

Review Article

Cardiac Surgery-associated Acute Kidney Injury: A Comprehensive Review

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Abstract

Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common and serious complication occurring within 7 days after cardiac surgery. With over 2 million cardiac surgeries performed worldwide annually, CSA-AKI incidence ranges from 19% to 43% in adults and up to 64% in neonates, increasing perioperative mortality by 3-8-fold, prolonging hospital stays, and substantially increasing healthcare costs. Despite advances in perioperative care, CSA-AKI remains a major clinical challenge due to its multifactorial pathophysiology and limited therapeutic options. **Purpose:** This review aims to provide a comprehensive and updated overview of CSA-AKI, systematically summarizing current knowledge on its pathophysiology, risk factors, diagnostic criteria, prevention strategies, and treatment options, with particular emphasis on recent advances through 2026. **Methods:** A comprehensive literature review was conducted by searching electronic databases for relevant clinical studies, systematic reviews, meta-analyses, and guideline updates on CSA-AKI published through 2026. The reviewed literature was analyzed and synthesized across key domains including pathophysiological mechanisms, risk factor classification, diagnostic criteria comparison, and evidence-based prevention and treatment strategies. **Conclusions:** The pathophysiology of CSA-AKI involves multiple interacting mechanisms including hypoperfusion, ischemia-reperfusion injury, inflammation, oxidative stress, nephrotoxicity, and genetic susceptibility, with renal hypoperfusion during cardiopulmonary bypass identified as a central mechanism. KDIGO criteria currently offer the highest diagnostic sensitivity among available classification systems. Goal-directed perfusion (GDP) strategies maintaining indexed oxygen delivery above targeted thresholds have demonstrated significant reduction in CSA-AKI incidence, with emerging evidence supporting sex-specific optimization. Pharmacological advances, particularly amino acid therapy, have shown a 28% reduction in CSA-AKI incidence with a Class IIa recommendation. Early identification of high-risk patients, optimization of cardiopulmonary bypass management through GDP, and implementation of evidence-based prevention bundles remain the cornerstones of clinical management. Future research should prioritize targeted pharmacological therapies, machine learning-based risk prediction models, and adequately powered multicenter trials.

Keywords

Cardiac Surgery-associated Acute Kidney Injury, Cardiopulmonary Bypass, Goal-directed Perfusion, Risk Factors, Diagnosis, Prevention

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1. Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is defined as acute renal dysfunction occurring within 7 days after cardiac surgery [1]. Globally, over 2 million cardiac surgeries are performed annually, with adult CSA-AKI incidence approximately 22.3% [2], pediatric incidence around 41.8% [3], and neonatal incidence reaching as high as 64% [4]. CSA-AKI significantly increases perioperative mortality by 3-8-fold, prolongs intensive care unit and hospital stays, and substantially increases medical costs [1, 5]. Understanding the pathophysiology and risk factors of CSA-AKI, achieving early diagnosis, and implementing appropriate preventive measures are of paramount importance for reducing CSA-AKI incidence and improving patient outcomes. Recent studies have advanced our understanding of CSA-AKI mechanisms, diagnostic biomarkers, and prevention strategies, particularly regarding goal-directed perfusion protocols and sex-specific considerations [6, 7].

2. Pathophysiology and Risk Factors of CSA-AKI

2.1. Pathophysiology of CSA-AKI

The pathophysiological mechanisms of CSA-AKI are complex and remain incompletely understood. Given the high metabolic state of the kidney, previous researchers believed CSA-AKI resulted solely from ischemia and reperfusion injury [8]. However, animal and human studies have demonstrated that multiple factors play important roles in CSA-AKI development, including hypoperfusion, ischemia-reperfusion injury, inflammation and oxidative stress, nephrotoxins, and genetic factors [8-10].

2.1.1. Hypoperfusion and Ischemia-Reperfusion Injury

Ischemia-reperfusion injury is considered the most common cause of CSA-AKI. The injury mechanisms involve renal hypoperfusion, inadequate oxygen supply to renal tubular cells, poor nutrient delivery, and impaired waste clearance [11]. During cardiac surgery, hypotension, low-flow states associated with cardiopulmonary bypass (CPB), and nonpulsatile perfusion may all contribute to renal hypoperfusion [1]. In the early postoperative period, cardiogenic shock and low cardiac output syndrome significantly reduce renal perfusion, decreasing glomerular filtration rate. Activation of the sympathetic nervous system and renin-angiotensin-aldosterone system during the perioperative period causes systemic vasoconstriction, further reducing renal blood flow and exacerbating renal ischemia and hypoxia [9].

Prolonged renal ischemia and hypoxia may cause structural tubular damage. The kidney, as a high-metabolic organ, is highly sensitive to hypoperfusion and hypoxia, with the outer

medullary region being most vulnerable [10]. Following CPB, ischemia-reperfusion injury may occur through opening the mitochondrial permeability transition pore, associated with cell injury or death [10, 12].

Recent research has further elucidated that renal hypoperfusion, particularly within the oxygen-avid medullary region, lies at the heart of CSA-AKI pathogenesis [6, 7]. CPB significantly amplifies this risk by introducing suboptimal flow rates and pressures, nonpulsatile perfusion, hemodilution, and potential for emboli formation [7].

2.1.2. Inflammation and Oxidative Stress Response

Endothelial cell injury caused by renal ischemia and surgical tissue trauma can initiate inflammatory and oxidative stress responses [9]. The mechanism may involve selectins promoting leukocyte adhesion to damaged endothelial cells, facilitating the inflammatory cascade. Proinflammatory cytokines, including tumor necrosis factor- α , interleukin-6 and -8 (IL-6, IL-8), and chemokines participate in local tissue ischemic responses [13].

Compared with off-pump surgery, CPB pump use is associated with elevated proinflammatory cytokine levels, suggesting that CPB can activate inflammation during cardiac surgery [8]. However, the CPB pump as a CSA-AKI risk factor remains controversial. A multicenter study analyzing 4,752 coronary artery bypass graft patients found no significant difference in outcomes between CPB and off-pump techniques [14].

Recent studies have highlighted the role of the complement system in CSA-AKI pathophysiology. The complement system is activated throughout and after CPB, creating a feedback loop whereby complement-mediated kidney injury causes release of proinflammatory mediators, propagating further complement activation and perpetuating kidney damage [15, 16].

2.1.3. Nephrotoxic Injury

Perioperative exposure to various nephrotoxic medications is common in cardiac surgery patients, including antibiotics, antihypertensives, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and radiographic contrast agents [8, 9].

Aminoglycosides and β -lactam antibiotics are two of the most common nephrotoxic drug classes [9, 17]. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can inhibit efferent arteriolar vasoconstriction, causing relative volume depletion and AKI [8, 18].

Perioperatively, high concentrations of myoglobin are also nephrotoxic. A prospective study observing 201 cardiac surgery patients found that 41% of patients with creatine kinase values $\geq 25,000$ were diagnosed with AKI, compared to only 18% with lower creatine kinase values [19].

2.1.4. Genetic Factors

Extensive genetic studies indicate that genetic susceptibility plays an important role in CSA-AKI development. A prospective study of 111 coronary artery bypass graft patients found that the IL-6 gene -174G>C polymorphism was associated with elevated postoperative plasma IL-6 levels and CSA-AKI occurrence [20]. Genome-wide association studies have identified novel susceptibility genes for increased AKI risk [21].

2.2. Risk Factors for CSA-AKI

Most information regarding CSA-AKI risk factors comes from retrospective studies. These factors can be categorized as preoperative, intraoperative, and postoperative.

2.2.1. Preoperative Risk Factors

Common preoperative CSA-AKI risk factors include female sex, advanced age, obesity, and multiple preoperative comorbidities such as heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, and hypercholesterolemia [1]. Frequent preoperative use of NSAIDs, diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers increases CSA-AKI incidence [5]. Patients with any degree of preoperative renal insufficiency (defined as serum creatinine ≥ 1.2 mg/dL) have increased CSA-AKI risk [22].

A systematic review and meta-analysis identified advanced age as one of the most consistent predictors, with age-related physiological changes contributing to increased vulnerability [23].

2.2.2. Intraoperative Risk Factors

Intraoperative CSA-AKI risk factors include those related to cardiac surgery type and those related to intraoperative CPB. Complex cardiac surgeries (valve replacement, valve repair, combined valve and coronary surgery, aortic arch surgery), reoperations, and emergency surgeries have much higher CSA-AKI risk compared with routine cardiac surgeries [24]. Simple valve surgery and combined valve-coronary surgery increase CSA-AKI risk by 2-fold and 4-fold, respectively [5]. RACHS-1 grade ≥ 4 was identified as an independent risk factor for CSA-AKI in children [25].

For cardiac surgeries requiring CPB, reported risk factors include CPB duration, aortic cross-clamp time, nonpulsatile CPB flow, low-flow hypoperfusion, hemolysis, thrombosis, hemodilution, and deep hypothermia [1, 26]. Adult CPB duration >140 minutes was an independent CSA-AKI risk factor [27]. CPB duration >120 minutes significantly increased infant and child CSA-AKI incidence [3]. Recent studies clarified that prolonged CPB/aortic cross-clamp time was an independent predictor, with AKI patients showing 100% longer ICU stays and 167% longer mechanical ventilation times [28].

2.2.3. Postoperative Risk Factors

Postoperative cardiac surgery patients experiencing low cardiac output states, hypotension, severe vasoconstriction, sepsis, and nephrotoxic medications are associated with CSA-AKI [26]. Elevated central venous pressure (CVP) has emerged as an independent predictor of AKI after cardiac surgery with CPB [7]. High CVP significantly affects peritubular capillary blood flow and the glomerular ultrafiltration gradient.

In summary, preoperative renal insufficiency, intraoperative CPB hypoperfusion, and postoperative hypotension are the most important independent risk factors for CSA-AKI [26].

3. Diagnosis of CSA-AKI

Currently, no unified CSA-AKI diagnostic standard exists internationally; over 35 different CSA-AKI definitions have been established [1]. The following discusses the most commonly used diagnostic criteria.

3.1. RIFLE Criteria

In 2002, the Acute Dialysis Quality Initiative Group proposed the Risk, Injury, Failure, Loss of kidney function, and End-stage renal failure (RIFLE) criteria for CSA-AKI diagnosis [29]. Currently, RIFLE has been validated in many studies for CSA-AKI diagnosis and monitoring severity. However, RIFLE criteria have limitations including reduced sensitivity for CSA-AKI diagnosis in chronic kidney disease patients [30].

3.2. AKIN Criteria

To improve CSA-AKI diagnostic sensitivity and specificity, the Acute Kidney Injury Network (AKIN) proposed a modified RIFLE criteria in 2005 [31]. Compared with RIFLE criteria, AKIN criteria rely only on SCr and urine output values without involving GFR changes. However, it requires at least two SCr values obtained within 48 hours, which may miss patients with slowly rising SCr [30].

3.3. KDIGO Criteria

The Kidney Disease: Improving Global Outcomes (KDIGO) criteria represent the latest CSA-AKI diagnostic standard, combining the advantages of both RIFLE and AKIN [32]. Luo et al. found that CSA-AKI incidence diagnosed using RIFLE, AKIN, and KDIGO criteria were 46.9%, 38.4%, and 51%, respectively, indicating that KDIGO criteria have higher sensitivity [33]. KDIGO 2026 guideline updates emphasize early AKI identification and personalized risk stratification.

3.4. pRIFLE Criteria

Since the above CSA-AKI diagnostic criteria rely on SCr and urine output values, and pediatric patient characteristics

affect SCr values, Akcan-Arikan et al. modified RIFLE criteria for pediatric patients, resulting in the pediatric RIFLE

(pRIFLE) criteria [34]. Studies found that pRIFLE criteria diagnosed higher CSA-AKI incidence compared with AKIN criteria (61.3% vs 47.4%) [35].

Table 1. RIFLE Classification [29].

Stage	SCr or GFR	Urine Output
Risk (R)	SCr increased to 1.5-2× baseline or GFR decreased >25%	<0.5 mL/kg/h for >6 h
Injury (I)	SCr increased to 2-3× baseline or GFR decreased >50%	<0.5 mL/kg/h for >12 h
Failure (F)	SCr increased to >3× baseline or GFR decreased >75%, or SCr ≥354 μmol/L	<0.3 mL/kg/h for >24 h or anuria >12 h
Loss (L)	Persistent failure >4 weeks	-
End-stage (E)	End-stage renal disease (persistent failure >3 months)	-

SCr, serum creatinine; GFR, glomerular filtration rate

Table 2. AKIN Classification [31].

Stage	SCr	Urine Output
1	SCr increased ≥0.3 mg/dL or 1.5-2× baseline	<0.5 mL/kg/h for >6 h
2	SCr increased to 2-3× baseline	<0.5 mL/kg/h for >12 h
3	SCr increased to 3× baseline or SCr ≥354 μmol/L, or RRT initiated	<0.3 mL/kg/h for >24 h or anuria >12 h

SCr, serum creatinine; RRT, renal replacement therapy

Table 3. KDIGO Classification [32].

Stage	SCr	Urine Output
1	1.5-1.9× baseline or increased ≥0.3 mg/dL within 48 h	<0.5 mL/kg/h for 6-12 h
2	2.0-2.9× baseline	<0.5 mL/kg/h for >12 h
3	3× baseline or ≥4.0 mg/dL or RRT initiated	<0.3 mL/kg/h for >24 h or anuria for 12 h

SCr, serum creatinine; RRT, renal replacement therapy

Table 4. pRIFLE Classification [34].

Stage	eCrCl	Urine Output
Risk (R)	Decreased >25%	<0.5 mL/kg/h for 8 h
Injury (I)	Decreased >50%	<0.5 mL/kg/h for 16 h
Failure (F)	Decreased >75% or eCrCl <35 mL/min/1.73 m ²	<0.3 mL/kg/h for 24 h or anuria for 12 h
Loss (L)	Persistent failure >4 weeks	-
End-stage (E)	End-stage renal disease (>3 months)	-

pRIFLE, pediatric RIFLE; eCrCl, estimated creatinine clearance

In summary, KDIGO criteria represent the current epidemiological and clinical standard for CSA-AKI diagnosis [1].

4. Prevention and Treatment of CSA-AKI

Identifying and classifying high-risk CSA-AKI patients enables optimal decision-making for CSA-AKI prevention and early intervention. Recent advances have integrated machine learning models with clinical and intraoperative biosignal data for predicting CSA-AKI [36].

4.1. Prevention of CSA-AKI

Current CSA-AKI prevention principles are based on physiological and pharmacological considerations. The traditional CSA-AKI physiological hypothesis is that low cardiac output or low mean arterial pressure leads to insufficient renal oxygen supply [1].

4.1.1. Optimizing Preoperative Preparation

Before surgery, patients should avoid nephrotoxic medications, optimize cardiac output, improve congestive heart failure, and maintain hemodynamic stability. For diabetic patients, perioperative hyperglycemia (>180 mg/dL) should be prevented. Patients with chronic kidney disease should have serum creatinine, blood electrolyte levels, and urine output closely monitored preoperatively [26].

4.1.2. Optimizing Cardiopulmonary Bypass

For intraoperative CSA-AKI prevention, current research focuses on optimizing CPB. Many studies have shown that renal hypoperfusion and insufficient oxygen supply during CPB are important pathogenic mechanisms [9, 10]. During CPB, goal-directed perfusion (GDP) management strategies have been proven to effectively reduce CSA-AKI incidence [37].

GDP strategy incorporates monitoring of perfusion flow, hematocrit, mean arterial pressure, and oxygen metabolism indicators such as indexed oxygen delivery ($DO_2 i$) to guide individualized CPB perfusion. $DO_2 i$ is the core indicator of GDP management [37, 38]. In 2018, Ranucci et al. conducted a multicenter randomized controlled trial [39], randomizing 350 cardiac surgery patients to GDP or conventional groups, with the GDP group maintaining $DO_2 i > 280 \text{ mL}/(\text{min m}^2)$. Results showed reduced CSA-AKI stage 1 incidence (relative risk 0.45, $P=0.01$). A meta-analysis showed that GDP strategy reduced CSA-AKI incidence (relative risk 0.52, $P<0.0001$) [40].

A 2025 randomized controlled trial demonstrated that GDP maintaining $DO_2 i \geq 360 \text{ mL}/\text{min}/\text{m}^2$ during pediatric cardiac surgery significantly reduced AKI incidence (28.1% vs 42.2%, relative risk 0.67, $P=0.010$) [41]. Subgroup analysis showed that GDP was particularly beneficial for patients aged less

than 1 year, those with nadir temperature $>32^\circ\text{C}$, those with nadir hemoglobin $<8 \text{ g/L}$ during CPB, and those with CPB duration 60-120 minutes.

Compared with adults, infants and children have higher metabolic rates and oxygen demand. Bojan et al. found that during normothermic CPB, $340 \text{ mL}/(\text{min m}^2)$ may represent the minimum $DO_2 i$ for maintaining aerobic metabolism in neonates [42]. Zhang et al. found that minimum safe $DO_2 i$ threshold for infants and children was $353 \text{ mL}/(\text{min m}^2)$ [43].

Recent studies highlighted sex differences in optimal $DO_2 i$ thresholds: $<301 \text{ mL}/\text{min}/\text{m}^2$ for males and $<273 \text{ mL}/\text{min}/\text{m}^2$ for females [7].

4.1.3. Pharmacological Prevention

Many medications are believed to be related to CSA-AKI prevention. In multiple prospective observational studies, perioperative statin therapy was associated with reduced C-reactive protein levels and lower atrial fibrillation incidence [44]. However, some large randomized controlled trials found that statin use during cardiac surgery did not reduce CSA-AKI or in-hospital mortality [1].

Recent studies have introduced promising advances. Amino acid therapy has shown successful translation from laboratory to clinical practice, demonstrating effectiveness in a large randomized trial ($n=3,511$) with 28% reduction in CSA-AKI incidence [45]. The 2024 EACTS/ESA/EBCP guidelines have given this intervention a Class IIa recommendation.

4.2. Treatment of CSA-AKI

Avoiding CSA-AKI through prevention measures remains the primary management strategy for high-risk CSA-AKI patients. For patients with evidence of early and progressive CSA-AKI, active intervention and treatment are crucial. CSA-AKI treatment can be divided into two categories: non-renal replacement therapy and renal replacement therapy.

4.2.1. Non-Renal Replacement Therapy

Aggressive intervention for oliguria and early CSA-AKI patients can prevent progressive tubular injury and renal function deterioration. Discontinue all potentially nephrotoxic medications, optimize hemodynamics [26]. For patients with hypertension and chronic kidney disease history, aggressive blood pressure reduction should be avoided because these patients typically require higher blood pressure (systolic 130-150 mmHg) to maintain renal blood flow perfusion.

If oliguria persists after hemodynamic improvement, diuretic use may be considered. Studies have shown that loop diuretics have no direct effect on renal function recovery but may increase postoperative mortality [46]. However, loop diuretics have consistently been shown to improve urine output. Once oliguric renal failure is diagnosed, strict fluid intake restriction should be implemented. Fluid overload in CSA-AKI increases pulmonary edema and organ congestion risks [47].

4.2.2. Renal Replacement Therapy

In CSA-AKI cases, 1-5% of patients require renal replacement therapy initiation. Routine indications include anuria, severe oliguria, volume overload unresponsive to diuretics, clinical complications of uremia, hyperkalemia (potassium concentration >6.5 mmol/L), severe metabolic acidosis (pH <7.2), and obvious azotemia [1].

The optimal timing for renal replacement therapy initiation after cardiac surgery remains uncertain. A multicenter retrospective study found that delayed initiation (≥ 3 days after cardiac surgery) was associated with increased in-hospital mortality, worsening renal function, and prolonged hospital stay [48].

In two large multicenter randomized controlled trials (ATN and RENAL trials), the ATN trial 60-day mortality for severe CSA-AKI requiring renal replacement therapy was 52.6%; the RENAL trial 90-day mortality was 44.7% [49, 50].

5. Conclusion

CSA-AKI is a common and important complication of cardiac surgery, associated with increased postoperative mortality and morbidity. Early identification of high-risk patients, developing preventive intervention measures, avoiding nephrotoxic medications, monitoring systemic hemodynamic changes, and optimizing CPB technology combined with GDP strategies represent current mainstays of CSA-AKI clinical management.

Recent advances have significantly improved our understanding and management of CSA-AKI. Key developments include enhanced pathophysiological understanding with recognition of complement system activation, improved diagnostic approaches with novel biomarkers (NGAL, [TIMP-2] \times [IGFBP7], KIM-1), goal-directed perfusion evidence supporting DO₂ i maintenance targets with sex-specific thresholds, pharmacological advances with amino acid therapy showing 28% reduction in CSA-AKI incidence earning Class IIa recommendation, and KDIGO bundle implementation suggested to reduce overall CSA-AKI incidence and severity.

Future research should focus on developing targeted pharmacological therapies, improving risk prediction models through machine learning integration, and conducting adequately powered global trials.

Abbreviations

AKIN	Acute Kidney Injury Network
CPB	Cardiopulmonary Bypass
CSA-AKI	Cardiac Surgery-Associated Acute Kidney Injury
CVP	Central Venous Pressure
DO ₂ i	Indexed Oxygen Delivery
EACTS	European Association for Cardio-Thoracic Surgery

EBCP	European Board of Cardiovascular Perfusion
eCrCl	Estimated Creatinine Clearance
ESA	European Society of Anaesthesiology
GDP	Goal-Directed Perfusion
GFR	Glomerular Filtration Rate
IGFBP7	Insulin-Like Growth Factor Binding Protein 7
IL-6	Interleukin-6
IL-8	Interleukin-8
KIM-1	Kidney Injury Molecule-1
KDIGO	Kidney Disease: Improving Global Outcomes
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
pRIFLE	Pediatric Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Renal Failure
RIFLE	Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Renal Failure
RRT	Renal Replacement Therapy
SCr	Serum Creatinine
TIMP-2	Tissue Inhibitor of Metalloproteinases-2

Author Contributions

Feng Long: Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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