

Risk factors for Sudden Cardiac Death in Childhood Hypertrophic Cardiomyopathy: A systematic review and meta-analysis.

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Abstract

Aims: To perform a systematic literature review and meta-analysis of clinical risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy.

Methods: Medline and PubMed databases were searched for original articles published in English from 1963 through to December 2015 which included patients under 18 years with a primary or secondary end-point of either sudden cardiac death (SCD) or equivalent (aborted cardiac arrest or appropriate ICD discharge) or cardiovascular death (CVD).

Results: Twenty five studies (3394 patients) met inclusion criteria. We identified four conventional major risk factors which were evaluated in at least 4 studies and found to be statistically associated with an increased risk of death in at least 2 studies: previous adverse cardiac event (pooled hazard ratio 5.4 (95% CI 3.67-7.95), $p < 0.001$); non-sustained ventricular tachycardia (pooled hazard ratio 2.13 (95% CI 1.21-3.74), $p = 0.009$); unexplained syncope (pooled hazard ratio 1.89 (95% CI 0.69-5.16), $p = 0.22$); and extreme left ventricular hypertrophy (pooled hazard ratio 1.80 (95% CI 0.75-4.32), $p = 0.19$). Left atrial diameter did not meet the major risk factor criteria, however is likely to be an additional significant risk factor. 'Minor' risk factors included a family history of sudden cardiac death, gender, age, symptoms, ECG changes, abnormal blood pressure response to exercise and left ventricular outflow tract obstruction.

Conclusions: A lack of well-designed, large population based studies in childhood hypertrophic cardiomyopathy means the evidence-base for individual risk factors is not robust. We have identified four clinical parameters which are likely to be associated with increased risk of SCD, SCD-equivalent event or CVD. Multi-centre prospective studies are needed to further determine their relevance in predicting SCD in childhood HCM and to identify novel risk markers.

Condensed abstract:

A systematic review and meta-analysis of clinical risk factors predicting sudden cardiac death (SCD) in childhood hypertrophic cardiomyopathy (HCM) was performed identifying four 'major' factors: previous adverse cardiac event; non-sustained ventricular tachycardia; syncope and extreme left ventricular hypertrophy. Well-designed multi-centre studies are required in the future to confirm these findings.

Background

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy (LVH) in the absence of loading conditions (hypertension, valve disease or congenital heart disease) sufficient to cause the observed abnormality¹. The true prevalence of HCM in childhood is unknown but is estimated to be in the region of 2.9 per 100,000²⁻⁴. The aetiology of paediatric HCM is heterogeneous, and includes inborn errors of metabolism, malformation syndromes and neuromuscular disorders. However, most cases of HCM are caused by mutations in cardiac sarcomere protein genes, even in young children^{5,6}.

The long-term prognosis of HCM in childhood is highly variable and depends to a large degree on the underlying aetiology. Estimates for sudden cardiac death (SCD) rates in childhood HCM vary widely and recent epidemiological studies have reported rates of between 1 and 7.2% per year⁷⁻¹². One of the greatest challenges in managing young patients with HCM is the identification of individuals at highest risk of adverse events. Risk factors for SCD in adult HCM patients are well described and, recently, a novel risk model (HCM RISK-SCD) has been developed to improve the targeting of implantable cardioverter-defibrillators (ICDs)¹⁴. However, this is not validated for patients under 16 years of age and the value of conventional “adult” risk markers in children is uncertain. ICDs have been shown to be effective at aborting malignant arrhythmias in childhood HCM^{8,13} but this is at the expense of a much higher rate of complications compared to adults¹⁵. This highlights the need for a greater understanding of risk factors for SCD in childhood HCM to allow clinicians to robustly identify patients for primary prevention therapy. We, therefore, performed a systematic review and meta-analysis of the published literature to evaluate published risk factors in childhood HCM.

Methods

Study selection

The online MEDLINE database was searched using PubMed through the *MeSH* (Medical Subject Headings) terms “((hypertrophic cardiomyopathy) AND (death OR sudden death OR cardiac death OR outcome OR prognosis OR risk factors) AND (children OR childhood OR young OR paediatric)). All searches were limited to: original articles written in English, patients <18 years, published from 1963 through to December 2015. This initial search strategy was supplemented by a manual search of the references for included papers and the most recent review articles.

Inclusion criteria

Studies reporting on a cohort of HCM patients with a primary or secondary end-point of either sudden cardiac death (SCD), SCD-equivalent event (aborted cardiac arrest or appropriate ICD discharge) or cardiovascular death (CVD) were included. Studies with an end-point of CVD secondary to heart failure alone were excluded.

We required that studies explored possible associations between clinical risk factors and survival, therefore studies with no estimates of association were excluded (this included case-reports and letters). We excluded those in which the patient cohort were exclusively infants (<1 year), or had a mixed adult and paediatric population with <75% of cohort under 18 years without separate analysis of paediatric data, or limited to rarer phenocopies such as Noonan syndrome or related disorders. As the study focused on clinical risk factors, studies exploring the use of genotyping or invasive markers to predict survival were excluded.

Data collection:

The titles and abstracts of all studies identified by the search strategy were reviewed by two independent researchers (GN and NC) to determine eligibility. All eligible studies were read in full by the same two independent researchers. The following data were extracted from all included

studies: patient characteristics (age and sex); study design; risk factor definition; length of follow up and number of patients lost to follow-up; univariate and/or multivariable Cox regression analysis; event count data and type of endpoint (SCD, SCD-equivalent event, CVD). A quality assessment for each included study was performed in line with the QUORUM (Quality of Reporting of Meta-analyses) statement¹⁶.

Survival analyses were not reported in all studies and for these count data were extracted in order to compute odds ratios for SCD. For the major risk factors, pooled estimates for the hazard ratio and/or odds ratio are reported. Average hazard ratios/odds ratios were not calculated for minor risk factors because of the low number of studies.

Statistics:

Random-effects meta-analysis was performed to combine the data from the included studies while accounting for between-study heterogeneity. The outcome of time to SCD (event of interest as described above) was addressed. SCD was also considered as a dichotomous outcome. In the first case, the results from each study's Cox proportional hazards regression analysis were combined using the generic inverse-variance (IV) method. Adjusted and unadjusted hazard ratios were pooled together. When SCD was considered as a dichotomous outcome, the event counts and the numbers of those with and without the risk factor under investigation were extracted from the included studies in order to estimate the study odds ratio. Pooled odds ratios were calculated using the Mantel-Haenszel (M-H) method. We report the pooled odds ratio and pooled hazard ratio for each risk factor with a 95% confidence interval for each summary estimate. We also report I^2 , the percentage of variability in estimates due to heterogeneity between the studies. A significance level of 5% (p value < 0.05) was used for analysis. The analysis was carried out using Review Manager (version 5.3)³⁷

Results

Figure 1 summarises the search result. Briefly, the initial search identified 820 unique studies. By reading the titles and abstracts 787 were excluded. The full text version was evaluated for the remaining 33 articles. This excluded a further 8 articles. Reasons for exclusion are detailed in *Figure 1*. Data were extracted from the remaining 25 articles which met inclusion criteria (*table 1*). Of the included studies, the end-point measured was SCD in 10 studies (40%), all cause CVD in 7 studies (28%) and both SCD and CVD in the remaining 8 studies (32%). In total, 23 clinical risk factors were studied. The definition of risk factors used in included studies is detailed in *table 2*.

For the purpose of analysis we divided the reported risk factors into 2 groups: probable/major risk factors (defined as being investigated as a potential risk factor in at least 4 studies and significantly associated with the end point in at least 2 univariate or multivariable analyses); and possible/minor risk factors (defined as being significantly associated with the end-point in 1 univariate or multivariable analysis study).

Major risk factors

Previous adverse cardiac event (aborted cardiac arrest or sustained VT)

Five studies^{12,17-20} evaluated the prognostic value of a previous adverse event (AE) for SCD^{12,18-20} or CVD¹⁷. A significant association with SCD was shown in two univariate analyses ($p < 0.0001$ ¹⁹, $p = 0.004$ ²⁰), and one multivariable analysis ($p < 0.001$ ²⁰). Kamp et al.¹⁸ described a small cohort of patients with previous ICD implantation in which a previous AE was not significant for SCD, however this study was underpowered to detect a difference. Decker et al.¹⁷ did not find an association with all CVD, however SCD was not analysed separately. The hazard ratio is 5.4 (95%

CI 3.67-7.95), $p < 0.001$, $I^2 = 0\%$ (figure 2a). The odds ratio estimate for previous AE is 5.06 (95% CI 2.11-12.17), $p < 0.001$, $I^2 = 0\%$ (figure 2b).

Syncope

Syncope was investigated as a potential risk factor for SCD in seven studies^{10,12,15,18-21} and for CVD in one study¹⁷. Three of the identified studies reported a significant relationship between unexplained syncope/pre-syncope and SCD^{10,19,21}. No significant association was seen between syncope and CVD¹⁷. The hazard ratio is 1.89 (95% CI .69-5.16), $p = 0.22$, $I^2 = 46\%$ (figure 3a). The odds ratio estimate for syncope is 2.64 (95% CI 1.21-5.79), $p = 0.02$, $I^2 = 40\%$ (figure 3b).

Non-sustained ventricular tachycardia (NSVT)

Six studies evaluated the predictive value of NSVT detected during ambulatory electrocardiographic (ECG) monitoring for SCD^{12,15,19,20} or CVD^{17,22}. Two found a significant relationship between NSVT and SCD^{12,15}, with a further study reporting non-significance of NSVT but significance for inducible VT during an electrophysiology study (EPS)¹⁹. No studies reported a significant association of NSVT and CVD^{17,22}.

The pooled hazard ratio was 2.13 (95% CI 1.21-3.74), $p = 0.009$, $I^2 = 19\%$ (figure 4a). The pooled odds ratio estimate for NSVT is 2.05 (95% CI .98-4.28), $p = 0.06$, $I^2 = 11\%$ (figure 4b).

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) was the mostly frequently assessed risk marker^{12,15,17–20,22–28}, however the measurement of LVH was highly variable. The most common measure of LVH was interventricular septal thickness (IVST)^{12,19,20,22–27}, for which 2 studies reported a significant association with SCD^{19,26} and a further study a correlation with CVD²². Six studies evaluated the predictive value of LV posterior wall thickness (LPWT)^{20,22,23,25,27,28} of which 4 showed a significant correlation between increasing LPWT and all cause CVD^{22,23,27,28} and 1 study showed an association with SCD²³. A left ventricular wall thickness/cavity ratio >0.3 was found to be significantly associated with CVD in the two studies reporting this measurement^{20,26}. No studies analysed its relationship with SCD. Finally, extreme LVH (as defined table 2) was evaluated in five studies^{15,17,18,20,22} and found to be statistically associated with SCD in one third of studies using this outcome measure¹⁵ and both studies looking at CVD^{17,22}. Another study showed increased risk of SCD with increasing LV wall thickness²⁵. The hazard ratio for extreme LVH is 1.80 (95% CI .75-4.32), p=0.19, I²=21% (Figure 5a). The odds ratio estimate for extreme LVH is 1.70 (95% CI .85-3.40), p=0.13, I²=31% (Figure 5b).

Minor risk factors

Family History of Sudden Cardiac Death

A family history (FHx) of sudden cardiac death (SCD) was evaluated as a risk factor in seven studies^{12,17–20,22,27}. Only one study reported a statistically significant association with SCD (HR 10.6, 95% CI 1.2-90.2, p=0.03)¹⁸.

Gender

Gender was investigated as a predictive factor for death in five studies^{18,22,23,26,27}. The majority did not demonstrate a significant relationship, However, Lipshultz et al.²⁷ reported an increased risk of CVD in female patients (HR 2.4, CI: 1.09-5.17, p=0.03).

Age

Age at presentation or diagnosis was investigated as a potential risk factor for death in eleven studies^{7,11,12,19,20,22–24,26–28}. Presentation in infancy (<1 year) was consistently associated with an increased risk of CVD, likely secondary to congestive cardiac failure^{7,22,28}; however, outside infancy, the majority of studies found no association between age and the risk of death^{12,20,22–24,27}. Ostman Smith *et al.* reported an increased risk of SCD if younger at presentation²⁶. In contrast, one study reported an increased risk of CVD in children presenting above 13 years¹⁹, and another if between the ages of 9-14 at presentation¹¹.

Symptoms

Eight studies compared the risk of death in symptomatic and asymptomatic patients^{12,17,20,21,24,26–28}, however the definition of symptomatic patients was highly variable. The presence of symptoms of congestive cardiac failure at presentation was significant in predicting an increased risk of CVD in 3 out of 4 studies with this end-point^{20,21,27}. One study reported that other symptoms (including chest pain and palpitations) were also significantly associated with increased risk of CVD²⁶. Only 3 studies assessed symptoms as a risk factor for SCD^{12,24,26}, of which only one found a significant association with SCD (HR1.7 (95% CI 0.80–3.6) p = 0.17²⁴). However, this was a composite measure including syncope, previous AE, chest pain, tachycardia and dizziness and therefore may not be an independent risk factor.

ECG changes

Five studies^{12,20,26,29,30} that assessed the prognostic value of ECG changes were identified. QTc dispersion was analysed in two studies and found to be associated with SCD in both (HR 3.2, CI: 1.5-6.6, $p=0.0042$ ²⁰, RR 1.61, CI; 1.24-2.08, $p=0.0003$ ¹²). Other ECG parameters included RS sum, which was analysed in one study and found to be significantly associated with SCD (HR 8.4 (95% CI 2.2-33.2) $p=0.0012$)²⁶, and heart rate variability, which correlated with SCD in both studies^{29,30}, however only reached statistical significance in one²⁹.

Abnormal blood pressure response to exercise

Blood pressure response to exercise was evaluated as a potential risk factor in 4 studies¹⁷⁻²⁰, however an abnormal blood pressure response to exercise (ABPE) as defined in table 2 was not found to be significantly associated with SCD. One study reported a significant relationship between ABPE and cardiovascular death (HR 9.6 (95% CI 1.0-93.1) $p<0.03$)¹⁷.

Left ventricular outflow tract obstruction (LVOTO)

Left ventricular outflow tract obstruction (LVOTO) was assessed as a potential risk factor for SCD in two studies, and CVD in four studies^{12,17,20,22,28,31}. A significant association with CVD was reported in one study ($p=0.04$)²². Ziowlowska et al.²⁰ reported a higher risk of SCD with increasing LVOTO gradient ($p=0.04$); however, whilst in the adult literature a gradient above 30mmHg is predictive for SCD, a gradient above 30mmHg was not predictive for SCD in this study.

Left atrial (LA) size

Left atrial size was investigated as a risk factor for SCD in three studies^{20,24,25} and CVD in two studies^{20,24}. Increased left atrial size was significantly correlated with SCD in two studies (HR 3.125 (95%CI 1.45-6.74) $p=0.001$ ²⁰, HR 3.4, CI: 1.1-11.2, $p=0.049$ ²⁴). Therefore, although LA size does not meet the criteria for classification as a major risk factor, it is likely to be a significant predictor for SCD.

Restrictive physiology

Three studies^{20,24,25} analysed the predictive value of echocardiographic markers of restrictive physiology for SCD. The measurement of restrictive physiology varied and included: septal E/E'^{24,25}, mitral inflow Doppler E/A ratio^{20,24} and LA enlargement without evidence of LV dilatation²⁴. McMahon et al.²⁵ reported that early transmitral left ventricular filling velocity (E)/septal Ea ratio predicted the risk of SCD (HR 6, $p<0.001$) and Maskatia et al.²⁴ reported echocardiographic findings associated with restrictive physiology to be associated with a 3.8 fold increase in the risk of SCD (HR 3.8, $p=0.302$).

Strain

Strain as assessed by echocardiography was investigated as a risk factor for SCD in only one study which reported a significant association of reduced global strain and increased risk of SCD (OR 1.13, CI 1.00-1.27) but a non-significant relationship between SCD and longitudinal or radial strain³².

24 hour blood pressure monitoring

Abnormal 24 hour ambulatory blood pressure monitoring was investigated as a risk factor for SCD in a single study in which a significant association was shown between an abnormal BP ratio (lower systolic BP in the morning) and risk of SCD³⁰.

Late Gadolinium Enhancement on Cardiac Magnetic Resonance (CMR) imaging

3 studies^{38,39,40} were identified that looked at the predictive value of late gadolinium enhancement on CMR as a risk factor for SCD in childhood HCM. They reported an increased incidence of LGE in patients with adverse outcomes. However, this did not reach statistical significance. In contrast the presence of LGE was statistically associated with increased LV wall thickness/mass.

Discussion

Risk factors for SCD in adult HCM patients are well-described and current European and American guidelines describe validated risk stratification algorithms for primary prevention. The American College of Cardiology Foundation/American Heart Association currently recommends that ICD implantation is reasonable if one major risk factor (Family history of SCD, LV wall thickness >30mm or unexplained syncope) is present and could be considered if two or more other risk factors are present³⁴. In comparison, the European Society of Cardiology has endorsed the use of a new SCD risk prediction model (HCM Risk-SCD)¹⁴ which provides an individualised estimate for 5 year SCD risk utilising predictor variables associated in multi-variable analyses. However, these algorithms have not been validated in children and younger teenagers.

This study is, to our knowledge, the first systematic review of potential risk factors for SCD in childhood HCM. Although a large number of potential risk factors for SCD in childhood HCM have been reported in the literature over the past 30 years, the lack of consistent definitions and

well-designed, large population based studies means that the evidence for individual risk factors is not robust.

Within both current European and American guidelines for the management of adults with HCM, short sections on the risk of SCD in childhood HCM³³⁻³⁵ recommend the use of four major risk factors to predict SCD: maximum left ventricular wall thickness >30mm or z score >+6; unexplained syncope; NSVT; and family history of SCD. ICD implantation is recommended for primary prevention of SCD for those with 2 or more major risk factors^{8,15,17,26,35,36}. The present systematic review supports the inclusion of unexplained syncope and NSVT as likely major risk factors for SCD in paediatric HCM. The measurement and definition of LVH varied between studies; however, severe LVH was found to be associated with SCD in several studies although pooled odds/hazard ratios were not significant at the 5% significance level. Interestingly, only one study showed a significantly increased risk of death with a LV wall thickness >30mm/Z score >+6, the definition endorsed by the ESC guidelines. The most clinically important measure of LVH and appropriate cut off to measure increased risk in paediatric HCM needs further investigation.

A family history of SCD was not classified as a major risk factor for paediatric HCM in our analysis as only one paper reported a statistical relation with sudden death. The ESC recommendations for the use of family history in children was based on a study³⁶ that was excluded from our review because less than 75% patients were below 18 years of age in the cohort. There is significant evidence supporting a family history of SCD as a risk factor in adult HCM; however there is currently a lack of data to support its role in paediatric HCM. Possible explanations for this observation may include a higher prevalence of *de novo* mutations in paediatric HCM, a small proportion of sarcomeric positive patients and insufficient reporting of family history in included studies. This needs further evaluation in future large scale paediatric cohort studies.

In adults, evidence supports additional risk factors such as left atrial diameter, left ventricular outflow tract obstruction or an abnormal blood pressure response to exercise, which can modify an individuals' risk. Our data suggest that, in addition to the four 'major' risk factors described, other clinical variables are also likely to be useful for risk stratification in childhood. These additional risk factors may be the same in adulthood and childhood, for example left atrial size, which was significantly associated with SCD in 2 out of 3 studies. However, other variables such as LVOTO and an abnormal BP response to exercise may not be as important in childhood compared to adulthood. Further studies are required to explore the potential association between these risk factors and risk of SCD in childhood HCM.

The validated SCD risk prediction model (HCM RISK-SCD)¹⁴ described above, which provides an individualised estimate for 5 year SCD risk, is not validated for patients under 16 years of age. Additionally, although it is validated for patients aged 16-18years, this group of patients constituted a small proportion of the cohort (n=82/3675, 2%), and therefore this group of patients require further evaluation. This systematic review has provided evidence that, whilst some of the validated adult risk factors may be applicable to risk stratification in childhood HCM, such as LVH or syncope, others, such as abnormal blood pressure response to exercise, may be less relevant. The results of this systematic review suggest that further research is needed to develop a validated paediatric-specific risk prediction model for SCD in HCM.

The number of studies included in this meta-analysis is small, and of these, all but one was a retrospective cohort study. It is, therefore, limited by the intrinsic problems of retrospective studies, including missing and incomplete information. Childhood HCM is a rare disease and many of the included studies were small; all but 3 of the studies had less than 150 participants. Furthermore, the patient populations were heterogeneous, making comparisons between groups challenging. Adverse outcomes in this population are rare and outcomes are highly variable depending on the underlying

aetiology, necessitating long follow up periods to identify prognostic risk factors. Many of the included studies had low event counts, which is likely to have reduced their power to detect differences between groups. Additionally, as the patients in included studies were often recruited from a small number of highly specialised tertiary services, which care for highly symptomatic individuals, it is possible that this patient group may have more severe disease and that duplication of patient data may have occurred in different studies. Collectively these limitations mean that the applicability of the results of this study to individual patients and the wider HCM population is difficult to determine.

Finally, comparison between studies was complicated by differences in the study design, definition of individual risk factors (including different Z score calculators) and study end-points. Diverse definitions were a particular problem for studies investigating the predictive role of ‘symptoms’ and ‘LVH’ for SCD. The use of ‘appropriate ICD therapy’ as a surrogate marker for SCD, although well established in both adult and paediatric studies, is a possible source of error as it does not account for inappropriate ICD therapy which has been reported to be more common in the paediatric population. Pooled estimates for average hazard and odds ratios were calculated; however the precision of estimates reported in the included studies is low as is the number of studies included. This is reflected in the width of the confidence interval for the pooled ratios. These estimates should be interpreted with caution due to the small number of studies and heterogeneity of included studies, and exclusion of studies with no estimates of association.

Conclusions:

We have identified 4 ‘Major’ risk factors that have been evaluated in at least 4 studies and found to be statistically associated with increased risk of death in at least 2 studies: Previous adverse cardiac event; NSVT, syncope and LVH. Pooled estimates of risk (odds/hazard ratio) were significant for previous adverse cardiac event, NSVT and syncope, however did not reach significance at 5% level

for extreme LVH. A significant number of other potential 'Minor' risk factors have been described, however many of these need further evaluation to determine their relevance in predicting SCD in childhood HCM.

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GN and JPK reports grants from British Heart Foundation during the conduct of the study. All other authors report no conflict of interest.

Author's contributions:

GN, NC and JPK contributed to the conception or design of the work.
GN, NC and EP contributed to the acquisition, analysis, or interpretation of data for the work.
GN and NC drafted the manuscript.
PE, GL, DR and JPK critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy."

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