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Review Article

# Acute kidney injury after pediatric cardiac surgery

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Acute kidney injury (AKI) is a common complication of pediatric cardiac surgery and is associated with increased morbidity and mortality. Literature of AKI after pediatric cardiac surgery is comprehensively reviewed in terms of incidence, risk factors, biomarkers, treatment and prognosis. The novel RIFLE (pediatric RIFLE for pediatrics), Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) criteria have brought about unified diagnostic standards and comparable results for AKI after cardiac surgery. Numerous risk factors, either renal or extrarenal, can be responsible for the development of AKI after cardiac surgery, with low cardiac output syndrome being the most pronounced predictor. Early fluid overload is also crucial for the occurrence of AKI and prognosis in pediatric patients. Three sensitive biomarkers, neutrophil gelatinase-associated lipocalin, cystatin C (CysC) and liver fatty acid-binding protein, are regarded as the earliest (increase at 2—4 h), and another two, kidney injury molecule-1 and interleukin-18 represent the intermediate respondents (increase at 6—12 h after surgery). To ameliorate the cardiopulmonary bypass techniques, improve renal perfusion and eradicate the causative risk factors are imperative for the prevention of AKI in pediatric patients. The early and intermediate biomarkers are helpful for an early judgment of occurrence of postoperative AKI. Improved survival has been achieved by prevention, renal support and modifications of hemofiltration techniques. Further development is anticipated in small children.


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## 1. Introduction

Acute kidney injury (AKI) is a common complication of pediatric cardiac surgery, which negatively impacts short- and long-term outcomes, and carries increased morbidity and mortality. The incidence of acute kidney injury in children after cardiac surgery under cardiopulmonary bypass (CPB) varied from report to report. It was reported to be 9.6–42% in children,[1–3] 52% in infants (<90 days),[4] and 64% in neonates (aged ≤6 weeks) with biventricular cardiac repairs.[5] In particular, patients younger than 2 years exhibited an increased risk for AKI.[3] AKI is associated with significantly increased mortality and morbidity. Despite updates of evaluation criteria for pediatric AKI utilized in clinical practice, improvements achieved in management and prognosis are still limited. The influencing factors and clinical importance of different biomarkers utilized in early diagnosis of pediatric AKI warrant further elucidation. The purpose of this article is to provide a comprehensive review of pediatric AKI after cardiac operations.

## 2. Classification and staging of acute kidney injury

In 2002, the Acute Dialysis Quality Initiative (ADQI) proposed evidence-based guidelines for the treatment and prevention of acute kidney injury (AKI), namely the RIFLE criteria (Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease). This classification was modified for pediatric patients as the pediatric RIFLE by using estimated creatinine clearance and urine output criteria and has been validated in pediatric cardiac surgery patients (Table 1).[6] Based on this novel classification, Meersch et al.[2] reported that among AKI patients, 83.3% of the patients were pediatric RIFLE-R, 16.7% were pediatric RIFLE-I, and none of the patients developed pediatric RIFLE-F.

**Table 1** Pediatric RIFLE Classification for acute kidney injury.

| pRIFLE Classification | | |
|---|---|---|
| Stage | GFR Criteria | Urine Output Criteria |
| Risk | eCCr decreased >25% | <0.5 mL/kg/h for 8 h |
| Injury | eCCr decreased >50% | <0.5 mL/kg/h for 16 h |
| Failure | eCCr decreased >75% or eCCr <35 mL/min/1.73 $m^2$ | <0.3 mL/kg/h for 24 h (oliguria) Or anuria for 12 h |
| Loss of function | Persistent acute renal failure >4 weeks | |
| End-stage renal disease | Complete loss of kidney function >3 month | |

eCCr = estimated creatinine clearance; GFR = glomerular filtration rate.

**Table 2** Acute Kidney Injury Network (AKIN) criteria.

| Stage | Serum Creatinine | Urine Output |
|---|---|---|
| 1 | Increase ≥0.3 mg/dL (≥26.4 μmol/L), or Increase ≥150–200% (1.5-∼2-fold) from baseline | <0.5 mL/kg/h for 6 h |
| 2 | Increase ≥200–300% (2-∼3-fold) from baseline | <0.5 mL/kg/h for 12 h |
| 3[a] | Increase > 300% (>3-fold) from baseline, or Serum creatinine to ≥4 mg/dL (≥354 μmol/L) with an acute increase ≥0.5 mg/dL (≥44 μmol/L) | <0.3 mL/kg/h for 24 h, or Anuria for ≥12 h |

[a] Patients receiving renal replacement therapy are included in Stage 3.

The second classification system developed by the Acute Kidney Injury Network (AKIN) classifies AKI into stages I–III on the basis of small increases in serum creatinine or decreases in urine output (Table 2).[7] The third classification of AKI is the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (Table 3).[8] There are several equations that are important for the evaluation of AKI: Schwartz formula[9] for the calculation of the estimated creatinine clearance (eCCr) is,

$$eCCr = 0.413 \times height\ (cm)/serum\ creatinine$$

It was reported that the eCCr values during the three days of the intensive care unit (ICU) stay showed a significant difference among the three groups of non-AKI, AKI-R and AKI-I groups.[10] according to the updated Schwartz formula. The creatinine value was measured by enzymatic method, which is rarely used in Taiwan, where most labs use the Jaffe method. The constant K should vary with age,

$$Glomerular\ filtration\ rate\ (mL/min/1.73\ m^2) = 0.55\ Length\ (cm)/Plasma\ creatinine\ (mg/dL)$$

The estimated results generated from this formula showed excellent agreement with glomerular filtration rate estimated by the renal clearance of endogenous creatinine or clearance of insulin.[11]

**Table 3** Kidney Disease Improving Global Outcomes (KDIGO) criteria.

| Stage | Serum Creatinine | Urine Output |
|---|---|---|
| 1 | 1.5–1.9 times baseline, or ≥0.3 mg/dL increase | <0.5 mL/kg/h for 6 h |
| 2 | 2–2.9 times baseline | <0.5 mL/kg/h for 12 h |
| 3 | 3 times baseline, or Increase in serum creatinine to ≥4 mg/dL, or Initiation of renal replacement therapy | <0.3 mL/kg/h for 24 h, or anuria for ≥12 h |

Adjusting serum creatinine (SCr) values for fluid balance is essential in predicting the subtle early signs of AKI.[12]

*Adjusted SCr* $=$ *measured SCr* $\times$ *(1* $+$ *[cumulative net fluid balance (L)/total body water (kg)])*

where total body water was calculated as 0.6 $\times$ body weight.

Percent fluid overload (FO) was calculated as,

*FO* $=$ *([volume of fluid in (L)* $-$ *volume of fluid out (L)]/weight)* $\times$ *100*

By using this equation, 5% FO is equivalent to a positive fluid balance of 50 mL/kg, a threshold that was recommended by Basu et al.[13] This was served as a cutoff point for higher AKI risk in "very high-risk patients," *i.e.*, those requiring prolonged mechanical ventilation and vasoactive agents.[14] Early postoperative FO, defined as a fluid balance 5% above body weight by the end of first postoperative day, occurred in 31% of the patients. As FO usually develops ahead of AKI, and 8% FO represents 80 mL/kg, this indicator was therefore 90% specific for subsequent AKI-I or AKI-F.[14] Patients with early FO had a protracted recovery from surgery as evidenced by 3.5 more days in hospital, two more days on inotropes, and increased prevalence of prolonged mechanical ventilation.[14] Pediatric cardiac surgery patients with longer CPB times ($>$100 min) and FO had double the risk of prolonged mechanical ventilation than those with shorter CPB times ($<$100 min) and FO. In children following arterial switch operation, FO is associated with increased postoperative ICU length of stay.[15]

## 3. Literature retrieval

The search terms for literature retrieval were "acute kidney injury" and "cardiac surgical procedures" with filters of article type (Clinical Study, Clinical Trial, Multicenter Study, Observational Study and Randomized Controlled Trial), publication data (From 2000/01/01 to 2017/12/31) and Human, English language and Child (from birth to 18 years). With the above-mentioned filters, only 25 articles were retrieved. By excluding unrelated ones, 13 articles were totally included (Table 4). Bibliographic references helped the completeness of literature collection.

As indicated by Ricci et al.,[26] according to pRIFLE criteria, the incidence of postoperative AKI was 50% in those receiving fenoldopam and 72% in those receiving placebo. Lee et al.[29] reported that this incidence was 14.1% in 19 patients: 17 had AKI Stage Risk (R) and 2 had AKI Injury (I). However, the incidence increased to 90% in the children after ECMO initiation.[30] According to AKIN criteria, the incidence of cardiac surgery-associated AKI was 36%, and most patients had stage II or III disease (72%).[32] Tanyildiz et al.[31] compared between the two criteria revealed that 84 (61.3%) patients developed AKI by pRIFLE criteria and 65 (47.4%) of patients developed AKI according to the AKIN criteria; children younger than 11 months were more likely to develop AKI. Lex et al.[33] reported that AKI was present in 285 (20%), 481 (34%), and 409 (29%) patients according to the AKIN, pRIFLE and KDIGO systems, respectively. The pRIFLE system was the most sensitive test in detecting AKI, which is especially suitable for infants and in the early identification of AKI in low-risk patients. The AKIN system was more specific and detected in high-risk patients of all age groups.

## 4. Risk factors for acute kidney injury

Risk factors for AKI after cardiac surgery can be classified into two types: renal and extrarenal. The latter includes constitutional, hemodynamic, or inflammatory causes (Table 5). In pediatric patients, younger age, a prolonged CPB time, a prolonged ventilation time, pump failure, sepsis and hematological complications predisposed to AKI after cardiac surgery. Of these, younger age was a stronger predictor of postoperative AKI, a longer ICU stay and mortality.[1] In addition to emphasizing the younger age at surgery, Morgan et al.[5] also described CPB duration $>$180 min and deep hypothermic circulatory arrest were independent risk factors for AKI. However, as Basu et al.[37] reported, in pediatric patients undergoing arterial switch operation a conclusion was also drawn with regard to the younger age; however, the predictive values of duration of CPB and crossclamp time for postoperative AKI were refuted.

It is noteworthy mentioning that in case of severe coarctation of aorta, the decreased blood flow to the kidney could be caused by the decreased patent ductus arteriosus flow and left ventricle dysfunction below the aortic arch level.[10] The decrease in milrinone dose and/or addition of a pure vasoconstrictor increased mean arterial pressure while decreasing inotrope score, and thereby potentially reduce the risk of AKI.[38]

## 5. Biomarkers for acute kidney injury

### 5.1. Traditional biomarkers

SCr is a traditional marker of renal function; however, it does not rise before a 50% loss of renal function. SCr is also affected by many extrarenal factors, for example, hemodilution during CPB. SCr is not sensitive for evaluation of postoperative AKI due to a delayed peak until 1–3 days after cardiac surgery.[39] The pattern of SCr rise in both magnitude and rate correlated significantly with clinical outcomes including mortality and long-term kidney functional alteration.[40] Urine output, another traditional marker of renal function, also has a low specificity for AKI after cardiac surgery, as it is also influenced by several factors, including renal blood flow or renal perfusion pressure, neurohormonal factors and functional changes.[2] Urine output is not a sensitive biomarker until reaching a cutoff value of $>$1.5 mL/kg/h for evaluating patients' outcomes, such as mortality and duration of mechanical ventilation and hospital stay.[41] According to a recent investigation, abrupt postoperative variation of SCr ($\Delta$SCr) is also a nonsensitive marker because of its delayed rise and lack of differential function between survivors and deceased.[42]

**Table 4** Literature retrieval.

| Year | Author | Case number | Age | Study design | AKI criteria | Major findings | Outcome |
|---|---|---|---|---|---|---|---|
| 2016 | Park et al.[16] | 220 | 10 days–19 years | Single-center, retrospective cohort study | KDIGO | 92 patients (41.8%) developed AKI and 18 (8.2%) required renal replacement therapy within the first postoperative week | Hemoglobin concentration increase (>3 g/dL) was an independent risk factor for AKI. Correction of preoperative anemia and prevention of hemoconcentration might ameliorate postoperative AKI |
| 2016 | Axelrod et al.[17] | 72 (randomized to receive aminophylline) & 72 (received placebo) | All patients <18 years of age | Double-blinded, randomized, placebo-controlled clinical trial | KDIGO | Aminophylline administration was not associated with mortality, and rates of adverse events were similar to placebo | Aminophylline did not show effect to prevent AKI in children |
| 2016 | Svarrer et al.[18] | 50 | Median age: 0.5 years (0.01–14.9 years) | Clinical trial | KDIGO | Apolipoprotein M was excreted into the urine at 0–4 postoperative hour | Urinary apolipoprotein M might be a biomarker of AKI in children undergoing heart surgery |
| 2014 | Simpson et al.[19] | 30 | 2–144 months | Single center prospective randomized double blinded study | AKIN | The magnitude of increase in plasma isofurans was greater than the magnitude in increase in plasma F2-isoprostanes during operation Acetaminophen attenuated the increase in plasma isofurans compared with placebo | Acetaminophen attenuated lipid peroxidation in children undergoing CPB |
| 2014 | Hornik et al.[20] | 165 | <2 years | Three-center, prospective study | AKIN | Postoperative AKI occurred in 165 children (60%), with 118 cases (43%) being mild and 47 cases (17%) severe | Preoperative B-type natriuretic peptide was not associated with increased risk of mild or severe postoperative AKI, and did not predict postoperative AKI |
| 2014 | Riley et al.[21] | 20 infants | <90 days | Randomized controlled trial | Not stated | Median biomarker concentrations did not differ between peritoneal dialysis and control groups | Renal replacement therapy did not change the time course of kidney function recovery |
| 2013 | Koyner et al.[22] | 1203 adults and 299 children | 1203 adults and 299 children | Prospective cohort study | AKIN and RIFLE | Correlation of urinary CysC level in the early postoperative period with both mild and severe AKIs in adults was attenuated for both forms of AKIs in both cohorts after adjusted for other factors | Urinary CysC values were not associated significantly with the development of AKI |
| 2012 | Cantinotti et al.[23] | 135 | Median age 7 (interquartile range 1–49) months | Prospective clinical trial | Defined as 1.5 serum creatinine increase | AKI occurred in 39% of patients (65% neonates and 32% older children) | The peak of uNGAL values occurred at 2 h. The uNGAL values at 2 h had a good diagnostic accuracy for early diagnosis of AKI |
| 2012 | Ricci et al.[24] | 160 | <1 year | Single-center prospective cross-sectional study | pRIFLE | The patients with abnormal uNGAL did not significantly correspond to level of renal damage by pRIFLE | uNGAL might be helpful for renal replacement therapy prediction |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2012 | Pedersen et al.[25] | 105 patients: remote ischemic preconditioning group, (n = 54); control group, (n = 51) | 0–15 years | Randomized single-center study | pRIFLE | Remote ischemic preconditioning did not improve the renal biomarkers and the secondary end points | Remote ischemic preconditioning did not provide protection of kidney function |
| 2011 | Ricci et al.[26] | 80 patients: 40 received fenoldopam during CPB, and 40 received placebo | <1 year | Prospective single-center randomized double-blind controlled trial | pRIFLE | Fenoldopam significantly reduced dosages of diuretics and vasodilators and decreased uNGAL and CysC | High-dose fenoldopam during CPB protected renal function |
| 2011 | Zappitelli et al.[27] | 288 | 3.8 ± 4.5 years (half the cohort was <2 years old) | Multicenter, prospective study | AKIN | The highest tertile of percent change in CysC independently predicted AKI, whereas the highest tertile of serum creatinine predicted Stage I but not Stage II AKI | Postoperative serum CysC was useful to risk-stratify patients for AKI |
| 2008 | Ricci et al.[28] | 40 | Neonates | Prospective controlled clinical trial | pRIFLE | Low dose fenoldopam in neonates undergoing cardiac surgery with CPB did not produce effects on urine output, fluid balance and AKI incidence | Low dose fenoldopam infusion did not show beneficial effects on renal function |
| 2017 | Lee et al.[29] | 135 | 480 days | Retrospective study | pRIFLE | 19 patients (14.1%) developed AKI: 17 had AKI with a severity classified as risk (R) and 2 had AKI classified as injury (I) | Higher pRIFLE classification positively correlated with increased incidence of peritoneal dialysis, increased postoperative mechanical ventilation duration, and longer hospital stay |
| 2017 | Elella et al.[30] | 59 | 11 months | Retrospective study | pRIFLE | 53 patients (90%) developed AKI after ECMO initiation | AKI patients had longer ECMO duration and intensive care unit stay in comparison to non-AKI patients |
| 2017 | Tanyildiz et al.[31] | 137 | <18 years | Retrospective study | pRIFLE and AKIN | 84 (61.3%) patients developed AKI by pRIFLE criteria; 65 (47.4%) of patients developed AKI according to the AKIN criteria; children younger than 11 months were more likely to develop AKI | pRIFLE identified AKI more frequently than AKIN criteria. pRIFLE identified patients at risk for AKI early and was more sensitive in pediatric patients. |
| 2017 | Blinder et al.[32] | 799 | 0-36 months | Prospective randomized study | AKIN | Cardiac surgery-associated AKI occurred in 289 patients (36%), most of whom had Stage II or III disease (72%) | Cardiac surgery-associated AKI was associated with longer mechanical ventilation and intensive care unit and hospital stays and increased mortality. Tight glycemic control did not reduce the cardiac surgery-associated AKI |

AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; CPB: cardiopulmonary bypass; CysC: cystatin C; ECMO: extracorporeal membrane oxygenation; KDIGO: Kidney Disease: Improving Global Outcomes; pRIFLE: Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease criteria; uNGAL: neutrophil gelatinase-associated lipocalin.

**Table 5** Risk factors for acute renal injury after cardiac surgery.

| Risk factors |
|---|
| **Renal** |
| • Reduced renal perfusion |
| • Decreased glomerular filtration, |
| • Dysfunctional renal tubule |
| • Nephrotoxic medications |
| **Extrarenal** |
| ***Constitutional*** |
| • Younger age and smaller body weight at surgery[10] |
| • Hypothermia[12] |
| ***Hemodynamic*** |
| • Higher risk adjustment for congenital heart surgery (RACHS-1) scores (3 and above)[12,13] |
| • Presence of cyanotic lesions[10] |
| • Uncorrected or residual cardiac defects[4] |
| • Cardiopulmonary bypass (nonpulsatile flow; inflammatory cascade)[12] |
| • Longer cardiopulmonary bypass time[12] |
| • Hypothermic circulatory arrest[34] |
| • Requirement of inotropic support[10,12] |
| • Low cardiac output syndrome[12] |
| • Prolonged ventilator requirement[14] |
| • Need for extracorporeal membrane oxygenation (ECMO)[35] |
| • Early fluid overload[14] |
| ***Inflammatory*** |
| • General systemic inflammatory response syndrome (SIRS)[36] |
| • Sepsis and septic shock[4] |

### 5.2. Proximal tubules biomarkers

Neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid-binding protein (L-FABP) and cystatin C (CysC) are biomarkers depending directly or indirectly on the proximal tubule functions. Research revealed that urine NGAL increased in AKI patients 4 h after surgery with a sharp decrease thereafter.[2] Urine NGAL levels at 4 h were significantly higher in patients with a CPB time >150 min than in those with a CPB time <150 min.[43] The NGAL at 6 h after cardiac operation best predicted severe AKI with an AUC of 0.88.[44] Among adults and children immediately after CPB surgery, plasma but not urine NGAL was predictive of AKI in adults, while urine but not plasma NGAL was predictive in pediatric patients. As Peco et al.[45] reported, serum CysC, urine NGAL and urine L-FABP increased 2 h after cardiac surgery and 24–48 h before SCr increased. Urine L-FABP level at 4 h was an independent risk factor for the development of AKI, with an AUC of 0.81.[46] Urine L-FABP showed the best cost-effectiveness among investigated biomarkers including serum CysC, urine NGAL and urine L-FABP.

Human kidney injury molecule-1 (KIM-1) is a type 1 transmembrane protein that is not detectable in normal kidney tissue or urine but is expressed highly in the proximal tubule epithelial cells after ischemic or toxic insult. KIM-1 is a sensitive urinary biomarker for AKI. It increased in the urine at 6–12 h after CPB and remained high up to 48 h after CPB. It was significantly higher in AKI than in non-AKI patients at 12 h, 24 h and 36 h. The AUC for KIM-1 was 0.90.[47]

### 5.3. G1 cell cycle arrest biomarkers

Both urine tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are inducers of G1 cell cycle arrest, and they are early markers of AKI. TIMP-2 and IGFBP7 are elevated 24–48 h in patients with AKI secondary to cardiac surgery.[2] [TIMP-2] × [IGFBP7], an early predictive biomarker of AKI after pediatric congenital heart disease repair, increased at 4 h after CPB in children with later AKI, followed by a strong decrease at 24 h.[2] In the pediatric patients, the higher baseline urine [TIMP-2] × [IGFBP7] concentrations could not be interpreted by renal immaturity or venous congestion as a result of congenital heart disease in the younger population.[2]

### 5.4. Inflammatory biomarkers

IL-6 is a 26 kDa glycoprotein, secreted by lymphocytes T and B, macrophages, fibroblasts, endothelium cells, mesangium and by renal tubule cells, and it increases rapidly in the serum of AKI patients.[48] Liu et al.[49] observed that serum IL-6 level increased at 2 h after cardiac surgery, and its concentration at 2 h and 12 h correlated with the subsequent AKI. Dennen et al.[48] found that urine IL-6 levels could predict AKI, whereas other inflammatory cytokines, such as IL-8, IL-10 and IL-1$\alpha$, could not. On the other hand, Morgan et al.[50] interpreted that upregulation of IL-6, IL-8, TNF-$\alpha$ and C-reactive protein seemed to be a inflammatory response to CPB, but unrelated to AKI. Moreover, IL-18 is a pro-inflammatory cytokine that is induced and cleaved in the proximal tubule, and easily detected in the urine after ischemic AKI. In children undergoing cardiac surgery and developing AKI, urine IL-18 levels increased around 6 h and peaked at over 25-fold at 12 h after CPB with an AUC of 0.75. In addition, urine microalbumin (MA) levels must be at least 5–6 times of $\alpha_1$-microglobulin ($\alpha_1$-MG) to indicate glomerular injury.[43]

In general, NGAL and L-FABP are the earliest respondents at 2–4 h after the start of CPB, and KIM-1 and IL-18 represent the intermediate respondents, which are increased 6–12 h after cardiac surgery. All these biomarkers are more sensitive than serum creatinine.

## 6. Treatment and outcomes

Renal support regimens of AKI include use of balanced crystalloid solution, avoidance of potentially nephrotoxic agents, institution of continuous venous–venous renal replacement, strict glycaemic control and enteral/parenteral nutrition.[51]

Potential therapies for AKI include diuretics, dopamine, fenoldopam, theophylline/aminophylline and rasburicase. Of these, furosemide may increase urine output, but it is less effective in preventing AKI progression. Dopamine and fenoldopam are feasible in the prevention and treatment of

AKI owing to their vasodilatory effects on the renal vasculature.[52]

Investigational therapies have shown success in the prevention of AKI.[53] Fenoldopam, a highly selective dopamine-1 agonist, significantly reduced the need of continuous renal replacement therapy (CRRT) after cardiac surgery with a dose of 0.03–0.1 μg/kg/min given at 2–72 h postoperatively. It was more effective than low-dose dopamine in reversing renal hypoperfusion. Natriuretic peptides are systemic and renal dilators, and the synthetic analogues have shown promise for AKI treatment in experiments. N-Acetylcysteine, a thiol-containing antioxidant, also improved ischemic renal dysfunction in laboratory settings. Erythropoietin (EPO) has tissue-protective effects by preventing tissue ischemia and inflammation, and it has been used in the prevention of AKI after cardiac surgery.

A variety of renal replacement therapy modalities may be used including peritoneal dialysis, intermittent hemodialysis, and CRRT. Peritoneal dialysis is preferred in neonates due to simple devices and ease of implementation. Peritoneal dialysis has been a primary form of CRRT after cardiac operations. Patients undergoing peritoneal dialysis had decreased levels of IL-6 and IL-8, suggesting removal of inflammatory cytokines by peritoneal dialysis.[12] Intermittent hemodialysis is suitable for children with intoxications. CRRT serves as controlled fluid removal in critically ill children.[52] The hemofiltration techniques are capable of controlling fluid balance. However, to perform CRRT is sometimes difficult because of the complexity of canalization, the smaller caliber of the vascular access and catheters, and the greater hemodynamic response. Pediatric patients receiving CRRT after cardiac surgery had a higher mortality than those receiving CRRT after non-cardiac surgery.[54] Böök et al.[55] reported on a group of 15 patients who were managed with early institution of high-volume rapidly cycled peritoneal dialysis and had a mortality rate of 33%. Zobel et al.[56] reported improvement of mortality rate for 11 patients treated with the early institution of continuous arteriovenous hemofiltration or slow continuous ultrafiltration. Greenberg et al.[57] demonstrated that 18% of the children with perioperative AKI after pediatric cardiac surgery had chronic kidney disease at 5-year follow-up. For children with AKI after cardiac surgery, both continuous arteriovenous hemofiltration (CAVH) and continuous venovenous hemofiltration (CVVH) were reported to be associated with high mortality rates; however, an early initiation of renal replacement therapy could lead to a better prognosis.[58]

Age, single ventricle status and pRIFLE stage F were significantly associated with mortality. As age increases from 3 months to 3.5 years, mortality risk decreases. The mortality risk for patients with a single ventricle was greater than those with two ventricles.[59] Seguin et al.[60] noted a close correlation between fluid overload and more severe AKI. Fluid overload has been regarded as risk factor of morbidity, especially in small children following heart operation, and therefore management of fluid overload would improve patients' outcomes.[58] Pediatric patients undergoing heart operations receiving CRRT early displayed significantly decreased mortality.

## 7. Conclusions

AKI is a common complication of pediatric cardiac surgery and is associated with increased morbidity and mortality. To ameliorate the cardiopulmonary bypass techniques, improve renal perfusion and eradicate the causative risk factors are imperative for prevention of AKI in pediatric patients. Early and intermediate biomarkers are helpful for an early judgment of occurrence of postoperative AKI. Improved survival has been achieved by modification of hemofiltration techniques. Further development of AKI management strategies is anticipated in small children.

## Conflict of interest

None.

## References

1. Sethi SK, Kumar M, Sharma R, Bazaz S, Kher V. Acute kidney injury in children after cardiopulmonary bypass: risk factors and outcome. *Indian Pediatr* 2015;**52**:223–6.
2. Meersch M, Schmidt C, Van Aken H, Rossaint J, Görlich D, Stege D, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury after pediatric cardiac surgery. *PLoS One* 2014;**9**:e110865.
3. Li S, Krawczeski CD, Zappitelli M, Devarajan P, Thiessen-Philbrook H, Coca SG, et al. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study. *Crit Care Med* 2011;**39**:1493–9.
4. Blinder JJ, Goldstein SL, Lee VV, Baycroft A, Fraser CD, Nelson D, et al. Congenital heart surgery in infants: effects of acute kidney injury on outcomes. *J Thorac Cardiovasc Surg* 2012;**143**:368–74.
5. Morgan CJ, Zappitelli M, Robertson CM, Alton GY, Sauve RS, Joffe AR, et al. Risk factors for and outcomes of acute kidney injury in neonates undergoing complex cardiac surgery. *J Pediatr* 2013;**162**:120–7. e1.
6. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 2007;**71**:1028–35.
7. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute dialysis quality initiative workgroup. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. *Crit Care* 2004;**8**:R204–12.
8. Hughes PJ. Classification systems for acute kidney injury. Available at http://emedicine.medscape.com/article/1925597-overview. Accessed September 11, 2017.
9. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;**20**:629–37.
10. Jang WS, Kim WH, Choi K, Nam J, Jung JC, Kwon BS, et al. Incidence, risk factors and clinical outcomes for acute kidney injury after aortic arch repair in paediatric patients. *Eur J Cardiothorac Surg* 2014;**45**:e208–14.
11. Schwartz GJ, Haycock GB, Edelmann Jr CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;**58**:259–63.

12. DeSena HC, Nelson DP, Cooper DS. Cardiac intensive care for the neonate and child after cardiac surgery. *Curr Opin Cardiol* 2015;**30**:81–8.
13. Basu RK, Chawla LS, Wheeler DS, Goldstein SL. Renal angina: an emerging paradigm to identify children at risk for acute kidney injury. *Pediatr Nephrol* 2012;**27**:1067–78.
14. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. *Pediatr Crit Care Med* 2014;**15**:131–8.
15. Wheeler DS, Dent CL, Manning PB, Nelson DP. Factors prolonging length of stay in the cardiac intensive care unit following the arterial switch operation. *Cardiol Young* 2008;**18**:41–50.
16. Park SK, Hur M, Kim E, Kim WH, Park JB, Kim Y, et al. Risk factors for acute kidney injury after congenital cardiac surgery in infants and children: a retrospective observational study. *PLoS One* 2016;**11**:e0166328.
17. Axelrod DM, Sutherland SM, Anglemyer A, Grimm PC, Roth SJ. A double-blinded, randomized, placebo-controlled clinical trial of aminophylline to prevent acute kidney injury in children following congenital heart surgery with cardiopulmonary bypass. *Pediatr Crit Care Med* 2016;**17**:135–43.
18. Svarrer EM, Andersen HØ, Helvind M, Slagman MC, Navis G, Dullaart RP, et al. Urinary apolipoprotein M as a biomarker of acute kidney injury in children undergoing heart surgery. *Biomark Med* 2016;**10**:81–93.
19. Simpson SA, Zaccagni H, Bichell DP, Christian KG, Mettler BA, Donahue BS, et al. Acetaminophen attenuates lipid peroxidation in children undergoing cardiopulmonary bypass. *Pediatr Crit Care Med* 2014;**15**:503–10.
20. Hornik CP, Krawczeski CD, Zappitelli M, Hong K, Thiessen-Philbrook H, Devarajan P, et al. Serum brain natriuretic peptide and risk of acute kidney injury after cardiac operations in children. *Ann Thorac Surg* 2014;**97**:2142–7.
21. Riley AA, Jefferies JL, Nelson DP, Bennett MR, Blinder JJ, Ma Q, et al. Peritoneal dialysis does not adversely affect kidney function recovery after congenital heart surgery. *Int J Artif Organs* 2014;**37**:39–47.
22. Koyner JL, Garg AX, Shlipak MG, Patel UD, Sint K, Hong K, et al. Urinary cystatin C and acute kidney injury after cardiac surgery. *Am J Kidney Dis* 2013;**61**:730–8.
23. Cantinotti M, Storti S, Lorenzoni V, Arcieri L, Moschetti R, Murzi B, et al. The combined use of neutrophil gelatinase-associated lipocalin and brain natriuretic peptide improves risk stratification in pediatric cardiac surgery. *Clin Chem Lab Med* 2012;**50**:2009–17.
24. Ricci Z, Netto R, Garisto C, Iacoella C, Favia I, Cogo P. Whole blood assessment of neutrophil gelatinase-associated lipocalin versus pediatric RIFLE for acute kidney injury diagnosis and prognosis after pediatric cardiac surgery: cross-sectional study*. *Pediatr Crit Care Med* 2012;**13**:667–70.
25. Pedersen KR, Ravn HB, Povlsen JV, Schmidt MR, Erlandsen EJ, Hjortdal VE. Failure of remote ischemic preconditioning to reduce the risk of postoperative acute kidney injury in children undergoing operation for complex congenital heart disease: a randomized single-center study. *J Thorac Cardiovasc Surg* 2012;**143**:576–83.
26. Ricci Z, Luciano R, Favia I, Garisto C, Muraca M, Morelli S, et al. High-dose fenoldopam reduces postoperative neutrophil gelatinase-associated lipocaline and cystatin C levels in pediatric cardiac surgery. *Crit Care* 2011;**15**:R160.
27. Zappitelli M, Krawczeski CD, Devarajan P, Wang Z, Sint K, Thiessen-Philbrook H, et al. Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery. *Kidney Int* 2011;**80**:655–62.
28. Ricci Z, Stazi GV, Di Chiara L, Morelli S, Vitale V, Giorni C, et al. Fenoldopam in newborn patients undergoing cardiopulmonary bypass: controlled clinical trial. *Interact Cardiovasc Thorac Surg* 2008;**7**:1049–53.
29. Lee SH, Kim SJ, Kim HJ, Son JS, Lee R, Yoon TG. Acute kidney injury following cardiopulmonary bypass in children-risk factors and outcomes. *Circ J* 2017;**81**:1522–7.
30. Elella RA, Habib E, Mokrusova P, Joseph P, Aldalaty H, Ahmadi MA, et al. Incidence and outcome of acute kidney injury by the pRIFLE criteria for children receiving extracorporeal membrane oxygenation after heart surgery. *Ann Saudi Med* 2017;**37**:201–6.
31. Tanyildiz M, Ekim M, Kendirli T, Tutar E, Eyileten Z, Ozcakar ZB, et al. Acute kidney injury in congenital cardiac surgery: pediatric risk-injury-failure-loss-end-stage renal disease and Acute Kidney Injury Network. *Pediatr Int* 2017;**59**:1251–60.
32. Blinder JJ, Asaro LA, Wypij D, Selewski DT, Agus MSD, Gaies M, et al. Acute kidney injury after pediatric cardiac surgery: a secondary analysis of the safe pediatric euglycemia after cardiac surgery trial. *Pediatr Crit Care Med* 2017;**18**:638–46.
33. Lex DJ, Tóth R, Cserép Z, Alexander SI, Breuer T, Sápi E, et al. A comparison of the systems for the identification of postoperative acute kidney injury in pediatric cardiac patients. *Ann Thorac Surg* 2014;**97**:202–10.
34. Miklaszewska M, Korohoda P, Sobczak A, Horbaczewska A, Filipiak A, Zachwieja K, et al. Acute kidney injury in a single pediatric intensive care unit in Poland: a retrospective study. *Kidney Blood Press Res* 2014;**39**:28–39.
35. Alabbas A, Campbell A, Skippen P, Human D, Matsell D, Mammen C. Epidemiology of cardiac surgery-associated acute kidney injury in neonates: a retrospective study. *Pediatr Nephrol* 2013;**28**:1127–34.
36. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005;**365**:1231–8.
37. Basu RK, Andrews A, Krawczeski C, Manning P, Wheeler DS, Goldstein SL. Acute kidney injury based on corrected serum creatinine is associated with increased morbidity in children following the arterial switch operation. *Pediatr Crit Care Med* 2013;**14**:e218–24.
38. Esch JJ, Salvin JM, Thiagarajan RR, Del Nido PJ, Rajagopal SK. Acute kidney injury after Fontan completion: risk factors and outcomes. *J Thorac Cardiovasc Surg* 2015;**150**:190–7.
39. Park M, Coca SG, Nigwekar SU, Garg AX, Garwood S, Parikh CR. Prevention and treatment of acute kidney injury in patients undergoing cardiac surgery: a systematic review. *Am J Nephrol* 2010;**31**:408–18.
40. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol* 2009;**20**:672–9.
41. Bezerra CT, Vaz Cunha LC, Libório AB. Defining reduced urine output in neonatal ICU: importance for mortality and acute kidney injury classification. *Nephrol Dial Transplant* 2013;**28**:901–9.
42. Bojan M, Lopez-Lopez V, Pouard P, Falissard B, Journois D. Limitations of early serum creatinine variations for the assessment of kidney injury in neonates and infants with cardiac surgery. *PLoS One* 2013;**8**:e79308.
43. Zheng J, Xiao Y, Yao Y, Xu G, Li C, Zhang Q, et al. Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. *Pediatr Cardiol* 2013;**34**:880–6.
44. Koyner JL, Vaidya VS, Bennett MR, Ma Q, Worcester E, Akhter SA, et al. Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. *Clin J Am Soc Nephrol* 2010;**5**:2154–65.
45. Peco-Antić A, Ivanišević I, Vulićević I, Kotur-Stevuljević J, Ilić S, Ivanišević J, et al. Biomarkers of acute kidney injury in pediatric cardiac surgery. *Clin Biochem* 2013;**46**:1244–51.

46. Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, et al. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2008;**73**:465—72.
47. Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. *Kidney Int* 2008;**73**:863—9.
48. Dennen P, Altmann C, Kaufman J, Klein CL, Andres-Hernando A, Ahuja NH, et al. Urine interleukin-6 is an early biomarker of acute kidney injury in children undergoing cardiac surgery. *Crit Care* 2010;**14**:R181.
49. Liu KD, Altmann C, Smits G, Krawczeski CD, Edelstein CL, Devarajan P, et al. Serum interleukin-6 and interleukin-8 are early biomarkers of acute kidney injury and predict prolonged mechanical ventilation in children undergoing cardiac surgery: a case-control study. *Crit Care* 2009;**13**:R104.
50. Morgan CJ, Gill PJ, Lam S, Joffe AR. Peri-operative interventions, but not inflammatory mediators, increase risk of acute kidney injury after cardiac surgery: a prospective cohort study. *Intensive Care Med* 2013;**39**:934—41.
51. Krzych Ł, Wybraniec M, Chudek J, Bochenek A. Perioperative management of cardiac surgery patients who are at the risk of acute kidney injury. *Anaesthesiol Intensive Ther* 2013;**45**:155—63.
52. Jetton JG, Rhone ET, Harer MW, Charlton JR, Selew DT. Diagnosis and treatment of acute kidney injury in pediatrics. *Curr Treat Options Peds* 2016;**2**:56—68.
53. Lameire N, van Biesen W, Hoste E, Vanholder R. The prevention of acute kidney injury an in-depth narrative review. Part 2: drugs in the prevention of acute kidney injury. *NDT Plus* 2009;**2**:1—10.
54. Lin JJ. Renal support for pediatric patients with acute kidney injury after cardiac surgery. What do we know now? *Rev Esp Cardiol (Engl Ed)* 2012;**65**:785—7 [Article in English, Spanish].
55. Böök K, Ohqvist G, Björk VO, Lundberg S, Settergren G. Peritoneal dialysis in infants and children after open heart surgery. *Scand J Thorac Cardiovasc Surg* 1982;**16**:229—33.
56. Zobel G, Stein JI, Kuttnig M, Beitzke A, Metzler H, Rigler B. Continuous extracorporeal fluid removal in children with low cardiac output after cardiac operations. *J Thorac Cardiovasc Surg* 1991;**101**:593—7.
57. Greenberg JH, Zappitelli M, Devarajan P, Thiessen-Philbrook HR, Krawczeski C, Li S, et al. Kidney outcomes 5 Years after pediatric cardiac surgery: the TRIBE-AKI study. *JAMA Pediatr* 2016;**170**:1071—8.
58. Kwiatkowski DM, Krawczeski CD. Acute kidney injury and fluid overload in infants and children after cardiac surgery. *Pediatr Nephrol* 2017;**32**:1509—17.
59. Watkins SC, Williamson K, Davidson M, Donahue BS. Long-term mortality associated with acute kidney injury in children following congenital cardiac surgery. *Paediatr Anaesth* 2014;**24**:919—26.
60. Seguin J, Albright B, Vertullo L, Lai P, Dancea A, Bernier PL, et al. Extent, risk factors, and outcome of fluid overload after pediatric heart surgery. *Crit Care Med* 2014;**42**:2591—9.