



Review Article

Cardiac Surgery–Associated Acute Kidney Injury: Integrative Perspectives on Pathogenesis, Phenotyping, and Precision Management

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Article info

Article History:

Received: May 21, 2025

Revised: November 11, 2025

Accepted: January 10, 2026

published: July 25, 2026

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Abstract

Acute kidney injury (AKI) following cardiac surgery, termed cardiac surgery-associated AKI (CSA-AKI), is a frequent and serious complication that significantly increases patient morbidity, mortality, hospital stay, and healthcare costs. Even when apparent renal recovery occurs, a considerable number of patients are at heightened long-term risk for developing chronic kidney disease (CKD). While much is known about general AKI, there remains a critical knowledge gap concerning persistent AKI—instances where injury does not resolve quickly and may evolve into acute kidney disease (AKD). The pathophysiological mechanisms, long-term sequelae, and management strategies for persistent AKI, especially after cardiac surgery, are poorly understood. Failure to achieve timely renal recovery, as in persistent AKI, is linked to a worse prognosis than transient episodes. This narrative review critically assesses the current understanding of persistent and severe AKI following cardiac surgery, outlines key challenges in early recognition and differentiation, discusses the complex mechanisms underlying renal non-recovery, and explores novel diagnostic, therapeutic, and research avenues. The ultimate aim is to highlight the potential of precision medicine strategies to improve outcomes for patients with persistent and severe CSA-AKI.

Keywords: Renal phenotypes, Precision nephrology, Renal risk stratification, Cardiac surgery, Acute kidney injury

Introduction

Acute kidney injury (AKI) remains a serious and prevalent complication among patients undergoing cardiac surgery. The incidence of cardiac surgery-associated AKI (CSA-AKI) varies considerably, with estimates ranging from 20% to 30% and reaching up to 43% depending on the diagnostic criteria and patient demographics employed.¹⁻⁵ Globally, approximately 25.9% of adult patients undergoing cardiac surgery develop CSA-AKI.⁶⁻⁹ Large cohort studies consistently confirm this burden, with a prospective study reporting an overall AKI incidence of 31.2%,¹⁰ and a recent investigation in a Chinese cohort documenting an incidence of 29.6%.¹¹ This incidence translates into a significant clinical and economic burden. CSA-AKI is strongly linked to adverse outcomes. Patients who develop AKI experience markedly higher short-term mortality, reaching up to 10.9%, compared with negligible mortality among those without AKI.¹¹ In cases requiring renal replacement therapy (AKI-RRT), mortality rates may rise to 36.5%.¹⁰ Moreover, CSA-AKI is linked to

prolonged ICU and hospital stays, increased healthcare costs, and a heightened risk of progression to chronic kidney disease (CKD), with long-term dialysis required in approximately 2–6% of cases.¹² The long-term mortality risk is also significantly elevated, with hazard ratios around 1.68 for any degree of AKI.¹³

A critical element in the clinical trajectory of AKI is its duration, particularly the distinction between transient and persistent forms. Transient AKI typically resolves within 48–72 hours or by the time of hospital discharge.¹⁴ In contrast, persistent AKI is characterized by sustained renal dysfunction beyond this period, often exceeding seven days or persisting at discharge, thus meeting criteria for AKD.¹⁵ Some analyses indicate that prolonged AKI, lasting from over seven days to less than three months, occurs in approximately 13% of patients undergoing cardiac surgery.⁶ Critically, the prognostic implications of these two trajectories diverge substantially. While transient AKI may not independently worsen in-hospital outcomes compared to patients with no AKI,¹⁶ persistent



AKI is consistently and strongly associated with a significantly poorer prognosis, including higher mortality and greater risk of long-term renal impairment.¹⁴ For example, one study reported a 26% mortality rate in patients with persistent AKI at discharge versus only 4% in those with transient AKI.¹⁶ These findings underscore that delayed renal recovery may be more detrimental than the initial injury itself.

The focus on persistent AKI is particularly pertinent in the context of cardiac surgery. This surgical setting often involves a significant and somewhat predictable renal insult, making it a unique model for studying the mechanisms of AKI persistence and non-recovery.⁶ The transition from AKI to CKD represents a significant long-term complication, and persistent AKI or AKD serves as a critical intermediary in this progression.¹⁵ Studies have shown that even AKI with early recovery can increase the risk of subsequent CKD, but persistent AKI dramatically amplifies this risk.¹⁵ The pathophysiological mechanisms underlying non-recovery, including sustained inflammation, failed tubular repair, maladaptive regeneration, and fibrosis, are particularly pronounced in the cardiac surgical setting, where cardiopulmonary bypass (CPB), ischemia-reperfusion injury, and systemic inflammatory responses play central roles.⁵

A major barrier to progress in this field is the lack of a standardized, cardiac surgery-specific definition of persistent AKI. The term is variably applied, sometimes equated with AKI at discharge or simply defined by duration, which hinders cross-study comparisons and limits the development of targeted interventions. Establishing a consensus definition is therefore critical for identifying high-risk populations and designing robust clinical trials.

This review provides a comprehensive and analytical synthesis of current evidence on persistent and severe AKI following cardiac surgery. It aims to clarify existing definitions, summarize epidemiological data, and examine the underlying pathophysiological mechanisms. In addition, it critically addresses diagnostic and management challenges, highlights emerging therapeutic approaches, and outlines future research priorities, with particular emphasis on precision medicine strategies to improve patient outcomes.

Materials and Methods

Search strategy

This narrative review examines and synthesizes the current body of literature on persistent and severe CSA-AKI. Through an extensive search of scientific databases, including PubMed, Web of Science, and Scopus, we identified relevant studies published over the past decade. These studies focused on the epidemiology, pathophysiology, diagnostic biomarkers, management strategies, and recovery trajectories of CSA-AKI. This review also evaluates existing evidence to identify therapeutic limitations and research gaps, with a particular focus on biomarker-guided precision

medicine approaches. Keywords used in the search include: Persistent Acute Kidney Injury, Cardiac Surgery-Associated AKI, Acute Kidney Disease, AKI Phenotypes, Biomarkers, Precision Nephrology, Postoperative Renal Dysfunction.

Definition and Classification

KDIGO and AKD Definitions

The Kidney Disease: Improving Global Outcomes (KDIGO) criteria remain the most commonly accepted standard for defining AKI. According to KDIGO, AKI is defined as an increase in serum creatinine (SCr) of ≥ 0.3 mg/dL within 48 hours, a rise to ≥ 1.5 times the baseline within 7 days, or urine output < 0.5 mL/kg/h for at least 6 hours. While these criteria capture the acute phase, they fall short when it comes to describing the persistence of renal dysfunction.

The term “persistent AKI” is commonly used to describe kidney injury that persists beyond 48–72 hours following the initial insult.⁶ However, the lack of a universally accepted consensus, particularly in the cardiac surgery setting, often leads to conceptual overlap with AKD. The latter, AKD, defined by the Acute Dialysis Quality Initiative (ADQI), refers to kidney dysfunction persisting for 7 to 90 days following an AKI event.¹⁷

Limitations of Existing Models

In the context of cardiac surgery, persistent AKI often overlaps with the AKD timeline. This overlap reflects impaired recovery mechanisms and represents a critical window for intervention to prevent irreversible damage and the progression to CKD.¹⁵ In fact, lack of renal recovery during the first postoperative week has consistently been linked to poor outcomes.

Definitions of transient versus persistent AKI vary across studies. Some studies define transient AKI as resolution of diagnostic criteria by hospital discharge, whereas persistent AKI is defined by the continued fulfillment of AKI criteria at discharge (e.g., SCr increase > 0.5 mg/dL or $> 25\%$ from baseline).¹⁴ Duration-based definitions are also common; for instance, AKI resolving within 48 hours is labeled transient, while persistence beyond that point, especially in neonates’ post-cardiac surgery, indicates persistent AKI.¹⁸ This lack of consensus complicates comparisons across studies and highlights the urgent need for a standardized definition, preferably tailored to cardiac surgery patients.

The distinction between transient and persistent AKI is not merely academic but carries important clinical implications. Persistent AKI is associated with markedly worse short- and long-term outcomes, including higher mortality, greater risk of CKD progression, increased dialysis dependence, and more frequent major adverse cardiovascular events (MACE). In contrast, transient AKI tends to have an outcome similar to that of non-AKI patients. For example, the hazard ratio for long-term mortality is 2.71 in patients with unresolved AKI at discharge, compared with 1.31 in those with recovered

renal function.¹³ Early recognition of persistent AKI may facilitate appropriate follow-up care, timely nephrology referral, and more effective allocation of clinical resources.⁵

The requirement for temporary or permanent RRT, including intermittent hemodialysis or continuous renal replacement therapy (CRRT), represents a critical marker of severity in CSA-AKI. Initiation of RRT is incorporated into the KDIGO criteria as a diagnostic threshold for stage 3 AKI, identifying the most severe form of the syndrome, regardless of creatinine or urine output changes.^{19,20} Beyond its diagnostic role, the requirement for RRT strongly predicts adverse clinical outcomes, including higher short- and long-term mortality, increased risk of CKD progression, prolonged intensive care and hospital stay, and greater long-term health care costs.²¹ In the context of persistent AKI, the requirement for temporary RRT may indicate a reversible trajectory, while prolonged or permanent dialysis dependence reflects irreversible renal injury and transition to CKD or ESRD.²² Therefore, assessment of RRT need is integral to both the staging and longitudinal risk stratification of CSA-AKI, guiding clinical decision-making, management intensity, and long-term follow-up strategies.

Epidemiology and Outcomes in Cardiac Surgery

AKI Incidence by Surgery Type

AKI remains a highly prevalent and impactful complication following cardiac surgery. The type of cardiac procedure is a major determinant of AKI risk. Isolated coronary artery bypass grafting (CABG) generally carries the lowest risk, followed by isolated valve replacement. In contrast, more complex procedures—including combined CABG with valve surgery, aortic aneurysm repair (particularly involving the ascending aorta or arch), and heart transplantation—are associated with markedly higher rates of postoperative AKI. In one large prospective cohort of 4007 patients, AKI occurred in 57.8% of combined CABG/valve cases, 52.0% of aneurysm surgeries, and 73.0% of heart transplantations, compared with an overall incidence of 31.2%.¹⁰ Although any-stage AKI is relatively common, AKI-RRT occurs in a smaller but vulnerable subset, typically between 1% and 5%.¹²

Mortality, CKD Progression, and Long-Term Outcomes

Understanding the difference between transient and persistent AKI is crucial. While transient AKI appears to be more frequent,¹⁶ a substantial portion of CSA-AKI progresses to a persistent form. One study reported that although AKI was diagnosed in 14.6–17.5% of patients, 3.6–4.5% continued to meet AKI criteria at discharge, consistent with persistent AKI.¹⁶ In a related clinical setting involving acute coronary syndrome, persistent AKI occurred in 9.1% of patients, compared with 7.2% who developed transient AKI.¹⁴ More directly in cardiac surgery, a large observational study reported that 13% of patients had prolonged AKI (>7 days but <3 months), meeting the definition of AKD.⁶

Persistent or severe AKI is closely associated with

adverse outcomes:

1. **Mortality:** In-hospital mortality is significantly higher among patients who develop AKI.¹⁰ For those requiring renal replacement therapy (RRT), mortality can reach 36.5% and even 50–60% in some cohorts.^{10,23} Persistent AKI at discharge is associated with a mortality rate of 26%, compared with 4% in transient AKI.¹⁶ Long-term mortality is significantly associated with postoperative AKI, with HRs ranging from 1.6 to 3.9 across studies.²⁴ Patients who recover renal function before discharge fare better (HR 1.31) than those with persistent AKI (HR 2.71).¹³ Meta-analyses report 1–5 year mortality rates of up to 30% among CSA-AKI survivors.²⁵
2. **Dialysis and CKD Progression:** Persistent AKI increases the likelihood of RRT and progression to end-stage renal disease (ESRD).^{5,24} Even if serum creatinine normalizes, subclinical injury may predispose to CKD. For example, in valvular surgery, even early-recovery AKI increased the odds of CKD (OR 2.86; 95% CI 1.68–4.86), while persistent AKI raised the odds to 10.54 (95% CI 4.01–27.76).¹⁵ In a secondary analysis of the STARRT-AKI trial, which included patients with severe AKI in the ICU, 39% progressed to CKD within 90 days, with aortic surgery identified as a major risk factor.²⁶

Beyond renal outcomes, CSA-AKI has been linked to higher risks of myocardial infarction, stroke, and heart failure.²⁷ Altogether, these findings highlight persistent AKI, especially when severe, as a distinct high-risk clinical entity. Its early recognition, close follow-up, and the development of targeted interventions are critical steps for improving outcomes in this vulnerable patient population.

Pathophysiology of Persistent AKI in Cardiac Surgery Mechanistic Pathways in CSA-AKI

Persistent AKI following cardiac surgery, often termed CSA-AKI, results from a complex network of pathophysiologic events, including hemodynamic instability, ischemia-reperfusion injury, systemic inflammation, and maladaptive tissue responses. These events can begin even before surgery, escalate during CPB, and continue postoperatively, eventually leading to failed renal recovery and potential progression to CKD^{8,10,28}

Hemodynamic Mechanisms

CPB, a central component of many cardiac surgeries, exerts significant stress on the kidneys. Factors such as non-pulsatile blood flow, hemodilution, systemic hypothermia with subsequent rewarming, and blood exposure to artificial surfaces activate both inflammatory and coagulation pathways. Longer CPB durations are strongly associated with higher AKI risk.^{5,10,28}

Experimental models have shown that CPB can cause sustained cortical and medullary hypoxia, even weeks postoperatively, with accompanying histological evidence

of fibrosis and tubular injury.²⁸ Renal oxygen delivery is particularly compromised in the medulla, a region already prone to hypoxia. This vulnerability is further exacerbated by intra- and postoperative hypotension and elevated central venous pressure (CVP).^{5,29} Moreover, CPB can trigger systemic inflammatory response syndrome (SIRS), characterized by the release of pro-inflammatory cytokines (e.g., IL-6, TNF- α) and damage-associated molecular patterns (DAMPs), such as cold-inducible RNA-binding protein (CIRP). These mediators contribute directly to injury of the renal microvasculature and parenchyma.^{5,30}

Ischemia-Reperfusion Injury and Oxidative Stress

Episodes of ischemia, often caused by aortic cross-clamping, hypotension, or microemboli, followed by reperfusion, play a major role in CSA-AKI. Although reperfusion is essential, it paradoxically intensifies injury by generating reactive oxygen species (ROS).⁵ These ROS disrupt cellular structures, amplifying inflammation and impairing endogenous repair mechanisms.⁵

Immune Dysregulation and Maladaptive Repair

Initial renal injury activates both innate and adaptive immune responses, with infiltration of neutrophils, macrophages, and lymphocytes. Macrophages exhibit dual roles: the M1 subtype exacerbates inflammation, whereas the M2 subtype may promote repair or fibrosis depending on the local environment.³¹ In persistent AKI, unresolved inflammation and failed tubular regeneration result in maladaptive repair,²⁴ characterized by:

1. **Recurrent Tubular Injury:** Repeated insults lead to cellular senescence and loss of differentiation capacity.³²
2. **Cell Cycle Arrest:** Sustained G2/M phase arrest in tubular epithelial cells leads to secretion of pro-fibrotic mediators (e.g., TGF- β 1, CTGF), a process in which JNK signaling is implicated.³²
3. **Senescence and SASP:** Senescent cells, marked by p16^{INK4a}, accumulate and secrete pro-inflammatory and pro-fibrotic factors collectively referred to as the senescence-associated secretory phenotype (SASP).³³

Mitochondrial Dysfunction and Epigenetic Modifications

Renal tubular cells depend heavily on mitochondrial function for energy. During ischemia-reperfusion and oxidative stress, mitochondria are particularly vulnerable. Mitochondrial injury leads to ATP depletion, excessive ROS production, and release of pro-apoptotic signals such as cytochrome C.³⁴ In patients with CSA-AKI, biomarkers reflecting mitochondrial stress, such as urinary mitochondrial DNA, plasma acylcarnitine profiles, and GDF-15, are often elevated, indicating a central role for mitochondrial dysfunction in persistent injury.³⁵⁻³⁷

Additionally, epigenetic changes, such as altered DNA methylation, histone modification, and dysregulated microRNAs, can imprint a long-lasting “injury memory” on renal cells. These modifications affect genes involved

in inflammation, apoptosis, and fibrosis, reinforcing maladaptive pathways.^{32,38}

Challenges in Early Detection and Differentiation

A major obstacle in mitigating the impact of persistent AKI after cardiac surgery is the difficulty in early and accurate detection, as well as differentiation from transient AKI, which carries a substantially better prognosis. Traditional diagnostic tools have notable limitations in this acute and dynamic setting.

Role of Traditional Markers (Serum Creatinine, Urine Output)

Serum creatinine (SCr) remains the most widely used marker for diagnosing and staging AKI according to KDIGO criteria. Nevertheless, its effectiveness during the early postoperative phase after cardiac surgery is limited by multiple factors. SCr is primarily a marker of renal function (glomerular filtration) rather than renal injury. Its levels typically rise only after a substantial loss of GFR, often 24-72 hours after the initial renal insult, making it a delayed indicator of damage.⁵ Moreover, SCr levels are influenced by numerous non-renal factors, including muscle mass, age, sex, and protein intake. Most critically in the surgical setting, fluid status and hemodilution resulting from intra- and postoperative resuscitation may mask early rises in SCr or even artificially lower its concentration, thereby delaying diagnosis.¹¹ Notably, estimation of GFR (eGFR) adds a quantitative assessment of kidney filtration function, and some studies suggest that reduced eGFR may predict AKI earlier than SCr alone. For example, in cardiac surgery patients, eGFR by the modification of diet in renal disease study 4 (MDRD-4) formula was found to be a reliable predictor of AKI onset.³⁹ However, eGFR estimation relies on SCr (or cystatin C) and demographic or anthropometric assumptions, and becomes unreliable in the non-steady-state conditions characteristic of evolving AKI.^{23,40} Therefore, both SCr and eGFR reflect renal filtration function rather than real-time tubular injury or stress. This limitation highlights the need for early biomarkers of injury and stress that can detect subclinical renal damage before a measurable decline in function.⁴¹

Novel Biomarkers for Early Detection, Differentiation, and Prognostication

The limitations of SCr have triggered extensive research into novel biomarkers that can detect kidney injury earlier, reflect specific pathophysiological processes, and help predict the course of AKI, including its likelihood of persistence. Several candidates have been investigated in the context of CSA-AKI (summarized in [Table 1](#)).

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is released from injured renal tubular cells and neutrophils and can be detected in plasma (pNGAL) and urine (uNGAL) within 2–6 hours of renal insult.⁴² While promising for early AKI detection, its performance

Table 1. Performance Characteristics of Selected Novel Biomarkers for AKI after Cardiac Surgery

Biomarker	Type	Optimal Timing (Post-Op) / Pre-Op	Reported AUC	Key Advantages	Key Limitations/Cons	Role in Predicting Persistence/Progression
NGAL (plasma/urine) ^{42,43}	Damage	2–8h post-CPB	pNGAL: ~0.70–0.80 (variable); uNGAL: ~0.70–0.75	Early rise after injury.	CPB effect, assay variability, different molecular forms, cost. Optimal cutoff unclear.	pNGAL measured at AKI diagnosis may predict progression; uNGAL is associated with adverse clinical outcomes ⁴²
TIMP-2 × IGFBP7 (urine) ⁴⁴	Stress	2–4h post-CPB/ICU admission	~0.72–0.81	Very early marker of cell cycle arrest, FDA-cleared for risk assessment.	Moderate overall accuracy; performance varies with cutoff values and timing; relatively high cost. ⁴⁴	Limited specific data on predicting persistence in CSA-AKI, primarily used for early risk stratification.
KIM-1 (urine) ⁴⁵	Damage	Early postoperative period (hours to days)	Variable, not well defined in CSA-AKI cohorts	Specific for proximal tubular injury.	Limited data from large CSA-AKI cohorts compared with NGAL or TIMP-2 × IGFBP7; optimal timing and cutoffs remain unclear.	Potential, but needs more validation specifically for predicting persistence in CSA-AKI.
IL-18 (urine) ²⁸	Damage/Inflammation	Within 6 h post-CPB	~0.76 (with clinical model)	Early rise, reflects inflammation and tubular injury.	Influenced by systemic inflammation.	Elevated levels at AKI diagnosis are associated with progression (OR ≈ 3.0) ⁴⁶ ; early elevations predict AKI and adverse outcomes. ²⁸
Cystatin C (serum) ^{47,48}	Function	Preoperative; early postoperative	Preoperative: ~0.72–0.86	Less affected by muscle mass than SCr, good GFR marker. Preoperative value predictive.	Influenced by age, inflammation, thyroid function, and steroid use; more costly than SCr.	Primarily a functional marker; pre-op levels predict overall AKI risk. Role in differentiating persistence not well established post-op.
CCL14 (urine) ^{11,49}	Stress/Repair signaling	At AKI diagnosis or early postoperative period	High for severe persistent AKI in critically ill cohorts	Specific for predicting persistent severe AKI.	Limited performance in mild AKI; not validated in adult CSA-AKI; pediatric CSA-AKI studies negative; limited availability and high cost.	Highly promising for persistent severe AKI, but needs robust validation in adult CSA-AKI cohorts.
DKK3 (urine) ⁵⁰	Chronic Stress/fibrosis	Preoperative	OR ≈ 1.6–1.9 for AKI and persistent CKD	Pre-op levels may indicate underlying renal vulnerability and predict non-recovery.	Not an early acute damage marker. Reflects chronic stress/fibrosis risk.	Preoperative levels associated with postoperative AKI and persistent CKD, suggesting a role in identifying patients prone to non-recovery/fibrosis.

Abbreviations: AKI: Acute Kidney Injury; AUC: Area Under the Receiver Operating Characteristic Curve; CCL14: C-C Motif Chemokine Ligand 14; CPB: Cardiopulmonary Bypass; CSA-AKI: Cardiac Surgery-Associated Acute Kidney Injury; DKK3: Dickkopf-3; IGFBP7: Insulin-like Growth Factor Binding Protein 7; IL-18: Interleukin-18; KIM-1: Kidney Injury Molecule-1; NGAL: Neutrophil Gelatinase-Associated Lipocalin; OR: Odds Ratio; pNGAL: plasma NGAL; SCr: Serum Creatinine; TIMP-2: Tissue Inhibitor of Metalloproteinases-2; uNGAL: urine

in predicting persistence is less clear. A meta-analysis suggested pNGAL measured 4–8 hours post-CPB had superior diagnostic performance for AKI, but results were variable, and overall utility was deemed inconclusive due to study heterogeneity and assay standardization issues.⁵¹ Some studies suggest pNGAL may be better than uNGAL for predicting AKI progression.⁴⁶ However, CPB itself can elevate NGAL levels, potentially confounding interpretation.⁴³

Tissue Inhibitor of Metalloproteinases-2 (TIMP-2) and Insulin-like Growth Factor Binding Protein 7 (IGFBP7)

These urinary biomarkers (commercially available as Nephrocheck®) signal G1 cell cycle arrest, an early cellular response to stress or injury.⁵ They typically rise within hours of insult. A meta-analysis demonstrated moderate diagnostic accuracy, with optimal cutoffs varying according to sampling time; a threshold of 0.3 (ng/mL) ²/1000 has been recommended for measurements obtained within 4 hours of insult.⁴⁴ In some cardiac surgery cohorts, TIMP-2 × IGFBP7 showed good predictive performance for AKI when measured early (e.g., 2 hours post-ICU admission).⁵² However, its superiority over other markers such as preoperative Cystatin C has been questioned in specific settings like thoracic aortic surgery

with hypothermic circulatory arrest.⁴⁷

Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a transmembrane protein highly upregulated in proximal tubular cells upon injury, making it a specific marker of acute tubular necrosis.⁴⁵ It is detectable in urine and has been recognized by the FDA as a preclinical AKI biomarker. While KIM-1 shows promise for early AKI diagnosis, its specific role in predicting *persistent* AKI or differentiating AKI trajectories after cardiac surgery requires more dedicated validation.

Interleukin-18 (IL-18)

Urinary IL-18 (uIL-18) is a pro-inflammatory cytokine released from injured proximal tubular cells.⁴² Levels peak within 6 hours post-cardiac surgery and are associated with subsequent AKI development and adverse outcomes.⁴² Elevated uIL-18 at the time of AKI diagnosis has also been linked to a higher risk of AKI progression.⁴⁶

Cystatin C

Serum Cystatin C is a small protein produced by all nucleated cells, freely filtered by the glomerulus, and then reabsorbed and catabolized by proximal tubular cells. Its serum concentration is less affected by muscle mass

than SCr, making it a potentially more reliable marker of GFR, especially in acute settings.⁵³ Pre-surgical serum Cystatin C has demonstrated better predictive ability for post-cardiac surgery AKI compared with SCr or eGFR.⁵⁴ A meta-analysis confirmed its good sensitivity and high specificity for predicting the risk of post-cardiac surgery AKI, with optimal detection 24 hours before surgery.⁴⁸

C-C Motif Chemokine Ligand 14 (CCL14)

Urinary CCL14 is an emerging biomarker specifically investigated for its potential to predict *persistent severe AKI*.⁵⁵ In heterogeneous critically ill populations with moderate to severe AKI, uCCL14 showed excellent predictive performance for persistence.⁴⁹ However, a study in pediatric cardiac surgery patients did not find an association between uCCL14 and persistent severe AKI, indicating the need for further validation in specific cardiac surgery populations and age groups.⁵⁶

Dickkopf-3 (DKK3)

Urinary DKK3 is a secreted glycoprotein whose levels are associated with chronic kidney stress, tubular atrophy, and interstitial fibrosis.⁵⁰ Notably, elevated *preoperative* urinary DKK3 levels have been linked to an increased risk of developing AKI after cardiac surgery and also with persistent CKD postoperatively, suggesting it may identify patients with pre-existing subclinical kidney vulnerability that predisposes them to non-recovery.⁵⁰

Functional Tests (FST, RRI, Doppler)

Beyond soluble biomarkers, functional tests offer insights into renal reserve and tubular integrity:

Furosemide Stress Test (FST)

The FST involves administering a standardized dose of furosemide and monitoring the subsequent urine output response. A robust diuretic response suggests preserved tubular function and a lower risk of AKI progression or need for RRT, while a poor response indicates significant tubular dysfunction and a higher risk of adverse outcomes.⁵⁷ Meta-analyses have shown good diagnostic accuracy for FST in predicting AKI progression (AUC $\approx$ 0.88) and the need for RRT (AUC $\approx$ 0.86) in general critically ill populations, with some evidence supporting its utility post-cardiac surgery.⁵⁷

Renal Resistive Index (RRI)

Measured by Doppler ultrasound, the RRI reflects intrarenal vascular resistance. An RRI >0.70 is often considered indicative of impaired renal perfusion or function.⁵⁸ Studies in cardiac surgery patients have yielded mixed results. While postoperative RRI may be associated with AKI development, its predictive value for individual patients can be limited, and conditions such as aortic insufficiency can confound measurements.⁵⁸ Combining RRI with intrarenal venous flow patterns might improve predictive accuracy.⁵⁹

Challenges in Biomarker Implementation: Standardization, Confounders, and Validation Gaps

While novel biomarkers hold substantial promise for early detection and phenotyping of persistent CSA-AKI, several critical challenges must be addressed before their routine clinical implementation. These challenges encompass assay standardization, interpretation of confounding factors inherent to cardiac surgery, and the need for robust validation in cardiac surgery-specific populations.

Assay Standardization and Inter-Laboratory Variability

A major obstacle to biomarker translation is the lack of standardized assays and universal cutoff values across different platforms and institutions. For NGAL, multiple molecular forms exist: monomeric (25 kDa, primarily kidney-derived), homodimeric (45 kDa, predominantly neutrophil-derived), and heterodimeric forms, each with distinct biological significance. Current commercially available assays often measure total NGAL without distinguishing these forms, limiting specificity for renal tubular injury.⁶⁰ A systematic review and meta-analysis of plasma NGAL for diagnosing AKI after cardiac surgery demonstrated substantial heterogeneity across studies, with area under the receiver operating characteristic curve (AUC) ranging from 0.60 to 0.87, largely attributable to assay variability, inconsistent timing of measurement, and differing AKI definitions.⁵¹ Prediction regions and confidence intervals were notably large due to clinical and statistical heterogeneity, rendering reliable conclusions difficult.

Similarly, although TIMP-2 $\times$ IGFBP7 (commercially available as NephroCheck®) is FDA-cleared for AKI risk assessment, optimal timing of measurement and cutoff values vary across clinical settings. Studies in cardiac surgery populations have reported detection of elevations at 4 hours post-CPB in some cohorts, while other investigations found elevations delayed until 24 hours postoperatively. Furthermore, the test expenses raise cost-effectiveness concerns for widespread implementation, particularly in resource-limited settings.⁶¹⁻⁶³

Cardiopulmonary Bypass and Systemic Inflammation as Confounders

The systemic inflammatory response triggered by CPB represents a significant confounder for multiple biomarkers, most notably NGAL. Extracorporeal circulation activates circulating neutrophils, leading to degranulation and release of neutrophil-derived NGAL independent of kidney injury.^{64,65} Studies have demonstrated that NGAL concentrations correlate directly with CPB duration and aortic cross-clamp time, with the homodimeric form predominating post-CPB, suggesting neutrophils rather than renal tubular cells as the primary source. This confounding renders interpretation problematic: elevated NGAL in the absence of creatinine-based AKI criteria may represent either subclinical renal injury (associated with increased mortality and RRT requirements) or simply reflect the magnitude of systemic

inflammatory response.^{51,60,66}

Beyond NGAL, inflammatory cytokines such as interleukin-6 (IL-6) rise substantially during cardiac surgery due to surgical trauma, sternotomy, myocardial incision, and blood contact with extracorporeal circuits, activating complement, coagulation, and cytokine cascades. Elevated preoperative IL-6 levels have been associated with a six-fold increased risk of stage 2/3 AKI in pediatric cardiac surgery patients (adjusted OR 6.41, 95% CI: 1.16-35.35), suggesting that baseline inflammation may predispose to worse renal outcomes.⁶⁷ However, distinguishing renal-specific injury biomarkers from systemic inflammatory markers remains challenging.

Additional confounders specific to cardiac surgery include hemodilution from intraoperative fluid resuscitation (which may artificially lower serum creatinine and delay AKI diagnosis), hypothermia during CPB (affecting biomarker kinetics), hemolysis (releasing free hemoglobin with nephrotoxic potential), administration of nephrotoxic medications (aminoglycosides, vancomycin, contrast agents), and variable renal perfusion related to hemodynamic instability.^{68,69} The complexity and heterogeneity of these factors underscore the necessity for cardiac surgery-specific validation of biomarkers rather than extrapolation from general ICU or sepsis populations.

Validation Gaps in Cardiac Surgery Populations

A critical limitation is that many biomarker studies derive from heterogeneous ICU, sepsis, or general AKI cohorts, with limited representation of post-CPB or post-cardiac surgery populations. Urinary CCL14, for instance, demonstrated excellent predictive performance for persistent severe AKI in critically ill patients (AUC 0.81, 95% CI: 0.72-0.89), but subsequent validation in pediatric cardiac surgery patients yielded negative results, finding no association between CCL14 and persistent severe AKI.^{56,70} This discrepancy highlights that biomarkers validated in one clinical context may not translate to cardiac surgery populations due to distinct pathophysiology.

Similarly, urinary mitochondrial DNA (mtDNA) has emerged as a marker of mitochondrial injury and AKI severity, correlating with peak serum creatinine and hospital stay duration. However, data specifically in adult cardiac surgery cohorts remain limited, and optimal cutoff values have not been established for this population.

Furthermore, few studies have rigorously evaluated biomarker performance specifically for predicting persistent AKI or differentiating transient from non-recovering trajectories in the cardiac surgery setting. A prospective study comparing CCL14, TIMP-2 $\times$ IGFBP7, and NGAL for predicting renal non-recovery found that CCL14 alone had an AUC of only 0.71 (95% CI: 0.63-0.77), lower than anticipated, potentially due to inclusion of functional (prerenal) AKI without true tubular damage.⁷¹ NGAL showed no predictive value for renal non-recovery (AUC 0.53), while TIMP-2 $\times$ IGFBP7 performed moderately well (AUC 0.74).⁷¹ These findings

emphasize the need for context-specific validation and acknowledgment that no single biomarker may suffice for the complex task of trajectory prediction.

Pediatric-Specific Considerations in Cardiac Surgery-Associated Acute Kidney Injury

While CSA-AKI presents significant challenges across all age groups, the pediatric population exhibits distinct pathophysiological characteristics, biomarker profiles, and clinical outcomes that warrant specialized consideration.^{72,73} The incidence of CSA-AKI in pediatric patients is notably high, ranging from 30% to 64% depending on the diagnostic criteria employed and the age distribution of the studied population.⁷⁴⁻⁷⁶ Neonates and infants younger than 12 months face particularly elevated risk, with AKI incidence reaching 50–60% following complex congenital heart surgery, especially after procedures such as the Norwood operation (stage 1 palliation).^{77,78} This heightened vulnerability stems from several developmental factors, including immature renal function with lower baseline GFR, smaller blood volume leading to more pronounced hemodilution during CPB, and an exaggerated systemic inflammatory response to CPB compared to adults.^{79,80} Younger age (particularly < 12 months), longer CPB duration, preoperative anemia, higher surgical complexity scores (RACHS-1), and single-ventricle physiology have consistently been identified as independent risk factors for pediatric CSA-AKI.^{76,77,81}

Importantly, biomarker performance and kinetics differ substantially between pediatric and adult populations. While urinary NGAL normalized to creatinine (uNGAL-to-Cr ratio) demonstrates excellent diagnostic accuracy in children with an estimated sensitivity of 91.3% and specificity of 89.7%, superior to its performance in adults, other biomarkers show variable utility.^{74,82} Urinary interleukin-18 (uIL-18) appears more effective in predicting AKI in pediatric patients compared to adults (diagnostic odds ratio of 7.33 versus 5.75; AUC 0.81 versus 0.77), though it exhibits sex-related differences in adolescents, with females over 10 years showing higher baseline concentrations than males.^{72,83} KIM-1 has emerged as particularly promising in young children, with urinary KIM-1/Cr peaking at 24 hours post-surgery and demonstrating a significant elevation at 6 hours in AKI patients, whereas NGAL and IL-18 showed variable time-to-peak kinetics despite their diagnostic value.^{82,84} Conversely, some biomarkers validated in adults may not translate to pediatric populations. As discussed earlier, urinary CCL14 demonstrated no association with persistent severe AKI in pediatric cardiac surgery patients, highlighting the critical need for age-specific biomarker validation.⁸⁴ The long-term implications of pediatric CSA-AKI extend far beyond the immediate postoperative period, with affected children facing decades of potential progression toward CKD, hypertension, and proteinuria, emphasizing the importance of extended surveillance and intervention strategies tailored to this population.⁷⁴

Performance characteristics of selected novel

biomarkers for AKI after cardiac surgery are presented in Table 1. Notably, these performance estimates are approximate and may vary substantially depending on the study population, AKI definition, biomarker assay, and cutoff values used. The data primarily reflect the CSA-AKI context where available.

As presented in Figure 1, the bar chart compares the diagnostic accuracy (Area Under the Receiver Operating Characteristic Curve, AUC) of key biomarkers representing distinct biological pathways in CSA-AKI. AUC reflects the ability of a biomarker to discriminate between patients with and without AKI or to predict AKI progression. Values closer to 1.0 indicate higher diagnostic accuracy. The values shown are derived from published studies and meta-analyses summarized in Table 1 and reflect average reported AUCs in CSA-AKI settings. Some biomarkers, such as pNGAL, TIMP-2×IGFBP7, and Cystatin C, demonstrate promising predictive value, while others (e.g., KIM-1, DKK3) require further validation for use in clinical practice.^{11,28,42-45, 47-50}

Proposed Classification and Management Strategies

Current Standard of Care

Despite advances in understanding the pathophysiology and diagnosis of CSA-AKI, current management predominantly relies on supportive measures. There remains a significant lack of targeted therapies capable of reversing injury or promoting recovery once AKI, particularly persistent AKI, is established.

Supportive Care

The cornerstone of managing patients at risk for or with established CSA-AKI involves meticulous attention to supportive care principles, largely guided by general AKI recommendations such as those from KDIGO.¹²

Hemodynamic Optimization

Maintaining adequate renal perfusion is paramount. This involves optimizing cardiac output and ensuring appropriate mean arterial pressure (MAP) targets, which may need to be individualized based on patient characteristics and baseline blood pressure.⁸⁵ Goal-directed therapy (GDT) approaches, utilizing fluids and vasoactive agents to achieve predefined hemodynamic targets, are recommended to improve oxygen delivery to the kidneys.⁸⁶

Fluid Management

Judicious fluid administration is crucial to maintain euvolemia, as both hypovolemia (impairing renal perfusion) and hypervolemia (leading to renal venous congestion and increased interstitial pressure) can exacerbate kidney injury.²⁹ Balanced crystalloid solutions, with lower chloride content, are generally preferred over 0.9% saline to minimize the risk of hyperchloremic acidosis and potential renal vasoconstriction.⁸⁷

Avoidance of Nephrotoxins

A critical component of care is the avoidance or cautious use of potentially nephrotoxic medications. This includes non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycoside antibiotics, and certain antiviral agents. Radiocontrast media exposure should be minimized or avoided if possible, especially in high-risk patients.⁸⁸ Preoperatively, it is often recommended to withhold angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) to reduce the risk of intraoperative hypotension.⁸⁵ The KDIGO care bundle for high-risk AKI patients explicitly includes these nephrotoxin avoidance strategies.¹²

Timing of Renal Replacement Therapy (RRT)

For patients who develop severe AKI, the decision to initiate RRT is complex. There is no definitive consensus

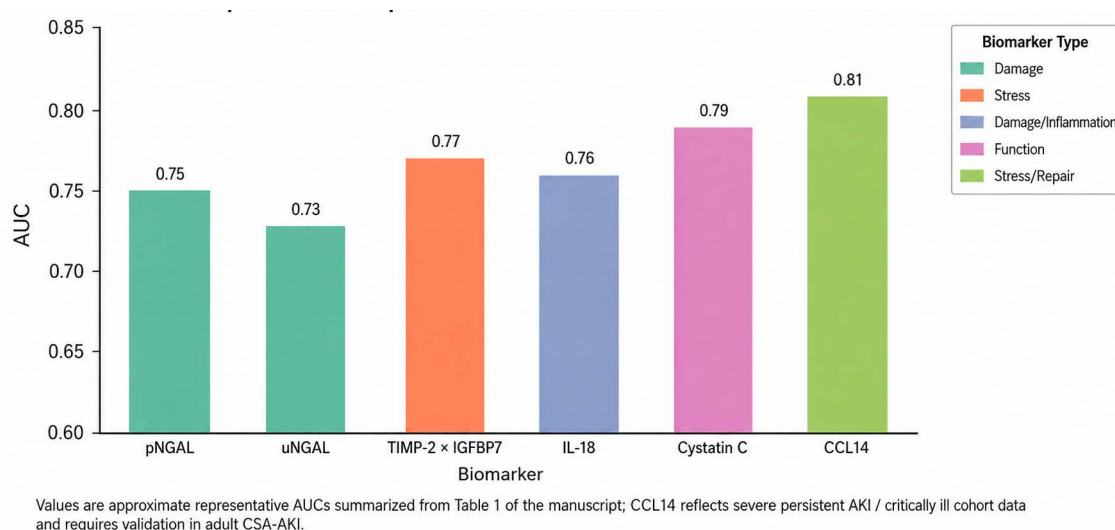


Figure 1. Representative Reported AUC of Selected Biomarkers in CSA-AKI

Abbreviations: CSA-AKI – cardiac surgery–associated acute kidney injury; AUC – area under the curve; pNGAL – plasma neutrophil gelatinase-associated lipocalin; uNGAL – urinary neutrophil gelatinase-associated lipocalin; TIMP-2 – tissue inhibitor of metalloproteinases-2; IGFBP7 – insulin-like growth factor binding protein-7; IL-18 – interleukin-18; CCL14 – C-C motif chemokine ligand-14.

on the optimal timing (i.e., “early” versus “standard” or “late” initiation) for RRT in the general critically ill population with AKI, and even less specific guidance exists for CSA-AKI. Several large randomized controlled trials (RCTs) such as AKIKI, ELAIN, IDEAL-ICU, and STARRT-AKI have yielded conflicting results or shown no clear survival benefit for routine early RRT initiation compared to a more conservative approach where RRT is started for urgent indications. The STARRT-AKI trial, one of the largest, found no benefit with an accelerated RRT strategy.⁸⁹

Current KDIGO guidelines recommend initiating RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist (e.g., severe hyperkalemia, metabolic acidosis, uremic complications, or pulmonary edema refractory to diuretics).⁸⁶ Beyond these absolute indications, the decision should be individualized, taking into account the overall clinical context, trends in kidney function, presence of oliguria, severity of illness, and the potential for renal recovery.⁸⁹ Functional tests such as the Furosemide Stress Test may help identify patients with severe AKI who are less likely to recover kidney function and may subsequently require RRT.⁵⁷

Lack of Targeted Treatments for Persistent AKI

A significant challenge in managing established CSA-AKI, particularly when it becomes persistent, is the scarcity of specific pharmacological therapies proven to reverse kidney damage, accelerate recovery, or prevent the transition to CKD.⁹⁰ Management remains largely supportive, focusing on maintaining physiological homeostasis and treating complications. Numerous pharmacologic agents have been evaluated as potential therapies for AKI, including low-dose dopamine, loop diuretics (used for treatment rather than diagnostic purposes), mannitol, fenoldopam, and atrial natriuretic peptide (ANP). Despite initial rationale, these agents have not shown consistent benefit in well-designed clinical trials. Moreover, some interventions have been associated with adverse effects.⁸⁶ While a short perioperative infusion of a balanced amino acid solution has shown promise in preventing AKI in one high-quality RCT by recruiting renal functional reserve,⁹⁰ this is a preventive measure and does not address the treatment of established or persistent injury.

This lack of effective disease-modifying interventions means that once AKI becomes clearly persistent, significant renal injury may have already occurred, and the pathological processes driving non-recovery (e.g., sustained inflammation, ongoing mitochondrial dysfunction, initiation of fibrotic pathways) are often not directly addressed by current standard care. This highlights a critical therapeutic gap, as the window for preventing long-term renal damage and progression to CKD may be narrowing rapidly in patients with persistent AKI. The current paradigm is thus largely reactive rather than proactive in modifying the course of established, persistent kidney injury.

Proposed Classification

Given the current absence of a standardized and cardiac surgery-specific definition for persistent AKI, a clinically oriented classification scheme is proposed, comprising Early Persistent AKI (EPAKI), Progressive Persistent AKI (PPAKI), and Fibrosis-Transitioning AKI (FTAKI), which integrates temporal duration, biomarker signatures, and pathophysiological context (Table 2). It should be emphasized that the proposed EPAKI/PPAKI/FTAKI framework is a conceptual, hypothesis-generating model derived from current pathophysiological and biomarker evidence. It has not yet been validated in prospective clinical cohorts and should therefore be considered a foundation for future research rather than a tool for routine clinical decision-making. This cardiac surgery-specific perspective recognizes that renal injury mechanisms and recovery kinetics are heavily influenced by intraoperative factors such as CPB duration, ischemia-reperfusion episodes, and the postoperative inflammatory milieu, distinguishing CSA-AKI from medical or septic AKI phenotypes. Although estimated GFR (eGFR) is routinely used to assess kidney function, it becomes unreliable during the non-steady-state phase of CSA-AKI because serum creatinine lags behind real-time filtration changes.

Management Based on Phenotypic Classification of Persistent AKI

The clinical management of persistent AKI after cardiac surgery can be significantly enhanced by adopting a phenotype-driven approach. Stratifying patients into EPAKI, PPAKI, and FTAKI subtypes enables more precise, timely, and mechanism-specific interventions. Below, we detail management strategies tailored to each phenotype:

Early Persistent AKI (EPAKI)

EPAKI represents renal dysfunction persisting beyond 48 hours but resolving within 7 days, typically with minimal structural damage.

Management

- Maintain hemodynamic stability and avoid nephrotoxic agents.^{90,91}
- Consider judicious fluid management and diuretic use in case of volume overload.^{92,93}
- Monitor urine output and serum creatinine every 12–24 hours.
- Use early stress biomarkers (e.g., NGAL, TIMP-2 × IGFBP7) to guide prognosis.^{94–96}
- Nephrology referral is not typically necessary unless renal function worsens.⁹⁷

Progressive Persistent AKI (PPAKI)

PPAKI is defined as renal dysfunction lasting more than 7 days with ongoing damage or cellular stress.

Table 2. Phased Management of CSA-AKI After Cardiac Surgery

Phase	Timing	Biomarkers	Functional Indices	Clinical Interventions and Key Management	Consultation / Referral	Monitoring Schedule	Clinical Implication	Monitoring Tools
EPAKI	48h–7d	- TIMP-2 × IGFBP7 - NGAL (rises within 2–6h)	- Mild ↓ in eGFR - Urine Output ↓ - FeNa > 1% (limited reliability post-CPB)	- Avoid nephrotoxins - Maintain MAP 65–75 mmHg - Monitor urine & sCr - Optimize hemodynamics - Fluid balance with/without diuretics - Supportive care only	ICU team manages primarily	- TIMP-2 × IGFBP7 at 4–6h - sCr/ UO every 12–24h	Often reversible with supportive care	- Daily sCr & UO - Early biomarkers (NGAL, TIMP-2 × IGFBP7)
PPAKI	>7d	- KIM-1 (tubular injury) - IL-18 (inflammatory) - Consider repeat TIMP-2 × IGFBP7	- eGFR ↓ ≥ 50% - Poor FST - FeNa > 2% (limited reliability post-CPB and in diuretic use)	- Nephrology referral - Renal ultrasound - Initiate RRT if needed - Experimental / investigational anti-inflammatory & fluid strategies - Biomarker-guided monitoring - Assess for RRT indication	ICU + Nephrology collaboration	- KIM-1/IL-18 on Day 7, 10–14 - eGFR weekly	Sustained injury; risk of fibrotic transition	- Serial stress/damage biomarkers (NGAL, KIM-1) - FST in hemodynamically stable patients - Renal ultrasound
FTAKI	>14d	- CCL14 investigational (marker of AKI persistence) - DKK3 (fibrosis transition)	- Persistent ↓ in eGFR - Proteinuria - BP ↑	- after hemodynamic stabilization and partial renal recovery initiate ACEi/ARB, SGLT2i - Lifestyle and BP management - Long-term renal care plan - Assess fibrosis risk (DKK3, mtDNA) - Enroll in precision nephrology trials	Nephrology-led long-term management	- eGFR every 2 weeks - CCL14 (research setting) & DKK3 at day 14, then monthly	High risk of progression to CKD	- Fibrosis markers - CKD screening labs - Imaging & long-term eGFR follow-up

This table summarizes a phase-based framework for management of persistent acute kidney injury (AKI) after cardiac surgery. Each phase (EPAKI, PPAKI, FTAKI) is defined by duration, biomarker profile, functional indices, and clinical management priorities. Abbreviations: AKI: Acute Kidney Injury; EPAKI: Early Persistent AKI (48 h–7 d); PPAKI: Prolonged Persistent AKI (> 7 d); FTAKI: Fibrotic Transition AKI (> 14 d); TIMP-2 × IGFBP7: Tissue Inhibitor of Metalloproteinases-2 × Insulin-like Growth Factor-Binding Protein 7 (early cell-cycle arrest biomarkers); NGAL: Neutrophil Gelatinase-Associated Lipocalin (early tubular stress biomarker); KIM-1: Kidney Injury Molecule-1 (proximal tubular injury marker); IL-18: Interleukin-18 (inflammatory biomarker); CCL14: Chemokine (C-C motif) Ligand 14 (predictor of AKI persistence and RRT need); DKK3: Dickkopf-related Protein 3 (fibrosis-transition biomarker); mtDNA: Mitochondrial DNA (oxidative stress marker); eGFR: Estimated Glomerular Filtration Rate; FeNa: Fractional Excretion of Sodium; MAP: Mean Arterial Pressure; RRT: Renal Replacement Therapy; FST: Furosemide Stress Test; UO: Urine Output; ACEi: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; SGLT2i: Sodium-Glucose Cotransporter-2 Inhibitor; ICU: Intensive Care Unit; CKD: Chronic Kidney Disease. Table Legend: Phase-specific management of persistent AKI after cardiac surgery, integrating biomarker kinetics, renal function indices, and targeted clinical interventions for early, prolonged, and fibrotic-transition phases.

Management

- Initiate early nephrology consultation.
- Consider imaging (renal ultrasound).
- Perform biomarker-based assessment (CCL14, NGAL, KIM-1, IL-18) to evaluate ongoing injury.^{85,98,99}
- Use the Furosemide Stress Test (FST) to anticipate the need for RRT.^{100,101}
- Evaluate for fluid overload and consider ultrafiltration or individualized fluid removal.¹⁰²
- Consider novel therapeutic trials (e.g., anti-inflammatory agents, mitochondrial protection).^{103–105}

Fibrosis-Transitioning AKI (FTAKI)

FTAKI refers to persistent renal dysfunction beyond 14 days accompanied by biomarker evidence of fibrosis or transition to CKD.

Management

- Initiate CKD-preventive strategies including renin-angiotensin system blockers or SGLT2 inhibitors if appropriate.^{106–108}
- Long-term follow-up with renal imaging and fibrosis biomarkers (e.g., DKK3, urinary mtDNA).^{109–113}
- Enroll in clinical trials targeting anti-fibrotic or senolytic therapies.^{114–116}
- Ensure continuity of care under nephrology for outpatient CKD surveillance and risk reduction.

To help situate this classification within the broader landscape, we compared it with existing AKI frameworks, including the KDIGO criteria and the ADQI/AKD concept (Table 3). Unlike these models, which focus primarily

on temporal or functional markers, our classification incorporates phenotypic patterns and biomarker-based insights specifically tailored to the post-cardiac surgery population. Notably, the proposed classification is not intended to replace KDIGO or ADQI definitions, but to complement them as a post-cardiac surgery-specific phenotypic and management framework.

This phenotypic approach shifts AKI care from a one-size-fits-all model to a precision nephrology paradigm, enabling earlier intervention, personalized therapy, and better long-term outcomes.

Preventive Measures for Post-Cardiac Surgery AKI

Given the high incidence and adverse long-term consequences of AKI following cardiac surgery, implementing structured preventive strategies is essential. These strategies span the preoperative, intraoperative, and postoperative phases and focus on optimizing renal perfusion, avoiding additional renal insults, and early recognition of renal stress or injury. Preoperatively, risk stratification is key: patients with reduced baseline eGFR, chronic kidney disease, older age, hypertension or other comorbidities should be identified and optimized prior to surgery. Nephrotoxic medications (e.g., NSAIDs, certain antibiotics) should be withheld or adjusted, and use of contrast media should be minimized or delayed when possible.^{5,85,118} Intraoperatively, maintaining adequate renal perfusion and oxygen delivery is critical. This includes goal-directed perfusion during CPB, minimizing hemodilution, and avoiding volume overload and venous congestion.¹¹⁸ Non-pharmacologic methods such as

Table 3. Comparison of KDIGO, ADQI/AKD, and Proposed EPAKI/PPAKI/FTAKI Framework for Cardiac Surgery Population

Feature	KDIGO (2012) ¹¹⁷	ADQI/AKD (2017) ⁸⁶	Proposed classification
Primary Focus	AKI	AKD, encompassing AKI and subacute kidney disorders	Persistent AKI phenotypes specific to cardiac surgery, integrating duration, biomarker profile, and recovery trajectory
Definition Criteria	- Increase in SCr ≥ 0.3 mg/dL within 48 hours - Increase in SCr to ≥ 1.5 times baseline within the prior 7 days - Urine output < 0.5 mL/kg/h for 6 hours	- AKI criteria as per KDIGO - GFR < 60 mL/min/1.73 m² for < 3 months - Decrease in GFR by $\geq 35\%$ or increase in SCr by $> 50\%$ for < 3 months - Evidence of kidney damage (e.g., structural abnormalities) lasting < 3 months	- EPAKI: Renal dysfunction lasting 48 hours–7 days, mild biomarker elevation (NGAL), often reversible with supportive care. - PPAKI: Dysfunction > 7 days with elevated stress/damage biomarkers (e.g., TIMP-2 $\times$ IGFBP7, NGAL), risk of maladaptive repair. - FTAKI: Dysfunction > 14 days with fibrosis or maladaptive repair markers (e.g., DKK3; mitochondrial injury markers such as urinary mtDNA), high risk of CKD transition.
Staging System	- Stage 1: SCr increase ≥ 0.3 mg/dL or 1.5–1.9 times baseline - Stage 2: SCr increase 2.0–2.9 times baseline - Stage 3: SCr increase ≥ 3.0 times baseline or SCr ≥ 4.0 mg/dL or initiation of renal replacement therapy	- No standardized staging; emphasizes the continuum from AKI to CKD and the need for monitoring and intervention during the subacute phase	Phenotype-based stratification (EPAKI $\rightarrow$ PPAKI $\rightarrow$ FTAKI) reflects progression severity rather than SCr magnitude, integrating biomarker dynamics and duration of renal dysfunction
Use of Biomarkers	Not incorporated into the diagnostic criteria	Recognizes the potential role of novel biomarkers (e.g., NGAL, KIM-1) for early detection and prognosis but not formally integrated into criteria	Explicitly integrates biomarkers for early identification and trajectory prediction of persistent AKI
Clinical Application	Widely adopted for AKI diagnosis and staging in various clinical settings	Aims to bridge the gap between AKI and CKD, highlighting the importance of the subacute phase for intervention and monitoring	Designed specifically for post-cardiac-surgery AKI to guide early nephrology referral, biomarker testing, and personalized management
Recovery Assessment	Focuses on the acute phase; limited guidance on recovery trajectories	Highlights the need to monitor recovery and progression to CKD during the AKD phase	Differentiates early recovery (EPAKI) from delayed or fibrotic progression (PPAKI/FTAKI); supports longitudinal risk stratification
Integration with CKD	Distinct from CKD; does not address the transition from AKI to CKD	Emphasizes the continuum from AKI through AKD to CKD, advocating for early interventions to prevent chronic progression	Identifies high-risk patients likely to transition from AKI to CKD after cardiac surgery; potentially enables preventive and targeted interventions

Abbreviations: AKI, acute kidney injury; AKD, acute kidney disease; CKD, chronic kidney disease; CSA-AKI, cardiac surgery–associated acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; ADQI, Acute Dialysis Quality Initiative; EPAKI, early persistent acute kidney injury; PPAKI, progressive persistent acute kidney injury; FTAKI, fibrosis-transitioning acute kidney injury; SCr, serum creatinine; GFR, glomerular filtration rate; RRT, renal replacement therapy; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor binding protein-7; DKK3, Dickkopf-3; CCL14, C–C motif chemokine ligand-14; mtDNA, mitochondrial DNA.

remote ischemic preconditioning (RIPC) have shown promise in reducing renal ischemia–reperfusion injury in selected high-risk patients.¹¹⁹ Postoperatively, vigilant monitoring of renal function (including SCr, urine output and trend-based eGFR, acknowledging limitations in acute settings) is vital, alongside stringent fluid balance management, hemodynamic optimization, and strict avoidance of nephrotoxin exposure.^{5,85} A bundled approach, such as the KDIGO AKI prevention bundle, has been associated with reductions in AKI incidence and severity in selected surgical populations; data in cardiac surgery remain limited. While pharmacologic interventions (e.g., dexmedetomidine, fenoldopam) have been explored, results remain heterogeneous and are not yet definitive.¹¹⁹ Overall, no single intervention suffices; rather, a multimodal prevention bundle tailored to high-risk cardiac surgery patients is likely to yield the greatest benefit. Further research is needed to define the optimal timing, combination and patient selection for preventive therapy.

Therapeutic Development Opportunities

The current lack of specific treatments for persistent CSA-AKI underscores an urgent need for innovative therapeutic strategies. Research is increasingly focusing on targeting the underlying pathophysiological mechanisms that drive renal non-recovery and progression to chronic

injury.

Targeting Inflammation: Precision Anti-inflammatory Strategies

Given that uncontrolled and persistent inflammation is a key driver of CSA-AKI and its transition to chronicity,⁵ therapies aimed at modulating specific inflammatory pathways are of considerable interest. Pro-inflammatory cytokines such as IL-6 rise significantly during and after cardiac surgery and are associated with poor outcomes. For instance, elevated preoperative IL-6 levels have been linked to a higher risk of severe AKI in pediatric cardiac surgery patients.⁶⁷ While IL-6 inhibitors such as tocilizumab, clazakizumab, and siltuximab are effective in various autoimmune and inflammatory conditions,¹²⁰ their specific efficacy and safety for preventing or treating CSA-AKI have not yet been established in large clinical trials. However, other agents with anti-inflammatory properties are being explored. For instance, sodium-glucose cotransporter 2 inhibitors (SGLT2i), such as empagliflozin (currently under investigation in the VERTIGO trial for CSA-AKI prevention), are known to exert anti-inflammatory effects, partly by inhibiting the NLRP3 inflammasome.¹²¹ The success of such approaches will likely depend on identifying the correct inflammatory targets and the optimal timing for intervention in specific patient subgroups.

Mitochondrial Protectants

Mitochondrial dysfunction is a critical driver of persistent AKI, characterized by ATP depletion, excessive ROS production, and impaired mitophagy. Mitochondria-targeted therapies have emerged as mechanistically promising interventions. Elamipretide (SS-31, Bendavia), a mitochondria-targeting tetrapeptide, selectively binds cardiolipin on the inner mitochondrial membrane, stabilizing cristae structure, reducing oxidative stress, and enhancing ATP production.¹²²⁻¹²⁵

Preclinical studies demonstrate that SS-31 accelerates ATP recovery, reduces tubular apoptosis and necrosis, and protects against ischemia-reperfusion injury in kidney models. Similarly, MitoQ, another mitochondria-targeted antioxidant, has shown protective effects against renal ischemia-reperfusion injury in preclinical studies. Elamipretide has advanced to multiple clinical trials including PROGRESS-HF, TAZPOWER, and MMPOWER-3 for heart failure and mitochondrial diseases, demonstrating its safety profile and potential therapeutic benefits.¹²⁵⁻¹³⁰

However, critical challenges impede clinical translation for CSA-AKI. First, no large-scale randomized controlled trials have specifically evaluated mitochondrial protectants for preventing or treating AKI in cardiac surgery populations. Second, optimal dosing, timing of administration (preoperative versus perioperative versus postoperative), and identification of patients most likely to benefit remain undefined. Third, biomarker-guided patient selection strategies are needed to identify individuals with predominant mitochondrial dysfunction phenotypes who would derive maximum benefit. Fourth, the high cost and limited availability of these agents pose implementation barriers, particularly in resource-limited settings.

Senolytic Therapies

Cellular senescence plays a causative role in the transition from AKI to CKD, with senescent cells accumulating in injured kidneys and secreting pro-inflammatory and pro-fibrotic mediators via the senescence-associated secretory phenotype (SASP). Senolytic drugs, including dasatinib, quercetin, fisetin, and navitoclax (ABT-263), selectively eliminate senescent cells by transiently disabling senescent cell anti-apoptotic pathways (SCAPs).¹³¹⁻¹³³

Preclinical evidence is compelling. In cisplatin-induced nephrotoxicity models, senolytic drugs (ABT-263 and fisetin) attenuated renal fibrosis, restored tubular regeneration, and improved renal function by suppressing tubular senescence. First-generation senolytics have demonstrated efficacy across multiple organs in preclinical models, delaying frailty and alleviating cardiovascular, kidney, and musculoskeletal disorders.¹³⁴⁻¹³⁶

Early clinical translation has begun. A pilot trial demonstrated that a 3-day course of dasatinib plus quercetin (D+Q) decreased senescent cell burden in adipose tissue of patients with diabetic kidney disease. The

combination also improved physical function in patients with idiopathic pulmonary fibrosis. More than 30 clinical trials using senolytics are currently underway or planned, targeting age-related diseases including cardiovascular disease, frailty, and CKD.^{114,137,138}

Nevertheless, substantial challenges remain for CSA-AKI application. First, no trials have specifically evaluated senolytics in the cardiac surgery or acute AKI setting; most studies focus on chronic conditions. Second, identification of appropriate patient populations (e.g., those with biomarker evidence of cellular senescence or fibrosis-transitioning AKI phenotypes) requires validated senescence biomarkers. Third, optimal timing, whether senolytics should be administered during the acute phase, subacute phase, or chronic phase post-AKI, is unknown. Fourth, potential off-target effects, long-term safety profiles, and drug interactions in the complex cardiac surgery population require rigorous investigation. Fifth, the intermittent “hit-and-run” dosing strategy, while theoretically advantageous, needs validation in the AKI context where temporal dynamics differ from chronic aging processes.^{139,140}

Regenerative Cellular Therapies: MSCs and Extracellular Vesicles

Cellular therapies represent a novel approach to promote renal repair and regeneration. Mesenchymal stem cells (MSCs) have demonstrated therapeutic potential in various preclinical AKI models, primarily through paracrine mechanisms that include the secretion of anti-inflammatory, pro-angiogenic, anti-apoptotic, and immunomodulatory factors.¹⁴¹ More recently, attention has shifted towards MSC-derived extracellular vesicles (EVs), including exosomes, as the primary mediators of the beneficial effects of MSCs.¹⁴¹ EVs are nano-sized vesicles containing a cargo of proteins, lipids, mRNAs, and microRNAs (miRNAs) that can be transferred to recipient cells, thereby modulating their function.

Preclinical studies have shown that MSC-EVs can protect against AKI induced by ischemia-reperfusion, nephrotoxins (e.g., cisplatin), and sepsis.¹⁴¹ Their protective mechanisms are diverse and include the transfer of specific miRNAs that can regulate mitochondrial function (e.g., miR-200a-3p, miR-30), inhibit apoptosis (e.g., miR-125b-5p targeting p53), reduce inflammation (e.g., miR-21 targeting PDCD4/NF- κ B, miR-146b inhibiting IRAK1/NF- κ B), and promote cell proliferation.¹⁴¹ As a cell-free therapy, EVs may offer advantages over whole-cell transplantation, including lower immunogenicity and easier manufacturing and storage. However, significant challenges remain in standardizing EV production, ensuring consistent cargo, developing effective delivery strategies to the injured kidney, and translating these promising preclinical findings into effective treatments for CSA-AKI in humans.

Nanoplatfoms for Kidney-Targeted Drug Delivery

Nanotechnology offers a transformative approach to

improving renal drug delivery by enhancing target specificity, minimizing off-target effects, and enabling controlled drug release.¹⁴² Various nanoplatforms, including polymeric nanoparticles, liposomes, and inorganic nanoparticles, can be engineered to carry diverse payloads such as anti-inflammatory drugs, antioxidants, small interfering RNAs (siRNAs) for gene silencing, or agents that promote renal repair.¹⁴³ Nanomedicine approaches are being explored to specifically target pathological processes involved in the AKI-to-CKD transition, such as oxidative stress, inflammation, ferroptosis, and apoptosis.¹⁴³ The ability to design multifunctional nanocarriers that can overcome biological barriers and selectively accumulate in injured renal tissue holds considerable promise for future AKI therapies.

Biomarker-Guided Treatment: Towards Personalized Intervention

One of the most promising strategies is integrating biomarker data into therapeutic decisions.¹⁴⁴ Biomarkers can play multiple roles: identifying patients at high risk for developing CSA-AKI or for progression to persistent AKI, stratifying patients based on underlying pathophysiological phenotypes (e.g., predominant inflammation, severe mitochondrial stress, or high fibrotic risk), guiding the timing and selection of targeted therapies, and monitoring therapeutic response. For example, the PrevAKI multicenter trial protocol involves biomarker-guided implementation of the KDIGO care bundle for high-risk patients.¹⁴⁵ In the future, biomarker panels could match individual patients with the most appropriate investigational therapy, such as anti-inflammatories for those with elevated IL-6 or NGAL levels, mitochondria-targeted agents for those with altered acylcarnitine profiles, and anti-fibrotics for those with elevated DKK3 or urinary collagen fragments.

The heterogeneity of underlying mechanisms in persistent AKI presents a formidable challenge for therapeutic development. It is unlikely that a single agent will be effective for all patients. Therefore, future successful therapies will likely need to either target common downstream pathways critical for non-recovery, such as maladaptive repair processes or fibrosis, or be applied in a phenotype-specific or even endotype-specific manner. This would involve using sophisticated biomarker profiles, potentially incorporating multi-omic data, to identify the dominant pathological process in an individual patient and tailor the intervention accordingly.

Toward Precision Medicine in AKI

The traditional approach to AKI, which often treats AKI as a monolithic entity defined by changes in sCr and urine output, has yielded limited success in developing effective targeted therapies. The inherent heterogeneity of AKI in its etiology, clinical presentation, severity, duration, and underlying pathophysiology necessitates a shift towards precision medicine strategies.¹⁴⁶ A more refined

approach is urgently needed, especially in the context of persistent AKI following cardiac surgery, where tailoring interventions to distinct patient subgroups could markedly improve outcomes.

Patient Phenotyping: Bridging Clinical and Biomarker Data

AKI subphenotyping seeks to classify patients into more homogeneous categories based on a combination of clinical features, functional markers, and biomarkers.¹⁴⁶ Traditional indicators such as oliguria, KDIGO stage, and the rate of creatinine change can be useful for initial stratification. For instance, patients with oliguric AKI typically face worse outcomes than those with non-oliguric AKI.

Recent advances in biomarker science allow for deeper granularity. The “function-damage matrix”, which combines functional markers (e.g., sCr) with damage markers (e.g., NGAL, KIM-1) enables identification of subclinical AKI (damage present, function preserved) or hemodynamic AKI (function impaired, damage absent), each representing distinct pathophysiological pathways and prognoses.¹⁴⁶ Moreover, certain biomarkers measured at AKI onset, such as IL-18, albumin-to-creatinine ratio (ACR), or plasma NGAL, can help flag progressor phenotypes, i.e., patients more likely to deteriorate. These phenotypes offer a foundation for personalized therapeutic strategies targeting shared biological drivers within each subgroup.⁴⁶ Such phenotyping can help identify subgroups with similar modifiable biological mechanisms or differential responses to potential therapies.

Artificial Intelligence and Machine Learning (AI/ML) for Predicting AKI Types and Therapy Response

The vast amount of data generated from electronic health records, continuous physiological monitoring, and biomarker assays provide an opportunity for AI and ML algorithms to uncover complex patterns and predict AKI-related outcomes with greater accuracy than traditional statistical models.¹⁴⁷ ML models, such as random forests, gradient boosting machines, and neural networks, can integrate numerous variables to predict the likelihood of developing CSA-AKI, its potential severity, the probability of persistence, and even, in the future, the likelihood of responding to specific therapies.¹⁴⁸

Numerous original studies have specifically focused on predicting AKI following cardiac surgery using AI/ML approaches. Lee et al. (2018) developed and validated multiple ML algorithms, including decision trees, random forests, SVM, and XGBoost in 2,010 cardiac surgery patients, with XGBoost achieving an AUC of 0.74–0.78.¹⁴⁹ Penny-Dimri et al. (2021) demonstrated that gradient boosting machines and neural networks achieved superior performance (AUC 0.84–0.85) compared to conventional risk scores for predicting renal replacement therapy requirements after cardiac surgery.¹⁵⁰ Li et al. (2025) specifically targeted elderly patients undergoing CABG, developing a random forest

model that achieved an AUC of 0.737 in 2,155 patients.¹⁴⁷ Rank et al. (2020) created a recurrent neural network for real-time prediction of postoperative AKI within 7 days after cardiothoracic surgery, significantly outperformed experienced physicians.¹⁵¹ Fan et al. (2023) incorporated early postoperative biomarkers including soluble ST2 (sST2), N-terminal pro-brain natriuretic peptide (NT-proBNP), heart-type fatty acid binding protein (H-FABP), lactic dehydrogenase (LDH), and uric acid (UA) into three tree-based ML models (XGBoost, random forest, and deep forest), achieving AUC values of 0.836–0.856.¹⁵² Jiang et al. (2023) developed interpretable ML models in 2,310 adult cardiac surgery patients, with logistic regression achieving an AUC of 0.812 for postoperative AKI and a gradient boosting classifier reaching 0.86 for severe AKI.¹⁵³ Chen et al. (2025) developed specialized models for acute type A aortic dissection surgery, with the LightGBM model demonstrating superior performance (AUC 0.874).¹⁵⁴ Ryan et al. (2022) advanced the field by creating an ensemble ML model for dynamic and early prediction, providing hourly predictions of future AKI risk within 48 hours using preoperative, operative, and ICU data.¹⁵⁵ Luo et al. (2023) addressed pediatric cardiac surgery populations across three medical centers in China, with XGBoost achieving AUC values of 0.85–0.90.¹⁵⁶ These studies collectively demonstrate that machine learning approaches consistently outperform traditional risk scores for predicting cardiac surgery-associated AKI. Machine learning applications in pediatric CSA-AKI prediction face unique challenges, including smaller sample sizes, the need for age-stratified modeling approaches to account for developmental physiology, and limited availability of large, annotated pediatric datasets.^{156,157} Across multiple studies, gradient boosting methods (XGBoost, LightGBM, GBM) consistently demonstrated superior or comparable performance to other machine learning algorithms.^{154,158–161} Deep learning approaches, particularly recurrent neural networks and convolutional neural networks, showed excellent performance in continuous and dynamic prediction tasks.^{162,163}

Designing RCTs Based on Phenotypes, Not Only Severity

The failure of many AKI clinical trials may stem from their inclusion of biologically heterogeneous patient populations, in which only a subset of patients may have been responsive to the intervention. Precision trials aim to overcome this by selecting participants based on phenotypes or biomarker-defined characteristics, thereby improving statistical power and clinical relevance.¹⁶⁴ For example, a trial of an anti-inflammatory drug could enroll patients with biomarker evidence of high systemic or renal inflammation. Similarly, therapies targeting mitochondrial dysfunction could be tested in patients with biomarkers indicating significant mitochondrial stress. This approach can increase statistical power and efficiency of clinical trials, reduce the number of participants needed, and enhance the likelihood of identifying effective treatments for specific AKI subphenotypes.¹⁶⁴ This contrasts with past trials that often used broad inclusion criteria based

primarily on AKI severity, leading to diluted treatment effects.¹⁶⁵

Advancing true precision medicine for persistent AKI will necessitate a deeper understanding that goes beyond observable phenotypes to the underlying molecular mechanisms. This will likely require the integration of dynamic, multi-omic biomarker data, including genomics (to identify susceptibility variants), transcriptomics (to understand gene expression changes), proteomics (to identify protein pathway dysregulation), and metabolomics (to reveal metabolic disturbances, such as altered acylcarnitine profiles³⁶), along with comprehensive clinical information. AI and ML will be indispensable for analyzing these high-dimensional datasets to define actionable endotypes and link them to specific, mechanism-based therapeutic interventions. This represents a bold shift from current phenotyping approaches and aims to tailor treatments not just to a group with similar characteristics, but to the individual's unique pathological state.

To enhance feasibility, we propose a phenotype-enriched RCT design using early biomarker stratification immediately after surgery. By combining markers of injury, stress, and functional decline, patients can be identified as likely to follow one of the predefined phenotypes (EPAKI, PPAKI, or FTAKE). Only those patients who meet high-risk phenotypic criteria would be randomized, thereby reducing the required sample size while improving statistical efficiency. The trial would incorporate both intermediate endpoints (such as biomarker change, early functional decline, and AKI duration) and definitive clinical outcomes (dialysis, persistent AKI, and CKD progression), allowing shorter follow-up with greater power. An adaptive or platform trial structure would enable stratification by phenotype, interim analyses, and flexible enrollment across phenotypic subgroups, ensuring both scientific rigor and operational feasibility.

Figure 2 illustrates the cascade of pathophysiological events leading from cardiac surgery to persistent AKI, culminating in CKD and ESRD, along with potential therapeutic intervention points.

Unmet Needs and Future Research Priorities in Persistent CSA-AKI

Despite significant progress, numerous research gaps and unmet needs persist in the field of persistent and severe AKI following cardiac surgery. Addressing these is crucial for improving patient outcomes.

Toward a Consistent Definition of Persistent AKI in Cardiac Surgery

A pressing need exists for a uniformly accepted and validated definition of persistent AKI (or AKD) specifically for the cardiac surgery population.⁵ Current definitions vary widely across studies, impeding meaningful comparisons and meta-analyses and limiting the generalizability of findings. A future consensus should go beyond duration and sCr thresholds to incorporate

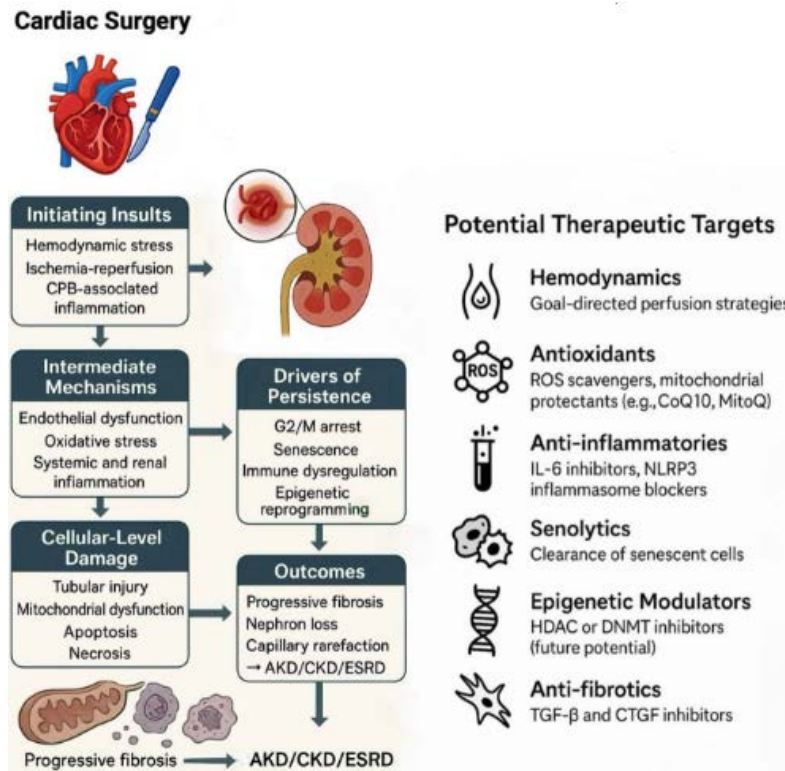


Figure 2. Pathophysiological Pathways and Therapeutic Targets in Persistent AKI Following Cardiac Surgery.

Abbreviations: CPB – cardiopulmonary bypass; ROS – reactive oxygen species; IL-6 – interleukin-6; NLRP3 – NOD-like receptor family pyrin domain-containing 3; HDAC – histone deacetylase; DNMT – DNA methyltransferase; TGF- β – transforming growth factor-beta; CTGF – connective tissue growth factor; AKD – acute kidney disease; CKD – chronic kidney disease; ESRD – end-stage renal disease

biomarker-based criteria reflecting ongoing injury or failed repair. Such a definition would improve patient identification for both research and clinical decision-making.

Biomarker-Guided Clinical Trials: A Precision Medicine Approach

The future of therapeutic development in CSA-AKI depends on biomarker-guided clinical trials that allow for a more precise and efficient therapeutic strategy.⁸⁷ Biomarkers can be used to enrich study populations by identifying patients at high risk of persistent or severe AKI, or with specific pathophysiological profiles most likely to benefit from targeted interventions. They can also support treatment stratification according to biomarker-defined subgroups, enable real-time monitoring of therapeutic response, and serve as surrogate endpoints to accelerate trial completion, provided that their validity is rigorously confirmed. In particular, future studies should focus on biomarkers predictive of non-recovery and those reflecting critical mechanisms such as inflammation, mitochondrial dysfunction, and early fibrotic remodeling.

Development of Cardiac-Surgery-Specific Biobanks

To support discovery and validation efforts, large-scale biobanks with biospecimens collected prospectively from cardiac surgery patients are essential.³⁶ These should be tightly integrated with granular clinical data, including operative variables and long-term follow-up. Blood,

urine, and, where possible, renal tissue samples will enable exploration of molecular AKI subtypes, genetic predisposition, and novel therapeutic targets.

Longitudinal Studies on the Outcomes and Trajectory of Persistent AKI

While it is known that persistent AKI is associated with poor long-term outcomes, more robust and detailed longitudinal studies are needed.⁸⁷ Future research must track the trajectory of renal function (e.g., eGFR slope), incidence of CKD, cardiovascular events, mortality, and health-related quality of life. Understanding post-discharge risk factors and identifying windows for intervention will be essential for post-ICU care models.

Elucidating Mechanisms of Maladaptive Repair and Fibrosis

The progression from acute injury to fibrosis hinges on a complex interplay of cellular dysfunction and maladaptive repair mechanisms. Key areas requiring deeper investigation include:

- Persistent G2/M cell cycle arrest and senescence in tubular cells;
- Mitochondrial dysfunction and impaired mitophagy as barriers to recovery;
- Epigenetic reprogramming, including changes in DNA methylation, histone modifications, and non-coding RNA expression;
- The diverse roles of immune cells, particularly macrophage subtypes, in modulating inflammation

and fibrosis.

These insights are vital for uncovering novel therapeutic targets for interrupting fibrosis at its earliest stages.

Development and Validation of Interventions for Persistent AKI

Based on an improved mechanistic understanding, novel interventions targeting these pathways need to be developed and rigorously tested. This includes therapies aimed at resolving inflammation, protecting mitochondria, clearing senescent cells (senolytics), reversing detrimental epigenetic programming, and directly inhibiting fibrotic pathways.

A particularly critical but underexplored research area is the identification of the “point of no return” in persistent AKI – the threshold beyond which renal injury becomes largely irreversible and transitions to established CKD. Such understanding could be pivotal when and how this transition occurs, possibly through serial biomarker measurements, advanced renal imaging techniques, or repeated functional assessments. Identifying this threshold could refine prognosis, optimize the timing of interventions aimed at preventing CKD, and help in designing clinical trials with realistic endpoints for patients with established persistent injury. Figure 3 illustrates the cascade of pathophysiological mechanisms leading from AKI to fibrosis, as well as the multi-level precision management strategies proposed to interrupt this trajectory.

Discussion

Persistent and severe AKI following cardiac surgery

remains a formidable clinical challenge, exacting a heavy toll in terms of patient morbidity, mortality, and healthcare resources. Its development is not merely an extension of the initial insult but rather a complex pathophysiological cascade involving sustained inflammation, ischemia-reperfusion injury, profound mitochondrial dysfunction, failed or maladaptive cellular repair mechanisms, and lasting epigenetic alterations that collectively drive the kidney towards chronic damage and fibrosis.

Early recognition of high-risk AKI phenotypes should not end at diagnosis but rather serve as the foundation for longitudinal care models that mitigate CKD progression.¹⁶⁶⁻¹⁶⁸ Recent evidence underscores that persistent AKI and incomplete renal recovery markedly increase the risk of long-term CKD and mortality.¹⁶⁸⁻¹⁷² Biomarker-based phenotyping, using early indicators such as NGAL, TIMP-2×IGFBP7, IL-18, or DKK3, enables identification of patients with ongoing tubular stress or maladaptive repair who would benefit from extended follow-up and nephrology-led management.¹⁷²⁻¹⁷⁵ Such integration allows for timely interventions, including optimization of hemodynamics, avoidance of nephrotoxins, and initiation of renoprotective agents (e.g., SGLT2 inhibitors or RAS blockers).^{167,176,177} Furthermore, serial monitoring of eGFR, albuminuria, and fibrosis biomarkers during follow-up can provide actionable insights for preventing AKI-to-CKD transition.¹⁷⁸ This precision medicine framework, linking early phenotyping with tailored longitudinal management, represents a critical step toward improving survival and renal outcomes after cardiac surgery.

Despite its clinical significance, early detection of

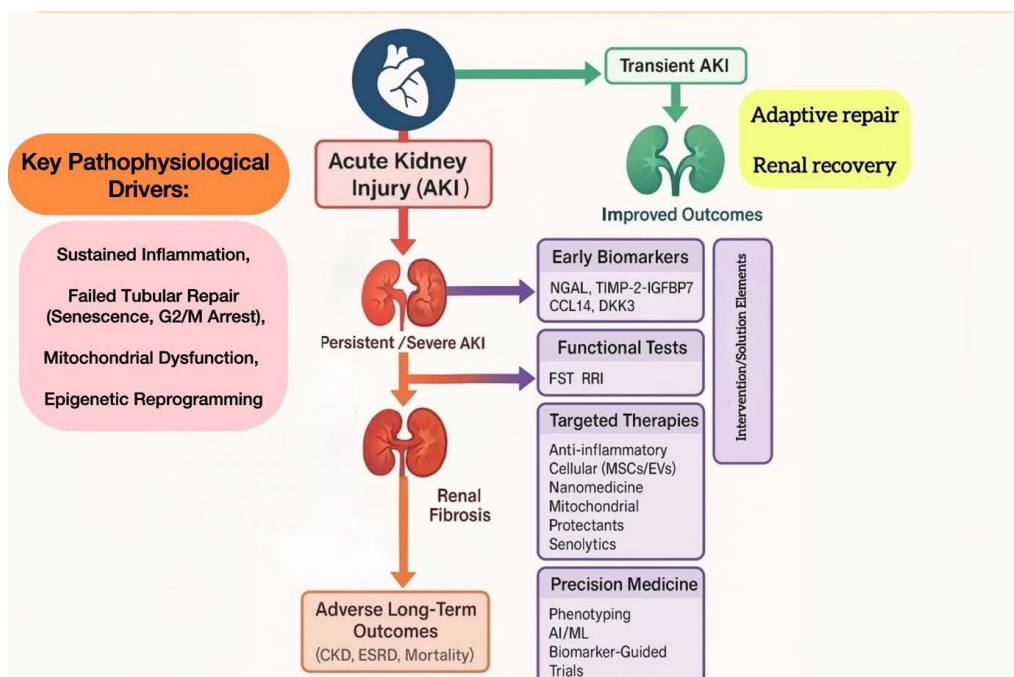


Figure 3. Persistent AKI Post-Cardiac Surgery: From Complex Pathophysiology to Precision Management for Improved Renal Outcomes.

Abbreviations: AKI – acute kidney injury; CPB – cardiopulmonary bypass; CKD – chronic kidney disease; ESRD – end-stage renal disease; NGAL – neutrophil gelatinase-associated lipocalin; TIMP-2 – tissue inhibitor of metalloproteinases-2; IGFBP7 – insulin-like growth factor binding protein-7; CCL14 – C-C motif chemokine ligand-14; DKK3 – Dickkopf-related protein 3; FST – furosemide stress test; RRI – renal resistive index; MSC – mesenchymal stem cell; EV – extracellular vesicle; AI/ML – artificial intelligence/machine learning

persistent AKI remains inadequate, as current diagnostic strategies largely depend on delayed functional markers such as serum creatinine. Although emerging biomarkers and functional assessments hold promise for earlier risk stratification and trajectory differentiation, their precise role, particularly in forecasting AKI persistence after cardiac surgery, requires further validation in context-specific settings.

It should also be emphasized that the framework proposed in this work is a conceptual and exploratory model introduced for the first time by the authors. Although it is founded on the mechanistic and temporal understanding of renal injury in the cardiac surgery setting, its clinical applicability requires future prospective validation and consensus among nephrology and cardiac surgery experts. Therefore, it should be regarded as a hypothesis-generating classification designed to stimulate further research and serve as a foundation for developing a unified, surgery-specific definition of persistent AKI.

Management of established persistent CSA-AKI remains predominantly supportive, with no targeted therapies currently proven to halt or reverse progression toward CKD. This therapeutic void underscores the need for a fundamental shift from generalized approaches to personalized medicine. Such a shift calls for a deeper understanding of patient-specific phenotypes and endotypes, identified through clinical profiles and biomarker signatures that reflect the dominant pathophysiological mechanisms. Timely recognition of individuals at risk for persistent renal injury could pave the way for mechanism-based interventions, targeting inflammation, enhancing mitochondrial function, promoting adaptive repair, and preventing fibrosis, ideally guided by predictive and dynamic biomarkers.

Moving forward, addressing the burden of persistent CSA-AKI will require integrated, multidisciplinary collaboration. Nephrologists, cardiac surgeons, intensivists, pathologists, and basic and translational researchers must join forces through well-structured clinical trials, the establishment of biobanks, and dedicated exploration of renal injury and recovery pathways. Only through such collective efforts can we translate scientific insights into effective clinical solutions that improve outcomes for this high-risk patient population.

Conclusion

Persistent AKI after cardiac surgery represents a distinct and high-risk clinical entity rather than a simple extension of transient renal injury. Early recognition, phenotypic stratification, and biomarker-guided care are key to improving renal recovery and reducing progression to chronic kidney disease. Establishing standardized definitions, validating biomarkers, and designing phenotype-based clinical trials will be critical steps toward implementing precision nephrology in this domain.

Acknowledgements

None.

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Competing Interests

The authors declare no competing interests.

Ethical Approval

Ethical approval and informed consent were not required for this narrative review as it is based solely on previously published data and contains no identifiable patient information.

Funding

This work received no specific grant from any funding agency, commercial, or not-for-profit sector.

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