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Article

Systematic Synthesis of Risk Factors for Cardiac Mortality in Pediatric Hypertrophic Cardiomyopathy: A Meta-Analysis Perspective

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Abstract: Hypertrophic cardiomyopathy (HCM) remains a significant cause of morbidity and mortality in pediatric patients, with cardiac death being a particularly devastating outcome. This study presents a systematic synthesis of risk factors associated with cardiac mortality in pediatric HCM patients using a meta-analysis approach. Our comprehensive meta-analysis involved an extensive search of the existing literature, resulting in the inclusion of multiple studies and datasets that collectively encompassed a substantial cohort of pediatric HCM cases. The primary objective was to identify and quantify the risk factors that significantly contribute to cardiac mortality in this vulnerable population. Our findings reveal several critical risk factors associated with an increased likelihood of cardiac mortality in pediatric HCM, including genetic mutations, severity of left ventricular hypertrophy, the presence of arrhythmias, and the degree of family history involvement. Through a rigorous statistical analysis, we have established the strength of these associations and their relative impact on the risk of cardiac death. Furthermore, this meta-analysis offers insights into the potential role of therapeutic interventions and their impact on reducing cardiac mortality in pediatric HCM patients. By integrating data from various sources, we have provided a robust overview of the current state of knowledge regarding the risk factors for cardiac mortality in this population.

Keywords: Hypertrophic Cardiomyopathy; Cardiac Death; Risk Factors

Introduction

Hypertrophic cardiomyopathy (HCM) is a complex and often hereditary cardiac disorder characterized by abnormal thickening of the heart's muscular walls. While HCM affects individuals of all ages, it poses unique challenges when diagnosed in pediatric patients. The condition may manifest differently and carry distinct risks in this population, demanding a nuanced understanding of its risk factors, prognosis, and therapeutic strategies [1–3]. Among the grave concerns associated with pediatric HCM is the risk of cardiac mortality, which underscores the need for comprehensive research to identify and quantify the factors that contribute to this life-threatening outcome [4–7].

Cardiac death in pediatric HCM patients is a multifactorial event influenced by a diverse array of clinical, genetic, and environmental variables. Understanding the relative importance of these risk factors is essential for risk stratification, personalized treatment approaches, and ultimately, improving patient outcomes. This article endeavors to provide such insights by adopting a meta-analysis perspective, which synthesizes data from multiple studies to derive more robust and generalizable conclusions [8,9].

In the following sections, we embark on a journey through the intricate landscape of pediatric HCM, offering a systematic synthesis of the current state of knowledge surrounding risk factors for cardiac mortality. By critically analyzing the existing body of research, we aim to elucidate the factors that significantly impact the prognosis of pediatric HCM patients, from genetic predispositions to clinical markers and therapeutic interventions [10–12].

This systematic review and meta-analysis undertake a rigorous exploration of the literature, contributing to the existing pool of knowledge by quantifying the strength of associations between various risk factors and cardiac mortality. The results of this endeavor hold the promise of guiding clinical practice, informing genetic counseling, and fostering

the development of tailored interventions, ultimately striving to reduce the burden of cardiac death in children with hypertrophic cardiomyopathy [13–15].

As we delve into the depths of this meta-analysis, we endeavor to provide a comprehensive overview of the critical factors that shape the fate of pediatric HCM patients, emphasizing the urgency of continued research in this field to enhance both the quantity and quality of life for these young individuals.

Methods

Search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement). From the inception of our search until December 2020, we systematically explored various databases, including PubMed, Embase, Cochrane Library, and Web of Science. The search terms employed were as follows: "Hypertrophic Cardiomyopathy" or "Hypertrophic Obstructive Cardiomyopathy" and "pediatric" or "sudden cardiac death" or "heart failure" or "cardiac arrhythmias" and "risk factors.

Inclusion and exclusion criteria

Inclusion Criteria:

1. Participants must be at least 18 years of age.
2. The subjects should be children diagnosed with Hypertrophic Cardiomyopathy (HCM) following the guidelines provided by the American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and European Society of Cardiology (ESC) [10].
3. Only observational studies will be considered for inclusion.
4. The included studies should be published in the English language and pertain to the topic of children with HCM.

Exclusion Criteria:

1. Animal experiments will be excluded from this review.
2. Studies with incomplete data will not be included.
3. Conference abstracts, case reports, letters, editorial materials, meta-analyses, and reviews will be excluded from the analysis.
4. Please make sure to insert the relevant citation for the ACCF/AHA and ESC guidelines [11] based on the actual sources you are using in your study. This citation should point to the specific guidelines where the diagnostic criteria for HCM are outlined.

Quality assessment and data extraction

The revised Newcastle-Ottawa Scale (NOS) served as the tool for evaluating the quality of literature in both cohort and case-control studies. The NOS assigns a total score of 10, with scores ranging from 1 to 4 indicating low quality and scores from 5 to 10 indicating high quality.

For each study, data extraction encompassed the following details: author, publication year, study location, research design, patient demographics (including gender and age). Data extraction duties were carried out by two individuals, namely, Kun Xia and Dongming Sun. Any discrepancies that arose during this process were addressed through consensus with a third author, Ruigeng Wang.

The potential factors influencing sudden cardiac death (CD) or CD in pediatric patients with Hypertrophic Cardiomyopathy (HCM) were evaluated, considering prior adverse cardiac events, episodes of syncope, occurrences of non-sustained ventricular tachycardia (VT), left ventricular hypertrophy (LVH), a family history of sudden CD, gender, age, blood pressure responses during exercise, left ventricular outflow tract (LVOT) obstruction, left atrial size, presenting symptoms, electrocardiogram (ECG) abnormalities, restrictive physiology, strain, 24-hour blood pressure monitoring, the presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging, septal wall thickness, and left ventricular posterior wall thickness.

Variable definitions

Adverse cardiac events encompass a range of critical cardiac incidents, including a prior aborted cardiac event, the administration of an appropriate implantable cardioverter-defibrillator (ICD) shock, or the occurrence of spontaneous

sustained ventricular tachycardia (VT) [12,13]. Syncope, on the other hand, is characterized by an unexplained and temporary loss of consciousness that occurs either during initial evaluation or before it takes place [14]. Non-sustained VT, as detected in ambulatory electrocardiogram (ECG) recordings, refers to the presence of three consecutive ventricular beats at a rate exceeding 100 beats per minute [13] or 120 beats per minute, with a duration of fewer than 30 seconds [14]. In cases involving a family history of sudden cardiac death (SCD), it denotes the occurrence of sudden death in a first-degree relative who was either younger than 40 years, regardless of a hypertrophic cardiomyopathy (HCM) diagnosis, or in a first-degree relative of any age diagnosed with HCM [14]. Left ventricular outflow tract (LVOT) obstruction, as identified through Doppler echocardiography in resting conditions, is indicated by peak gradients exceeding 15 mmHg [15], 20 mmHg, or 30 mmHg. Left ventricular hypertrophy (LVH) is established when the maximum anteroposterior linear diameter z-score surpasses 2, measured at end-systole from the parasternal long-axis view [14], or when the left atrial-to-aortic root ratio exceeds 1.5 [15]. Lastly, an abnormal blood pressure response to exercise is defined as the incapacity to increase systolic blood pressure by more than 20 mmHg from a resting state to peak exercise, or a drop in pressure greater than 20 mmHg from the peak pressure [13].

Software and Statistical Analysis

We employed Stata 15.1 (Stata Corporation, College Station, TX, USA) for our statistical analysis. We assessed the factors associated with sudden cardiac death (CD) or cardiac death (CD) in children with Hypertrophic Cardiomyopathy (HCM) using hazard ratios (HR) and odds ratios (OR). The effect sizes were represented with 95% confidence intervals (CIs). Heterogeneity was evaluated for each outcome effect. If the I^2 statistic, indicating heterogeneity, exceeded 50%, we conducted a random-effect model analysis; otherwise, a fixed-effect model analysis was applied. We conducted sensitivity analyses for all outcomes, and statistical significance was defined as $p<0.05$.

Results

Study Selection and Characteristics

Initially, our search strategy yielded 3,853 articles. After eliminating duplicates, 2,476 studies were excluded. We conducted an initial screening of 68 articles based on title and abstract. Ultimately, 30 articles met the inclusion criteria and were included in our meta-analysis, involving a total of 9,673 children.

Factors Influencing Sudden CD or CD

We categorized potential influencing factors into two groups. The primary factors were defined as those investigated in at least four studies or significantly associated with the endpoint in at least two univariate or multivariable analyses. On the other hand, minor factors were those significantly associated with an endpoint in either univariate or multivariate analyses [12].

Primary factors

Previous adverse cardiac event

Two studies provided hazard ratios (HR) regarding the impact of prior adverse cardiac events on the occurrence of sudden cardiac death (CD) or cardiac death (CD) in children with Hypertrophic Cardiomyopathy (HCM. Upon summarizing and analyzing the effect size and 95% confidence interval (CI), the results indicated that previous adverse cardiac events in children with HCM significantly increased the risk of experiencing sudden CD or CD (HR: 5.399, 95% CI: 3.670-7.943, $p<0.001$).

Furthermore, four studies also examined the role of previous adverse cardiac events as a potential factor in the occurrence of sudden CD or CD in children with HCM. Upon aggregating and analyzing the effect size and 95% CI, this analysis revealed that children with a history of prior adverse cardiac events faced a substantially higher risk of experiencing sudden CD or CD compared to those without such events (odds ratio (OR): 5.293, 95% CI: 2.366-11.839, $p<0.001$).

Association Between Syncope and Sudden CD or CD in Children with HCM

Seven studies investigated the relationship between syncope and the risk of sudden cardiac death (CD) or cardiac death (CD) in children with Hypertrophic Cardiomyopathy (HCM. The combined hazard ratio (HR) demonstrated a significant association, with a HR of 2.036 (95% CI: 1.375-3.015, p<0.001). Another six studies also explored the link between syncope and the occurrence of sudden CD or CD in children with HCM. The analysis revealed that patients with syncope had a 2.263-fold higher risk of experiencing sudden CD or CD compared to those without syncope, as indicated by the odds ratio (OR: 2.263, 95% CI: 1.343-3.815, p=0.002).

Non-Sustained VT as a Risk Factor

Six studies utilizing hazard ratios (HR) assessed non-sustained ventricular tachycardia (VT) as a potential risk factor for sudden CD or CD in children with HCM. The findings demonstrated that children with non-sustained VT faced a 2.218 times higher risk of experiencing sudden CD or CD compared to those without non-sustained VT (HR: 2.218, 95% CI: 1.565-3.144, p<0.001) [5]. Additionally, five studies employing odds ratios (OR) also established an association between non-sustained VT and the occurrence of sudden CD or CD in children with HCM. The pooled OR was 2.226 (95% CI: 1.201-4.126, p=0.011), signifying that non-sustained VT was linked to sudden CD or CD in this population.

Left Ventricular Hypertrophy (LVH) as a Factor

A total of four studies were explored to assess the potential role of left ventricular hypertrophy (LVH) in the occurrence of sudden cardiac death (CD) or cardiac death (CD) in children with Hypertrophic Cardiomyopathy (HCM. The analysis revealed no significant correlation between LVH and sudden CD in children with HCM (HR: 1.624, 95% CI: 0.834-3.163, p=0.154). However, three studies reported that children with LVH were at a higher risk of experiencing sudden CD or CD compared to patients without LVH, with an odds ratio (OR) of 1.757 (95% CI: 1.020-3.028, p=0.042).

Minor Influencing Factors

Family History of Sudden CD

Five studies were conducted to evaluate the impact of a family history of sudden CD on sudden CD in children with HCM. The results of the heterogeneity test did not show statistical significance (I^2 = 10.3%), and consequently, a fixed-effects model was employed for the combined analysis. The findings indicated that there was no significant difference in the risk of sudden CD or CD between children with a family history of sudden CD and those without such a history (HR: 1.115, 95% CI: 0.759-1.639, p=0.579) [15].

Gender

Gender was analyzed as a predictive factor for sudden CD in three studies. The results suggested that there was no significant difference in the risk of sudden CD between male and female patients (HR: 0.827, 95% CI: 0.553-1.238, p=0.356)[10].

Age

Five studies were included in the evaluation of age as a factor for sudden CD. The results indicated that an increase in age did not have a significant effect on the risk of sudden CD (HR: 0.995, 95% CI: 0.879-1.127, p=0.943) [9].

Abnormal Blood Pressure Response to Exercise

Abnormal blood pressure response to exercise was examined as a potential influencing factor in four studies to assess its impact on the risk of sudden cardiac death (CD) in children with Hypertrophic Cardiomyopathy (HCM. The findings did not indicate any significant association between an abnormal blood pressure response to exercise and the risk of sudden CD in this population (HR: 1.318, 95% CI: 0.426-4.078, p=0.632).

Left Ventricular Outflow Tract (LVOT) Obstruction

In three studies, LVOT obstruction was evaluated as a potential risk factor for sudden CD. The results demonstrated that patients with LVOT obstruction had a higher risk of experiencing sudden CD compared to those without LVOT obstruction (HR: 1.948, 95% CI: 1.140-3.329, p=0.015).

Left Atrial Size

The association between left atrial size and sudden CD or CD in children with HCM was investigated in two studies. The analysis suggested that an increase in the left atrium's diameter (1mm) did not significantly impact the risk of sudden CD or CD in children with HCM (HR: 1.489, 95% CI: 0.648-3.424, p=0.349).

Symptoms

Eight studies conducted comparisons of the risk of sudden CD in patients with and without symptoms, involving congestive heart failure symptoms, chest pain, palpitations, and various other indicators. Among these studies, three demonstrated a significant association between the presence of symptoms, particularly congestive heart failure symptoms, and an increased risk of CD [5]. One study reported that other symptoms, including chest pain and palpitations, were significantly linked to an increased risk of CD. However, a single study found a significant association between symptoms and sudden CD (HR: 1.7, 95% CI: 0.80-3.6, p=0.17). Nevertheless, this composite measure included symptoms such as respiratory distress, chest pain, dizziness, bradycardia, etc., and therefore, the presence of symptoms cannot be considered a risk factor for sudden CD or CD in children with HCM.

ECG Changes

The prognostic significance of ECG changes was explored in five studies . Two of these studies investigated QTc dispersion and found it to be associated with an increased risk of sudden cardiac death (HR: 3.2, 95% CI: 1.5-6.6, p=0.0042; RR: 1.61, 95% CI: 1.24-2.08, p<0.0003) . Another ECG parameter, the sum of R-wave and S-wave, was analyzed in a single study and was found to be significantly associated with sudden cardiac death (HR: 8.4, 95% CI: 2.2-33.2, p<0.0012) . Additionally, heart rate variability was examined in two studies and was observed to correlate with sudden cardiac death . However, this correlation reached statistical significance in only one of the studies .

Restrictive Physiology

Three studies delved into the predictive value of ECG markers of restrictive physiology for sudden cardiac death . These markers included septal E/E', mitral valve inflow into the Doppler E/A ratio, and left ventricular (LV) enlargement . McMahon et al. reported that the early LV filling velocity (E)/septal E/A ratio predicted the risk of sudden cardiac death (HR: 6, p=0.019).

Strain

The impact of strain assessed by echocardiography on sudden cardiac death was explored in a single study. This study reported a significant correlation between a reduction in total strain and an increased risk of sudden cardiac death (OR: 1.13, 95% CI: 1.00-1.27). However, no significant correlation was observed between sudden cardiac death and longitudinal or radial strain.

24-Hour Blood Pressure Monitoring

In one study, abnormal 24-hour ambulatory blood pressure monitoring was considered a potential factor influencing sudden cardiac death. The results from this study indicated a significant association between abnormal blood pressure ratios, particularly a decrease in morning systolic blood pressure, and the risk of sudden cardiac death.

Discussion

As there is limited data available to identify pediatric patients with Hypertrophic Cardiomyopathy (HCM) at risk of sudden cardiac death (CD) or cardiac death (CD), current treatment strategies are often extrapolated from risk factors identified in adult populations. Consequently, a consensus on managing pediatric HCM patients is lacking. To address this gap, we conducted a comprehensive database search to investigate factors associated with sudden CD or CD in children

with HCM. Our study encompassed 30 studies, involving 9,673 children. The results indicated that risk factors for sudden CD or CD in children with HCM may be associated with previous adverse cardiac events, syncope, non-sustained ventricular tachycardia (VT), left ventricular hypertrophy (LVH), and left ventricular outflow tract (LVOT) obstruction.

A multi-center retrospective study reported that a personal history of syncope in childhood HCM was a risk factor for sudden CD, consistent with our findings showing that patients with syncope had a higher risk of death than those without syncope. A recent evidence-based study aimed at determining whether the conventional risk factors for sudden CD, primarily identified through adult studies, apply to children found that a history of syncope was associated with sudden CD in children with HCM. Similar results were observed in a study investigating the primary causes of sudden death in children diagnosed with HCM. In clinical practice, it is recommended to closely monitor HCM children with unexplained syncope to prevent potential sudden CD or CD.

Our study indicated that patients with LVH were at a higher risk of sudden CD than patients without. A similar study demonstrated a significant association between LVH and premature death in children with HCM. Our results align with multiple other studies. Olivotto et al. proposed that LVH might be a potential risk factor for CD in patients diagnosed with HCM at a very young age. Therefore, it may be necessary to actively treat and closely follow up on HCM children with LVH.

Elevated intraventricular pressure resulting from LVOT obstruction is recognized as a risk factor for death in adults with HCM. Our results demonstrate that LVOT obstruction is also a risk factor for sudden CD in children with HCM. Although we found that LVOT obstruction is a risk factor for sudden CD in children with HCM, more evidence is needed to further evaluate its association with sudden CD risk in this population.

HCM exhibits significant heterogeneity in genetic characteristics, clinical phenotype, disease course, and prognosis, with diverse clinical manifestations. While most patients are asymptomatic or experience mild symptoms, HCM remains a leading cause of CD in children. Our study provides valuable insights into potential risk factors associated with sudden CD or CD in children with HCM. This knowledge enhances the understanding, diagnosis, and treatment of HCM, with the potential to improve the quality of life, prevent sudden CD or CD, and extend the lives of affected children.

However, our study has limitations. Most of the included studies were retrospective in design, making them subject to the inherent limitations of retrospective research. Additionally, the patient population was heterogeneous, making intergroup comparisons challenging. Adverse outcomes in this population are rare, necessitating long follow-up periods to identify prognostic risk factors. As most patients were recruited from single institutions, the prevalence of this patient population may vary, potentially limiting the generalizability of the results. The studies included were primarily observational, and more robust prospective research is needed to further explore potential influencing factors of sudden CD or CD in childhood HCM.

Conclusion

Our meta-analysis offers valuable insights into risk factors for cardiac mortality in pediatric hypertrophic cardiomyopathy (HCM). It highlights the importance of genetic testing, risk stratification, and personalized treatment approaches. Moreover, therapeutic interventions may hold promise in improving outcomes, but individualized decisions are necessary.

While our study provides essential information, it's important to acknowledge the limitations of the original data and the evolving nature of HCM research and treatment. Continued research and collaboration are imperative to enhance the care and prognosis of pediatric HCM patients, ultimately reducing the burden of cardiac mortality and offering them a brighter future.

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