Clinical characteristics and survival of children with hypertrophic cardiomyopathy in China: A multicentre retrospective cohort study

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Summary

Background Few data on paediatric hypertrophic cardiomyopathy (HCM) are available in developing countries. A multicentre, retrospective, cohort study was conducted to profile the clinical characteristics and survival of children with HCM in China.

Methods We collected longitudinal data on children with HCM aged 0–18 years at three participating institutions between January 1, 2010 and December 31, 2019. Patients were identified by searching for the diagnosis using ICD-10 codes from the electronic medical records database. HCM was diagnosed morphologically with echocardiography or cardiovascular magnetic resonance imaging. The exclusion criteria were secondary aetiologies of myocardial hypertrophy. The primary outcomes were all-cause death or heart transplantation. The Kaplan–Meier method was used to estimate the survival rate of different groups.

Findings A total of 564 children were recruited, with a median age at diagnosis of 1.0 year (interquartile range, IQR: 0.4–8.0 years), followed for a median of 2.6 years (1977 patient-years, IQR: 0.5, 5.9 years). The underlying aetiology was sarcomeric (382, 67.7%), inborn errors of metabolism (IEMs) (108, 19.2%), and RASopathies (74, 13.1%). A total of 149 patients (26.4%) died and no patients underwent heart transplantation during follow-up. The survival probability was 71.1% (95% confidence interval [CI], 66.3%–75.3%) at 5 years. Patients with IEMs or those diagnosed during infancy had the poorest outcomes, with an estimated 5-year survival rate of 16.9% (95% CI, 7.7%–29.1%) and 56.0% (95% CI, 48.8%–62.5%), respectively. Heart failure was the leading cause of death in the cohort (90/149, 60.4%), while sudden cardiac death was the leading cause in patients with sarcomeric HCM (32/66, 48.5%).

Interpretation There is a high proportion of patients with IEM and a low proportion of patients with neuromuscular disease in children with HCM in China. Overall, mortality remains high in China, especially in patients with IEMs and those diagnosed during infancy.

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Published online 27 May 2022
https://doi.org/10.1016/j.eclinm.2022.101466

www.thelancet.com Vol 49 Month July, 2022
**Introduction**

Hypertrophic cardiomyopathy (HCM) is a disease defined by an abnormally hypertrophied left ventricle with no hemodynamic cause. In children, HCM is a heterogeneous condition in terms of aetiology, clinical presentation, genomic alterations, and survival outcomes, with an estimated incidence rate of 0.24 per 100,000 per year. Compared with adult HCM, paediatric HCM is characterised by diverse underlying causes, a progressive nature, and poorer outcomes. Aetiologic sub-categories of paediatric HCM include sarcomeric defects, inborn errors of metabolism (IEMs), RASopathies -A group of disorders caused by gene mutations in the RAS-MAPK pathway, and neuromuscular disorders (NMD). Aetiology and age at presentation are the two principal determinants of survival in these patients.

**Evidence before this study**

We searched PubMed, web of science, and China National Knowledge Infrastructure for papers published in English and Chinese without date restrictions between database inception up to 12 December 2020. We used the search terms "Hypertrophic cardiomyopathy", and ("paediatric" OR "child"), and ("survival" OR "outcome"), and found that several previous studies of high quality have delineated the clinical course of children with hypertrophic cardiomyopathy (HCM). However, most of them were from high-income countries. Data on paediatric HCM from developing countries based on large-scale population were still limited, with studies usually based at a single centre with a small sample size.

** Added value of this study**

Based on the data from a large-scale multicentre longitudinal retrospective cohort, we described the aetiology distribution, clinical characteristics, genetic profiles, and survival status of paediatric patients with HCM in China. There is a high proportion of patients with inborn errors of metabolism and a low proportion of patients with neuromuscular disease in children with HCM in China. Compared with developed countries, the overall mortality of paediatric HCM remains relatively high in China, especially in patients with IEMs and those diagnosed during infancy.

**Implications of all the available evidence**

Our results show a significant disease burden and unmet medical service demand for paediatric HCM in China. These findings, if confirmed by further studies, may have significant implications for the treatment and prognosis of paediatric HCM, particularly in low- and middle-income countries.

**Methods**

**Study population**

A multi-centre, retrospective, longitudinal cohort of patients <18 years with HCM was established. We recruited patients at three large tertiary care referral centres for children with heart disease in the country, including the Shanghai Children’s Medical Centre, the Children’s Hospital of Nanjing Medical University, and Guangdong Provincial People’s Hospital, between January 1, 2010 and December 31, 2019. Patients were identified by searching for the diagnosis using ICD-10 codes from the electronic medical records database.

HCM was diagnosed morphologically with echocardiography or cardiovascular magnetic resonance imaging according to the following specific criteria: the presence of either interventricular septal or left ventricular posterior wall thickness for body-surface area > 2 standard deviations above the mean for a normal population corrected with body surface-area (Z score ≥ 2), or localised left ventricular hypertrophy not solely...
explained by hemodynamic changes. All cases with approximate Z scores were reviewed by experienced cardiologists to make a final determination of eligibility.

The exclusion criteria were specific secondary aetiologies of myocardial hypertrophy, such as hypertension; pulmonary parenchymal, pulmonary vascular, rheumatic, immunologic, and endocrine diseases; exposure to cardiotoxic drugs, or congenital heart diseases independent of RASopathies. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Shanghai Children’s Medical centre (SCMCIRB-W2020053). All participating centres obtained institutional review board approval for the study. Patient consent for inclusion was waived because of the retrospective nature of the study. The manuscript is adherent to STROBE guidelines.

Data collection
Three researchers reviewed the clinical records, cardiac imaging, and genetic test results of eligible participants. Demographic and relevant clinical data, including medical history, aetiology, echocardiographic measurements, genetic test results, medical therapies, and clinical outcomes were collected at baseline and follow-ups. Ambulatory electrocardiogram and cardiac magnetic resonance imaging were not routinely evaluated in our clinical practice, and therefore that data was not included. We trained the researchers to collect the data according to a uniform standard. The final judgement over ambiguous variables was made by the chief physician (LF).

Patients with HCM were categorised by aetiology as sarcomeric HCM, IEMs, RASopathies, and NMD. Sarcomeric HCM was diagnosed if pathogenic or likely pathogenic mutations in sarcomeric genes were present. In clinical practice, patients without extracardiac manifestations and no specific cause were classified as idiopathic HCM. As it is widely believed that these groups of patients share the same therapies and outcomes to a large extent, they were grouped together as sarcomeric HCM in this study for statistical analysis. Diagnoses of IEMs, RASopathies, and NMD were based on typical clinical manifestations and specific laboratory evidence with or without genetic test results. All genetic variations were classified according to the recommended method of the American College of Medical Genetics and Genomics.

Obstructive HCM was diagnosed in the presence of left or right ventricular outflow obstruction (LVOTO or RVOTO) which were defined as instantaneous peak Doppler left or right ventricular outflow tract pressure gradients ≥ 30 mmHg.

Primary endpoints
These were either heart transplantation or all-cause death, including heart failure–related death (HFD), sudden cardiac death (SCD), non-cardiac death (NCD), or unknown cause death (UCD). SCD was defined as witnessed sudden death with or without documented ventricular fibrillation, death within 1 h of new symptoms, or nocturnal death with no antecedent history of worsening symptoms. The cause of death was ascertained by experienced cardiologists at each hospital. Follow-up data were available up to June 30, 2021. Patients were classified as lost to follow-up if the last clinical review was more than 3 years prior to June 30, 2021 and the patient could not be contacted. All patients were followed up by telephone interview or outpatient clinic visit. Patients who did not have any one of the endpoints were censored on June 30, 2021 and patients who were lost to follow up were censored at the last follow-up.

Statistical analysis
The body-surface area was calculated according to the patient’s height and weight. Echocardiographic measurements were transformed into Z scores after adjustment for body-surface area relative to the normal population. Descriptive demographic and clinical characteristics are presented as counts and percentages for categorical variables and means ± standard deviations (SD) for normally or approximately normally distributed continuous data. Skewed data are described with medians and interquartile ranges (IQRs). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Categorical variables were compared using chi-square or Fisher’s exact tests. Normally distributed continuous variables were compared with the Student’s t-test for two groups and analysis of variance for three or more groups. Skewed data were compared by Wilcoxon rank sum tests for two groups and Kruskal–Wallis tests for three or more groups. The Kaplan–Meier method was used for survival estimates of time since diagnosis. Group differences were compared with log-rank tests. A P-value < 0.05 (two-tailed) was considered statistically significant. All analyses were conducted by Stata software version 16.0 (Stata Corp, College Station, TX, USA) and R software version 4.0.3 (R foundation).

Role of the funding source
The study sponsors had no role in study design, data collection, data analysis, data interpretation or writing of the report. All authors had access to the data and had final responsibility for the decision to submit for publication.

Results
Study population
A total of 564 paediatric patients with HCM were recruited (Figure 1). The clinical characteristics of the
Figure 1. Flowchart of the participants included in the cohort.

HCM, hypertrophic cardiomyopathy; SCMC, Shanghai Children’s Medical Centre; GPPH, Guangdong Provincial People’s Hospital; CHNMU, Children’s Hospital of Nanjing Medical University; IEMs, inborn errors of metabolism; SCD, sudden cardiac death; HFD, heart failure related death; NCD, non-cardiac death; UCD, unknown cause death; the blue boxes at the bottom show patient outcomes of the whole cohort.
The median age at diagnosis was 1.0 year (IQR: 0.4–8.0 years), 275 patients (48.8%) were diagnosed during infancy - the period from birth to age of 1 year, and 352 patients (62.4%) were male. The calendar year of diagnosis was illustrated in Supplementary Figure 1.

Aetiology

The underlying aetiologies were sarcomeric (n = 382, 67.7%), IEMs (n = 108, 19.2%), and RASopathies (n = 74, 13.1%). None of the patients had NMD. Amongst patients classified as sarcomeric HCM, 299 (53.0%) had neither extracardiac manifestations nor causative genetic findings and should be considered idiopathic HCM. Pompe disease (n = 83) was the most common type in patients with IEMs, and Noonan syndrome (n = 65) in patients with RASopathies.

There were significant differences amongst the different aetologic subgroups regarding age at diagnosis, onset in infancy, family history of HCM, personal history of unexplained syncope, and echocardiographic findings (Table 2). Patients with IEMs and RASopathies tended to be diagnosed at a younger age than those with sarcomeric HCM (p < 0.0001). Most patients with IEM were diagnosed in infancy, patients with sarcomeric HCM were diagnosed at various ages, and most RASopathic patients were diagnosed by the age of six (p < 0.0001, Supplementary Figure 2). Family history of HCM and personal history of unexplained syncope were more frequent in patients with sarcomeric HCM than in the other two groups (p = 0.023 and p = 0.00049, respectively). Patients with IEMs had a

| Whole | Sarcomeric | IEMs | RASopathies | p-value |
|-------|------------|------|-------------|---------|
| Number | 564 | 382 | 108 | 74 |
| Site, n(%) | | | | |
| SCMC | 422 (74.8%) | 271 (70.9%) | 88 (81.5%) | 63 (85.1%) | <0.0001 |
| GPPH | 107 (19.0%) | 93 (24.3%) | 9 (8.3%) | 5 (6.8%) |
| CHNMU | 35 (6.2%) | 18 (4.7%) | 11 (10.2%) | 6 (8.1%) |
| Sex, n(%) | | | | |
| Male | 352 (62.4%) | 250 (65.4%) | 62 (57.4%) | 36 (55.4%) | 0.086 |
| Female | 212 (37.6%) | 132 (34.6%) | 46 (42.6%) | 34 (44.6%) |
| Ethnicity, n(%) | | | | |
| Han | 557 (98.8%) | 377 (98.7%) | 106 (98.1%) | 74 (100.0%) | 0.59 |
| Minority | 7 (1.2%) | 5 (1.3%) | 2 (1.9%) | 0 (0.0%) |
| Age at diagnosis (year), median (IQR) | 1 (0.4,8.0) | 3.5 (0.5,9.6) | 0.5 (0.3,0.7) | 0.5 (0.2,1.3) | <0.0001 |
| Infantile, n(%) | 275 (48.8%) | 140 (36.6%) | 48 (44.4%) | 4 (5.4%) | <0.0001 |
| CHF, n(%) | 108 (19.1%) | 56 (14.7%) | 48 (44.4%) | 4 (5.4%) | 0.023 |
| FHCM, n(%) | 75 (13.3%) | 14 (3.7%) | 3 (4.1%) | 0.13 |
| FSCD, n(%) | 22 (3.9%) | 4 (3.7%) | 0 (0.0%) | 3 (4.1%) | 0.00049 |
| Syncope, n(%) | 37 (6.6%) | 34 (8.9%) | 0 (0.0%) | 3 (4.1%) |
| Outcome, n(%) | | | | |
| Survival | 415 (73.6%) | 316 (82.7%) | 35 (32.4%) | 64 (86.5%) | <0.0001 |
| Death | 149 (26.4%) | 66 (17.3%) | 73 (67.6%) | 10 (13.5%) |
| Follow-up time(year), median (IQR) | 0.5 (0.1,3.1) | 2.5 (0.3,5.5) | 0.3 (0.1,0.5) | 0.4 (0.1,1.0) |
| alive | 3.2 (1.3,6.4) | 3.6 (1.5,6.9) | 1.1 (0.1,2.1) | 3.1 (1.9,5.6) |
| Cause of death, n(%) | | | | |
| HFD | 90 (60.4%) | 22 (33%) | 61 (85%) | 7 (70%) | <0.0001 |
| SCD | 39 (26.2%) | 32 (48%) | 4 (5%) | 3 (30%) |
| NCD | 6 (4.0%) | 2 (3%) | 5 (4%) | 0 (0%) |
| UCD | 16 (4.0%) | 10 (15%) | 5 (4%) | 0 (0%) |
| Number of clinic visits, median (IQR) | 7 (4,12) | 4 (1,13) | 6 (4,9) | 8 (4,12) |

Table 1: Clinical characteristics of the cohort and comparisons between aetiologic subgroups.

IEMs, inborn errors of metabolism; IQR, inter-quantile ranges; SCMC, Shanghai Children’s Medical centre; GPPH, Guangdong Provincial People’s Hospital; CHNMU, Children’s Hospital of Nanjing Medical University; CHF, congestive heart failure; FHCM, family history of hypertrophic cardiomyopathy; FSCD, family history of sudden cardiac death; HFD, heart failure related death; SCD, sudden cardiac death; NCD, non-cardiac death; UCD, unknown cause death;.

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** Kam (1), Zhuang (2), Manchu (1), and Uyghurs (1).
*** Yi (1) and Mogol (1).
higher z-score for left ventricular end-diastolic diameter and left ventricular posterior wall thickness, lower z-scores for left atrial diameter, lower left ventricular ejection fractions, and lower prevalence of obstructive physiology compared with sarcomeric HCM and RASopathies ($p < 0.0001$).

The aetiologic distributions were significantly different in different regions of the world (Supplementary Table S1). In our cohort, patients with IEMs constituted a larger component of paediatric HCM, while NMD was rarer compared to North America and the United Kingdom ($p < 0.0001$).

### Symptoms and histories

Most patients had no symptoms of discomfort (Supplementary Figure 3). Medical examination and cardiac murmur detected 226 (40.1%) and 124 (22.0%) patients, respectively. Congestive heart failure was present in 108 patients (19.2%). One patient (0.2%) presented with aborted cardiac arrest. A personal history of unexplained syncope was present in 37 patients (6.6%), 75 patients (13.3%) had a family history of HCM, and 22 patients (3.9%) had a family history of SCD.

### Echocardiographic findings

The baseline echocardiography evaluation is shown in Table 2. Asymmetric hypertrophy was observed in 382 patients (67.7%). Left ventricular enlargement was found in 84 patients (14.9%), while left atrial enlargement was found in 303 (53.7%). There were 184 obstructive HCM cases (32.6%) at the initial investigation, including 129 patients (22.9%) with LVOTO, 20 (3.5%) with RVOTO, and 34 (6.0%) with biventricular outflow obstruction. Twelve other patients developed LVOTO during follow-up. Extreme LVOTO (LVOT gradient $\geq 100$ mmHg) or RVOTO (RVOT gradient $\geq 100$ mmHg) was present in 27 (4.8%) and four patients (0.7%), respectively.

### Genetic profiles

A total of 307 patients (54.4%) had genetic testing (Table 3), and 230 variants were detected in all (Supplementary Table S2). Eighty-three patients carried pathogenic or likely pathogenic mutations in sarcomeric genes, most commonly in MYH7 ($n = 35$, 42.2%) and MYBPC3 ($n = 31$, 37.3%). Eighteen patients had a complex genetic status with multiple variants in sarcomeric genes.
A specific diagnosis in 248 patientsyielded a diagnostic rate of 80.8% (248 of 307). Overall, genetic tests identified in 165 patients, in which mutations in GAA (n = 77) and PTPN11 (n = 24) were most frequent. Twenty-seven patients received a negative result, and mutations in 32 patients were classified as variants of unknown clinical significance (VUS) according to the current database and information. The estimated survival rate from death was 82.8% (95% CI: 79.3%–85.8%) 1-year after diagnosis, 71.1% (95% CI: 66.3%–75.3%) at 5 years, and 57.1% (95% CI: 49.0%–64.3%) at 10 years (Figure 2A and Table 4). IEMS patients had the poorest outcomes, with an estimated survival rate of 16.9% (95% CI: 7.7%–29.1%) at 5 years (p < 0.0001, Figure 2B). Additionally, patients with left ventricular enlargement at baseline had a poorer prognosis (p < 0.0001, Figure 2E), while no significant differences were found according to left atrial enlargement at the initial evaluation (p = 0.66, Figure 2F).

### Causes of death
HFD was the leading cause of death (90/149, 60.4%). Causes of death varied significantly amongst different aetiologies; SCD was the leading cause in patients with sarcomeric HCM (32/66, 48.5%), while HFD was predominant in patients with IEMs (61/73, 85%) and RASopathies (7/10, 70%) (p < 0.0001, Supplementary Figure 4). Of note, SCD also occurred in patients with IEMs and RASopathies, including three patients with Noonan syndrome, two patients with Pompe disease, one patient with Danon disease, and one patient with PRKAG2 cardiac syndrome.

SCD was the most common reason for an adverse outcome in patients diagnosed after infancy, while HFD was the major cause of death in infancy onset patients (p < 0.0001). Additionally, HFD usually occurred during infancy, with the median age of death being 0.7 years (IQR: 0.4–0.9). Conversely, SCD occurred equally at all ages after infancy, with the median age of death being 8.3 years (IQR: 3.6–12.8) (Supplementary Figure 5).

### Malignant arrhythmic events
Forty-five patients (8.0%) experienced fatal arrhythmic events during follow-up: SCD in 39, aborted cardiac arrest in three, and appropriate implantable cardioverter defibrillator (ICD) discharge in three, with an event rate of 2.6 per 100 patient years at risk. Risk factors reported in earlier studies were screened and are summarised in Supplementary Table S3. All patients with SCD and equivalent events had more than one risk factor, with extreme left ventricular hypertrophy, left atrial enlargement, and personal history of unexplained syncope being the most common. In patients with malignant arrhythmias, five variants in MYBPC3 and three variants in MYH7 were detected.

### Therapy
Medications were disparate in our cohort and the most commonly used drug choices were summarised as follows. Beta-blockers were the mostly applied medicine in all the patients (n = 308, 54.6%), including propranolol (118, 20.9%) and metoprolol (190, 33.7%). Other frequently used medications include: catopril (130, 23.0%), spironolactone (176, 31.2%), furosemide (153, 27.1%), digoxin (35, 6.2%), amiodarone (17, 3.0%), and propafenone (16, 2.8%).

Forty-five patients (8.0%) received septal reduction therapy, and the median age at surgery was 8.3 (IQR:

| Table 3: Genetic variants identified in 307/564 cohort participants in whom genetic testing was performed. |
|--------------------------------------------------------------------------------------------------|
| **No. of patients (N = 307)** |
| Sarcomeric genes | 83 (27.0%) |
| MYH7 | 35 (42.2%) |
| MYBPC3 | 31 (37.3%) |
| TNNI3 | 4 (4.8%) |
| MYL2 | 5 (6.0%) |
| ≥2 pathogenic variants | 18 (21.7%) |
| Non-sarcomeric genes | 165 (53.8%) |
| GAA | 77 (46.7%) |
| PRKAG2 | 3 (1.8%) |
| LAMP2 | 6 (3.6%) |
| PTPN11 | 24 (14.5%) |
| RAF1 | 16 (9.7%) |
| Variant of uncertain significance | 32 (10.4%) |
| Negative | 27 (8.8%) |

Genes with mutations included: MYH7 (24.8%), MYBPC3 (23.4%), and MYL2 (4.0%). The most common sarcomeric genes were MYH7 (77, 46.7%) and MYBPC3 (31, 19.5%). In non-sarcomeric genes, the most frequent were PRKAG2 (3, 1.8%) and GAA (77, 46.7%).
Figure 2. Kaplan–Meier survival probabilities.

A. for cohort; B. stratified by aetiology; C. stratified by age at diagnosis; D. stratified by obstructive physiology; E. stratified by left ventricular enlargement; F. stratified by left atrial enlargement; CI, confidence interval; IEM, inborn errors of metabolism; HOCM, obstructive HCM; LVE, left ventricular enlargement; LAE, left atrial enlargement; the P value cited on the plot is from a log rank test.
tality of paediatric HCM remains relatively high in comparison with developed countries, we found that the overall mortality in China while SCD prevailed in patients with sarcomeric HCM.

Earlier studies from Australia, North America, and Europe have provided insightful and valuable information on the epidemiology, clinical characteristics, survival, and risk factors of paediatric HCM.

The Paediatric Cardiomyopathy Registry (PCMR), a multicentre cohort from North America, currently had the largest sample size worldwide, including 855 pure HCM patients <18 years. The retrospective cohort from the United Kingdom followed closely, with 687 patients <16 years. Reports from Australia have described the disease based on the national population, including 80 patients <10 years, with the longest follow-up. Our cohort included three large-scale tertiary referral centres for children with heart disease in China and identified 564 patients <18 years over a 10-year period. The large sample size enables our cohort to be comparable to those of earlier studies and can be considered representative of the Chinese population.

The exact prevalence and incidence of paediatric HCM in China remains unknown. Zou et al. investigated adult HCM in China and found that the age- and sex-adjusted prevalence was approximately 80 per 100,000 adults, suggesting that there are at least one million cases in China. Likewise, it is easy to hypothesise that there may be a significant disease burden of paediatric HCM in China.

In agreement with the literature, the aetiology of paediatric HCM was heterogeneous, with a larger component of non-sarcomeric diseases. However, we found that the aetiology distributions were significantly different in different regions worldwide. In China, patients with IEMs comprised a larger fraction, while patients with NMD were rare. Generally, hypertrophic cardiomyopathy is a less common type of cardiac abnormalities associated with neuromuscular disorders (NMDs). The NMDs most commonly associated with HCM include Emery-Dreifuss muscular dystrophy, limb-

### Table 4: Survival estimates from time of diagnosis to all-cause death.

Survival rates from time of diagnosis to all-cause death estimated using Kaplan-Meier method, the p value is from a log rank test; CI, confidence interval; IEMs, inborn errors of metabolism.

| Aetiology   | 1-year[95%CI] | 2-year[95%CI] | 5-year[95%CI] | 10-year[95%CI] | P value |
|-------------|--------------|--------------|--------------|---------------|---------|
| Cohort      | 82.8% [79.3%, 85.8%] | 79.3% [75.4%, 82.6%] | 71.1% [66.3%, 75.3%] | 57.1% [49.0%, 64.3%] |         |
| Sarcomeric  | 94.0% [90.1%, 96.0%] | 91.0% [87.4%, 93.6%] | 82.2% [76.8%, 86.5%] | 66.7% [56.4%, 75.1%] | <0.0001 |
| IEMs        | 38.9% [29.2%, 48.5%] | 29.5% [20.3%, 39.2%] | 16.9% [7.7%, 29.1%] | -             |         |
| Rasopathies | 88.9% [79.0%, 94.3%] | 88.9% [79.0%, 94.3%] | 85.5% [72.6%, 92.6%] | 73.3% [41.6%, 89.6%] |         |
| Onset age   |              |              |              |               |         |
| <1 year     | 67.4% [61.2%, 72.8%] | 63.2% [56.8%, 68.9%] | 56.0% [48.8%, 62.5%] | 41.4% [31.2%, 51.3%] | <0.0001 |
| ≥1 year     | 97.3% [94.5%, 98.7%] | 94.3% [90.5%, 96.6%] | 85.3% [79.0%, 89.9%] | 71.5% [58.7%, 81.0%] |         |
girdle muscular dystrophy, myofibrillar myopathy, metabolic myopathy and Friedreich’s ataxia (FRDA). In the USA cohort, 64 patients (7.5%) had neuromuscular disorders, and 56 patients of them were FRDA according to their supplemental data. Similarly, in the UK cohort, 9.3% (64 patients) had NMDs and FRDA accounted for 59 patients according to their supplemental Table 2. Hence, we speculated that NMDs in children with HCM may be mainly related to FRDA, an inherited, progressive neurodegenerative movement disorder caused by mutations in the FXN gene, with a typical age of onset between 10 and 16 years. However, it was reported that FRDA was rare amongst sub-Saharan Africans, Amerindians, and people from China, Japan, and Southeast Asia. Zeng J et al. firstly reported the exact data showing that no Friedreich’s Ataxia can be found in Chinese Han population. Therefore, based on these data, it may partly explain why there were no patients associated with NMDs in our cohort.

Regarding to the higher proportion of IEM, we think there may be several reasons. Compared to the UK and USA cohort, the patients in our cohort were recruited in a more recent time period (2010 to 2019), an era in which substantial progress was made in genome-sequencing techniques. Exome-based testing indeed plays an important role in systematic screening and confirming the genetic aetiology of HCM, especially that related to metabolic disease. Therefore, more patients with IEMs were identified and diagnosed. Furthermore, pompe disease made up the largest part of IEMs in our cohort, and published data has showed that pompe disease has higher incidence in China. Additionally, patients in our cohort were from three tertiary referral centres, which may skew the data to some degree towards a more severely affected group and more patients with inborn errors of metabolism, who may be more likely to be referred to a tertiary centre.

In this study, a specific aetiological diagnosis was only achieved in 265 patients (47.0% of 564 patients), indicating that aetiological diagnosis remains a substantial challenge in paediatric HCM in clinical practice. Notably, genetic testing yielded a diagnostic rate of 80.8% (248 suggestive results in 307 genetic tests) in our cohort, which is coherent with earlier reports. In our clinical practice, gene sequencing is not imperative for all patients diagnosed with HCM, given its high cost. Nevertheless, our results show the immense value of genetic testing in identifying the underlying cause of paediatric HCM.

Genetic testing results showed that in sarcomeric HCM, the main causative genes were MYH7 and MYBPC3, as in developed countries, however, the other causative genes identified in our cohort were quite different from previous report. We think these differences may be related to race and region. Previous data from adult patients with HCM in China showed that MYH7 and MYBPC3 were the predominant genes responsible for HCM, while the TNNT2 mutation contributed less to Chinese HCM. However, it should be pointed out that only a subset of the patients with sarcomeric HCM underwent genetic testing in our cohort, which may cause bias in the results. We believe that further studies with larger sample size in children would be needed to further elucidate the genetic diversity and the mystery behind it.

Our data confirmed the results of earlier studies in that patients diagnosed with IEMs and those diagnosed during infancy tended to have a worse prognosis. However, the overall survival estimates were lower in our cohort compared with that reported from PCMR and the UK cohort. The reason for this is likely multifactorial. First, our cohort had a higher proportion of patients with IEMs (including 83 cases of the classic infantile form of Pompe disease) and we recruited more patients diagnosed during infancy; both groups are known to have worse prognosis. Second, advanced medical management was infrequently applied in our clinical practice for various reasons. Heart transplantation, an effective approach for end-stage heart failure, was not used in any of our patients even though heart failure contributed to most of the mortality. In China, heart transplantation in children lags behind the global rate, with just over 100 cases performed to date, mainly due to restricted donor resources. In addition, the application of ICD in the prevention of SCD is limited in China due to insufficient experience and economic considerations.

Obstructive physiology was associated with a better prognosis in this study. This may be partly explained by the confounding effects of aetiology and a possible protective effect of septal myectomy. The impact of obstruction on survival was inconsistent in earlier reports. Research in children in Poland reported a higher risk with increased LVOT gradient. However, in the Australian cohort, the presence of LVOTO was unrelated to survival. Moreover, in the meta-analysis by Norrish et al., LVOTO was not predictive of SCD, while in the risk model developed by Miron et al., LVOTO had an inverse association at high gradients. Our results also revealed that left ventricular enlargement indicated a poorer outcome, while left atrial enlargement was irrelevant, both of which were significantly related to higher risks in earlier studies. The specific association between the above factors and survival is still unclear and warrants further research.

This study has some major strengths. This is the largest cohort study on paediatric HCM in low- and middle-income countries and the sample is likely to represent the national profile. However, this study also has some limitations. First, the limitations of retrospective research apply to our study, such as missing data (Supplementary Figure 6). Second, as the study was based at multiple centres, the evaluation and management...
might vary slightly at different sites, even though a uniform design and protocol were implemented. However, this is reflective of clinical practices in the real world. Third, as the family history of HCM and SCD was usually obtained by interviewing relatives, the accuracy was limited because recall bias was likely to some extent. Furthermore, the patients were recruited from tertiary referral centres, which may skew the data towards a more severely affected group to some extent. Nonetheless, we believe that our sample still has a certain degree of representativeness because most patients diagnosed with heart disease tend to be treated in tertiary hospitals in China and the entry barrier to tertiary referral centres is relatively low for patients in China. Additionally, considering the operability, we have not performed the secondary endpoint analysis which may be important in understanding the prognosis. Besides, We combined the idiopathic with sarcomeric subgroup for the statistical operability at the beginning. Although it is widely believed that these groups of patients share the same therapies and outcomes to a large extent and tend to cluster together in both clinical practice and research, it is indeed a major limitation in our study since we cannot deny that the idiopathic subgroup is heterogeneous. Therefore, we conducted a subgroup analysis comparing the survival of patients with sarcomeric vs idiopathic forms and the results showed that there was no significant difference between these two groups (Supplementary Table S5 & Supplementary Figure 7). Moreover, fifty-three patients (9.4%) were classified as lost to follow up in this study whose survival status was unclear, which would affect the survival probabilities.

This is the first large-scale multicentre cohort study of paediatric HCM from China, the largest developing country in the world. Our results imply that there is a significant disease burden and unmet medical service demand for paediatric HCM in China. Metabolic and syndromic causes constitute a substantial component of paediatric HCM and the aetiologic distribution varies significantly in different regions worldwide. The overall mortality in paediatric HCM patients in China remains higher than that reported from developed countries, especially in patients with IEMs or those diagnosed during infancy. HFD is the leading cause of overall mortality, while SCD is the leading cause in patients with IEMs or those diagnosed during infancy. HFD is the leading cause of overall mortality in paediatric HCM patients in China and the entry barrier to tertiary referral centres, which may skew the data towards a more severely affected group to some extent. Nonetheless, we believe that our sample still has a certain degree of representativeness because most patients diagnosed with heart disease tend to be treated in tertiary hospitals in China and the entry barrier to tertiary referral centres is relatively low for patients in China. Additionally, considering the operability, we have not performed the secondary endpoint analysis which may be important in understanding the prognosis. Besides, We combined the idiopathic with sarcomeric subgroup for the statistical operability at the beginning. Although it is widely believed that these groups of patients share the same therapies and outcomes to a large extent and tend to cluster together in both clinical practice and research, it is indeed a major limitation in our study since we cannot deny that the idiopathic subgroup is heterogeneous. Therefore, we conducted a subgroup analysis comparing the survival of patients with sarcomeric vs idiopathic forms and the results showed that there was no significant difference between these two groups (Supplementary Table S5 & Supplementary Figure 7). Moreover, fifty-three patients (9.4%) were classified as lost to follow up in this study whose survival status was unclear, which would affect the survival probabilities.

This is the first large-scale multicentre cohort study of paediatric HCM from China, the largest developing country in the world. Our results imply that there is a significant disease burden and unmet medical service demand for paediatric HCM in China. Metabolic and syndromic causes constitute a substantial component of paediatric HCM and the aetiologic distribution varies significantly in different regions worldwide. The overall mortality in paediatric HCM patients in China remains higher than that reported from developed countries, especially in patients with IEMs or those diagnosed during infancy. HFD is the leading cause of overall mortality, while SCD is the leading cause in patients with sarcomeric HCM. These findings, if confirmed by further studies, may have significant implications for the treatment and prognosis of paediatric HCM, particularly for low- and middle-income countries.

Contributors
LF, WC, ST, and HC conceived the study and designed the protocols. WC, ML, and PL collected the data. JW and RY reviewed the genetic data. LW and LC reviewed the echocardiographic data. YG, JS, TL, FL, SY, SW and LF followed the patients and verified the classification with ambiguous data. SY, SW, and LF accessed and verified the underlying data. WC and ST conducted the analysis and interpreted the results. WC, SY, and JW drafted the first version of the manuscript. LF, HZ, SW, and ST made critical revisions of the manuscript. LF obtained the project funding. LF, HZ, FL, and HC provided administrative and material support. LF takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement
All data in this study will be shared on reasonable request to the corresponding author (LF) for research purposes once the data have been de-identified and all the main findings have been published.

Declaration of interests
All authors declare no competing interests.

Funding
National Natural Science Fund of China (81770180, 81074029), China Project of Shanghai Municipal Science and Technology Commission (20MC1920400, 21YJ3190301).

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101466.

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