Genetic Etiology and Mortality Risk Factors in Pediatric Primary Dilated Cardiomyopathy (Postprint)

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Abstract

Background Dilated cardiomyopathy (DCM) is one of the common causes of sudden cardiac death and heart failure in children. Different etiologies are significantly associated with the prognosis of pediatric DCM patients; however, there currently lacks precise etiological diagnosis and effective risk stratification protocols. Primary DCM accounts for the highest proportion and has a relatively poor prognosis, particularly in patients associated with genetic factors. Therefore, analysis of mortality risk factors based on genetic background will facilitate precise prognostic assessment and risk stratification for pediatric DCM patients.

Objective To investigate the proportion of genetic etiology, genetic characteristics, and factors associated with poor prognosis in pediatric primary DCM.

Methods Clinical data of 42 pediatric patients with primary DCM who were hospitalized at Hebei Children's Hospital from July 2018 to December 2022 and completed genetic testing were retrospectively included. Genetic testing results of the patients were collected. After discharge, patients were regularly followed up at the cardiology outpatient clinic of Hebei Children's Hospital. The follow-up endpoint was either the time of patient death or December 31, 2022. Based on follow-up outcomes, patients were divided into a death group (9 cases) and a survival group (33 cases). Kaplan-Meier method was used to plot survival curves, and Log-rank test was used for inter-group comparisons. Multivariate COX regression analysis was used to identify risk factors for patient mortality.

Results The median age at first diagnosis was 12 (7, 96) months, and the median follow-up duration was 24 (9, 36) months. The median follow-up duration in the death group was 8 (0, 11) months, while in the survival group it was 30 (12, 39) months, with a statistically significant difference ($Z=-2.19$, $P<0.05$). The

positive rate of gene mutations was 38.1% (16/42), among which de novo mutations accounted for 25.0% (4/16), and negative gene mutations accounted for 61.9% (26/42). All 9 patients in the death group died within 1 year after diagnosis. Among gene mutation-positive patients, 8 died (50.0%, 8/16), while among gene mutation-negative patients, 1 died (3.8%, 1/26), with a statistically significant difference between groups (P<0.05). The gene mutation-negative patient who died had a CSRP3 (c.190C>T) heterozygous variant with a pathogenic classification of uncertain clinical significance. Kaplan-Meier survival curves were plotted, and Log-rank test results showed that gene mutation-negative patients had higher survival rates than gene mutation-positive patients (2=18.1, P<0.001). Multivariate COX regression analysis results indicated that gene mutation [HR=23.91, 95%CI=(1.80~317.21), P=0.016] and cardiac function class III/IV [HR=11.29, 95%CI(1.13~112.68), P=0.039] were risk factors for mortality in pediatric DCM patients.

Conclusion In this study, 38.1% of pediatric patients with primary DCM were associated with genetic etiology. The first year after diagnosis is a high-risk period for mortality in pediatric DCM patients, and those with positive gene mutations have a worse prognosis. The presence of pathogenic gene mutations and cardiac function class III-IV at first diagnosis are independent risk factors for patient mortality.

Full Text

Genetic Etiology and Risk Factors for Mortality in Primary Dilated Cardiomyopathy in Children

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Abstract

Background: Dilated cardiomyopathy (DCM) is a leading cause of sudden cardiac death and heart failure in children. Prognosis varies significantly depending on etiology, yet precise diagnostic tools and effective risk stratification protocols remain lacking. Primary DCM accounts for the majority of cases and carries a relatively poor prognosis, particularly among children with underlying genetic factors. Analyzing mortality risk factors within a genetic framework could therefore facilitate more accurate prognosis assessment and risk stratification for pediatric DCM patients.

Objective: To investigate the proportion of genetic etiology, genetic characteristics, and factors associated with poor prognosis in children with primary DCM.

Methods: We retrospectively enrolled 42 children with primary DCM who were hospitalized at Hebei Children's Hospital between July 2018 and December 2022 and completed genetic testing. Clinical data and genetic test results were collected, and patients were followed regularly at the cardiology outpatient clinic after discharge. Using death or December 31, 2022 as the endpoint, patients were divided into a death group (9 cases) and a survival group (33 cases). Kaplan-Meier survival curves were constructed, and between-group comparisons were performed using the Log-rank test. Multivariate Cox regression analysis was employed to identify mortality risk factors.

Results: The median age at first diagnosis was 12 (7, 96) months, and the median follow-up duration was 24 (9, 36) months. The death group had a median follow-up of 8 (0, 11) months, significantly shorter than the survival group's 30 (12, 39) months ($Z = -2.19$, $P < 0.05$). The positive mutation rate was 38.1% (16/42), including 25.0% (4/16) de novo mutations, while 61.9% (26/42) were mutation-negative. All nine deaths occurred within one year of diagnosis. Among mutation-positive children, 8 died (50.0%, 8/16), compared to only 1 death (3.8%, 1/26) in the mutation-negative group ($P < 0.05$). The single mutation-negative death involved a CSRP3 (c.190C>T) heterozygous variant classified as a variant of uncertain significance (VUS). Kaplan-Meier analysis revealed significantly higher survival rates in mutation-negative versus mutation-positive children ($^2 = 18.1$, $P < 0.001$). Multivariate Cox regression identified gene mutation [HR = 23.91, 95%CI = (1.80–317.21), P = 0.016] and cardiac function grade III/IV [HR = 11.29, 95%CI = (1.13–112.68), P = 0.039] as independent risk factors for mortality.

Conclusion: In this cohort, 38.1% of children with primary DCM had an underlying genetic etiology. The first year post-diagnosis represents a critical high-risk period, with mutation-positive patients showing significantly worse outcomes. Pathogenic gene mutations and grade III–IV cardiac function at initial diagnosis are independent predictors of death in pediatric DCM.

Keywords: Dilated cardiomyopathies; Genic mutation; Child; Genetic testing; Prognosis; Root cause analysis

Introduction

Dilated cardiomyopathy (DCM) is the most common form of pediatric cardiomyopathy, characterized by left ventricular dilation and systolic dysfunction that cannot be explained by hemodynamic causes, with physiological or anatomical etiologies excluded [1]. The incidence of pediatric cardiomyopathy has been rising annually in China [2]. Lacking specific clinical manifestations, DCM is of-

ten difficult to diagnose early and represents a frequent cause of sudden cardiac death (SCD) and heart failure (HF) in children [3,4].

The first year following diagnosis is a critical survival period, with approximately 33% of children with primary DCM dying within this timeframe [3,5]. The etiology of pediatric DCM is complex and prognosis varies considerably across different causes. Genetic factors play a substantial role, with approximately 40% of cases showing hereditary links and patients harboring pathogenic variants experiencing worse outcomes [4,6]. Notably, DCM caused by TTN and LMNA mutations carries a particularly high risk of life-threatening arrhythmias or SCD during early disease stages [6].

Although diagnostic and therapeutic approaches have advanced, early precise diagnosis remains challenging, and high mortality and morbidity persist without effective risk stratification protocols. Therefore, investigating mortality risk factors for pediatric DCM within a genetic context will facilitate accurate risk stratification, prognosis assessment, and individualized management.

1. Materials and Methods

1.1 Study Population

We retrospectively enrolled 42 children with primary DCM who were hospitalized at Hebei Children's Hospital between July 2018 and December 2022 and completed genetic testing. All diagnoses conformed to the *AHA Scientific Statement on the Classification and Diagnosis of Cardiomyopathies in Children* [1], with secondary causes including inflammation, chemotherapy, tachycardia, vitamin D deficiency, hypertension, valvular disease, congenital heart disease, and ischemic heart disease excluded. The study was approved by the Hebei Children's Hospital Ethics Committee (approval No. 202136), and informed consent was obtained from all parents.

1.2 Data Collection

Baseline data were extracted from electronic medical records, including age at first diagnosis, sex, clinical manifestations, cardiac function grade, medical history, family history (of cardiomyopathy or SCD), CK-MB, troponin I (cTnI), B-type natriuretic peptide (BNP), electrocardiogram, and echocardiographic parameters [left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), mitral regurgitation]. Malignant arrhythmias included ventricular tachycardia and third-degree atrioventricular block.

Heart failure classification used the modified Ross score for children aged 0–14 years: 0–2 points = grade I, 3–6 = grade II, 7–9 = grade III, and 10–12 = grade IV; patients >14 years were classified using NYHA criteria [7]. Genetic testing employed whole-exome sequencing (WES) performed by MyGenostics or Sinobio Genetics, with parental validation via Sanger sequencing. Variant pathogenicity was classified according to the 2015 American College of Medical Genetics and

Genomics (ACMG) guidelines [8], with pathogenic or likely pathogenic variants defined as mutation-positive and variants of uncertain significance (VUS) as mutation-negative.

1.3 Follow-up and Grouping

All patients received standard anti-heart failure therapy (milrinone, digoxin, ACE inhibitors, diuretics) and were followed regularly at the cardiology outpatient clinic. Using death or December 31, 2022 as the endpoint, patients were divided into a death group (9 cases) and survival group (33 cases).

1.4 Statistical Analysis

Data were analyzed using SPSS 25.0. Normally distributed continuous variables are presented as mean ± SD and compared using independent t-tests; non-normally distributed variables are expressed as median (P25, P75) and compared using nonparametric rank-sum tests. Categorical data are reported as percentages and compared using ^{2} tests or Fisher's exact test. Kaplan-Meier survival curves were constructed with Log-rank comparisons. Multivariate Cox regression identified mortality risk factors. Statistical significance was set at $P < 0.05$.

2. Results

2.1 Baseline Characteristics

The median age at first diagnosis was 12 (7, 96) months, with a median follow-up of 24 (9, 36) months. The death group had a significantly shorter median follow-up duration of 8 (0, 11) months compared to 30 (12, 39) months in the survival group ($Z = -2.19$, $P < 0.05$).

2.2 Genetic Testing Results

The mutation-positive rate was 38.1% (16/42), including 25.0% (4/16) de novo mutations, while 61.9% (26/42) were mutation-negative. All nine deaths occurred within one year of diagnosis. Among mutation-positive children, 8 died (50.0%, 8/16) versus only 1 death (3.8%, 1/26) in the mutation-negative group ($P < 0.05$). The single mutation-negative death involved a CSRP3 (c.190C>T) heterozygous variant classified as VUS. [Figure 1: see original paper]

The 16 mutation-positive cases included: 3 TTN [c.78938delA (p.His26313Profs*2), c.5072_{5074del} (p.1691_{1692del}), c.4714C>T (p.R1572X)], 2 LMNA [c.917T>G (p.L306R), c.1621C>T (p.R541C)], 2 TAZ [c.646+2T>C (N/A), c.364_{370}+23delTGCCGAGGTGAGCTGCTCCTCC (p.C122fs*15)], 2 MYH7 [c.602T>C (p.I201T), c.3956T>C (p.L1319P)], and one each of PCCB [c.31_c.40delGGGGCAAGGC (p.G11fs*51)], CTNNA3 [c.1126C>T (p.Q376X)], FBN1 [c.3596A>G (p.D1199G)], TNNI3 [c.335insT (p.Y112Lfs)],

FLNC [c.261_{262delTC} (p.P88Afs*63)], ATAD3A [c.517C>T (p.Q137*, 462)], and SGCD [c.290G>A (p.Arg97Gln)].

2.3 Survival Analysis of Mortality Risk Factors

Kaplan-Meier survival curves demonstrated significantly higher survival in mutation-negative versus mutation-positive children (^{2} = 18.1, P < 0.001). [Figure 2: see original paper] [Figure 3: see original paper] Multivariate Cox regression analysis, with survival outcome as the dependent variable (survival = 0, death = 1) and including variables showing statistical significance in univariate analysis [sex (female = 0, male = 1), gene mutation (negative = 0, positive = 1), cardiac function grade (I/II = 1, III/IV = 2), LVFS (actual value)], identified gene mutation and grade III/IV cardiac function as independent risk factors for mortality.

Discussion

DCM is the most common pediatric cardiomyopathy and a major cause of heart failure and sudden death. While FADL et al. [4] reported an incidence of 0.77/100,000 for pediatric DCM and left ventricular noncompaction in Sweden, corresponding data are lacking in China. The precise etiology and pathogenesis remain unclear. The AHA classification system categorizes pediatric DCM as primary (idiopathic or genetic/familial) or secondary (inflammatory, metabolic, toxic, structural, tachycardia-induced, or nutritional) [1]. Studies show that DCM secondary to infection, chemotherapy, carnitine, or vitamin D deficiency carries better prognosis, whereas idiopathic and pathogenic mutation-associated DCM have poor outcomes [3,5,6]. Etiology significantly impacts prognosis, and early definitive diagnosis enables individualized treatment and risk stratification.

Despite diagnostic advances, 50–70% of cases remain idiopathic [9,10]. In our cohort of 42 primary DCM patients, WES identified pathogenic variants in 38.1% (16/42), similar to the 34.8% reported by WANG et al. [6] in 46 pediatric DCM cases. The most common variants were TTN (18.8%), followed by LMNA (12.5%), TAZ (12.5%), and MYH7 (12.5%). This contrasts with adult DCM, where TTN truncating variants (TTNtv) account for ~25% of familial and ~18% of sporadic cases [12,13]. Our finding of 7.1% (3/42) TTN mutations aligns with KHAN et al. [14], who reported ~9% TTN mutations in 109 pediatric DCM cases.

Pediatric DCM often presents with nonspecific symptoms, frequently involving gastrointestinal or respiratory manifestations that can lead to missed diagnoses without chest X-ray or echocardiography [3,11]. In our cohort, poor appetite, vomiting, diarrhea, cough, and dyspnea were common, without significant differences between survival and death groups (P > 0.05). The mortality rate remains high, with LIU et al. [5] reporting 33% one-year mortality in 183 primary DCM cases. Our 21.4% (9/42) one-year mortality suggests some improvement, likely

reflecting advances in intensive care and heart failure management. However, the mutation-positive group showed 50% (8/16) mortality versus only 3.8% (1/26) in the mutation-negative group ($P < 0.05$), confirming worse outcomes in genetically mediated DCM.

Over 60 genes involving sarcomeric, nuclear envelope, cytoskeletal, and ion channel proteins have been implicated in pediatric DCM, with pathogenic variants detectable in 30–40% of patients [6,10]. Compared to MYH7-related DCM, TTN and LMNA mutations confer higher early risk of life-threatening arrhythmias or SCD [2,6,15]. In our study, all three TTN and both LMNA mutation carriers had poor outcomes, while two TAZ mutation carriers died from ventricular fibrillation, suggesting TAZ may also carry high arrhythmic risk. Conversely, patients with MYH7, PCCB, FLNC, CTNNA3, FBN1, TNNI3, and SGCD mutations showed relatively favorable outcomes and remain alive.

The first year post-diagnosis represents a critical high-risk period, with all nine deaths occurring within this window. Multivariate analysis identified pathogenic gene mutations and grade III–IV cardiac function at diagnosis as independent mortality risk factors. While some studies report male sex as an independent risk factor in adult DCM [16], and FRANASZCZYK et al. [17] found better outcomes in TTNtv-carrying females, our multivariate analysis did not identify sex as an independent predictor, though males comprised 77.8% (7/9) of the death group and 87.5% (7/8) of mutation-positive deaths, suggesting male sex may be a risk factor in the mutation-positive subgroup.

Age at diagnosis has been associated with prognosis, with older age at onset predicting higher mortality [3,5]. Our cohort showed no significant age difference between groups ($P > 0.05$), possibly due to the high proportion of genetic etiology, particularly in the death group (8/9). Genetic-metabolic DCM often presents in infancy with earlier death [1,11]. While elevated natriuretic peptides may indicate poor prognosis even in asymptomatic DCM [18], WANG et al. [6] found no significant prognostic value for BNP in pediatric DCM, consistent with our finding of no significant BNP difference between groups ($P = 0.07$). Other reported risk factors including family history, moderate-to-severe mitral regurgitation, LVFS <15%, abnormal Q waves, malignant ventricular arrhythmias, and QT prolongation [3–5] showed no significant differences in our cohort, possibly due to small sample size.

Limitations include the single-center design, small sample size, and relatively short follow-up period, limiting assessment of long-term prognosis. Future large-scale, multicenter studies are warranted to validate these findings and improve risk stratification.

In conclusion, high mortality in pediatric primary DCM correlates with pathogenic gene mutations, male sex, grade III–IV cardiac function at diagnosis, and low LVFS. Notably, the first year post-diagnosis is a high-risk period, with mutation-positive patients showing significantly worse prognosis. Pathogenic gene mutations and grade III–IV cardiac function at initial diagnosis

are independent risk factors for death in primary DCM.

Author Contributions: ZHENG Kui conceptualized the study, performed data analysis, and drafted the manuscript; LIU Lu, WANG Yongli, LI Hui, and WANG Xuan collected cases and organized data; HAO Jingxia and LI Bo participated in patient diagnosis; ZHANG Yingqian supervised the study, provided guidance, and revised the manuscript.

Conflict of Interest: None declared.

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Note: Figure translations are in progress. See original paper for figures.