Failure to thrive in pediatric patients with congenital heart disease: a cross-sectional study of 13,256 patients

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The Lancet Regional Health - Western Pacific 2024;44: 101002

Published Online xxx https://doi.org/10.1016/j.lanwpc.2023.101002

Summary

Background The prevalence and risk factors for failure to thrive (FTT) in pediatric patients with congenital heart disease (CHD) remain ambiguous. We aimed to investigate the prevalence, growth profiles, risk factors, and vulnerable subtypes of CHD associated with FTT in pediatric patients with CHD.

Methods This was a cross-sectional study based on Chinese Database for Congenital Heart Surgery. FTT was defined as either stunting or underweight (height or weight standard deviation score <−2), and they were standardized by references of normal Chinese population. Risk factors was determined with logistic regression model, and growth profiles were delineated in each subgroup.

Findings A total of 13,256 CHD patients were included in this study, with 3994 patients of mild CHD, 7195 patients of moderate CHD and 2067 patients of complex CHD. The prevalence of stunting, underweight and FTT was 24%, 29.3% and 36.9%, respectively. Preoperative anaemia, left ventricle systolic dysfunction, younger age, more complex CHD types, lower birth weight and genetic syndrome were found to be the risk factors for FTT in CHD patients. Interrupted aortic arch was revealed to be the most severe group associated with FTT.

Interpretation FTT is ubiquitous in patients with CHD and exacerbated in high-risk subgroups. Our findings hinted the necessity of early identification and intervention for FTT in patients with CHD during daily practice of pediatrics, as it has the potential to improve outcomes and enhance their quality of life. Furthermore, we advocate for the initiation of prospective research with longitudinal data to comprehensively investigate the association between FTT and CHD across the lifespan.

Funding This study was supported by National High Level Hospital Research Funding (2022-GSP-GG-19), Capital Health Research and Development of Special Fund (2022-1-4032) and National Key R&D Program of China (2022YFC3600202 and 2022YFC3600203).

Keywords: Congenital heart disease; Growth profile; Failure to thrive; Stunting; Underweight

Introduction

Failure to thrive (FTT) is characterized by inadequate growth during childhood, typically defined as stunting or underweight with a standard deviation score (SDS) less than −2.[1–5] Without intervention, FTT can lead to various physical, emotional, and behavioral issues.[6] Among patients with congenital heart disease (CHD), FTT is highly prevalent,[7] resulting in detrimental clinical outcomes such as prolonged hospitalization, increased risk of comorbidities, and elevated in-hospital mortality.[3,4] CHD represents the largest category of congenital defects globally, with approximately 3.12

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Research in context

Evidence before this study

We thoroughly searched in PubMed by using the queries of "congenital heart disease" AND ("failure to thrive" OR "malnutrition" OR "growth disorder" OR "poor growth" OR "growth retardation" OR "growth failure" OR "HAZ <−2" OR "WAZ <−2" OR "stunting" OR "underweight" OR "developmental delay" OR "developmental disorder" OR "developmental retardation"). Several studies investigated the association between failure to thrive (FTT) and congenital heart disease (CHD), while they were limited with sample size and spectrum of cardiac defects. In addition, there is scarcity of study systemically investigating FTT among CHD patients with large sample size and appropriate anthropometric reference for Chinses population.

Added value of this study

A total of 13,256 patients with CHD were included into this cross-sectional study from the Chinese Database for Congenital Heart Surgery (Registry No. ChiCTR1800014577) to systemically investigate the association between FTT and CHD, and potential risk factors. With the largest sample size, we reported the prevalence of FTT, potential risk factors, and the most vulnerable subgroups among patients with CHD.

Implications of all the available evidence

CHD, the leading global birth defect, is frequently accompanied by FTT in pediatric patients. FTT in CHD patients is associated with prolonged hospitalization, increased postoperative comorbidities, and elevated mortality rates. This study provides evidence that FTT is prevalent and particularly severe in younger CHD patients with lower birth weight and complex CHD conditions. The prevalence of FTT also varies across different types of complex CHD. These findings have important implications for early identification and intervention of FTT by clinical professionals, potentially improving outcomes for CHD patients. Furthermore, this study serves as a call to initiate prospective studies with longitudinal data to establish the relationship between FTT and CHD.

million live births[8] and 195,000 deaths[9] in 2019. Given the heightened susceptibility to FTT, CHD-related FTT presents a significant challenge, particularly in high-risk subgroups such as infants and those with complex CHD.[2,10]

However, the association between FTT and CHD remains to be fully understood. Several studies have speculated that increased energy consumption in pulmonary hypertension, persistent heart failure or cyanosis,[11,12] along with inadequate calorie intake due to feeding difficulties,[7,13] may be the potential contributing factors. Researches on CHD-related FTT have been limited in terms of sample size and spectrum of defects.[2,10,14] The previous studies in China did not utilize anthropometric measurements from a standardized healthy Chinese population, which may not accurately reflect the actual condition.[2,5] In addition, various types of CHD with different hemodynamic status may contribute to disparities in FTT, yet there is a scarcity of study systematically investigate this issue, and the condition remains controversial.[15,16]

To address the limitations of previous studies, we conducted this cross-sectional study with an adequate sample size to investigate the association between FTT and CHD. This study aimed to address the following objectives: (i) described the prevalence of FTT in pediatric CHD patients using an anthropometric reference derived from the Chinese population; and (ii) explored the risk factors associated with FTT in different subgroups. By doing so, our study provides valuable insights into the prevalence and determinants of FTT in CHD patients. Furthermore, our findings can raise awareness among pediatricians regarding the importance of monitoring growth and development in patients with CHD, facilitating early nutritional support and ultimately improving the quality of life for this population. Lastly, the results of this study also serve as an appeal to initiate a prospective study with longitudinal data, which would further enhance our understanding of the relationship between CHD and FTT.

Methods

Study design and participants

All CHD surgery records at Pediatric Cardiac Surgery Center, National Center for Cardiovascular Diseases, Fuwai Hospital, between January 1, 2018 and December 31, 2022, were identified from the Chinese Database for Congenital Heart Surgery (CDCHS, Registry No. ChiCTR1800014577).[17] All hospitalized patients underwent congenital cardiac surgery were included and clinic patients were excluded due to incomplete profile. The CHD diagnoses were confirmed by ultrasonography and surgical notes, and standardized by the *International Classification of Disease and Injuries 10*th *edition (ICD-10)* during their entry to CDCHS. The baseline demographic characteristics included gender, ethnicity, surgery history, height, weight, body mass index (BMI), age at surgery, gestational age, birth weight and comorbid genetic syndrome. One patient might undergo multiple operations during the same hospitalization, and only information from the first procedure would be retrieved. Flowchart was shown in eFigure 1 in the Supplement. This study was approved by the Ethnic Committee of Fuwai Hospital (2017–977), and followed Strengthening the Reporting of Observational Studies in

Epidemiology (STROBE) guidelines[18] (eTable 1 in the Supplement).

Anthropometric measurements

Height and weight were measured in the morning in each ward after admission. For children under 3 years, height was measured in the supine position (recumbent length). BMI was calculated as weight (kg)/height $(m)^2$. Height SDS and weight SDS were calculated as height SDS = (actual height − mean height for age and sex)/standard deviation of height, and weight SDS = (actual weight − mean weight for age and sex)/standard deviation of weight. For those under 7 years, the mean height and weight based on age and sex were referencing the growth standard for children under 7 years published by the National Health Commission of China in 2022,[19] and for those age 7 or older, reference of the national survey data of China published in 2009 was utilized.[20,21]

Definition

All the data were collected at admission (i.e., before surgery). According to World Health Organization,[1] stunting was defined as height SDS <−2 and underweight was defined as weight SDS <−2. Additionally, FTT, a composite indicator, was defined as either stunting or underweight. Han was defined as the major ethnicity and other fifty-five were defined as the minority. Hypoalbuminemia was defined as the preoperative albumin (automatic biochemical analyzer [HITACHI, LABOSPECT 008AS]) lower than 37 g/L in patients below the age of 6 months, 43 g/L in patients aged 6 months to 6 years, 44 g/L in patients aged 6–13 years, and 46 g/L in patients beyond the age of 13 years.[22] Anaemia was defined as the preoperative hemoglobin (automated hematology analyzer [Sysmex XN-10]) lower than 130 g/L in patients below the age of 1 month, 95 g/L in patients aged 1–6 months, 110 g/L in patients aged 6 months to 5 years, 115 g/L in patients aged 5–12 years, 120 g/L in patients aged 12–15 years, 120 g/L in female patients beyond the age of 15 years, and 130 g/L in male patients beyond the age of 15 years.[23,24] Left ventricle (LV) systolic dysfunction was defined as the left ventricular ejection fraction (LVEF) lower than 55%.[25] According to the different growth characteristics across age groups, we categorized them into six groups: 0–1, 1–3, 3–6, 6–12, 12–18, and above 18 years (final adult height as reference). Gestational age was classified into four categories: extremely preterm birth (<28 weeks), preterm birth (28–37 weeks), normal term birth (37–42 weeks) and post term birth (>42 weeks). Birth weight was divided into four categories: very low birth weight (VLBW, <1500 g), low birth weight (LBW, 1500–2500 g), normal birth weight (NBW, 2500–4000 g) and macrosomia (>4000 g). Genetic syndrome was a composite variable encompassing DiGeorge syndrome, Sotos syndrome, Down syndrome, Kawasaki syndrome, Leopard syndrome, Marfan syndrome, Noonan syndrome, PHACE syndrome, Turner syndrome, Williams syndrome, and G-6-PD deficiency. According to previous studies,[26,27] mild CHD was defined as isolated atrial septal defect (ASD), ventricular septal defect (VSD) or patent ductus arteriosus (PDA), complex CHD was defined as transposition of the great arteries (TGA), total anomalous pulmonary venous return (TAPVR), double-outlet right ventricle (DORV), coarctation of the aorta (CoA), interrupted aortic arch (IAA), pulmonary atresia (PA), Ebstein anomaly, tricuspid atresia (TA), truncus arteriosus, hypoplastic left heart syndrome (HLHS), hypoplastic right heart syndrome (HRHS), and single ventricle (SV) and others were defined as moderate CHD.

Planned analyses

First, we presented the descriptive analysis on baseline demographics and growth characteristics of the entire cohort. Second, we delineated the growth profile curve according to gender as well as age groups, including height, weight and their SDS using the cross-sectional anthropometric data, which was widely adopted in the field of pediatrics for the growth and development patterns of children with a particular disease.[28,29] The group of age greater than 18 years was utilized to be the reference for final adult height of patients with CHD. Third, we explored the potential risk factors to FTT. Fourth, based on the identified risk factors, we depicted weight SDS and height SDS density distribution diagrams in each subgroup. Moreover, we further analyze the potential alterations of these risk factors across three relative high-risk groups: aged 6 months–3 years (Patients under 6 months of age have been excluded from this group due to the inclusion of laboratory indicators and these indicators tend to fluctuate significantly in infants, and there is a lack of well-established reference values specifically for this age group), complex CHD and LBW/VLBW.

Statistical analysis

Continuous variables were presented with median (interquartile range, IQR) and compared with Kruskal–Wallis rank sum test. Categorical variables were presented with counts (percentage) and compared with $\chi 2$ test. A univariate logistic regression model with threshold of P-values <0.1, a stepwise regression with "both" method, and clinical considerations were used to select variables for the final logistic regression model. Due to the possibility of missing values for several patients and adequate sample size, the model would only include patients with intact profile. Odd ratio (OR) with 95% confidence intervals (CI) was demonstrated via forest plots. In subgroup analyses, we evaluated the distribution of height SDS and weight SDS in different subgroups via Ridgeline plots and established the multivariate logistic regression models in three relative high-risk groups. All of the analyses and data visualization were conducted using the R (version 4.2.2) and a

two-sided P < 0.05 was considered as statistical significance.

Role of the funding source

The funders played no role in the study design, data collection, data analysis, interpretation or writing of this report.

Results

Baseline characteristics

A total of 13,256 CHD patients were included in this study, with 3994 of mild CHD, 7195 of moderate CHD and 2067 of complex CHD. Male patients were prominent in complex CHD group (60.3%). Patients with complex CHD had evidently higher previous operation rate (22.9%), LV systolic dysfunction (5.2%), and hypoalbuminemia (60%). Approximately 90% of the patients were preschool children (i.e., children younger than 6 years), with the most prominent in infants (i.e., children younger than 1 year). Pre-term birth consisted of 9.4% of the whole cohort. Only minority patients were reported with genetic syndrome (0.7%). The prevalence of stunting, underweight and FTT was 24.0%, 29.3% and 36.9% in this cohort, respectively, and patients with complex CHD had a higher prevalence in stunting (41.1%), underweight (42.9%) and FTT (54.2%). The detailed information of baseline characteristics was documented in Table 1, and the prevalence of FTT among other subgroups were presented in eTable 2 in the Supplement and eTable 3 in the Supplement.

Overall growth profile

With increasing of age, an upward trajectory of height and weight was observed in CHD patients. After standardization, height SDS had been fluctuating around zero since the age of 12, and weight SDS gradually approached zero as age increased, reaching to normal by the age of 18 (Fig. 1).

Factors related to FTT

In the multivariate logistic regression model, gender, BMI, preoperative anaemia, LV systolic dysfunction, age, preterm birth, birth weight, genetic syndrome, and CHD type were found to be associated factors (Fig. 2; eFigure 2 and 3 in the Supplement). Compared to patients aged greater than 6 years, risk of FTT increased with younger age (OR for 0–1, 19.10 [95% CI, 15.08–24.40]; P < 0.001). Lower birth wight (OR for VLBW, 4.33 [95% CI, 2.49–7.73]; P < 0.001) was a risk factor for FTT, whereas macrosomia conferred a protective effect (OR, 0.39 [95% CI, 0.30–0.49]; P < 0.001). Genetic syndrome was a contributing factor for FTT (OR, 2.90 [95% CI, 1.69–4.98]; P < 0.001). Moreover, a higher risk of FTT were related to patients with more complex cardiac defects (OR for complex CHD, 2.94, [95% CI, 2.52–3.44]; P < 0.001). The contributing effects of ethnicity, previous operation, and hypoalbuminemia were adjusted in the multivariate model.

Subgroup analyses

Age

Infancy was the most critical period for FTT with the prevalence of 62.6%, followed by 32.6% in patients aged 1–3 years (Fig. 3; eTable 2 in the Supplement). Due to the worse situation in younger patients, we further analyzed the risk factors in the subgroup aged 6 months to 3 years. Risks of FTT increased with more complex cardiac defects (OR for complex CHD, 3.52 [95% CI, 2.83–4.39]; P < 0.001). Lower birth weight (OR for LBW, 3.07 [95% CI, 2.42–3.91]; P < 0.001), anaemia (OR, 2.13 [95% CI, 1.83–2.48]; P < 0.001) and LV systolic dysfunction (OR, 1.98 [95% CI, 1.21–3.30]; P = 0.007) also increased risks of FTT. However, no significant association between preterm birth, genetic syndrome and FTT was observed in this subgroup analysis (eFigure 4 in the Supplement).

CHD types

Complex CHD patients had the highest prevalence of FTT, reaching 54.2% (Fig. 4; eTable 2 in the Supplement). We further performed subgroup analysis on risk factors, and found that the risk of FTT was higher for younger age (OR for 0–1, 14.01 [95% CI, 9.24–21.61]; P < 0.001) than those over 6 years. Similarly, preterm birth and extremely preterm birth as well as LBW and VLBW contributed to FTT, while macrosomia seemed to be protective (eFigure 5 in the Supplement).

Considering the conundrum in clinical practice, we further explored subtypes of complex CHD. Among them, CoA stood out with the highest prevalence of 3.4%, while HLHS exhibited the lowest of 0.1% (eTable 4 in the Supplement). The IAA was the most severe complex CHD with FTT (77.1%), while Ebstein's anomaly was found to be the relatively mildest (22.0%) (eFigure 6 and eTable 3 in the Supplement). Owing to the limited number of specific complex CHD, we did not perform risk factor analysis.

Birth weight

The prevalence of FTT increased with lower birth weight (eFigure 7 and eTable 2 in the Supplement). In subgroup analysis of LBW and VLBW, patients with lower BMI and under preschool ages were found to be risky. In addition, more complex cardiac defects (OR for complex CHD, 2.78 [95% CI, 1.62–4.82]; P < 0.001) contributed to FTT. Not surprisingly, genetic syndrome contributed to FTT (OR, 6.16 [95% CI: 1.42–38.02]; P = 0.025) (eFigure 8 in the Supplement).

Genetic syndrome

CHD patients with genetic syndrome had a relatively higher prevalence of FTT (54.2% vs. 36.6%) (eFigure 9 and eTable 2 in the Supplement). Due to the

Characteristic	No. (%)				
	Overall (n = 13,256)	Mild CHD (n = 3994)	Moderate CHD (n = 7195)	Complex CHD (n = 2067)	P-value
Male	6695 (50.5)	1889 (47.3)	3560 (49.5)	1246 (60.3)	<0.001[g]
Ethnic minority	1205 (9.1)	362 (9.1)	643 (8.9)	200 (9.7)	0.583
With surgery history	862 (6.5)	34 (0.9)	357 (5.0)	471 (22.9)	<0.001[g]
Height, m, median (IQR)	0.85 (0.70–1.03)	0.93 (0.80–1.06)	0.79 (0.67–1.00)	0.77 (0.60–1.02)	<0.001[g]
Weight, kg, median (IQR)	11.00 (7.50–15.30)	13.00 (10.00–17.00)	9.60 (7.00–14.50)	9.00 (5.20–15.00)	<0.001[g]
BMI, kg/m^2, median (IQR)	14.94 (13.81–16.33)	15.03 (13.98–16.32)	14.97 (13.77–16.38)	14.72 (13.46–16.02)	<0.001[g]
Hypoalbuminemia[a]	6196 (49.6)	1890 (48.6)	3189 (47.3)	1117 (60.0)	<0.001[g]
Anaemia[b]	1509 (11.8)	342 (8.7)	941 (13.7)	226 (11.5)	<0.001[g]
LV systolic dysfunction[c]	266 (2.0)	9 (0.2)	149 (2.1)	108 (5.2)	<0.001[g]
Age					<0.001[g]
0–1	4340 (32.7)	566 (14.2)	2855 (39.7)	919 (44.5)	
1–3	4194 (31.6)	1642 (41.1)	2116 (29.4)	436 (21.1)	
3–6	3413 (25.7)	1459 (36.5)	1530 (21.3)	424 (20.5)	
6–12	1006 (7.6)	291 (7.3)	503 (7.0)	212 (10.3)	
12–18	151 (1.1)	23 (0.6)	80 (1.1)	48 (2.3)	
>18	152 (1.1)	13 (0.3)	111 (1.5)	28 (1.4)	
Gestational age[d]					<0.001[g]
Normal term birth	11,328 (88.7)	3523 (91.0)	6084 (88.1)	1721 (86.6)	
Preterm birth	1197 (9.4)	282 (7.3)	700 (10.1)	215 (10.8)	
Extremely preterm birth	12 (0.1)	6 (0.2)	5 (0.1)	1 (0.0)	
Post term birth	228 (1.8)	60 (1.5)	117 (1.7)	51 (2.6)	
Birth weight[e]					
NBW	10,462 (85.7)	3246 (88.1)	5618 (85.0)	1598 (83.9)	
LBW	987 (8.1)	210 (5.7)	581 (8.8)	196 (10.3)	<0.001[g]
VLBW	96 (0.8)	26 (0.7)	58 (0.9)	12 (0.6)	
Macrosomia	657 (5.4)	203 (5.5)	355 (5.4)	99 (5.2)	
Genetic syndrome[f]	94 (0.7)	2 (0.1)	86 (1.2)	6 (0.3)	<0.001[g]
Stunting	3174 (24.0)	501 (12.6)	1825 (25.4)	848 (41.1)	<0.001[g]
Underweight	3889 (29.3)	630 (15.8)	2372 (33.0)	887 (42.9)	<0.001[g]
FTT	4876 (36.9)	848 (21.3)	2908 (40.5)	1121 (54.2)	<0.001[g]

Abbreviations: CHD, Congenital heart disease; BMI, Body mass index; LV, Left ventricle; NBW, Normal birth weight; LBW, Low birth weight; VLBW, Very low birth weight; FTT, Failure to thrive; IQR, Interquartile range. [a]A total of 760 missing data in albumin. [b]A total of 491 missing data in hemoglobin. [c]A total of 8 missing data in left ventricular ejection fraction. [d]A total of 491 missing data in gestational age. [e]A total of 1054 missing data in birth weight. [f]Genetic syndrome includes DiGeorge syndrome (n = 1), Sotos syndrome (n = 1), Down syndrome (n = 23), Kawasaki syndrome (n = 10), Leopard syndrome (n = 2), Marfan syndrome (n = 3), Noonan syndrome (n = 11), PHACE syndrome (n = 1), Turner syndrome (n = 2), Williams syndrome (n = 36) and G-6-PD deficiency (n = 5). [g]Indicates statistically significant.

Table 1: **Baseline characteristics of participants.**

inadequate identification (i.e., under-diagnosis) of genetic syndrome in this cohort, we did not perform risk factors exploration on this subgroup.

Discussion

To the best of our knowledge, this retrospective cross-sectional study represented the largest investigation of FTT in pediatric patients with CHD. The study provided detailed profiles of somatic growth in different subgroups and across various CHD spectrums. Here, three major findings were documented: (i) FTT was a common condition in pediatric CHD patients and presented a more significant challenge in high-risk subgroups; (ii) risk factors for FTT included preoperative anaemia, LV systolic dysfunction, younger age, more complex CHD, lower birth weight and genetic syndrome; and (iii) the prevalence of FTT exceeded over 50% in most complex CHD cases, with IAA being the most severe defect.

Prevalence

A notably increased prevalence of FTT was observed in CHD patients with factors such as immaturity, complex CHD, comorbid genetic syndrome, preterm birth and feeding difficulty.[2,10,14,30] In a Chinese study involving 3252 CHD patients, the prevalence of stunting and underweight was reported as 23.3%, which increased to 45% for stunting and 73.4% for underweight in infants.[2] Another cross-sectional study conducted among 428 Chinese CHD patients aged 1–10 years reported a prevalence of chronic malnutrition (Z-score of height for age <–2) of only 19.9%.[5] The lower prevalence

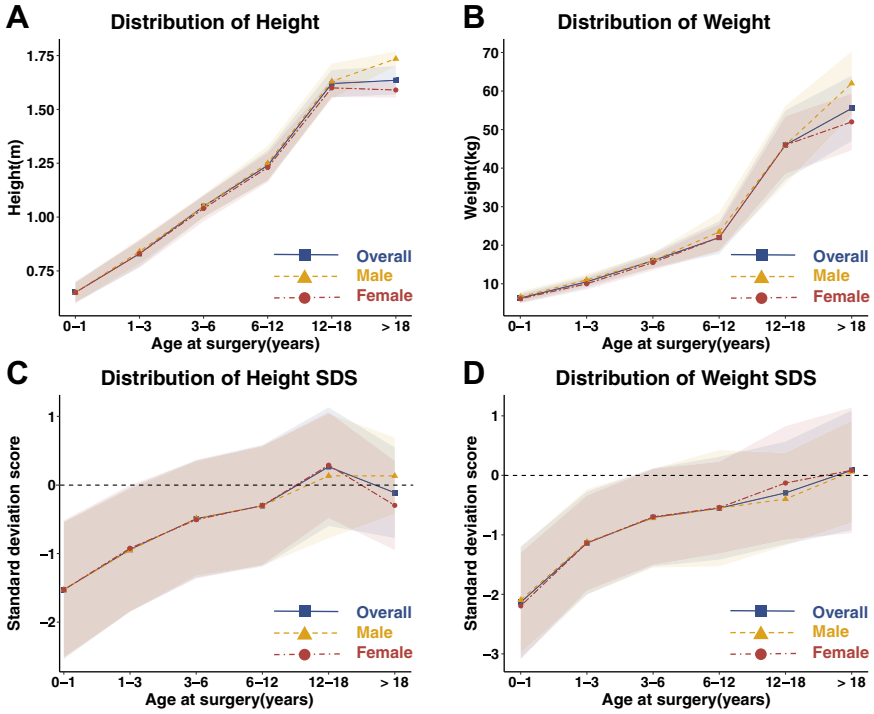

Fig. 1: **Curve of growth profile according to gender and age at surgery.** (A) The distribution of height; (B) The distribution of weight; (C) The distribution of height SDS; (D) The distribution of weight SDS. Shade indicates the interquartile range. Each point was plotted with median and interquartile range of each group (i.e., 0–1, 1–3, 3–6, 6–12, 12–18, and above 18 years). SDS, Standard deviation score.

compared to our study could be explained by the following reasons: (i) the utilization of an anthropometric reference from normal Chinese population released by an authority for standardization in our study; (ii) a large number of patients included in our study; and (iii) a higher proportion of complex CHD cases in our cohort, which closely reflected the actual condition in China.[17] Therefore, our results may provide a more accurate reflection of the real prevalence of FTT. In other countries, Palleri et al. reported a prevalence of stunting and underweight in Italy of only 6.5% and 7.4%, respectively, which increased to 12.3% for stunting and 17% for underweight among patients with complex CHD.[10] In the United Kingdom, the prevalence of stunting was 18.5%, increasing to 28.4% in infants.[14] Medoff-Cooper et al. reported that 30% of neonates within 30 days of birth had underweight at 3 months of age after congenital cardiac surgery in the United States.[31] In Nigeria, the situation of FTT among children with CHD was notably more severe, with a staggering 37.8% experiencing stunting.[32] Taken together, CHD patients in China and other developing countries may have a higher vulnerability to FTT compared to developed countries.[10,14,33] This could be attributable to factors such as ignorance or underestimation of FTT, while the developed countries place emphasis on nutritional intervention alongside primary CHD treatment.[33] High-energy feeding,[34] enteral nutrition, expressed breast milk,[35] and the involvement of dietitians[36] have been shown to be beneficial for somatic growth and clinical outcomes in patients with CHD. Therefore, early assessment of nutritional status and corresponding interventions should be considered in the management of CHD in China and other developing countries.

Younger age

Younger age was identified as a risk factor for FTT, with infants being the most challenging group.[2,14] The condition of FTT tended to improve with increasing age, which can be explained by the nature of CHD, where more severe defects require surgery during early life. Infancy is a critical period for neurodevelopment and establishment of metabolic, endocrine, and immune pathways.[37,38] The adverse impacts of malnutrition on brain development have been demonstrated, showing that malnourished infants have fewer brain cells and decreased dendritic span and arborization.[37,39,40] Infants with complex CHD often require cardiac surgery, catheter intervention or medication early in life, which can further impact neurodevelopment.[41] Infections and suboptimal feeding also interfere with the development of metabolic, endocrine, and immune pathways development, affecting the trajectory of child growth.[37] In this study, infants with CHD were found to be at a high-risk

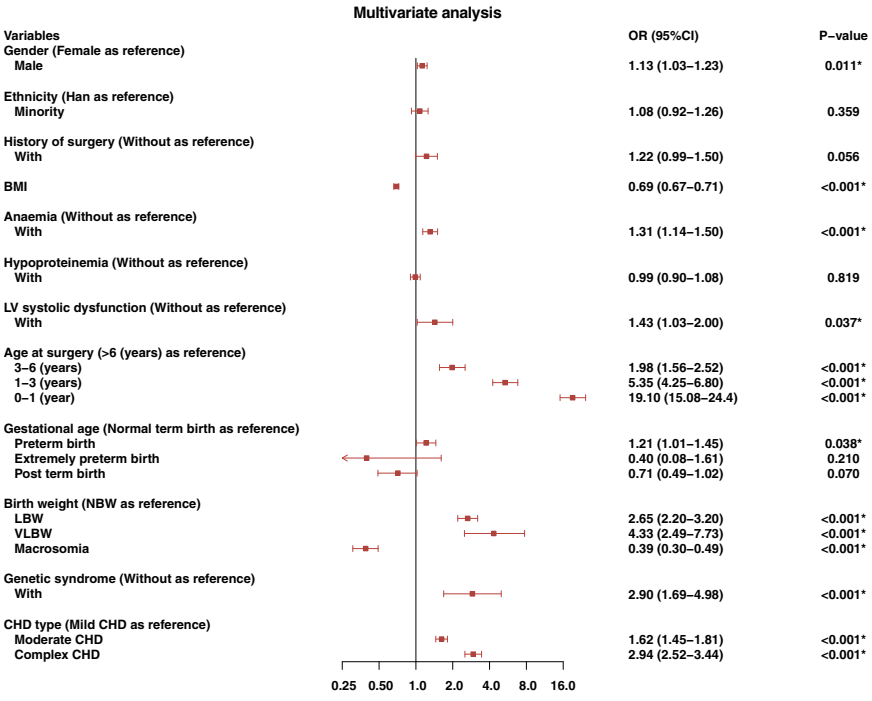

***Fig. 2:* Multivariate logistic regression model of the overall cohort.** Although FTT is defined based on the measures of height and weight, BMI is easily obtained during daily practice. Thus, we still treated it as one of the variables. BMI, Body mass index; LV, Left ventricle; NBW, Normal birth weight; LBW, Low birth weight; VLBW, Very low birth weight; CHD, Congenital heart disease; OR, Odd ratio; CI, Confidence intervals.

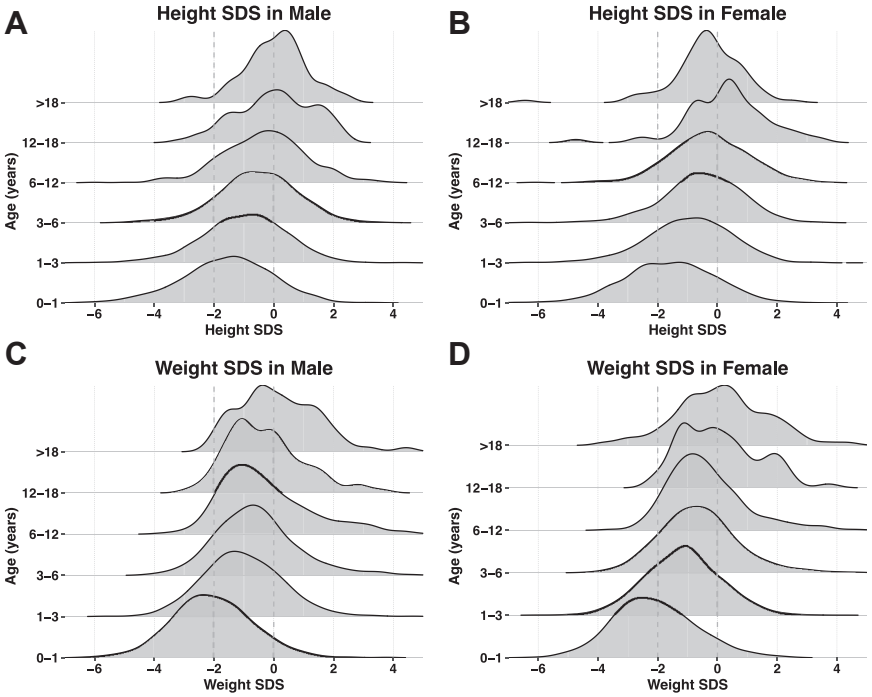

***Fig. 3:* Distribution of SDS according to gender and age at surgery.** (A) Height SDS in male; (B) Height SDS in female; (C) Weight SDS in male; (D) Weight SDS in female. SDS, Standard deviation score.

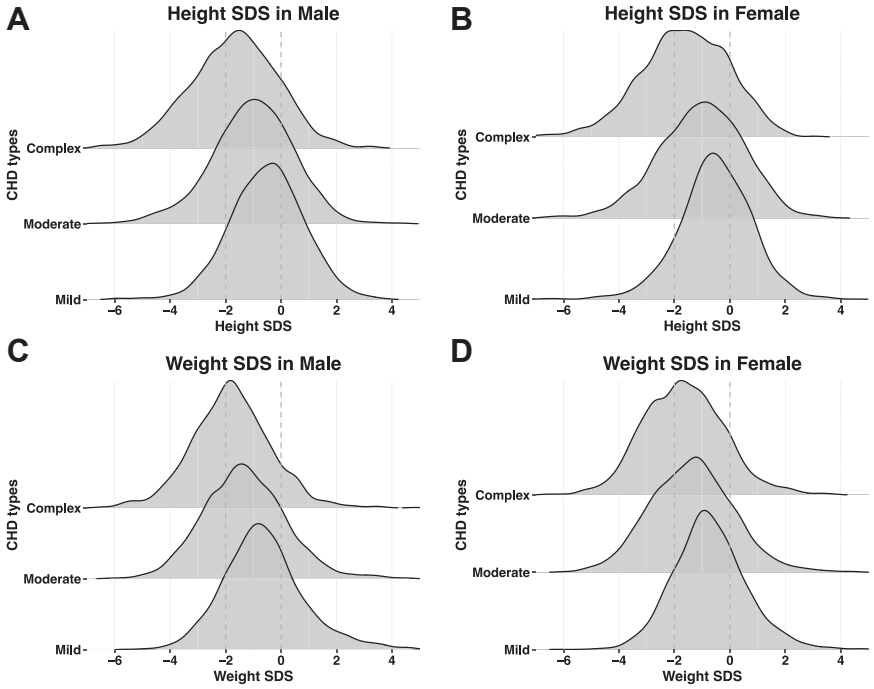

Fig. 4: **Distribution of SDS according to gender and CHD types.** (A) Height SDS in male; (B) Height SDS in female; (C) Weight SDS in male; (D) Weight SDS in female. SDS, Standard deviation score; CHD, Congenital heart disease.

for FTT, and the underlying cause may be the significant proportion of complex CHD cases that require multiple surgeries but have not yet undergone the final corrective procedure, thereby impeding the establishment of stable hemodynamics necessary for normal growth.[10] Even with final procedure, FTT may still persist due to the inherent challenges associated with complex CHD.[42] Preoperative trophic feeds were reported to be beneficial, such as decreasing hospital length of stay and time to reach target caloric intake, among patients with complex CHD.[36] Anaemia, one of the most common comorbidities in CHD, was also identified as a risk factor for FTT among younger CHD patients. Hemoglobin plays a crucial role in oxygen transport, which is an essential substrate for mitochondrial oxidative phosphorylation. Anaemia can compromise the ability of mitochondria to generate ATP,[43] which may contribute to somatic development delays in CHD patients. Therefore, it is advocated to involve nutritional experts for feeding consultations for infants with CHD before surgery. With early identification and intervention, these patients have the potential to grow and develop as normal population.[44]

Complex CHD

Complex CHD is a significant risk factor for FTT,[10,16,36,45] frequently presenting with precarious hemodynamics or genetic syndrome that make these patients more susceptible to FTT. Varan et al. indicated that cyanotic CHD with pulmonary hypertension had the highest risk to FTT, as these patients experienced hypoxia and pulmonary hypertension, leading to limited nutrient intake.[16] Mignot et al. reported that infants with left-to-right shunts faced a higher risk due to decreased nutrient absorption caused by poor gastrointestinal perfusion and increased energy expenditure.[15] Interestingly, our study revealed, for the first time, that the prevalence of FTT was highest in patients with IAA. IAA is characterized by an interrupted aorta, resulting in discrepant visceral blood supply. The inadequate gastrointestinal blood supply may impair the absorption from digestive tract, which could contribute to FTT in these patients. In addition, IAA is frequently reported in patients with DiGeorge syndrome (approximately 50%),[46] in which prevalence of FTT reaching 58.6%.[47] Thus, the high prevalence of FTT in patients with IAA may be further exacerbated by the presence of DiGeorge syndrome. However, due to the limited data, our study refrained from drawing further conclusions, and the association among IAA, DiGeorge syndrome and FTT remained to be elucidated. Apart from IAA, other forms of complex CHD, such as TGA, DORV, TAPVR, HLHS and truncus arteriosus, also exhibited notably severe growth profiles, which aligned with previous studies.[16,48]

Low birth weight

Our study demonstrated that CHD patients with LBW were more vulnerable to FTT, which was in line with

previous studies.[15,49] It is well recognized that neonates with CHD face an increased risk of LBW, potentially due to abnormal circulation during the fetal period.[50] Following birth, unstable hemodynamics can further impact the nutrition and oxygen supplementation until anatomical correction, which may worsen the somatic growth. Moreover, a prospective study revealed that infants with LBW would continue to suffer significant malnutrition even after corrective surgery.[42] Therefore, for CHD patients with LBW, FTT remains a persistent issue that can extend into adulthood. Early identification, timely intervention and routine surveillance are crucial to address this ongoing challenge.

Genetic syndrome

Genetic syndrome was identified as a risk factor for FTT, albeit inadequate identification in our center. As a specialized cardiovascular center, we only conducted genetic testing for a subset of patients with evident multiple systemic abnormalities, following a cost-saving policy. However, individuals with genetic syndrome are highly susceptible to experiencing both FTT and CHD.[41,51] For instance, Turner syndrome is characterized by short stature, skeletal abnormalities, lower intelligent quotient and potentially serious CHD (e.g., bicuspid aortic valve, coarctation aorta).[41,51,52] Noonan syndrome is frequently with developmental delay, growth failure, short stature, cognitive impairment and cardiac abnormity (e.g., pulmonary valve stenosis, ASD).[41,51,53] The inherent impact of genetic defects on skeletal system can contribute to poor somatic growth and may exacerbate FTT among CHD patients.[54] However, in this study, only 0.7% CHD patients were identified as having genetic syndrome, which could be explained by pregnancy termination once diagnosed and the screening of genetic syndrome not performed routinely in cardiovascular centers in China. Therefore, the isolated effect of CHD on FTT cannot be accurately determined from this study.

Preterm birth

Preterm birth was identified as a risk factor for FTT, which aligned with the previous studies.[30,55] Parents of preterm infants are often reported to experience anxiety,[56] and in severe cases of prematurity, they may be susceptible to perinatal depression.[55,57] Maternal depression was negatively associated with the quality of parenting,[58] which can contribute to FTT. Therefore, it is important to consider the psychological well-being of parents with lactating CHD infants and provide them with appropriate feeding guidance. Addressing the psychological condition of parents may offer a potential avenue to mitigate FTT to some extent. By providing support and guidance, healthcare professionals can help parents navigate the challenges of feeding and ensure optimal nutrition for their CHD infants, which can positively impact their growth and development.

Limitations

Several limitations should be addressed in this study. First, the nature of retrospective and cross-sectional study limited the integration of data, impeding further analysis on causal relationship between CHD and FTT. Second, due to the multifactorial nature of FTT, additional information such as feeding history, dietary habits, regional distribution and economic conditions would have been valuable for adjusting the analysis; however, these variables were missing due to the retrospective design of the study. Third, there was a lack of sufficient longitudinal follow-up data to further understand the developmental status of the CHD population after surgery. Fourth, although the cohort was obtained from the largest CHD center in China, the condition of FTT in the CHD population may be exacerbated when including centers from underdeveloped regions. Fifth, diagnosis of genetic syndrome was inadequate in our center, which may have led to an underestimation of the actual prevalence of genetic syndrome in the study population. Last, further subgroup analyses are limited due to insufficiently corresponding sample size.

Conclusion

FTT is ubiquitous in patients with CHD, with a prevalence of 36.8% in our cohort, and it tends to aggregate in high-risk subgroups. Preoperative anaemia, LV systolic dysfunction, younger age, more complex CHD, lower birth weight, and comorbid with genetic syndrome were the risk factors for FTT. Over half of patients with complex CHD exhibited notably severe growth profiles, and our study revealed, for the first time, that IAA was the most severe complex CHD associated with FTT. We advocate early identification and intervention to address FTT and it may have a positive impact on improving outcomes in patients with CHD. Future prospective studies including more indices reflecting growth profiles should be performed to validate the results obtained from this study.

Contributors

QH, XL and ZZ: conceptualisation, methodology, data analysis, manuscript writing; HS: methodology, data analysis, laboratory indices provision; KM, ZD and YL: investigation; HP and SL: supervision, professional suggestion, revision.

Data sharing statement

Data used to generate the results of this study could be obtained from the corresponding author at reasonable request.

Declaration of interests

All authors declare no conflict of interest.

Acknowledgements

We thank all patients enrolled in this study.

We sincerely appreciate Dr. David M. Zheng AP for his valuable assistance in polishing our article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.101002.

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