



Review Article

Risk Factors for Acute Kidney Injury in Surgical Patients - A Review

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Introduction

Acute Kidney Injury (AKI) is a well-recognized post-operative complication and occurs in almost one-third of inpatients [1]. The risk factors for the development of AKI in these patients are different from the usual culprits seen in other hospitalized patients. AKI carries a high mortality, and this risk extends even to survivors of acute kidney injury (AKI) after leaving the hospital [2]. The increased ICU stays could cause other complications [3]. Moreover, there is a high risk for progression to chronic kidney disease (CKD) and hemodialysis [4]. AKI can be avoided and treated with prompt intervention, but the problem nevertheless poses a significant burden and cost to healthcare. There exist several definitions for AKI, such as the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease), AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease: Improving Global Outcomes) criteria. Among these definitions, the KDIGO definition is the most utilized, and an arbitrary window of 7 days post-surgery is widely used as the timeline to define post-operative AKI (PO-AKI) [5]. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) is the most extensive database tracking surgical outcomes after major procedures. It provides detailed information on the risk-adjusted outcomes of patients within 30 days of their surgery. According to their definition, AKI is defined as a post-operative increase in blood creatinine above 2 mg/dl or the requirement for renal replacement treatment. The American College of Surgeons Committee on Trauma defines Acute Kidney Injury (AKI) in trauma patients as an increase in creatinine above 3.5 mg/dl [6]. But these definitions based on creatinine cut-offs alone may lack sensitivity and result in under detection of AKI in some patients [4]. Recognizing the immense burden of AKI,

the International Society of Nephrology (ISN) initiative “0 by 25 Initiative” project was proposed that aims to decrease avoidable fatalities attributable to Acute Kidney Injury (AKI) worldwide by the year 2025 [7]. The risk for developing PO-AKI could be related to patient, surgery, and peri-operative factors. This article aims to provide clinicians with a comprehensive review of the various risk factors that contribute to AKI in surgical patients to help identify high-risk patients.

Patient-Related Factors

Age and Gender

Age >50 years has been described as a risk factor for (PO-AKI) [5]. Both Renal Plasma Flow (RPF) and Glomerular Filtration Rate (GFR) decrease with age. It has been demonstrated that elderly patients have increased intrarenal vascular resistance, likely due to arteriosclerosis in smaller intrarenal vasculature, along with increased interstitial fibrosis and tubular atrophy [8]. Females have lower hematocrit and blood volumes and have been found to have increased transfusion requirements and PO-AKI after cardiac surgeries [9].

Pre-Existing Kidney Disease

CKD is a widely recognized condition that increases the risk of PO-AKI following cardiac, bariatric, and other surgeries [10,11]. The decreased kidney reserve in CKD leads to an increased risk of injury. The incidence of CKD increases in older patients, for example, preoperative Chronic Kidney Disease (CKD) was found to be highly prevalent in older patients who have hip fracture surgery, with an incidence rate of up to 40% [12]. It is, therefore, essential to know the baseline creatinine of these patients [9]. CKD not only increases the risk of PO-AKI, but also other post-

surgical complications and causes increased hospital stays. PO-AKI is a causative factor for CKD and faster progression to ESRD in patients with pre-existing CKD. This progression to CKD occurs within one year of surgery [13]. Albuminuria and hypoalbuminemia have been identified as risk factors for PO-AKI, and these are also frequently associated in CKD patients [5].

Comorbid Conditions

Patients with hypertension and diabetes mellitus are known to have an increased risk of AKI after cardiac surgery, major abdominal surgery, bariatric surgery, and orthopedic surgeries [12,14-16]. Both chronic and acute hyperglycemia are linked to heart dysfunction, increased susceptibility to infections, and impaired endothelial function [17]. Pre-existing low left ventricular ejection fraction is a significant risk factor [15]. The presence of CKD also independently increases the incidence of cardiovascular disease [18]. High Body Mass Index (BMI) is associated with both early and late PO-AKI after most surgeries [19]. There are conflicting associations between high BMI and AKI after cardiac surgery. Patients with a higher Body Mass Index (BMI), although having a higher risk of cardiovascular problems and more additional health conditions, do not always experience unfavorable outcomes following cardiac surgery. This is referred to as the ‘‘obesity paradox’’[15]. Such a paradox has not been found in patients undergoing other surgeries, in patients undergoing bariatric surgery, higher BMI is associated with an increased AKI risk [14]. Preexisting liver disease also increases the risk for PO-AKI, and the risk is even higher in patients with cirrhosis [1,20]. Even in the early phases of liver disease, there exists splanchnic vasodilation, which is usually counterbalanced by increased cardiac output. When the cardiac response is blunted by cardiomyopathy or other cardiac diseases, patients are prone to developing AKI [20]. The American Society of Anesthesiologists (ASA) Physical Status Classification System III–IV has been found to increase the risk for AKI, likely due to their decreased cardiac reserve [21]. Patients with a history of congestive heart failure could develop renal venous congestion, causing compression of renal tubules and decreased Glomerular Filtration Rate (GFR), which worsens post-surgery [22].

Surgical Factors

Type of Surgery

The risk of AKI post cardiac surgeries is higher compared to others and occurs in up to 30% of the patients [1,23]. Even slight elevations in Serum Creatinine (SCr) levels following heart surgery have been found to be linked to a substantial rise in mortality within 30 days. Various models exist to predict AKI post-cardiac surgeries, such as the Cleaveland clinic score, the Society of Thoracic Surgeons (STS) Bedside Risk Tool, and the Simplified Renal Index (SRI). The risk models predicting AKI requiring dialysis are the most reliable and validated [23]. Renal atheroembolism can be the primary cause of Acute Kidney

Injury (AKI) in cardiac surgery, but these cases are usually not detected early and are found incidentally on autopsies. Post-operative use of intra-aortic balloon pumps can contribute to AKI by disrupting atheromas [9]. Biomarkers such as tissue inhibitors of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), inducers of G1 cell cycle arrest, have been validated in detecting AKI. The concentrations of [TIMP-2] [IGFBP7] in the urine of individuals who have cardiac surgery are highly sensitive and specific in predicting Acute Kidney Injury (AKI). Although cardiac surgeries portend a higher AKI risk to patients, the risk of AKI due to other surgeries is not low. Research studies investigating AKI related to surgery have established different timelines to identify AKI, such as 48 hours, 72 hours, or 7 days after the surgical procedure [24]. AKI may not be apparent in the immediate post-operative period but may worsen later [5]. A large retrospective study that included 54,810 patients who underwent non-cardiac surgeries such as cranial, chest or abdominal surgeries showed that 41.7% developed AKI within 48 hours after surgery. Among various factors that resulted in a high risk for AKI, patients with sepsis carried the highest risk. Other risk factors were a requirement for blood transfusion, vasopressors, and mechanical ventilation [19]. There are risk prediction models available for predicting AKI following major noncardiac surgery; however, these models have not been validated [24]. Extended periods of elevated intra-abdominal pressure by pneumoperitoneum during laparoscopic surgeries are linked to a reduction in urine production. While acute renal impairment typically resolves entirely following the completion of surgery in healthy people, there is a concern that these temporary changes may have a significant impact on patients with pre-existing renal illness [25]. Intra-abdominal surgeries cause AKI due to various mechanisms. Along with the risk due to prolonged pneumoperitoneum, increased blood losses during surgery can worsen AKI [10]. Major abdominal surgeries like colon resection are at high risk for PO-AKI. Conventional intravenous-fluid protocols used in abdominal surgery administer almost 7 liters of liquids on the day of the surgical procedure due to the increased need for fluids, but some patients may require more [26]. Orthotopic Liver Transplant (OLT) recipients are at high risk, and the pathogenesis of AKI is complex and involves various factors such as exposure to elevated amounts of harmful free radicals, renal ischemia, administration of nephrotoxic drugs, and the impact of liver disease on the kidney.

The presence of female sex as a risk factor for Acute Kidney Injury (AKI) in liver transplant patients may appear counterintuitive, considering the known protective benefits of estrogens in cardiovascular and renal conditions. The estrogens’ ability to provide protection is typically reduced or absent in women who are premenopausal or menopausal [27]. This elevated risk was not seen in females undergoing other surgeries [1]. Orthopedic surgeries are generally considered low-risk surgeries but still carry a risk of AKI [1]. Previous research has shown that the occurrence of Acute Kidney Injury (AKI) following hip fracture

surgery ranges from 8% to 24%, depending on the characteristics of the study participants and the specific criteria used to define AKI [12]. Obstructive uropathy due to benign prostatic hypertrophy or complications of urological procedures should be diagnosed early and intervened early to avoid complications [10,22].

Duration of Surgery

Surgeries conducted within the initial 5 days of admission had a notably reduced likelihood of Acute Kidney Injury (AKI) compared to those performed later during the hospital stay [22]. The duration of surgery is important in some surgeries, such as coronary artery bypass graft surgery. The duration of time on Cardiopulmonary Bypass (CPB) of ≥ 180 minutes has been identified as a risk factor for the occurrence of Acute Kidney Injury (AKI) following CPB. This is commonly known as “on the pump”. These patients have an elevated mortality that remains elevated for up to 10 years, even after blood creatinine levels return to their original levels. Additional factors contributing to patient risk and surgical complications include older age, preexisting kidney dysfunction before surgery, ejection fraction less than 40%, and utilization of intra-aortic balloon pumps [28]. There is a suggestion that inhalational anesthetics possess characteristics that protect the kidneys. Sevoflurane and enflurane, containing fluorine, seem to be well-tolerated by people with kidney issues. The use of dexmedetomidine can have a protective effect on the kidneys by decreasing vasopressin secretion and improving renal blood flow and glomerular filtration [22].

Nephrotoxic Agents

The commonly identified causes of PO-AKI are ischemia, nephrotoxic medications, obstructive uropathy, inflammation, and oxidative stress [5]. Nephrotoxic medications account for almost 20-30% of PO-AKI [5]. The use of Angiotensin-Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARB), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and antibiotics are the common agents linked to PO-AKI. The precise processes underlying the link between the utilization of ACE-I/ARB medicines and AKI remain incompletely understood. The preoperative use of these medications may hinder the kidneys' ability to manage abrupt alterations in renal hemodynamics autonomously. This, together with other risk factors, can render the kidneys susceptible to experiencing ischemia injury [14]. An examination of 949 patients who underwent significant gastrointestinal or hepatobiliary surgery revealed no discernible difference in the occurrence of Acute Kidney Injury (AKI) between individuals who had their ACE inhibitors and ARBs discontinued before surgery and those who did not. Nonetheless, it is recommended to hold these drugs peri-operatively. NSAIDs should be generally avoided in high-risk individuals [5]. Preoperative use of diuretics has been considered a modifiable risk factor for AKI and should only be used when indicated [15].

The use of diuretics and radioiodine contrast can provoke AKI in a high-risk patient with pre-existing conditions or volume depletion [5]. Nephrotoxic medications are usually implicated in late AKI [22]. Multiple studies have provided evidence of nephrotoxicity using a combination of vancomycin and piperacillin-tazobactam. There is a notable correlation between a longer duration of antibiotic use and a higher likelihood of experiencing renal injury. Aminoglycosides are another class of antibiotics associated with renal failure and can cause AKI in 10-20% of the cases [29]. The use of Sodium-Glucose Transport 2 (SGLT2) inhibitors has increased over the last few years. While there is no consensus about using SGLT2i peri-operatively, their use must be evaluated on a case-by-case basis. The renal natriuretic and osmotic effects caused by SGLT2 inhibitors impact the overall hemodynamics. Providers should be cautious of the low probability of developing Diabetic Ketoacidosis (DKA) related with SGLT2i use, which presents in a different manner [30]. SGLT2 inhibitors, by causing renal glycosuria, promote the growth and colonization of organisms in the genital tract. This phenomenon is intensified in patients with obstructive uropathy due to benign prostatic hypertrophy or neurogenic bladder and can result in infections [31]. Healthcare professionals should exercise prudence when prescribing medications to individuals at high risk, particularly those that have the potential to worsen renal vasoconstriction.

Perioperative Factors

Anemia and Hypotension

Anemia plays a role in Acute Kidney Injury (AKI) by decreasing oxygen delivery to tissues [15]. A prior history of anemia before surgery has been solely linked to early Acute Kidney Injury (AKI), but blood transfusion during surgery is associated with late AKI [19]. Hypotension in the peri-operative period affects the kidneys in many ways. Apart from the direct effect of renal tissue hypoperfusion, other cascading events also worsen injury to the kidney. The inflammatory changes, impaired renal autoregulation, peritubular capillary narrowing, and oxidative stress cause reversible or irreversible injury depending upon the degree of hypoperfusion. The only preventative action depends on maintaining a sufficient intravascular volume and close monitoring. The intraoperative requirement for vasopressors and the detection of lactic acidosis usually precede PO-AKI [21]. A mean arterial pressure (MAP) < 55 mmHg has been shown to be an independent risk factor for PO-AKI [22]. However, hypotension was not found to be a risk factor in a large multicenter study, but the use of vasopressors was related to PO-AKI [11]. The RELIEF Randomized Controlled Trial (RCT) involved 3,000 patients undergoing major elective non-cardiac surgery. The results showed that the fluids-restricted group had a higher risk of Acute Kidney Injury (AKI), demonstrating the need for appropriate fluid resuscitation [26].

Hemodynamic Status

Renal autoregulation is an intricate mechanism involving multiple limbs that are ever-rapidly changing. These involve neurohormonal interactions between the sympathetic nervous system, several vasoconstrictors, and vasodilators [22]. Severe derangements to the hemodynamic status requiring endotracheal intubation, cardiogenic shock, and Intra-Aortic Balloon Pump (IABP) have been associated with PO-AKI. These risk factors affect young and older adults alike [15]. The requirement of renal replacement therapy among these post-surgical patients with AKI varies between 3.3-10% [3]. Machine learning algorithms have been recently developed to aid in noninvasive measurements of cardiorespiratory physiology gathered in the operating room and ICU and to risk stratify patients at high risk for developing AKI [4].

Infections

Sepsis is a well-known factor associated with late AKI, similar to the requirement for vasopressors and mechanical ventilation [22]. Endothelial dysfunction and the release of cytokines are a critical factor in the impairment of blood flow in small blood vessels during sepsis [22]. Bacterial endocarditis leads to AKI via embolization of vegetation and thrombus [9]. COVID-19 has also been found to incite PO-AKI. The systemic inflammatory response and the accompanying cytokine storm caused by COVID-19 infection could result in AKI due to Acute Tubular Necrosis (ATN) [32]. The increased duration between a positive SARS-CoV-2 test result and surgery has been linked to less AKI and mortality [33].

Conclusion

PO-AKI is associated with poor outcomes, longer length of stay, and readmissions [1]. The most effective preventative measures for Acute Kidney Injury (AKI) are early identification of high-risk individuals, increased clinical monitoring, appropriate fluid delivery, and avoidance of nephrotoxic exposure. Researchers are now studying biomarkers for Acute Kidney Injury (AKI) to assist providers in promptly and accurately detecting kidney damage. It is also crucial to plan for elective surgeries in patients with co-morbidities to prevent AKI. Refraining from the use of renal vasoconstrictors can offer immediate benefits in decreasing the incidence of PO-AKI.

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