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ORIGINAL RESEARCH

Persistent Markers of Kidney Injury in Children Who Developed Acute Kidney Injury After Pediatric Cardiac Surgery: A Prospective Cohort Study

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BACKGROUND: Acute kidney injury (AKI) after pediatric cardiac surgery is common. Longer-term outcomes and the incidence of chronic kidney disease after AKI are not well-known.

METHODS AND RESULTS: All eligible children (aged <16 years) who had developed AKI following cardiac surgery at our tertiary referral hospital were prospectively invited for a formal kidney assessment ≈5 years after AKI, including measurements of estimated glomerular filtration rate, proteinuria, α_1-microglobulin, blood pressure, and kidney ultrasound. Longer-term follow-up data on kidney function were collected at the latest available visit. Among 571 patients who underwent surgery, AKI occurred in 113 (19.7%) over a 4-year period. Fifteen of these (13.3%) died at a median of 31 days (interquartile range [IQR], 9–57) after surgery. A total of 66 patients participated in the kidney assessment at a median of 4.8 years (IQR, 3.9–5.7) after the index AKI episode. Thirty-nine patients (59.1%) had at least 1 marker of kidney injury, including estimated glomerular filtration rate <90 mL/min per 1.73 m^2 in 9 (13.6%), proteinuria in 27 (40.9%), α_1-microglobinuria in 5 (7.6%), hypertension in 13 (19.7%), and abnormalities on kidney ultrasound in 9 (13.6%). Stages 1 to 5 chronic kidney disease were present in 18 (27.3%) patients. Patients with CKD were more likely to have an associated syndrome (55.6% versus 20.8%, P=0.015). At 13.1 years (IQR, 11.2–14.0) follow-up, estimated glomerular filtration rate <90 mL/min per 1.73 m^2 was present in 18 of 49 patients (36.7%), suggesting an average estimated glomerular filtration rate decline rate of –1.81 mL/min per 1.73 m^2 per year.

CONCLUSIONS: Children who developed AKI after pediatric cardiac surgery showed persistent markers of kidney injury. As chronic kidney disease is a risk factor for cardiovascular comorbidity, long-term kidney follow-up in this population is warranted.

Key Words: acute kidney injury ■ cardiac surgery ■ children ■ chronic kidney disease ■ congenital heart disease ■ long-term outcomes

Acute kidney injury (AKI) in the immediate postoperative period is common, occurring in 30% to 60% of children undergoing pediatric cardiac surgery for congenital heart disease (CHD). A recent meta-analysis demonstrated that AKI after pediatric cardiac surgery was associated with increased short-term morbidity and mortality, including higher rates of in-hospital mortality, need for kidney replacement therapy, and cardiac arrhythmias, as well as longer ventilation time and hospital length of stay.[1]

Longer-term outcomes of AKI after pediatric cardiac surgery, however, are not well known. Adult studies have found robust associations of cardiac surgery-associated AKI with a 9-fold increased risk of

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CLINICAL PERSPECTIVE

What Is New?

- In this prospective cohort of 66 children with congenital heart disease who developed acute kidney injury after pediatric cardiac surgery, evidence of kidney injury was present in 39 (59.1%) and chronic kidney disease stage 1 to 5 was present in 18 (27.3%) after a median follow-up of 4.8 years.
- Kidney function measurements obtained in 49 children at a median of 13.1 years after the index acute kidney injury episode revealed overall ongoing kidney function deterioration with an average decline in estimated glomerular filtration rate of –1.8 mL/min per 1.73 m^2 per year.

What Are the Clinical Implications?

- Our findings provide incremental evidence that persistent markers of kidney injury are common after postoperative acute kidney injury in children with congenital heart disease at mid- and long-term follow-up.
- Children may develop absolute or relative hyperfiltration in response to acute kidney injury, thus initially "masking" the injury; however, kidney injury progresses and eventually becomes evident, especially in those with syndromes or univentricular physiology.
- As chronic kidney disease, proteinuria, and hypertension are important cardiovascular risk factors, structured follow-up of the kidneys in this vulnerable population is warranted and prevention of kidney disease should start in childhood to ensure optimal outcomes in the growing population of adults with congenital heart disease.

Nonstandard Abbreviations and Acronyms

ACHD	adults with congenital heart disease
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
KDIGO	Kidney Disease Improving Global Outcomes

developing chronic kidney disease (CKD) and a 2-fold increased risk of long-term mortality when compared with those without AKI.[2] In contrast, prior studies in children with CHD have been inconclusive with regard to the risk of persistent kidney injury and CKD and there is a scarcity of data in this population.[3–8]

While CHD was a lethal condition several decades ago, >90% of infants with CHD currently survive into adulthood.[9] The rising number of adults with CHD (ACHD) now accounts for two thirds of the CHD population.[10] As early mortality continues to decrease, it becomes more clear that CHD is never cured and results in multiple complications accumulated over the lifespan.[11] CKD is an important issue in the growing ACHD population, occurring in 30% to 50% of these patients[12] and being responsible for an excess burden in health care utilization.[13] Furthermore, as CKD represents an important cardiovascular risk factor, it needs to be managed and followed up as part of the standard care of this population.[14] Currently, AKI guidelines in children offer no recommendations on structured kidney follow-up. Therefore, this prospective cohort study investigated the mid- and long-term kidney consequences of AKI after pediatric cardiac surgery.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

This study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the local ethical committee of the University Hospitals Leuven (project number S52045). All consecutive children (aged <16 years) with CHD who had developed AKI following cardiac surgery with extracorporeal circulation between December 2004 and December 2008 were identified through the local Pediatric Cardiology database and the hospitals electronic database. AKI was defined according to the Acute Kidney Injury Network (AKIN) classification[15] as an increase in serum creatinine ≥0.3 mg/dL or ≥50% within 48 hours after surgery. AKI was further subdivided into stage 1 (increase of ≥0.3 mg/dL or 50%–100%), stage 2 (increase of 100%–200%), and stage 3 (increase of ≥4 mg/dL with an acute increase of ≥0.5 mg/dL, or >200%, or requiring renal replacement therapy). AKIN was the leading classification for AKI at the time of protocol validation of this study (ie, June 2010). Demographic, perioperative, and postoperative data were retrieved from information available in their electronic medical records, as well as hospitalizations and outpatient consultations.

CHD was classified into the following types: intracardiac left-to-right shunts (atrial septal defect, ventricular septal defect, atrioventricular septal defect), obstructive left heart lesions (coarctation of the aorta, aortic stenosis, small left hearts, Shone complex, and other lesions with evolution to biventricular circulation), transposition of the great arteries ("simple" types, with or without ventricular septal defect), conotruncal

lesions (tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus, complex transpositions with pulmonary stenosis or coarctation), univentricular hearts (hypoplastic left heart syndrome, tricuspid atresia, mitral atresia, hypoplastic right heart, complex atrioventricular connections, and other lesions with evolution to Fontan circulation), totally anomalous pulmonary venous return, and other. Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) scores as a marker for surgery complexity and the mortality risk after congenital surgery were assigned according to O'Brien et al.[16]

Study Design and Objectives

Patients who had developed AKI after pediatric cardiac surgery and were still alive were contacted by mail and invited for a formal kidney assessment between June 2010 and December 2012. Patients who did not respond were contacted by telephone. Informed consent was obtained from the parents or caregivers of all patients. All assessments were performed on an outpatient basis on the same day as a planned cardiology consultation.

During the study visit, height, weight, and vital signs were collected and a full physical examination was performed. Blood pressure was measured at the upper extremity using an automated Dinamap monitor and cuff of appropriate size. The lowest of 3 readings taken 5 minutes apart was recorded. Hypertension was defined as systolic and/or diastolic blood pressure >95th percentile for sex, age, and height.[17] Children with previously diagnosed hypertension who were on antihypertensive therapy were also considered to have hypertension.

Kidney outcome was assessed by means of estimated glomerular filtration rate (eGFR), proteinuria, α_1-microglobinuria, and kidney ultrasound. Serum creatinine was determined and eGFR was estimated using the 2009 Schwartz formula (eGFR=0.413×height [cm]/creatinine [mg/dL]).[18] A clean catch or bagged urine sample was collected. Proteinuria was defined as a urine protein/creatinine ratio >0.2 g/g. α_1-Microglobulinuria, an indicator of proximal tubular dysfunction, was defined as a urinary level of α_1-microglobuline >12.5 mg/L. Kidney ultrasound with Doppler was performed to assess kidney length, aspect of kidney parenchyma, and kidney perfusion. Kidney length was standardized to height-matched normal ranges.[19] A kidney was considered small or large if its length was inferior or superior to 2 SDs compared with controls.

The primary objective of the study was to determine midterm kidney outcomes of AKI after pediatric cardiac surgery. CKD was defined according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines: eGFR 90 mL/min to 100 mL/min per 1.73 m^2 with abnormalities on kidney ultrasound or biochemistry (stage 1), or eGFR <90 mL/min per 1.73 m^2 (stages 2–5).[20] Hyperfiltration was defined as an eGFR >140 mL/min per 1.73 m^2. A secondary objective was to evaluate the progressive decline in kidney function at long-term follow-up. To this end, the latest occasional eGFR measurement available from electronic medical records was evaluated. Most blood samples were obtained during routine checkups before catheterization. Samples taken at the time of intercurrent acute disease were excluded.

Statistical Analysis

Continuous variables were checked for normality using Shapiro-Wilk test. Normally distributed variables are presented as mean±SD and were compared using Student *t* test; non-normally distributed variables are presented as median (interquartile range [IQR]) and were compared using Mann-Whitney *U* test. Categorical variables are expressed as frequency (percentage) and were compared with chi-square test. All analyses were performed using R Statistical Software (version 4.0.2 2020-06-22, Foundation for Statistical Computing). A 2-tailed $P<0.05$ was considered statistically significant.

RESULTS

Prevalence of AKI, Patient Characteristics, and Survival

A total of 640 cardiac operations in 571 children with CHD were performed at our tertiary referral hospital between December 2004 and December 2008. AKI occurred following 122 procedures (19.1%) in 113 patients (19.7%). The patients underwent the index operation at a median age of 79.0 days (IQR, 9.0–230 days) and 68 (60.2%) were male. Nine patients experienced a second AKI episode between this index operation and the kidney assessment visit. According to their highest AKIN classification, 64 patients (56.6%) had stage 1 AKI, 40 (35.4%) had stage 2 AKI, and 10 (8.8%) had stage 3 AKI. Renal replacement therapy was required in 2 patients (1.6%), one for a period of 45 days and another for 4 days. Fifteen patients (13.3%) died at a median of 31.0 days (IQR, 9.0–57.0 days) after surgery and at a median age of 93.0 days (IQR, 56.0–211 days). The cause of death was cardiorespiratory failure in 11 patients (80.0%) and severe infections in 3 patients (20.0%).

The 98 surviving patients were contacted to participate in a formal kidney assessment. Thirteen patients (13.3%) declined and 19 (19.4%) were lost to follow-up, mostly attributable to further follow-up abroad. Thus, a total of 66 children were included in the current study (Figure 1). The study visits were performed at a median follow-up of 4.8 years (IQR, 3.9–5.7 years) after the index AKI episode. At that time, the median age was

5.6 years (IQR, 4.1–6.4 years). Patient demographics are presented in Table 1. Patients included in the prospective cohort did not differ from those who were not included, apart from lower birth weight (3030±652 g versus 3381±614 g, *P*=0.012) and higher number of CHD surgeries (median, 2 [IQR, 1–2] versus 1 [IQR, 1–1], *P*=0.002) in the former.

Kidney Assessment Visit

Anthropometric Data

Findings at the kidney assessment visit are presented in Table 2. The patients had a mean length of 110±12.2 cm and a median weight of 18.2 kg (16.0–20.5 kg). The median percentiles for length and weight were 32.0 (10.0–50.0) and 25.0 (3.0–50.0), respectively. The median body mass index was 14.9 kg/m^2 (14.1–16.0 kg/m^2). Patients with AKIN stage 2 had a significantly lower weight than those with AKIN stage 1 (16.0 kg [IQR, 13.4–18.0 kg] versus 19.0 kg [IQR, 17.0–20.6 kg]; *P*=0.025).

Kidney Function

The mean eGFR at the formal assessment visit was 114±25 mL/min per 1.73 m^2. Hyperfiltration was observed in 8 children (12.1%). Eight children (12.1%) had a mildly decreased eGFR between 60 and 90 mL/min per 1.73 m^2 (CKD stage 2) and 1 child (1.5%) had an eGFR of 51 mL/min per 1.73 m^2 (CKD stage 3a). Two of these patients had known kidney hypodysplasia and reduced kidney function since the neonatal period and their eGFR at the kidney assessment visit was comparable with their baseline eGFR before the index surgery. There were no differences in kidney function between AKIN stages (*P*=0.474).

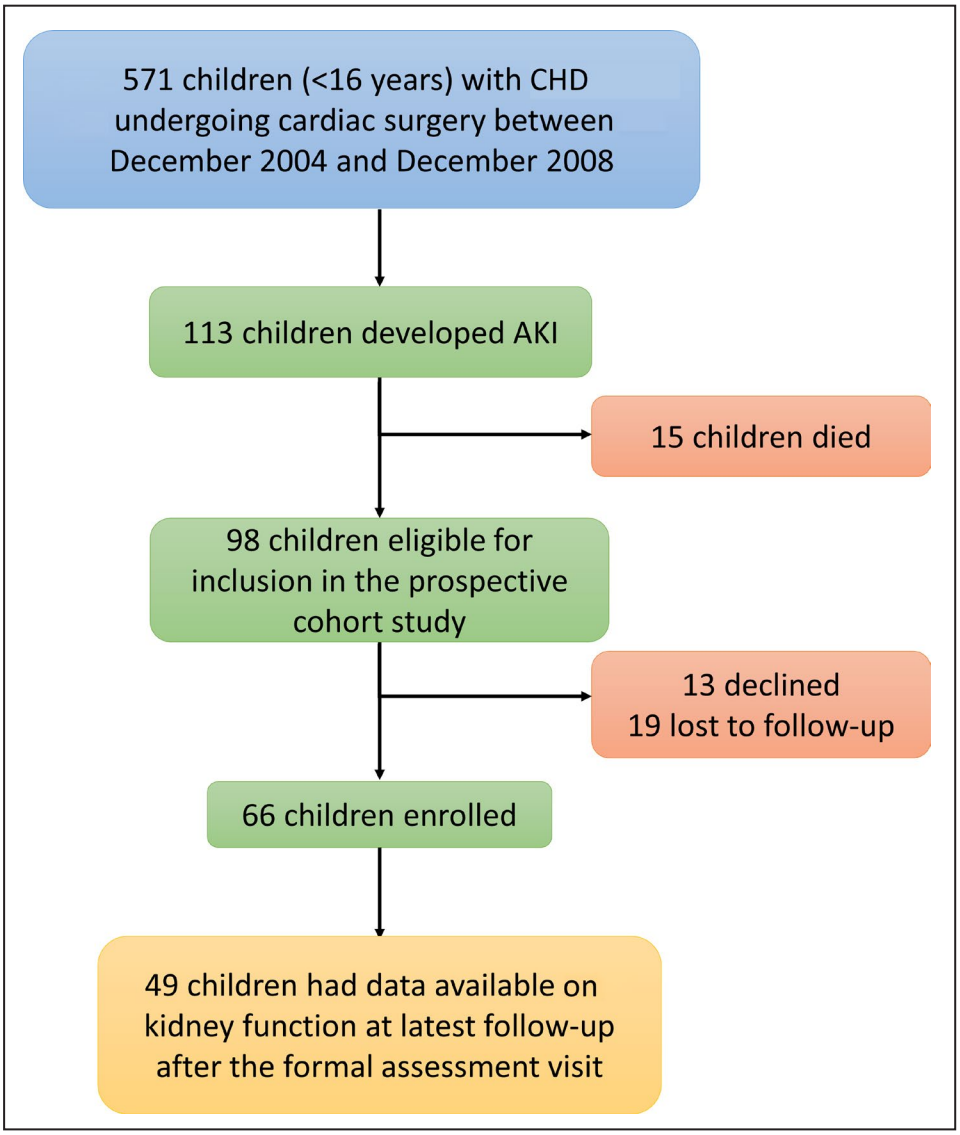

Figure 1. Flow diagram of the cohort study.
AKI indicates acute kidney injury; and CHD, congenital heart disease.

Table 1. Demographics of Patients Included and Not Included in the Prospective Cohort

Variable	Included (n=66)	Not included (n=47)
Female sex	28 (42.4)	18 (38.3)
Prematurity (<37 wk)	9 (13.6)	2 (4.3)
Delivery at tertiary hospital	19 (28.8)	10 (21.3)
Birth weight, g	3030±652	3381±614
Birth weight <2.5 kg	8 (12.1)	2 (4.3)
Prenatal diagnosis of CHD	17 (25.8)	12 (25.5)
Type of CHD		
Intracardiac left-to-right shunts	7 (10.6)	11 (23.4)
Obstructive left heart lesions	5 (7.6)	6 (12.8)
Transposition of the great arteries	18 (27.3)	10 (21.3)
Conotruncal lesions	19 (28.8)	8 (17.0)
Univentricular heart	16 (24.2)	7 (14.9)
TAPVR	1 (1.5)	3 (6.4)
Other	0 (0.0)	2 (4.3)
Comorbidities		
Syndrome	20 (30.3)	14 (29.8)
CAKUT	5 (7.6)	3 (6.4)
No. of surgeries for CHD	2 (1–2)	1 (1–1)
1	30 (45.5)	37 (78.7)
2	21 (31.8)	7 (14.9)
3	12 (18.2)	3 (6.4)
4	3 (4.5)	0 (0.0)
Age at index CHD surgery, d	87 (9–316)	79 (8–136)
Neonates (<28 d)	27 (40.9)	19 (40.4)
Characteristics of index CHD surgery		
CPB time, min	133±77	131±69
CPB time >120 min	27 (40.9)	18 (38.3)
Cross clamp time, min	72±31	69±34
STAT score	3 (2–4)	3 (2–4)
1	7 (10.6)	7 (14.9)
2	19 (28.8)	13 (27.7)
3	18 (27.3)	15 (31.9)
4	18 (27.3)	10 (21.3)
5	4 (6.1)	2 (4.3)
ICU length of stay, d	8 (5–14.8)	7 (6–13.9)
Total number of CHD surgeries with AKI episode		
1	59 (89.4)	45 (95.7)
2	7 (10.6)	2 (4.3)
AKI severity		
AKIN stage 1 (mild)	42 (63.6)	22 (46.8)
AKIN stage 2 (moderate)	19 (28.7)	21 (44.7)
AKIN stage 3 (severe)	5 (7.6)	5 (10.6)

Data are presented as frequency (percentage), mean±SD, or median (interquartile range). AKI indicates acute kidney injury; AKIN, Acute Kidney Injury Network; CAKUT, congenital anomalies of the kidney and urinary tract; CHD, congenital heart disease; CPB, cardiopulmonary bypass; ICU, intensive care unit; STAT, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery; and TAPVR, totally anomalous pulmonary venous return.

Proteinuria and α_1-Microglobinuria

Proteinuria was identified in 27 patients (40.9%). One child with known kidney hypodysplasia and reduced kidney function had overt proteinuria (2.1 g/g); the proteinuria was in the same range as before the AKI surgery. Proteinuria did not differ between AKIN stages (P=0.146). Urinary α_1-microglobulin concentration was increased in 5 patients (7.6%), indicating tubular dysfunction. Three patients had associated proteinuria.

Hypertension

Hypertension was detected in 13 patients (19.6%): 9 had hypertension (including 3 patients who were taking antihypertensive treatment) and 4 were normotensive but taking antihypertensive medications for blood pressure control. There was no difference between AKIN stages with regard to hypertension (P=0.477).

Kidney Ultrasound

Kidney ultrasound with Doppler detected abnormalities in 9 patients (13.6%). Five of these children had preexisting congenital anomalies of the kidney and urinary tract, which had already been documented on ultrasound during the neonatal period. Kidney intraparenchymal acceleration times and resistance indices were within normal ranges in all patients.

Markers of Kidney Injury

Of the 66 patients who came to the kidney assessment visit, 39 (59.1%) had at least 1 marker of kidney injury (ie, reduced kidney function, proteinuria, α_1-microglobinuria, abnormalities on ultrasound, and/or hypertension). Nineteen (28.8%) had 1 positive marker of kidney injury, 17 (25.8%) had 2 positive markers, and 3 (4.5%) had abnormalities in 3 markers.

CKD Stages 1 to 5

CKD stages 1 to 5, defined as eGFR <90 mL/min per 1.73 m^2 or eGFR 90 mL/min per 1.73 m^2 to 100 mL/min per 1.73 m^2 with laboratory/ultrasound abnormalities, was present in 18 patients (27.3%) at the kidney assessment visit. Patients with CKD were more likely to have an associated syndrome (55.6% versus 20.8%, P=0.015). However, no other differences in demographic data were observed (Table 3). While overall the types of CHD were different between both groups (P=0.049), no significant differences for individual types were observed. Nonetheless, trends were observed towards more univentricular hearts (38.9% versus 18.8%, P=0.089) and intracardiac left-to-right shunts (22.2% versus 6.3%, P=0.061) and less transposition of the great arteries (11.1% versus 33.3%, P=0.071) in the CKD group. No significant associations to the characteristics

Table 2. Kidney Assessment Visit at 5-Year Follow-Up

Variable	All patients (N=66)	AKIN stage 1 (n=42)	AKIN stage 2 (n=19)	AKIN stage 3 (n=5)	*P* value
Anthropometric data					
Height, cm	110±12.2	112±10.9	105±14.3	108±9.3	0.087
Height percentile	32.0 (10.0–50.0)	33.5 (10.0–50.0)	25.0 (6.5–50.0)	35.0 (3.0–50.0)	0.736
Weight, kg	18.2 (16.0–20.5)	19.0 (17.0–20.6)	16.0 (13.4–18.0)	18.3 (16.4–19.3)	0.031
Weight percentile	25.0 (3.00–50.0)	33.0 (7.00–50.0)	10.0 (3.0–29.5)	34.0 (3.0–75.0)	0.312
BMI, kg/m^2	14.9 (14.1–16.0)	15.0 (14.0–16.0)	15.0 (14.2–15.9)	16.0 (14.9–16.7)	0.668
Serum creatinine, mg/dL	0.42±0.12	0.44±0.13	0.37±0.07	0.40±0.13	0.066
eGFR, mL/min per 1.73 m^2	114±25	111±27	120±20	118±33	0.474
eGFR <90 mL/min per 1.73 m^2	9 (13.6)	8 (19.1)	0 (0.0)	1 (20.0%)	0.121
eGFR 90–140 mL/min per 1.73 m^2	49 (74.2)	30 (71.4)	17 (89.5)	2 (40)	0.063
eGFR >140 mL/min per 1.73 m^2	8 (12.1)	4 (9.5)	2 (10.5)	2 (40)	0.138
Proteinuria (>0.2 g/g)	27 (40.9)	17 (40.5)	6 (31.6)	4 (80)	0.146
α_1-Microglobinuria (>12.5 mg/L)	5 (7.6)	3 (7.1)	1 (5.3)	1 (20)	0.533
Hypertension	13 (19.7)	10 (23.8)	3 (15.8)	0 (0.0)	0.395
Kidney ultrasound					
Small kidney	8 (12.1)	3 (7.1)	4 (21.1)	1 (20.0)	0.260
Large kidney	4 (6.1)	3 (7.14)	1 (5.3)	0 (0.0)	0.807
Abnormal medullary reflectivity	2 (3.0)	1 (2.4)	1 (5.3)	0 (0.0)	0.764
Abnormal cortical reflectivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Abnormalities					0.304
Present at neonatal ultrasound (CAKUT)	5 (7.6)	1 (2.4)	3 (15.8)	1 (20.0)	
Newly diagnosed	4 (6.1)	3 (4.5)	1 (1.5)	0 (0.0)	
No abnormalities	57 (86.4)	38 (90.5)	15 (78.9)	4 (80.0%)	

Data are presented as frequency (percentage), mean±SD, or median (interquartile range). *P* value is given for the comparison between Acute Kidney Injury Network (AKIN) stages. BMI indicates body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; and eGFR, estimated glomerular filtration rate.

of the surgery (number of surgeries before kidney assessment, number of surgeries with AKI episode, clamp and bypass time of the index surgery, STAT score, and intensive care unit length of stay) could be found, but caution is warranted because of low power. At the time of the visit, patients in the CKD group had a lower height percentile (10 [IQR, 1.88–34.2] versus 50 [IQR, 10–53.2]; *P*=0.005), despite similar weight percentile (17.5 [IQR, 3–35.2] versus 25 [IQR, 5.25–50]; *P*=0.181), when compared with those without CKD (Table 4).

Kidney Function at Latest Follow-Up

Between the formal kidney assessment and latest follow-up, 2 patients died: one 13.1-year-old patient at 7.5 years after the assessment attributable to sudden collapse after Potts shunt for severe pulmonary hypertension, and another 17.2-year-old patient at 10.0 years after the assessment following complications of COVID-19 in a failing Fontan circulation. In a total of 49 of the 66 patients originally included in the assessment, kidney function tests were obtained from the latest available visit after the formal assessment, at a median follow-up of 13.1 years (IQR, 11.2–14.0 years) after the index AKI episode. The median age was 13.6 years (IQR, 12.2–15.3 years). At that time, the mean eGFR had declined to 99±23 mL/min per 1.73 m^2 (*P*=0.001 compared with 114±25 mL/min per 1.73 m^2 at the kidney assessment visit) (Figure 2A). This suggests an average eGFR decline rate of –1.81 mL/min per 1.73 m^2 per year. If the decline would proceed at the same rate, it is predicted that 50% of our patients will have developed an eGFR <90 mL/min per 1.73 m^2 by early adulthood (at 18.1 years of follow-up), which corresponds to data in ACHD.[12] Hyperfiltration was observed in only 1 child

Table 3. Comparison of Demographic Data in Patients Who Had Developed CKD at the Kidney Assessment Visit at 5-Year Follow-Up Versus Those Who Did Not

Variable	No CKD (n=48)	CKD (n=18)	SMD*	*P* value
Female sex	20 (41.7)	8 (44.4)	0.061	1.000
Prematurity (<37 wk)	6 (12.5)	3 (16.7)	0.187	0.696
Delivery at tertiary hospital	14 (29.2)	5 (27.8)	−0.038	0.913
Birth weight, g	3210 (2732–3440)	2955 (2692–3415)	−1.205	0.496
Birth weight <2.5 kg	6 (12.5)	2 (11.1)	−0.074	1.000
Prenatal diagnosis of CHD	14 (29.2)	3 (16.7)	−0.398	0.301
Type of CHD				
Intracardiac left-to-right shunts	3 (6.3)	4 (22.2)	0.797	0.061
Obstructive left-sided heart lesions	5 (10.4)	0 (0.0)	NA	0.154
Transposition of the great arteries	16 (33.3)	2 (11.1)	−0.764	0.071
Conotruncal lesions	15 (31.3)	4 (22.2)	−0.258	0.471
Univentricular heart	9 (18.8)	7 (38.9)	0.558	0.089
TAPVR	0 (0.0)	1 (5.6)	NA	0.100
Comorbidities				
Syndrome	10 (20.8)	10 (55.6)	0.861	0.015
CAKUT	3 (6.25)	2 (11.1)	0.341	0.608
No. of surgeries for CHD	2 (1–2)	2 (1–3)	0.949	0.368
1	23 (47.9)	7 (38.9)	−0.203	0.512
2	16 (33.3)	5 (27.8)	−0.143	0.666
3	7 (14.6)	5 (27.8)	0.448	0.216
4	2 (4.2)	1 (5.6)	0.167	0.810
Age at index CHD surgery, d	35.5 (9.0–213)	167 (28.2–1068)	2.277	0.125
Neonates (<28 d)	22 (45.8)	5 (27.8)	−0.433	0.295
Characteristics of index CHD surgery				
CPB time, min	118 (88–156)	104 (86–141)	−1.091	0.480
CPB time >120 min	21 (43.8)	6 (33.3)	−0.246	0.627
Cross clamp time, min	77±30	69±42	−0.219	0.500
STAT score	3 (2–4)	3 (2–4)	−0.011	0.889
1	5 (10.4)	2 (11.1)	0.040	0.933
2	14 (29.2)	5 (27.8)	−0.038	0.508
3	13 (27.1)	5 (27.8)	0.019	0.956
4	14 (29.2)	4 (22.2)	−0.203	0.573
5	2 (8.3)	2 (11.1)	0.177	0.292
ICU length of stay, d	6.5 (3.3–9)	8 (5–15.3)	1.982	0.107
Total number of CHD surgeries with AKI episode				0.327
1	44 (91.7)	15 (83.3)	−0.438	
2	4 (8.3)	3 (16.7)	0.438	
AKI severity				0.038
AKIN stage 1 (mild)	27 (56.2)	15 (83.3)	0.749	
AKIN stage 2 (moderate)	18 (37.5)	1 (5.6)	−1.276	
AKIN stage 3 (severe)	3 (6.3)	2 (11.1)	0.341	

Data are presented as frequency (percentage), mean±SD, or median (interquartile range). AKI indicates acute kidney injury; AKIN, Acute Kidney Injury Network; CAKUT, congenital anomalies of the kidney and urinary tract; CHD, congenital heart disease; CPB, cardiopulmonary bypass; ICU, intensive care unit; NA, not available; STAT, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery; and TAPVR, totally anomalous pulmonary venous return.

*Standardized mean differences (SMDs) are presented for chronic kidney disease (CKD) compared with no CKD.

(2.0%, *P*=0.047). A total of 11 of 49 patients (22.4%) who had normal kidney function at the assessment visit eventually developed kidney dysfunction (Figure 2B). Thus, 17 children (34.7%, *P*=0.008) had a mildly decreased eGFR between 60 mL/min per 1.73 m^2 and 90 mL/min per 1.73 m^2 (CKD stage 2) and

Table 4. Comparison of Data From Kidney Assessment Visit in Patients Who Had Developed CKD at 5-Year Follow-Up Versus Those Who Did Not

Variable	No CKD (n=48)	CKD (n=18)	SMD*	*P* value
Anthropometric data				
Height, cm	110±12.1	109±12.8	−0.080	0.800
Height percentile	50.0 (10.0–53.2)	10.0 (1.88–34.2)	−4.212	0.005
Weight, kg	18.1 (15.7–20.6)	18.2 (17.5–19.9)	0.505	0.655
Weight percentile	25.0 (5.25–50.0)	17.5 (3.0–35.2)	−1.233	0.181
BMI, kg/m^2	15.0 (14.0–16.0)	15.0 (14.5–16.6)	0.805	0.924
Serum creatinine, mg/dL	0.36 (0.33–0.41)	0.52 (0.47–0.58)	9.826	<0.001
eGFR, mL/min per 1.73 m^2	125±19.2	84.9±13.6	−2.410	<0.001
eGFR <90 mL/min per 1.73 m^2	0 (0.0)	9 (50.0)	NA	<0.001
eGFR 90–140 mL/min per 1.73 m^2	40 (83.3)	9 (50.0)	−0.886	0.006
eGFR >140 mL/min per 1.73 m^2	8 (16.7)	0 (0.0)	NA	0.065
Proteinuria (>0.2 g/g)	19 (39.6)	8 (44.4)	0.109	0.939
α_1-Microglobinuria (>12.5 mg/L)	3 (6.3)	2 (11.1)	0.341	0.608
Hypertension	9 (18.8)	4 (22.2)	0.115	0.906
Kidney ultrasound				
Small kidney	5 (11.9)	3 (18.8)	0.297	0.499
Large kidney	3 (7.1)	1 (6.3)	−0.071	0.906
Abnormal medullary reflectivity	1 (2.2)	1 (5.6)	0.535	0.484
Abnormal cortical reflectivity	0 (0.0)	0 (0.0)	NA	1.000
Abnormalities				0.382
Present at neonatal ultrasound (CAKUT)	3 (6.3)	2 (11.1)	0.341	
Newly diagnosed	4 (8.3)	0 (0.0)	NA	
No abnormalities	41 (85.4)	16 (88.9)	0.173	

Data are presented as frequency (percentage), mean±SD, or median (interquartile range). BMI indicates body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; eGFR, estimated glomerular filtration rate; and NA, not available.

*Standardized mean differences (SMDs) are presented for chronic kidney disease (CKD) compared with no CKD.

1 child (2.0%, *P*=0.832) had an eGFR of 42 mL/min per 1.73 m^2 (CKD stage 3b; this was the same child who had an eGFR of 51 mL/min per 1.73 m^2 at the kidney assessment visit). Apart from this one child, none of the patients were in nephrology follow-up.

DISCUSSION

In this cohort study, 66 children with CHD who had developed AKI after cardiac surgery underwent a formal kidney assessment 5 years after the index event (Figure 3). Our findings at 5-year follow-up revealed that 59.1% of patients had at least 1 marker of kidney injury, including reduced kidney function (eGFR <90 mL/min per 1.73 m^2) in 13.6%, proteinuria in 0.9%, α_1-microglobinuria in 7.6%, hypertension in 19.7%, and abnormalities on kidney ultrasound in 13.6%. CKD stages 1 to 5, defined as eGFR <90 mL/min per 1.73 m^2 or eGFR 90 mL/min per 1.73 m^2 to 100 mL/min per 1.73 m^2 with laboratory/ultrasound abnormalities, was present in 18 (27.3%). Kidney function measurements obtained in 49 children 13 years after the index event revealed overall ongoing kidney function deterioration and suggested an average eGFR decline rate of −1.8 mL/min per 1.73 m^2 per year. These results show that persistent markers of kidney injury are common after postoperative AKI in children with CHD and warrant the initiation of structured kidney follow-up in this patient population.

Kidney Function and CKD

A number of studies have examined kidney outcomes during follow-up of children who developed AKI after pediatric cardiac surgery.[3–7] Most of these have focused on the prevalence of CKD at variable lengths of follow-up and using different definitions. In a population of children undergoing heart transplantation, Hollander et al[4] reported a 6- and 12-month prevalence of CKD stages 3 to 5 (eGFR <60 mL/min per 1.73 m^2) of 5% and 6% of patients, respectively. At a median of 1 year after AKI during the Fontan completion, CKD (defined in this study as eGFR <80 mL/min per 1.73 m^2) was observed in 11%

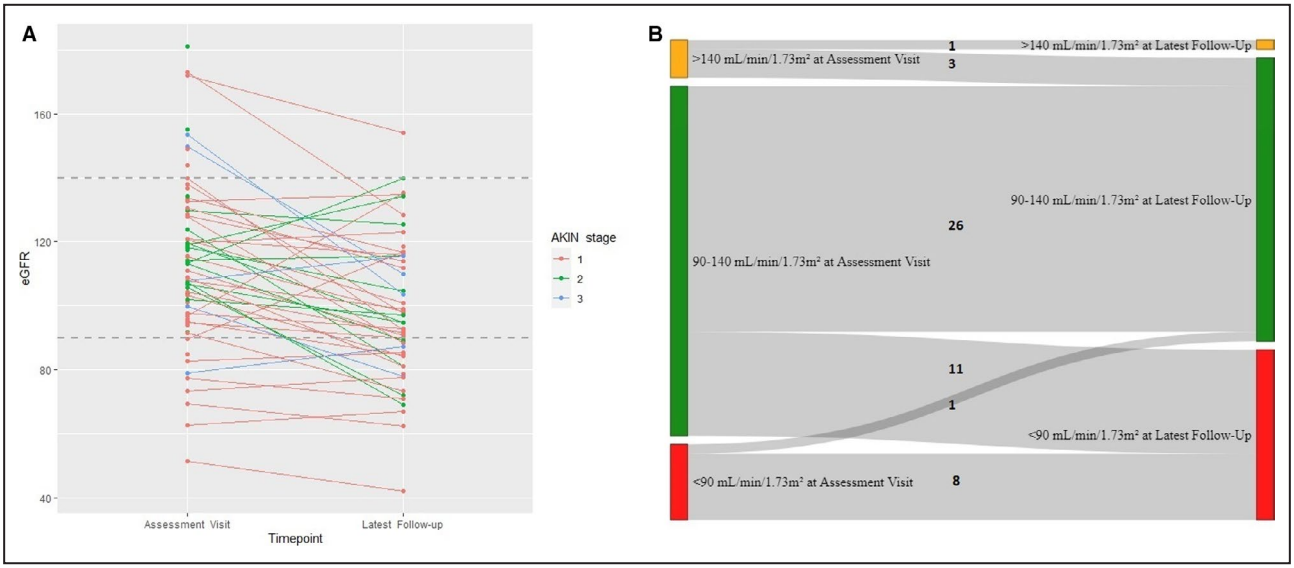

Figure 2. Change in kidney function between kidney assessment visit (5-year follow-up) and latest follow-up (>10-year follow-up).

A, Line graph showing estimated glomerular filtration rate (eGFR; in mL/min per 1.73 m²) at each timepoint. Globally, a progressive decline in kidney function was observed from 114±25 mL/min per 1.73 m² at the kidney assessment visit to 99±23 mL/min per 1.73 m² at latest follow-up (*P*=0.001). **B**, Sankey diagram showing transition in kidney function class between both timepoints. A total of 11 of 49 patients (22.4%) who had normal kidney function at the assessment visit eventually developed kidney dysfunction. AKI indicates acute kidney injury.

of the cohort by Esch et al.[5] In the multicenter TRIBE-AKI (Translational Research Investigating Biomarker Endpoints in AKI) study,[7] 6% of children with AKI had CKD stages 2 to 5 (<90 mL/min per 1.73 m²) at 5-year follow-up. Using Danish regional population-based registries, Madsen et al[3] found that CKD stages 2 to 5 (eGFR <90 mL/min per 1.73 m²) occurred in 14% of patients at 5 years after AKI following surgery for CHD. Finally, Huynh et al[6] evaluated children 6 years after neonatal cardiac surgery and found CKD (defined as eGFR <90 mL/min per 1.73 m² or albumin/creatinine ≥3 mg/mmol) in 9.5% of patients. The prevalence of CKD stages 2 to 5 (eGFR<90 mL/min per 1.73 m²) in our study (13.6%, 9 of 66 at 5-year follow-up) is in line with these prior investigations. In contrast, however, the comprehensive assessment in our study also allowed us to consider CKD stage 1 (eGFR 90–100 mL/min per 1.73 m² with abnormalities on kidney ultrasound or biochemistry), showing an even greater overall burden of CKD (27.3%, 18 of 66).

Notably, a relatively high proportion of children with hyperfiltration was observed in our study (12.1%). Following the early landmark experimental studies by Brenner and colleagues,[21] hyperfiltration became recognized as a mechanism where the loss of functional nephrons leads to maladaptive hemodynamic changes, which increase glomerular capillary pressure and elevate single-nephron glomerular filtration rate. This has been observed in diabetes, solitary or remnant kidneys, and various forms of acquired kidney disease. Similarly, it has been suggested by Greenberg et al[7] that children may develop absolute or relative hyperfiltration in response to AKI, thus initially "masking" the injury. In support of this idea, Cooper et al[8] revealed that biomarkers of kidney injury such as interleukin 18 and liver-type fatty acid–binding protein remained elevated 7 years after AKI even in the absence of conventional evidence of CKD. This might explain why most previous studies (with length of follow-up of ≤7 years) in children with CHD could not reveal an association of AKI with the development of CKD,[5–8] while studies in adults have established AKI as a risk factor for CKD with much shorter follow-up.[2]

Further expanding on these observations, our study revealed a progressive decline in eGFR between 5 and 13 years of follow-up in our study. During this period, the group with hyperfiltration decreased (from 12.1% to 2.0%) and the group with CKD stages 2 to 5 increased (from 13.6% to 36.7%). Interestingly, the latter percentage is closer to the 30% to 50% reported in ACHD.[12] Taken together, these results suggest that the excess burden of CKD in ACHD might already start in childhood. While initially masked by hyperfiltration, kidney injury progresses and eventually becomes evident later (in adolescence or adulthood).

Hypertension and Proteinuria

The prevalence of hypertension in our study (19.7%) was comparable to that found in the multicenter TRIBE-AKI study[7] (16.8%) and single-center FRAIL-AKI (Follow-Up Renal Assessment of Injury Long-Term After Acute Kidney Injury) study[8] (17.6%). This is ≈5-fold higher than

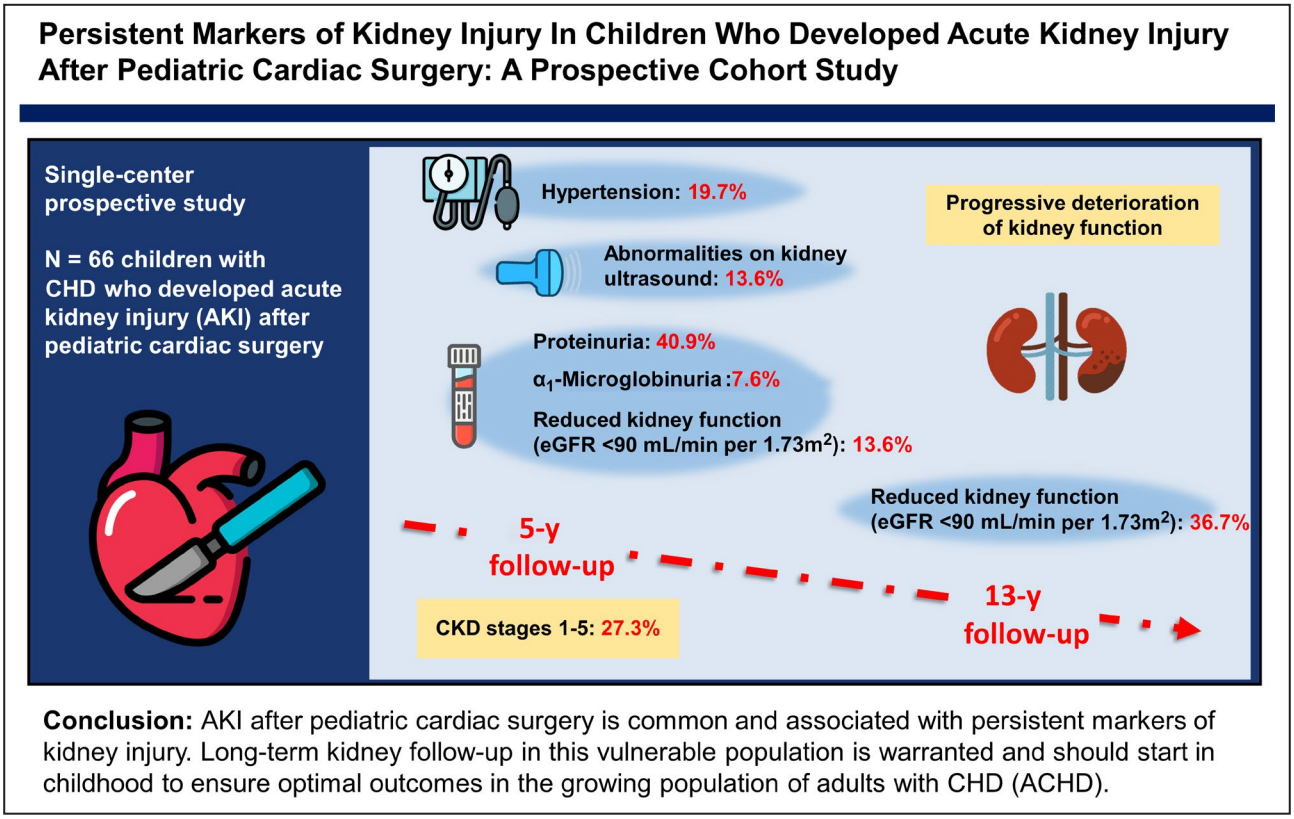

Figure 3. Graphical representation of the main study results.
In this cohort study, 66 children with congenital heart disease (CHD) who had developed acute kidney injury (AKI) after pediatric surgery underwent a formal kidney assessment 5 years after the index event. Our findings revealed that reduced kidney function (estimated glomerular filtration rate [eGFR] <90 mL/min per 1.73 m²) was present in 9 patients (13.6%), proteinuria in 27 patients (40.9%), α_1-microglobinuria in 5 patients (7.6%), hypertension in 13 patients (19.7%), abnormalities on kidney ultrasound in 9 patients (13.6%), and chronic kidney disease (CKD) in 18 patients (27.3%). Occasional eGFR measurements obtained in 49 children 13 years after the index event revealed ongoing kidney function deterioration. These results suggest that persistent markers of kidney injury are common after postoperative AKI in children with CHD and warrant the initiation of structured kidney follow-up in this patient population.

the prevalence in children of the same age in the general population (4.3%).[22] While hypertension is a common presentation of (re)coarctation of the aorta,[23] only 2 of 5 children with coarctation in our cohort were hypertensive. The cause of hypertension was most likely multifactorial, including enhanced sympathetic activity and upregulation of other neurohormonal pathways,[24] in addition to underlying CKD.

Proteinuria has been previously reported in CHD and has been associated mainly with cyanotic CHD, Fontan circulation, shunts lesions complicated by pulmonary hypertension, and conditions with a systemic right ventricle.[25] The pathophysiology might include cyanosis, erythrocytosis, limited perfusion, and kidney congestion. Notably, albuminuria is associated with major adverse outcomes in ACHD.[26] We demonstrated that even α_1-microglobulinuria is seen in 7.6%, which suggests an associated proximal tubular dysfunction.[27] The present study revealed that both abnormalities may already be present in childhood.

Cause of Kidney Injury Following Pediatric Cardiac Surgery

One potential explanation for the presence of CKD in this population is persistent damage after AKI resulting from aortic clamping or hemodynamic imbalances during cardiopulmonary bypass.[28] However, we did not observe any differences in cardiopulmonary bypass or cross clamp time in those who developed CKD and those who did not. Although not measured in this study, cardiopulmonary bypass can lead to fluid shifts, increased blood vessel permeability, and depressed myocardial contractility, resulting in fluid overload.[29] The latter has been demonstrated to be a factor that may incite and worsen AKI, but can also independently affect morbidity and mortality.[30] Strikingly, there were also no differences in kidney outcomes between AKIN stages in our study, in contrast to adult studies where the risk of CKD increased in a graded fashion when AKI was more severe.[2] While the hyperfiltration theory

might help explain why such relationships between AKI and CKD are only observed at an older age, it should also be considered that several other factors, apart from the index AKI episode, can contribute to the kidney phenotype in children with CHD. In our study, a significant association of CKD with syndromic diagnoses was revealed. It is known that certain mutations underlying syndromes such as trisomy 21 and 22q11.2 microdeletions might lead to both CHD and dysfunction of other organs.[31] Of note, 5 of 6 patients (83.3%) with trisomy 21 and 1 of 4 patients (25%) with 22q11.2 microdeletions in our cohort had CKD. Studies have identified genetic links between birth defects of the kidney and CHD.[32]

Furthermore, CHD itself can alter hemodynamics and put pressure on the kidneys, both preoperatively (eg, ischemic hit in neonates with coarctation) and postoperatively (eg, venous congestion after Fontan completion). In the cohort by Huynh et al,[6] cyanosis postoperatively was the only independent predictor of kidney dysfunction, while Esch et al[5] reported that 25% of patients already had kidney dysfunction before Fontan completion. In addition, several studies have described a "cyanotic nephropathy" characterized by proteinuria.[33] Venous congestion, as seen in patients with univentricular hearts or those with pulmonary hypertension, atrial fibrillation, neurohormonal activation, endothelial dysfunction, and drug and procedure toxicity among others, have all been related to kidney dysfunction in both acquired and congenital cardiovascular diseases.[34] Univentricular heart defects were 2-fold more common among patients with CKD in our cohort (38.9% in patients with CKD versus 18.8% in patients with no CKD). Finally, also intermittent catheterizations (using potentially nephrotoxic contrast agents) and surgical interventions (other than the index surgery) might contribute to progressive kidney function decline.

The finding that persistent markers of kidney injury are common in patients who developed AKI after pediatric cardiac surgery does not necessarily imply that these observations are entirely attributable to the effect of AKI alone. This is an important consideration, because a causal relationship between AKI and CKD progression cannot be directly inferred from our study, as suggested above. In fact, prior studies in children have been unable to consistently demonstrate such a relationship in the pediatric population.[3–8] There might be several reasons for why this is different from findings in adults,[2] including adaptive capacities of the kidneys in children (cfr. hyperfiltration) and the need for relatively longer follow-up to find a significant effect, or the possibility that other factors might play a more important role in driving kidney injury in these patients. Regardless of this discussion, our findings clearly demonstrate the large extent of kidney disease in this vulnerable population. Therefore, arguably more important than trying to tease out the exact contribution that AKI has in CKD progression, we should strive towards a better overall understanding of context wherein these patients find themselves at elevated risk of poor kidney health. AKI might only be one episodic piece of the puzzle that drives kidney injury in these patients, along with various other factors along the lifespan.

Need for Structured Kidney Follow-Up in Children With CHD

Except for one, none of the children in our cohort were seen or followed up by a nephrologist, despite sometimes clear kidney function deterioration in early adolescence. Detection and treatment of CKD, proteinuria, and hypertension in children is critical because these are risk factors for cardiovascular diseases and progressive kidney damage in adults.[35,36] Patients with CHD are at especially high risk for long-term cardiac events, and the superposition of comorbidities such as coronary artery disease, diabetes, smoking, and hypertension in adulthood leads to an excess of health care utilization in ACHD.[13] This study, showing progressive kidney injury arising as early as in childhood, highlights the need for long-term and structured kidney follow-up after pediatric cardiac surgery in general and following AKI in particular.[37] During nephrology visits, patients and families should be educated about kidney dysfunction and its risk factors, lifestyle changes should be discussed, medications should be reviewed, and screening along with timely initiation of treatment should be pursued. The ideal window of opportunity is in the pediatric cardiology practice, ie, before any decline in kidney function, but optimization of the transition from pediatric cardiology to ACHD will be at least equally essential to ensure continuity of care.[38] With the emergence of novel, more sensitive biomarkers such as cystatin C and neutrophil gelatinase-associated lipocalin, detection and monitoring of kidney injury as well as personalized approaches to the prevention and treatment of kidney dysfunction will become available.[39,40]

Supporting the effectiveness of structured kidney follow-up, a study by Harel et al[41] demonstrated that mortality can be reduced if adult survivors of severe AKI are seen by a nephrologist within 90 days of discharge (8.4 versus 10.6 per 100 patient-years). Translating these insights into a coordinated care model, Ly et al[42] reported their piloting experience with the implementation of AKI clinics and similarly found reductions in rehospitalizations, morbidity, and mortality. Certainly, these studies pave the way for a more integrated approach towards AKI. In a similar manner, our present study proposes the need for a lifespan approach to kidney health for those who underwent cardiac surgery

in childhood. This is in line with a growing understanding that CHD is never cured or reversed, but requires a lifetime of treatment and careful monitoring.[43]

Limitations

It should be noted that this study was performed in a select population of patients with AKI after cardiac surgery with extracorporeal circulation, which is not necessarily representative of the whole CHD population. Only 25% of all people living with CHD undergo surgery in childhood,[44] and caution should be made in the extrapolation of our results. Of note, the number of CHD surgeries was higher in the patients included in the formal kidney assessment compared with those who were not. As a second limitation, we did not include a control group without AKI such that the exact contribution of AKI to kidney dysfunction could not be estimated; this was, however, not the main focus of the present study and has been investigated by other studies, as discussed above.[3–8] Furthermore, no direct relationship between the kidney phenotype and the index surgery can be assumed, as most children underwent other surgeries, interventions, and cardiac catheterizations. The subgroup analyses should also be interpreted with caution, given limitations in statistical power.

CONCLUSIONS

This study revealed that AKI after pediatric cardiac surgery in children with CHD is common and that persistent and progressive markers of kidney injury are present in these children at mid- and long-term follow-up. Especially those with syndromes or univentricular physiology might be at risk. As the data on long-term kidney follow-up in children with CHD are scarce, no current recommendations are available regarding the follow-up of CKD, proteinuria, and hypertension. Based on our findings, we suggest a structured kidney follow-up in this vulnerable population and recommend that prevention of kidney disease should start in childhood to ensure optimal outcomes in the growing population of ACHD.

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