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ORIGINAL ARTICLE

Pre-operative level of FGF23 predicts severe acute kidney injury after heart surgery in children

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Abstract

Background Early detection of acute kidney injury (AKI) after cardiac surgery has improved recently with the discovery and validation of novel urinary biomarkers. However, objective tools to predict the risk of AKI before the insult are still missing. We tested the hypothesis that pre-operative serum fibroblast growth factor 23 (FGF23) concentrations would be elevated in children who develop AKI after heart surgery with cardiopulmonary bypass (CPB). We also compared post-operative FGF23 concentrations to other biomarkers for early detection of AKI.

Methods Blood and urine samples were collected in a prospective observational study from 83 children with congenital heart disease. Severe AKI (sAKI) development (KDIGO stages II–III) in the first seven days after surgery was the primary outcome.

Results Thirty of 76 (39.5%) and 11/76 (14.5%) of patients developed AKI and sAKI, respectively. Pre-operative serum creatinine, cystatin C, and urine biomarker concentrations did not differ between sAKI patients and controls. Pre-operative serum FGF23 levels were higher in patients who developed sAKI (median [IQR] value of 819 RU/ml [397.7, 1196.8] vs. 324.3 RU/ml [124.6, 679.8] ($p = 0.02$). FGF23 12–24 h after the termination of CPB was also associated with sAKI in the first week after surgery (498 RU/ml [226, 928] vs. 1435 RU/ml [831, 12,996]).

Conclusions Pre- and post-operative FGF23 levels are higher in children who develop sAKI after cardiac surgery. We suggest FGF23 may be able to detect sub-clinical kidney injury and can be used with demographic AKI risk factors to enhance post-operative sAKI risk prediction.

Keywords Acute kidney injury · Biomarkers · Cardiac surgery · FGF23 · Pediatric

Introduction

Acute kidney injury (AKI) remains one of the most significant prognostic factors for morbidity and mortality in children who undergo cardiac surgery (CS) even after adjustment for other comorbidities [1–5]. As the clinical use of troponin has revolutionized the treatment of patients with myocardial infarction, early identification of AKI by biomarkers has the potential to improve AKI management, although this goal has not been fully realized [6–10].

To date, identifying children with a higher risk of developing AKI prior to cardiac surgery has relied on demographic factors such as complexity of cardiac surgery, age, and expected cardiopulmonary bypass time [11, 12]. Prevention of fluid overload, avoidance of nephrotoxic medications, and earlier renal replacement therapy (RRT) in susceptible patients may decrease the severity of the impact of AKI and improve outcomes [12–14]. In addition, improved prediction and early diagnosis have the potential for development of new technologies and trials of preventive therapies.

Children undergoing CS with cardiopulmonary bypass (CPB) provide an informative population to test predictive markers for kidney injury. Acute kidney injury as an incidence of 30–40% after cardiac surgery and the timing of the insult is known and predictable [3–5]. Low cardiac output, as well as insults with previous exposure to nephrotoxic medications and contrast media, may lead to sub-clinical kidney injury which cannot be distinguished by the conventional markers of kidney function, which are based mainly on the filtration

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capacity of the kidney. If pre-operative predictive AKI biomarkers, using a known or new biomarker, could be incorporated into clinic models, this would increase the potential to improve identification of high-risk patients and their outcomes.

Fibroblast growth factor 23 (FGF23), an osteoblast-produced hormone, affects the kidney in order to control phosphorus homeostasis by inhibiting its reabsorption in the proximal tubules and by inhibiting the hydroxylation of vitamin D [15, 16]. Serum FGF23 increases in early stages of chronic kidney disease (CKD) and is associated with cardiovascular morbidity and mortality [17]. It appears that serum FGF23 increases also in early stages of AKI, as demonstrated in animal models as well as in recent adult studies [18, 19]. Two small studies in children have also shown that *post-operative* serum FGF23 can be used as an AKI biomarker—a nested case-control study in 14 patients and a small prospective study in 32 patients [20, 21]. We have recently demonstrated, using a retrospective multicenter study in 41 infants, that serum FGF23 level rises 4–8 h after cardiac surgery and it improves the prediction of AKI by other AKI biomarkers as neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid-binding protein (LFABP) when combined with them [22].

We conducted a prospective study to determine if *pre-operative* serum FGF23 concentrations are associated with post-operative severe AKI (sAKI) development in children who undergo heart surgery. In addition, we assessed if post-operative serum FGF23 concentrations are associated with AKI prediction in this population.

Methods

Study participants

This was a single-center prospective study enrolling children up to 18 years of age who had a scheduled CS with CPB between February 2016 and February 2017 at Cincinnati Children's Hospital Medical Center (CCHMC). The exclusion criteria included abnormal pre-operative serum levels per age of calcium, phosphorus, and creatinine.

Laboratory assessments

Pre-operative blood and urine samples were collected within 3 days of surgery. Post-operative samples were collected 12–24 h after termination of CPB. Daily serum calcium, phosphorus, creatinine, blood urea nitrogen, and hemoglobin levels were measured as part of routine clinical care. Blood specimens for FGF23, cystatin C, C-reactive protein (CRP), and urine for NGAL, kidney injury molecule 1 (KIM1), LFABP, and interleukin-18 (IL18) were obtained for research purposes pre- and post-operatively. Serum 25-hydroxyvitamin D was assessed only pre-operatively. Blood and urine samples for research purposes were centrifuged at 3500 RPM and 4 °C for 15 min. The serum or urine supernatants were extracted and immediately stored at − 80 °C. Serum biomarkers were measured at the CCHMC central research lab, and urine biomarkers were processed and measured by ELISA by the CCHMC Division of Nephrology and Hypertension Biomarker Laboratory (M. Bennett, Director) as previously described [23]. Biomarker levels, either corrected or corrected to creatinine level, had similar statistical significance. Therefore, uncorrected ratios are presented in the tables. The serum FGF23 level was measured using a human C-terminal FGF23 kit (Immutopics, Inc., San Clemente, CA, USA) in the CCHMC central research lab. All biomarkers and FGF23 levels were measured in duplicate after a single freeze-thaw cycle.

Clinical variables

The complexity of the surgery was defined using RACHS-1 (risk-adjusted classification for congenital heart surgery classification) [24]. The glomerular filtration rate was estimated by the revised Schwartz formula ($k = 0.413$) [25] as well as the cystatin C value based on Larsson's formula [26]. Serum creatinine level and use of renal replacement therapy were monitored in the first week after the surgery. In addition, hourly urine output and daily patient fluid gain or loss were monitored in the first 24 h. Patient heart disease was classified as cyanotic vs. non-cyanotic based on the physiology of the underlying cardiovascular anatomy at the time of cardiac surgery. AKI development and severity were defined by the Kidney Disease Improving Global Outcomes (KDIGO) classification based on creatinine level, urine output, and use of RRT in the first week after CS [8]. Severe AKI was defined as KDIGO stage 2 or 3 by both creatinine and urine output criteria while the patients with stage I AKI and those who did not develop AKI were included in the non-severe AKI (nsAKI) group. Acute kidney injury stages included in sAKI have been associated repeatedly with worsening morbidity and mortality in pediatric cardiac and non-cardiac ICU populations, whereas stage 1 AKI has not [4, 10, 27]. The higher KDIGO stage of creatinine or urine output was used if there was a discrepancy between the two criteria. nsAKI was defined as either no AKI or KDIGO stage 1 AKI.

Analytical and statistical methods

All statistical analyses were performed using Stata (version 14, College Station, Texas). The primary outcome was sAKI development within the first week after cardiac surgery. Global bivariate comparisons among groups (sAKI vs.

nsAKI) were performed by Mann-Whitney *U* and chi-square tests for continuous and categorical variables, respectively. Receiver operator characteristic (ROC) analyses were used to evaluate the association between the different markers and the development of sAKI. Pre-operative clinical and log-transformed biomarker results with a $p < 0.15$ were entered into non-parametric multivariable linear regression models to test for independent associations with sAKI. Post-operative log-transformed biomarker results with a $p < 0.05$ entered into non-parametric multivariable linear regression models to test for an independent association with sAKI. A p-value of <0.05 was considered to be significant for all analyses.

Results

Patients with severe and non-severe AKI had similar characteristics

Eighty-three subjects were recruited and consented, and 76 patients had available lab results for the study (Fig. 1). Thirty of the 76 subjects developed AKI (39.5%), and 11 (14.5%) developed sAKI in the first week after CS. RACHS-1 score ($p = 0.07$), the presence of cyanotic heart disease physiology ($p = 0.007$), and lower patient age ($p = 0.09$) were the only demographic variables entered into the multivariable models (Table 1).

Pre-operative serum FGF23 was elevated in subjects who developed sAKI

Pre-operative comparisons of biomarker concentrations in patients who did vs. did not develop post-operative sAKI are shown in Table 1. Median pre-operative estimated glomerular filtration rate (eGFR), serum phosphorus, and 25-hydroxyvitamin D did not differ between sAKI and nsAKI subjects. Median pre-operative serum FGF23 levels were higher in subjects who developed sAKI (819 RU/ml [397.7, 1196.8] vs. 324.3 RU/ml [124.6, 679.8], ($p = 0.02$)). In contrast, the pre-operative concentration of urinary AKI biomarkers did not differ between sAKI and nsAKI subjects.

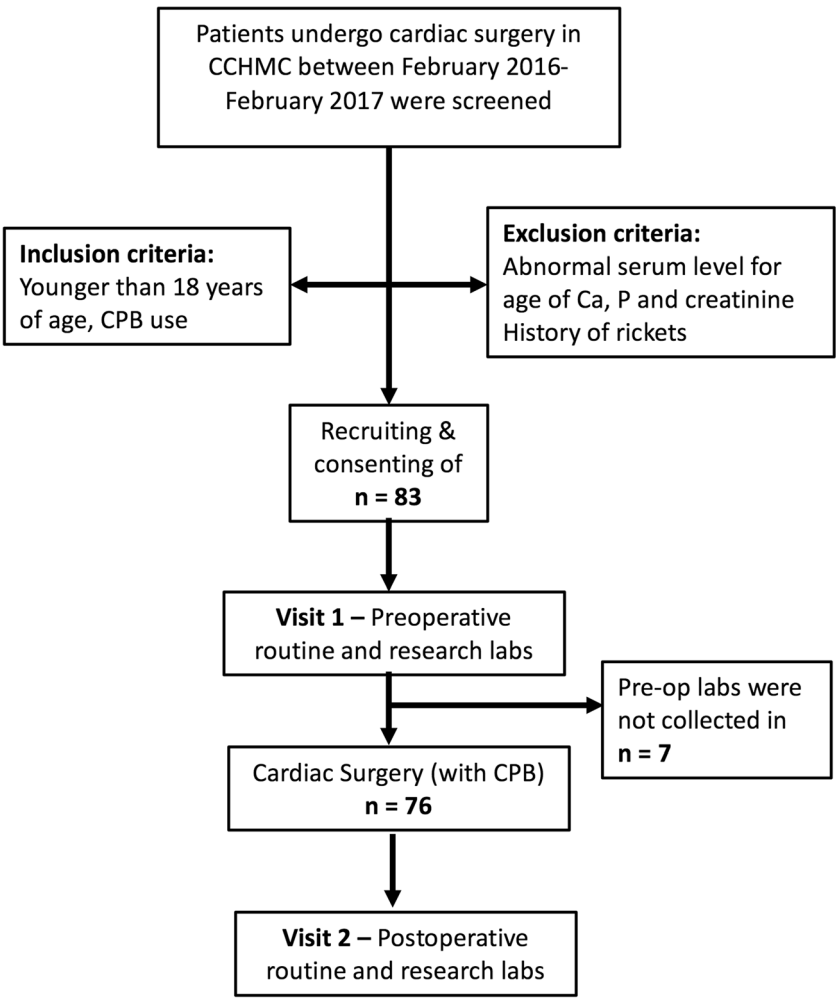

Fig. 1 Study design. *Ca/P* calcium/phosphorus, *CCHMC* Cincinnati Children's Hospital Medical Center, *CKD* Chronic kidney disease, *CPB* cardiopulmonary bypass.

Table 1 Pre-operative patient characteristics and laboratory data

Characteristic	All ($n = 76$)	Non-severe AKI ($n = 65$)	Severe AKI ($n = 11$)	p value
Age (years)	0.7 [0.3, 4.7]	0.8 [0.4, 4.9]	0.4 [0.02, 2.3]	0.09
Males (n, %)	42 (55.5%)	36 (55%)	6 (55%)	0.96
Caucasian (n, %)	64 (84%)	55 (85%)	9 (82%)	0.81
Cyanotic heart disease (n, %)	11 (14%)	5 (8%)	6 (55%)	0.007
RACHS-1	3 [2, 3]	2 [2, 3]	3 [2, 4]	0.07
Serum creatinine (mg/dl)	0.36 [0.28, 0.45]	0.36 [0.28, 0.44]	0.41 [0.26, 0.52)	0.75
Cystatin GFR (ml/min)	96 [68, 122]	96 [68, 122]	88 [66, 126]	0.76
Schwartz GFR (ml/min/173 m^2)	93 [67, 120]	95 [70, 122]	77 [41, 104]	0.17
Calcium (mg/dl)	9.2 [9, 9.5]	9.2 [9, 9.5]	9.1 [8.8, 9.6]	0.56
Hemoglobin (gm/dl)	14.0 [13.0, 15.3]	14.0 [13.0, 15.3]	13.8 [13, 14.5]	0.9
Phosphorus (mg/dl)	5.1 [4.3, 5.6]	5.0 [4.4, 5.5]	5.1 [4.1, 6.1]	0.72
25-OH vitamin D (mg/dl)	30.5 [24.3, 30.5]	30.5 [24.5, 36.6]	32.3 [16.6, 50.6]	0.84
Serum FGF23 (RU/ml)	374 [134, 739]	324.3 [125,680)	820 [398, 1197)	0.02
Urine NGAL (ng/ml)	3.5 [2, 7.4]	3.5 [2, 6.9]	3.1 [2.7, 29.2]	0.60
Urine IL18 (pg/ml)	30.1 [12.7, 66.6]	28.6 [12.7, 63.2]	97.8 [16.1, 108.2]	0.27
Urine KIM1 (pg/ml)	470 [236, 757]	534 [239, 831]	273 [194, 390]	0.08
Urine LFABP (ng/ml)	2.2 [0.7, 4.4]	2.2 [0.7, 4]	2.5 [0.7, 4.4]	0.89

Values are presented as n (%) or median (interquartile range [IQR], 25th–75th percentile). A p value for global comparisons among groups was calculated using Mann-Whitney and chi-square tests for continuous and categorical variables, respectively. GFR was calculated using Schwartz formula ($k = 0.413$). *AKI* acute kidney injury, *CPB* cardiopulmonary bypass, *GFR* glomerular filtration rate, *KIM1* kidney injury molecule-1, *LFABP* liver-type fatty acid-binding protein, *NGAL* neutrophil gelatinase-associated lipocalin, *RACHS* risk-adjusted classification for congenital heart surgery, *FGF23* fibroblast growth factor 23. The number of subjects in the non-severe AKI and severe AKI groups was respectively 65 and 11 in the non-urine biomarker data and 41 and 5 in the urine biomarker data

Post-operative serum FGF23 was elevated early after cardiac surgery in sAKI subjects

Intraoperative and post-operative results are depicted in Table 2. Subjects who developed sAKI had longer CPB and aortic cross-clamp times, as well as higher post-operative urinary NGAL, LFABP, and serum hemoglobin compared to controls. In addition, post-operative serum FGF23 was higher in subjects who developed sAKI. Similar to pre-operative results, there was no difference in post-operative calcium or phosphorus levels in patients with vs. without sAKI. Normalization of biomarkers with urine creatinine concentrations did not change the associations (data not shown).

Serum FGF23 and urinary biomarkers for sAKI prediction

Serum FGF23 demonstrated moderate to good prediction pre-operatively (AUC-ROC, SEM 0.73, 0.09) and post-operatively (0.79, 0.08) for sAKI (Fig. 2). A multivariable logistic regression model incorporating patient age, RACHS-1 score, the presence of cyanotic heart disease, and pre-operative FGF23 level demonstrated that pre-operative FGF23 was associated with increased risk of post-operative sAKI (OR 7.5 (1.03–79.3), $p = 0.047$) (Table 3). A multivariable logistic regression model was developed incorporating CPB time, post-operative FGF23, NGAL, and LFABP (Table 3); only CPB time retained a significant association with sAKI development in this model.

Discussion

As precise objective pre-operative tools for prediction of severe AKI are still lacking, we tested the hypothesis that pre-operative serum FGF23 can predict sAKI development in children who undergo cardiac surgery with cardiopulmonary bypass. We found in this prospective study that pre-operative FGF23 concentrations were higher in patients who developed sAKI after CS with CPB, while other pre-operative conventional tests to assess kidney function did not demonstrate any difference between the groups. Moreover, well-studied novel structural biomarkers, which have performed well to detect AKI assessed post-operatively in multiple studies, were not associated with AKI in CS when assessed pre-operatively [6, 11, 28, 29]. The duration of CPB was strongly associated with sAKI. However, this can only be known after the surgery and cannot help the clinician to determine the risk of sAKI pre-operatively.

Table 2 Post-operative patient characteristics

Characteristic	All ($n = 76$)	Non-severe AKI ($n = 65$)	Severe AKI ($n = 11$)	p value
CPB duration (min)	135 [89, 205]	123 [82,77]	227 [182, 266]	0.0006
Phosphorus	5.3 [4.6, 6.4]	5.3 [4.6, 6.3]	6.3 [3.6, 6.5]	0.25
Hemoglobin	12.5 [10.7, 14.6]	12.3 [10.7, 13.8]	14.3 [13.3, 17.6]	0.008
Fluid overload (% of original weight)	2.16 [− 0.38,4.86]	2.04 [0.04–4.63]	2.29 [− 6.58, 8.29]	0.72
Cystatin GFR (ml/min)	83.5 [59, 112.5]	89 [63, 119]	54, [49, 79]	0.004
Schwartz GFR (ml/min)	79 [55,103]	71.4 [52, 96]	43 [30, 59]	0.0002
FGF23 (RU/ml)	572 [275, 1294]	498 [226, 928]	1435 [831, 12,996]	0.008
Urine NGAL (ng/ml)	16 [5.1, 34.5]	16.0 [5.1, 34.5]	94.3 [17.5, 203.6]	0.004
Urine IL18 (pg/ml)	29.83 [13.5, 85.8]	26.9 [11.4, 79.5]	55.4 [18.1, 130.8]	0.17
Urine KIM1 (pg/ml)	646 [224, 1149]	508 [194, 1149]	886 [510, 1552]	0.14
Urine LFABP (ng/ml)	8.3 [3, 23.6]	7.5 [2.6, 22.2]	65.8 [65.9, 168.9]	0.007

Values are presented as n (%) or median (interquartile range [IQR], 25th–75th percentile). A p value for global comparisons among groups was calculated using Mann-Whitney and chi-square tests for continuous and categorical variables, respectively. GFR was calculated using Schwartz formula ($k = 0.413$) for creatinine-based assessment or Larsson formula for cystatin C-based assessment. The number of subjects in the non-severe AKI and severe AKI groups was respectively 65 and 11 in the non-urine biomarker data and 59 and 10 in the urine biomarker data. *AKI* acute kidney injury, *CPB* cardiopulmonary bypass, *GFR* glomerular filtration rate, *KIM1* kidney injury molecule-1, *LFABP* liver-type fatty acid-binding protein, *NGAL* neutrophil gelatinase-associated lipocalin, *CPB* cardiopulmonary bypass, *FGF23* fibroblast growth factor 23

In addition, we found that post-operative serum FGF23 concentrations were higher, 12–24 h after surgery in patients who developed sAKI. While the rise of FGF23 is affected by functional aspects of kidney failure, its level was associated with sAKI post-operatively with a similar performance of the structural markers NGAL and LFABP. Although post-operative serum FGF23 was the biomarker most strongly associated with sAKI development, it did not retain statistical significance when CPB time was added to the model. We suggest that a larger cohort would be needed to assess for a post-operative FGF23 association with sAKI independent of CPB time.

There are a number of factors that regulate and are associated with serum FGF23 concentrations. Calcium, phosphorus, and vitamin D are the main regulators of serum FGF23 levels. Active vitamin D increases the expression level of FGF23 in the bone by binding to the responsive element in the hormone's promoter. The high FGF23 level leads to decreased renal hydroxylation of vitamin D thereby causing a feedback loop. The mechanism by which calcium and phosphorus regulate FGF23 level is more obscure. In our study, we did not find any difference in serum calcium and phosphorus levels between the two groups which could explain the difference in FGF levels.

FGF23 is also known to be independently related to increased inflammation by a possible increase in transcription of the hormone in the bone cells by increased activity of hypoxia-inducible factor 1α (HIF-1α) and by other mechanisms [30, 31]. It has been suggested that the increased level of FGF23 can be induced also by an inflammatory state of CKD [32]. In order to assess an inflammatory-mediated process affecting FGF23 in our study, CRP was measured pre-operatively and post-operatively, yet no difference in the inflammation was found which may have also explained the difference in FGF23.

Increased FGF23 levels have been reported in cell lines and animal models under hypoxic conditions and have been observed in human subjects as well. In our study, a higher rate of

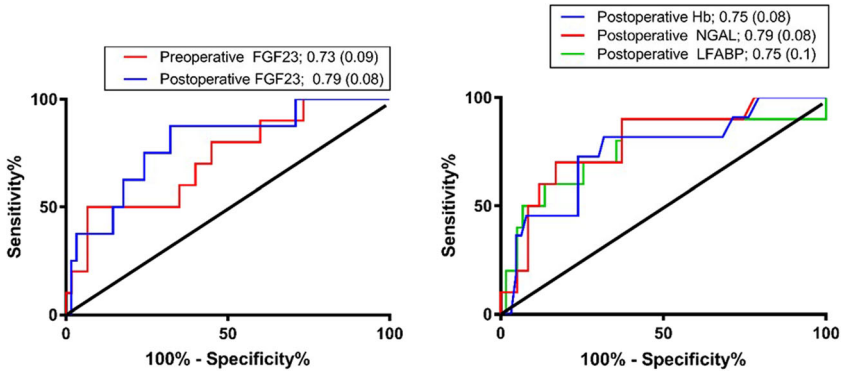

Fig. 2 Receiver operating characteristic analyses of the prediction of severe acute kidney injury. Numeric values in the legend represent area under the curve and standard error. *AUC* area under the curve, *Hb* hemoglobin, *NGAL* neutrophil gelatinase-associated lipocalin, *LFABP* liver-type fatty acid-binding protein, *ROC* receiver operating characteristic, *SEM* standard error of mean

Table 3 Multivariable model for pre-operative risk factors and post-operative biomarkers associated with severe AKI

Timing	Variable	Odds ratio for severe AKI (95% CI)	*p* value
Pre-operative	Cyanotic heart disease	0.7 (0.1–3.5)	0.65
	Age (years)	1.0 (0.8–1.3)	0.99
	RACHS-1	1.4 (0.8–2.3)	0.31
	Log FGF23 (RU/ml)	7.5 (1.1–79.2)	0.047
Post-operative	CPB (hours)	2.1 (0.9–4.5)	0.07
	Log FGF23 (RU/ml)	3.3 (0.6–17.3)	0.16
	Log NGAL (ng/ml)	2.1 (0.3–15)	0.48
	Log LFABP (ng/ml)	0.6 (0.2–2.2)	0.47

A multivariable logistic regression model was developed incorporating risk factors with $p < 0.15$ or pre-operative risk factors and for post-operative biomarkers with $p < 0.05$ on bivariate analysis

RACHS risk-adjusted classification for congenital heart surgery, *AKI* acute kidney injury, *FGF23* fibroblast growth factor-23, *CPB* cardiopulmonary bypass, *NGAL* neutrophil gelatinase-associated lipocalin, *LFABP* liver-type fatty acid-binding protein, *CI* confidence interval

cyanotic heart disease was seen in patients with sAKI compared to the group without sAKI [21]. However, FGF23 was associated with sAKI independent of cyanotic heart disease in multivariable analysis.

Iron deficiency anemia is also associated with increased level of FGF23. It has been suggested that iron deficiency stimulates the transcription level of the hormone in the osteocytes and impairs cleavage of the hormone. Clinical studies have demonstrated that iron deficiency anemia is associated with high level of FGF23 [30, 33, 34] and that iron transfusion may have been beneficial in decreasing FGF23 in CKD patients [35, 36]. No difference in pre-operative hemoglobin levels was found in the groups we studied. However, increased hemoglobin levels were noted in the sAKI group rather than the anemia that has been associated with FGF23 levels. However, it should be noted that iron and ferritin levels were not measured in our study, so low iron states without anemia could have been missed. In addition, it is possible that the patients with cyanotic heart disease have higher hemoglobin level, and therefore anemia can be missed as well.

Our study has a number of strengths. First, the AKI and sAKI rates are similar to what has been published previously in cardiac surgery studies, so our study may be considered representative [3, 4, 29, 37]. This is the largest prospective study in the pediatric population to assess for the clinical utility of FGF23 as an AKI biomarker and the first to compare pre-operative FGF23 to other structural biomarkers for prediction of post-operative AKI development in children. While similar FGF23 findings were suggested in adults, and a small case-control study in children [20–22], no comparison was made to other biomarkers in these studies. In addition, our study demonstrated that elevated pre-operative FGF23 level is associated with higher risk of sAKI after heart surgeries independent of possible confounders as cyanotic heart disease and inflammation [21].

The study has some limitations. First, it is a single-center study, and should be repeated as a multicenter study to confirm our findings. Although this is the largest prospective study in this field in children, the sample size is still relatively low to exclude multiple other potential confounders. We have used KDIGO criteria to diagnose sAKI which is based not only on creatinine level and urine output but also on estimated kidney function using the revised Schwartz equation and need for RRT. Different approaches in initiating RRT may vary in different institutions and may affect the result. Calcium, phosphorus, and vitamin D are the main regulators of FGF23. However, there are other factors which are supposedly involved in the regulation of FGF23 but were not tested in this study such as parathyroid hormone, different types of cytokines and soluble klotho level, a necessary coreceptor for activation of FGF receptor by FGF23.

Currently, no other biomarkers have been found to be able to predict AKI pre-operatively, and FGF23 was superior to current demographic data or laboratory results. The question why the FGF23 level is elevated while the kidney function appears normal using other tests is still unresolved. While the filtration capacity of the kidney appears normal and thereby the level of other markers appears normal, other functions of the kidney may have already compensated. Our results suggest that FGF23 may be detecting sub-clinical kidney injury and can be used with demographic AKI risk factors to enhance sAKI risk prediction.

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Authors' contributions Dr. Volovelsky, Dr. Cooper, and Dr. Goldstein have designed the study. All the authors were involved in analysis and interpretation of the data, drafting of the article, and provision of intellectual content of critical importance to the work.

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Compliance with ethical standards

The study was approved by the CCHMC Institutional Review Board. Written informed consent was obtained from all patient caregivers, and assent from all patients 11 years and older was obtained prior to enrollment.

Conflict of interest The authors declare no conflict of interest in this study.

Disclosures Dr. Goldstein receives consulting fees from Bioporto, Incorporated, which owns the NGAL assay. Bioporto Inc. had no involvement in any aspect of this study.

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