Journal of the American Heart Association

ORIGINAL RESEARCH

Age-Based Classification and Outcomes in Pediatric Heart Failure: Findings From a Retrospective Multicenter Cohort Study

Yuxing Yuan, MD*; Bo Pan, MD*; Fangjie Wang, MD; Zhi Chen, MD; Ying Guo, MD; Xing Shen, MD; Xuecun Liang, MD; Yanyan Liang, MD; Yanlin Xing, MD; HuiLi Zhang, MD; Yingqian Zhang, MD; Chunhong Xie, MD; Li Li, MD; Zhilin Huang, MD; Huichao Sun, MD; Min Zheng, MD; Lingjuan Liu, MD; Tiewei Lv, MD; Zipu Li, MD; Xiaohua Liang, MD; Jie Tian, MD

BACKGROUND: Although heart failure is a well-known major global public health concern, the general understanding of the clinical status of pediatric heart failure (PHF) is inadequate. Therefore, this study aims to enhance the general understanding of clinical characteristics across different PHF age groups and provide references for improving PHF treatment strategies.

METHODS: This multicenter retrospective cohort study involved patients from 20 Chinese provinces, primarily including hospitalized patients (aged ≤18 years) diagnosed with heart failure between January 2013 and December 2022. The study subjects were categorized into 4 groups: neonatal, infant and toddler, young children, and adolescent.

RESULTS: Herein, 2903 hospitalized patients with PHF were included. Significant differences were observed across age groups in clinical characteristics, auxiliary examination results, comorbid diagnoses, and hospitalization outcomes. After adjusting for covariates, the odds of in-hospital death were significantly lower in the infant and toddler (odds ratio [OR], 0.46 [95% CI, 0.25–0.85]), young children (OR, 0.39 [95% CI, 0.18–0.85]), and adolescent (OR, 0.34 [95% CI, 0.13–0.87]) groups compared with the neonatal group. Furthermore, the odds of cardiovascular adverse events were significantly higher in the young children (OR, 1.91 [95% CI, 1.62–2.88]) and adolescent (OR, 2.16 [95% CI, 1.15–4.06]) groups compared with the neonatal group. Additionally, regarding the odds of a bad Ross class, the adolescent group had 1.85 times higher odds (95% CI, 1.11–3.09) compared with the neonatal group, 2.36 times (95% CI, 1.67–3.35) higher odds compared with the infant and toddler group, and 1.45 times (95% CI, 1.05–2.02) higher odds compared with the young children group (P<0.05).

CONCLUSIONS: This study emphasizes the importance of age-specific stratification in PHF management, revealing distinct clinical and prognostic differences across various developmental stages.

REGISTRATION: URL: https://www.chictr.org.cn. Unique identifier: ChiCTR2300078262.

Key Words: age-based stratification ■ all-cause mortality rate ■ cardiovascular adverse event ■ HF class ■ pediatric heart failure

Correspondence to: Jie Tian, MD, Department of Cardiology Children's Hospital of Chongqing Medical University 136 Zhongshan Er Road, Yu Zhong District, Chongqing, 400014, P.R. China. Email: jietian@cqmu.edu.cn and Xiaohua Liang, MD, Department of Clinical Epidemiology and Biostatistics, Children's Hospital of Chongqing Medical University 136 Zhongshan Er Road, Yu Zhong District, Chongqing, 400014, P.R. China. Email: xiaohualiang@hospital.cqmu.edu.cn; liangxiaohua666@sina.com and Zipu Li, MD, Heart Center, Qingdao Women and Children's Hospital, Qingdao University Qingdao 266034, China. Email: apuqd@sina.com

*Y. Yuan and B. Pan are co-first authors.

This manuscript was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.038129

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This study reveals significant age-related differences in clinical characteristics and outcomes among patients with pediatric heart failure, highlighting the need for age-stratified management strategies.

What Are the Clinical Implications?

- Age-based treatment approaches may mitigate the risks of adverse events inherent to each developmental stage, improving the clinical outcomes in patients with pediatric heart failure.
- Through prospective cohort studies, future research should explore the pathophysiological mechanisms of age-specific variations in heart failure and assess the clinical efficacy of age-stratified pediatric heart failure management strategies, which will guide the formulation and refinement of evidence-based treatment protocols.

Nonstandard Abbreviations and Acronyms

BRC	bad Ross class
CAE	cardiovascular adverse event
CCHD	Complex Congenital Heart Disease
GR	growth retardation

Heart failure (HF) is a condition that occurs when the heart is unable to pump adequate blood due to structural or functional cardiac abnormalities.[1,2] Although medical advancements have improved outcomes among patients with HF, the global HF prevalence continues to rise, a phenomenon primarily attributable to population aging, prolonged survival among critically ill patients, and adverse drug reactions. Consequently, HF remains a significant public health concern.[3,4]

Multiple studies have been conducted on HF, significantly enhancing our understanding of the disease.[5–8] However, current research predominantly focuses on adult HF and overlooks pediatric HF (PHF), resulting in limited PHF-related research. This phenomenon could primarily be attributed to the paucity of large-scale PHF cohorts. The current PHF guidelines, which are yet to be updated, were proposed by the Canadian Cardiovascular Society (2013)[9] and the International Society for Heart and Lung Transplantation (2014).[10] Furthermore, besides lacking in-depth evidence, recently published PHF treatment and management recommendations or consensus statements[11–13] mostly draw on results from adult HF research, a gap that was also highlighted in the American Heart Association's July 2024 scientific statement on chronic HF in children and adolescents with congenital heart disease (CHD).[14]

Although recommendations for PHF diagnosis and treatment have been proposed on the basis of relevant professional guidelines, due to pathogenetic complexities and lack of large-scale research-based medical evidence, current treatment strategies are largely extrapolated from adult HF research; hence, they lack specificity and empirical support. Recent research has also shown significant differences between pediatric and adult HF in terms of pathogenesis, clinical manifestations, and prognosis. However, most of these clinical investigations were conducted in Europe and America, and systematic studies examining the characteristic differences across various PHF age groups remain elusive.[15–24] In contrast with the age-related decline in organ function and metabolic rates observed in adulthood,[25–30] child growth and development is a continuous, dynamic process, in which the body undergoes gradual refinement after birth.[19] According to research, PHF often presents with distinct age-related characteristics, such as feeding difficulties or interrupted feeding in infants and digestive issues in adolescents.[13] Moreover, age may constrain pharmacotherapy selection for PHF treatment. Birth history and body mass index (BMI), which were found to affect HF in adult studies,[31–35] may also influence children's growth and development, highlighting the potential PHF implications.

Despite the crucial need for age-based PHF treatment strategies, there is a paucity of research-based medical evidence tailored to different PHF age groups. Consequently, this multicenter retrospective cohort study aimed to delineate age-related differences in PHF characteristics and outcomes, providing evidence for age-specific management strategies.

METHODS

Study Design and Cohort

This multicenter retrospective cohort study, supported by the National Center for Children's Health Clinical Research (Data S1), involved 30 medical centers from 20 Chinese provinces. Medical experts and statisticians collaboratively developed the survey questionnaire and manual used herein and created a database using Access software (Microsoft, Redmond, WA). All researchers at each center underwent standardized, high-quality training. Data were extracted from the hospital information systems. Trained personnel verified the data, which were entered in a double-blinded approach.

The Ethics Committee of Chongqing Medical University approved the study protocol (File No.

2020.160). The right to informed consent was waived owing to the nature of the study. Data supporting our findings are available from the corresponding author upon reasonable request.

Patients

Herein, all hospitalized patients with HF (aged ≤18 years) diagnosed between January 2013 and December 2022 in the involved institutions were included. Patients were stratified into 4 age groups: neonatal (≤1 month), infant and toddler (>1 month and ≤3 years), young children (>3 years and ≤12 years), and adolescent (>12 years and ≤18 years). These age groups reflect the distinct stages of children's growth and development, which have various HF implications. For instance, neonates often undergo the transition from fetal to independent circulation, making them particularly susceptible to CHD or infection-induced HF. On the other hand, infants and toddlers, as well as adolescents, often experience rapid growth. Consequently, HF in infants and toddlers is often linked to CHD and increased metabolic demands and hormonal changes in adolescents. Finally, when entering a period of slowed growth, young children may experience HF due to long-term hemodynamic changes.

Herein, PHF diagnosis was defined as outlined in the Chinese recommendations,[13,36] primarily on the basis of pathogenesis, medical history, clinical manifestations, and auxiliary examinations, and confirmed through a 3-level physician ward examination system. Regarding data collection, invalid questionnaires included duplicates, those filled by patients aged >18 years, those not matching the admission period, or those with a missing rate of ≥20%. These questionnaires were excluded from the final analysis.

Variables and Outcomes

Demographic characteristics, clinical features, auxiliary examinations, diagnoses, and outcomes were the collected data. Variables such as height, weight, BMI, and blood pressure (BP) were categorized on the basis of age and sex reference values.[37–41]

The primary outcome measure was the all-cause mortality rate. On the other hand, the secondary outcome measures were cardiovascular adverse events (CAEs; defined as malignant arrhythmias or patients requiring advanced life support), and bad Ross class (BRC; means classified as modified Ross class III–IV at discharge; Data S2).

Statistical Analysis

Data were processed using RStudio 4.3.0 software (R Foundation for Statistical Computing, Vienna, Austria). Variables with ≥70% missing values were excluded from the analysis. The missing data in variables with <70% missing values were not filled in. Differences with $P<0.05$ were considered statistically significant. Continuous variables were expressed as medians and interquartile ranges, and intergroup differences were compared using the Wilcoxon rank-sum test. On the other hand, categorical variables were presented as frequencies (percentages), and intergroup differences were compared using the χ^2 or Fisher's exact test.

Logistic and linear regression models were used to assess differences in PHF outcomes across various age groups. Variables with significant differences ($P<0.05$) between outcomes groups (all-cause mortality rate, CAE, and BRC) in univariate analyses were included in the final model (Table S1). Moreover, clinically relevant covariates were also selected on the basis of expert consensus and existing literature. These variables included sex, gestational week (GW; we conducted a multiple model regression analysis considering the collinearity between GW and birth weight; Table S2), surgical history, BMI, BP, modified Ross classification on admission, HF type (acute HF or chronic HF [CHF]), and primary combined diseases (simple CHD [SCHD], complex CHD [CCHD], cardiomyopathy, infection, and other), auxiliary examination data (left ventricular ejection fraction [LVEF], moderate to severe valvular regurgitation, NT-proBNP [N-terminal pro-B-type natriuretic peptide], alanine transaminase, aspartate aminotransferase, albumin, creatine, blood urea nitrogen, uric acid, serum potassium concentration, serum calcium concentration, prothrombin time [PT], activated partial thromboplastin time, triglyceride, total cholesterol, fasting blood glucose, P_{O_2}, and P_{CO_2}). Subgroup analyses (eg, by sex, blood pressure) were conducted to explore potential variations in the effect of age group on the main outcomes (all-cause mortality rate, CAEs, and BRC). Further multivariable regression analyses were performed to identify factors influencing PHF outcomes. In all analyses, $P<0.05$ was considered statistically significant.

Since the LVEF–age and growth retardation (GR)–age relationship may be nonlinear, these associations were modeled using restricted cubic splines flexibly. The reference value was established at the median position, and knots were positioned at the 5th, 35th, 65th, and 95th percentiles of the variable distribution. The 95% CIs were represented by shaded areas. The P value for nonlinear was calculated using a likelihood ratio test, comparing the goodness of fit between the nonlinear model and a simpler linear model. A P value for nonlinear <0.05 was considered to indicate significant nonlinearity.

RESULTS

Herein, 3557 PHF questionnaires were collected, of which 2903 (212, 1618, 766, and 307 questionnaires

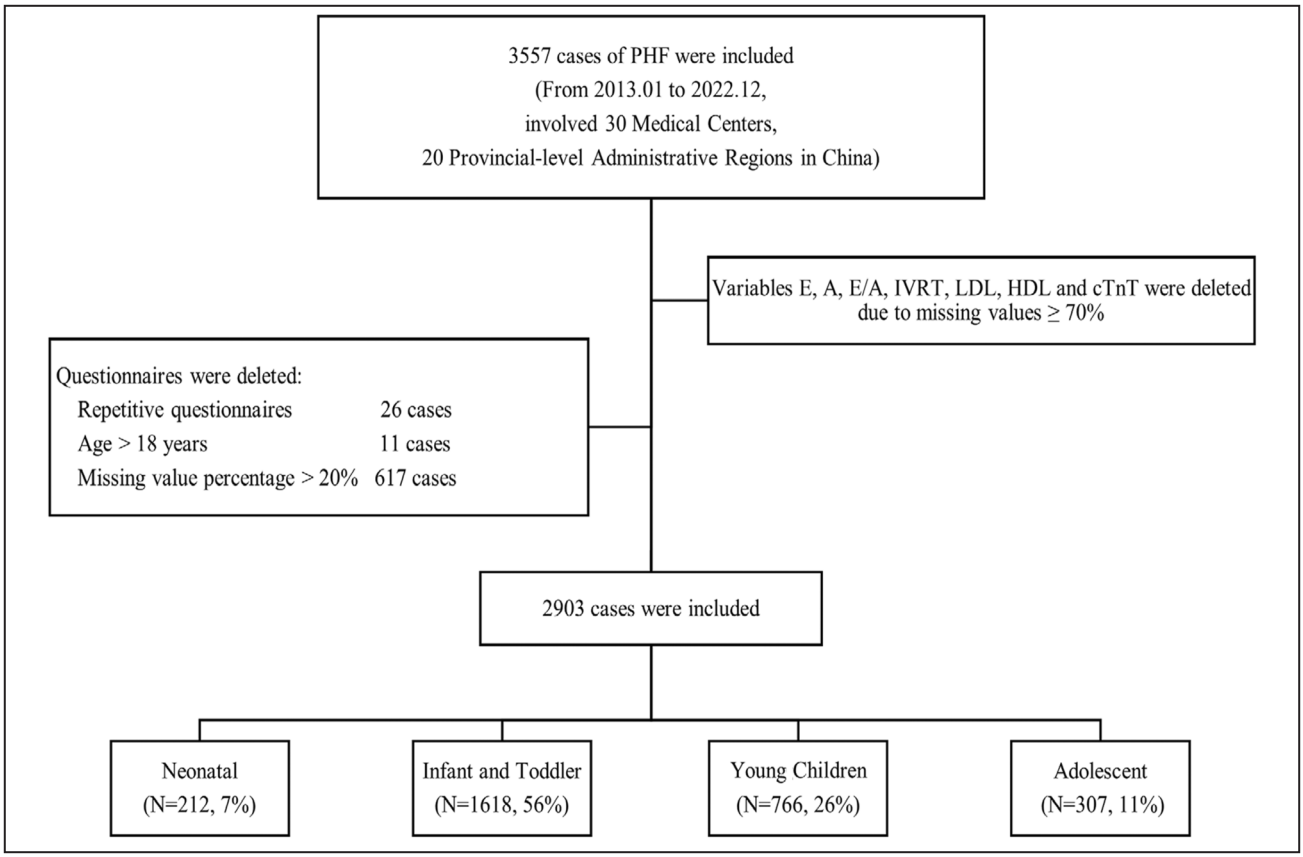

Figure 1. Flowchart of subject selection.
A indicates late diastolic mitral flow peak velocity; cTnT, cardiac troponin T; E, early diastolic mitral flow peak velocity; HDL, high-density lipoprotein; IVRT, isovolumic relaxation time; LDL, low-density lipoprotein; and PHF, pediatric heart failure.

for the neonatal, infant and toddler, young children, and adolescent groups, respectively) were included in the final analysis after data cleaning. The infant and toddler (56%) and young children (26%) groups made up the majority of the hospitalized patients with PHF (Figure 1).

General Characteristics

The majority of hospitalized patients with PHF (63.6%) were categorized as acute HF, with an almost equal sex distribution and a median age of 12.8 (3.4–82.7) months. Furthermore, more than one third of all patients with PHF (39.4%) had GR, and the most prevalent clinical manifestations of PHF were respiratory symptoms (75.3%) and systemic venous congestion (74.9%). Additionally, more than one third of all PHF cases were diagnosed with CHD (36.6%) or cardiomyopathy (33.7%), with infections complicating 29.3% of all cases. Moreover, the median LVEF was 54% (35%–68%) and more than half (51.0%) of all patients with PHF had LVEF <55% (49.9% of patients with CHF had LVEF <55%), with an even lower percentage of PHF cases having comorbid CHD (33.7%; Figure S1). All differences were statistically significant (P<0.05; Table).

Characteristics of Different Age Groups

There was no sex difference in younger groups (infant and toddler and young children groups), whereas a higher proportion of boys had PHF in older groups (neonatal [57.1%] and adolescent groups [58.3%]). More than one quarter of neonatal group patients with PHF had a GW of <37 weeks (28.1%) and a birth weight of <2.5 kg (28.0%). Furthermore, both the infant and toddler (27.1%) and adolescent (29.0%) groups had significantly higher proportions of low BMI, while the infant and toddler group had the highest proportion of GR (46.4%). Compared with other groups, the neonatal group had a significantly greater proportion of patients with PHF with hypotension (14.7%), whereas the young children (24.0%) and adolescent (19.1%) groups had higher proportions of patients with PHF with hypertension. The most prominent symptom in the neonatal (41.5%) and infant and toddler (45.0%) groups was interrupted feeding, and these groups exhibited a significantly higher prevalence of respiratory symptoms at 89.6% and 81.5%, respectively. Meanwhile, the infant and toddler group had the highest proportion of systemic venous congestion cases (82.1%). Compared with the other 2 groups, digestive symptoms were significantly more prevalent in the adolescent (38.8%) and young children (39.2%) groups.

Table. General Characteristics of PHF and Comparisons Between Different Age Groups

Variables	Total (n=2903)	Neonatal (n=212)	Infant and toddler (n=1618)	Child (n=766)	Teenager (n=307)
Demographic characteristics					
Sex, n (%)					
Girl	1402 (48.3)	91 (42.9)	787 (48.6)*	396 (51.7)*	128 (41.7)†,‡
Boy	1501 (51.7)	121 (57.1)	831 (51.4)*	370 (48.3)*	179 (58.3)†,‡
Age, mo, median (IQR)	12.83 (3.42–82.68)	0.30 (0.03–0.70)	5.62 (2.78–12.19)*	87.60 (60.51–117.61)*,†	180.23 (162.77–186.82)*,†,‡
GW, wk, median (IQR)	38.57 (37.00–39.86)	38.29 (36.14–39.43)	38.43 (37.00–39.71)*	39.00 (37.43–40.00)*,†	39.00 (38.00–40.00)*,†
Birth weight, kg, median (IQR)	3.20 (2.90–3.50)	3.05 (2.31–3.50)	3.20 (2.80–3.50)*	3.20 (3.00–3.50)*,†	3.25 (3.00–3.60)*,†
Family history, n (%)	258 (8.9)	11 (5.2)	122 (7.5)*	88 (11.5)*,†	37 (12.1)*,†
Surgical history, n (%)	232 (8.0)	1 (0.5)	80 (4.9)*	97 (12.7)*,†	54 (17.6)*,†,‡
Clinical features					
BMI, n (%)					
Underweight	493 (23.2)	26 (14.4)	317 (27.1)*	86 (15.5)*,†	64 (29.0)*,†,‡
Normal	1461 (68.7)	141 (77.9)	739 (63.2)*	428 (77.0)*,†	153 (69.2)*,†,‡
Overweight	173 (8.1)	14 (7.7)	113 (9.7)*	42 (7.6)†	4 (1.8)*,†,‡
Growth retardation, n (%)	1059 (39.4)	N*	751 (46.4)	206 (26.9)†	102 (33.2)†,‡
Blood pressure					
SBP, mm Hg, median (IQR)	91 (82–104)	72 (65–80)	88 (80–96)*	98 (90–108)*,†	106 (98–116)*,†,‡
DBP, mm Hg, median (IQR)	56 (48–65)	41 (34–52)	52 (45–60)*	61 (55–70)*,†	68 (60–75)*,†,‡
Hypotension, n (%)	152 (6.0)	28 (14.7)	55 (4.2)*	43 (5.8)*	26 (8.7)*,†,‡
Hypertension, n (%)	406 (16.0)	19 (9.9)	152 (11.6)	178 (24.0)*,†	57 (19.1)*,†
Modified Ross classification on admission, n (%)					
I–II	783 (37.5)	49 (41.2)	422 (38.8)*	240 (37.9)	72 (28.9)*,‡
III–IV	1308 (62.6)	70 (58.8)	667 (61.2)*	394 (62.1)	177 (71.1)*,‡
Symptoms and signs					
Respiratory, n (%)	2185 (75.3)	190 (89.6)	1319 (81.5)	465 (60.7)*,†	211 (68.7)*,†,‡
Digestive, n (%)	717 (24.7)	22 (10.4)	276 (17.1)	300 (39.2)*,†	119 (38.8)*,†
SVC, n (%)	2173 (74.9)	145 (68.4)	1328 (82.1)*	492 (64.2)†	188 (61.2)†
Interrupted feeding, n (%)	816 (28.1)	88 (41.5)	728 (45)	N*	N*
Diagnostic related					
HF type, N (%)					
AHF	1801 (63.6)	202 (100)	962 (60.7)*	443 (59.4)*	194 (65.5)*
CHF	1029 (36.4)	N*	624 (39.3)	303 (40.6)	102 (34.5)
Primary combined disease, n (%)					
CHD, n (%)	1062 (36.6)	101 (47.6)	769 (47.5)	133 (17.4)*,†	59 (19.2)*,†
Simple CHD	331 (11.4)	23 (10.8)	251 (15.5)*	37 (4.8)*,†	20 (6.5)†
Complex CHD	731 (25.2)	78 (36.8)	518 (32)	96 (12.5)*,†	39 (12.7)*,†
Infection	107 (3.7)	15 (7.1)	77 (4.8)*	12 (1.6)*,†	3 (1)*,†
Cardiomyopathy, n (%)	978 (33.7)	15 (7.1)	491 (30.3)*	325 (42.4)*,†	147 (47.9)*,†
Infection	100 (3.4)	4 (1.9)	60 (3.7)*	18 (2.3)	18 (5.9)*,‡
Infection, n (%)	850 (29.3)	100 (47.2)	439 (27.1)*	216 (28.2)*	95 (30.9)*
Other, n (%)	322 (11.1)	18 (8.5)	129 (8.0)*	139 (18.1)†	36 (11.7)*,†,‡

(*Continued*)

Table 1. Continued

Variables	Total (n=2903)	Neonatal (n=212)	Infant and toddler (n=1618)	Child (n=766)	Teenager (n=307)
Outcomes					
AMR, n (%)	115 (4.0)	23 (10.8)	57 (3.5)*	24 (3.1)*	11 (3.6)*
CAEs, n (%)	413 (14.23)	12 (5.7)	115 (7.1)*	76 (9.9)*,†	40 (13)*,†,‡
BRC, n (%)					
I–II	1349 (72.1)	83 (74.1)	738 (76)	408 (70.1)	120 (58.3)*,†,‡
III–IV	522 (27.9)	29 (25.9)	233 (24.0)	174 (29.9)	86 (41.8)*,†,‡
LHS, d, median (IQR)	12 (8–19)	13 (8–24)	12 (8–19)*	12 (8–18)*	12 (7–18)*
Cost, RMB, median (IQR)	20445 (10770–44442)	33504 (17048–82804)	19904 (10702–41570)*	20060 (10206–41122)*	19517 (10327–45780)*,y

AHF, acute heart failure; AMR, all-cause mortality rate; BMI, body mass index; BRC, bad Ross class; CAE, cardiovascular adverse event; CHD, congenital heart disease; CHF, chronic heart failure; DBP, diastolic blood pressure; GW, gestational weeks; IQR, interquartile range; LHS, length of hospital stay; PHF, pediatric heart failure; SBP, systolic blood pressure; and SVC, systemic venous congestion.

Family history: Cardiovascular diseases have been observed among immediate blood relatives within 3 generations (such as CHD, cardiomyopathy, hypertension, coronary artery disease, primary pulmonary hypertension, or sudden death, etc); surgical history: cardiovascular-related surgeries, including interventional, open-heart, radiofrequency ablation, pacemaker etc; growth retardation: weight, height, or BMI below the third percentile of healthy children of the same age and sex; CAEs: malignant arrhythmias or requiring advanced life support (pacemaker implantation, heart transplantation, cardioversion, extracorporeal membrane oxygenation, blood purification; BRC: means classified as modified Ross class III–IV at discharge).

*Comparison with neonatal group, $P<0.05$.

†Comparison with infant and toddler group, $P<0.05$.

‡Comparison with child group, $P<0.05$.

Significant variations in the combined disease prevalence was observed across various age groups. Although CHD was the most common combined disease in the neonatal (47.6%) and infant and toddler (47.5%) groups, cardiomyopathy was significantly more prevalent in the young children (42.4%) and adolescent (47.9%) groups. Additionally, the neonatal group showed a significantly higher prevalence of infections (47.2%), whereas the young children (18.1%) and adolescent (11.7%) groups showed a higher prevalence of other diseases (noncardiovascular/noninfection). Furthermore, in echocardiography, the indices of the heart's structural size and ventricular systolic function increased and decreased significantly with age, respectively (Table).

Significant intergroup differences were also observed in other auxiliary examination indicators (Table S3). After adjusting for covariates, there were still significant differences in symptoms and signs, LVEF, left ventricular fractional shortening, brain natriuretic peptide, and NT-proBNP ($P<0.05$; Table S4).

Outcomes Across Different Age Groups

The median length of hospital stay and hospitalization cost for PHF were 12 (8–19) days and 20400 (10800–44400) RMB, respectively. Notably, 4.0% of the included patients with PHF died, while 53% and 27.9% had CAEs and BRC, respectively. Compared with other groups, the neonatal group had the highest length of hospital stay (13 days), all-cause mortality rate (10.8%), and hospitalization costs (33504 RMB), while the adolescent group had the highest proportion of CAE (13.0%) and BRC (41.8%) cases ($P<0.05$; Table).

Mortality Rates Across Different Age Groups

After adjustment, compared with the neonatal group, the infant and toddler (odds ratio [OR], 0.46 [95% CI, 0.25–0.85]), young children (OR, 0.39 [95% CI, 0.18–0.85]), and adolescent (OR, 0.34 [95% CI, 0.13–0.87]) groups showed a significantly lower in-hospital mortality odds for PHF ($P<0.05$; Figure 2, Table S5). Furthermore, subgroup analyses revealed consistent neonatal mortality odds rates in terms of sex, GW, BP, modified Ross class on admission, CHD, cardiomyopathy, infection, and LVEF ($P>0.05$), although the odds were significantly higher in cases classified as acute HF (OR, 2.29 [95% CI, 1.40–3.76]; $P<0.05$; Figure 3).The independent risk factors for death were a GW of <34 weeks (neonatal: OR, 21.34 [95% CI, 1.80–253.63]; nonneonatal: OR, 8.72 [95% CI, 3.91–19.45]), III–IV modified Ross classification on admission (neonatal: OR, 1.72 [95% CI, 1.10–5.11]; nonneonatal: OR, 2.99 [95% CI, 1.43–6.23]), CCHD (neonatal: OR, 1.92 [95% CI, 1.22–16.77]; nonneonatal: OR, 2.50 [95% CI, 1.19–5.26]) and moderate to severe valvular regurgitation (neonatal: OR, 1.38 [95% CI, 1.25–7.57]; nonneonatal: OR, 1.94 [95% CI, 1.18–3.18]). On the other hand, calcium (neonatal: OR, 0.33 [95% CI, 0.05–0.89]; nonneonatal: OR, 0.55 [95% CI, 0.35–0.87]) was a protective factor. Additionally, infections (OR, 2.26 [95% CI, 1.26–19.68]) were an independent risk factor for

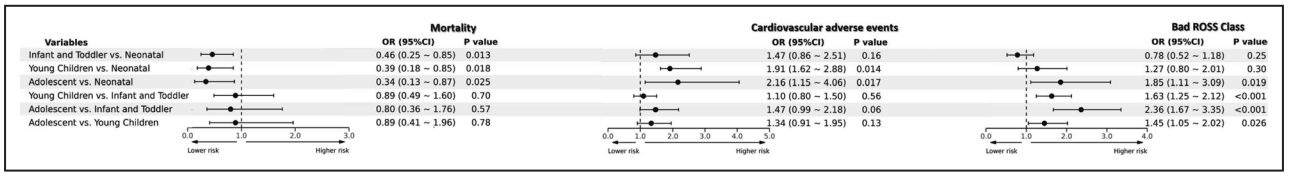

Figure 2. The relationship between age and clinical outcomes of PHF after adjustment (total sample regression analysis).
Adjust: sex, gestational weeks, surgical history, body mass index, HBP, LBP, modified Ross classification on admission, heart failure type, simple congenital heart disease, complex congenital heart disease, cardiomyopathy, infection, other, left ventricular ejection fraction, moderate to severe valvular regurgitation, N-terminal pro-B-type natriuretic peptide, alanine transaminase, aspartate transaminase, albumin, creatine, blood urea nitrogen, uric acid, potassium, calcium, prothrombin time, activated partial thromboplastin time, Po_2, Pco_2, triglyceride, total cholesterol, and fasting plasma glucose. PHF indicates pediatric heart failure.

neonatal death, while hypotension (OR, 4.53 [95% CI, 2.35–8.73]) and NT-proBNP (OR, 1.01 [95% CI, 1.01–1.01]) were independent risk factors for nonneonatal death (P<0.05; Table S6).

CAEs in Different Age Groups

After adjustment, CAE odds were significantly higher in the young children (OR, 1.91 [95% CI, 1.62–2.88]) and adolescent (OR, 2.16 [95% CI, 1.15–4.06]) groups than in the neonatal group (Figure 2, Table S5). Furthermore, subgroup analyses revealed consistent CAE odds in young children and adolescent groups in terms of sex, GW, BP, modified Ross class on admission, SCHD, and cardiomyopathy (P>0.05), although the odds was significantly higher in cases classified as acute HF (OR, 1.98 [95% CI, 1.53–2.57]), non-CCHD (OR, 1.94 [95% CI, 1.51–2.50]), infection (OR, 3.29 [95% CI, 2.23–4.86]), and LVEF ≥55% (OR, 2.21 [95% CI, 1.52–3.22]; P<0.05; Figure 3).

The independent risk factors for CAE were SCHD (neonatal and infant and toddler groups: OR, 2.24 [95% CI, 1.15–3.40]; young children and adolescent groups: OR, 2.90 [95% CI, 1.52–5.52]), and cardiomyopathy (neonatal and infant and toddler groups: OR, 2.26 [95% CI, 1.15–2.46]; young children and adolescent groups: OR, 3.15 [95% CI, 2.02–4.91]). Meanwhile, LVEF (neonatal and infant and toddler groups: OR, 0.96 [95% CI, 0.95–0.97]; young children and adolescent groups: OR, 0.99 [95% CI, 0.98–0.99]) and calcium (neonatal and infant and toddler groups: OR, 0.59 [95% CI, 0.42–0.82]; young children and adolescent groups: OR, 0.61 [95% CI, 0.43–0.86]) were protective factors. Moreover, underweight (OR, 14.06 [95% CI, 9.94–19.89]), overweight (OR, 2.20 [95% CI, 1.07–4.55]), modified Ross class III to IV on admission (OR, 1.79 [95% CI, 1.25–2.59]), and NT-proBNP (OR, 1.01 [95% CI, 1.01–1.01]) were independent risk factors for CAEs in the young children and adolescent groups,

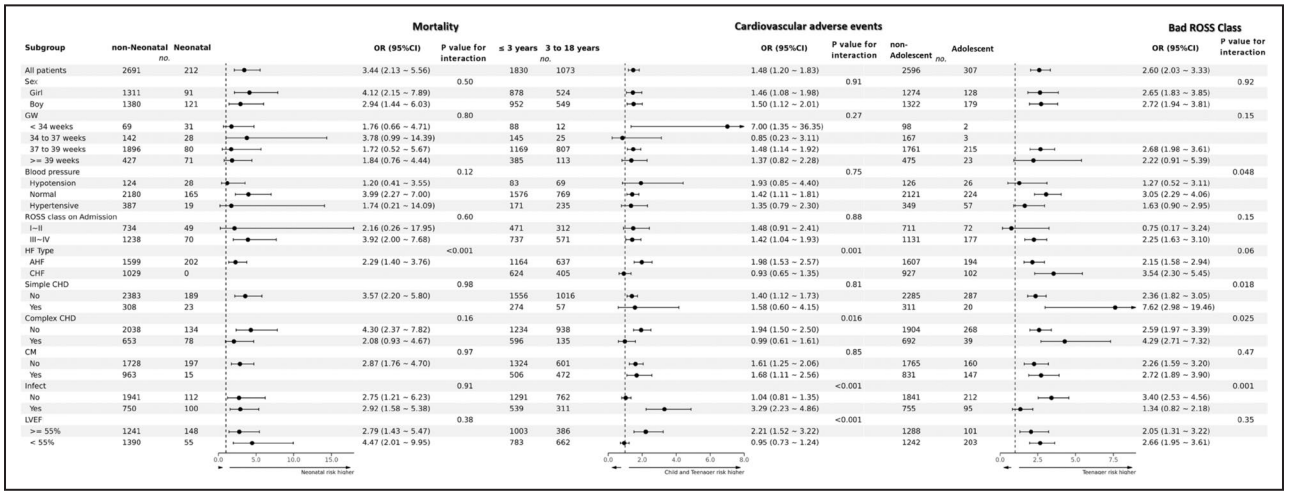

Figure 3. The relationship between age and clinical outcomes of PHF after adjustment (subgroup analysis).
Adjust: sex, gestational weeks, surgical history, body mass index, HBP, LBP, modified Ross classification on admission, heart failure type, simple congenital heart disease, complex congenital heart disease, cardiomyopathy, infection, other, left ventricular ejection fraction, moderate to severe valvular regurgitation, N-terminal pro-B-type natriuretic peptide, alanine transaminase, aspartate transaminase, albumin, creatine, blood urea nitrogen, uric acid, potassium, calcium, prothrombin time, activated partial thromboplastin time, Po_2, Pco_2, triglyceride, total cholesterol, and fasting plasma glucose. AHF indicates acute heart failure; CHD, congenital heart disease; CHF, chronic heart failure; CM, cardiomyopathy; GW, gestational weeks; LVEF, left ventricular ejection fraction; OR, odds ratio; and PHF, pediatric heart failure.

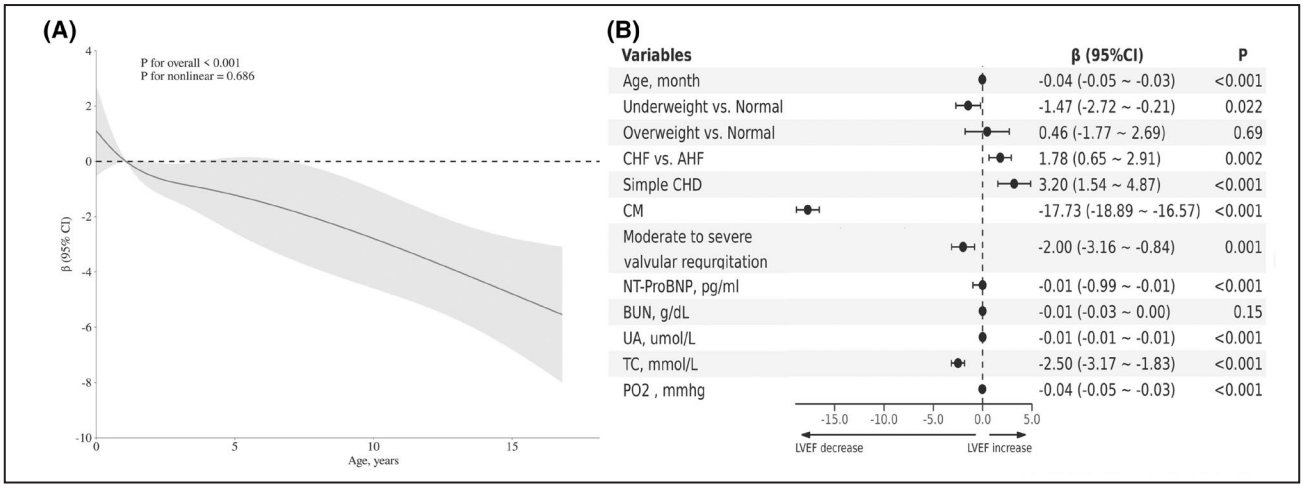

Figure 4. The relationship between age and LVEF of PHF after adjustment.
A, Restricted cubic splines analysis of adjusted age and LVEF. **B**, Multivariate linear analysis of LVEF for PHF. Adjust: sex, gestational weeks, surgical history, BMI, blood pressure, Modified Ross classification on admission, heart failure type, simple CHD, complex CHD, cardiomyopathy, infection, other, LVEF, moderate to severe valvular regurgitation, alanine transaminase, aspartate transaminase, NT-proBNP, albumin, creatine, BUN, UA, potassium, calcium, prothrombin time, activated partial thromboplastin time, Po_2, Pco_2, triglyceride, TC, and fasting plasma glucose. AHF indicates acute heart failure; BUN, blood urea nitrogen; CHD, congenital heart disease; CHF, chronic heart failure; CM, cardiomyopathy; LVEF, left ventricular ejection fractions; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PHF, pediatric heart failure; PT, prothrombin time; TC, total cholesterol; and UA, uric acid.

while CCHD (OR, 2.38 [95% CI, 1.34–4.21]) was an independent risk factor for CAEs in the neonatal and infant and toddler groups (P<0.05; Table S6).

BRC Risk in Different Age Groups

Regarding BRC risk, after adjustment, the adolescent group had 1.85 times (95% CI, 1.11–3.09) higher odds compared with the neonatal group, 2.36 times (95% CI, 1.67–3.35) higher odds compared with the infant and toddler group, and 1.45 times (95% CI, 1.05–2.02) higher odds compared with the young children group (Figure 2, Table S4). Subgroup analyses revealed consistent BRC odds in adolescents in terms of sex, GW, modified Ross classification on admission, HF type, cardiomyopathy, and LVEF (P>0.05). However, the odds were significantly higher in individuals with normal BP (OR, 3.05 [95% CI, 2.29–4.06]), SCHD (OR, 7.62 [95% CI, 2.98–19.46]), CCHD (OR, 4.29 [95% CI, 2.71–7.32]), and noninfections (OR, 3.40 [95% CI, 2.53–4.56]; P<0.05; Figure 3).

The independent risk factors for BRC were modified Ross classif III to IV on admission (nonadolescents: OR, 9.84 [95% CI, 6.68–14.51]; adolescents: OR, 40.18 [95% CI, 9.49–170.09]), CCHD (nonadolescents: OR, 1.61 [95% CI, 1.12–2.31]; adolescent: OR, 1.93 [95% CI, 1.26–3.40]), cardiomyopathy (nonadolescents: OR, 1.89 [95% CI, 1.32–2.72]; adolescents: OR, 1.69 [95% CI, 1.07–2.68]), and NT-proBNP (nonadolescents and adolescents: OR, 1.01 [95% CI, 1.01–1.01]). Meanwhile, the male sex (nonadolescents: OR, 0.78 [95% CI, 0.63–0.96]; adolescents: OR, 0.50 [95% CI, 0.26–0.96]) was a protective factor in both groups. Furthermore, while LVEF (OR, 0.98 [95% CI, 0.96–0.99]) was a protective factor for BRC in the adolescent group, calcium (OR, 0.78 [95% CI, 0.62–0.98]) was a protective factor in the nonadolescent groups. We also found that GW <34 weeks (OR, 2.43 [95% CI, 1.48–3.97]) and surgical history (OR, 1.61 [95% CI, 1.10–2.36]) were independent risk factors for BRC in the nonadolescent groups (P<0.05; Table S6).

GR and LVEF of Different Age Groups

The adjusted restricted cubic splines revealed that LVEF correlated linearly with age. In other words, LVEF decreased gradually with increasing age (P for overall <0.001, P for nonlinear=0.69; Figure 4A). Conversely, GR correlated nonlinearly with age as it underwent 2 periods of increase and 1 period of decrease as age progressed (P for nonlinear <0.001; Figure 5A).While GR and LVEF were not the primary outcome measures of this study, these findings prompted further exploration of their relationship with age. The multivariable linear analysis indicated that LVEF negatively correlated with age (β=−0.04 [95% CI, −0.05 to −0.03]) and various comorbid conditions, such as underweight (β=−1.47 [95% CI, −2.72 to −0.21]) and cardiomyopathy (β=−17.73 [95% CI, −0.05 to −0.03]), while it positively correlated with CHF (β=1.78 [95% CI, −0.65 to −2.91]) and SCHD (β=3.20 [95% CI, 1.54–4.87]; P<0.05; Figure 4B).

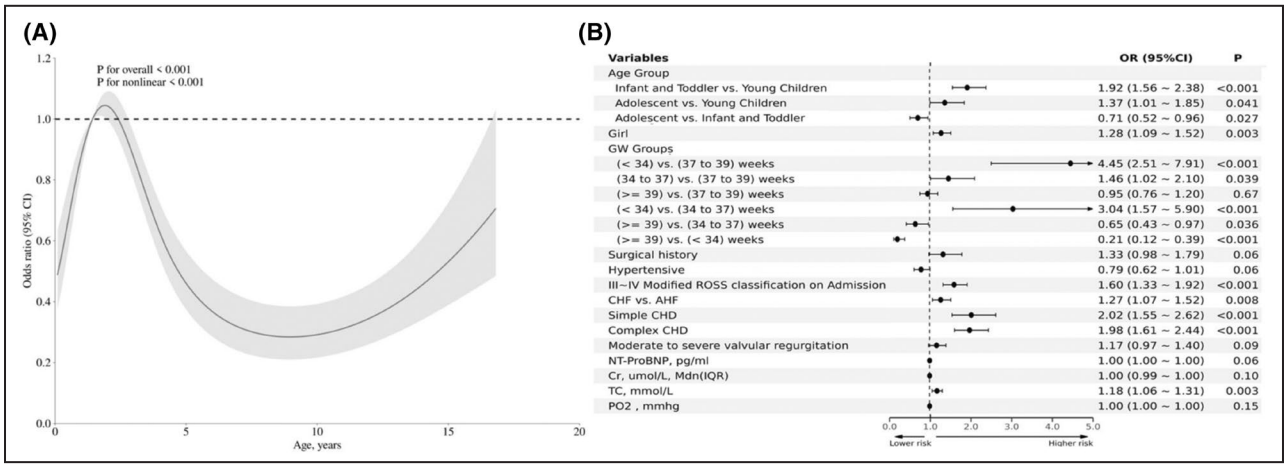

Figure 5. The relationship between age and GR of PHF after adjustment.
A, Restricted cubic splines analysis of adjusted age and GR. **B**, Multivariate regression analysis of GR for PHF. Adjusted for: sex, GW, surgical history, body mass index, blood pressure, modified Ross classification on admission, heart failure type, simple CHD, complex CHD, cardiomyopathy, infection, other, LVEF, moderate to severe valvular regurgitation, NT-proBNP, alanine transaminase, aspartate transaminase, albumin, creatine, BUN, UA, potassium, calcium, prothrombin time, activated partial thromboplastin time, Po_2, Pco_2, triglyceride, TC, and fasting plasma glucose. AHF indicates acute heart failure; CHD, congenital heart disease; CHF, chronic heart failure; Cr, creatine; GW, gestational weeks; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PHF, pediatric heart failure; and TC, total cholesterol.

Regarding GR, the multivariable regression analysis revealed significantly higher odds of PHF in the adolescent (OR, 1.37 [95% CI, 1.01–1.85]) and infant and toddler (OR, 1.92 [95% CI, 1.56–2.38]) groups compared with the young children group. Additionally, GR was positively correlated in girls (OR, 1.28 [95% CI, 1.09–1.52]), GW <34 weeks (OR, 4.45 [95% CI, 2.51–7.91]), modified Ross class III to IV on admission (OR, 1.60 [95% CI, 1.33–1.92]), CHF (OR, 1.27 [95% CI, 1.07–1.52]), SCHD (OR, 2.02 [95% CI, 1.55–2.62]) and CCHD (OR, 1.98 [95% CI, 1.61–2.44]; $P<0.05$; Figure 5B).

Outcomes Across Sexes and LVEF Differences

Considering the variability in clinical outcomes among adult patients with HF stratified by sex and LVEF, we performed a regression analysis on patients with PHF using the same stratified parameters. Adjusted results showed no correlation between sex and odds of in-hospital death or CAEs. However, reduced BRC odds were observed in boys (OR, 0.76 [95% CI, 0.62–0.93]). Although the LVEF category did not predict in-hospital mortality or BRC risk, PHF with LVEF <55% showed an elevated risk of CAEs ($P<0.05$; Tables S7 and S8).

DISCUSSION

To the best of our knowledge, this multicenter retrospective cohort study is the first large-scale investigation to comprehensively examine the clinical characteristics and PHF outcomes across different age groups in China. Our findings revealed significant differences in PHF characteristics and outcomes across various age groups. Specifically, the neonatal group exhibited the highest mortality risk, while the young children and adolescent groups were more prone to CAEs. Furthermore, adolescents often showed BRC at discharge, and GR was more prevalent in infants, toddlers, and adolescents with PHF. Moreover, LVEF showed a decreasing trend with increasing age in PHF.

In adult studies, HF was found to primarily affect middle-aged and older individuals, with its incidence increasing with age.[25–31] Herein, PHF was primarily observed in the infant and toddler and young children groups, highlighting potential age-based differences in its underlying mechanisms. According to research, CHD is the most common cause of PHF, followed by cardiomyopathy.[15–18] During the neonatal period, most patients with CHD and cardiomyopathy do not present with symptoms. They instead progress to symptomatic HF as the children grow older, a phenomenon primarily attributable to hemodynamic demands. Long-term hemodynamic changes could result in ventricular remodeling or increased cardiac burden due to infections. Furthermore, CHD cases are commonly diagnosed shortly after birth and can be addressed via surgical intervention before the early childhood stage, whereas cardiomyopathy is often diagnosed after childhood and progressively worsens.[42–44] These differences in pathogenesis and disease progression could explain the variations in comorbidities observed herein across different PHF age groups.

In neonates, GW <34 weeks is a high-risk factor for death, a phenomenon attributable to the adverse effects of preterm birth on heart development.[34,35] Most neonatal patients with HF are a result of CHD or infections,[16,17] which, along with immature development, could lead to rapid disease progression, severe symptoms, increased risk of shock, organ damage, and even death in cases of insufficient effective blood volume. Therefore, assessing and intervening in risk factors for death (such as GW and underlying diseases), CHD screening, preventing infections, and providing pathogenetic treatments, are imperative for reduced mortality rates.

On the other hand, GR was established as the most prominent issue for infants and toddlers. Besides the effects of preterm birth (GW <34 weeks), CHF-associated long-term hemodynamic changes could also affect oxygen supply, cellular function, and energy metabolism in the body, impacting overall growth and development processes.[45,46] This phenomenon is particularly relevant in cases of CHD-induced PHF given that long-term hemodynamic changes may occur before symptomatic HF onset. Furthermore, the infant and toddler group goes through the first peak period of childhood growth and development, potentially exacerbating the degree of growth delay. Consequently, in this stage, additional attention to the impacts of adverse birth history, standardized CHD management, and assessment of both physical growth and nutritional support would be required.

The significant CAE risk in young children and adolescents with PHF highlights the need for more aggressive treatment. Based on mechanisms of cardiomyopathy-associated ventricular remodeling,[42,43] older children with PHF are more likely to exhibit severe symptoms, necessitating advanced life support. Furthermore, abnormal BMI may increase the risk of CAEs in older groups, although additional rigorous controlled studies will be required to verify this phenomenon. Moreover, our findings revealed that respiratory and systemic venous congestion symptoms were less common in older children than younger ones. Based on these findings, we came up with several deductions. First, the more mature neurohumoral regulatory ability in the young children and adolescent categories could somewhat compensate for the effects of pathological changes such as hypoxia. Second, older children's cognitive development may confer greater tolerance, potentially masking their symptoms. Overall, the young children and adolescent groups may require early diagnosis and precise treatments for cardiomyopathy, which are crucial to prevent or delay HF progression. Moreover, assessing the impact of BMI would be crucial for identifying atypical symptoms,[47,48] and exploring other valuable evaluation methods or indicators, such as bendopnea, the 6-minute walking test, and quality of life assessments, could be beneficial.[49–51]

In adolescents, the impacts of cardiomyopathy and CHD on the heart gradually worsen with age, and effective drug treatment options that could halt HF progression in such cases remain elusive. As a result, adolescents with HF often present with worse cardiac dysfunction, and may experience GR, a phenomenon attributed to the second peak of growth and development. Consequently, additional attention is also required for adolescents to assess their growth and development, as well as to emphasize long-term management and rehabilitation guidance after discharge. Researchers should also consider the impact of the physiological and psychological changes at this stage on HF progression.[52,53]

Developing a guided direct medical therapy based on LVEF classification could also be crucial. Adult guidelines define LVEF <50% as HF with mildly reduced ejection fraction.[1] However, there are no standard guidelines for classifications concerning PHF. Consequently, some scholars have often followed adult guidelines, while others have often defined PHF with reduced ejection fraction as LVEF <55%.[9,14,37] These modifications have complicated the distinction and treatment of reduced or preserved LVEF in PHF. Herein, LVEF correlated significantly with CAE risk. Moreover, LVEF values correlated significantly with age, CHD, and cardiomyopathy, highlighting the clinical relevance of LVEF classification in PHF and the fact that it should not rely solely on a single cutoff value but also consider the combined impact of underlying diseases and age.

Some laboratory tests could also provide valuable insights. For instance, NT-proBNP demonstrated significant clinical value in the diagnosis, risk stratification, and prognostic evaluation of HF.[54–56] However, our findings revealed that NT-proBNP was associated with outcomes only in certain age groups. Therefore, additional clinical research will be required to determine the value and diagnostic threshold of NT-proBNP in PHF. Furthermore, we found that serum calcium concentration correlated with PHF outcomes, indicating that calcium-regulating agents may ameliorate HF. However, calcium channel blockers and sensitizers have not been effectively used in children, and their safety and efficacy in PHF remain unclear, thus necessitating additional research. Moreover, our findings suggested that girls had a higher risk of BRC and GR than boys, a phenomenon attributable to differences in underlying diseases. According to research, boys CHD tend to have more complex and severe conditions, whereas SCHD[57] is more common among girls. Furthermore, a recent study suggested that the sex specificity of HF may be associated with hormonal differences between sexes,[58] although this deduction

warrants additional research involving larger cohort studies.

Strengths and Limitations

To the best of our knowledge, this study is the first to thoroughly examine the influence of age on PHF using large-scale sample data collected from 30 medical centers across China. Our study's sample size ensures the stability and representativeness of the results. Furthermore, the variables discussed were all conventional clinical indicators, conferring a practical clinical application value on our findings. Nonetheless, this study also had limitations. For instance, since follow-up was terminated at discharge, this study did not examine long-term outcomes, thus precluding the evaluation of the sustained prognostic impact. Consequently, future large-scale prospective studies are needed to further validate the present findings.

CONCLUSIONS

This multicenter study systematically reveals the distinct clinical phenotypes and prognosis profiles of PHF in various age groups. Moreover, the influence of age on pathophysiological changes, clinical manifestations, and outcomes in PHF is demonstrated. Although there is significant heterogeneity within the PHF population, this study also highlights the critical need for developing diagnostic and therapeutic approaches customized to the age-specific characteristics of PHF.

ARTICLE INFORMATION

Received October 21, 2024; accepted January 9, 2025.

Affiliations

Department of Cardiology, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Pediatric Metabolism and Inflammatory Diseases, Key Laboratory of Children's Important Organ Development and Diseases of Chongqing Municipal Health Commission, National Clinical Key Cardiovascular Specialty, Children's Hospital of Chongqing Medical University, Chongqing, China (Y.Y., B.P., Z.H., H.S., M.Z., L.L., T.L., X.L., J.T.); Children's Hospital Affiliated to Zhengzhou University, Henan Children's Hospital (F.W.); Department of Cardiology, Hunan Children's Hospital, Changsha, China (Z.C.); Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China (Y.G.); Department of Pediatric, The Affiliated Hospital of Southwest Medical University (X.S.); Heart Center, Children's Hospital of Fudan University (X.L.); Inner Mongolia People's Hospital, China (Y.L.); Department of Pediatrics, Shengjing Hospital of China Medical University, Chongqing, China (Y.X.); Pediatric Cardiac Surgery Centre, Fuwai Hospital, National Centre for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Chongqing, China (H.Z.); Hebei Children's Hospital, China (Y.Z.); Department of Cardiology, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Chongqing, China (C.X.); West China Second Hospital, Chongqing, China (L.L.); Qingdao Women and Children's Hospital, West China Second Hospital, Chongqing, China (Z.L.); and Department of Clinical Epidemiology and Biostatistics, Children's Hospital of Chongqing Medical University, Chongqing, China (X.L.).

Acknowledgments

The authors thank the survey teams from different centers for their valuable support in collecting the high-quality data used in this study. A list of the researchers is presented in Data S3. The authors thank all the reviewers who participated in the review and MJEditor (www.mjeditor.com) for editing the language of this manuscript.

Author contributions: Drs Yuan and Pan are co-first authors of the article. They had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Drs Pan and Yuan. Acquisition of data: Drs Pan, Yuan, Wang, Chen, Guo, Shen, X. Liang, Y. Liang, Xing, H. Zhang, Y. Zhang, Xie, Huang, Sun, Zhen, Liu, Lv, and Z. Li. Analysis and interpretation of data: Drs Yuan and Liang. Drafting of the manuscript: Dr Yuan. Critical revision of the manuscript for important intellectual content: Dr Pan, Z. Li, X. Liang, and Tian. Statistical analysis: Drs Yuan and X. Liang. Obtained funding: Drs Sun and Tian. Study supervision: Drs Z. Li, X. Liang, and Tian.

Sources of Funding

This study was supported by the National Clinical Research Center for Child Health and Disorders (Grant No.: NCRCCHD-2021-KP-01 to JT) and the Special Fund for Cardiovascular Diseases, China International Medical Foundation (Grant No.: Z-2019-42-1908-2 to Dr Sun).

Disclosures

None.

Supplemental Material

Tables S1–S8
Figure S1

REFERENCES

1. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the Management of Heart Failure: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2022;145:e876–e894. doi: 10.1161/CIR.0000000000001062
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44:3627–3639. doi: 10.1093/eurheartj/ehad195
3. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;118:3272–3287. doi: 10.1093/cvr/cvac013
4. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, Younis A, Dai H. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol*. 2021;28:1682–1690. doi: 10.1093/eurjpc/zwaa147
5. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, heart failure Association of the European Society of cardiology, Japanese heart failure society and writing Committee of the Universal Definition of heart failure: endorsed by the Canadian heart failure society, heart failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese heart failure association. *Eur J Heart Fail*. 2021;23:352–380. doi: 10.1002/ejhf.2115
6. Ducharme A, Zieroth S, Ahooja V, Anderson K, Andrade J, Boivin-Proulx LA, Ezekowitz J, Howlett J, Lepage S, Leong D, et al. Canadian cardiovascular society-Canadian heart failure society focused clinical practice update of patients with differing heart failure phenotypes. *Can J Cardiol*. 2023;39:1030–1040. doi: 10.1016/j.cjca.2023.04.022
7. Tamargo M, Martínez-Legazpi P, Espinosa MÁ, Lyon A, Méndez I, Gutiérrez-Ibañes E, Fernández AI, Prieto-Arévalo R, González-Mansilla A, Arts T, et al. Increased chamber resting tone is a key determinant of left ventricular diastolic dysfunction. *Circ Heart Fail*. 2023;16:e010673. doi: 10.1161/CIRCHEARTFAILURE.123.010673
8. Ide T, Kaku H, Matsushima S, Tohyama T, Enzan N, Funakoshi K, Sumita Y, Nakai M, Nishimura K, Miyamoto Y, et al. Clinical characteristics and

outcomes of hospitalized patients with heart failure from the large-scale Japanese registry of acute decompensated heart failure (JROADHF). *Circ J*. 2021;85:1438–1450. doi: 10.1253/circj.CJ-20-0947
9. Kantor PF, Lougheed J, Dancea A, McGillion M, Barbosa N, Chan C, Dillenburg R, Atallah J, Buchholz H, Chant-Gambacort C, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian cardiovascular society guidelines. *Can J Cardiol*. 2013;29:1535–1552. doi: 10.1016/j.cjca.2013.08.008
10. Kirk R, Dipchand AI, Rosenthal DN, McGillion M, Barbosa N, Chan C, Dillenburg R, Atallah J, Buchholz H, Chant-Gambacort C, et al. The International Society for Heart and Lung Transplantation guidelines for the management of pediatric heart failure: executive summary. *J Heart Lung Transplant*. 2014;33:888–909. doi: 10.1016/j.healun.2014.06.002
11. El-Saiedi SA, Fathalla A, Gaber H, El Shershaby M, AbdelMassih AF. New strategies in the treatment of advanced heart failure in children and the current consensus of Cairo University children hospital heart failure working group. *Curr Probl Cardiol*. 2023;48:101389. doi: 10.1016/j.cpcardiol.2022.101389
12. Watanabe K, Shih R. Update of pediatric heart failure. *Pediatr Clin North Am*. 2020;67:889–901. doi: 10.1016/j.pcl.2020.06.004
13. Subspecialty Group of Cardiology, the Society of Pediatrics, Chinese Medical Association; Pediatric Cardiovascular Disease Committee, College of Cardiovascular Physicians, Chinese Medical Doctor Association; Editorial Board, Chinese Journal of Pediatrics. Recommendations for diagnosis and treatment of heart failure in children (2020 revised edition). *Zhonghua Er Ke Za Zhi*. 2021;59:84–94. doi: 10.3760/cma.j.cn112140-20200619-00737
14. Amdani S, Conway J, George K, Martinez HR, Asante-Korang A, Goldberg CS, Davies RR, Miyamoto SD, Hsu DT, American Heart Association Council on Lifelong Congenital Heart Disease and Heart Health in the Young, et al. Evaluation and Management of Chronic Heart Failure in children and adolescents with congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2024;150:e33–e50. doi: 10.1161/CIR.0000000000001245
15. Adebiyi EO, Edigin E, Shaka H, Hunter J, Swaminathan S. Pediatric heart failure inpatient mortality: a cross-sectional analysis. *Cureus*. 2022;14:e26721. doi: 10.7759/cureus.26721
16. Morales-Demori R, Montañes E, Erkonen G, Chance M, Anders M, Denfield S. Epidemiology of pediatric heart failure in the USA-a 15-year multi-institutional study. *Pediatr Cardiol*. 2021;42:1297–1307. doi: 10.1007/s00246-021-02611-3
17. Amdani S, Marino BS, Rossano J, Lopez R, Schold JD, Tang WHW. Burden of pediatric heart failure in the United States. *J Am Coll Cardiol*. 2022;79:1917–1928. doi: 10.1016/j.jacc.2022.03.336
18. Shaddy RE, George AT, Jaecklin T, Lochlainn EN, Thakur L, Agrawal R, Solar-Yohay S, Chen F, Rossano JW, Severin T, et al. Systematic literature review on the incidence and prevalence of heart failure in children and adolescents. *Pediatr Cardiol*. 2018;39:415–436. doi: 10.1007/s00246-017-1787-2
19. Guo Y, Pu WT. Cardiomyocyte maturation: new phase in development. *Circ Res*. 2020;126:1086–1106. doi: 10.1161/CIRCRESAHA.119.315862
20. Wall JB, Garcia AM, Jacobsen RM, Miyamoto SD. Important considerations in pediatric heart failure. *Curr Cardiol Rep*. 2020;22:141. doi: 10.1007/s11886-020-01383-1
21. Monda E, Lioncino M, Pacileo R, Rubino M, Cirillo A, Fusco A, Esposito A, Verrillo F, Di Fraia F, Mauriello A, et al. Advanced heart failure in special population-pediatric age. *Heart Fail Clin*. 2021;17:673–683. doi: 10.1016/j.hfc.2021.05.011
22. Andrews RE, Fenton MJ, Ridout DA, Burch M, British Congenital Cardiac Association. New-onset heart failure due to heart muscle disease in childhood: a prospective study in the United Kingdom and Ireland. *Circulation*. 2008;117:79–84. doi: 10.1161/CIRCULATIONAHA.106.671735
23. Wilkinson JD, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ, Cox GF, Canter CE, Hsu DT, Webber SA, et al. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. *Heart Fail Clin*. 2010;6:401-vii. doi: 10.1016/j.hfc.2010.05.002
24. Qasim A, Dam T, Kim JJ, Valdes SO, Howard T, Diaz MA, Morris SA, Miyake CY. Trends in hospitalization and factors associated with in-hospital death among pediatric admissions with implantable cardioverter defibrillators. *J Cardiovasc Electrophysiol*. 2022;33:502–509. doi: 10.1111/jce.15347
25. Emmons-Bell S, Johnson C, Roth G. Prevalence, incidence and survival of heart failure: a systematic review. *Heart*. 2022;108:1351–1360. doi: 10.1136/heartjnl-2021-320131
26. Albert NM. Heart failure is everywhere: insuring diversity in care across gender, age, race and ethnicities. *J Card Fail*. 2021;27:722–723. doi: 10.1016/j.cardfail.2021.05.004
27. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. *JAMA*. 2023;329:827–838. doi: 10.1001/jama.2023.2020
28. Masoli JAH, Mensah E, Rajkumar C. Age and ageing cardiovascular collection: blood pressure, coronary heart disease and heart failure. *Age Ageing*. 2022;51:afac179. doi: 10.1093/ageing/afac179
29. Elbadawi A, Dang A, Elgendy IY, Thakker R, Albaeni A, Omer MA, Mohamed AH, Gilani S, Chatila K, Khalife WI, et al. Age-specific trends and outcomes of hospitalizations with acute heart failure in the United States. *Int J Cardiol*. 2021;330:98–105. doi: 10.1016/j.ijcard.2021.02.031
30. Chan DZL, Kerr AJ, Doughty RN. Temporal trends in the burden of heart failure. *Intern Med J*. 2021;51:1212–1218. doi: 10.1111/imj.15253
31. Yang F, Janszky I, Gissler M, Cnattingius S, Roos N, Miao M, Yuan W, Li J, László KD. Preterm birth, small for gestational age, and large for gestational age and the risk of atrial fibrillation up to middle age. *JAMA Pediatr*. 2023;177:599–607. doi: 10.1001/jamapediatrics.2023.0083
32. Fonseca GWPD, Garfias-Veitl T, von Haehling S. Birth weight and heart failure: hindsight as an exact science? *Eur J Prev Cardiol*. 2022;29:968–970. doi: 10.1093/eurjpc/zwac012
33. Bygdell M, Ohlsson C, Lilja L, Celind J, Martikainen J, Rosengren A, Kindblom JM. Birth weight and young adult body mass index for predicting the risk of developing adult heart failure in men. *Eur J Prev Cardiol*. 2022;29:971–978. doi: 10.1093/eurjpc/zwab186
34. Greer C, Troughton RW, Adamson PD, Harris SL. Preterm birth and cardiac function in adulthood. *Heart*. 2022;108:172–177. doi: 10.1136/heartjnl-2020-318241
35. Crump C, Groves A, Sundquist J, Sundquist K. Association of Preterm Birth with Long-term Risk of heart failure into adulthood. *JAMA Pediatr*. 2021;175:689–697. doi: 10.1001/jamapediatrics.2021.0131
36. Chinese Pediatric Cardiology Society, Chinese Medical Association, Editorial Board, Chinese Journal of Pediatrics. Guideline of diagnosis and treatment for heart failure in children. *Zhonghua Er Ke Za Zhi*. 2006;44:753–757. doi: 10.3760/cma.j.issn.0578-1310.2006.10.111
37. Li H, Ji CY, Zong XN, Zhang YQ. Height and weight standardized growth charts for Chinese children and adolescents aged 0 to 18 years. *Zhonghua Er Ke Za Zhi*. 2009;47:487–492. doi: 10.3760/cma.j.issn.0578-1310.2009.07.003
38. Li H, Ji CY, Zong XN, Zhang YQ. Body mass index growth curves for Chinese children and adolescents aged 0 to 18 years. *Zhonghua Er Ke Za Zhi*. 2009;47:493–498. doi: 10.3760/cma.j.issn.0578-1310.2009.07.004
39. Zong XN, Li H, Zhang YQ, Zhang YQ. Updated growth standards for Chinese children under 7 years of age. *Zhonghua Er Ke Za Zhi*. 2023;61:1103–1108. doi: 10.3760/cma.j.cn112140-20230925-00219
40. Joffe AR. Importance of hypotension and its definition after cardiac arrest. *JAMA Pediatr*. 2018;172:120–122. doi: 10.1001/jamapediatrics.2017.4099
41. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, et al. Clinical practice guideline for screening and Management of High Blood Pressure in children and adolescents. *Pediatrics*. 2017;140:e20171904. doi: 10.1542/peds.2017-1904
42. Bogle C, Colan SD, Miyamoto SD, Choudhry S, Baez-Hernandez N, Brickler MM, Feingold B, Lal AK, Lee TM, Canter CE, et al. Treatment strategies for cardiomyopathy in children: a scientific statement from the American Heart Association. *Circulation*. 2023;148:174–195. doi: 10.1161/CIR.0000000000001151
43. Tsatsopoulou A, Protonotarios I, Xylouri Z, Papagiannis I, Anastasakis A, Germanakis I, Patrianakos A, Nyktari E, Gavras C, Papadopoulos G, et al. Cardiomyopathies in children: an overview. *Hellenic J Cardiol*. 2023;72:43–56. doi: 10.1016/j.hjc.2023.02.007
44. Yuan W, Jia Z, Li J, Liu L, Tian J, Huang X, Quan J. The clinical profile, genetic basis and survival of childhood cardiomyopathy: a single-center retrospective study. *Eur J Pediatr*. 2024;183:1389–1401. doi: 10.1007/s00431-023-05358-6
45. Tsintoni A, Dimitriou G, Karatza AA. Nutrition of neonates with congenital heart disease: existing evidence, conflicts and concerns. *J Matern Fetal Neonatal Med*. 2020;33:2487–2492. doi: 10.1080/14767058.2018.1548602
46. Scott M, Neal AE. Congenital heart disease. *Prim Care*. 2021;48:351–366. doi: 10.1016/j.pop.2021.04.005
47. Hollander SA, Addonizio LJ, Chin C, Lamour JM, Hsu DT, Bernstein D, Rosenthal DN. Abdominal complaints as a common first presentation

of heart failure in adolescents with dilated cardiomyopathy. *Am J Emerg Med*. 2013;31:684–686. doi: 10.1016/j.ajem.2012.12.009
48. Capin I, Capone CA, Taylor MD. Acute on chronic heart failure secondary to left ventricular noncompaction. *Case Rep Pediatr*. 2020;2020:6369806. doi: 10.1155/2020/6369806
49. Chen J, Aronowitz P. Congestive heart failure. *Med Clin North Am*. 2022;106:447–458. doi: 10.1016/j.mcna.2021.12.002
50. Agarwala P, Salzman SH. Six-minute walk test: clinical role, technique, coding, and reimbursement. *Chest*. 2020;157:603–611. doi: 10.1016/j.chest.2019.10.014
51. Johansson I, Joseph P, Balasubramanian K, McMurray JJV, Lund LH, Ezekowitz JA, Kamath D, Alhabib K, Bayes-Genis A, Budaj A, et al. Health-related quality of life and mortality in heart failure: the global congestive heart failure study of 23 000 patients from 40 countries. *Circulation*. 2021;143:2129–2142. doi: 10.1161/CIRCULATIONAHA.120.050850
52. John AS, Jackson JL, Moons P, Uzark K, Mackie AS, Timmins S, Lopez KN, Kovacs AH, Gurvitz M, American Heart Association Adults With congenital Heart Disease Committee of the Council on Lifelong congenital Heart Disease and Heart Health in the Young and the Council on Clinical Cardiology, et al. Advances in managing transition to adulthood for adolescents with congenital heart disease: a practical approach to transition program design: a scientific statement from the American Heart Association. *J Am Heart Assoc*. 2022;11:e025278. doi: 10.1161/JAHA.122.025278
53. Lindgren M, Robertson J, Adiels M, Schaufelberger M, Åberg M, Torén K, Waern M, Åberg ND, Rosengren A. Elevated resting heart rate in adolescent men and risk of heart failure and cardiomyopathy. *ESC Heart Fail*. 2020;7:1178–1185. doi: 10.1002/ehf2.12726
54. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, Coats AJS, Metra M, Mebazaa A, Ruschitzka F, et al. Heart failure Association of the European Society of cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail*. 2019;21:715–731. doi: 10.1002/ejhf.1494
55. Meijers WC, Bayes-Genis A, Mebazaa A, Bauersachs J, Cleland JGF, Coats AJS, Januzzi JL, Maisel AS, McDonald K, Mueller T, et al. Circulating heart failure biomarkers beyond natriuretic peptides: review from the biomarker study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur J Heart Fail*. 2021;23:1610–1632. doi: 10.1002/ejhf.2346
56. Tawiah KD, Franks CE, Tang J, Gazit A, Dietzen DJ, Farnsworth CW. Comparison between BNP and NT-proBNP in pediatric populations. *Clin Biochem*. 2022;109-110:74–78. doi: 10.1016/j.clinbiochem.2022.08.003
57. Yoo BW. Epidemiology of congenital heart disease with emphasis on sex-related aspects. *Adv Exp Med Biol*. 2018;1065:49–59, Springer International Publishing. doi: 10.1007/978-3-319-77932-4_3
58. Rosano GMC, Stolfo D, Anderson L, Abdelhamid M, Adamo M, Bauersachs J, Bayes-Genis A, Böhm M, Chioncel O, Filippatos G, et al. Differences in presentation, diagnosis and management of heart failure in women. A scientific statement of the heart failure association of the ESC. *Eur J Heart Fail*. 2024;26:1669–1686. doi: 10.1002/ejhf.3284