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Fibroblast growth factor 23 in children with or without heart failure: a prospective study

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ABSTRACT

Background Elevated fibroblast growth factor 23 (FGF23) levels have been associated with mortality in adults with heart failure (HF), but data on FGF23 levels in paediatric HF are limited. In this prospective cohort study, we aimed to assess the prognostic value of FGF23 in children with chronic HF.

Methods We prospectively enrolled 40 children with chronic HF and 20 matched healthy controls. In each patient, a complete diagnostic workup was performed, including transthoracic echocardiography to evaluate cardiac systolic and diastolic functions. Serum FGF23, renal function tests, parathyroid hormone, serum calcium and phosphate were measured in patients and controls. N-terminal probrain natriuretic peptide (NT-proBNP) was measured in patients. The severity of symptoms was assessed using the modified Ross HF classification for children. Patients were followed for 1 year, and clinical worsening events such as death and HF hospitalisation were recorded.

Results Patients with HF had significantly higher FGF23 levels compared with controls (355.68±97.27 pg/mL and 60.20±11.04 pg/mL, respectively; p<0.001). Three patients died and 11 were admitted with HF. In comparison with patients without clinical worsening events, these 14 patients exhibited significantly higher FGF23 levels (320.04±89.56 pg/mL and 421.86±75.50 pg/mL, respectively; p<0.001). FGF23 was positively correlated with NT-proBNP and left ventricular end-diastolic diameter and negatively correlated with ejection fraction and fractional shortening. The ability of FGF23 to predict clinical worsening events in patients was analysed using a receiver operating characteristic curve. The optimal cut-off point was 375 pg/mL, with 85.71% sensitivity, 84.62% specificity, positive predictive value of 75.0, negative predictive value of 91.7 and area under the curve (AUC) of 0.878. Multivariable regression analysis revealed that FGF23 is the only independent predictor of clinical worsening events in children with chronic HF.

Conclusion FGF23 levels were elevated in children with chronic HF and increased significantly as Ross score class increased. FGF23 levels increased in patients who experienced clinical worsening events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increased fibroblast growth factor 23 (FGF23) levels have been associated with left ventricular (LV) hypertrophy and impaired LV function.
⇒ Adult studies showed that FGF23 is related to adverse cardiovascular events in patients with heart failure (HF) and that it could be used to predict the clinical outcome of these patients, but data about FGF23 in children with HF are limited.

WHAT THIS STUDY ADDS

⇒ FGF23 levels increase significantly with increasing HF clinical severity and in patients experiencing clinical worsening events.
⇒ FGF23 may have a potential prognostic value as a novel biomarker in paediatric HF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The prognostic significance of FGF23 in children with HF may help in the identification of high-risk patients who are more prone to complications and need closer monitoring and more aggressive therapy.

INTRODUCTION

Paediatric heart failure (HF) is a complex disease process that can occur secondary to a variety of aetiologies, including congenital heart diseases, cardiomyopathy and also acquired conditions. It remains a major cause of morbidity and mortality in childhood, with significant health and economic burden worldwide.[1]

Exploring new cardiac biomarkers for HF helps clinicians identify disease progression, predict clinical outcomes, provide protective strategies, select the proper treatment and monitor therapy.[2] Fibroblast growth factor 23 (FGF23) is a bone-derived hormone secreted by osteoblasts and osteocytes in response to increased phosphate levels, regulating renal phosphate homeostasis and vitamin D metabolism by stimulating phosphaturia and inhibiting calcitriol synthesis.[3]

Besides its role in mineral metabolism, FGF23 has a direct effect on the cardiovascular system. It has been recently linked to adverse cardiovascular events in adult

patients with HF and is involved in cardiac remodelling.[4–7] Increased FGF23 levels have been associated with left ventricular (LV) hypertrophy and impaired LV function.[8–11] It has been linked with alterations in myocyte calcium handling[12] and upregulation of the renin–angiotensin system.[13] Interestingly, adult studies showed that FGF23 not only predicted clinical outcomes in patients with acute and stable HF[14 15] but was also independently associated with all-cause death and HF in community-living older persons.[16]

Comparable data about FGF23 in children with HF are limited. Therefore, we aimed to measure and compare the FGF23 levels of children with chronic HF with those of healthy children, to correlate them with indicators of HF severity and to assess the prognostic significance of FGF23 in children with chronic HF.

METHODS

This prospective cohort study was carried out at the Pediatric Cardiology Unit of Menoufia University Hospital between January 2019 and February 2020. Informed consent was obtained from the guardian of each participant included in the study.

Patient and public involvement statement

Patients and/or the public were involved in the design, conduct, reporting and dissemination plans of this research. Public healthcare clinics, but not families, were involved in the content and design.

Eligibility criteria

Inclusion criteria

For the case group, we targeted children with chronic HF, defined by the International Society for Heart and Lung Transplantation Practice Guidelines for Management of Heart Failure in Children[17] as a syndrome resulting from ventricular dysfunction, volume overload or pressure overload, alone or in combination. The definition of chronic HF has changed from the traditional definition of a syndrome that results from inadequate cardiac output to maintain end-organ perfusion to the new definition in adults, which incorporates disorders of ventricular filling, that is, diastolic dysfunction or HF with preserved ejection fraction (EF).[18]

Therefore, patients with systolic and diastolic chronic HF who fulfilled one or more of the following criteria were included in the study:

- Patients with reduced LV EF%, fractional shortening (FS) and/or tricuspid annular plane systolic excursion (TAPSE).
- Symptomatic patients with evidence of structural cardiac abnormality. (Symptoms and signs of HF were respiratory distress, dyspnoea on exertion, feeding problems, failure to thrive, diaphoresis, hepatomegaly, cool extremities and poor peripheral perfusion.[19])
- Asymptomatic patients with prior symptoms and signs of HF controlled on antifailure medications with evidence of structural cardiac abnormality.

All patients included in the study did not have their structural cardiac abnormalities corrected.

The control group included a group of age-matched and sex-matched healthy children who were referred to the cardiology clinic for innocent murmurs and found to be free of any cardiac disease.

Exclusion criteria

Exclusion criteria included diseases that affect FGF23 such as chronic kidney disease and rickets, any congenital anomalies other than congenital heart disease, and age less than 2 months and more than 18 years.

All included patients and controls were subjected to detailed history taking, including collecting patient demographics and a comprehensive clinical examination. Patients were assessed for functional status of HF using the modified Ross classification system for HF in infants and children.[20] Patients were followed for 1 year for an endpoint of all-cause mortality or HF hospitalisation, and patients were classified accordingly into two groups: patients with clinical worsening events (death or hospitalisation with HF) and patients without clinical worsening events.

Investigations

Blood samples were collected, then centrifuged, aliquoted, labelled and stored at −80°C until batch assays were performed. Samples were withdrawn from patients and controls once they were included in the study according to the previously mentioned inclusion criteria during their visit to the cardiology clinic. Because of the well-defined role of FGF23 in renal and bone diseases, investigations using standard procedures were performed, including complete blood count (CBC), renal function, serum calcium, serum phosphate and parathyroid hormone. Estimated glomerular filtration rate (eGFR; in mL/min/1.73 m^2) was determined using an established formula: eGFR=k×height (cm)/serum creatinine (mg/dL).[21] Serum intact FGF23 levels were measured by an ELISA commercial kit from Elabscience (USA). There is no clear FGF23 cut-off value for the paediatric population and the available assays are not standardised. So we used the most similar assay reference values (Kainos Laboratories, Japan) with a normal FGF23 cut-off level in children of less than 71 pg/mL.[22] To correlate FGF23 with other biomarkers of HF, we measured N-terminal probrain natriuretic peptide (NT-proBNP) using ELISA kits in children with HF.

Echocardiography

On enrolment, Philips HD11XE equipment (Philips, Bothell, Washington) was used for transthoracic echocardiography imaging with tissue Doppler study, using transducers of 3–8 and 1–3 MHz, depending on patient size. Two authors (first and last), who have more than

10 years of expertise in echocardiography, performed the echocardiographic examination and were not aware of the serum test results. To reduce interobserver variability, both were present during each echo examination to double-check the echo results separately. Only agreed-upon results were recorded. M-mode tracing was obtained in the parasternal short-axis view at the level of the papillary muscles of the LV, and the LV end-systolic and end-diastolic diameters were measured. LV EF was measured using the modified Simpson's method, as recommended by the American Society of Echocardiography.[23] EF% and FS were considered reduced if <55% and ≤25 %, respectively.[24] TAPSE was considered reduced if <10 mm.[25]

Statistical analysis

The data collected were tabulated and statistically analysed using Statistical Package for Social Science (SPSS) V.22. The Kolmogorov-Smirnov, Shapiro and D'Agostino tests were used to verify the normality of the distribution of variables. χ^2 test or the Fisher's exact test was used to compare categorical variables. The Student's t-test was used to compare two groups for normally distributed quantitative variables, whereas the Mann-Whitney U test was used to compare two groups for abnormally distributed quantitative variables. Pearson coefficient was used to correlate between quantitative variables. The receiver operating characteristic (ROC) curve was performed to assess the prognostic performance of FGF23, with respective maximum accuracy points for both sensitivity and specificity (an area of more than 50% gives acceptable performance, and an area of about 100% is the best performance for the test). Positive predictive value (PPV) and negative predictive value (NPV) were also calculated. Univariable and multivariable logistic regression analyses were done to detect the most independent factors that predict clinical worsening events in children with chronic HF (all-cause mortality and HF hospitalisation). Due to the small sample size, variance inflation factors (VIF) were calculated for the statistically significant variables in the univariable analysis to measure multicollinearity among the independent variables in the multiple regression model. Only variables with a low VIF (less than 5) were included in the multivariable regression analysis.[26] The significance of the obtained results was judged to be at the 5% level. The sample size was calculated using the following formula:

$$n \geq \left[\frac{z_{1-\alpha/2}+z_{1-\beta}}{\frac{1}{2}\log_e \frac{1+r}{1-r}}\right]^2 + 3$$

where n=sample size, Z1−α/2=1.96 (the critical value that divides the central 95% of the Z distribution from the 5% in the tail), r=0.63 (correlation coefficient between FGF23 and LV end-diastolic diameter in a previous study by Isakova *et al*[27]) and β=0.05. The required sample size to conduct this study was at least 27 patients and 13 controls. We exceeded the sample size (40 patients and 20 controls) to increase the accuracy and significance of the results.

Table 1 Clinical characteristics of patients with chronic heart failure (n=40)

Characteristics	n
Aetiology of heart failure	
Congenital heart diseases	19
VSD	5
PDA	4
Large ostium secundum ASD	2
Parachute mitral valve causing severe MS	1
Parachute mitral valve causing severe MS and moderate MR	1
Dysplastic mitral valve causing severe MS and MR	1
Fallot tetralogy with mild pulmonary stenosis	1
Subaortic VSD causing severe AR	1
PDA+VSD	1
Congenital moderate aortic stenosis and severe AR	1
VSD+ASD	1
Dilated cardiomyopathy	15
Hypertrophic cardiomyopathy	4
Rheumatic heart diseases	2
Severe MR and mild AR	1
Moderate MR and AR	1
Medications	
Diuretics	36
ACE inhibitors	33
Betablockers	17
Digoxin	5
Anticoagulants	2
Modified Ross class	
I	14
II	15
III	11
Duration of heart failure (months), median (IQR)	10 (6–27)
Duration of follow-up until occurrence of endpoint (months), median (IQR)	12 (10–12)

AR, aortic regurgitation; ASD, atrial septal defect; MR, mitral regurgitation; MS, mitral stenosis; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

RESULTS

The study included 60 children divided into two independent groups. The case group included 40 children with chronic HF, with a median age of 12.0 months (IQR=6.5–108), and the control group included 20 matched clinically healthy children, with a median age of 12.0 months (IQR=6.5–108).

Table 1 displays the clinical features of patients with HF. Congenital heart disease was the cause of HF in 19 patients, dilated cardiomyopathy in 15, hypertrophic

cardiomyopathy in 4 and rheumatic heart disease in 2, with a median HF duration of 10 months (IQR=6–27). According to the modified Ross score, 14 patients (35%) were placed in class I, 15 patients (37.5%) in class II and 11 patients (27.5%) in class III.

Table 2 Comparison of demographic, clinical, laboratory and echocardiographic data between case and control groups

Parameters	Case group (n=40)	Control group (n=20)	P value
Demographic and clinical parameters			
Age (months)*	12.0 (6.50–108.0)	12.0 (6.50–102.0)	0.863
Female†, n (%)	21 (52.5)	12 (60	0.582
Heart rate (beats per minute)‡	128.50±22.99	110.30±17.76	**0.001**
Respiratory rate (per minute)*	53.50 (40.0–60.0)	38.0 (20.0–41.0)	**<0.001**
Systolic blood pressure (mm Hg)‡	95.95±10.40	95.75±10.14	0.944
Diastolic blood pressure (mm Hg)‡	59.82±6.71	63.10±7.48	0.091
Weight (kg)*	9 (8.75–25.0)	10.50 (7.0–26.50)	0.445
Length or height (m)*	0.77 (0.68–1.24)	0.81 (0.71–1.21)	0.433
Body mass index (kg/m^2)‡	16.16±2.94	16.98±3.38	0.342
Laboratory parameters			
Haemoglobin (g/L)‡	108.81±09.23	111.72±09.61	0.252
White cell count (×10^9/L)‡	7.03±1.80	6.80±1.57	0.629
Platelet count (×10^9 /L)‡	265.55±67.16	258.0±62.12	0.676
Serum creatinine (mg/dL)‡	0.63±0.16	0.67±0.18	0.332
BUN (mg/dL)‡	14.18±3.21	13.40±2.91	0.367
eGFR‡	77.51±30.80	77.95±39.52	0.536
Serum calcium (mg/dL)‡	9.35±0.64	9.30±0.52	0.788
Serum phosphate (mg/dL)‡	2.98±0.56	3.0±0.36	0.542
PTH (pg/mL)‡	42.85±6.34	40.20±4.73	0.131
Serum FGF23 (pg/mL)‡	355.68±97.27	60.20±11.04	**<0.001**
NT-proBNP (pg/mL)	380.2±103.9	–	
Echocardiographic parameters			
IVSd (cm)*	0.50 (0.40–0.60)	0.50 (0.40–0.60)	0.733
IVSs (cm)*	0.60 (0.50–0.75)	0.60 (0.50–0.70)	0.350
LVEDD (cm)*	4.0 (3.0–4.45)	2.80 (2.35–3.85)	**0.001**
LVESD (cm)*	2.75 (1.90–3.30)	1.75 (1.55–2.70)	**0.003**
LVPWd (cm)*	0.50 (0.40–0.60)	0.50 (0.40–0.70)	0.611
LVPWs (cm)*	0.70 (0.60–0.80)	0.65 (0.6–0.85)	0.642
EF%*	58.95 (44.0–72.0)	67.60 (63.5–73.0)	**0.001**
FS*	29.45 (21.75–36.0)	34.80 (32.0–36.25)	**0.047**
E/A*	1.33 (1.21–1.50)	1.47 (1.22–1.56)	0.106
E/e′*	9.82 (7.93–11.89)	7.33 (6.14–8.81)	**0.005**
TAPSE (cm)*	1.81 (1.20–2.70)	1.60 (1.05–2.13)	0.295

Data are presented as number, percentage, mean±SD or median (IQR).
P value in bold refers to a statistically significant result.

*Mann-Whitney test was used.
†χ^2 test/Fisher's exact test was used.
‡Student's t-test was used.
BUN, blood urea nitrogen; E/A, ratio of peak early to late mitral inflow diastolic velocities; E/e′, ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity measured by tissue doppler imaging; EF%, ejection fraction; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; FS, fractional shortening; IVSd, interventricular septum thickness in diastole; IVSs, interventricular septum thickness in systole; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVPWd, left ventricular posterior wall thickness in diastole; LVPWs, left ventricular posterior wall thickness in systole; NT-proBNP, N-terminal probrain natriuretic peptide; PTH, parathyroid hormone; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Comparison of demographic, clinical, laboratory and echocardiographic data between patients with and without clinical worsening events

Parameters	Patients with events (n=14)	Patients without events (n=26)	P value
Sex*, n (%)			
Male	7 (50.0)	12 (46.2)	0.816
Female	7 (50.0)	14 (53.8)	
Age (months)†	67.79±72.57, 24.0 (3.0–192.0)	41.96±53.52, 12.0 (2.0–144.0)	0.130
Mortality, n (%)	3 (21.4)	0 (0)	
Diagnosis, n (%)‡			
Congenital heart disease	2 (14.3)	17 (65.4)	0.002
Dilated cardiomyopathy	10 (71.4)	5 (19.2)	
Hypertrophic cardiomyopathy	2 (14.3)	2 (7.7)	
Rheumatic heart disease	0 (0.0)	2 (7.7)	
Modified Ross class*, n (%)			0.003
I	1 (7.1)	13 (50.0)	
II	5 (35.7)	10 (38.5)	
III	8 (57.1)	3 (11.5)	
Duration of HF (months)†	19.07±21.57, 12.0 (2.0–60.0)	19.77±24.86, 6.5 (2.0–96.0)	0.967
Heart rate (beats per minute)§	126.07±24.35, 130.0 (90.0–170.0)	129.81±22.60, 135.0 (85.0–165.0)	0.630
Respiratory rate†	47.0±15.0, 51.0 (20.0–65.0)	49.46±14.09, 55.0 (20.0–65.0)	0.664
Systolic blood pressure§	95.36±8.65, 95.0 (85.0–110.0)	96.27±11.38, 95.0 (80.0–120.0)	0.795
Diastolic blood pressure§	60.0±6.50, 60.0 (50.0–70.0)	59.73±6.94, 60.0 (50.0–80.0)	0.905
Weight (kg)†	20.29±16.66, 12.0 (5.0–55.0)	14.73±13.07, 9.0 (4.0–45.0)	0.130
Length (m)†	1.0±0.36, 0.83 (0.65–1.61)	0.88±0.32, 0.74 (0.55–1.50)	0.220
Body mass index (kg/m^2)§	17.08±2.29, 16.69 (11.83–21.48)	15.67±3.17, 16.20 (8.65–20.66)	0.150
Haemoglobin (g/L)§	106.40±10.51, 106.52 (85.0–125.0)	109.92±08.30, 111.51 (85.0–125.0)	0.124
White cell count (×10^9/L)§	7.19±2.02, 7.10 (4.30–12.0)	6.93±1.71, 6.80 (4.30–10.50)	0.671
Platelet count (×10^9/L)§	263.93±75.60, 265.0 (170.0–400.0)	266.42±63.74, 255.0 (156.0–400.0)	0.913
Serum creatinine (mg/dL)§	0.59±0.09, 0.60 (0.50–0.80)	0.65±0.19, 0.60 (0.40–1.0)	0.182
BUN (mg/dL)§	14.14±3.18, 13.50 (10.0–20.0)	14.19±3.29, 13.0 (10.0–20.0)	0.964
eGFR†	87.23±34.36, 75.63 (53.57–160.0)	72.28±28.01, 65.88 (37.0–145.0)	0.190
Calcium (mg/dL)†	9.34±0.63, 9.15 (8.50–10.20)	9.36±0.66, 9.20 (8.40–11.0)	0.989
Phosphate (mg/dL)†	3.16±0.88, 2.90 (2.60–6.0)	2.88±0.24, 2.85 (2.60–3.50)	0.528
Parathyroid hormone (pg/mL)†	45.79±6.61, 48.0 (34.0–55.0)	41.27±5.70, 40.0 (32.0–52.0)	0.055
NT-proBNP (pg/mL)§	457.57±82.61, 416.0 (340.0–600.0)	338.54±90.19, 350.0 (210.0–560.0)	<0.001
FGF23 (pg/mL)§	421.86±75.50, 397.50 (329.0–560.0)	320.04±89.56, 326.0 (200.0–550.0)	<0.001
IVSd (cm)†	0.74±0.48, 0.50 (0.40–1.90)	0.54±0.25, 0.50 (0.30–1.50)	0.123
IVSs (cm)†	0.85±0.50, 0.70 (0.40–2.0)	0.68±0.26, 0.60 (0.47–1.50)	0.305
LVEDD (cm)†	4.41±0.72, 4.20 (3.50–5.90)	3.56±0.93, 3.20 (2.30–5.90)	0.005
LVESD (cm)†	3.10±0.69, 3.0 (2.0–4.0)	2.32±0.75, 2.0 (1.40–3.90)	0.002
LVPWd (cm)†	0.74±0.42, 0.55 (0.50–1.70)	0.55±0.24, 0.50 (0.40–1.50)	0.023
LVPWs (cm)†	0.87±0.42, 0.70 (0.40–1.80)	0.73±0.29, 0.65 (0.40–1.80)	0.180
EF%§	46.86±18.38, 42.0 (22.0–80.0)	65.46±10.88, 68.0 (42.0–82.0)	0.003
FS†	23.43±9.19, 21.0 (11.0–40.0)	33.15±6.25, 34.0 (21.0–50.0)	0.002
E/A§	1.30±0.48, 1.37 (0.50–2.25)	1.34±0.31, 1.35 (0.52–1.92)	0.776
†E/e′	11.87±3.87, 11.54 (4.40–17.40)	8.71±2.64, 8.78 (3.55–13.25)	0.012
TAPSE (cm)†	2.07±0.79, 1.90 (0.90–3.20)	1.67±0.79, 1.30 (0.80–3.20)	0.067

Continued

Table 3 Continued

Parameters	Patients with events (n=14)	Patients without events (n=26)	P value

Data are described as number (%) or as mean±SD, median (range).
*χ^2 test/Fisher's exact test was used.
†Mann-Whitney test was used.
‡Monte Carlo test was used.
§Student's t-test was used.
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BUN, blood urea nitrogen; E/A, ratio of peak early to late mitral inflow diastolic velocities; E/e′, ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity measured by tissue doppler imaging; EF%, ejection fraction; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; FS, fractional shortening; HF, heart failure; IVSd, interventricular septum thickness in diastole; IVSs, interventricular septum thickness in systole; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVPWd, left ventricular posterior wall thickness in diastole; LVPWs, left ventricular posterior wall thickness in systole; NT-proBNP, N-terminal probrain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion.

Table 2 compares the case and control groups' demographic, clinical, laboratory and echocardiographic data. Age, sex, body mass index (BMI), height, weight and blood pressure (systolic and diastolic) did not significantly differ between the groups. Both heart rate and respiratory rate were significantly greater in the case group. There was no statistically significant difference between the groups in terms of laboratory data for CBC parameters, blood urea nitrogen, serum creatinine, serum calcium, serum phosphorus and eGFR. FGF23 levels were significantly higher in patients with HF than in healthy controls (355.68 97.27 pg/mL vs 60.20 11.04 pg/mL; p<0.001). Compared with controls, cases had significantly higher left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD) and ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity measured by tissue doppler imaging (E/e′), and lower EF% and FS.

Table 3 shows the comparison of demographic, clinical, laboratory and echocardiographic data between patients with and without clinical worsening. The median duration of follow-up was 12 months. Of the 14 children who experienced clinical worsening events, 11 needed hospital admission for HF and 3 passed away during the study. The three children were suffering from dilated cardiomyopathy. One of them had a sudden death shortly after complaining of palpitation and chest pain at home. The other two patients presented with cardiogenic shock and were admitted to our intensive care unit. Their condition worsened until they eventually passed away. One died on the sixth day and the other on the eighth.

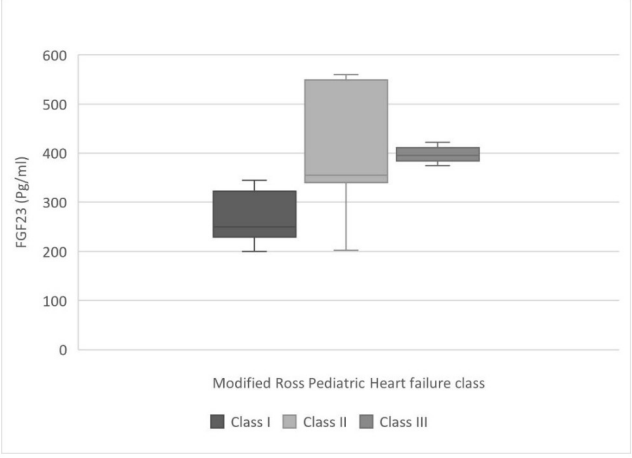

Figure 1 Boxplots showing comparison between FGF23 levels among different Ross classes (p<0.001). Pairwise comparison between each two classes was done using post-hoc test (Tukey). The p value for comparing class I and class II was <0.01; the p value for comparing class I and class III was <0.01; and the p value for comparing class II and class III was 0.048. P value for analysis of variance test. FGF23, fibroblast growth factor 23.

Regarding age, sex, duration of HF, heart rate, respiratory rate, blood pressure, weight, height and BMI, there were no statistically significant differences between the groups. The modified Ross classification placed the majority of patients with clinical worsening events in class III (eight patients). When compared with patients without clinical worsening events, participants with clinical worsening events had statistically significantly higher troponin I, NT-proBNP and FGF23 levels. Patients with clinical worsening events showed significantly greater LVEDD, LVESD and E/e′ ratio, as well as poorer EF and FS, than those without clinical worsening events in terms of echocardiographic measures.

FGF23 serum levels increased significantly as Ross score class increased (p<0.001) (figure 1).

FGF23 was positively correlated with LVEDD (r=0.437, p<0.001) and NT-proBNP (r=0.977, p<0.001) and negatively correlated with EF (r=−0.328, p=0.039) and FS (r=−0.365, p=0.021).

The prognostic performance of FGF23 was analysed using a ROC curve (figure 2). The area under the curve (AUC) was 0.878 (95% CI 0.767 to 0.989, p 0.001). The optimal cut-off point to predict clinical worsening events was >375 pg/mL, with 85.71% sensitivity, 84.62% specificity, PPV of 75.0 and NPV of 91.7. Table 4 depicts the univariable and multivariable regression analyses for variables that may influence patients' prognosis. Statistically significant parameters with a low VIF (less than 5) from the univariable analysis were incorporated in a multivariable regression analysis model after exclusion of NT-proBNP due to multicollinearity between FGF23 and NT-proBNP. The FGF23 level was the only independent predictor of clinical worsening events in children with chronic HF (p=0.027).

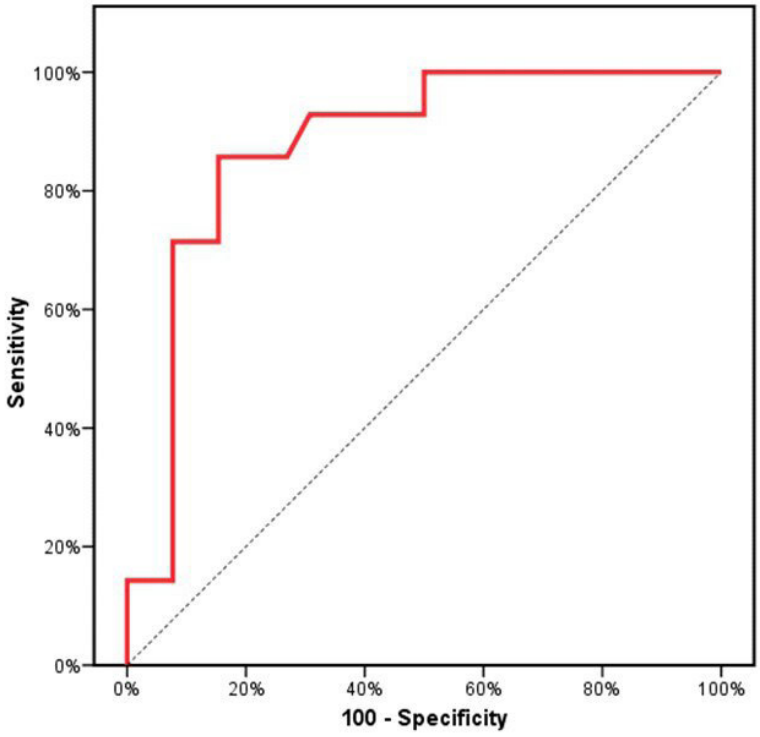

Figure 2 Receiver operating characteristic curve for the ability of FGF23 (pg/mL) to predict clinical worsening events in children with heart failure. The area under the curve was 0. 878 (95% CI 0.767 to 0.989, p<0.001). FGF23, fibroblast growth factor 23.

DISCUSSION

The current study showed that children with chronic HF had a significantly higher level of FGF23 compared with controls and that FGF23 levels increased significantly with increasing Ross score class and in patients with clinical worsening events.

Isakova *et al*[27] compared the FGF23 levels of 20 children suffering from chronic HF caused by various aetiologies and 17 healthy controls. They reported about a twofold increase in FGF23 levels in patients compared with healthy controls and found a significant association between FGF23 levels and both the clinical severity of HF (assessed by New York Heart Association (NYHA)/Ross class and NT-proBNP level) and LV dilatation. Both associations were independent of eGFR.[27] Studies in the adult population demonstrated that FGF23 was elevated in patients who had HF with preserved EF[28] and with reduced EF.[4] Additionally, Andersen *et al*[29] found elevated serum levels of FGF23 in patients with acute decompensated HF. In our study, elevated FGF23 could not be explained by impaired renal function, as has been largely described,[7 30] indicating another underlying mechanism. Studies revealed that FGF23 is expressed in the heart and that, regardless of renal function, it is markedly increased in clinical and experimental conditions of cardiac remodelling and HF. FGF23 may promote cardiac injury through endocrine, paracrine/autocrine and other mechanisms.[31 32]

Risk stratification for HF is greatly influenced by NYHA classification, biomarkers including NT-proBNP and LV systolic function.[33 34] Our study demonstrated that FGF23 increased with increasing disease severity assessed by the modified Ross classification, NT-proBNP and ventricular function indices. FGF23 had been postulated to have direct cardiac and vascular toxicity.[35 36] Another possibility is that FGF23 suppresses calcitriol synthesis, which then activates the renin–angiotensin–aldosterone system.[37 38]

Our study's novel conclusion is that FGF23 levels are significantly higher in children with HF with clinical worsening events (death and hospitalisation) than in children with HF without such events. FGF23 level was found to be the only independent predictor of clinical worsening events in a multivariable logistic regression model. This was in line with adult studies conducted by Gruson *et al*,[4] who found that FGF23 was the strongest predictor of long-term cardiac death, and Plischke *et al*,[15] who showed that FGF23 level was significantly higher in patients reaching the combined endpoint of cardiac hospitalisation or death. Imazu *et al*[39] reported that FGF23 levels in hospitalised patients with HF were higher than in non-hospitalised patients and that elevated FGF23 is associated with poor outcomes (death, LV assist device implantation and rehospitalisation).

The optimal cut-off value in our study to distinguish patients with clinical worsening events from those without was >375 pg/mL, with 85.71% sensitivity, 84.62% specificity, PPV of 75.0, NPV of 91.7 and AUC of 0.878. In the study by Cornelissen *et al*,[14] FGF23 measured on days 1 and 2 after admission of patients with acute HF accurately predicted 1-year outcomes, as did the Seattle HF model.

Table 4 Univariable and multivariable logistic regression analyses for predictors of clinical worsening events in children with chronic heart failure

	Univariable		Multivariable	
	P value	OR (95% CI)	P value	OR (95% CI)
Sex (male)	0.816	1.167 (0.318 to 4.284)		
Age (months)	0.205	1.007 (0.996 to 1.018)		
Heart rate (beats per minute)	0.620	0.993 (0.965 to 1.022)		
Respiratory rate	0.599	0.988 (0.944 to 1.034)		
Systolic blood pressure	0.789	0.991 (0.930 to 1.057)		
Diastolic blood pressure	0.902	1.006 (0.912 to 1.110)		
Ross class III	0.021*	13.0 (1.478 to 114.358)	0.084	4.850 (0.809 to 29.081)
Duration of HF	0.928	0.999 (0.971 to 1.027)		
Weight (kg)	0.250	1.027 (0.982 to 1.074)		
Length (m)	0.270	2.991 (0.427 to 20.933)		
Body mass index (kg/m^2)	0.153	1.201 (0.934 to 1.554)		
IVSd (cm)	0.129	4.895 (0.631 to 37.938)		
IVSs (cm)	0.182	3.515 (0.556 to 22.231)		
LVEDD (cm)	0.013*	3.076 (1.265 to 7.482)		
LVESD (cm)	0.007*	3.874 (1.446 to 10.376)		
LVPWd (cm)	0.111	6.373 (0.655 to 61.975)		
LVPWs (cm)	0.228	3.254 (0.479 to 22.113)		
EF%	0.002*	0.919 (0.871 to 0.970)		
FS	0.002*	0.846 (0.760 to 0.943)		
E/A	0.769	0.769 (0.133 to 4.446)		
E/e′	0.011*	1.382 (1.076 to 1.775)	0.736	1.022 (0.899 to 1.163)
TAPSE (cm)	0.129	1.909 (0.828 to 4.403)		
Calcium (mg/dL)	0.944	0.964 (0.346 to 2.688)		
Phosphate (mg/dL)	0.238	2.943 (0.490 to 17.657)		
Parathyroid hormone (pg/mL)	0.037*	1.135 (1.008 to 1.277)	0.320	1.073 (0.934 to 1.233)
Troponin	0.051	10.0 (0.992 to 100.821)		
NT-proBNP (pg/mL)	0.004*	1.015 (1.005 to 1.026)		
Serum creatinine (mg/dL)	0.262	0.073 (0.001 to 7.027)		
BUN (mg/dL)	0.962	0.995 (0.810 to 1.222)		
Haemoglobin (g/L)	0.437	0.982 (0.938 to 1.028)		
White cell count (×10^9/L)	0.662	1.085 (0.753 to 1.562)		
Platelet count (×10^9/L)	0.910	0.999 (0.990 to 1.009)		
eGFR	0.150	1.016 (0.994 to 1.038)		
FGF23 (pg/mL)	0.009*	1.014 (1.004 to 1.025)	0.027*	1.011 (1.001 to 1.021)

*Statistically significant at p≤0.05.
BUN, blood urea nitrogen; E/A, ratio of peak early to late mitral inflow diastolic velocities; E/e′, ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity measured by tissue doppler imaging; EF%, ejection fraction; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; FS, fractional shortening; HF, heart failure; IVSd, interventricular septum thickness in diastole; IVSs, interventricular septum thickness in systole; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVPWd, left ventricular posterior wall thickness in diastole; LVPWs, left ventricular posterior wall thickness in systole; NT-proBNP, N-terminal probrain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion.

In addition, a later study by the same authors showed that, in patients with acute myocardial infarction and concomitant HF, FGF23 levels outperformed the Global Registry of Acute Coronary Events (GRACE) score in 1-year mortality prediction. FGF23, however, lacked any discriminative capacity for predicting survival in patients without acute HF.[40] They demonstrated that in patients with acute HF caused by myocardial infarction, logFGF23

levels of 1.71 pg/mL accurately predicted death at 1 year with a sensitivity of 75% and a specificity of 74%.

Our study has some limitations. First, it was a single-centre study with a small sample size. Second, data analysis may be limited by the diverse aetiologies of HF in our patients with predominantly unoperated structural heart diseases. Previous research, however, has shown that FGF23 levels are elevated in patients with HF regardless of the cause. Third, the multivariable model's interpretation may be limited by the small number of patients. Thus, multicentric studies involving a larger number of participants may be warranted. Additionally, further research is needed to fully comprehend the precise pathophysiological function of FGF23 in paediatric HF.

CONCLUSION

Children with chronic HF had elevated serum FGF23 levels, which increased significantly with increasing modified Ross score class. FGF23 may have a potential prognostic value as a novel biomarker in paediatric HF, allowing for identification of high-risk patients who are more prone to complications and need a closer follow-up and more aggressive treatment.

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Patient consent for publication Parental/guardian consent obtained.

Ethics approval This study involves human participants and the study protocol was approved by the Ethics Committee of Menoufia Faculty of Medicine (IRB 9/2022PEDI9). The study was conducted in accordance with the Helsinki Declaration of 1964, as revised in 2013. Participants gave informed consent to participate in the study before taking part.

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