Early prediction of acute kidney injury
in neonates with cardiac surgeryShanshan Shi,¹ Jiajie Fan,¹ Qiang Shu²

To cite: Shi S, Fan J, Shu Q. Early prediction of acute kidney injury in neonates with cardiac surgery. *World Jnl Ped Surg* 2020;3:e000107. doi:10.1136/wjps-2019-000107

Received 29 December 2019

Revised 12 May 2020

Accepted 14 May 2020

ABSTRACT

Background Acute kidney injury (AKI) occurs in 42%–64% of the neonatal patients experiencing cardiac surgery, contributing to postoperative morbidity and mortality. Current diagnostic criteria, which are mainly based on serum creatinine and hourly urine output, are not sufficiently sensitive and precise to diagnose neonatal AKI promptly. The purpose of this review is to screen the recent literature, to summarize the novel and cost-effective biomarkers and approaches for neonatal AKI after cardiac surgery (CS-AKI), and to provide a possible research direction for future work.

Data sources We searched PubMed for articles published before November 2019 with pertinent terms. Sixty-seven articles were found and screened. After excluding 48 records, 19 articles were enrolled for final analysis.

Results Nineteen articles were enrolled, and 18 possible urinary biomarkers were identified and evaluated for their ability to diagnose CS-AKI. Urinary neutrophil gelatinase-associated lipocalin (uNGAL), serum cystatin C (sCys), urinary human kidney injury molecule-1 (uKIM-1), urinary liver fatty acid-binding protein (uL-FABP) and interleukin-18 (uIL-18) were the most frequently described as the early predictors of neonatal CS-AKI.

Conclusions Neonates are vulnerable to CS-AKI. uNGAL, sCys, uL-FABP, uKIM-1 and uIL-18 are potential biomarkers for early prediction of neonatal CS-AKI. Renal regional oxygen saturation by near-infrared spectroscopy is a non-invasive approach for early identification of neonatal AKI. Further work should focus on exploring a sensitive and specific combined diagnostic model that includes novel biomarkers and other complementary methods.

the development of CS-AKI. Neonates are vulnerable to CS-AKI. Neonatal renal physiological features and several comorbidities and associated conditions have proved to be high-risk factors for neonatal CS-AKI (box 1). The reported incidence of AKI following pediatric cardiac surgery was 30%–50%, whereas in the neonatal population the incidence was 42%–64%, depending on the definition of AKI and the enrolled cardiac lesions (table 1). The occurrence of CS-AKI has been proven to be associated with short-term and long-term outcomes in neonates. Neonates with CS-AKI require longer duration in mechanical ventilation, intensive care unit stay and hospitalization. The mortality rate of neonates receiving dialysis after cardiac surgeries is 6.4 times higher than that of neonates without AKI. Furthermore, a 2-year follow-up study indicates that the infants surviving from Acute Kidney Injury Network stage 2 and 3 in their neonatal period have lower Z score for height.^{4 6} Establishing an ‘alarm system’ to identify patients at high risk for AKI might facilitate the initiation of prompt intervention and might improve the outcomes. The purpose of this review is to summarize the recent literature and to describe the novel and cost-effective biomarkers and tools for early diagnosis of neonatal CS-AKI.

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Cardiac Intensive Care Unit, The Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China

²Department of Thoracic and Cardiovascular Surgery, The Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China

Correspondence to

Dr Qiang Shu; shuqiang@zju.edu.cn

INTRODUCTION

Acute kidney injury (AKI), also known as acute kidney failure, covers a wide spectrum of clinical states, from subtle increase of serum creatinine (sCr) to serious injury that requires renal replacement.^{1 2} AKI is a common complication of patients after cardiac surgery both in adults and in children, and is recognized as one of the most important factors contributing to postoperative morbidity and mortality.^{3–5}

The mechanism of acute kidney injury after cardiac surgery (CS-AKI) is not well understood and can involve multiple factors. Hemodynamic fluctuation, inflammatory/immune factors, coagulation and neurohumoral regulation disorder might play essential roles in

DIAGNOSIS OF CS-AKI IN NEONATAL PATIENTS

Several definitions for AKI have been launched since 2004, including the Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE), Acute Kidney Injury Network (AKIN), and the Kidney Disease: Improving Global Outcomes (KDIGO) classifications.^{7–10} The disparities and similarities among these definitions are listed in table 2. In the case of patients with cardiac procedures, severe AKI stages are related to adverse outcome and higher mortality; however, the debate on the standard criteria for CS-AKI remains unsettled and depends on the patient population enrolled and the validated version of each criterion (such as adding a diagnostic

Box 1 The mechanisms of neonatal CS-AKI

Pathophysiology:

- ▶ Hemodynamic fluctuation
 - CPB and cross-clamping of aorta⁴⁷
 - Perioperative LCOS⁴⁸
 - Vasoactive drug application⁴⁹
 - Transfusion⁵⁰
- ▶ Inflammation/immunity
 - Inflammatory mediators^{33 34}
 - Free hemoglobin^{51 52}
 - Free iron⁵¹
 - ROS⁵²
- ▶ Others
 - Coagulopathy⁵³
 - Neurohumoral regulation disorder⁵⁴

Risk factors:

- ▶ VLBW/ELBW⁵⁵
- ▶ Nephrotoxic drug application⁵⁶
- ▶ Lesion types/comorbidity
 - Single ventricular physiology⁵
 - Duct-dependent CHD⁵⁷
 - Abdominal complications⁵⁷
 - Intraventricular hemorrhage⁵⁷
 - Fluid overload⁶
 - Sepsis⁵⁷
- ▶ Perioperative therapies
 - Complex surgical procedures^{47 58}
 - Preoperative ventilation⁴
 - Longer CPB time⁴⁷
 - DHCA application⁵⁹
 - ECMO⁶⁰

CHD, congenital heart disease; CPB, cardiopulmonary bypass; CS-AKI, acute kidney injury after cardiac surgery; DHCA, deep hypothermia cardiac arrest; ECMO, extracorporeal membrane oxygenation; ELBW, extremely low birth weight (birth weight <1000 g); LCOS, low cardiac output syndrome; ROS, reactive oxygen species; VLBW, very low birth weight (birth weight <1500 g).

period to AKIN and KDIGO systems).^{11 12} Generally, RIFLE is much more sensitive in identifying the risk-stage patients, and the AKIN and KDIGO may be more specific in diagnosing AKI, particularly in recognizing stage 3 patients. Nevertheless, all three classifications are based on the change of sCr directly and indirectly. The main challenges of diagnosing neonatal AKI are focused on the following items:

- ▶ The promptness of sCr: sCr obviously will not change until 25%–50% of renal function is lost, and the effect of fluid dilution may conceal the real change in sCr. Therefore, the rise in sCr in neonatal patients always delays until 36–48 hours after surgery. Patients in an early phase of AKI might not be discerned and would miss timely intervention.
- ▶ Some neonates present non-oliguric AKI, especially preterm neonates due to higher proportion of body water.¹³ Thus, urine output (UO) less than 0.5 mL/kg/hour is not sufficient, and some researchers refuse to take UO as a reliable indicator of CS-AKI.
- ▶ The number of nephrons and the tubular maturity are closely related to gestational age.^{11 12 14} The renal blood flow improves gradually within the initial several weeks after birth. However, glomerular filtration rate (GFR) will not be steady until 2 years of age.¹⁵ Accordingly, gestational age, birth weight and postnatal age all have a potential impact on the susceptibility of neonates to AKI.

EARLY PREDICTION OF CS-AKI IN NEONATAL PATIENTS

Regarding the limitations of sCr and UO in early recognition of CS-AKI in neonatal patients, tremendous research has been performed to explore possible serum and urine biomarkers and other non-invasive methods for discriminating patients at high risk for AKI.

Serum and urine biomarkers predicting neonatal CS-AKI

We searched PubMed with terms ‘neonate, cardiac surgery, acute kidney injury’, ‘neonate, cardiac surgical procedure, acute kidney injury’ and ‘neonate, cardiopulmonary bypass, acute kidney injury’ separately. Clinical trial, clinical study, controlled clinical trial, multicenter study, observational study and randomized controlled trial published before November 2019 were considered. A total of 67 articles were screened. After excluding 48 of these records, 19 articles were analyzed. The methodology is explicated in figure 1.

It is notable that, in the case of neonates, the application of urinary biomarkers for early prediction or for adding diagnostic value to sCr is prevalent. Urine samples were applied in a total of 15 of the 19 studies

Table 1 Incidence of CS-AKI in neonates

Study	Population	Cases	Cardiac lesion	AKI definition	Incidence (%)
Alabbas <i>et al</i> ⁶⁰	<28 days	122		AKIN	62
Morgan <i>et al</i> ⁴	≤6 weeks	264		AKIN	64
Piggott <i>et al</i> ⁶	6–29 days	95		AKIN	45
Park <i>et al</i> ⁵⁰	<30 days	60		KDIGO	48
Carlo <i>et al</i> ⁶¹	<30 days	56		KDIGO	75
SooHoo <i>et al</i> ⁶²	<30 days	95	HLHS	KDIGO	42

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CS-AKI, acute kidney injury after cardiac surgery; HLHS, hypoplastic left heart syndrome; KDIGO, Kidney Disease: Improving Global Outcomes.

Table 2 Definition and classification of neonatal acute kidney injury

AKIN			RIFLE			KDIGO		
Stage	sCr	UO	Stage	eGFR	UO	Stage	sCr	UO
1	Rise of ≥ 0.3 mg/dL or 1.5–1.9 times the baseline.	< 0.5 mL/kg/hour for 6 hours.	Risk	25% decrease in eGFR.	< 1.5 mL/kg/hour for 24 hours.	0	No change or rise of < 0.3 mg/dL.	≥ 0.5 mL/kg/hour.
2	2–3 times the baseline.	< 0.5 mL/kg/hour for > 12 hours.	Injury	50% decrease in eGFR.	< 1.0 mL/kg/hour for 24 hours.	1	Rise of ≥ 0.3 mg/dL or 1.5–1.9 times the baseline.	< 0.5 mL/kg/hour for 6–12 hours.
3	3 times the baseline or rise of ≥ 4.0 mg/dL with acute rise of at least 0.5 mg/dL.	< 0.3 mL/kg/hour for 24 hours or anuria for 12 hours.	Failure	75% decrease in eGFR.	< 0.7 mL/kg/hour for 24 hours or anuria for 12 hours.	2	2–2.9 times the baseline.	< 0.5 mL/kg/hour for ≥ 12 hours.
			Loss	Persistent failure of > 4 weeks.		3	3 times the baseline or rise of ≥ 2.5 mg/dL or initiation of RRT.	< 0.5 mL/kg/hour for ≥ 24 hours or anuria for ≥ 12 hours.
			End stage	Persistent failure of > 3 months.				

Baseline refers to the lowest previous level of sCr.

AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, and End-Stage Kidney Disease; RRT, renal replacement treatment; sCr, serum creatinine; UO, urine output.

we collected. The plausible explanations are that urine-oriented biomarkers can reflect both the structural damage and the functional injury of the kidney directly and that urinary samples can be obtained non-invasively from Foley catheter after cardiac surgery. The utilities of novel biomarkers in neonates are illustrated in [table 3](#).

Figure 1 Literature retrieval process. AKI, acute kidney injury; CPB, cardiopulmonary bypass; CS, cardiac surgical procedure.

Proximal tubular cell biomarkers

Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and liver fatty acid-binding protein (L-FABP) are secreted by the proximal tubular epithelial cells. Increases in concentration indicate tubular injury.

Elevating serum and urinary NGAL levels have been widely identified in patients with AKI with multiple etiologies. The relationship between NGAL and CS-AKI in neonates was also evaluated recently. In four studies including neonates, the rise in urinary NGAL (uNGAL) occurs as early as about 2 hours after surgery and shows good diagnostic ability for CS-AKI regardless of AKI definitions, even normalized by creatinine, and can be one of the independent risk factors for adverse clinical outcomes.^{16–22} Other studies also indicate that the value of uNGAL within 12 hours after surgery is a strong predictor of CS-AKI, and it is significantly associated with poor outcomes.^{21 23 24} A study including 30 neonatal patients concludes that, besides postoperative serum NGAL (sNGAL), preoperative sNGAL is also a potential indicator of CS-AKI.²⁵ But the conclusions are not always on the same page. A study published in 2018 with 59 neonates and infants reveals that both uNGAL and sNGAL are not indicators of CS-AKI. But in the cases experiencing longer cardiopulmonary bypass (CPB) time (≥ 75 min), uNGAL increases significantly as early as 2 hours after surgery.²⁶

KIM-1, a type 1 transmembrane protein, could not be detected in urine normally, but increases promptly after

Table 3 Literature review of novel biomarkers predicting CS-AKI in neonates

Author, year	Population	AKI definition	Novel biomarkers predicting CS-AKI
Krawczeski <i>et al</i> , 2011 ¹⁶	35/375	AKIN	uNGAL, sNGAL
Cantinotti <i>et al</i> , 2012 ¹⁷	26/135	AKIN	uNGAL, BNP, uNGAL/urinary creatinine ratio
Ricci <i>et al</i> , 2012 ¹⁸	50/160	RIFLE	uNGAL
Peco-Antić <i>et al</i> , 2012 ²³	20/112	≥25% decrease in eCCI	sCys C, sNGAL, uNGAL, uKIM-1, uL-FABP
Hassinger <i>et al</i> , 2012 ³¹	100*	RIFLE	sCys C
Zappitelli <i>et al</i> , 2012 ⁴¹	294*	AKIN	Urine albumin to creatinine ratio
Hazle <i>et al</i> , 2013 ²⁴	42*	AKIN/KDIGO	uNGAL, uIL-18, uKIM-1, sCys C
Seitz <i>et al</i> , 2013 ³²	139*	RIFLE	uNGAL, sCys C
Zheng <i>et al</i> , 2013 ³⁵	58*	AKIN	uMA, NAG and α1-MG-MG, uNGAL and uIL-18
Mamikonian <i>et al</i> , 2014 ¹⁹	40*	RIFLE	uNGAL
Alcaraz <i>et al</i> , 2014 ²⁰	106*	RIFLE	uNGAL, uNGAL/Cr
Bojan <i>et al</i> , 2016 ²¹	75/200	AKIN	uNGAL, urine creatinine normalized uNGAL
Herbert <i>et al</i> , 2015 ²²	17*	RIFLE	uNGAL, sCys C
Tew <i>et al</i> , 2017 ⁴⁰	187/814	AKIN	Nadir value of platelet
Reiter <i>et al</i> , 2018 ²⁶	59*	RIFLE	uNGAL
Gist <i>et al</i> , 2018 ²⁷	31*	KDIGO	uTIMP2*IGFBP-7, uKIM-1
Burra <i>et al</i> , 2018 ³⁸	51*	KDIGO	Serum phosphorus
Volovelsky <i>et al</i> , 2018 ³⁹	81*	KDIGO	Serum FGF23
Schroeder <i>et al</i> , 2019 ²⁵	30	KDIGO	sNGAL

The population enrolled in the studies is presented as neonate/total cases.

*Specific number of neonates was not described in the study.

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; BNP, brain natriuretic peptide; BNP, brain natriuretic peptide; CS-AKI, acute kidney injury after cardiac surgery; eCCI, estimated creatinine clearance; FGF23, fibroblast growth factor 23; IGFBP-7, insulin-like growth factor-binding protein type 7; KDIGO, Kidney Disease: Improving Global Outcomes; α1-MG, α1-microglobulin; RIFLE, Risk, Injury, Failure, Loss, and End-Stage Kidney Disease; sCys C, serum cystatin C; sNGAL, serum neutrophil gelatinase-associated lipocalin; uIL-18, urinary IL-18; uKIM-1, urinary KIM-1; uL-FABP, urinary L-FABP; uMA, urinary microalbumin; uNGAL, urinary neutrophil gelatinase-associated lipocalin; uTIMP2, urinary tissue inhibitor metalloproteinase type 2.

proximal tubular epithelial cells injury, boosting epithelial repair and phagocytosis. In a study with patients younger than 1 year old (including neonates), urinary KIM-1 at 6 hours after CPB has predictive power for AKI, with an AUC of 0.66.²⁷ L-FABP, which is involved in fatty acid metabolism, expresses highly in ischemic insult and is a sensitive predictor of kidney diseases. Urinary L-FABP (uL-FABP) increases at 2, 6 and 24 hours after surgery and proves to be a strong indicator of CS-AKI in neonatal and infants, and the AUC for uL-FABP is 0.89, 0.75 and 0.87, respectively.²³

Biomarkers of GFR

Cystatin C, a low-molecular-weight protein, is filtered freely by the glomerulus. Compared with creatinine, the serum cystatin C (sCys C) level would not be influenced by maternal level, gestational age, sex and muscle mass. Taking these theoretical properties into consideration, Cys C sounds an ideal marker of renal function in neonates in different clinical situations.^{28–30}

In the studies of neonates undergoing cardiac surgery, significant upregulation of sCys C is found at 2 and 8 hours following CPB and has been proven to be an independent

predictor of AKI.^{31 32} Likewise, elevating urinary cystatin C is also detected at a very early period after surgery (0, 2 hours) in patients with poor outcomes.²⁴

Inflammatory biomarkers

Systemic inflammatory response is a major cause of CS-AKI. Research studies have indicated that the traditional inflammatory mediators, including interleukins (ILs), interferon-gamma, tumor necrosis factor-alpha, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, C reactive protein and so on, do upregulate early after cardiac surgery. Theoretically, these phenomena are more likely to be a reaction to CPB than to the renal insult per se.^{33 34} IL-18, a proinflammatory cytokine, is activated and released into urine after ischemic insult of proximal tubules. However, the role of urinary IL-18 (uIL-18) in predicting AKI is still controversial. Zheng *et al*³⁵ reveal that in patients developing AKI uIL-18 has the best predictive ability at 4 hours after surgery, with an AUC of 0.835. In contrast, Morgan *et al*³³ do not find a significant difference in IL-18 between AKI and non-AKI patients.

Other biomarkers

In addition to the mainstream biomarkers mentioned, several other biomarkers are reported as potential predictors of CS-AKI. Tissue inhibitor metalloproteinase type 2 (TIMP-2) and insulin-like growth factor-binding protein type 7 (IGFBP-7) are two molecules provoking G1 cell cycle arrest, playing key roles in the development of and recovery from AKI.³⁶ Meersch *et al*³⁷ identified that urinary TIMP-2*IGFBP-7 concentration demonstrates a highly early predictive value for AKI (4 hours after surgery) in infants and children. Likewise, a recent study including infants and neonates reports that urinary TIMP-2*IGFBP-7 concentration at 12 hours after CPB strongly indicates the occurrence of AKI, with an AUC of 0.71.²⁴

Electrolytic and metabolic disorders are also involved in the kidney insult after cardiac surgery, and persistent hyperphosphatemia may prognose severe renal impairments. Burra *et al*'s³⁸ study found that serum phosphorus level increased significantly at 24 hours postoperatively in patients with AKI and could be another alternative predictor of CS-AKI. The rise in the preoperative and postoperative levels of fibroblast growth factor 23, a hormone which regulates renal phosphate reabsorption, has also been proven to be associated with severe AKI.³⁹

Furthermore, thrombocytopenia has been identified as a risk factor for CS-AKI, and the degree of the nadir platelet count has a strong relationship with the severity of AKI.⁴⁰ First postoperative urine albumin to creatinine ratio is also an available marker predicting stage 2 and 3 AKI in patients younger than 2 years old.⁴¹ Serum gelsolin is significantly decreased at 6 hours following CPB in patients with AKI and has been proven to be an excellent predictor of CS-AKI in neonates and young infants.⁴²

In general, NGAL, cystatin C, L-FABP, KIM-1 and IL-18 were the most frequently detected for early prediction of CS-AKI. Table 4 illustrates the common time period for each biomarker, all of which occur much earlier than the rise in sCr. However, it is unavoidable that these findings have some limitations. First, the majority of studies were conducted in single-center manners with non-uniform AKI criteria and with limited sample sizes. Second, the findings in this review are obtained from

studies including both neonatal and pediatric patients and lack systematic evaluation, particularly in the case of neonates. Third, although the novel biomarkers express rapidly after surgery, the discrepancies in sensitivity and specificity in different clinical settings are huge. Further work aiming to develop a joint application of traditional and novel biomarkers is needed in order to improve diagnostic accuracy.

Renal near-infrared spectroscopy predicting neonatal CS-AKI

Near-infrared spectroscopy (NIRS), a non-invasive, continuous and real-time monitor device, is used to detect regional oxygen saturation (rSO_2), namely the oxygen content within the local tissue. This new technology is based on the different absorptions of near-infrared wavelengths by oxygenated and deoxygenated hemoglobin, known as the Beer-Lambert principle. The sensor could be placed on the forehead, the surface of the abdomen, or the left or right side of the spine at the T10–L2 level to detect the cerebral, abdominal and kidney rSO_2 , respectively. The neonatal cerebral rSO_2 was recorded by Jobsis for the first time in 1977.⁴³ In 1991, NIRS was used as a non-invasive tool for evaluating the effect of hypothermic CPB and total circulatory arrest on pediatric cerebral metabolism.⁴⁴ Since then, tremendous research has been implemented to assess the influence of ischemic insult on the neurological, renal and other organic functions by NIRS in neonates.

A study including 40 neonates and young infants indicates that patients with renal rSO_2 <50% more than 2 hours within the first 24 hours after surgery are more susceptible to AKI. In addition, patients with permanently low renal rSO_2 need longer mechanical ventilation and inotropic support.^{24,45} Ruf *et al*⁴⁶ continuously monitored the renal rSO_2 intraoperatively and 24–48 hours postoperatively and found that intraoperative persistently low renal oximetry (<65%) or significant decrease of oximetry (>25%) was related to the occurrence of AKI and poor outcomes and that the diagnostic value of NIRS might surpass NGAL and cystatin C. These findings indicate that NIRS can be another promising non-invasive bedside monitor for the development of CS-AKI in neonates. Despite the inspiring results, NIRS still has several imperative shortcomings. First, the normal and pathological baseline for renal rSO_2 is still lacking, and the variance between individuals is significant. Second, the value of renal rSO_2 is easily influenced by the position, exogenous light, and cyanotic and non-cyanotic congenital heart diseases. Therefore, exploring a sensitive and specific combined diagnostic model consisting of NIRS and other chemical markers is inevitable in future work.

CONCLUSION

Neonatal patients are vulnerable to CS-AKI. Identifying the patients at high risk for CS-AKI facilitates timely intervention and improves outcome. UNGAL, serum cystatin C, uL-FABP, uKIM-1 and uIL-18 are the potential

Table 4 Common time period of biomarkers predicting neonatal CS-AKI

Biomarker	Time
uNGAL	2–12 hours postoperatively
sCys C	2–8 hours postoperatively
uL-FABP	2–6 hours postoperatively
uKIM-1	6–12 hours postoperatively
uIL-18	4–12 hours postoperatively

CS-AKI, acute kidney injury after cardiac surgery; sCys C, serum cystatin C; uIL-18, urinary interleukin-18; uKIM-1, urinary kidney injury molecule-1; uL-FABP, urinary liver fatty acid-binding protein; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

biomarkers for early prediction of CS-AKI in neonates. Continuous monitoring of renal rSO₂ by NIRS could be a cost-effective complement in the early diagnosis of neonatal AKI. Further work should focus on exploring a sensitive and specific combined diagnostic model that includes novel biomarkers and non-invasive tools.

Acknowledgements We sincerely appreciate the Key Laboratory for Diagnosis and Therapy of Neonatal Diseases, the Children's Hospital of Zhejiang University School of Medicine for serving as the scientific advisers.

Contributors SSS collected the data and drafted the manuscript. FJJ analyzed the data and assisted in revising the manuscript. SQ designed the study and supervised the drafting of the manuscript. All authors had read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not required for this review paper.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no data sets generated and/or analyzed for this study. No data, models or codes were generated in this review paper.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005;294:814–8.
- Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012;380:756–66.
- Li S, Krawczeski CD, Zappitelli M, 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.
- Morgan CJ, Zappitelli M, Robertson CMT, et al. Risk factors for and outcomes of acute kidney injury in neonates undergoing complex cardiac surgery. *J Pediatr* 2013;162:120–7.
- Blinder JJ, Goldstein SL, Lee VV, et al. Congenital heart surgery in infants: effects of acute kidney injury on outcomes. *J Thorac Cardiovasc Surg* 2012;143:368–74.
- Piggott KD, Soni M, Decampli WM, et al. Acute kidney injury and fluid overload in neonates following surgery for congenital heart disease. *World J Pediatr Congenit Heart Surg* 2015;6:401–6.
- Bellomo R, Ronco C, Kellum JA, et al. 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.
- Jetton JG, Guillet R, Askenazi DJ, et al. Assessment of worldwide acute kidney injury epidemiology in neonates: design of a retrospective cohort study. *Front Pediatr* 2016;19:68.
- Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.
- Ricci Z, Ronco C. Neonatal rifle. *Nephrol Dial Transpl* 2013;28:2211–4.
- Lex DJ, Tóth R, Cserép Z, 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.
- Sutherland L, Hittesdorf E, Yoh N, et al. Acute kidney injury after cardiac surgery: a comparison of different definitions. *Nephrology* 2020;25:212–8.
- Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. *Curr Opin Pediatr* 2012;24:191–6.
- Hinchliffe SA, Sargent PH, Howard CV, et al. Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the disector method and Cavalieri principle. *Lab Invest* 1991;64:777–84.
- Abitbol CL, Seeherunvong W, Galarza MG, et al. Neonatal kidney size and function in preterm infants: what is a true estimate of glomerular filtration rate? *J Pediatr* 2014;164:1026–31.
- Krawczeski CD, Woo JG, Wang Y, et al. Neutrophil gelatinase-associated lipocalin concentrations predict development of acute kidney injury in neonates and children after cardiopulmonary bypass. *J Pediatr* 2011;158:1009–15.
- Cantinotti M, Storti S, Lorenzoni V, 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.
- Ricci Z, Netto R, Garisto C, et al. Whole blood assessment of neutrophil gelatinase-associated lipocalin versus pediatric RIFLE for acute kidney injury diagnosis and prognosis after pediatric cardiac surgery. *Pediatr Crit Care Med* 2012;13:667–70.
- Mamikonian LS, Mamo LB, Smith PB, et al. Cardiopulmonary bypass is associated with hemolysis and acute kidney injury in neonates, infants, and children*. *Pediatr Crit Care Med* 2014;15:e111–9.
- Alcaraz AJ, Gil-Ruiz MA, Castillo A, et al. Postoperative neutrophil Gelatinase-Associated lipocalin predicts acute kidney injury after pediatric cardiac surgery*. *Pediatr Crit Care Med* 2014;15:121–30.
- Bojan M, Basto Duarte MC, Ermak N, et al. Structural equation modelling exploration of the key pathophysiological processes involved in cardiac surgery-related acute kidney injury in infants. *Crit Care* 2016;20:171.
- Herbert C, Patel M, Nugent A, et al. Serum cystatin C as an early marker of neutrophil gelatinase-associated Lipocalin-positive acute kidney injury resulting from cardiopulmonary bypass in infants with congenital heart disease. *Congenit Heart Dis* 2015;10:E180–8.
- Peco-Antić A, Ivanišević I, Vulićević I, et al. Biomarkers of acute kidney injury in pediatric cardiac surgery. *Clin Biochem* 2013;46:1244–51.
- Hazle MA, Gajarski RJ, Aiyagari R, et al. Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age. *J Thorac Cardiovasc Surg* 2013;146:861–7.
- Schroeder LW, Buckley JR, Stroud RE, et al. Plasma neutrophil gelatinase-associated lipocalin is associated with acute kidney injury and clinical outcomes in neonates undergoing cardiopulmonary bypass. *Pediatric Critical Care Medicine* 2019;20:957–62.
- Reiter K, Balling G, Bonelli V, et al. Neutrophil gelatinase-associated lipocalin reflects inflammation and is not a reliable renal biomarker in neonates and infants after cardiopulmonary bypass: a prospective case-control study. *Cardiol Young* 2018;28:243–51.
- Gist KM, Cooper DS, Wrona J, et al. Acute kidney injury biomarkers predict an increase in serum methylmalonic acid concentration earlier than serum Creatinine-Defined acute kidney injury in infants after cardiac surgery. *Ther Drug Monit* 2018;40:186–94.
- Elmas AT, Tabel Y, Elmas ON. Serum cystatin C predicts acute kidney injury in preterm neonates with respiratory distress syndrome. *Pediatr Nephrol* 2013;28:477–84.
- Li Y, Li X, Zhou X, et al. Impact of sepsis on the urinary level of interleukin-18 and cystatin C in critically ill neonates. *Pediatr Nephrol* 2013;28:135–44.
- Yang Y, Wu Y, Pan JJ, et al. Change of cystatin C values in preterm infants with asphyxia-From two centers of China. *J Clin Lab Anal* 2017;31:e22070.
- Hassinger AB, Backer CL, Lane JC, et al. Predictive power of serum cystatin C to detect acute kidney injury and pediatric-modified rifle class in children undergoing cardiac surgery. *Pediatr Crit Care Med* 2012;13:435–40.
- Seitz S, Rauh M, Gloeckler M, et al. Cystatin C and neutrophil gelatinase-associated lipocalin: biomarkers for acute kidney injury after congenital heart surgery. *Swiss Med Wkly* 2013;143:w13744.
- Morgan CJ, Gill PJ, Lam S, et al. 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.
- Liu KD, Altmann C, Smits G, 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.
- Zheng J, Xiao Y, Yao Y, 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.

- 36 Kashani K, Al-Khafaji A, Ardiles T, *et al.* Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 2013;17:R25.
- 37 Meersch M, Schmidt C, Van Aken H, *et al.* Validation of cell-cycle arrest biomarkers for acute kidney injury after pediatric cardiac surgery. *PLoS One* 2014;9:e110865.
- 38 Burra V, Nagaraja PS, Singh NG, *et al.* Early prediction of acute kidney injury using serum phosphorus as a biomarker in pediatric cardiac surgical patients. *Ann Card Anaesth* 2018;21:455–9.
- 39 Volovelsky O, Terrell TC, Swain H, *et al.* Pre-Operative level of FGF23 predicts severe acute kidney injury after heart surgery in children. *Pediatr Nephrol* 2018;33:2363–70.
- 40 Tew S, Fontes ML, Greene NH, *et al.* Natural history of nonimmune-mediated thrombocytopenia and acute kidney injury in pediatric open-heart surgery. *Paediatr Anaesth* 2017;27:305–13.
- 41 Zappitelli M, Coca SG, Garg AX, *et al.* The association of albumin/creatinine ratio with postoperative AKI in children undergoing cardiac surgery. *CJASN* 2012;7:1761–9.
- 42 Shi SS, Yue XJ, Zhao DY, *et al.* Plasma gelsolin level predicts acute kidney injury after cardiopulmonary bypass in infants and young children. *World J Pediatr* 2018;14:143–50.
- 43 Jobsis F. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977;198:1264–7.
- 45 Greeley WJ, Bracey VA, Ungerleider RM, *et al.* Recovery of cerebral metabolism and mitochondrial oxidation state is delayed after hypothermic circulatory arrest. *Circulation* 1991;84:III400–6.
- 45 Owens GE, King K, Gurney JG, *et al.* Low renal oximetry correlates with acute kidney injury after infant cardiac surgery. *Pediatr Cardiol* 2011;32:183–8.
- 46 Ruf B, Bonelli V, Balling G, *et al.* Intraoperative renal near-infrared spectroscopy indicates developing acute kidney injury in infants undergoing cardiac surgery with cardiopulmonary bypass: a case–control study. *Crit Care* 2015;19:27.
- 47 DeSena HC, Nelson DP, Cooper DS. Cardiac intensive care for the neonate and child after cardiac surgery. *Curr Opin Cardiol* 2015;30:81–8.
- 48 Salmasi V, Maheshwari K, Yang D, *et al.* Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery. *Anesthesiology* 2017;126:47–65.
- 49 Gaies MG, Gurney JG, Yen AH, *et al.* Vasoactive–inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass*. *Pediatr Crit Care Med* 2010;11:234–8.
- 50 Park SK, Hur M, Kim E, *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.
- 51 Billings FT, Ball SK, Roberts LJ, *et al.* Postoperative acute kidney injury is associated with hemoglobinemia and an enhanced oxidative stress response. *Free Radic Biol Med* 2011;50:1480–7.
- 52 Billings FT, Yu C, Byrne JG, *et al.* Heme oxygenase-1 and acute kidney injury following cardiac surgery. *Cardiorenal Med* 2014;4:12–21.
- 53 Meersch M, Zarbock A. Prevention of cardiac surgery-associated acute kidney injury. *Curr Opin Anaesthesiol* 2017;30:76–83.
- 54 Jönsson S, Agic MB, Narfström F, *et al.* Renal neurohormonal regulation in heart failure decompensation. *Am J Physiol Regul Integr Comp Physiol* 2014;307:R493–7.
- 55 Arcinue R, Kantak A, Elkhwad M. Acute kidney injury in ELBW infants. *J Neonatal Perinatal Med* 2015;8:349–57.
- 56 Selewski DT, Charlton JR, Jetton JG, *et al.* Neonatal acute kidney injury. *Pediatrics* 2015;136:e463–73.
- 57 Jang WS, Kim WH, Choi K, *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.
- 58 Basu RK, Chawla LS, Wheeler DS, *et al.* Renal angina: an emerging paradigm to identify children at risk for acute kidney injury. *Pediatr Nephrol* 2012;27:1067–78.
- 59 Miklaszewska M, Korohoda P, Sobczak A, *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.
- 60 AlAbbas A, Campbell A, Skippen P, *et al.* Epidemiology of cardiac surgery-associated acute kidney injury in neonates: a retrospective study. *Pediatr Nephrol* 2013;28:1127–34.
- 61 Carlo WF, Clark ST, Borasino S, *et al.* Impact of contrast exposure from computed tomography angiography on acute kidney injury after neonatal cardiopulmonary bypass surgery. *Congenit Heart Dis* 2017;12:540–5.
- 62 SooHoo M, Griffin B, Jovanovich A, *et al.* Acute kidney injury is associated with subsequent infection in neonates after the Norwood procedure: a retrospective chart review. *Pediatr Nephrol* 2018;33:1235–42.