



# Postoperative acute kidney injury

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Acute kidney injury (AKI) after cardiac surgery is a common and serious complication. Several definitions of AKI have been proposed recently, and include both increases in serum creatinine levels and decreases in urine output as diagnostic criteria. The pathophysiology of postoperative AKI is complex and involves both ischemic injury and systemic inflammation. Identifying risk factors, such as old age, underlying diabetes, heart failure, and obesity, may aid in the application of preventative methods for postoperative AKI. Additionally, recognizing different risks after different types of surgical procedures would be valuable. Novel biomarkers that could detect AKI more precisely at an earlier time point are being investigated. Several new biomarkers have been assessed in large multi-center studies and are believed to accommodate conventional clinical findings in diagnosing postoperative AKI. In high-risk patients, preventative measures, such as the maintenance of adequate hemodynamics and sufficient fluid resuscitation, could lower the incidence of postoperative AKI. Avoiding nephrotoxic agents and optimizing preoperative hemoglobin levels to avoid excessive transfusions would also be beneficial. In situations in which medical management fails to maintain sufficient urine output and acid–base and electrolyte homeostasis, early initiation of renal replacement therapy should be considered.

**Key Words:** Acute kidney injury, Postoperative complications, Renal protection, Surgery.

## Introduction

Acute kidney injury (AKI), a condition characterized by persistent oliguria and elevated serum creatinine levels, is a common complication in patients undergoing surgery. The incidence of AKI varies from 5.0–7.5% in hospitalized patients receiving acute care, and can reach up to 20% in patients in the intensive care unit [1,2]. Although the incidence of postoperative AKI depends greatly on the type of surgery, overall, 40% of in-hospital AKI cases are related to surgical procedures [3]. Reported incidence rates of AKI associated with cardiac surgery

range from 7.7–40%, depending on the patient population [4–8]. Improvements in surgical procedures and perioperative management have increased the number of surgical patients with severe comorbidities and older age, which has led to an increase in patients who are at a high risk of postoperative complications, such as infections, gastrointestinal dysfunction, acute lung injury, and postoperative AKI. Recent investigations have shown that postoperative AKI increases the risk of morbidity after surgery and in-hospital mortality [6,9–11]. Patients who develop postoperative AKI have been found to develop sepsis and coagulopathy more often than those who do not develop postoperative AKI [12]. Additionally, patients with postoperative AKI are at higher risk of needing mechanical ventilation [12]. Moreover, a recent study found that the mortality rate at 30 days after intra-abdominal surgery was 15-fold higher in patients with AKI than in those without, indicating that the risk of mortality is higher in patients with AKI even after the recovery of renal function [13].

This review discusses the definition and pathophysiology of postoperative AKI and explores current methods of identifying postoperative AKI, including the role of novel biomarkers. Finally, it provides recommendations for preventative measures and management strategies.

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## Definition of AKI

Various definitions have been applied to effectively determine the extent of renal function decline that affects patient morbidity and mortality. The glomerular filtration rate (GFR) is the most accurate representation of renal function. However, estimating the GFR using a 24-h urine creatinine clearance test is troublesome and time-consuming in acute situations when immediate treatment decisions are needed. Thus, most recent definitions use urine output and serum creatinine levels as surrogates of renal function because of their easy-to-measure characteristics.

The first consensus on the definition of AKI, the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE) criteria, was reported in 2004 by the Acute Dialysis Quality Initiative [14]. The RIFLE system classifies AKI into three stages of severity, determined by serum creatinine levels or changes in urine output, and two outcome stages, decided by the duration of kidney function loss. This system also introduced the term 'AKI' to replace the formerly used term 'acute renal failure.' This change in terminology reflects the fact that structural injury to the kidney precedes the loss of kidney function, highlighting the importance of salvaging actions even before actual failure of function occurs.

In 2007, the RIFLE system was revised by the Acute Kidney Injury Network (AKIN) [15]. With increasing evidence showing that even small elevations in serum creatinine levels may be associated with increases in morbidity and mortality [16], the AKIN system allows the definition of AKI without knowledge of baseline serum creatinine levels.

Studies comparing these two classification systems have shown that both definitions can effectively identify AKI within the first 24 h [17,18]. Additionally, the severity of AKI clearly predicts clinical outcomes in both systems [19]. However, overdiagnosis can occur when AKI is defined solely on the basis of the degree of serum creatinine change [19]. Choosing the appropriate baseline creatinine level for comparison is key in these situations.

The most recent consensus on the definition and staging of AKI was reached in 2012 by the Kidney Disease: Improving Global Outcomes (KDIGO) Foundation [20]. It defined AKI as any of the following: an increase in serum creatinine by  $\geq 0.3$  mg/dl ( $\geq 26.5$   $\mu$ mol/L) within 48 h; or an increase in serum creatinine to  $\geq 1.5$  times the baseline value, which is known or presumed to have occurred within the prior 7 days; or urine volume  $< 0.5$  ml/kg/h for 6 h. In particular, the KDIGO criteria eliminated the use of GFR and added a timeframe according to the absolute level or relative increase of serum creatinine. Additionally, this system added a new class to recognize patients with acute kidney damage superimposed on an underlying chronic kidney disease. Moreover, KDIGO recommends staging AKI according to severity, based on investigations demonstrating that mortality and renal replacement therapy risks increase with each stage [21]. Table 1 compares the three different definition criteria.

Despite these efforts to detect AKI effectively and in a timely manner, definitions that include serum creatinine levels still have limitations. Most importantly, serum creatinine levels begin to increase after the pathological changes of kidney injury

**Table 1.** Comparison of the Three Classifications and Staging of AKI

Classification	RIFLE	AKIN	KDIGO
Stage		Stage 1	Stage 1
Risk	Increased sCr $\times 1.5$ or GFR decrease $> 25\%$ or urine output $< 0.5$ ml/kg/h for 6 h	Increased sCr $\times 1.5$ or $\geq 0.3$ mg/dl from baseline or urine output $< 0.5$ ml/kg/h for 6 h	Increased sCr $\times 1.5$ to 1.9 baseline or $\geq 0.3$ mg/dl from baseline or urine output $< 0.5$ ml/kg/h for 6 to 12 h
Injury	Increased sCr $\times 2$ or GFR decrease $> 50\%$ or urine output $< 0.5$ ml/kg/h for 12 h	Stage 2 Increased sCr $\times 2$ or urine output $< 0.5$ ml/kg/h for 12 h	Stage 2 Increased sCr $\times 2.0$ to 2.9 baseline or urine output $< 0.5$ ml/kg/h for 12 h
Failure	Increased sCr $\times 3$ or GFR decrease $> 75\%$ or sCr $\geq 4$ mg/dl (acute rise of sCr $\geq 0.5$ mg/dl) or urine output $< 0.3$ ml/kg/h for 24 h or anuria for 12 h	Stage 3 Increased sCr $\times 3$ or $\geq 4$ mg/dl with acute rise of sCr $\geq 0.5$ mg/dl or urine output $< 0.3$ ml/kg/h for 24 h or anuria for 12 h	Stage 3 Increased sCr $\times 3$ baseline or $\geq 4$ mg/dl or initiation of RRT, or GFR decrease $< 35$ ml/min/1.73 m <sup>2</sup> for patients $< 18$ years of age or urine output $< 0.3$ ml/kg/h for 24 h or anuria for 12 h
Loss	Persistent AKI $> 4$ weeks		
ESRD	ESRD		
End-stage renal disease	End-stage renal disease		

RIFLE: Risk, Injury, Failure, Loss and End-stage Kidney, AKIN: Acute Kidney Injury Network, KDIGO: Kidney Disease: Improving Global Outcomes, sCr: serum creatinine level, GFR: glomerular filtration rate, AKI: acute kidney injury, ESRD: end-stage renal disease.

are already well established. Thus, timely measures to prevent the progression of kidney injury at an early time point may not be possible. Additionally, the serum creatinine level is affected by volume status, infectious conditions, steroid use, and muscle mass [22]. Therefore, recent investigations have focused on developing biomarkers that can effectively detect AKI at earlier time points.

## Pathophysiology

Traditionally, the causes of AKI have been classified into prerenal, intrinsic, and postrenal factors. These classifications provide practical information about the underlying pathophysiology of the etiology of AKI, but to date the causes of AKI have not been differentiated clearly in a clinical setting. When the duration of AKI induced by a prerenal cause is prolonged, renal parenchymal damage progresses, eventually giving rise to intrinsic kidney injury [22].

Prerenal AKI occurs when the perfusion of the kidney is altered. The kidney, which has the highest tissue perfusion rate relative to organ weight, normally receives 15–20% of total cardiac output [23]. This high perfusion rate makes the kidney vulnerable to hemodynamic injury. Prerenal AKI is found most commonly in patients undergoing cardiac surgery who have undergone cardiopulmonary bypass procedures [24,25]. However, recent investigations have shown that in addition to hemodynamic alterations, inflammation and direct nephrotoxic effects on tubular cells play crucial roles in inducing AKI in patients after cardiac surgery [26]. Additionally, factors not related to the surgical procedure itself, such as the presence of valvular disease, inotropic use, or postoperative intra-aortic balloon pump support, can reduce renal blood flow, subsequently aggravating the damage caused by cardiopulmonary bypass. Moreover, impaired glomerular hemodynamics resulting from the use of non-steroidal anti-inflammatory drugs, diuretics, and renin-angiotensin-aldosterone system blockades may further exacerbate renal damage.

Intrinsic AKI accompanies injury of the major structural components of the kidney. Embolic events and vasculopathies

caused by malignant hypertension or microangiopathies induce damage to the renal vasculature. Allergic reactions to medications or infectious organisms can generate renal interstitial injury. Damage to the renal tubules can occur due to profound hemodynamic deterioration in the kidney, or nephrotoxic substances, such as antibiotics or contrast media. Tubular damage is the most common underlying cause of intrinsic AKI occurring after surgery [20]. However, all of the events mentioned above can occur postoperatively. Table 2 summarizes the common etiologies of postoperative AKI.

## Risk Factors

Several factors are known to contribute to postoperative AKI. Identifying these factors could aid in avoiding nephrotoxic drugs and providing close monitoring for renal derangements in high-risk patients.

## Comorbidities

Demographic factors, such as age and gender, have been found to be closely related with the development of postoperative AKI. The capacity of the kidney to adapt to hemodynamic changes declines with age [27]. Not only is renal plasma flow lower, but renal responses to vasodilating factors are also weaker in older patients [28]. Additionally, older patients are more often exposed to medications that can affect renal function, such as diuretics and contrast media. In a recent prospective evaluation of 9,400 patients, female gender was also noted as a significant risk factor for postoperative AKI [29].

Underlying medical conditions, such as chronic kidney disease, diabetes mellitus, hypertension, cardiovascular disease, liver disease, and chronic obstructive pulmonary disease, are well-documented risk factors predisposing a patient to postoperative AKI [5,11,27,30,31]. In a prospective evaluation of 43,642 patients undergoing cardiac surgery, the risk of postoperative AKI was increased significantly among patients with cardiomegaly (odds ratio, OR = 1.74; 95% CI = 1.43–2.12), cerebrovascular disease (OR = 1.89; 95% CI = 1.48–2.41), chronic obstructive

**Table 2.** Factors Associated with Postoperative AKI

Preoperative	Intraoperative	Postoperative
Nephrotoxic drugs	Cardiopulmonary bypass	Decreased cardiac function
Inflammation	Anemia	Vasoactive drugs
Underlying CKD	Shock	Nephrotoxic drugs
Decreased effective volume	Hemodilution	Inflammation
Renovascular disease	Embolic events	Unstable hemodynamic state
Congestive heart failure		

AKI: acute kidney injury, CKD: chronic kidney disease.

pulmonary disease (OR = 1.55; 95% CI = 1.28–1.88), diabetes mellitus (OR = 1.43; 95% CI = 1.08–1.89), and New York Heart Association class IV status (OR = 2.12; 95% CI = 1.78–2.54). However, the risk of AKI was unrelated to remote myocardial infarction or a history of percutaneous coronary artery angioplasty [5].

## Obesity

Obesity, particularly severe obesity, defined by a body mass index (BMI) of  $> 40 \text{ kg/m}^2$ , is associated with a higher risk of postoperative AKI than lower BMI [32,33]. The reason for this increased risk is known to be related to the changes in renal hemodynamics induced by adipose tissue in obese patients [34,35]. The type and location of adipose tissue is also suspected to affect renal function after surgery. In a recent investigation, abdominal obesity, quantified using computed tomography scans, was particularly associated with postoperative AKI [36].

## Metabolic acidosis

A recent investigation evaluating factors associated with AKI development after cardiac surgery revealed that low preoperative serum bicarbonate levels ( $< 23 \text{ mEq/L}$ ) were independently associated with a two-fold increased risk of postoperative AKI [37]. The underlying mechanism for the association between low serum bicarbonate concentrations and postoperative AKI is unclear, but several possibilities can be considered on the basis of previous animal experiments. Metabolic acidosis is known to induce medullary ammonia production, which in turn activates the alternative complement pathway and aggravates tubular inflammation in an animal model of AKI [38]. Additionally, excessive acid loading in mice resulted in activation of the intrarenal renin-angiotensin-aldosterone system [39]. Moreover, sodium bicarbonate is known to increase renal medullary oxygen delivery and to reduce renal iron-mediated free radical formation [40]. Based on these findings, some investigators have attempted to prevent AKI through urine alkalization by means of sodium bicarbonate infusion; however, the results of these trials have been inconsistent [41,42].

## Type of surgery

The type of surgery has a significant effect on the risk of postoperative AKI occurrence. The risk of postoperative AKI is increased in emergency surgery versus elective operations [30,31]. Compared with other surgical procedures, intraperitoneal surgery, especially exploratory laparotomy and small-bowel resection operations, is known to increase the risk of postoperative AKI [31,43,44]. Increased intra-abdominal pressure, caused

by excessive fluid administration in these operations, results in a situation in which the intra-abdominal pressure compresses the renal veins and constricts the renal arteries, activating the sympathetic system; this is known as abdominal compartment syndrome [45–47]. This condition ultimately leads to a reduction in renal perfusion and can cause ischemic damage to the kidneys [45]. Similarly, urine output decreases during a laparoscopy due to increased abdominal pressure resulting from intra-abdominal gas insufflation [48]. However, the reduction in urine output during laparoscopy has not been found to increase the risk of postoperative AKI [49,50]. Nonetheless, increasing intra-abdominal pressure should be avoided in older and high-risk patients, such as those with underlying CKD.

Major vascular surgery and cardiac operations also increase the risk of postoperative AKI in particular [8,51]. Previous studies have demonstrated that AKI occurs in almost 30% of patients who have undergone cardiac surgery, although the incidence of AKI associated with cardiac surgery varies somewhat depending on the characteristics of the study population [8,19,51]. Although several pathophysiological factors have been identified, such as ischemic-reperfusion injury, inflammation, microembolism, decreased renal perfusion, and the use of nephrotoxic drugs, the mechanism of the increased postoperative AKI risk in patients undergoing cardiac operation is not yet fully understood [52]. The type of cardiac operation is also linked to different effects in inducing postoperative AKI. Because cardiopulmonary bypass per se is a known risk factor for AKI, coronary artery bypass graft (CABG) operations using cardiopulmonary bypass were associated with a higher incidence of AKI compared with off-pump CABG [24,25]. Patients receiving cardiac valve surgery also have higher incidences of postoperative AKI than those undergoing on-pump CABG operations [24,25,53].

## Drugs

Preoperative and intraoperative uses of medications have been evaluated extensively as a cause of postoperative AKI. Medications that block the renin-angiotensin-aldosterone system and non-steroidal anti-inflammatory drugs increase the risk of postoperative AKI [54,55]. The influence on the compensatory mechanism that maintains the GFR under hemodynamically compromised conditions is the main mechanism for this increased risk. Aminoglycosides induce renal damage via mitochondrial dysfunction [35]. The combination of two or more nephrotoxic drugs, consisting of diuretics with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and non-steroidal anti-inflammatory drugs, was found to increase the risk of AKI considerably in an evaluation of a large cohort of patients with hypertension [54].

Patients who undergo radiological examinations involving

contrast media before surgery are at an increased risk of developing postoperative AKI [56]. The mechanism of contrast-induced nephropathy is not understood, but it is believed to include direct damage from reactive oxygen species [57,58]. Because hypovolemia aggravates the renal damage induced by contrast media, it is important to maintain effective blood volume in patients exposed to contrast media before surgery.

## Biomarkers

Detecting AKI by using serum creatinine levels is problematic because serum creatinine levels are elevated after renal function has declined, and do not reflect injury. Therefore, recent investigations have focused on finding practical serum and urine biomarkers that could reveal early injury before profound functional damage occurs.

Neutrophil gelatinase-associated lipocalin (NGAL) is released from neutrophils and is induced by inflammation. Studies have shown that elevated urine and serum NGAL levels reflect tubular injury [59,60]. In a study of children undergoing cardiopulmonary bypass, urine concentrations of NGAL increased 2 h after cardiopulmonary bypass, whereas AKI diagnosis with serum creatinine was only possible 1–3 days after the procedure. In this study, the amount of NGAL in urine at 2 h after cardiopulmonary bypass was the most powerful independent predictor of acute renal injury [61]. However, because NGAL is produced throughout the body, it is difficult to distinguish systemic inflammation from localized renal inflammation with elevated levels of NGAL [62]. This limitation has restricted the use of NGAL in detecting AKI. Cystatin C (CyC) is a protease inhibitor produced by nucleated cells at a constant rate. This is filtered freely by the glomerulus and reabsorbed completely by the renal tubules. CyC is not normally found in urine, so detection of CyC in urine may indicate renal injury [63,64]. Kidney injury molecule-1 (KIM-1) is highly upregulated in proximal tubular cells after kidney injury. A recent study reported that plasma KIM-1 levels increased within 2 days after surgery only in patients who developed AKI, suggesting KIM-1 as a biomarker capable of early AKI detection [65].

Recently, some researchers have assessed combinations of two or more biomarkers to improve the diagnostic power for AKI. This approach is promising in that different biomarkers indicate different aspects of renal injury. In a prospective evaluation of 90 patients undergoing cardiac surgery, Han et al. [66] reported that the combination of urinary KIM-1, *N*-acetyl-beta-D-glucosaminidase, and NGAL enhanced the sensitivity of early detection of postoperative AKI compared with individual biomarkers.

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) are cell-cycle

arrest proteins. In events of tubular injury due to toxin exposure, hypoxia, and inflammation, these proteins are released into the urine [67]. Recent multi-center studies have demonstrated that TIMP-2 and IGFBP7 are superior to existing markers, and provide additional information in detecting AKI to that provided by clinical variables [68,69]. The US Food and Drug Administration recently approved the combination of these two novel urinary biomarkers to assess the risk of AKI in critically ill patients.

## Therapeutic Approach

Maintaining adequate hemodynamics to prevent tissue hypoperfusion and renal ischemic injury is the primary goal of perioperative management [70]. Blood pressure is a practical surrogate indicating hemodynamic status. Prolonged periods of perioperative hypotension have been found to be significantly associated with postoperative AKI. An investigation evaluating the perioperative data of 33,330 patients undergoing non-cardiac surgery revealed that 1–5 min of an intraoperative mean arterial pressure of < 55 mmHg was significantly associated with the development of postoperative AKI [71].

Adequate fluid management is a key component in maintaining intravascular volume and cardiac hemodynamics in patients undergoing surgery. However, although under resuscitation increases the risk of renal hypoperfusion, excessive fluid administration is capable of decreasing renal blood flow and GFR by increasing renal subcapsular pressure and inducing abdominal compartment syndrome [72]. Recent non-invasive methods for monitoring hydration status, such as chest ultrasound for detecting pulmonary congestion and body composition monitoring through bioimpedance spectroscopy techniques, may help to maintain appropriate hydration status [73,74].

The type of fluid used for volume resuscitation also affects postoperative renal function. Because normal saline actually contains supraphysiological levels of chloride, infusion of large volumes of normal saline may cause hyperchloremic acidosis, which can lead to a decrease in renal perfusion. Animal studies have shown that hyperchloremia produces progressive renal vasoconstriction and decreases in GFR [75]. In an investigation comparing the effects of intravenous administration of normal saline and a balanced crystalloid solution, only normal saline resulted in a reduction in renal cortical tissue perfusion [76].

Anemia induces renal medullary hypoxia, which is one of the key mechanisms leading to AKI [77]. In an observational study of patients undergoing non-cardiac surgery, low preoperative and early postoperative decreases in hemoglobin concentrations were strongly associated with postoperative AKI in a graded manner [78]. Additionally, intraoperative transfusions have been found to increase the risk of postoperative AKI development. An investigation of a cohort of patients who underwent cardiac



surgery with cardiopulmonary bypass revealed that AKI rates increased in direct proportion to the amount of erythrocytes transfused, and this increase was more pronounced in patients with anemia [79]. It is uncertain whether anemia induced renal hypoxia, or whether toxic effects of transfusion itself increased the risk of postoperative AKI in these patients. Considering that stored red blood cells undergo irreversible changes, making them more adherent to the vascular endothelium, resulting in a decrease in microvascular flow, both low hemoglobin levels and increased amounts of transfusions could play a role in inducing postoperative AKI [80,81]. Thus, optimizing the preoperative hemoglobin levels as suggested by the recent 'patient blood management protocol' would be helpful in lowering the risk of postoperative AKI [82].

Once oliguria occurs, interventions improving renal hemodynamics, such as maintaining vascular contractility with inotropes and optimizing heart rate, should be implemented to maintain urine volume. However, if oliguria persists despite these actions, diuretics should be used to maintain urine output. Nonetheless, it should be noted that a recent meta-analysis found that although the use of furosemide may be beneficial in achieving fluid balance, it did not reduce mortality in patients with AKI [83]. Additionally, furosemide can aggravate renal failure by inducing prerenal injury in patients with reduced effective volume.

Renal replacement therapy should be considered when the

effort to maintain renal function has failed. The general indications for renal replacement therapy are volume overload, hyperkalemia, and medically unresolved metabolic acidosis. However, early initiation of renal replacement therapy may be beneficial in some cases. In a recent investigation of patients who developed severe AKI after cardiac surgery, early and aggressive continuous venovenous hemofiltration was associated with better-than-predicted survival [84,85].

## Conclusions

AKI is a common complication in patients undergoing surgery. The clinical significance of postoperative AKI is substantial in that the incidence is growing with the increase in operations in older and severely comorbid patients. Additionally, the development of postoperative AKI increases mortality risks significantly, lengthens hospital stays, and worsens long-term morbidity. The recent definitions and classifications of AKI were intended to provide effective and timely detection of AKI. Nonetheless, assessments based on serum creatinine levels have limitations. The development of novel biomarkers may provide a more accurate and faster way of detecting postoperative AKI, which could eventually lead to earlier intervention. Additionally, recognizing the risk factors of postoperative AKI and understanding the management options would be beneficial in preventing postoperative AKI and improving patient outcomes.

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