Severe Heart Failure and Outcomes in 121 Children With Dilated Cardiomyopathy: A Single-Center Retrospective Study from Southwest China

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Abstract

Objective

Heart failure is a common complication in children with dilated cardiomyopathy. The aim of this study was to determine whether severe heart failure at diagnosis was related to poor outcomes in children with dilated cardiomyopathy.

Methods

We analyzed medical data from 121 children with dilated cardiomyopathy in our hospital from 2003 to 2021. The children were grouped by the degree of heart failure. Cox regression analysis was performed to confirm whether severe heart failure was associated with poor outcomes.

Results

There were 121 patients with dilated cardiomyopathy in this research. The mean age of the 121 patients was 118.5 ± 63.0 months. Of these patients, 81 (67.8%) were sorted into a severe heart failure group and 39 (32.2%) were placed into a mild heart failure group. A comparison between the two groups showed that patients with severe heart failure were older and more likely to be male, have lower systolic blood pressure measurements, be admitted to the intensive care unit and be treated with β-blockers, loop diuretics, spironolactone and digoxin. In addition, they had larger systolic and diastolic left ventricular end-diastolic dimensional and lower left ventricular ejection fractional z-scores as well as being more prone to aortic and tricuspid regurgitations ($P < 0.05$ in all cases). After adjusting for age, sex, heart rate, left ventricular ejection fraction z-scores and drug, severe heart failure was found to be independently associated with an increased risk of death (hazard ratio [HR] 2.27; $P < 0.005$).

Conclusions

Severe heart failure at diagnosis was related to a greater risk of death in children with dilated cardiomyopathy. Further prospective studies are warranted to evaluate the efficacy between the treatment undertaken for heart failure and outcomes in children with dilated cardiomyopathy.

Introduction

Dilated cardiomyopathy (DCM) is a progressive and serious disorder of the heart muscle which is characterized by the dilation of the left ventricle accompanied by a reduction of systolic function[1]. DCM is diagnosed in 0.57 cases per 100 000 children /year in the United States and has a 20% mortality rate at 1 year and a 56% mortality rate at 4 years[2, 3]. Although the prognosis of children with DCM have

increased in the past 20 years[4], the management of patients with this condition needed to be more targeted and precise in order to raise long-term prognosis.

Heart failure (HF) is a severe complication of DCM and a major cause of heart transplantation or sudden death in children with DCM [2, 5]. Improvement of HF can reverse cardiac histologic remodeling and increase the prognosis of DCM[6, 7]. With the release of the European Society of Cardiology and American College of Cardiology Guidelines for HF in 2021, the management of HF has become more standardized and effective[8, 9]. Therefore, we performed a novel analysis comparing children with severe HF who were classified as ROSS/NYHA class III or class IV to those with mild HF who were classified as ROSS/NYHA class I or class II. We hypothesized that severe HF is related to poor prognosis in children with DCM.

Methods

Study Subjects

Children aged ≤ 18 years with a diagnosis of DCM admitted to the First Affiliated Hospital of Guangxi Medical University between March 2003 and September 2021 were enrolled into the study. The exclusion criteria included congenital heart disease, arrhythmia cardiomyopathy, ischemic heart disease, cardiac valve disease and hypertensive heart disease; DCM with known etiology, such as drug-induced cardiomyopathy and inherited metabolic cardiomyopathy such as primary carnitine deficiency.

Definitions

Diagnosis of DCM was indicated by a left ventricular end-diastolic dimension (LVEDD) of more than two standard deviations (SDs) above normal for the individual's body surface area (or *z*-score for age > 2) and a left ventricular ejection fraction (LVEF) or left ventricular fractional shortening (LVFS) of lower than 2 standard deviations for healthy children of the same age (or *z*-score for age < 2). Severe HF was defined as an improved ROSS scoring criteria (≥ 7score)[10] or NYHA class III/IV and mild HF was defined as an improved ROSS scoring criteria (7score) or NYHA class I/II.

Study Methods

General data involved age, race, sex and body mass index (BMI), HF at diagnosis, duration of symptoms, duration of stay in hospital, multiple hospitalizations (≥ 2 visits), admission to the intensive care unit, family history of DCM, heart rate at diagnosis, systolic and diastolic blood pressure measurements at diagnosis, echocardiographic measurements z-scores, medications, follow-up periods and outcomes. The patients were classified into either a severe and or a mild HF group based on the severity of HF. The primary adverse event was death.

Statistical Analysis

Data analyses were performed employing SPSS software (version 24.0 for Windows, SPSS, Inc., Chicago, Illinois). Data are presented either as means or percentages. Continuous variates were compared using

Student's *t* test (for normally distributed data) or Wilcoxon rank sum test (for non-normally distributed data), and categorical variates were compared with chi-square tests. Kaplan–Meier plots were established, and log-rank statistics were employed to evaluate survival differences at specific time points of 12, 24 and 60 months after enrollment as well as overall survival. Cox regression was performed to confirm the factors independently related to worse outcomes to reduce selection bias among children involved in the study. Hazard ratios (HR) and 95% confidence intervals (95% CI) were used to present the data. $P < 0.05$ was identified statistically significant.

Results

Clinical Characteristics

There were 121 DCM patients in this cohort. The mean age of the 121 patients was 118.5 ± 63.0 months. Of these, 81 (67.8%) patients were grouped as severe HF and 39 (32.2%) were placed in a mild HF group. Table 1 presents the demographic information, clinical indicators, echocardiographic characteristics, medications used at the time of cardiomyopathy diagnosis, time period of follow-up and the outcomes of patients who were classified as severe HF compared with those who were classified as mild HF. There were no significant differences between the groups when compared by race, duration of symptoms, duration in the first hospitalization, multiplicity of hospitalizations, family history of DCM, BMI, heart rate and systolic blood pressure. Nevertheless, patients with severe HF were older, more likely to be male, have lower systolic pressure, be admitted to the intensive care unit and be treated with β-blockers, loop diuretics, spironolactone and digoxin. Patient with severe HF were more likely to have lower LVEF z-scores, larger systolic and diastolic LV dimensional z-scores, and more likely to suffer from aortic and tricuspid regurgitations.

Table 1
Demographics, clinical indicators, echocardiographic measurement, drug use, time of follow-up and Outcomes of the patients in this study.

Parameter	Overall (n = 121)	Severe HF (n = 82)	Mild HF (n = 39)	*p*
Age, (mean ± SD), m	118.5 ± 63.0	129.5 ± 64.5	95.4 ± 53.5	**0.005**
Male, n (%)	69 (57.0%)	52 (63.4%)	17 (43.5%)	**0.04**
Race, n (%)				0.865
Han	58 (47.9%)	38 (46.3%)	20 (51.3%)	
Zhuang	57 (47.1%)	40 (48.8%)	17 (43.6%)	
Others	6 (5.0%)	4 (4.9%)	2 (5.1%)	
Duration of symptoms, (mean ± SD), m	4.0 ± 9.6	3.9 ± 8.9	4.2 ± 11.1	0.899
Duration in first hospitalization, (mean ± SD), d	11.8 ± 10.4	12.5 ± 11.3	10.5 ± 8.0	0.342
Multiple hospitalizations, n (%)	51 (42.1%)	39 (47.6%)	12 (30.8%)	0.08
Admission to intensive care unit, n (%)	53 (43.8%)	45 (54.8%)	8 (20.5%)	**< 0.001**
Family history of dilated cardiomyopathy, n (%)	10 (8.3%)	8 (9.7%)	2 (5.1%)	0.388
Body mass index, (mean ± SD)	16.3 ± 3.3	16.7 ± 3.5	15.6 ± 2.6	0.089
Heart rate at admission, (mean ± SD)	113.4 ± 21.9	114.2 ± 20.8	111.7 ± 24.3	0.574
systolic blood pressure at admission, (mean ± SD)	99.3 ± 14.4	97.2 ± 14.4	104.1 ± 13.4	**0.017**
diastolic blood pressure at admission, (mean ± SD)	64.8 ± 11.5	64.2 ± 11.5	66.1 ± 11.6	0.417
Medications at diagnosis N (%)				
ACEI/ARNI	103 (85.1%)	71 (86.5%)	32 (82.0%)	0.512
β-blocker	37 (30.5%)	30 (36.5%)	7 (17.9%)	**0.038**
Loop diuretic	114 (94.2%)	81 (98.7%)	33 (84.6%)	**0.002**
Spironolactone	111 (91.7%)	78 (95.1%)	33 (84.6%)	**0.05**
Digoxin	114 (94.2%)	81 (98.7%)	33 (84.6%)	**0.002**

HF, heart failure; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEDPWT, left ventricular end-diastolic posterior wall thickness; LVEDST, left ventricular end-diastolic septal thickness; ACEI, angiotensin-converting enzyme inhibitors; ARNI, angiotensin II receptor blocker neprilysin inhibitor.

Parameter	Overall (n = 121)	Severe HF (n = 82)	Mild HF (n = 39)	*p*
Intravenous inotropes	61 (50.4%)	46 (56.1%)	15 (38.4%)	0.07
LV echocardiographic z scores, (mean ± SD)				
LVEDD z scores	7.3 ± 2.8	7.7 ± 2.6	6.5 ± 2.8	**0.033**
LVESD z scores	10.4 ± 3.3	10.8 ± 3.1	9.4 ± 3.5	**0.035**
LVEDPWT z scores	0.9 ± 2.4	0.9 ± 2.7	0.9 ± 1.8	0.99
LVEDST z scores	0.2 ± 1.6	0.2 ± 1.7	0.2 ± 1.4	0.679
LV fractional shortening z scores	-8.9 ± 4.8	-9.1 ± 5.3	-8.4 ± 3.7	0.411
LV ejection fraction z scores	-6.5 ± 2.1	-7.0 ± 2.0	-5.6 ± 2.0	**0.001**
Mitral regurgitation, n (%)	80 (96.6%)	80 (97.5%)	37 (94.8%)	0.439
Aortic regurgitation, n (%)	10 (12.1%)	10 (12.1%)	0 (0.0%)	**0.023**
Tricuspid regurgitation, n (%)	104 85.9%)	74 (90.2%)	30 (76.9%)	**0.049**
Pulmonary regurgitation, n (%)	43 (35.5%)	32 (39.0%)	11 (28.2%)	0.245
Follow-up times	30.5 ± 42.9	24.4 ± 40.4	43.2 ± 45.7	**0.024**
Events	83 (68.5%)	65 (79.2%)	18 (46.1%)	**< 0.001**

HF, heart failure; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEDPWT, left ventricular end-diastolic posterior wall thickness; LVEDST, left ventricular end-diastolic septal thickness; ACEI, angiotensin-converting enzyme inhibitors; ARNI, angiotensin II receptor blocker neprilysin inhibitor.

Outcomes

The median follow-up time was 24.4 months for patients with severe HF and 43.2 months for patients with mild HF (P < 0.024). Of the 82 children with severe HF, 50 (60.9% at 12months), 56 (68.3% at 24 months), 65 (79.2% at 60 months) and 65 (79.2%, overall) died, whereas among the 39 children with mild HF, 9 (23.1% at 12 months), 12 (30.8% at 24 months), 18 (46.1% at 60 months) and 18 (46.1% overall) died (P < 0.001). Compared with those with mild HF, the time to death was shorter for children with severe HF (Fig. 1, P < 0.001). Cox regression analysis was employed to confirm the factors related to the overall probability of death (Table 2). Severe HF increased the risk of death in unmodulated and in all modulated Cox regression analyses. This relationship was not weakened after modulating for various factors. However, after modulating for use of loop diuretics, severe HF was independently related to a higher risk of death (hazard ratio [HR] 2.27; 95% CI, 1.28–4.03 in model 6). In model 6, use of loop diuretics was related to a decreased risk of death (Table 2, hazard ratio [HR] 0.074; 95% CI, 0.006–0.876, p<0.039).

Table 2
Multivariate Cox regression modeling of severe heart failure versus mild heart failure.

Outcome	Variates	Model 1 (n = 121)	Model 2 (n = 121)	Model 3 (n = 121)	Model 4 (n = 121)	Model 5 (n = 121)	Model 6 (n = 121)
Death	**Heart Failure (severe vs mild)**	**2.516 (1.488–4.255) <0.001**	**2.614 (1.538–4.440) <0.001**	**2.741 (1.603–4.686) <0.001**	**2.625 (1.524–4.620) <0.001**	**2.512 (1.448–4.357) <0.001**	**2.274 (1.280–4.038) <0.005**
	Age (months)		0.998 (0.995–1.002) 0.329	0.998 (0.995–1.002) 0.460	0.999 (0.996–1.003) 0.743	0.999 (0.995–1.003) 0.558	1.000 (0.995–1.004) 0.947
	Sex			1.330 (0.854–2.073) 0.207	1.318 (0.847–2.051) 0.221	1.283 (0.821–2.006) 0.273	0.766 (0.475–1.237) 0.276
	Heart Rate				1.005 (0.995–1.016) 0.335	1.004 (0.993–1.015) 0.445	1.005 (0.993–1.016) 0.418
	LVEF z scores					0.949 (0.857–1.052) 0.320	0.935 (0.838–1.043) 0.225
	ACEI/ARNI (yes vs no)						1.214 (0.569–2.588) 0.615
	β-blockers (yes vs no)						1.035 (0.551–1.942) 0.915
	Loop diuretics (yes vs no)						**0.074 (0.006–0.876) 0.039**
	Spirolactone (yes vs no)						2.338 (0.756–7.232) 0.140

Hazard ratios (95% CIs) and P values were used to show data. Variates were employed according to the statistics in Table 1 ($P < 0.05$) or prognostic indicator. Model 1 is a one-variable Cox regression analysis with heart failure (HF) variable (severe HF vs mild HF). Model 2 modulates for age. Model 3 ulteriorly modulates for sex (male/female) besides the variates in Model 2. Model 4 ulteriorly modulates for heart rate besides the variates in Model 3. Model 5 ulteriorly modulates for LV ejection fraction z score besides the covariates employed in Model 4. Model 6 ulteriorly modulates for drug (including either ACEI or ARNI, and beta blockers, loop diuretics, spironolactone, digoxin and intravenous inotropes) besides the variates employed in Model 5.

Outcome	Variates	Model 1 (n = 121)	Model 2 (n = 121)	Model 3 (n = 121)	Model 4 (n = 121)	Model 5 (n = 121)	Model 6 (n = 121)
	Digoxin (yes vs no)						2.421 (0.406–16.912) 0.311
	Intravenous inotropes (yes vs no)						0.943 (0.577–1.542) 0.815

Hazard ratios (95% CIs) and P values were used to show data. Variates were employed according to the statistics in Table 1 (P < 0.05) or prognostic indicator. Model 1 is a one-variable Cox regression analysis with heart failure (HF) variable (severe HF vs mild HF). Model 2 modulates for age. Model 3 ulteriorly modulates for sex (male/female) besides the variates in Model 2. Model 4 ulteriorly modulates for heart rate besides the variates in Model 3. Model 5 ulteriorly modulates for LV ejection fraction z score besides the covariates employed in Model 4. Model 6 ulteriorly modulates for drug (including either ACEI or ARNI, and beta blockers, loop diuretics, spironolactone, digoxin and intravenous inotropes) besides the variates employed in Model 5.

Discussion

The study demonstrates that children with DCM and severe HF at diagnosis were older, more likely to be male, have lower systolic blood pressure measurements, be admitted to the ICU and be treated with β-blockers, loop diuretics, spironolactone and digoxin. They are also more likely to have larger diastolic LV end-diastolic dimensional z-scores and poorer LV function. Compared with children with DCM and mild HF, those with DCM and severe HF at diagnosis were at a higher risk of death. Severe HF was related to an accumulated risk of death. These associations were not affected by sex, age at diagnosis, heart rate, ventricular function and use of medication.

These results are similar to those found in a study by Rusconi [11]. They showed similar results with respect to survival between family-associated DCM and idiopathic DCM after modulation for other variates. However, HF, older age, and larger left ventricular end-diastolic dimension (LVEDD) at diagnosis were independently related to increased risks of the major adverse events of heart transplantation or death. In a retrospective analysis, HF with NYHA III/IV were significantly associated with overall death risk[12]. A meta-analysis of 57 researches of medication adherence interventions for HF treatment from adults found an obvious association between improvement of HF and a decrease of mortality[13]. These findings lend support to the idea that an improvement in HF may be a key goal for DCM therapy.

Angiotensin-converting enzyme inhibitors (ACEI) is the cornerstone of HF treatment and can significantly improve cardiac remodeling. The beneficial effects of ACEI for HF in children with DCM have been proven in previous studies[14, 15]. One prospective and large-sample study which included 5,955 adult patients with DCM and LVEF < 40% also confirmed that use of ACEI was related to the recovery of the LVEF coupled with an improvement of HF at 3 years of follow-up[16]. In a European survey between pediatric HF and ACEI use patterns conducted between January and May 2015, ACEI appeared to be essential in

pediatric HF treatment strategies[17]. Nowadays, the angiotensin II receptor blocker, neprilysin inhibitor (ARNI), is more effective when compared with ACEI, and this drug has now been recommended to be the preferred treatment in patients with HF[8, 9, 18].

In children with DCM and HF, elevated heart rate is often accompanied by worsening HF. Thus, the heart rate may be a target for HF treatment. Beta blockers can reduce heart rate. Three meta-analysis on the use of beta-blockers for congestive HF in children showed that children with congestive HF might benefit from treatment with these drugs[19–21]. Additionally, ivabradine is a novel drug which can reduce the heart rate. A study randomized 116 patients diagnosed with DCM and class II to IV HF. In this study, the heart rate was reduced by ≥ 20% from baseline without leading to symptoms or bradycardia were more likely to occur in the patients taking ivabradine rather than taking the placebo. This reduction was accompanied with a significant increase in the LVEF, an improvement of the cardiac function as well as in the quality of life[22]. Another adult study also showed that the reduction of heart rate in the ivabradine group could improve the prognosis of HF[23].

In our study, loop diuretics was related to a decreased risk of death. Diuretics are also another important treatment for HF. A meta-analysis of 14 studies with 525 participants of the use of diuretic in HF suggested that these were able to reduce mortality and retard progression of HF [24]. In a study of 25,345 elder patients with HF, patients with loop diuretics as a discharge prescription had a better clinical improvement comparing with those not taking loop diuretics[25]. One study included 108 children and showed that an increase of loop diuretic responsiveness during the first 72 hours of treatment was accompanied by shorter length of hospital stays and a decrease of inpatient deaths or use of mechanical circulatory support[26]. In addition to loop diuretics, a mineralocorticoid receptor antagonist (MRA), such as spironolactone, which can also have a diuretic effect, is fundamental during the long-term management of HF[27].

There are several emerging treatments for HF in children with DCM. In a meta-analysis study, sodium-glucose co-transporter-2 (SGLT2) inhibitors were shown to reduce all-cause and cardiovascular death in patients with HF [28], and these drugs are recommended to be the preferred choice of treatment in patients with HF[8, 9]. Pulmonary artery banding (PAB) treatment, as a new indication for end-stage DCM in pediatric patients, has also been shown to be safe and effective[29, 30]. Left ventricular mechanical assist can be indicated as destination therapy for end-stage DCM[31]. Cardiac pacemaker can be an effective tool for treating HF, especially in patients who have a complete left bundle branch block[32]. Cardiac stem cell therapy is yet another feasible and safe treatment in children with DCM and HF, and can improve left ventricular function[33]. If none of the above methods work, heart transplantation could be considered as a last resort[34].

As we have already confirmed that severe HF is related to a higher risk of death in children with DCM, so therapies that improve HF can increase survival. Through a more comprehensive understanding of DCM, especially with respect to the genetics of DCM and the potential of finding new early markers and treatment for HF, it is envisaged that the treatment of HF caused by DCM will become more personalized

and lead to earlier interventions [35–37]. Thus, a larger and prospective study combining all these factors should be performed to evaluate the efficacy between the treatment of HF and outcomes in children with DCM.

Limitations

Several limitations were included in this study. Assessment of cardiac functions is often difficult and a lack of objectivity can occur due to non-cooperation of young children. Echocardiography was usually not performed by the same doctor. This may have introduced error measurements into the research. This just was a small-sample and retrospective research in one single center and therefore prone to biases and limitations. Further larger-sample and prospective researches are warranted to verify our conclusions. Finally, selection bias was existed due to the nature of the retrospective study.

Conlusions

It was concluded that severe HF at diagnosis was related to a higher risk of death. The result shows that improvement of HF may be a primary goal of therapy and can potentially increase the survival in children with DCM. Further prospective studies are warranted to evaluate the efficacy between the treatment of HF and outcomes in children with DCM.

Abbreviations

DCM
Dilated cardiomyopathy
HF
Heart failure
LVEDD
left ventricular end-diastolic dimension
SDs
standard deviations
LVESD
left ventricular end-systolic dimension
LVEDPWT
left ventricular end-diastolic posterior wall thickness
LVEDST
left ventricular end-diastolic septal thickness LVEF:left ventricular ejection fraction
LVFS
left ventricular fractional shortening
BMI
body mass index
HR

Hazard ratios
CI
confidence intervals
ACEI
Angiotensin-converting enzyme inhibitors
ARNI
neprilysin inhibitor
MRA
mineralocorticoid receptor antagonist
SGLT2
sodium-glucose co-transporter-2
PAB
pulmonary artery banding.

Declarations

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AUTHOR CONTRIBUTIONS

CC contributed to study design and drafted the article. DS, SQ, YH and WZ contributed to statistical analysis, BY, YH and DL collected data. YP contributed to the concept of the research and the edited manuscript. All authors took part in drafting article and had their permission for publication.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (NO. 2022(KY-E-007)) and carried out in accordance with the principles of the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from their legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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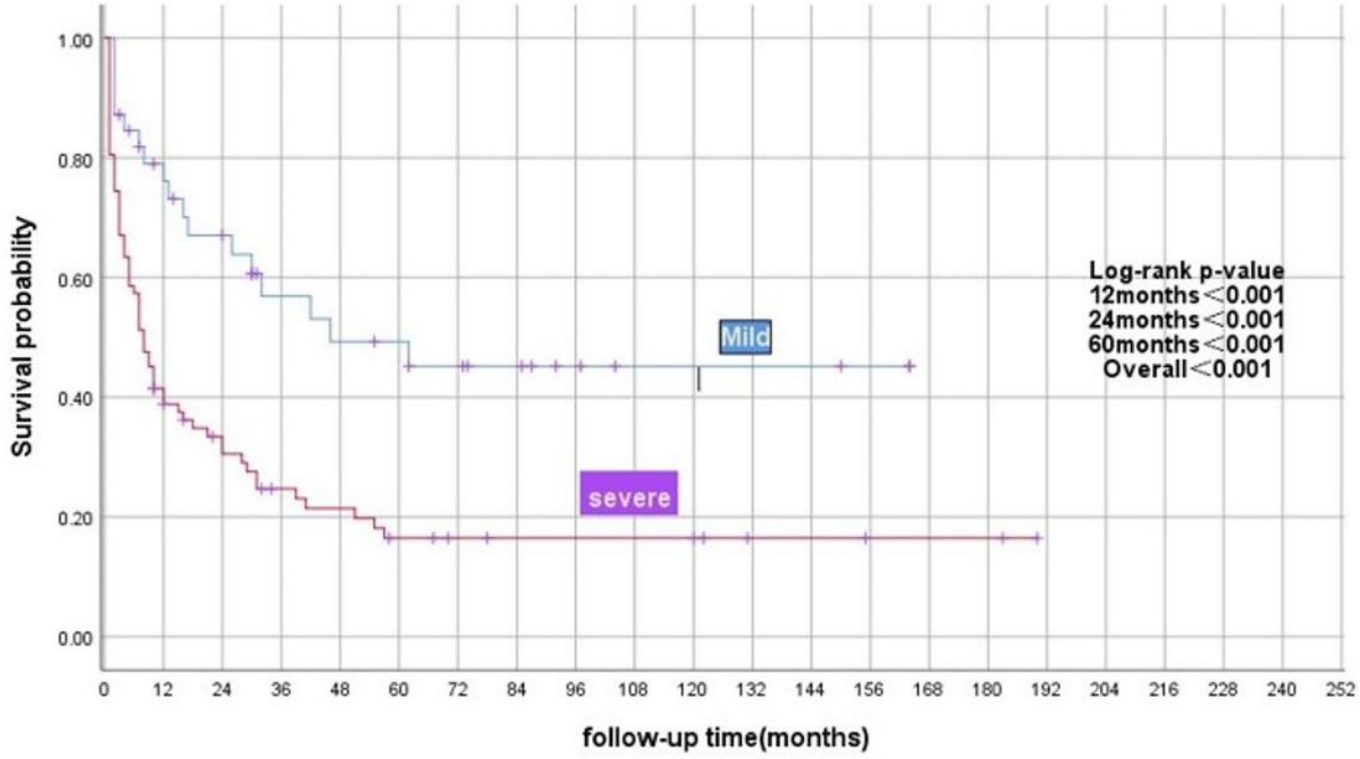
Figures



Number of accumulative death					
Severe	50	56	60	65	65
Mild	9	12	15	17	18

Figure 1

Survival analysis in severe and mild heart failure. The time to death was shorter for children with severe HF, compared with those having mild HF. Log-rank testing P values for survival at 12, 24, and 60 months

after diagnosis of dilated cardiomyopathy were <0.001.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- dataSevereHeartFailureandOutcomesin121ChildrenWithDilatedCardiomyopathy.xls