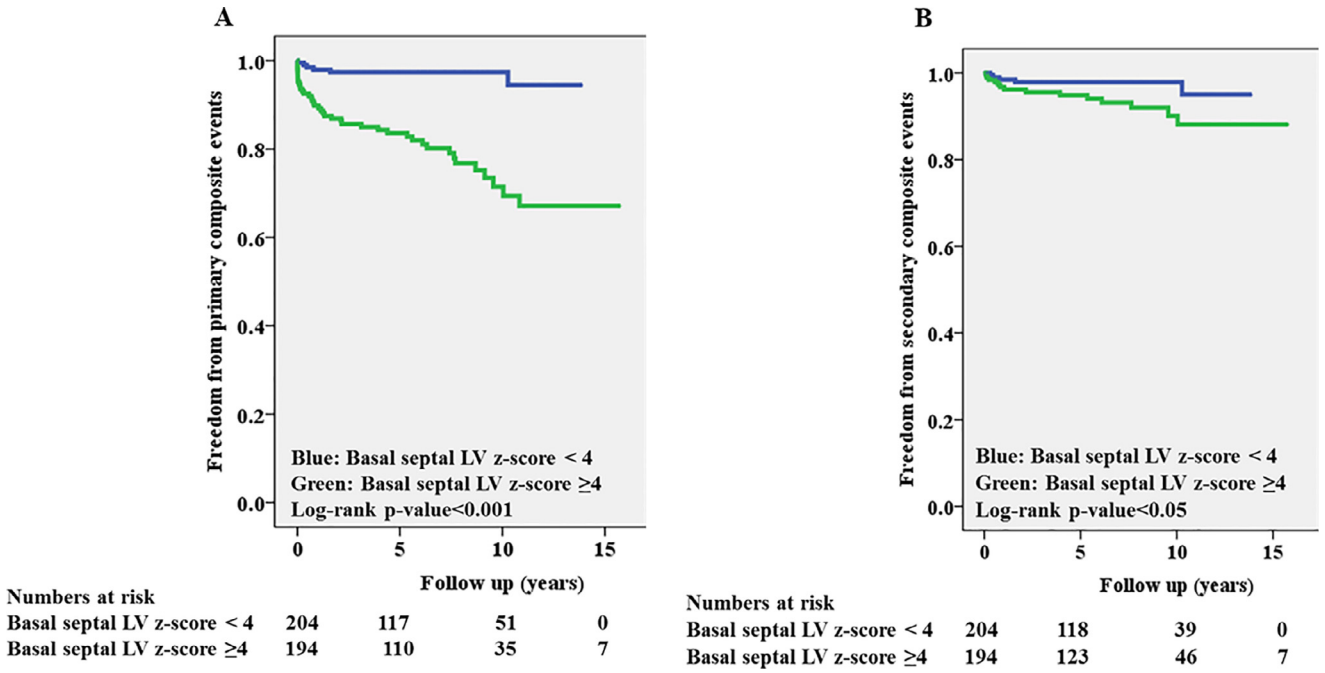

Figure 3. Kaplan-Meier survival curves demonstrating long term primary (a) and secondary (b) outcomes of the entire study sample (n = 398), separated on basis of LV septal z-score higher or lower than a cutoff of 4 (derived from spline analysis in Figure 2).

risk stratification. However, these data need further validation

Younger HC patients have typically been considered in the highest risk spectrum, especially for SCD. Indeed, previous reports have suggested that the annualized mortality in children with HC reached upto 6%/year.[3–9] In addition, a substantial amount of attention has been paid to HC-related deaths in younger individuals, as it often includes competitive athletes, often in peak physical shape.[11] The last decade has seen a major evolution in all facets of HC management, including improved diagnosis and risk stratification tools, increased primary prevention ICDs, improved postcardiac arrest revival strategies, improved surgical techniques to relieve LVOT obstruction, and post-transplantation survival. As a result, overall hard-event rate has dropped significantly to ~0.5%/year, similar to the current study.[12]

A previous report has also suggested that with modern management protocols, the hard event rate in younger HC patients is similar to what is reported in the current study. There were important differences between the 2 studies. That study included young adults up to 30 years of age, with only a small proportion (16%) less than 19 years of age.[13] In addition, ACC/AHA risk factors provided prognostic value, likely because majority (84%) of the patients were adults over 19 years of age. However, unlike another previous report from Italy, presence of a specific HC-related genetic mutation was not associated with primary or secondary outcomes in our study.[9] This might reflect regional and ethnic differences, as Italian population tends to be more homogeneous and Caucasian than average Americans. Indeed, in our study ~20% patients were non-Caucasian. Another report studied 411 pediatric HC patients and similar to the current study, demonstrated that adult risk stratification did not provide incremental prognostic value. However, it did not report pediatric specific criteria associated with longer-term events.[10]

This was an observational study from a single tertiary center, with potential selection bias. The results of testing were available to all clinicians at the time of decision-making, introducing further bias. CMR was not uniformly performed hence its detailed association with outcomes (including LGE quantification) is not presented. The current study only tests associations, not causality. Because the sudden death risk score recommended by European Society of Cardiology has been previously shown to be ineffective in pediatric HC population, we did not report that in the current study.[10] An argument can be made that, in terms of outcomes, myectomy should not have the same weight as harder endpoints of death, appropriate ICD discharge, or heart transplantation. However, undergoing heart surgery, especially for a child is a major psychological ordeal with long-term implications. However, the basic results were similar even if hard endpoints (death and appropriate ICD discharge) were included. We did not report survival analysis of individual events due to small numbers.

In a large group of HC patients' ≤18 years of age, we demonstrate that 1 presence of symptoms and higher LV septal thickness were independently associated with events. With modern management protocols, including pediatric surgical myectomy and primary prevention ICD, longer-term event rate was very low. Simple extrapolation of risk factors derived from adult HC patients may not be appropriate in children; and we need to develop tailored risk stratification tools for children. However, these data need further validation.

Credit Letter

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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