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Review article

## The Role of Perioperative Risk Factors and Prognostic Value of Leading Biomarkers in the Occurrence of Acute Kidney Injury in Children after Cardiac Surgery

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### Abstract

The issue of acute kidney injury in children after cardiac surgery remains topical despite the constant development of modern technologies and methods. Complications arising from cardiac surgery in children have serious adverse effects, leading to increased length of stay in the infant intensive care unit and increased mortality.

The aim of study: to analyse modern concepts on the role of perioperative risk factors and prognostic value of leading biomarkers in the development of acute kidney injury in children after cardiac surgery.

The review was prepared using the method of searching literature on databases Scopus, PubMed, MedLine, Cyberleninka, Google Scholar, Cochrane library, TripDataBase for the period 2012-2022.

Research in the academic setting has revealed that there are several risk factors associated with the development of acute kidney injury in children after cardiac surgery. These factors include early patient age, duration of artificial circulation, complexity of surgery, use of artificial ventilation and inotropic support. Despite the importance of these studies, they have not fully explored many of the issues that have recently become relevant and related to the search for new biomarkers. These biomarkers play an important role in early diagnosis and treatment of acute kidney injury.

Key words: acute kidney injury, children, cardiac surgical intervention, biomarkers, risk factors.

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## Introduction

According to the literature, acute kidney injury (AKI) is a common complication of cardiac surgery in children of high-risk groups [1,2]. AKI occurs in about 30-60% of children who have undergone cardiac surgery and is associated with increased in-hospital mortality and adverse short-term outcomes [3-5]. Advances in cardiac surgery have led to a reduction in the overall mortality associated with open-heart surgery, but it can still exceed 40% among those patients who develop postoperative complications of AKI, and can reach 50% in patients, need renal replacement therapy [6].

There are many factors influencing the development of SRBs in children after cardiac surgery, and the underlying mechanisms include hypoperfusion, ischemia reperfusion injury, neuro-humoral activation, inflammation and oxidative stress. All these can occur before, during and after surgery [7].

In many studies, the exact mechanism for post-heart surgery development of AKIs in children is unclear, as many factors are involved. The factors involved in the development of AKI include five major categories: preoperative, cardiac bypass, postoperative, inflammatory and neuroendocrinal factors. In children undergoing cardiac surgery for congenital heart disease, the reported incidences of AKI according to pRIFLE criteria ranged from 20 to 64.6% [8-10]. The reported cases of AKI according to the KDIGO classification ranged from 29 to 86% [11-13]. Possible reasons for the difference in frequency are differences in patient characteristics (age, type of defect,

### Impact of perioperative risk factors on the prognosis of AKI

According to Zappitelli M. et al. postoperative prognosis in young children with congenital heart defects is aggravated by low body weight, age, prior to cardiac surgery, blue bloater of congenital malformation, cardiac bypass over 180 minutes, circulatory arrest, fluid overload and use of higher doses of cardiotonins in the early postoperative period, preoperative artificial lung ventilation, development of acute kidney injury [14,15].

The problem of the occurrence of cardiosurgically-associated acute kidney injury (CS-AKI) in newborns and infants, it is caused by a number of pathological mechanisms, such as features of blood circulation in congenital heart defects (CHD) with the physiology of a single ventricle; age-related anatomical and functional features (increased pulmonary vascular resistance, higher level of metabolism and oxygen consumption, increased hyperpermeability capillary tube, elevated level of water in the extracellular sector); anatomical and functional features of the myocardium (immaturity of cardio myocytes with a low density of contractile proteins, immaturity of calcium channels, mitochondria, extracellular matrix, leading to imperfection of the functions of contraction and relaxation, as well as limited opportunities to increase cardiac output); anatomical and functional features of the kidneys (low glomerular filtration, bicarbonate reabsorption threshold in the proximal tubules and sensitivity V2 receptors of

### Early prognostic biomarker of AKI

Many biomarkers are available for early diagnosis of AKIs, and some are widely used in practice. One of the main advantages of such biomarkers is sensitivity. The authors of this article focus on the effectiveness of biomarkers for detecting AKI and diagnosing the severity of the disease such as lipocalin associated with neutrophilic gelatinase (NGAL), kidney damage molecule-1 (KIM-1), cystatin C and

cardiac distress), Surgeon's surgical skills, cardiac bypass duration, anaesthesia and postoperative care. There are many risk factors for Acute Kidney Injury after pediatric cardiac surgery for congenital heart disease: low body weight, young age, blue disease, previous cardiac surgery procedure, risk adjustment for congenital heart defects (RACHS-1), single ventricular anatomy, preoperative pulmonary hypertension and congestive heart failure, preoperative use of inotropic support, preoperative admission to intensive care, preoperative artificial lung ventilation [14]. Bettina Ruf et al. reasonably showed that low blood pressure in the first 24 hours after surgery was a risk factor, and again emphasized the importance of hemodynamics for the risk of AKI [10].

Heart surgery in children is one of the most technically difficult surgical interventions. The severity of the patient's condition and the complexity of the anatomy of the malformation, may need the early intervention associated with decompensation, which may be accompanied by physiologic equilibration disorders. homeostasis.

**The aim of study:** to analyse modern concepts on the role of perioperative risk factors and prognostic value of leading biomarkers in the development of acute kidney injury in children after cardiac surgery.

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basolateral membranes of cells of distal tubules and collecting tubes to antidiuretic hormone [16].

According to Seliverstova A.A., et al. the most frequent CHD in newborns and infants with an elevated pre-operative level of creatinine were defects with obstruction of the left heart and a reduced fraction of the ejection system ventricle (critical aortic stenosis, critical aortic coagulation, left-side hypoplasia syndrome). According to the results of the study, cardiac surgical associated AKI (CSA-AKI) was diagnosed according to the AKIN classification in 34 out of 60 children (56.7%), of which 15 (44.1%) — stage 1, 10 (29.4%) — stage 2, 9 (26.4%) — stage 3. An increase in the preoperative creatinine level was diagnosed in 14 out of 60 (23.3%) children, 12 of them developed CSA-AKI [16].

Acute renal failure (ARF) often occurs in children in critical condition, with a frequency of up to 26.9% and is associated with high morbidity and mortality in children's intensive care units (ICU). Currently, the reduction in the rate of glomerular filtration is calculated by the level of creatinine in the blood serum. However, 48 hours can elapse between kidney damage and a measurable increase in creatinine levels. Lipocalin associated with neutrophil gelatinase in urine (uNGAL) has been confirmed for intravenous circulation in children, as it can detect AKI prior to functional changes confirmed by an increase in serum creatine level [17].

albumin. There are many methods for the prevention and treatment of AKI after cardiac surgery in children, but there is still no systematic approach [18,19].

Several risk stratification systems exist for cardiac surgery patients. The most reliable scores predict severe DFS requiring dialysis and include the Cleveland Clinic Score by Thakar and the Dialysis Risk After Cardiac Surgery

(Mehta) score [20,21]. To date, most studies have evaluated the ability of lesions and functional markers to predict AKI compared with clinical risk factors, but, they have not yet been included in prediction rates for AKI after cardiac surgery [22].

Currently, the diagnosis and severity of PPD are determined by serum creatinine and diuresis. However, serum creatinine and diuresis are not timely markers. The usefulness of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin-C, hepatic fatty acid binding protein (L-FABP), and interleukin (IL)-18 as markers has been shown in many studies. NGAL is the most promising marker for detecting RPL in the early stage of the disease [18].

There is strong evidence that albumin urine is an old but promising biomarker in this field. Albumin in urine can be measured in a general hospital with low cost, and studying results can be immediately available. Typically, in normal kidneys, a small amount of serum albumin passes through the glomerular filter and almost all of the albumin in the tubules is reabsorbed. The simultaneous occurrence of increased albumin efflux from the tubules and decreased reabsorption of albumin in the tubules results in albuminuria. As an additional mechanism, it has been reported that the albumin gene is induced in the renal cortex [23]. AKI can be detected earlier by albumin in urine than by creatinine in serum, because albumin expression occurs earlier than NGAL or KIM-1 expression. For early and accurate detection of AKI, a combination of several AKI biomarkers should be used.

Oded Volovelsky et al. studied the biomarker FGF23, which predicts severe acute kidney injury after cardiac surgery in children. It is suggested that FGF23 can detect subclinical kidney injury and can be used with demographic risk factors for AKI to improve prediction of risk of postoperative AKI [24,25].

Another study showed that the usefulness of urinary biomarkers, tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7), in detecting acute kidney injury (AKI) in neonates after surgery for congenital heart defect TIMP-2 and IGFBP-7 are cell cycle arrest proteins detected in urine during periods of renal stress/damage. TIMP-2 and IGFBP-7 urine levels 24 hours after CPR are good predictors of RPE [26,27].

Jef Van den Eynde et al. conducted an informative meta-analysis where aimed at synthesising knowledge

## Conclusions

According to the literature analysis, it was found that the study of the problem of the influence of perioperative risk factors, as well as the importance of early predictive biomarkers in the development of AKI in children after cardiac surgery was considered quite widely. At the same time, a number of specific issues related to the risk factor of AKIs in children after cardiac surgery remain poorly developed. There are only a few works on new biomarkers to diagnose post-heart surgery AKIs in children, but it is unclear how they relate to each other in terms of diagnostic accuracy.

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of new biomarkers and comparing their ability to predict AKIs published by March 2021. 37 studies were available for meta-analysis. Many biomarkers have been proposed as predictors of AKI associated with cardiac surgery in children, of which uNGAL with excellent diagnostic qualities was the most important. However, further consolidating evidence will be required before these new biomarkers can eventually help realize the precision medicine in the treatment of AKI. However, in modern clinical practice, the definition and detection of AKI are often based on changes in serum creatinine and diuresis, which are late and insensitive markers of kidney damage [5].

In the following study, the concentration of the kidney injury molecule-1 (KIM-1)/ creatinine (Cr) is shown in urine can be considered a good biomarker for early prediction of AKI after open heart surgery using an artificial bypass in young children with congenital heart defects. Thirty patients with congenital heart defects who underwent heart surgery using cardiac bypass were selected for urine and blood samples taken initially and 6, 24 and 48 hours after the surgery. Serum creatinine and blood urea nitrogen levels were measured, as were NGAL, KIM-1 and IL-18 levels in urine samples, and clinical parameters were evaluated. Out of 30 patients, AKI was developed in 12 patients after 48 hours after heart surgery. In the AKI group, 8 out of 12 (66.6%) patients met the AKI criteria after 24 hours, and the level of KIM-1/creatinine in urine peaked after 24 hours with a significant difference from the baseline level. In addition, the level of KIM-1/Cr in urine in the group with AKI was significantly higher than in the group without AKI after 6 hours. However, the levels of NGAL/Cr and IL-18/Cr in urine did not show a specific trend within 48 hours after heart surgery [28,29].

A systematic review and meta-analysis was carried out to assess the effectiveness of new biomarkers in detecting acute kidney injury and predicting other relevant clinical outcomes. A total of 56 studies (17.967 participants), mostly prospective cohort studies, were selected for inclusion. No studies have been found on the clinical impact of biomarkers on patients' treatment outcomes compared to standard therapy. The main sources of bias in studies were the lack of information on blinding and the optimal threshold for NGAL. The available data are insufficient to make a full assessment of the role and economic value of these biomarkers and to determine whether they provide cost-effective improvements in clinical outcomes in patients with acute kidney injury [30].

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**Contribution of the authors.** Conceptualization – A.A.; methodology – A.A., M.M.; verification – M.M., T.I.-R.; formal analysis – A.A., B.B. and M.M.; writing (original draft preparation) – A.A.; writing (review and editing) – A.A., S.B.

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## Кардиохирургиялық отадан кейінгі балалардағы бүйректің жіті зақымдануының пайда болуындағы жетекші биомаркерлердің периоперациялық қауіп факторларының рөлі мен болжамдық құндылығы

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### Түйіндеме

Кардиохирургиялық отадан кейінгі балалардағы бүйректің жіті зақымдану проблемасының өзектілігі қазіргі заманғы технологиялар мен әдістердің үнемі дамуына қарамастан әлі де сақталуда. Балалардағы кардиохирургиялық араласудан кейінгі пайда болатын асқынулар ауыр, теріс салдарға әкеледі. Бұл науқастың балалар реанимациясы бөлімінде болу ұзақтығының ұзаруына және өлім-жітімнің артуына әкеледі.

Зерттеудің мақсаты: периоперациялық қауіп факторларының рөлі және кардиохирургиялық араласудан кейінгі балалардағы жіті бүйрек зақымдануының дамуындағы жетекші биомаркерлердің болжамдық маңызы туралы заманауи тұжырымдамаларға талдау жүргізу.

Шолуды дайындау кезінде Scopus, PubMed, MedLine, Cyberleninka, Google Scholar, Cochrane library, tripdatabase дерекқорлары бойынша әдебиеттерді іздеу әдісі 2012-2022 жылдар аралығында қолданылды.

Ғылыми ортада жүргізілген зерттеулер бойынша кардиохирургиялық отадан кейін балаларда бүйректің жіті зақымдануының дамуына байланысты бірнеше қауіп факторлары бар екенін анықталды. Бұл факторларға науқастың жасы, жасанды канайналымының ұзақтығы, операцияның күрделілігі, механикалық желдетуді қолдану және инотропты дәрілер қолдану жатады. Бұл зерттеулердің маңыздылығына қарамастан, соңғы уақытта өзекті болып келе жатқан және жаңа биомаркерлерді табумен байланысты көптеген мәселелерді толық ашылмаған. Бұл биомаркерлер бүйректің жіті зақымдануын ерте диагностикалауда және емдеуде маңызды рөл атқарады.

Түйін сөздер: жіті бүйрек жетіспеушілігі, кардиохирургиялық ота, биомаркер, қауіп фактор.

## Роль периоперационных факторов риска и прогностическая ценность ведущих биомаркеров в возникновении острого повреждения почек у детей после кардиохирургических вмешательств

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### Резюме

Актуальность проблемы острого повреждения почек у детей после кардиохирургических вмешательств сохраняется несмотря на постоянное развитие современных технологий и методов. Осложнения, возникающие после кардиохирургических операций у детей, имеют серьезные негативные последствия, что приводит к увеличению длительности пребывания пациента в отделении детской интенсивной терапии и увеличению смертности.

Цель исследования: провести анализ современных концепций о роли периоперационных факторов риска и прогностического значения ведущих биомаркеров в развитии острого почечного повреждения у детей после кардиохирургических вмешательств.

При подготовке обзора был использован метод поиска литературы по базам данных Scopus, PubMed, MedLine, Cyberleninka, Google Scholar, Cochrane library, TripDataBase за период 2012-2022 гг.

Исследования, проведенные в научной среде, выявили, что существуют несколько факторов риска, связанных с развитием острого повреждения почек у детей после кардиохирургических вмешательств. Данные факторы включают ранний возраст пациента, продолжительность искусственного кровообращения, сложность операции, использование искусственной вентиляции легких и инотропную поддержку. Несмотря на значимость этих исследований, недостаточно изучены многие проблемы, которые стали актуальными в последнее время и связаны с поиском новых биомаркеров. Обсуждаемые биомаркеры играют важную роль в ранней диагностике и лечении острого повреждения почек.

Ключевые слова: острое почечное повреждение, дети, кардиохирургическая вмешательства, биомаркеры, факторы риска.