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Long-term consequences of acute kidney injury after pediatric cardiac surgery: A systematic review

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Objective The objective of this study was to evaluate the available data on long-term kidney dysfunction, hypertension, and mortality after cardiac surgery–associated acute kidney injury (AKI) in the pediatric population.

Study design PubMed/MEDLINE, Embase, Scopus, and reference lists of relevant articles were searched for eligible studies published from inception through March 2022. Long-term outcomes after pediatric cardiac surgery complicated by AKI and those without were investigated.

Results We identified 14 studies published between 2013 and 2022 that included a total of 6701 patients (AKI: 1376 patients; no AKI: 5325 patients). These studies used different well-established classifications to define AKI. All the studies suggested that AKI after heart surgery is common in the pediatric patient population and reported a potential link between cardiac surgery–associated AKI and important clinical outcomes. However, only 4 out of 11 studies found a strong association between (absence of recovery from) cardiac surgery–associated AKI and risk of developing chronic kidney disease, and 3 out of 5 studies found a significant increase in mortality rates for pediatric patients who developed AKI after cardiac surgery. Only 1 out of 4 studies found an association between AKI and hypertension at 12 months postoperatively, but found no association at later follow-up times.

Conclusions Although there is a trend, evidence on the long-term consequences of cardiac surgery-associated AKI in the pediatric population is mixed. Genetic syndromes, preexisting kidney disease, univentricular or cyanotic heart conditions, and/or high-complexity surgery may be more important for the development of kidney dysfunction by adolescence and early adulthood. Regardless, these children may benefit from a long-term kidney follow-up. *(J Pediatr 2022;■:1-10)*.

Cardiac surgery–associated acute kidney injury (AKI) is associated with increased morbidity and mortality in both adults and children.[1,2] When compared with adults, pediatric kidney physiology differs with respect to kidney vasculature, maturity of the kidneys, and the impact of systemic processes such as inflammation and coagulation.[3] Consequently, the pace and extent at which AKI recovery occur may be different in pediatric patients. Knowledge about long-term consequences of AKI is essential in order to establish effective follow-up and preventive strategies for this patient population.[4]

Several observational studies have been conducted to investigate the long-term outcomes of cardiac surgery–associated AKI in children. The present systematic review aimed to summarize the current evidence regarding long-term outcomes of AKI following cardiac surgery in the pediatric population.

Methods

We followed the PRISMA[5] guidelines for the conduction and reporting of this systematic review (PROSPERO Registration CRD42022348545). Studies were included if the population consisted of pediatric patients, patients underwent

AKI	Acute kidney injury	pRIFLE	Pediatric RIFLE
AKIN	Acute Kidney Injury Network	RACHS-1	Risk Adjustment in Congenital Heart Surgery Surgical Severity Score
CHD	Congenital heart disease		
CKD	Chronic kidney disease		
eGFR	Estimated glomerular filtration rate	RIFLE	Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease
ESKD	End-stage kidney disease		
GFR	Glomerular filtration rate		
HR	Hazard ratio		
IL-18	interleukin 18	SCr	Serum creatinine
KDIGO	Kidney Disease Improving Global Outcomes		

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cardiac surgery, long-term outcomes (>1 year of follow-up) were analyzed according to the presence of cardiac surgery-associated AKI, and studies were prospective or retrospective observational studies or randomized controlled trials. Exclusion criteria were adult population, noncardiac surgery, or data not available for AKI and no AKI separately.

Databases were searched for articles meeting our inclusion criteria and published from inception through March 19, 2022: PubMed/MEDLINE, Embase, Scopus, and reference lists of relevant articles. The detailed search terms that were used for this search are given in **Appendix** (available at www.jpeds.com). The following steps were taken: (1) identification of titles of records through databases searching, (2) removal of duplicates, (3) screening and selection of abstracts, (4) assessment for eligibility through full-text articles, and (5) final inclusion in the study. Studies were selected by 2 independent reviewers. When concordance was absent, a third reviewer took the decision to include or exclude the study.

Data Items

The outcomes considered in this systematic review included long-term kidney dysfunction, hypertension, and long-term mortality. From each study, we extracted first authors' name, year of publication, country of origin, study design, years of enrollment, sample size, AKI incidence, definition of AKI, and mean or median age. Risk of bias of the selected studies was assessed using the Cochrane Risk of Bias in Nonrandomized Studies of Interventions tool.

Three main definitions for AKI currently exist. First, the Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease (RIFLE) classification was published by the Acute Dialysis Quality Initiative in 2004.[6] Staging in this classification is based on changes from baseline serum creatinine (SCr) or glomerular filtration rate (GFR) within 7 days. This classification has been modified for children in the pediatric RIFLE (pRIFLE) classification, adding estimated creatinine clearance.[7] Another modification of the RIFLE classification has led to the AKI Network (AKIN) criteria, which focuses on dynamic changes in creatinine.[8] Contrary to RIFLE, AKIN does not use premorbid baseline SCr, but the lowest SCr within a 48-hour period, as the reference SCr for calculations of absolute and relative increase in SCr values. The AKIN criteria also avoid the use of creatinine clearance. The third and last modification is the Kidney Disease Improving Global Outcomes (KDIGO) classification, which covers both the AKIN and RIFLE criteria.[9] This new classification combines the 1.5-fold relative increase in SCr and urine output over 7 days from the RIFLE criteria with the absolute increase in SCr of 0.30 mg/dL over the rolling 48-hour window from AKIN. Urine output criteria are common to all 3 classifications.

Results

A total of 2826 citations were identified; of which, 21 studies were potentially relevant and retrieved as full text. Fourteen publications fulfilled our eligibility criteria (**Figure 1**; available at www.jpeds.com). Study characteristics are shown in **Table I**. Patient and surgery characteristics are presented in **Tables II** and **III** (available at www.jpeds.com). We identified 14 studies published between 2013 and 2022 that included a total of 6701 patients (AKI: 1376 patients; no AKI: 5325 patients). All studies were nonrandomized observational studies, including 5 prospective multicenter studies, 4 prospective single-center studies, 1 retrospective multicenter study, and 4 retrospective single-center studies. The pooled mean age of participants at the AKI episode was 32.4 months. The population included a heterogeneous mix of congenital heart disease (CHD) and cardiomyopathies undergoing a range of procedure (**Tables II** and **III**). The pRIFLE criteria[7] were used for AKI diagnosis in 2 studies, 6 studies used the KDIGO guidelines,[9] and 6 studies used the AKIN criteria.[8] The overall internal validity of the analysis was considered moderate risk of bias (**Figure 2**; available at www.jpeds.com).

Synthesis of Results

Long-Term Kidney Dysfunction. Eleven studies compared the risk of long-term kidney dysfunction between patients who developed AKI following pediatric cardiac surgery and those who did not (**Table IV**). Definitions for chronic kidney disease (CKD) or kidney dysfunction are listed in **Table IV**, with all 11 studies using estimated glomerular filtration rate (eGFR; <90 mL/min/1.73 m^2 in 7 studies, <80, <60, and <15 mL/min/1.73 m^2 each in 1 study, and age-specific cutoffs in 1 study) and 5 studies using microalbuminuria (defined as microalbumin-to-creatinine ratio >30 μg/mg in 4 studies and age-specific cutoffs in 1 study). Three studies revealed a significantly higher risk for CKD development in patients who experienced cardiac surgery-associated AKI than in patients without cardiac surgery-associated AKI,[17,18,23] and another study demonstrated an association of absence of AKI recovery with long-term kidney outcomes.[15] The other studies could not show such associations.

Madsen et al[17] conducted a prospective cohort study of 382 children (ages 0-14 months) with CHD; of which, 33.2% developed cardiac surgery–associated AKI. After a median follow-up of 4.9 years, 14 patients (11%) with cardiac surgery–associated AKI progressed to CKD (eGFR <90 mL/min/1.73 m^2), compared with only 6 patients (2%) without cardiac surgery–associated AKI (hazard ratio [HR] 3.8, 95% CI 1.4-10.4). In addition, they found that the risk of developing CKD remained elevated even among the 94 children with renal recovery, defined as documented normalization of their SCr to levels in range of their pre-CS baseline between >5 days and <90 days post-CS (HR 3.5, 95% CI 1.2-9.8). In a recent prospective study, Van den Eynde et al[23] assessed the persistent markers of kidney injury in children who underwent cardiac surgery and developed cardiac surgery–associated AKI (median age 2.9 years). The authors included 571 patients who were operated over a 4-year period, where AKI occurred in 113 children (19.8%). At a

Table I. Characteristics of the included studies

Study (y)	Country of origin	Study design	Y of enrollment	Sample size	AKI incidence	Definition of AKI
Morgan (2013)[10]	Canada	P, NR, M	2002-2009	264	64.4%	AKIN
Watkins (2014)[11]	USA	NP, NR, NM	2004-2006	711	49.5%	pRIFLE (stage F)
Esch (2015)[12]	USA	NP, NR, NM	2003-2009	211	42.2%	AKIN
Cooper (2016)[13]	USA	P, NR, NM	2004-2007	51	64.7%	KDIGO (pRIFLE for AKI severity stratification)
Greenberg (2016)[14]	Canada/USA	P, NR, M	2007-2009	131	44%	AKIN
Hollander (2016)[15]	USA	NP, NR, NM	2007-2013	88	71.6%	KDIGO
Hirano (2017)[16]	Japan	NP, NR, NM	2007-2013	418	24.9%	pRIFLE
Madsen (2017)[17]	Denmark	P, NR, M	2005-2010	382	33%	KDIGO
Parikh (2019)[18]	Canada	NP, NR, M	2002-2015	3600	4%	AKIN
Huynh (2020)[19]	Canada	P, NR, M	2005-2012	58	57%	KDIGO
Zappitelli (2020)[20]	Canada/USA	P, NR, M	2010-2012	124	46%	KDIGO
Fredric (2021)[21]	Canada	P, NR, NM	2007-2009	23	35%	AKIN
Sethi (2021)[22]	India	P, NR, NM	2010-2017	93	9.8%*	KDIGO
Van den Eynde (2022)[23]	Belgium	P, NR, NM	2004-2008	547	19.7%	AKIN

M, multicenter; *NM,* single-center; *NP,* retrospective; *NR,* nonrandomized; *P,* prospective; *R,* randomized.
*These represent data from the full cohort (n = 2035); only 44 cases and 49 controls were included in the long-term study.

median follow-up of 4.8 years, 66 patients were studied. Thirty-nine (59%) had at least 1 marker of kidney injury, including eGFR, proteinuria, alpha-1-microglobinuria, hypertension, and abnormalities detected on kidney ultrasound. Interestingly, at the 13.1-year follow-up, reduced eGFR (<90 mL/min/1.73 m^2) was present in 36.7% of patients. The relevance of this study lies in its demonstration that established markers of kidney injury are common among children who developed cardiac surgery–associated AKI. It also shed a light on the persistently worsening nature of kidney disease in the years following the event. Interestingly, however, the authors acknowledged that AKI might not be the single most important risk factor: both genetic syndromes (55.6% vs 20.8%, $P = .015$) and univentricular heart conditions (38.9% vs 18.8%, $P = .089$) were more common among those with CKD at follow-up.

In a retrospective cohort by Hollander et al[15] of 88 children undergoing heart transplantation (median age 6.3 years), 71.6% developed cardiac surgery–associated AKI, a rate that is higher than most other types of CHD surgery. At the 12-month follow-up, no significant difference was found in CKD (eGFR <60 mL/min/1.73 m^2) incidence between patients who developed AKI postoperatively and those who did not (6% vs 5%, $P = .9$). However, CKD was significantly more common in the 17 patients who did not recover from AKI (18% vs 0%, $P = .03$) and recovery from AKI was less common in patients with moderate to severe AKI (50% vs 78%, $P = .04$). In a retrospective study of 3600 children who had undergone cardiac surgery within the first 10 years of birth (median age 0.41 years), Parikh et al[18] found that those who received dialysis for cardiac surgery–associated AKI during their index surgery admission were at a 5-fold higher risk of developing end-stage kidney disease (ESKD) (eGFR <15 mL/min/1.73 m^2) than those who did not receive dialysis (HR 5.0; 95% CI, 2.0 to 12.6). Furthermore, the authors found that patients undergoing surgery for hypoplastic left heart syndrome had a higher risk for developing ESKD, consistent with the findings by Van den Eynde et al.[23]

Five studies found no association between cardiac surgery–associated AKI and long-term CKD development.[12,13,19,20,22] Esch et al[12] conducted a retrospective cohort study including 211 patients who underwent Fontan completion (median age 2.7 years). After a median follow-up of 373 days, kidney dysfunction (eGFR <80 mL/min/1.73 m^2) was not significantly associated with presence nor degree of postoperative AKI ($P = .290$). In contrast, pre-Fontan kidney dysfunction was significantly associated with kidney dysfunction at follow-up ($P = .017$). In line with this, Sethi et al[22] compared 44 children who had postoperative cardiac surgery–associated AKI with 49 controls (median age 6.5 months) and showed that neither the presence of AKI nor AKI stage was significantly associated with low eGFR (<90 mL/min/1.73 m^2) at a median follow-up of 41 months. On the other hand, higher surgical complexity, as reflected by Risk Adjustment in Congenital Heart Surgery Surgical Severity Score (RACHS-1), was associated with lower eGFR at follow-up. Similar findings were presented by Huynh et al[19] who performed a prospective cohort study to evaluate the long-term outcomes of neonatal heart disease repair (median age 10 days). After a median of 6 years of follow-up, CKD (eGFR <15 mL/min/1.73 m^2 or microalbuminuria) was observed in 9 neonates (17%) and was not found to be significantly associated with cardiac surgery–associated AKI. On the other hand, higher RACHS-1 score ($P = .04$) and preoperative cyanosis ($P < .001$) were significantly associated with CKD at follow-up. Similarly, in the ASsessment, Serial Evaluation, and Subsequent Sequelae in AKI study, Zappitelli et al[20] investigated 124 participants (median age 27 months) and showed that from the 3- to 48-month follow-up, AKI was not significantly associated with development of CKD (low eGFR or microalbuminuria for age, according to KDIGO criteria). These results are also supported by Cooper et al[13] in the Follow-up Renal Assessment of Injury Long-term after AKI study in which they compared kidney findings in 51 children (median age 6.4 months at the time of surgery) at a mean follow-up of

Table IV. Summary of outcomes in studies reporting on long-term kidney dysfunction

Study (y)	AKI	No AKI	Follow-up, y	Definition of CKD or kidney dysfunction	Findings
Esch (2015)[12]	89	122	1.02	eGFR <80 mL/min/1.73 m^2	Kidney dysfunction occurred in 16 patients (8%) of the overall cohort. There was no significant association between kidney dysfunction and either presence or degree of postoperative AKI ($P = .29$).
Cooper (2016)[13]	33	18	7	eGFR <90 mL/min/1.73 m^2 or microalbuminuria	eGFR, proteinuria and blood pressure were normal and similar between patient groups. In contrast, urinary IL-18 ($P = .01$), NGAL ($P = .01$) and L-FABP ($P = .001$) were significantly higher in the AKI group.
Greenberg (2016)[14]	57	74	5	eGFR <90 mL/min/1.73 m^2 or microalbuminuria	AKI patients had a significantly ($P < .001$) lower incidence of CKD (6%) compared to patients without AKI (27%).
Hollander (2016)[15]	63	25	1	eGFR <60 mL/min/1.73 m^2 for >3 months	There was no significant difference ($P = .9$) in CKD incidence between AKI patients (6%) and non-AKI patients (5%). Incidence of CKD was significantly higher in the 17 patients who did not recover from AKI (18% vs 0%, $P = .03$).
Madsen (2017)[17]	127	255	4	eGFR <90 mL/min/1.73 m^2 for 2 or more SCr measures >90 days post-surgery without a normal value in the interim	AKI patients had a significantly higher incidence of developing CKD (11%) than patients who did not develop AKI (2%) (HR 3.8, 95% CI 1.4-10.4).
Parikh (2019)[18]	126	3474	13	End-stage kidney disease (eGFR <15 mL/min/1.73 m^2 or dialysis)	Children who received dialysis for AKI during their index surgery admission tended to have a 5-fold higher risk of mortality when compared to those who did not receive dialysis, although this was not statistically significant (HR 5.0, 95% CI, 2.0 to 12.6).
Huynh (2020)[19]	33	25	6.3	eGFR <90 mL/min/1.73 m^2 or microalbuminuria	Overall CKD prevalence was 17% and was not significantly associated with AKI.
Zappitelli (2020)[20]	57	67	4	Low eGFR or microalbuminuria for age, according to KDIGO criteria	AKI was not significantly associated with the development of CKD throughout follow-up.
Fredric (2021)[21]	8	15	9	eGFR <90 ml/min/1.73 m^2 or microalbuminuria	A total of 5 participants in the no AKI (33%) group developed CKD, compared to none in the AKI (0%) ($P = .065$)
Sethi (2021)[22]	44	49	3.4	eGFR <90 ml/min/1.73 m^2	Neither the presence of AKI nor AKI stage was associated with CKD
Van den Eynde (2022)[23]	113	434	4.8	eGFR <90 ml/min/1.73 m^2, proteinuria, α 1-microglobinuria, abnormalities on kidney ultrasound, hypertension	Children who developed AKI after heart surgery had persistent markers of kidney injury.

BP, blood pressure; *IL-18*, interleukin 18; *KIM-1*, kidney injury molecule-1; *L-FABP*, liver-type fatty acid–binding protein; *NGAL*, neutrophil gelatinase–associated lipocalin.

7 years after undergoing cardiopulmonary bypass. They found normal measurements of eGFR and proteinuria in patients with and without cardiac surgery–associated AKI. However, even though these conventional measures of CKD were unaffected, increased levels of the novel biomarkers interleukin 18 (IL-18, $P = .01$), neutrophil gelatinase–associated lipocalin ($P = .01$), and liver-type fatty acid–binding protein ($P = .001$) were significantly higher in the AKI group. Collectively, these studies seem to suggest that cardiac surgery–associated AKI may not be a definitive predictor of CKD and that other causes such as RACHS-1 score, genetic syndromes, preexisting kidney dysfunction, and cyanotic heart disease may be relatively more important. Nonetheless, AKI seems to cause kidney injury—as evidenced by persistently elevated markers—which may eventually in the long-term result in clinically evident CKD.

Two studies found a seemingly paradoxical lower rate of CKD in the AKI group. In a prospective cohort of 23 children (median age 24 months), Fredric et al[21] found that 35% developed postoperative AKI at the time of index surgery. Interestingly, a total of 5 out of 15 participants in the no-AKI (33%) group developed CKD (eGFR <90 mL/min/1.73 m^2 or microalbuminuria), compared with 0 out of 8 in the AKI (0%) ($P = .065$). This trend was confirmed in the Translational Research Investigating Biomarker Endpoints in AKI study. In this study, Greenberg et al[14] analyzed a prospective cohort of 131 pediatric patients who underwent cardiopulmonary bypass. Patients without AKI were more likely to have CKD (eGFR <90 mL/min/1.73 m^2 or microalbuminuria) after a 5-year follow-up (27% vs 6%, $P < .001$). The authors determined that these children also had an abnormal eGFR prior to cardiac surgery. Furthermore, they suggested that the superior kidney regenerative potential and the tendency toward hyperfiltration in response to nephron injury in children might help explain why no association between AKI and kidney outcomes was observed.

Hypertension

Four studies compared the risk of long-term hypertension between patients who developed AKI following pediatric cardiac surgery and those who did not (Table V). All studies defined hypertension as systolic or diastolic blood pressure ≥95th percentile for age, sex, and height, or above adolescent and adult blood pressure thresholds, as

Table V. Summary of outcomes in studies reporting on hypertension

Study (y)	AKI	No AKI	Follow-up, y	Findings
Greenberg (2016)[14]	57	74	5	Hypertension occurred in 17% at 5 y after pediatric cardiac surgery; in 11% of children with AKI compared to 22% in those without AKI ($P = .09$).
Zappitelli (2020)[20]	57	67	4	AKI was associated with hypertension development at 12 months after discharge (aRR 2.16; 95% CI 1.18-3.95), but not at subsequent visits.
Fredric (2021)[21]	8	15	9	At 9-y follow-up ambulatory blood pressure monitoring was feasible for all patients. A total of 6 participants in the no AKI (33%) group developed hypertension, compared to none in the AKI (0%) ($P = .037$).
Van den Eynde (2022)[23]	113	434	4.8	Hypertension was detected in 19.7% of patients, however, there was no difference between AKIN stages with regard to hypertension.

aRR, adjusted relative risk.

appropriate, or taking antihypertensive therapy. The study by Zappitelli et al[20] was the only one demonstrating a significant association between cardiac surgery–associated AKI and the development of hypertension at 12 months after discharge (adjusted relative risk 2.16, 95% CI 1.18-23.95), but failed to demonstrate such association between 12 and 48 months of follow-up. None of the other studies could establish a clear association. Van den Eynde et al[23] determined that hypertension was present in 19.7% of children who developed cardiac surgery–associated AKI; however, they found no differences across AKIN stages and did not include a control group without AKI. Again somewhat paradoxically, Fredric et al[21] found that 6 out of 15 participants in the no-AKI (33%) group developed hypertension, compared with 0 out of 8 in the AKI (0%) ($P = .037$). A similar trend was observed in the Translational Research Investigating Biomarker Endpoints in AKI study by Greenberg et al,[14] where hypertension was present in 11% of children with AKI compared with 22% in those without AKI ($P = .09$).

Long-Term Mortality

Five studies compared the long-term mortality rates between patients who developed cardiac surgery–associated AKI and those who did not (Table VI). All studies showed at least a trend toward higher long-term mortality rates in patients who developed cardiac surgery–associated AKI. However, only 1 study reported a significant difference between any stage of AKI and no AKI.[16] Two studies revealed an association with long-term mortality only in the highest stages of AKI.[10,11] Finally, 2 studies could not find an association between AKI and long-term mortality.[15,18]

A retrospective study by Hirano et al[16] investigated 2-year outcomes of AKI in 418 pediatric patients who underwent cardiac surgery (median age 5.5 months). The 2-year mortality rate was significantly higher in patients who developed

Table VI. Summary of outcomes in studies reporting on long-term mortality

Study (y)	AKI	No AKI	Follow-up, y	Mortality, %	Findings
Morgan (2013)[10]	170	94	2	AKI: 10.0% No AKI: 4.3%	Patients were divided in groups according to AKIN stage. At every stage of AKI, mortality rates were higher than in the non-AKI group. Only for AKIN stage 3, mortality rates were significantly elevated (HR 7.34, 95% CI 1.63-33.4, $P = .01$). In AKIN stage 3, 9 out of 42 patients (21.4%) died.
Watkins (2014)[11]	352	359	4.02	Overall: 11.4%	Mortality risk was significantly increased for patients with AKI (as defined by pRIFLE stage F) compared to those without AKI (HR 3.82, 95% CI 1.89-7.75, $P < .001$). Withdrawal of support including ECMO was the lead death cause (40.0%), followed by cardiac failure (30.8%) and respiratory processes including pneumonia and aspiration (9.2%).
Hollander (2016)[15]	63	25	2.7	AKI: 19% No AKI: 16%	There were no significant differences in mortality between patient groups ($P = .8$).
Hirano (2017)[16]	104	314	2	AKI: 22% No AKI: 3%	The 2-y mortality rate was significantly higher in patients who developed AKI compared to those who did not (HR 7.50, 95% CI 3.34-16.86, $P < .001$). Multivariate cox hazard regression analysis determined AKI to be the most significant contributor to risk of mortality, as AKI was identified as a more significant risk factor than gender (male), age (<1 y), cardiopulmonary bypass time (≥90 min), pRIFLE category (≥injury) or RACHS-1 category (≥4).
Parikh (2019)[18]	126	3474	13	Overall: 2.8% at 1 y, 3.9% at 5 y, 4.8% at 10 y, 5.4% at 13 y	Children who received dialysis for AKI during their index surgery admission tended to have a 1.5-fold higher risk of mortality when compared to those who did not receive dialysis, although this was not statistically significant (HR 1.5, 95% CI, 0.6 to 3.7).

AKI than in those who did not (HR 7.50, 95% CI 3.34-16.86, $P < .001$). In multivariate Cox proportional hazard regression analysis, AKI even proved to be the single significant contributor to risk of mortality, and other risk factors such as sex, age <1 years, RACHS-1 category ≥4, and cardiopulmonary bypass time ≥90 minutes were not significantly associated with mortality.

Watkins et al[11] conducted a retrospective chart review in which 711 children (mean age 33 months) were included. They found a significantly increased mortality risk for patients with severe AKI as defined by pRIFLE stage F, compared with those without AKI (HR 3.82, 95% CI 1.89-7.75, $P < .001$). Withdrawal of support including extracorporeal membrane oxygenation was identified as the leading known cause of death within the study population, followed by cardiac failure and respiratory processes such as pneumonia and aspiration. Other significant risk factors for mortality were age (HR 0.25 per year increase, 95% CI 0.07-0.85) and univentricular heart conditions (HR 2.46, 95% CI 1.18-5.13). Similar results were found by Morgan et al.[10] They included 264 neonates (mean age 0.57 months), and groups were made according to AKIN stage. At every stage of AKI, the mortality rate was higher than in the non-AKI group, but this only reached statistical significance for AKIN stage 3 (HR 7.34, 95% CI 1.63-33.4, $P = .01$), where 9 out of 42 patients (21.4%) died.

Hollander et al[15] could not confirm these findings. During a mean follow-up of 2.6 and 3 years, 12 (19%) of those who developed AKI died, compared with 4 (16%) among those who did not develop AKI, respectively, showing no significant difference between both groups ($P = .8$). Similarly, Parikh et al[18] found that children who received dialysis for cardiac surgery–associated AKI during their index surgery admission tended to have a 1.5-fold higher risk of mortality when than those who did not receive dialysis, although this was not statistically significant (HR 1.5, 95% CI, 0.6-3.7).

Discussion

Although other predictors may play a more important role, our extensive review identified long-term outcomes that may be associated with cardiac surgery–associated AKI. Significant evidence about the long-term consequences of cardiac surgery–associated AKI in the pediatric population remains controversial, and more studies are warranted to better elucidate the relative contributions of predictive risk factors on long-term sequalae.

The progression from AKI to CKD is well known and delineated in adults. A meta-analysis by Coca et al[24] showed that adults have an 8.8-fold higher risk of CKD and a 3.3-fold higher risk of ESKD after AKI development. The risk of CKD and ESKD increased in a graded fashion when AKI was more severe. The pathophysiology and mechanisms underlying this observed progression could be explained by a maladaptive repair in the tubular, vascular, and interstitial compartments of the kidney system caused by AKI, resulting in a higher susceptibility to the development of interstitial fibrosis, and CKD consequently.[25] G2/M cell-cycle arrest, cell senescence, activation of pericytes and myofibroblasts, and profibrogenic cytokine production have all been linked to this maladaptive repair that occurs following AKI.[26]

The interplay between comorbidities and risk factors of AKI and the subsequent progression of AKI to CKD is complex. For example, higher age, decreased baseline kidney function, diabetes mellitus, arterial hypertension, and preexisting cardiovascular disease are all risk factors for AKI but also for AKI progressing to CKD.[24,27-33] Adults with the highest risk of developing CKD after an episode of AKI also seem to be those who are already at a higher risk of having CKD, independent of an episode of AKI.[34] As these multifactorial comorbidities and risk factors are less prevalent in children, and because children have a longer life expectancy with a longer time to manifest outcomes after an AKI episode, pediatric patients could be a near-optimal study population to investigate the actual contribution of AKI to long-term outcomes such as CKD.[35]

Children who develop AKI at a pediatric intensive care unit are at increased risk for early adverse outcomes, such as mortality, longer duration of mechanical ventilation, and prolonged length of pediatric intensive care unit and hospital stay.[36-39] Greenberg et al[35] performed a systematic review and meta-analysis to investigate long-term outcomes in children after AKI, independent of its etiology. A total of 346 patients from 10 cohort studies were included. During a mean follow-up of 6.5 years, proteinuria, hypertension, eGFR <90 ml/min/1.73 m^2, GFR < 60 ml/min/1.73 m^2, ESKD, and mortality per 100 patient-years were 3.1 (95% CI 2.1-4.1), 1.4 (0.9-2.1), 6.3 (5.1-7.5), 0.8 (0.4-1.4), 0.9 (0.6-1.4), and 3.7 (2.8-4.5), respectively. Although no non-AKI comparator group was available in any of the included studies, these rates were high than those in the general population and suggested an association of AKI with worse long-term outcomes. A comprehensive analysis of province-wide health administrative databases in Canada by Robinson et al[40] subsequently confirmed that subjects who survived a dialysis-treated AKI episode in childhood (n = 1688) experienced significantly higher risk of death, CKD, and hypertension, compared with a matched hospitalized cohort (n = 6752), at a median follow-up of 9.6 years. Lebel et al[41] summarized the available pediatric studies indicating increased rates of albuminuria, hypertension, eGFR <90 mL/min/m^2, and CKD following AKI due to various etiologies (including very-low-birth-weight neonates, critical illness, nephrotoxic medication, stem cell and organ transplantation, cardiac surgery, infections, and cancer). These findings suggest that increased risks of long-term kidney dysfunction and mortality after AKI exist.

AKI has been described as a loose collection of syndromes with a sudden decrease in GFR, as it has various etiologies and is known to develop in different clinical settings including nephrotoxicity, sepsis, and cardiac surgery. Multiple broad classifications (according to the dominant etiology or anatomical site of the defect) have been proposed to demonstrate more consistent relationships regarding

pathophysiological processes.[42-44] Because of the heterogeneity within AKI, different long-term outcomes are observed in different study populations. For example, pediatric hematopoietic stem cell recipients who developed at least 1 AKI episode following the procedure had a higher risk of developing hypertension and CKD,[45,46] though children with solid tumors experienced worse long-term kidney outcomes only if they had more than 4 AKI episodes.[47] However, even within the same AKI setting, contradicting evidence exists, as illustrated by the ambiguous evidence regarding long-term outcomes of AKI after cardiac surgery in children in the present systematic review.

It remains largely unclear whether children with AKI following cardiac surgery are at higher risk of long-term kidney outcomes and mortality. The development of CKD was associated with any prior episodes of cardiac surgery–associated AKI in the studies of Madsen et al[17] and Van den Eynde et al,[23] with the most severe stages of cardiac surgery–associated AKI in the study by Parikh et al,[18] and with absence of recovery from cardiac surgery–associated AKI in the study by Hollander et al.[15] However, no significant associations were found between CKD and cardiac surgery–associated AKI in 5 other studies.[12,13,19,20,22] Fredric et al[21] and Greenberg et al[14] reported lower rates of CKD in those who suffered from postoperative AKI, which the authors attributed either to the regenerative capacity of nephrons in children or their ability to respond to kidney injury by means of glomerular hyperfiltration. Furthermore, cardiac surgery–associated AKI was overall a clearly significant predictor of long-term mortality in the study by Hirano et al,[16] and pRIFLE stage F and AKIN stage 3 significantly increased the mortality risk as shown by Watkins et al[11] and Morgan et al,[10] but no association could be found by Hollander et al[15] and Parikh et al.[18]

Different explanations for the ambiguous observations can be made. First, different definitions were used by different studies. The lack of uniformity regarding the use of AKI definitions is a universal obstacle both in clinic and in research. Different definitions stress different clinical characteristics, and different clinical characteristics can be indicative of differences in pathophysiological processes and thus long-term outcomes. In this regard, pRIFLE tends to be most sensitive and include the most stage 1 cases, though AKIN tends to be the most selective due to its restrictive time frame of 48 hours.[48] Because KDIGO results in an incidence between pRIFLE and AKIN, is strongly associated with outcomes in most cohorts, and carries the advantage of containing both pediatric and adult criteria, it seems to be the preferred AKI definition in the contemporary era. However, because only 2 studies included in this review relied upon the pRIFLE, the potential inclusion of clinically irrelevant AKI events (which would reduce the ability to find significant associations with outcomes) does not seem to have played a major role in most studies. Similarly, although most studies defined CKD based on eGFR <90 mL/min/1.73 m^2, other cutoffs and combinations with microalbuminuria or other markers were also used, which might have had an impact on their ability to find vsignificant associations. Second, there was heterogeneity within the study populations of the included studies. There was heterogeneity in terms of age, as most studies investigated a general pediatric population undergoing cardiac surgery though 2 studies analyzed outcomes of cardiac surgery–associated AKI specifically in neonates.[10,19] Heterogeneity regarding surgery type was present as well, as some studies investigated children undergoing a distinct cardiac surgery procedure and, consequently, children with distinct clinical characteristics. For example, Hollander et al[15] studied pediatric heart transplant recipients, a population that was excluded by Watkins et al.[11] Similarly, Esch et al[12] specifically studied a pediatric cohort undergoing the Fontan operation. Third, follow-up times varied among the studies. Longer follow-up times are thought to allow for more nephron loss, caused by AKI, to manifest itself. Only when as much as 50% of kidney function has been lost, changes in serum creatinine concentration take place, which is essential for eGFR calculation and thus CKD diagnosis.[14,49,50] Furthermore, as suggested by Greenberg et al[14] children can respond to kidney injury by means of glomerular hyperfiltration such that a decline in eGFR only becomes apparent later in life. Fourth, children who suffer from CHD are prone to long-term kidney sequelae, regardless of AKI. Perhaps AKI episodes are not the driving cause of CKD development in children with CHD.

Kidney function impairment is frequent in the CHD population, with 40%-50% of these patients having a compromised GFR (<90 mL/min/1.73 m^2) in young adulthood.[23,51,52] These high rates of kidney dysfunction are believed to be caused by both extrinsic factors such as cardiac surgery, cardiopulmonary bypass, and nephrotoxins and intrinsic factors such as polycythemia, chronic hypoxia, cardiac volume overload, impaired autonomic nervous system, and neurohormonal disturbances (**Figure 3**; available at www.jpeds.com).[53] Because of the variety and multiplicity of factors contributing to kidney dysfunction, questions arise regarding the importance of AKI episodes in the development of long-term CKD. Young adults with CHD and reduced GFR have higher mortality rates than those with normal GFR values.[52] This illustrates the importance of having a better understanding of the AKI-to-CKD transition and the etiology of CKD in pediatric CHD patients to develop targeted prevention and treatment of long-term adverse outcomes.

Data in adults suggest that nephrologist follow-up improves all-cause mortality of patients who developed AKI.[53] Although the present review did not allow to draw definitive conclusions about the existence of true AKI-to-CKD transition in children after pediatric cardiac surgery, we argued that a substantial decline in kidney function may take longer to manifest itself and children can respond to kidney injury by means of glomerular hyperfiltration. In addition, various other factors associated with CHD can lead to kidney dysfunction in young adulthood. Furthermore, both AKI and CKD are responsible for major

increases in health care expenditure for patients with CHD, with 1.21-fold higher perioperative costs for those with stage 1 AKI, 2.74-fold higher perioperative costs for those requiring acute dialysis,[54] and 1.31-fold higher cost for those with CKD.[55] Structured kidney follow-up thus seems justified in this population.[51,52,56] Follow-up after cardiac surgery–associated AKI development is currently a substantial unmet need: Greenberg et al[14] reported that only 4% of the patients had seen a nephrologist at the follow-up. This number is close to the 2% (1 of 49) estimated by Van den Eynde et al.[23] In order to bring about change in this field, more data about long-term outcomes of cardiac surgery-associated AKI are required. Such an approach will facilitate lifelong care, where the impact of childhood surgery on kidney dysfunction in adulthood is evaluated. The knowledge obtained from these studies may contribute to creating successful protocols for prevention and more personalized management. As identified by the present systematic review, most resources should likely be targeted toward patients with genetic syndromes, univentricular or cyanotic heart conditions, and/or preexisting kidney dysfunction as well as those undergoing high-complexity procedures (high RACHS-1 score).[11,19,22,23] From a clinical perspective, it might thus we wise to pay particular attention to this target population and enroll them into a systematic kidney follow-up program early on.

The lack of an optimal AKI definition continues to be a key shortcoming. Although the KDIGO criteria have been immensely helpful, they do not account for the variability within AKI subtypes. Moreover, a creatinine-based definition does not optimally reflect the structural kidney damage that proceeds its functional repercussions. Further work will be needed to integrate personalized medicine into the heterogeneous world of AKI, and to develop a more structure-driven definition of AKI. The search for early and precise biomarkers for AKI will certainly play a pivotal role in solving this problem.[57] In addition to providing more appropriate definitions for AKI, such biomarkers may facilitate earlier AKI detection. This could result in earlier and better preventive measures, which are targeted and can limit the adverse short-term and possible long-term adverse outcomes of AKI. Biomarkers of kidney injury such as neutrophil gelatinase–associated lipocalin, IL-18, and liver-type fatty acid–binding protein remain elevated several years after the AKI episode even in the absence of conventional evidence of CKD.[13] Such findings suggest that emerging biomarkers may provide a more sensitive tool for CKD risk stratification in these patients.[13,22]

Several limitations need to be considered when interpreting the results. First, this systematic review included mostly observational studies, meaning that our findings cannot demonstrate causality. Second, heterogeneity among included studies was ubiquitous. Sources of heterogeneity might include study design, age, AKI definition, kidney dysfunction or CKD definition, underlying type of CHD, type of cardiac surgery procedure, and follow-up period. Third, most study populations were relatively small and may have been underpowered to confirm and capture an accurate assessment of the effects of AKI. Fourth, most follow-up periods were relatively short, and CKD only occurs after considerable loss of kidney function and children can have mechanisms to compensate for kidney injury by increasing GFR.[14,49] Fifth, a meta-analysis to quantitatively assess long-term outcomes of cardiac surgery–associated AKI was deferred given the lack of uniform data.

Although clear effects of cardiac surgery–associated AKI on the development of CKD and mortality have been demonstrated in adults, evidence about the long-term consequences of cardiac surgery–associated AKI after pediatric cardiac surgery is mixed. It seems that underlying or preexisting kidney disease may be more relevant to the development of kidney dysfunction at long-term follow-up. Structured nephrological follow-up of these children is warranted. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table II. Patient characteristics

Study	Group	Male (%)	Age at AKI (mo)	Gestation (wk)	Weight at AKI (kg)	Types of heart disease	Baseline kidney function
Morgan 2013[10]	AKI	59.4	0.58 ± 0.58	38.7 ± 2.0	3.433 ± 0.732	NR	Baseline SCr (μmol/L): <30 (27%), 30-49 (52%), 50-70 (16%), >70 (6%)
	No AKI	63.8	0.57 ± 0.73	38.9 ± 1.7	3.453 ± 0.627	NR	Baseline SCr (μmol/L): <30 (3%), 30-49 (55%), 50-70 (30%), >70 (12%)
Watkins 2014[11]	All patients	55	33 ± 49.3	<37 (15.5%)	13.3 ± 16.4	ToF (16.3%), AV septal/canal defect (11.5%), VSD (12.6%), ASD (9%), HLHS (8%), TGA (7.4%), DORV (6.3), other (28.9%)	Baseline eCrCl (mL/h): 120 (56)
Esch 2015[12]	AKI	58	31.2 (26.4-38.4)	NR	12.2 (10.9-13.6)	Systemic RV (73%), HLHS (56%), AVV regurgitation > mild (18%), any ventricular dysfunction (28%)	Baseline eCrCl (mL/min/1.73 m^2): 116 (93-128)
	No AKI	61	32.4 (27.6-39.6)	NR	12.8 (11.4-14.6)	Systemic RV (60%), HLHS (45%), AVV regurgitation > mild (3%), any ventricular dysfunction (17%)	Baseline eCrCl (mL/min/1.73 m^2): 107 (88-124)
Cooper 2016[13]	AKI	48.5	6.1 (4.1-16.6)	NR	NR	NR	Baseline SCr (mg/dL): 0.3 [0.3-0.4], Baseline eCrCl (mL/min/1.73 m^2): 97.5 (85.5-134.75)
	No AKI	44.4	6.8 (3.0-37.8)	NR	NR	NR	Baseline SCr (mg/dL): 0.4 (0.3-0.6), Baseline eCrCl (mL/min/1.73 m^2): 96 (74.3-116.6)
Greenberg 2016[14]	AKI	56	13 (5.8-48.7)	NR	NR	NR	Baseline estimated SCr-GFR: 97 (78-126)
	No AKI	49	38 (7.4-68.9)	NR	NR	NR	Baseline estimated SCr-GFR: 89 (81-101)
Hollander 2016[15]	AKI	47	74.4 (3.1-222)		NR	Cardiomyopathy (56%), CHD (44%)	NR
	No AKI	52	62.4 (12-200)		NR	Cardiomyopathy (60%), CHD (40%)	NR
Hirano 2017[16]	AKI	65.4	2.0 (1.0-11.5)	NR	NR	NR	Baseline eCrCl (mL/min/1.73 m^2):
	No AKI	60.8	6.0 (2.0-21.0)	NR	NR	NR	63.6 (49.9-79.7)
Madsen 2017[17]	AKI	56	0-1 (96%). 2-14 (4%)	<37 (18%). >37 (82%)	NR	NR	eGFR >90 (>40 for children <3 mo of age): 100%
	No AKI	58	0-1 (67%). 2-14 (33%)	<37 (9%). >37 (91%)	NR	NR	eGFR >90 (>40 for children <3 mo of age): 100%
Parikh 2019[18]	All patients	56	4.9 (1.32-8.3)	NR	NR	Ventricular septal defects, Tetralogy of Fallot, atrioventricular septal defect	NR
Huynh 2020[19]	All patients	46	0.3 ± 0.3	≥ 37 (81%)	3.2 (0.8)	NR	NR
Zappitelli 2020[20]	AKI	54	8.4 (4.8-40.8)	NR	NR	NR	Baseline estimated SCr-GFR: 134 (107-155)
	No AKI	49	45.6 (6-158)	NR	NR	NR	Baseline estimated SCr-GFR: 111 (92-125)
Fredric 2021[21]	AKI	70	24 (12-96)	NR	NR	NR	NR
Sethi 2021[22]	AKI	78.7	3.5 (0.6-14.2)	NR	16 (13.2-21.9)	NR	Baseline creatinine (mg/dl): 0.4 (0.3-0.5)
	No AKI	84.8	9 (5-37)	NR	14.5 (11.7-18.6)	NR	Baseline creatinine (mg/dl): 0.3 (0.2-0.3)
Van den Eynde 2022[23]	All patients	57.6	2.9 (0.3-10.5)	NR	3.030 ± 0.652	Intracardiac left-to-right shunt (10.6%), Obstructive left heart lesions (7.6%), TGA (27.3%), univentricular heart (24.2%), TAPVR (1.5%)	NR

ASD, atrial septal defect; *AV*, atrioventricular; *AVV*, atrioventricular valve; *DORV*, double outlet right ventricle; *eCrCl*, estimated creatinine clearance; *HLHS*, hypoplastic left heart syndrome; *NR*, not reported; *RV*, right ventricle; *TGA*, transposition of the great arteries; *ToF*, tetralogy of Fallot; *VSD*, ventricular septal defect.

Table III. Surgery characteristics

Study	Group	Types of surgery	Cardiopulmonary bypass duration (min)	RACHS-1 scores
Morgan 2013[10]	AKI	ASO (39%), TAPVD repair (17%), Other (31%), Any with chromosome abnormality (12%)	≤60 (11%), 61-90 (22%), 91-120 (28%), 121-180 (27%), ≥181 (12%)	2 (21%), 3 (33%), 4 (44%), 5 (1%)
	No AKI	ASO (48%), TAPVD repair (26%), Other (19%), Any with chromosome abnormality (7%)	≤60 (17%), 61-90 (28%), 91-120 (26%), 121-180 (26%), ≥181 (4%)	2 (15%), 3 (44%), 4 (40%), 5 (1%)
Watkins 2014[11]	All patients	ASD closure (17.9%), AV septal defect/canal repair (11.3%), VSD closure (8.7%), Complete repair of ToF/pulmonary atresia or stenosis (8.7%), Valvotomy or valvuloplasty (8.4%), Fontan (7.2%), Bi-Directional Glenn (5.7%), ASO (4.5%), Other (27.6%)	117 ± 52	NR
Esch 2015[12]	AKI	Fontan (100%)	116 (95-140)	NR
	No AKI	Fontan (100%)	99 (81-116)	NR
Cooper 2016[13]	AKI	NR	NR	1 (0%), 2 (45.5%), 3 (45.5%), 4 (3%), 5 (6%), 6 (0%)
	No AKI	NR	NR	1 (11.1%), 2 (44.4%), 3 (27.8%), 4 (11.1%), 5 (5.6%), 6 (0%)
Greenberg 2016[14]	AKI	Septal defect repair (33%), Inflow/outflow tract or valve procedure (15%), Combined procedure (52%)	NR	1 (0%), 2 (46%), 3 (45%), 4 (9%)
	No AKI	Septal defect repair (38%), Inflow/outflow tract or valve procedure (22%), Combined procedure (41%)	NR	1 (9%), 2 (54%), 3 (36%), 4 (0%)
Hollander 2016[15]	AKI	Heart transplantation (100%)	NR	NR
	No AKI	Heart transplantation (100%)	NR	NR
Hirano 2017[16]	AKI	NR	≥90 (91.3%)	≥4 (21.1%)
	No AKI	NR	≥90 (57.0%)	≥4 (2.9%)
Madsen 2017[17]	AKI	NR	NR	1 (8%), 2 (42%), 3 (26%), 4-6 (24%)
	No AKI	NR	NR	1 (18%), 2 (46%), 3 (20%), 4-6 (16%)
Parikh 2019[18]	All patients	NR	NR	3 (29%), ≥4 (14%)
Huynh 2020[19]	All patients	NR	NR	1 (5%), 2 (21%), 3 (54%), 4 (10%), 5 (0%), 6 (10%)
Zappitelli 2020[20]	All patients	NR	NR	RACHS-1 ≥3: AKI (22, 39%); No AKI (38, 57%)
Fredric 2021[21]	All patients	NR	NR	1 (9%), 2 (65%), 3 (22%), 4 (4%)
Sethi 2021[22]	All patients	NR	65 (45-100)	3: 14 (93.3%) 4: 1 (6.7%)
Van den Eynde 2022[23]	All patients	NR	118 (88-56)	NR (reported STAT score)

ASO, arterial switch operation; *AV*, atrioventricular; *NR*, not reported; *TAPVD*, totally anomalous pulmonary venous drainage; *ToF*, tetralogy of Fallot; *VSD*, ventricular septal defect.

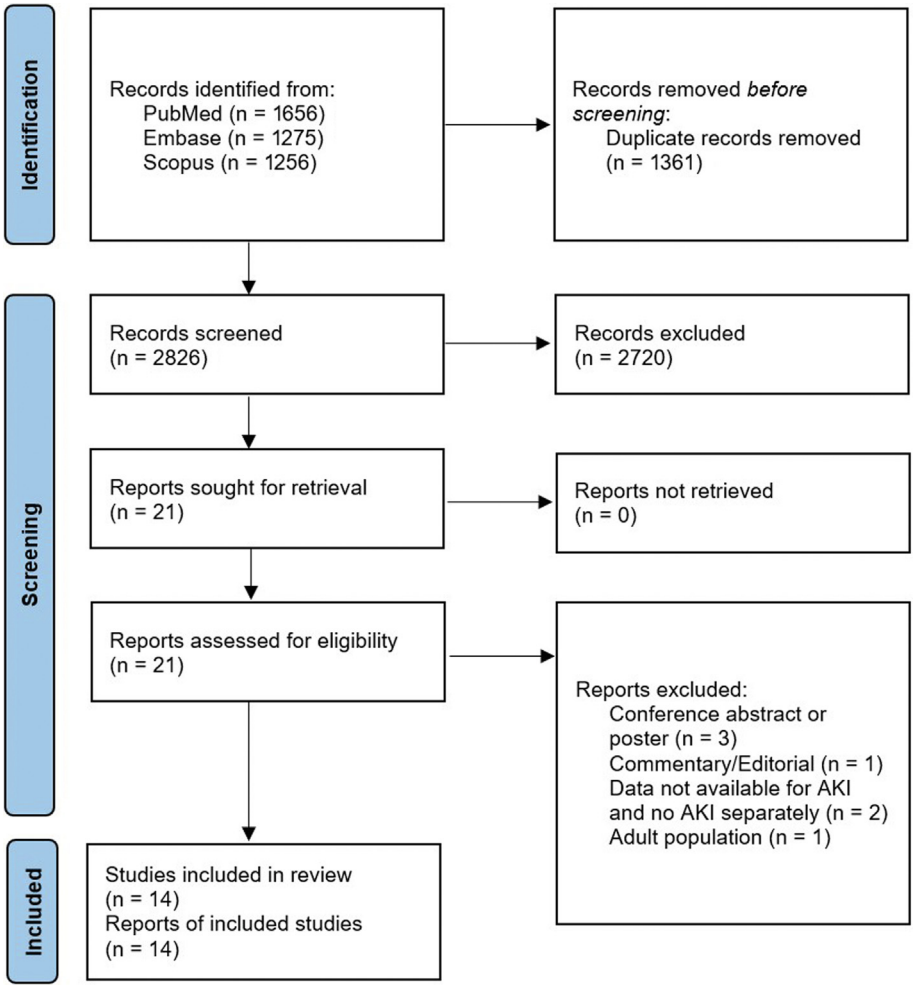

Figure 1. Flow diagram of studies included in data search.

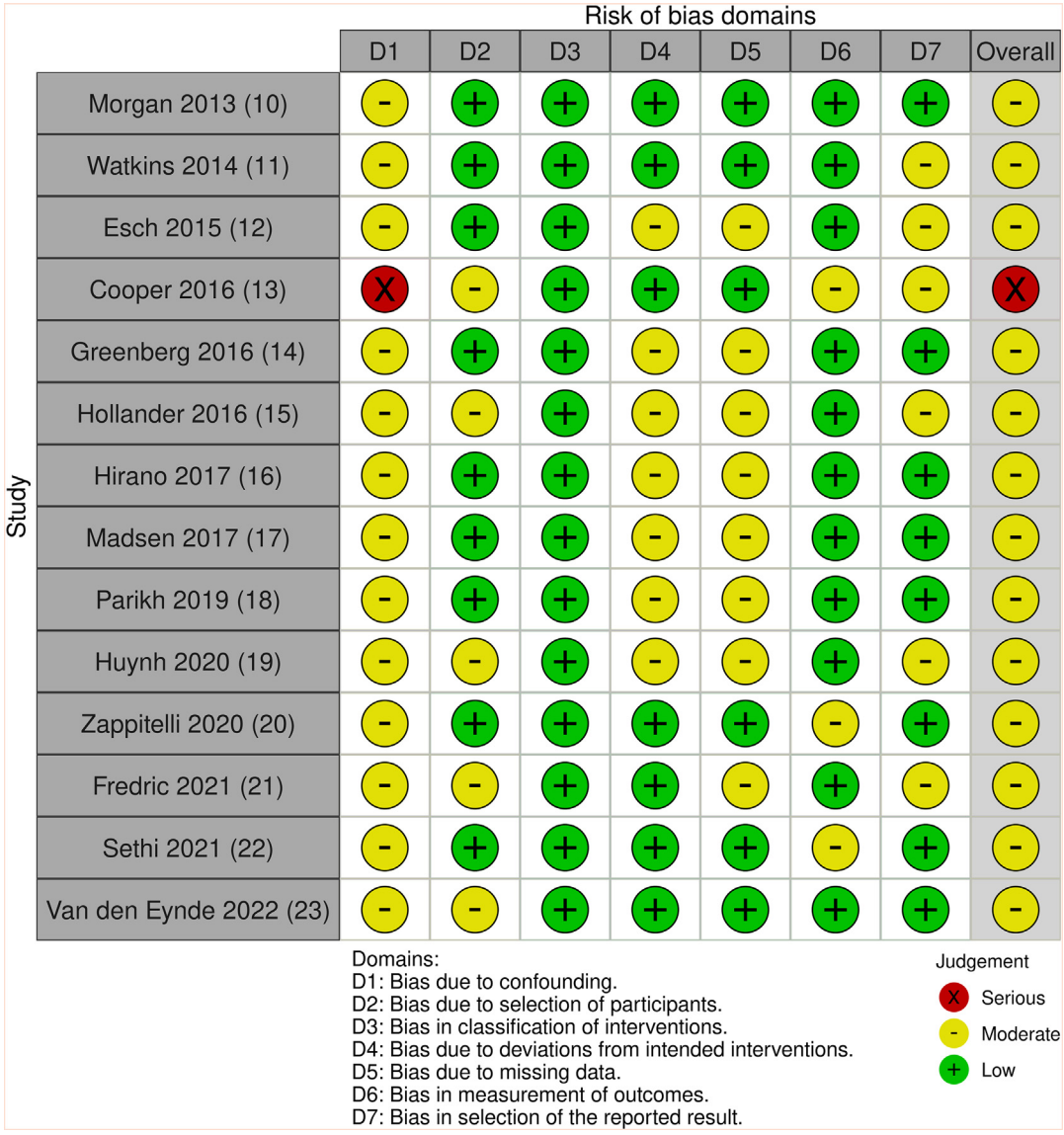

Figure 2. Risk-of-bias assessment of observational studies using the ROBINS-I tool. *ROBINS-I,* Risk of Bias in Nonrandomized Studies of Interventions.

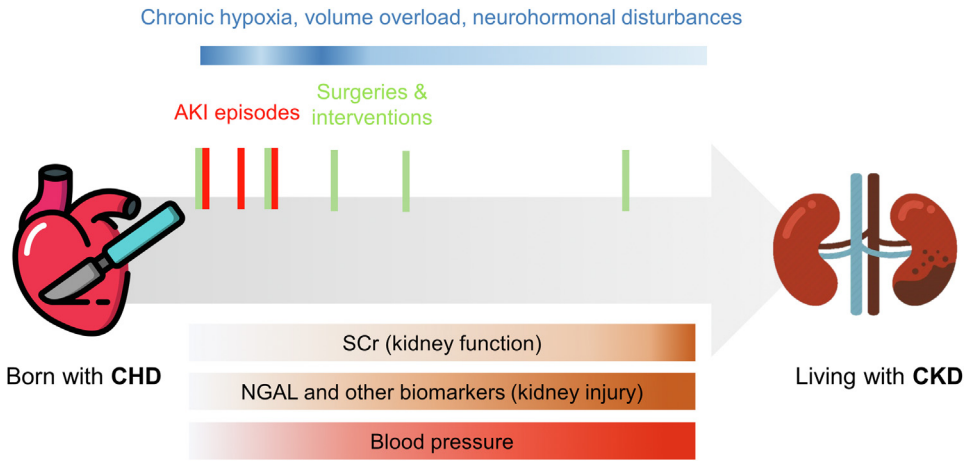

Figure 3. Framework to understand the long-term consequences of cardiac surgery-associated AKI and the complex relationship between CHD, AKI, and CKD. Episodes of cardiac surgery-associated AKI can lead to the development of hypertension, CKD, and increased risk of mortality. However, intercurrent surgeries and interventions as well as chronic hypoxia, volume overload, and neurohormonal disturbances may also contribute. Biomarkers such as NGAL might be able to detect kidney injury prior to kidney function decline. *NGAL*, neutrophil gelatinase–associated lipocalin.