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Homocysteine is a risk factor for reduced ejection fraction in children with myocarditis: a single-center study

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Background: The relationship between homocysteine (HCY) and ejection fraction (EF) has been demonstrated in diseases such as coronary artery disease, but the relationship between HCY and EF in pediatric patients with myocarditis remains unclear. The aim of this study was to investigate the relationship between HCY and EF in pediatric patients with myocarditis.

Methods: This single-center cross-sectional study included 164 pediatric myocarditis patients aged 1–18 years, including 104 males and 60 females, at Anzhen Hospital (2023–2024) in Beijing. Patient demographic characteristics were collected, and blood tests were performed to assess HCY, routine blood tests, and markers of myocardial damage. EF was measured using 3.0T cardiac magnetic resonance (CMR), and patients were grouped using EF < 55% as the cutoff value. Statistical analyses were performed using t-tests, Binary logistic regression and Restrict cubic spline (RCS), and subgroup analyses [age, sex, body mass index (BMI)].

Results: Of the 164 patients, 31% ($n = 51$) had EF values < 55%. High HCY concentration demonstrated a statistically positive relationship with the risk of occurrence of EF < 55% (OR = 1.033, $P = 0.034$). Subgroup analysis showed a stronger correlation in men (OR = 1.045, $P = 0.016$) and in those with a BMI ≥ 24 kg/m² (OR = 1.083, $P = 0.010$). The RCS showed a non-significant trend of increasing EF < 55% ($P > 0.05$).

Conclusion: The findings suggest that elevated HCY levels are a risk factor for EF < 55% in pediatric patients with myocarditis, especially in males and overweight individuals.

KEYWORDS

cardiac magnetic resonance, cardiac MRI, ejection fraction, homocysteine, myocarditis, pediatrics

1 Introduction

Homocysteine (HCY) is a sulfhydryl-containing amino acid that occupies a pivotal role in one-carbon metabolism, functioning as a critical intermediate in two interconnected pathways: remethylation to methionine and transsulfuration to cysteine (1, 2). Elevated plasma HCY levels, termed hyperhomocysteinemia, arise from a combination of genetic predispositions [e.g., mutations in methylenetetrahydrofolate

reductase (MTHFR) or cystathionine β -synthase (CBS) genes], nutritional deficiencies (particularly folate, vitamin B6, or vitamin B12), and impaired renal clearance, which is a common contributor in chronic kidney disease (3). Accumulating evidence underscores hyperhomocysteinemia as a robust biomarker for cardiovascular pathology. Specifically, elevated HCY levels have been mechanistically linked to endothelial dysfunction via oxidative stress-mediated depletion of nitric oxide bioavailability, vascular inflammation through NF- κ B activation and pro-inflammatory cytokine release, and thrombogenesis due to enhanced platelet aggregation and impaired anticoagulant pathways (4). These mechanisms collectively contribute to the pathogenesis of atherosclerosis, hypertension, and ischemic heart disease (5). Furthermore, clinical studies highlight a dose-dependent relationship between HCY levels and cardiovascular mortality, independent of traditional risk factors, solidifying its role as both a diagnostic and prognostic marker in cardiovascular medicine (6, 7).

Ejection fraction (EF) is a critical indicator for assessing cardiac systolic function, typically measured by echocardiography (8), with cardiac magnetic resonance (CMR) providing more accurate EF measurements (9, 10). Research indicates that when EF falls below 55%, patients experience significantly increased mortality and cardiovascular event risks (11). Furthermore, EF changes are closely related to prognosis, as an EF below 55% typically reflects substantial impairment of cardiac pumping capacity, potentially exacerbating heart failure symptoms and reducing quality of life (11). Consequently, a clinical threshold of 55% EF is commonly used to distinguish populations with normal EF from those with mildly abnormal cardiac function (12).

Myocarditis is clinically and pathologically defined as an inflammatory disease characterized by pathological changes predominantly confined to the myocardium, which can lead to cardiac dysfunction and ventricular remodeling (13, 14). Its etiology primarily includes infectious factors, such as viral and bacterial infections, and non-infectious causes, such as autoimmune diseases (15). In the pediatric population, myocarditis continues to exhibit high morbidity and significant disease burden. A nationwide epidemiological survey of hospitalized children in China revealed an increasing prevalence of myocarditis among pediatric inpatients, with a mortality rate of 4.13% (16).

Patients with severe myocarditis may develop ventricular remodeling, leading to a decrease in EF. The change in EF measured by the initial CMR performed early after acute myocarditis onset is an independent predictor of adverse outcomes in acute myocarditis (17, 18). Multiple studies have confirmed an inverse correlation between HCY levels and EF in patients with coronary artery disease, diabetes, and chronic heart failure (19–21). Nygard et al. (1997) observed in patients with coronary artery disease that elevated HCY levels were significantly associated with reduced LVEF, with a significantly higher mortality rate in the high HCY group ($\geq 15 \mu\text{mol/L}$), which suggests that HCY is not only a marker of cardiac insufficiency, but also an independent prognostic predictor (22). A negative correlation between HCY and LVEF was also

identified in patients undergoing coronary artery bypass grafting (CABG) surgery (23). A study by El-Amrousy et al. (2017) reporting an association between HCY and EF in pediatric acute heart failure, no study to date has specifically examined the association between HCY levels and reduced EF in children diagnosed with myocarditis using CMR imaging (24). Given the unique pathophysiological features of myocarditis and the enhanced accuracy of CMR for evaluating left ventricular function, this study addresses a critical gap in the pediatric cardiovascular literature. This study aims to investigate the association between elevated HCY levels and reduced EF in pediatric patients with myocarditis, explore the dose-response relationship between HCY concentration and the risk of reduced EF, and examine whether this association varies across clinically relevant subgroups stratified by age, sex, and body mass index (BMI). We hypothesize that elevated plasma HCY levels are associated with an increased risk of reduced EF (EF < 55%) in pediatric patients with myocarditis.

2 Methods

2.1 Study participants

We performed a single-center cross-sectional study involving 350 hospitalized patients admitted to Department of General Pediatrics in Anzhen Hospital in Beijing, China from January 2023 to January 2024. Inclusion criteria: (1) diagnosis consistent with the “Diagnostic recommendation for myocarditis in children (version 2018)” (14): A clinical diagnosis of myocarditis can be made when ≥ 3 major clinical diagnostic criteria are met, or when 2 major criteria plus ≥ 3 minor criteria are present, and other diseases are excluded.

(I) Major Diagnostic Criteria

- 1 Cardiac dysfunction, cardiogenic shock, or cardio-cerebral syndrome.
- 2 Cardiac enlargement.
- 3 Elevated serum cardiac troponin T or I (cTnI or cTnT) or creatine kinase MB subunit (CK-MB) with dynamic changes.
- 4 Significant electrocardiographic (ECG) changes (ECG or 24-hour Holter monitoring). Includes: ST-T segment changes in two or more primary leads (I, II, aVF, V5) dominated by R waves persisting for more than 4 days with dynamic variation; newly identified sinoatrial or atrioventricular block; complete right or left bundle branch block; sinus arrest; pairs, polymorphic, or multifocal premature contractions, ectopic tachycardia not caused by the AV node or AV reentrant circuits, atrial flutter, atrial fibrillation, ventricular flutter, ventricular fibrillation, low-voltage QRS complexes (excluding neonates), or abnormal Q waves.
- 5 CMR demonstrates typical myocardial inflammatory features. At least two of the following three criteria must be present: (1) Myocardial edema: focal or diffuse

hyperintensity on T2-weighted images; (2) myocardial hyperemia and capillary leakage: early gadolinium enhancement on T1-weighted images; (3) Myocardial necrosis and fibrosis: At least one focal area of late gadolinium enhancement on T1-weighted images, distributed in non-ischemic regions.

(II) Secondary Clinical Diagnostic Criteria

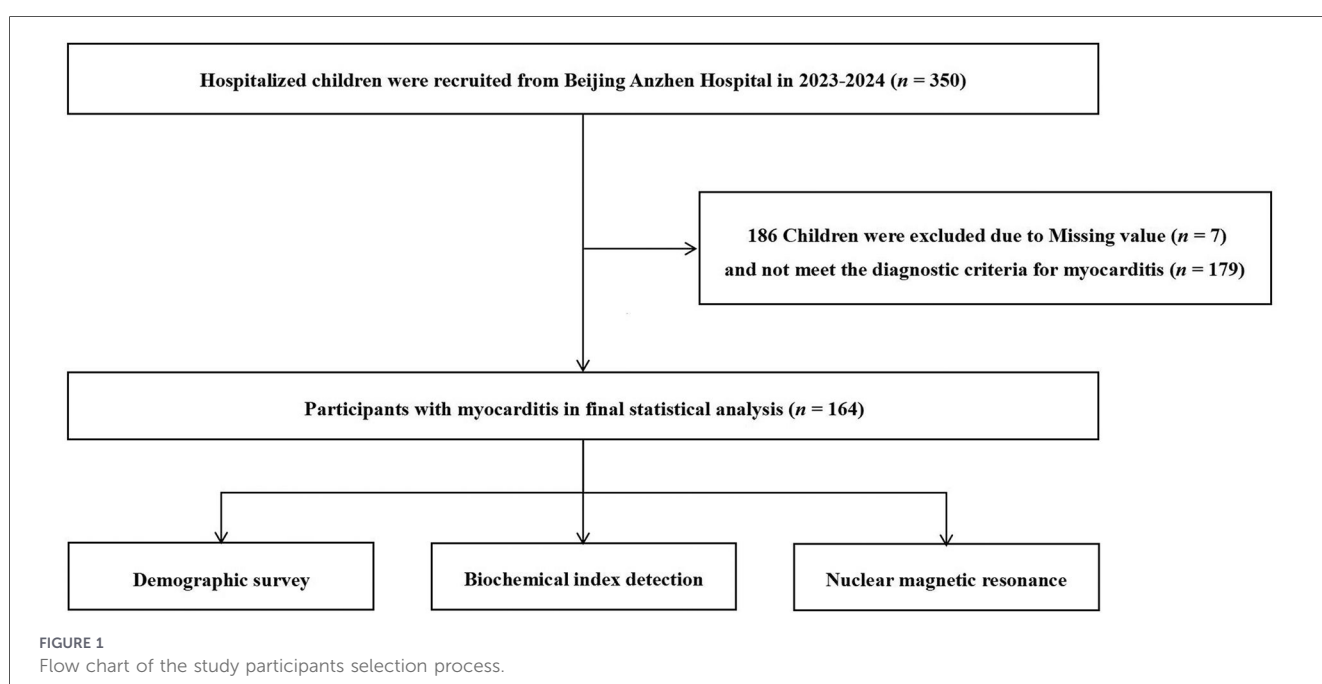
- (a) History of preceding infection, such as upper respiratory or gastrointestinal viral infection within 1–3 weeks prior to onset.
 - (b) 2. Symptoms including chest tightness, chest pain, palpitations, fatigue, dizziness, pallor, grayish complexion, or abdominal pain (at least 2 items).
 - (c) Elevated serum lactate dehydrogenase (LDH), α -hydroxybutyrate dehydrogenase (α -HBDH), or aspartate transaminase (AST).
 - (d) Mild electrocardiogram (ECG) abnormalities. This refers to ST-T changes that do not meet the criteria for “significant ECG changes” in the primary clinical diagnostic criteria for myocarditis.
 - (e) Positive anti-myocardial antibodies.
- (2) 1 year < age < 18 years; (3) informed consent from the guardians. Exclusion criteria: (1) other cardiovascular diseases, such as coronary artery disease, congenital heart disease, cardiomyopathies and congenital atrioventricular block; (2) metabolic disorders, including hyperthyroidism and other inherited metabolic diseases; (3) other disease such as ion channelopathies, orthostatic intolerance, beta-receptor hyperactivity, and drug-induced electrocardiographic changes. (4) missing value. 186 pediatric patients were excluded due to missing value ($n = 7$) and not meet the diagnostic criteria for myocarditis ($n = 179$). Ultimately, 164 subjects were included in

the final statistical analysis (Figure 1). This study was conducted in accordance with the Declaration of Helsinki and has been approved by the Ethics Committee of Beijing Anzhen Hospital (No.2025072x) on March 20, 2025. Written informed consent were obtained from all pediatric patients and their legal guardians before participation in the study.

2.2 Sample collection and laboratory analysis

All participants conducted routine examinations upon admission, including collection of demographic data, anthropometric measures (height and weight) and BMI was calculated as weight (kg)/height (m²). Serum biomarkers including white blood cell count (WBC), C-reactive protein (CRP), hemoglobin (HGB), platelet count (PLT), interleukin-6 (IL-6), creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB), troponin I (TnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), folate, vitamin B12, and the percentage of band neutrophils and segmented neutrophils were analyzed using standard laboratory methods. Serum HCY was measured using enzymatic cycling assay on DIASYS diagnostic systems (Shanghai, China). The reference range for HCY is 3–50 $\mu\text{mol/L}$. The intra-/inter-assay coefficient of variation (CV) is 3.02% and 4.81%, respectively. Currently, there is no established specific reference range for plasma HCY in children in China, and the reference range varies depending on age and detection methods (25). In the present study, the normal values of HCY under our measurement method were 6–14 $\mu\text{mol/L}$.

All pediatric patients completed CMR (3.0T, Discovery MR750, GE, USA) within 72 h of admission. The sequences types include TrueFisp; turboFlash; myocardial resting perfusion



imaging; myocardial delayed imaging sequences; cine MRI; TSE, T1WI, T2WI. After scout scanning, cine sequences were acquired to assess cardiac function. Left ventricular end-diastolic volume (LVEDV), EF, and systolic wall thickness (SWT) were measured. software used for EF was cvi42, version 5.17; Circle Cardiovascular Imaging. T2-weighted imaging was performed using a triple inversion recovery sequence to capture extent of high-signal areas within myocardial tissue, reflecting the presence of myocardial edema. The ratio of myocardial signal intensity to skeletal muscle signal intensity at the same level was calculated, with a ratio exceeding 2.0 indicating edema. The presence and distribution of myocardial edema were recorded according to 17-segment of the left ventricle. Subsequently, inject the contrast agent Gd- using a high-pressure injector. Following contrast administration, Early gadolinium enhancement (EGE) imaging was performed using a triple inversion recovery sequence. The extent of early enhancement was assessed by comparison with the signal intensity of adjacent skeletal muscle. Myocarditis was considered when the whole myocardial-to-skeletal muscle signal intensity ratio was ≥ 4.0 or when the absolute extent of myocardial enhancement was $\geq 45\%$. Late gadolinium enhancement (LGE) imaging was subsequently acquired 5–10 min after contrast administration using the same triple inversion recovery sequence. The presence of LGE was considered indicative of myocardial fibrosis or necrosis. The extent, frequency, and degree of myocardial involvement of LGE were recorded. When LGE demonstrated a subendocardial distribution corresponding to a coronary artery territory, myocardial infarction was considered, and such cases were excluded from the diagnosis of myocarditis.

This study employed a self-designed data collection form to systematically document each child with myocarditis' baseline status, serum biomarkers, and relevant CMR examination details.

2.3 Statistical analysis

SPSS 26.0 and R 4.2.3 were used for data analysis. Graphs were drafted by Graph pad Prism 8 and R 4.2.3. Quantitative data was expressed as mean \pm SD. Categorical data was expressed as number and percentage [n (%)]. The normal distribution test using SPSS. Although HCY values were not normally distributed based on the Shapiro–Wilk test, the sample size in each group exceeded 50, and logistic regression is robust to moderate violations of normality. Therefore, no data transformation was applied. Independent samples t-test and χ^2 test was used to compare the differences between two groups. General linear model (GLM) was used to compare the differences of biochemical parameters between groups. Binary logistic regression and restrict cubic spline (RCS) were conducted to explore the association between plasma parameters and the risk of the occurrence of EF < 55%. Confounding factors, including age, gender and BMI were adjusted during analysis. A two-sided $p < 0.05$ was considered statistically significant.

3 Results

3.1 Characteristic of participants

As shown in Table 1, Among 164 participates with myocarditis, 51 participants with EF < 55% and 113 participants with EF \geq 55%. There were no significant differences in age, BMI, or gender among the groups ($P > 0.05$). After adjusting for confounding factors (age, sex, BMI), the EF < 55% group demonstrated a statistically significant decrease in plasma band neutrophil percentage and a significant elevation in HCY concentration (15.48 ± 1.90 μ mol/L) compared to the EF \geq 55% group ($P < 0.05$). However, no statistically significant differences were found in other plasma parameters, including WBC, CRP, HGB, PLT, CK, CKMB, TNI, NT-proBNP, IL-6, folate, VB12, and the segmented neutrophil percentage ($P > 0.05$).

TABLE 1 Demographic characteristics and plasma parameters of pediatric myocarditis patients, grouped by EF < 55% and EF \geq 55%.

Variables	EF < 55% ($n = 51$)	EF \geq 55% ($n = 113$)	<i>P</i> value
Age (year)	12.33 \pm 0.54	12.16 \pm 0.34	0.778
BMI (kg/m ²)	22.73 \pm 1.00	21.67 \pm 0.51	0.348
Gender			0.905
Male	32 (62.7)	72 (63.7)	
Female	19 (37.3)	41 (36.3)	
Plasma parameters			
IL-6 (pg/mL)	2.72 \pm 0.37	2.51 \pm 0.26	0.925
HCY (μ mol/L)	15.48 \pm 1.90	11.45 \pm 9.03	0.025
WBC (10^9 /L)	7.01 \pm 0.25	6.89 \pm 0.21	0.910
Band Neutrophil (%)	51.12 \pm 1.97	54.46 \pm 1.10	0.048
Segmented Neutrophil (%)	36.96 \pm 1.58	35.97 \pm 1.03	0.296
CRP (mg/L)	2.50 \pm 0.60	2.49 \pm 0.57	0.699
HGB (g/L)	143.20 \pm 2.13	139.93 \pm 1.43	0.170
PLT (10^9 /L)	302.86 \pm 8.04	289.80 \pm 6.48	0.268
CK (U/L)	162.47 \pm 26.37	127.91 \pm 10.29	0.122
CKMB (ng/mL)	2.46 \pm 0.19	2.49 \pm 0.14	0.998
TNI (pg/mL)	32.56 \pm 22.38	27.52 \pm 15.72	0.903
NT-proBNP (pg/mL)	52.95 \pm 8.01	64.84 \pm 7.57	0.345
Folate (ng/mL)	7.66 \pm 0.62	7.44 \pm 0.32	0.458
VB12 (pg/mL)	393.00 \pm 23.82	405.00 \pm 18.70	0.823

Data was presented as mean \pm standard error or n (%). T-test was used to compare differences in age and BMI; χ^2 test was used to compare differences in gender between groups. General linear model was used to compare differences in plasma parameters, with adjusting for age, gender and BMI. $P < 0.05$ was considered statistically significant. BMI, body mass index; CRP, C-reactive protein; HGB, hemoglobin; PLT, platelet count; IL-6, Interleukin-6; CK, creatine kinase; CK-MB, creatine kinase-MB form; TNI, troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; HCY, homocysteine; VB12, vitamin B12.

3.2 Association between plasma parameters and the risk of EF<55%

The relationship between plasma parameters and the risk of EF < 55% is shown in Table 2. High HCY concentration demonstrated a statistically positive relationship with the risk of occurrence of EF < 55% [OR = 1.033 (95%CI, 1.002–1.064); $P = 0.034$]. The relationship remained statistically significant after adjusting for confounding factors [OR = 1.038 (95% CI, 1.003, 1.074); $P = 0.033$]. However, we did not find association between other plasma parameters and the occurrence of EF < 55% ($P > 0.05$).

We further conducted the RCS plot to investigate the relationship between plasma HCY concentration and the risk of EF < 55%. The RCS results showed that the risk of EF < 55% in children with myocarditis increased with the increase of plasma HCY (Figure 2). However, it was not statistically significant ($P > 0.05$). Suggesting that although a positive trend was observed, the current data do not provide sufficient evidence to confirm a nonlinear or threshold effect of HCY on EF reduction.

3.3 Subgroup analysis according to age, gender and BMI

A subgroup analysis stratified by age, gender, and BMI was conducted, with detailed outcomes presented in Figure 3. It revealed that Higher HCY levels emerged as a significant independent risk factor for reduced EF (EF < 55%), with particularly pronounced associations observed in specific demographic subgroups. This association demonstrated greater

significance in boys [OR = 1.045 (95%CI, 1.008–1.083); $P = 0.016$] and individuals with BMI ≥ 24 kg/m² [OR = 1.083 (95%CI, 1.019–1.151); $P = 0.010$].

4 Discussion

Myocarditis affects individuals across all age groups. Compared to adults, the incidence of myocarditis in children exhibits a bimodal distribution, infants exhibit a higher incidence, followed by a secondary increase in young adults (26). Two-thirds have a history of preceding viral infections, and over 50% present with fever (10). Viral infection is the primary etiology, with pathogenesis involving direct damage from viral replication in host cells and inflammatory responses mediated by both viral activity and immune reactions (15). The pathophysiology of myocarditis can be divided into three stages: acute viral-induced injury; host innate and adaptive immune responses; and recovery or progression to scarring and dilated cardiomyopathy (15). Compared to adults, the pathophysiological course of myocarditis in children is more rapid, with fulminant myocarditis occurring more frequently than in adults (10). This may stem from the active immune systems of adolescents (27). Therefore, early recognition of myocarditis in pediatric patients is crucial for prognosis.

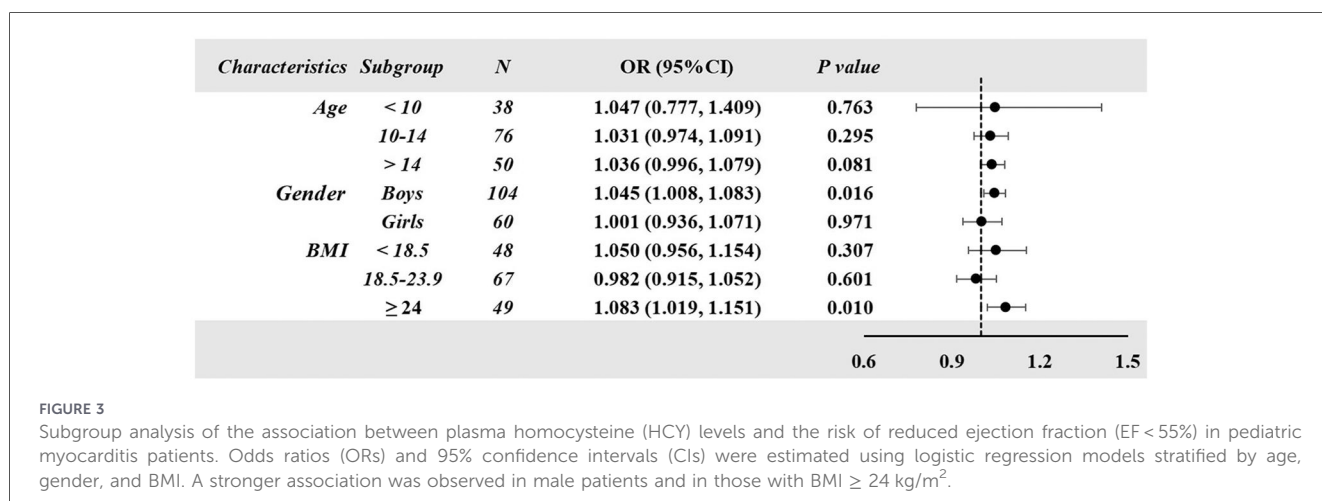
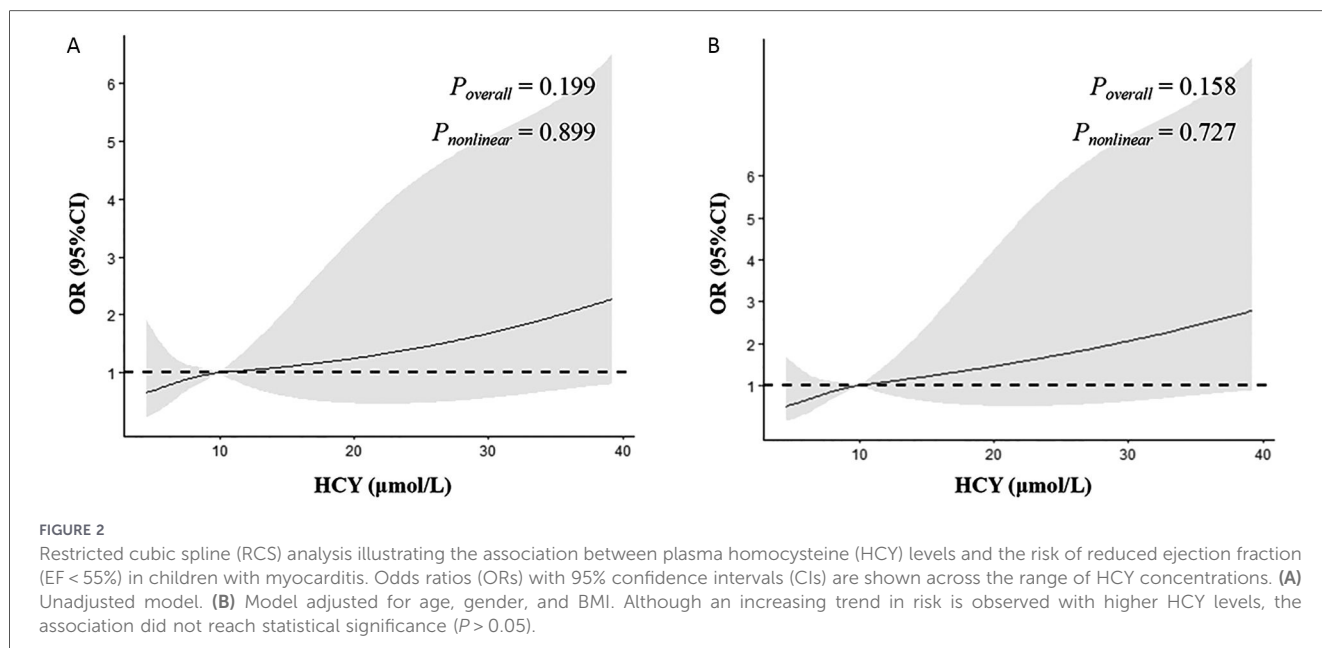
In this study, we investigated the association between elevated HCY levels and reduced EF in pediatric patients with myocarditis. we observed that elevated HCY levels were a risk factor for patients with EF < 55%. This result remained statistically significant after correcting for confounders such as gender, age, and BMI. In previous studies, multiple investigations have

TABLE 2 Logistic regression analysis of plasma parameters associated with the risk of reduced ejection fraction (EF < 55%) in children with myocarditis.

Parameters	Model 1		Model 2	
	OR 95%CI	P	OR 95%CI	P
IL-6 (pg/mL)	1.027 (0.914, 1.155)	0.653	1.006 (0.887, 1.141)	0.927
HCY (μ mol/L)	1.033 (1.002, 1.064)	0.034	1.038 (1.003, 1.074)	0.033
WBC ($10^9/L$)	1.028 (0.880, 1.202)	0.723	1.009 (0.858, 1.188)	0.909
Band Neutrophil (%)	0.979 (0.953, 1.005)	0.117	0.970 (0.941, 1.001)	0.057
Segmented Neutrophil (%)	1.008 (0.978, 1.039)	0.595	1.019 (0.983, 1.057)	0.294
CRP (mg/L)	1.000 (0.943, 1.062)	0.992	0.987 (0.924, 1.054)	0.700
HGB (g/L)	1.014 (0.992, 1.037)	0.204	1.021 (0.992, 1.050)	0.166
PLT ($10^9/L$)	1.003 (0.998, 1.008)	0.241	1.003 (0.998, 1.009)	0.263
CK (U/L)	1.002 (0.999, 1.004)	0.158	1.002 (0.999, 1.004)	0.129
CKMB (ng/mL)	0.987 (0.784, 1.244)	0.912	1.000 (0.786, 1.271)	0.998
TNI (pg/mL)	1.000 (0.998, 1.002)	0.855	1.000 (0.998, 1.002)	0.901
NT-proBNP (pg/mL)	0.998 (0.993, 1.003)	0.345	0.997 (0.992, 1.003)	0.351
Folate (ng/mL)	1.016 (0.931, 1.109)	0.720	1.039 (0.942, 1.146)	0.447
VB12 (pg/mL)	1.000 (0.998, 1.001)	0.707	1.000 (0.998, 1.002)	0.820

Model 1 was an unadjusted model.

Model 2 was adjusted for age, gender and BMI.



extensively demonstrated a negative correlation between HCY and EF, and this association exhibits remarkable consistency across different clinical populations (20, 22–24, 28). This is consistent with the conclusions of the aforementioned studies. This finding demonstrates that elevated HCY levels in pediatric patients with myocarditis are associated with more severe cardiac function impairment. As this is a cross-sectional study, even if we can only establish an association between reduced EF and elevated HCY levels, it still holds significant clinical importance. In the 2024 ACC Expert Consensus Decision Pathway on Strategies and Criteria for the Diagnosis and Management of Myocarditis, reduced EF is recognized as a definitive poor prognostic factor (17). Given the correlation between HCY and reduced EF, early HCY assessment in blood biochemistry can serve as a prognostic reference during the initial treatment phase of myocarditis. This holds significant importance for determining pediatric treatment plans and subsequent follow-up care.

Secondly, due to the uncertainty of causality, we cannot definitively determine whether elevated HCY levels during myocarditis result from the inflammatory response, thereby causing reduced EF, or whether individuals with high HCY levels inherently experience poorer outcomes when developing myocarditis. These questions require further clarification through cohort studies.

HCY is an independent risk factor for cardiovascular diseases (4). As a cross-sectional study, although this paper cannot establish a causal relationship between elevated HCY levels and reduced EF in children with myocarditis, we review the potential mechanisms underlying this association based on previous research. HCY has been demonstrated to possess cardiotoxicity, leading to myocardial remodeling and dysfunction (29). The underlying mechanisms involve multiple levels: at the genetic level, HCY decreases the S-adenosylmethionine (SAM)/S-adenosylhomocysteine (SAH)

ratio and induces DNA and histone hypomethylation, which alters gene expression and promotes cardiomyocyte hypertrophy (30). At the organelle level, HCY generates reactive oxygen species (ROS), triggers oxidative stress, and impairs mitochondrial protein content and function in cardiomyocytes. HCY also induces endoplasmic reticulum (ER) stress, which leads to Ca^{2+} accumulation, reduced ATP production, decreased membrane potential, and activation of mitosis and apoptosis (30). At the cellular level, HCY induces cardiomyocyte hypertrophy by up-regulating copper-transporting ATPase 1 (ATP7a) protein expression, decreasing copper content, and decreasing cytochrome c oxidase (COX) activity. Interactions between soluble epoxide hydrolase (sEH) and typical transient receptor potential 3 (TRPC3) channels, as well as the calreticulin-nuclear factor of activated T-cells (NFAT) pathway, may also contribute to HCY-mediated myocardial alterations (31–33). Additionally, elevated HCY levels may alter cell communication by regulating the expression of matrix metalloproteinases and connexins in myocardial tissue (34). In this study, patients with EF <55% exhibited higher HCY levels. These mechanisms provide a potential theoretical basis for the association between elevated HCY levels and more severe myocardial injury.

In our study, The RCS results showed an increased risk of EF <55% in children with myocarditis with increasing plasma HCY. However, this relationship was not statistically significant ($P > 0.05$) due to the small sample size, but this trend still provides some indication of the relationship between HCY and EF. Several factors may explain this finding. First, the overall sample size, particularly the limited number of patients with significantly elevated HCY levels, constrained the statistical power of the RCS analysis. Second, HCY levels in this dataset primarily fell within the upper range of normal values ($12.70 \pm 0.84 \mu\text{mol/L}$), exhibiting a relatively narrow distribution, which may have weakened the observable dose-response effect. Third, reduced EF in acute myocarditis is influenced by multiple interacting factors, including inflammatory activity, myocardial edema, viral infection. The presence of residual confounding factors may also obscure subtle nonlinear relationships. Therefore, the RCS results should be interpreted as hypothesis-generating findings, suggesting a potential risk pattern, requiring further validation through larger prospective studies.

Notably, in the subgroup analysis, the association between high HCY levels and EF <55% risk showed greater significance in boys OR = 1.045 [95%CI, 1.008–1.083]; $P = 0.016$ and individuals with BMI ≥ 24 OR = 1.083 [95%CI, 1.019–1.151]; $P = 0.010$. In pediatric populations, HCY exhibits a weak correlation with overweight status (35). Previous studies have found elevated levels of total cholesterol and low-density lipoprotein in children with homocysteinemia. Homocysteinemia is significantly associated with LDL levels (36). The association between elevated HCY levels and overweight appears to be mediated through adipose tissue dysfunction, with the mechanism involving the inhibition of lipolysis through the activation of adenosine monophosphate-sensitive protein kinase (37). MTHFR gene polymorphisms are closely associated with HCY concentrations in obesity (38). However, evidence

supporting this mechanistic link in pediatric populations remains insufficient, with only limited epidemiological data showing a conclusive association between hyperhomocysteinemia and excessive obesity in pediatric and adolescent populations (35). In previous studies, boys demonstrated higher HCY levels compared to girls (39), which may be attributed to sex-related differences in amino acid metabolism (40). HCY remethylation rates were found to be higher in females than in males, and this metabolic difference is consistent with sex differences in physiological requirements and utilization patterns of certain amino acids (41). Therefore, close monitoring of plasma HCY levels in overweight male children with myocarditis is essential to mitigate adverse outcomes.

This study has several limitations that should be acknowledged. First, it is a single-center study, which may limit the generalizability of the findings. Second, due to the cross-sectional design, causal inferences between HCY levels and cardiac function cannot be established. Third, the relatively small sample size may reduce the statistical power to detect certain associations. Finally, the absence of follow-up or longitudinal data precludes assessment of dynamic changes in HCY and cardiac function over time. Despite these limitations, our study provides novel insights into the association between HCY and left ventricular EF in pediatric patients with myocarditis. By identifying significant HCY–EF correlations and evaluating potential modifiers such as sex, age, and BMI, this work lays a foundation for future longitudinal studies.

5 Conclusion

The aim of this study was to investigate the relationship between HCY and EF in children with myocarditis. The results showed that elevated HCY levels were a risk factor for patients with EF <55%. In addition, the association between high HCY levels and EF <55% was more pronounced in two subgroups of patients with BMI ≥ 24 and in boys. HCY has great potential as a biomarker of myocarditis prognosis. Future studies should further investigate whether HCY lowering therapies improve cardiac function and establish a causal relationship between HCY and decreased EF in pediatric patients with myocarditis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Beijing Anzhen Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for

participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

CZ: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. XR: Data curation, Formal analysis, Methodology, Writing – review & editing. YX: Data curation, Investigation, Writing – review & editing. YD: Investigation, Resources, Writing – review & editing. YL: Investigation, Resources, Writing – review & editing. XY: Conceptualization, Resources, Supervision, Writing – review & editing. GL: Conceptualization, Methodology, Resources, Supervision, Writing – review & editing.

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