



## Unveiling the Landscape of Acute Kidney Injury in Surgical Patients: A Systematic Review of Risk Factors and Clinical Biomarkers

Nooreena Yusop<sup>1</sup>, Nooreena Yusop<sup>1\*</sup>, Muhammad Ishamuddin Ismail<sup>2</sup>, Ruslinda Mustafar<sup>3</sup>

<sup>1</sup> Faculty of Nursing, University College MAIWP International, 61800, Kuala Lumpur, Malaysia

<sup>2</sup> Head of Cardiothoracic, Head of Heart and Lungs Centre, Hospital Canselor Tuanku Muhriz, Malaysia

<sup>3</sup> Nephrology Unit, Hospital Canselor Tuanku Muhriz, Malaysia

### ARTICLE INFO

### ABSTRACT

#### Article history:

Received : 30 March 2024

Received in revised form : 3 May 2024

Accepted : 6 June 2024

Available online : 16 August 2024

#### Keywords:

Acute kidney injury, risk factors, clinical biomarkers, surgical patients

Acute Kidney Injury (AKI) is a critical complication with significant implications for surgical patients, leading to increased morbidity, mortality, and healthcare costs. Identifying the risk factors and clinical biomarkers associated with AKI in the surgical context is essential for timely intervention and personalized management. To address this knowledge gap, we conducted a systematic review to comprehensively analyze existing literature on AKI in surgical patients. In this paper, we provided a systemically review analysis based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) technique for AKI risk factors and clinical biomarkers. The advanced searching into two powerful databases which is Scopus, Pubmed and Mendeley. Based on searching, find finally main data n=30 and will be analyzed using the synthesis approach. Through a meticulous search and appraisal of studies in reputable scientific databases, we identified a diverse range of research articles, clinical trials, and cohort studies that met our rigorous inclusion criteria. Synthesizing the findings from these studies, we explored the multifactorial nature of AKI, encompassing patient-related factors, surgical variables, and exposure to potential nephrotoxic agents. Our review revealed that AKI in surgical patients is influenced by a complex interplay of risk factors, including patient demographics, comorbidities, surgical procedures, anaesthetic management, and exposure to nephrotoxic drugs. The systematic analysis identified the most common drug classes associated with drug-induced AKI, such as diuretics, ACE inhibitors/angiotensin receptor blockers (ACEIs/ARBs), and antibiotics. Understanding these associations is crucial in minimizing the risk of drug-induced AKI in surgical patients. In conclusion, our systematic review contributes to a deeper understanding of the landscape of AKI in surgical patients. The identified risk factors and clinical biomarkers provide valuable guidance for risk stratification, preventive strategies, and early intervention, ultimately enhancing patient safety and outcomes in the context of surgical care.

\* Corresponding author.

E-mail address: [nooreena@ucmi.edu.my](mailto:nooreena@ucmi.edu.my)

<https://doi.org/10.37934/jhqol.3.1.1332>

## 1. Introduction

Acute kidney injury (AKI) represents the updated and widely accepted term for acute renal failure. It denotes a clinical syndrome characterized by a swift decline in renal excretory function, occurring over a short period (ranging from hours to days) [1]. This results in the accumulation of nitrogen metabolism by-products, such as creatinine and urea, alongside other unmeasured waste products with potential clinical significance. Typical manifestations encompass reduced urine output (although not universally present), the build-up of metabolic acids, and elevated levels of potassium and phosphate [2].

The adoption of the term "acute kidney injury" over "acute renal failure" serves to emphasize the continuum of kidney injury that occurs well before significant loss of excretory kidney function becomes evident through conventional laboratory tests. This conceptual shift also underscores the varying prognoses associated with AKI, with escalating mortality risks linked to even slight increases in serum creatinine levels, and further elevated mortality rates as creatinine concentration rises. Acute Kidney Injury (AKI) is a critical and prevalent complication that poses significant challenges to the management and outcomes of surgical patients. AKI is characterized by a sudden and rapid decline in renal function, leading to the accumulation of waste products and electrolyte imbalances. It is associated with increased morbidity, prolonged hospital stays, elevated healthcare costs, and a heightened risk of mortality [3].

In recent years, the incidence of AKI in surgical patients has been on the rise, prompting researchers and clinicians to delve deeper into its underlying causes and potential predictive markers. The multifactorial nature of AKI involves a complex interplay of patient-related factors, surgical procedures, anesthetic management, and exposure to nephrotoxic agents [4]. Additionally, an evolving body of evidence suggests that certain clinical biomarkers may serve as early indicators of impending renal injury, facilitating timely intervention and preventive measures. AKI poses a significant challenge for healthcare providers due to its association with increased morbidity, mortality, prolonged hospital stays, and escalated healthcare costs [5]. The incidence of AKI in the surgical setting has garnered considerable attention over the years, prompting extensive research into identifying the determinants and understanding the pathophysiological mechanisms that underlie its occurrence. Surgical patients represent a particularly vulnerable population, as they often encounter a complex interplay of factors that can compromise renal function, including surgical stress, fluid imbalances, exposure to nephrotoxic medications, and ischemia-reperfusion injury during surgery [6,7].

Despite advances in medical science and surgical techniques, AKI remains a major cause of morbidity and mortality in the postoperative period [8]. The multifactorial nature of AKI presents a complex challenge, with various risk factors and clinical biomarkers contributing to its occurrence. Despite its clinical significance, there is still a lack of a comprehensive and systematic understanding of the specific risk factors and clinical biomarkers associated with AKI in the surgical patient population. The existing literature on AKI in surgical patients is vast and varied, comprising studies with varying methodologies, sample sizes, and outcomes. Previous research has often focused on specific aspects or risk factors, leading to fragmented and sometimes conflicting findings. Moreover, the lack of a unified approach to identifying and assessing clinical biomarkers for AKI has hindered the development of standardized preventive and management strategies in the surgical setting [9].

The process of kidney injury initiates before the loss of excretory function, which is commonly represented by a decreased glomerular filtration rate (GFR). In certain instances, such injuries can be identified through the assessment of specific biomarkers. These biomarkers not only have potential diagnostic applications but also hold promise for prognostic evaluations. The glomerular filtration

rate (GFR) is a crucial measure of kidney function. Several biomarkers have been identified to aid in the detection and assessment of kidney injury [10].

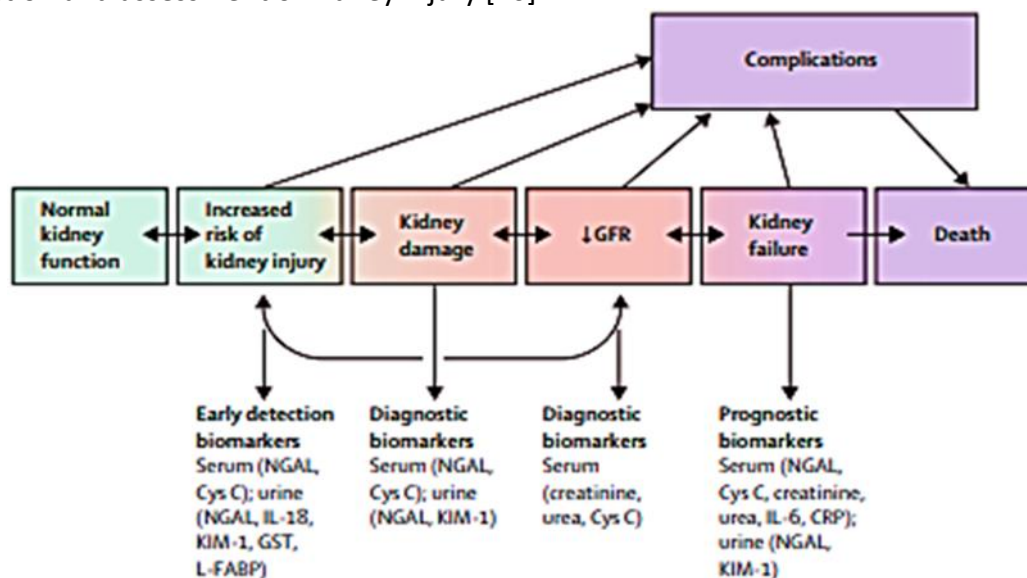


Fig. 1. Evolution of AKI [11]

These biomarkers play a crucial role in identifying early signs of kidney injury even before a decline in GFR becomes apparent. They offer valuable understanding for diagnostic purposes, aiding in the timely detection and management of kidney dysfunction. Additionally, these biomarkers can be utilized for prognostic assessments, helping to predict the severity of kidney injury and associated outcomes. By utilizing these biomarkers, clinicians can enhance their ability to monitor kidney health, implement preventive measures, and tailor treatment strategies to improve patient outcomes. Emphasizing the importance of these biomarkers offers a promising avenue for advancements in the early diagnosis and management of kidney injury. Therefore, early identification and understanding of the risk factors and clinical biomarkers associated with AKI are of paramount importance in optimizing patient care and surgical outcomes [12].

## 2. Material and methods

In choosing several appropriate papers for this report, the systematic review process consists of three main phases. The first step is keyword recognition and the quest for linked, similar terms based on the thesaurus, dictionaries, encyclopedia, and previous studies. Accordingly, after all the relevant keywords were decided, search strings on Scopus and PubMed (see Table 1) databases have been created. In the first step of the systematic review process, the present research work successfully retrieved 35 papers from both databases.

### 2.1 Screening

During the initial screening phase, duplicate papers should be disregarded. Based on various inclusion-and-exclusion criteria created by researchers, 7 papers were excluded in the first phase, whereas 44 articles were evaluated in the second phase. Because literature (research articles) is the main source of useful knowledge, it was the first criterion. Additionally, publications in the form of systematic reviews, reviews, meta-analyses, meta-synthesis, book series, books, chapters, and

conference proceedings are excluded from the current study. Additionally, the review was limited to English-language studies only. The schedule was established for a ten-year period (2021–2022), which is important to remember. Otherwise, to comply with the analytic purpose, only research conducted on Malaysian soil have been chosen. 56 publications overall based on predetermined criteria.

**Table 1**

Search and Screening Process

Scopus	TITLE-ABS-KEY ( "risk factors" AND "biomarkers*" AND "acute kidney injury" AND "surgical* patient" ) AND ( LIMIT-TO ( EXACTKEYWORD , "Acute Kidney Injury" ) OR LIMIT-TO ( EXACTKEYWORD , "Biomarkers" ) OR LIMIT-TO ( EXACTKEYWORD , "Surgical Patient" ) OR LIMIT-TO ( EXACTKEYWORD , "Adult" ) ) AND ( LIMIT-TO ( SUBJAREA , "MEDI" ) ) AND ( LIMIT-TO ( DOCTYPE , "ar" ) OR LIMIT-TO ( DOCTYPE , "re" ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) ) AND ( LIMIT-TO ( SRCTYPE , "j" ) ) AND ( LIMIT-TO ( PUBSTAGE , "final" ) )
Pubmed	(("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields]) AND ("biomarker s"[All Fields] OR "biomarkers"[Supplementary Concept] OR "biomarkers"[All Fields] OR "biomarker"[All Fields] OR "biomarkers"[MeSH Terms]) AND "AKI"[All Fields] AND ("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgical"[All Fields] OR "surgically"[All Fields] OR "surgicals"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) AND ((ffrft[Filter]) AND (review[Filter]))
Mendeley	Risk factors and clinical biomarkers of acute kidney injury AND surgical patients

2.2 Eligibility

For the third step, known as eligibility, a total of 44 articles have been prepared. All articles’ titles and key content were thoroughly reviewed at this stage to ensure that the inclusion requirements were fulfilled and fit into the present study with the current research aims. Therefore, 14 articles were omitted because they were not met the searching criteria’s. Finally, 30 articles are available for review (see Table 2).

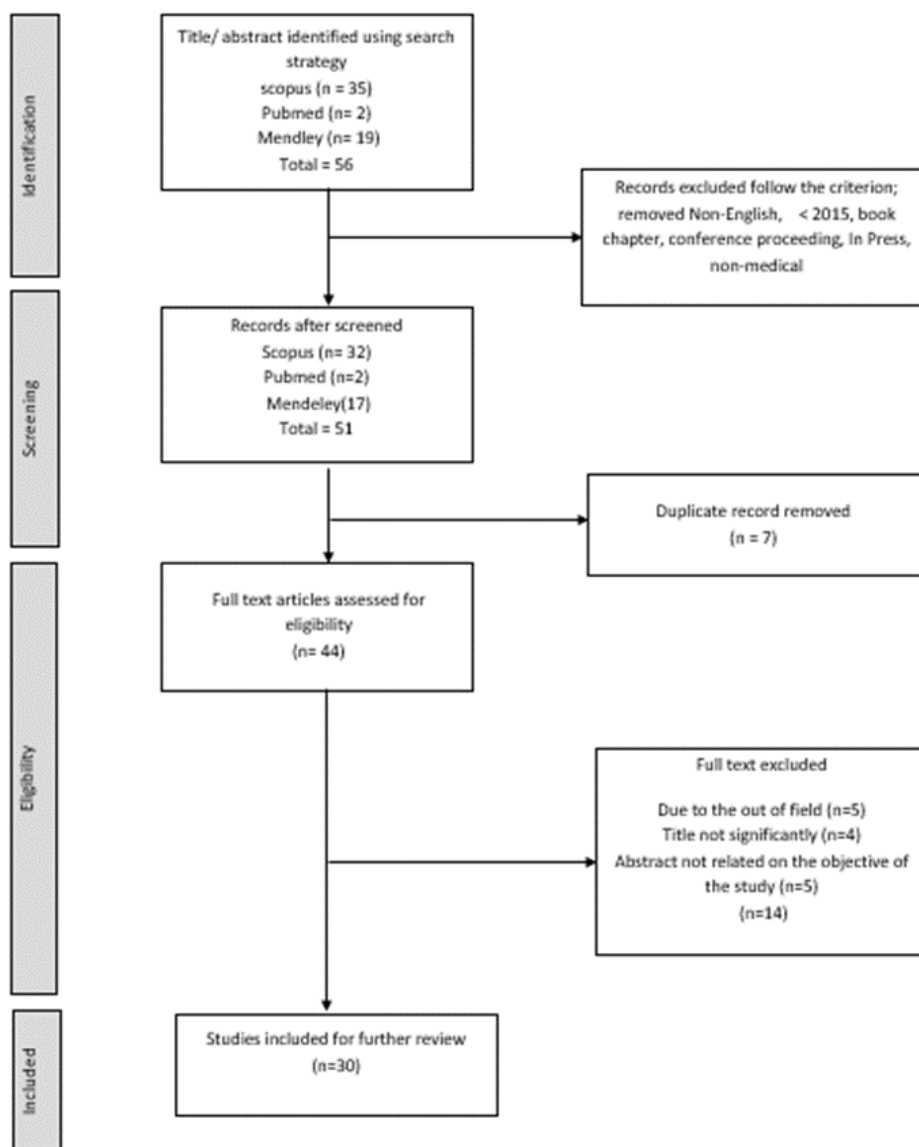
**Table 2**  
 Eligibility Process

Criterion	Inclusion	Exclusion
Language	English	Non-English
Time line	2015 – 2023	< 2015
Literature type	Journal (Article)	Conference, Book, Review
Publication Stage	Final	In Press
Subject Area	Medical	Non-medical

2.3 Data Abstraction and Analysis

An integrative analysis was used as one of the assessment strategies in this study to examine and synthesize a variety of research designs (cohort study, retrospective and prospective study). The goal of the competent study was to identify relevant topics and subtopics. The stage of data collection was the first step in generating the classifications of biomarkers and risk factors. Figure 2 shows how the authors meticulously analyzed a compilation of 30 publications for assertions or material relevant to the topics of the current study. The authors then evaluated the current significant studies related to surgical patients. The methodology used in all studies, as well as the research results, are being

investigated. Next, the author collaborated with other co-authors to classify the AKI biomarkers and risk factors based on the evidence in this study’s context. A log was kept throughout the data analysis process to record any analyses, viewpoints, riddles, or other thoughts relevant to the data interpretation. Finally, the authors compared the results to see if there were any inconsistencies in the theme design process. It is worth noting that, if there are any disagreements between the concepts, the authors discuss them amongst themselves. The produced biomarkers and risk factors of AKI were eventually tweaked to ensure consistency. The analysis selection was carried out by two experts, sexpert medical doctor in surgery and the other in nephrology who is nephrologist consultant and academican to determine the validity of the problems. The expert review phase ensures the clarity, importance, and suitability of each subtheme by establishing the domain.



**Fig. 2.** The flow of article using a search strategy

### 3. Result and Finding

AKI is a multifactorial and potentially serious complication affecting patients undergoing surgical procedures. Exploring the various clinical biomarkers and risk factors contributing to the

development of AKI among surgical patients is significant to understand the pathophysiological mechanisms that underlie its occurrence.

Based on the searching technique, 32 articles were extracted and analysed. All articles were categorised based on three main categories, which are clinical biomarkers (19 articles), surgery risk factors (6 articles), and Drugs induced AKI (5 articles) as presented at Table 3.

### 3.1 Clinical Biomarkers

#### 3.1.1 N-terminal pro-brain natriuretic peptide (NT-proBNP)

N-Terminal pro B-Type natriuretic peptide (NT-proBNP) is a biomarker used in medicine to assess the function and health of the heart. It is a fragment of a protein called B-type natriuretic peptide (BNP), which is released by the heart in response to stretching of the heart muscle walls, particularly in conditions of increased pressure or volume overload [13]. Moreover, at cardiac surgery the association between preoperative biomarkers that reflect cardiac, inflammatory, renal, metabolic disorders and cardiac surgery-Associated AKI (CSA-AKI) are crucial to improve identification of patients at risk for renal injury [14]. For example, a study done at 539 perioperative patients to identify novel risk factors for cardiac surgery-associated AKI (CSA-AKI) in elderly patients by analyzing preoperative biomarkers reflecting cardiac, inflammatory, renal, and metabolic disorders. In this study, it was found CSA-AKI occurred in 88 (16.3%) patients and was associated with increased risk of mortality (RR, 6.70 [95% confidence interval {CI}, 3.38-13.30]) and disability (RR, 2.13 [95% CI, 1.53-2.95]). Preoperative concentrations of N-Terminal pro B-Type natriuretic peptide (NT-proBNP), high-sensitive C-reactive protein (hs-CRP), hemoglobin, and magnesium had the strongest association with CSA-AKI [15].

A similar study but conducted involving 3,314 noncardiac surgical patients with preoperative N-terminal pro-brain natriuretic peptide (NT-proBNP) and left ventricular ejection fraction LVEF measurements to forecast postoperative AKI in noncardiac surgical patients AKI occurred in 223 patients (6.72%) within a week after surgery. Preoperative NT-proBNP concentrations and LVEF levels were found to be independent predictors of AKI, even after adjusting for clinical variables. The inclusion of these biomarkers resulted in significant improvements in reclassification, with 22.9% (95% CI 10.5–34.4%) for patients experiencing postoperative AKI and 36.3% (95% CI 29.5–43.9%) for those who did not, leading to an overall improvement in net reclassification (NRI: 0.591, 95% CI 0.437–0.752,  $p < 0.000$ ). The integral discrimination improvement was 0.100 (95% CI: 0.075, 0.125,  $p < 0.000$ ). These findings highlight the potential of NT-proBNP and LVEF as valuable biomarkers in predicting postoperative AKI and may aid in risk assessment and patient management during noncardiac surgical procedures [16].

Fan *et al.*, [17] performed a cohort study among a discovery cohort ( $n=452$ ) and a validation cohort ( $n=326$ ) for early identification of acute kidney injury (AKI) following cardiac surgery. Using a combination of least absolute shrinkage and selection operator, logistic regression, and machine learning techniques, five independent biomarkers were identified for the nomogram inclusive of 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). NT-proBNP, 5.50 [3.54–8.71] was found significantly correlated with AKI after adjusting clinical confounders (odds ratio and 95% confidence interval).

Zhoa *et al.*, [18] conducted a similar study to investigate the predictive role of pre-operative N-terminal pro-B-type natriuretic peptide (NT-proBNP) on postoperative AKI. A retrospective cohort study was conducted involving adult patients who underwent noncardiac surgery between February 2008 and May 2018. Of 7,248 patients, 6.1% (444) developed AKI within one week after surgery. Pre-

operative NT-proBNP was an independent predictor of AKI after adjustment for clinical variables (OR comparing top to bottom quintiles 2.29, 95% CI, 1.47 to 3.65,  $P < 0.001$  for trend; OR per 1-unit increment in natural log transformed NT-proBNP 1.27, 95% CI, 1.16 to 1.39). From this study, it can be observed that, NT-proBNP concentrations provided predictive information for AKI in a cohort of patients undergoing noncardiac surgery, independent of and incremental to conventional risk factors.

### 3.1.2 Kidney injury molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1), is a transmembrane glycoprotein and is primarily found in the proximal tubules of the kidney. KIM-1 plays a significant role in the response to kidney injury and is considered a biomarker for acute kidney injury (AKI) [19]. When the kidney is injured due to various factors such as ischemia, toxins, or infections, the expression of KIM-1 is upregulated. A cohort study of high-risk adults undergoing cardiac surgery, pre-operative plasma levels of sTNFR1, sTNFR2, and KIM-1 were examined for their association with long-term outcomes after discharge. Out of 1378 participants with a median follow-up of 6.7 years, 31% died, 19% experienced cardiovascular events, and 30% developed CKD. However, the individual biomarkers or their combination did not significantly discriminate outcomes compared to a clinical model. The study highlighted the significance of pre-operatively measured sTNFR1, sTNFR2, and KIM-1 in predicting long-term outcomes in high-risk individuals after cardiac surgery, suggesting their potential use in patient evaluation before cardiac surgery [20].

Another prospective cohort study (TRIBE-AKI) was aimed to examine whether specific kidney injury biomarkers in urine collected immediately after cardiac surgery are associated with the duration of serum creatinine elevation. This study involved 1199 adults undergoing cardiac surgery, the levels of five urinary biomarkers were analyzed. Among the patients, 407 (34%) experienced at least stage 1 AKI, with 251 (61.7%) having AKI lasting 1–2 days, 118 (28.9%) for 3–6 days, and 38 (9.3%) for  $\geq 7$  days. An AKI duration of 7 days or longer was associated with a 5-fold increased risk of mortality at 3 years. The most significant associations were observed for urine KIM-1 and IL-18, with each logarithmic increase in these markers being linked to a 36% and 22% higher likelihood of longer AKI duration, respectively (OR 1.36, 95% CI 1.21, 1.52 for KIM-1 and OR 1.22, 95% CI 1.13–1.32 for IL-18). The highest quintiles of KIM-1 and IL-18 showed a 2.3-fold and 2.9-fold increased likelihood of extended AKI duration, respectively. This study revealed an independent dose-response relationship between levels of urinary injury biomarkers immediately after cardiac surgery and the duration of AKI. Additionally, longer AKI duration was linked to higher long-term mortality risk [20].

Göger *et al.*, [21] performed a study among patients with acute unilateral obstructive stone disease (AUOSD) undergoing endoscopic surgery. Urine samples from 50 patients were collected preoperatively, postoperatively at 4 hours, and on the 7th postoperative day. The study found that urinary KIM-1/Cr and NGAL/Cr ( $p < 0.001$ ) were significantly higher in the early postoperative period and correlated with higher grades of hydronephrosis. Additionally, these biomarkers demonstrated predictive potential for identifying hydronephrosis as KIM-1 value of 1.24 ng/mL had a sensitivity of 78% and a specificity of 63%. Authors conclude that KIM-1 and NGAL are valuable biomarkers for assessing renal function and aiding in the management of AUOSD patients, including predicting hydronephrosis and monitoring patients with JJ stents even though SCr are normal.

A retrospective study conducted among 157 patients was enrolled to assess the early diagnosis of acute kidney injury (AKI) in patients with urosepsis following ureteroscopic lithotripsy (URL), using urine interleukin-18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1). Urine biomarkers were measured at various time intervals after surgery. AKI

group exhibited significantly higher levels of urine IL-8, NGAL, and KIM-1 at 4, 12, 24, and 48 hours post-surgery ( $p < 0.01$ ). Combined detection of urine IL-8, NGAL, and KIM-1 at 12 hours yielded an improved diagnostic performance (AUC: 0.997, 95% CI: 0.991–0.998), with 98.2% sensitivity and 96.7% specificity. The study concludes that elevated levels of these urine biomarkers can promptly identify AKI in patients with URL-related urosepsis, and their combined evaluation at 12 hours post-surgery can serve as an essential reference for early AKI diagnosis [22].

### 3.1.3 Serum Creatinine (SCr)

Jin *et al.*, [23] performed a retrospective study analysis on 1334 patients who underwent elective cardiac surgery between January 1 and December 31, 2015 to explore how serum SCr corrected for fluid balance influences the prognosis of cardiac surgery patients. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to identify CSA-AKI, with SCr measurements taken every 24 hours during the ICU period and adjusted for cumulative fluid balance. The difference between SCr before and after adjustment, termed  $\Delta\text{Crea}$ , was used to classify patients into three groups: the underestimation group ( $\Delta\text{Crea} \geq P75$ ), the normal group ( $P25 < \Delta\text{Crea} < P75$ ), and the overestimation group ( $\Delta\text{Crea} \leq P25$ ). After adjusting for fluid balance, the incidence of AKI increased from 29.5% to 31.8%. Patients in the underestimation group had a prolonged length of ICU stay compared to the normal and overestimation groups (3.2 [1.0–4.0] vs. 2.1 [1.0–3.0] days,  $P < 0.001$ ; 3.2 [1.0–4.0] vs. 2.3 [1.0–3.0] days,  $P < 0.001$ ). The underestimation group also experienced significantly longer hospital stays and mechanical ventilation dependency compared to the normal group ( $P < 0.001$ ). Multivariate analysis revealed that age, baseline SCr, and left ventricular ejection fraction were independently associated with the underestimation of creatinine. In this study revealed patients with underestimation of SCr were found to have a poorer prognosis. This finding also highlights the importance of considering fluid balance adjustments when assessing kidney function and predicting outcomes in patients undergoing cardiac surgery as cumulative fluid balance following cardiac surgery interferes with accurate measurement of serum creatinine [23].

A retrospective analysis of clinical data from 450 patients who underwent major abdominal surgery were assess the occurrence and predictive factors of both transient and persistent postoperative AKI as well as its impact on in-hospital mortality. The researchers considered AKI diagnosed within the first 48 hours after surgery, using the Kidney Disease: Improving Global Outcome (KDIGO) classification based on serum creatinine (SCr) and urine output criteria. Persistent and transient AKI were defined following the Acute Disease Quality Initiative (ADQI) workgroup definitions. The result revealed AKI was observed in 22.4% of patients ( $n = 101$ ) within the first 48 hours after surgery, with 48% of these patients ( $n = 49$ ) experiencing persistent AKI lasting for more than 48 hours. SCr were identified as independent predictors of persistent AKI (adjusted OR 22.67 [4.00-128.46],  $p < 0.001$ ) and patients with persistent AKI had a higher mortality rate compared to those with transient AKI (51.9% vs. 20.7%). Persistent AKI remained an independent predictor of in-hospital mortality after adjusting for other factors [24].

There was another study that aimed to identify risk factors for acute kidney injury (AKI) based on pre-operative variables in individuals aged 65 and older. The eligible participants were patients aged 65 or above who underwent non-cardiac, non-ambulatory scheduled surgeries. AKI cases were identified from hospital databases, and 300 patients with no AKI diagnosis were randomly selected as controls. A total of 81 AKI cases and 239 controls were identified, with a post-operative AKI incidence of 2.87%. Pre-operative creatinine level ( $p = 0.0001$ ), a history of respiratory insufficiency ( $p = 0.04$ ), prior vascular surgery ( $p = 0.0001$ ), and abdominal surgery ( $p = 0.03$ ) were associated with an increased risk of AKI after surgery. These factors were used to develop a score and a nomogram



to predict the occurrence of post-operative AKI. A history of renal disease was also linked to a higher risk of post-operative AKI, particularly in cases involving vascular or abdominal surgery [25].

#### 3.1.4 Urinary neutrophil gelatinase-associated lipocalin (NGAL)

Another vital biomarker to be considered to detect and assess the kidney injury through Urinary neutrophil gelatinase-associated lipocalin (NGAL) that is measured in urine by Patel *et al.*, [26] study. NGAL is a protein that is produced by neutrophils, a type of white blood cell, and it is also expressed by cells in the kidney tubules. During kidney injury or stress, the expression of NGAL increases, leading to elevated levels of NGAL in the urine [27]. A prospective cohort study was aimed to investigate and validate the potential endostatin as a predictor for failure to recover from AKI. This study was conducted on 198 patients without known chronic kidney disease (CKD) who underwent major noncardiac surgery and developed new-onset AKI within 48 hours of ICU admission. Plasma levels of endostatin, neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C were measured immediately after AKI diagnosis. The primary endpoint was nonrecovery from AKI within 7 days. Endostatin showed superior predictive capabilities for nonrecovery (AUC = 0.776, CI 0.654-0.892,  $p < 0.001$ ) compared to NGAL and cystatin C. The prediction model combining endostatin with clinical risk factors (SOFA score and AKI classification) significantly improved predictive ability (AUC = 0.887, CI 0.766-0.958,  $p < 0.001$ ). The endostatin-clinical risk model outperformed others, achieving a sensitivity of 94.6% and specificity of 72.7%. Plasma endostatin serves as a valuable predictor for nonrecovery from AKI in surgical patients, and combining it with clinical risk factors offers a promising approach for identifying higher-risk patients [28].

The prospective observational study aimed to investigate the development of acute kidney injury (AKI) in patients undergoing major abdominal surgery by comparing the rise in NGAL to that in creatinine. Sixty patients between 18 and 65 years old undergoing major abdominal surgery were included. Patients with certain medical conditions and those undergoing emergency surgery were excluded. Various laboratory values, including leukocyte and creatinine levels, NGAL, lactate, and urine output, were evaluated at different time points. Results showed that 15% of patients had increased NGAL values at 6 hours postoperatively, indicating early detection of AKI. Increased creatinine levels and decreased urine output were observed at 48 hours postoperatively, further confirming the development of AKI. NGAL proved to be an early predictive biomarker for AKI in patients undergoing major abdominal surgery [29].

A similar study to compare various serum and urinary markers (creatinine, kineticGFR, cystatin C, NGAL, NephroCheck, proteinuria, albuminuria, and acantocytes) for their predictive capabilities of AKI and long-term eGFR decline after robotic Nephron-Sparing Surgery (rNSS). The procedure was performed on 38 patients undergoing rNSS for suspected localized Renal Cell Carcinoma. Samples were collected before and after surgery, with kidney function assessed for up to 24 months. Of the participants, 42% developed clinical AKI, and those with postoperative AKI experienced a more significant eGFR decline at 24 months. In this study, 16 (42%) developed clinical AKI. The eGFR decline at 24 months was more pronounced after postoperative AKI ( $-20.75$  vs.  $-7.20$ ,  $p < 0.0001$ ). KineticGFR at 4 h ( $p = 0.008$ ) and NephroCheck at 10 h ( $p = 0.001$ ). At multivariable linear regression analysis, KineticGFR at 4 hours and NephroCheck at 10 hours emerged as efficient predictors of postoperative AKI and long-term eGFR decline, outperforming creatinine. These non-invasive and early biomarkers could enable early identification of patients at high risk for postoperative AKI and long-term eGFR decline, offering potential benefits for clinical practice [30].

### 3.1.5 C-reactive protein (CRP)

C-reactive protein (CRP), procalcitonin, and presepsin are suggested as important diagnostic and prognostic factors in critically ill sepsis patients. In normal individuals, procalcitonin is found in low concentrations. However, its levels significantly rise in response to different conditions such as infection, tumor, burn, inflammation, trauma, and surgery [31]. CRP, produced in hepatocytes due to inflammatory cytokines, increases in both infectious and non-infectious inflammation. Procalcitonin, a precursor of calcitonin, rises in various conditions, especially bacterial and fungal infections. Presepsin, released by activated monocytes in response to pathogens, is associated with infectious inflammation. The levels of presepsin and CRP increase with decreased renal function, and CRP can still predict infection accurately in patients with impaired kidney function [32].

A study to determine the procalcitonin (PCT), Sr Creatinine (SCr) and C-Reactive Protein (CRP) value to predict the development of AKI was enrolled with 105 patients and categorized them into AKI (37 cases) and non-AKI groups (68 cases). Various factors were compared between the groups. Results showed that age, number of bee stings, and vomiting after admission were different between the groups. AKI patients had higher levels of serum creatinine, PCT, interleukin-6 (IL-6), and hypersensitive C-reactive protein (hs-CRP). PCT levels were positively correlated with SCr, IL-6, and hs-CRP in AKI patients. The ROC curve analysis showed that the area under the ROC curve (AUC) of age, SCr, PCT, IL-6 and hs-CRP for predicting AKI in patients with bee stings were 0.622 [95% confidence interval (95%CI) was 0.516 to 0.727], 0.722 (95%CI was 0.601 to 0.843), 0.869 (95%CI was 0.781 to 0.958), 0.739 (95%CI was 0.627 to 0.851) and 0.799 (95%CI was 0.700 to 0.900). Multivariate analysis identified age, SCr, PCT, IL-6, and hs-CRP as independent risk factors for AKI after bee stings. PCT had better predictive efficacy (AUC=0.869) and could be used as a valid biomarker for clinical prediction [33].

The retrospective study involved 582 patients diagnosed with acute pancreatitis (AP), and the severity of AP was classified using the Atlanta classification. Patient's laboratory values were recorded upon their initial presentation to the emergency room. Subsequently, blood tests were performed at 48 hours and monitored daily until the day of discharge. Among them, 147 patients (25.2%) developed AKI. Patients who developed AKI were generally older, had lower albumin and calcium levels, and higher C-reactive protein (CRP)/albumin and neutrophil/lymphocyte ratios. The AKI group also showed higher levels of leukocytes, CRP, procalcitonin, and immature granulocytes, with decreased lymphocytes, hematocrit, and platelet levels. Additionally, urea and creatinine levels were higher in the AKI group at admission. The clinical picture of 13 patients with AP and AKI was severe. The study concluded that hematocrit, platelet, leukocyte, lymphocyte, albumin, CRP, CRP/albumin ratio, neutrophil/lymphocyte ratio, immature granulocytes, procalcitonin, urea, and creatinine levels at admission could serve as useful biomarkers to predict AKI development in AP patients, alongside age and accompanying diseases [34].

### 3.1.6 Urinary Output (UO)

Initially, Thomas *et al.*, [45] study revealed minimum hourly urine output of 0.5 mL/kg is commonly used for guiding perioperative fluid therapy. However, limited evidence supports this practice, and it may contribute to excessive fluid administration during the perioperative period. Interestingly, a randomized trial study was performed involving patients undergoing elective colectomy without significant risk factors for acute kidney injury to assess the safety and fluid-saving potential of a lower perioperative minimum urine output target compared to the standard target. The study was conducted with 40 participants completing the trial. The low group received 3170 mL

(95% confidence interval 2380-3960) of intravenous fluids compared to 5490 mL (95% confidence interval 4570-6410) in the standard group ( $p = 0.0004$ ). The low group was noninferior to the standard group regarding neutrophil gelatinase-associated lipocalin levels [14.7  $\mu\text{g/L}$  (interquartile range 7.60-28.9) vs. 18.4  $\mu\text{g/L}$  (interquartile range 8.30-21.2); Pnoninferiority = 0.0011], as well as serum cystatin C (Pnoninferiority < 0.0001), serum creatinine (Pnoninferiority = 0.0004), and measured glomerular filtration (Pnoninferiority = 0.0003). Effective renal plasma flow increased in both groups after surgery, with a slightly larger increase observed in the standard group (Pnoninferiority = 0.125). From this study showed, a perioperative urine output target of 0.2 mL/kg/h is noninferior to the standard target of 0.5 mL/kg/h and results in significant intravenous fluid sparing. This target should be considered for adoption in surgical patients without significant risk factors for kidney injury [35].

The potential relationship between a mild AKI observed shortly after major surgery and its impact on long-term renal function deserved for further investigation. Joosten *et al.*, [36] conducted a study to investigate whether patients who underwent intermediate-to-high-risk abdominal surgery and experienced mild AKI in the subsequent days would be at a higher risk of long-term renal injury compared to those without postoperative AKI. Result showed among the 815 patients included, 109 (13%) experienced postoperative AKI (81 mild and 28 moderate-to-severe). The median long-term follow-up was 360, 354, and 353 days for the three groups, respectively ( $p = 0.2$ ). Patients who developed mild AKI had a higher risk of long-term renal injury than those who did not (odds ratio 3.1 [95% CI 1.7–5.5];  $p < 0.001$ ). In multivariable analysis, mild postoperative AKI was independently associated with an increased risk of developing long-term renal injury (adjusted odds ratio 4.5 [95% CI 1.8–11.4];  $p = 0.002$ ). Study by Joosten *et al.*, concludes that, mild AKI following major abdominal surgery is associated with an increased risk of long-term renal injury that highly associated with poor urine output.

AKI is observed in approximately 22% of patients undergoing cardiac surgery, with around 2.3% requiring renal replacement therapy (RRT). Current diagnostic criteria based on increased serum creatinine levels have limitations, leading to the exploration of new biomarkers. Microscopic urinalysis, specifically the presence of renal tubular epithelial cells (RTEC) and granular casts (GC), is being investigated as a potential biomarker to differentiate pre-renal from renal AKI. This study aimed to evaluate the utility of urine sediment analysis in diagnosing AKI in patients undergoing cardiac surgery with cardiopulmonary bypass. Out of 114 patients analyzed, 23 (20.17%) developed AKI based on serum creatinine criteria, and 76 (66.67%) based on urine output criteria. Four patients required RRT, and the mortality rate was 3.51%. The presence of RTEC and GC in the urine sample demonstrated promising specificity for early AKI diagnosis after cardiac surgery [37].

After cardiovascular surgery, AKI is a common concern, typically diagnosed based on SCr levels and urinary output. A study conducted among 95 patients who underwent endovascular abdominal aortic aneurysm repair (EVAR) and 42 who underwent open repair to assess perioperative changes in urinary liver-type fatty-acid-binding protein (L-FABP) as a predictor for AKI during abdominal aortic repair. Urine and serum samples were collected at specific intervals for L-FABP and SCr measurements, respectively. These findings revealed EVAR, urinary L-FABP was significantly increased 4 h after the procedure ( $P = 0.014$ ). With open repair, urinary L-FABP increased significantly to its maximum by 2 h after AXC ( $P = 0.007$ ). OC analysis showed urinary L-FABP to be more sensitive than SCr for early detection of AKI. From this study demonstrates the urinary L-FABP demonstrated potential as a sensitive biomarker for AKI in patients undergoing this surgical procedure [38].

### 3.2 Risk Factor Surgery

During surgery, urine output might decrease due to factors unrelated to kidney injury or due to the presence of kidney injury, with or without fluid responsiveness. As a result, careful fluid management is essential to prevent both hypovolemia and hypervolemia. A sudden rise in Scr and/or a fall in urine output (UO) are used to make the diagnosis of AKI. Short- and long-term mortality and morbidity are both enhanced with even modest increases in Scr (National Institute for Health and Care Excellence, 2019). According to KDIGO, oliguria was defined as urine volume  $< 0.5\text{ml/kg/hour}$  for six hours has been shown to associate with AKI [39] & [45]. A large prospective multicentre study in Finland was conducted to investigate the association with oliguria and adverse outcomes among ICU patients. Out of 454 (23.1%) patients developed AKI from 1966 assessed patients. Within this AKI diagnosed patients, 68.7% developed AKI commenced renal replacement therapy. This study also reported that consecutive oliguria independently associated with 90-days mortality [40]. Another prospective study approached, combining clinical risk stratification and early postoperative evaluation of urinary biomarkers for AKI, to identify the high-risk patients. The study included all patients undergoing scheduled surgery with cardiopulmonary bypass between August 2015 and July 2016, except those on chronic hemodialysis. Patients were stratified based on Cleveland Clinic Score (CCS) and Leicester Score (LS), identifying high-risk patients with  $LS > 25$  or  $CCS > 6$ . Urinary biomarker concentrations for AKI ( $[\text{TIMP-2}] * [\text{IGFBP-7}]$ ) were evaluated four hours postoperatively in high-risk patients. AKI occurred in 54% of patients (352 out of 613), with higher incidence in high-risk compared to low-risk patients (66% vs. 49%;  $p = 0.001$ ). In-hospital mortality was significantly higher after AKI stage 2 (15%) or stage 3 (49%) compared to patients without AKI (1.8%;  $p = 0.001$ ). LS had modest predictive value for AKI (AUC 0.601), while CCS showed fair accuracy and predicted stage 2 or 3 AKI (AUC 0.669). In 133 high-risk patients, urinary  $[\text{TIMP-2}] * [\text{IGFBP-7}]$  had significant predictability for all-stage AKI within 24 hours (AUC 0.63), but not beyond 24 hours. Sensitivity for all-stage AKI within 24 hours was 0.38, specificity was 0.81, using a cutoff value of 0.3. This contrasts with findings by Vaara *et al.*, [40] findings. Following this study resulted CSA-AKI is a prevalent and relevant complication following cardiac surgery. However, clinical prediction scores can identify high-risk patients, their accuracy remains limited. Additionally, urinary  $[\text{TIMP-2}] * [\text{IGFBP-7}]$  quantification four hours postoperatively did not significantly improve the predictive value of clinical scores, especially for AKI cases occurring beyond the initial 24 hours. The findings from this study highlight the need for further research and enhanced diagnostic strategies to improve the early detection and management of CSA-AKI [41].

Identifying high-risk patients through biomarkers and implementing appropriate hemodynamic management strategies are key components of such an approach that essential to reduce the AKI risk and improving patient outcomes particularly in perioperative procedure [16]. Recent studies have shown that AKI occurs in approximately 1 in 10 surgical patients, with the highest risk observed in cardiac, orthopedic, and major abdominal surgeries. The use of cell cycle arrest biomarkers shows promise in identifying high-risk patients who could benefit from targeted interventions recommended by the Kidney Disease: Improving Global Outcomes guidelines. Implementing protocol-based fluid and vasopressor administration for hemodynamic management has been shown to reduce the incidence of AKI. Recent studies have also highlighted the benefits of personalized blood pressure targets based on individual resting reference values, avoiding both hypovolemia and fluid overload. Preliminary research indicates potential renoprotective effects of angiotensin II and nitric oxide, although further confirmation is needed. Additionally, urinary oxygenation monitoring has shown promise as a feasible method for predicting postoperative AKI [42].

On top of that, emergency surgeries are often performed under time constraints and in patients with compromised health status, which can contribute to a higher risk of AKI development. Hemodynamic instability, inadequate fluid resuscitation, and a lack of preoperative optimization are potential factors associated with AKI in emergency surgery cases [43]. Early recognition and prompt management of these factors are crucial in reducing the incidence of AKI in this setting. For instance, a retrospective cohort study in Austria was conducted among 6261 patients to determine the prevalence of AKI in postoperative ICU patients using the complete KDIGO criteria and the outcomes associated with various surgical procedures. According to all KDIGO criteria, the primary outcome was 28-day all-cause death in all stages of AKI. Primary effects 3497 (55.9%) postoperative ICU patients with AKI were identified. 235 (4%) individuals got RRT, with the severity distribution of AKI stage 1 to 3 being 19.7%, 28.4%, and 7.8%, respectively. (n = 205) The 28-day mortality rate was 3%. When other factors were considered, the severity of the AKI was linked to a higher 28-day mortality rate (AKI 2°: OR 2.81; 95% CI 1.55 to 5.24; p 0.001 and AKI 3°: OR 11.37; 95% CI 5.91 to 22.55; p 0.001). In multivariate analysis, there was a significantly higher risk of 28-day mortality following emergency surgery (OR 2.63; 95% CI 1.58 to 4.31, p = 0.001), vascular surgery (OR 2.01; 95% CI 1.06 to 3.98, p = 0.033), and orthopaedic and trauma surgery (OR 3.79; 95% CI 1.98 to 7.09, p 0.001). This study concludes that, within emergency surgery, type of surgery like vascular, orthopedic and trauma were linked to a stepwise rise in 28-day mortality following KDIGO guidelines [44]

Other study done at a tertiary academic hospital to determine the occurrence of acute kidney injury (AKI) following major non-cardiac surgery and to identify perioperative factors associated with a higher risk of postoperative AKI. This study involved retrospective collection of perioperative data for adult patients who underwent major non-cardiac surgery. Serum creatinine levels were recorded up to 7 days after surgery and compared to baseline measurements to diagnose AKI. The overall incidence of AKI was found to be 11.2% (95% confidence interval 9.8 - 12.6). After multivariate analysis, emergency surgery was observed to be an independent risk factor for AKI (OR 1.74; 95% CI 1.15 - 2.65; p=0.009) [45].

### 3.3 Drug induced AKI

Drug-induced kidney disease primarily affects patients with underlying risk factors. Patient-specific, kidney-related, and drug-related factors can all contribute to renal injury, leading to various clinical renal syndromes. Identifying these risk factors is essential to prevent renal complications caused by drugs and toxins [46]. The rising occurrence of drug-induced AKI requires a thorough comprehension of its underlying mechanisms and risk factors. Drug-induced AKI presents significant challenges in clinical settings, impacting both patient outcomes and healthcare systems. Identifying the risk factors related to nephrotoxic agents and AKI is crucial to prevent and reduce the impact of this severe condition [47]. Furthermore, medications that may build up in the body due to decreased kidney function should be avoided or adjusted, especially in patients with stage 2 or 3 AKI. This includes Aminoglycosides (tobramycin, gentamycin), NSAIDs (ibuprofen, naproxen, ketorolac, celecoxib), ACEi (captopril, lisinopril, benazepril, ramipril), ARB (losartan, valsartan, candesartan, irbesartan), Analgesics (morphine, meperidine, gabapentin, pregabalin), Antiepileptics (lamotrigine), Antivirals (acyclovir, gancyclovir, valgancyclovir), Antifungals (fluconazole), Antimicrobials (almost all antimicrobials need dose adjustment in AKI, with important exceptions of azithromycin, ceftriaxone, doxycycline, linezolid, moxifloxacin, nafcillin, rifampin), Diabetic agents (sulfonylureas, metformin) and others [48].

A retrospective analysis study done by Thomas *et al.*, to investigate the characteristics and outcomes of Amoxicillin (AMX)- induced crystal nephropathy (AICN). 101 AICN cases reported to

national pharmacovigilance databases were analyzed. Intravenous AMX/AMX–clavulanate was prescribed as surgical prophylaxis (32 surgical patients) or to treat infection (69 medical patients). AKI KDIGO stage 3 was observed in 70 patients and 24/70 patients required renal replacement therapy and/or intensive care unit admission. There was a significant increase in AICN cases was observed since 2010 (6 [0;7] and 77 [24;111] cases per 100 000 patient-years of exposure, before and after 2010 respectively;  $P < .001$ ). In surgical patients, the increase in AICN has been reported since 2010 and was mainly related to inadequate AMX administration. This study suggested monitoring AMX administration and identifying contributing factors could help mitigate the risk of AICN in patients receiving high doses of AMX [49].

Another study to determine the risk factors related to AKI caused by high-dose methotrexate (HDMTX) treatment ( $\geq 1$  g/m<sup>2</sup>), was conducted on 59 patients who had received 200 HDMTX courses between July 2014 and August at a medical centre. Data on demographics, lab results, and medications were collected and compared between groups with or without AKI. The findings revealed the incidence of HDMTX-induced nephrotoxicity was 9.5%. Male sex (odds ratio [OR], 4.20;  $P = 0.037$ ), the use of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), (OR, 5.18;  $P = 0.016$ ) and diuretics with urinary acidification (like loop diuretics) (OR, 4.91;  $P = 0.018$ ) were significantly associated with AKI [50].

Finally, Zainudheen *et al.*, [51] published a retrospective case-control study on 258 consecutive patients of elective total knee or hip replacement surgery. The aim of this study was to compare the incidence of intraoperative hypotension and adverse events between patients who received RAA and those who did not. Patients receiving RAA had higher preoperative systolic blood pressure, a higher prevalence of hypertension and chronic kidney disease, and a lower prevalence of ischaemic heart disease and cardiac risk compared to controls. Other factors such as age, gender, type of operation, operative fitness, mode and duration of anaesthesia, and prevalence of other cardiovascular diseases, dyslipidaemia, and diabetes were similar between the groups. However, patients receiving RAA had a higher incidence of intraoperative hypotension (76.0% vs 45.9%,  $P < 0.001$ ), AKI (11.6% vs 1.6%,  $P = 0.002$ ), and MACCE (6.2% vs 0%,  $P = 0.007$ ) compared to controls, and all adverse events were associated with intraoperative hypotension. This study provides further observational evidence of potential harm caused by RAA in patients undergoing elective surgery however a prospective randomized trials are suggested to determine the benefits and adverse clinical outcomes of preoperative withdrawal of RRA.

**Table3**

AKI Clinical biomarkers of Surgical Patients according to the listed authors

Author(s)	AKI Biomarkers					
	NGAL	NT-proBNP	KIM-1	SrC	CRP	Urinary Output (UO)
1 Verwijmeren et al (2021)	-	√	-	-	√	-
2 Yu et al (2023)	-	√	-	-	-	-
3 Fan et al (2023)	-	√	-	-	-	-
4 Zhao et al., 2021	-	√	-	-	-	-
5 Vasquez-Rios et al., 2022)	-	-	√	√	-	-
6 Göger et al (2022)	√	-	√	-	-	-
7 Tan et al., 2022	√	-	√	-	-	-
8 Jin et al., 2021)	-	-	-	√	-	-
9 Gameiro et al., 2020).	-	-	-	√	√	√
10 (De Guglielmo et al., 2022).	-	-	-	√	-	-
11 Jia et al., 2018	√	-	-	-	-	-
12 Mustafayeva et al., 2022).	√	-	-	√	-	√

13	Marco Allinovi et al., 2023	√	-	-	√	-	-
14	Xu et al., 2022)	-	-	-	√	√	-
15	Uğurlu & Tercan, 2023	-	-	-	√	√	-
16	Puckett et al., 2017	-	-	-	√	-	√
17	Joosten et al (2021)	-	-	-	-	-	√
18	Goldani et al., 2020)	-	-	-	√	-	√
19	Grieshaber et al., 2020	-	-	-	-	-	√
20	Canet & Bellomo, 2018).	-	-	-	-	-	-
21	Hu et al., 2022	-	-	-	-	-	-
22	Schiefer et al., 2023	-	-	-	-	-	-
23	Rossouw & Chetty, n.d.).	-	-	-	√	-	-
24	Moore et al., 2018	-	-	-	-	-	-
25	Thomas et al., 2020)	-	-	-	-	-	-
26	Liang et al., n.d.	-	-	-	-	-	-
27	Obata et al., 2016).	-	-	-	√	-	√
28	Xu et al., 2022	-	-	-	√	√	-
29	Vaara et al., 2016)	-	-	-	-	-	√
30	Zainudheen et al., 2017)	-	-	-	-	-	-

**Table 4**

AKI Clinical biomarkers of Surgical Patients according to the listed authors

Author(s)	AKI-risk factors			Other risk factors
	Surgery	Type of surgery	Drug induced AKI	
1. Verwijmeren et al (2021)	√	cardiac	-	Hb, magnesium
2. Yu et al (2023)	√	Non-cardiac	-	LVEF
3. Fan et al (2023)	√	cardiac	-	Soluble ST2, heart-type fatty acid protein (H-FABP), LDH, uric acid
4. Zhao et al., 2021	√	Non-cardiac	-	-
5. Vasquez-Rios et al., 2022)	√	cardiac	-	-
6. Göger et al (2022)	√	endoscopic surgery	-	-
7. Tan et al., 2022	√	ureteroscopic lithotripsy	-	-
8. Jin et al., 2021)	√	cardiac	-	Age
9. Gameiro et al (2020).	√	abdominal	-	-
10. De Guglielmo et al (2022).	√	vascular	-	Age >65 years
11. Jia et al (2018)	√	-	-	Plasma endostatin, Cystatin C
12. Mustafayeva et al (2022)	√	abdominal	-	-
13. Marco Allinovi et al (2023)	-	-	-	Cystatin C, eGFR
14. Xu et al (2022)	-	-	-	Age
15. Uğurlu & Tercan (2023)	√	-	-	Albumin, age, procalcitonin
16. Puckett et al (2017)	√	colectomy	-	GFR, Cystatin C
17. Joosten et al (2021)	√	abdominal	-	-
18. Goldani et al (2020)	-	-	-	-
19. Grieshaber et al (2020)	√	cardiac	-	-
20. Canet & Bellomo (2018).	√	Cardiac, ortho, major abdomen	√	-
21. Hu et al (2022)	√	emergency	-	Unstable hemodynamically, inadequate fluid resuscitation

22. Schiefer et al (2023)	√	Emergency, vascular, trauma, ortho	-	-
23. Rossouw & Chetty, (n.d.).	√	Emergency, non-cardiac	-	-
24. Moore et al (2018)	-	-	√Aminolycoside, NSAIDs, ACE, ARB, Analgesic	-
25. Thomas et al (2020)	√	General surgery	√antibiotic	-
26. iang et al., n.d.	-	-	√ Diuretic, ACE, ARB,	Male sex
27. Obata et al (2016).	√	EVAR	-	Age, PCT
28. Xu et al (2022)	-	-	-	-
29. Vaara et al (2016)	√	cardiac	-	-
30. Zainudheen et al (2017)	√	total knee or hip replacement	Renin-angiotensin-antagonist	-

#### 4. Discussion

AKI is a significant concern among surgical patients, as it is associated with increased morbidity and mortality. Timely detection and risk assessment are crucial for mitigating AKI-related complications. Early detection and risk stratification are pivotal for effective intervention and improved patient outcomes. This overview discusses the utility of clinical biomarkers and the identification of risk factors associated with AKI in surgical settings. Clinical biomarkers inclusive of NT-proBNP: N-Terminal pro B-Type natriuretic peptide (NT-proBNP) serves as a valuable biomarker for assessing heart function. It is particularly relevant in cardiac surgery, aiding in the identification of patients at risk of cardiac surgery-associated AKI (CSA-AKI). By facilitating risk assessment and early intervention, NT-proBNP contributes to enhanced patient management. Other than that, KIM-1: Kidney injury molecule-1 (KIM-1) is an essential biomarker for evaluating kidney function and predicting AKI. Predominantly found in the kidney's proximal tubules, KIM-1 exhibits upregulation in response to kidney injuries stemming from ischemia or toxin exposure. Significantly, KIM-1 elevation occurs before clinical symptoms or changes in serum creatinine levels manifest, enabling early detection of kidney injury. Various studies have corroborated KIM-1's ability to predict AKI across diverse clinical scenarios, underscoring its critical role in timely intervention and damage prevention.

SCr remains a cornerstone biomarker in the diagnosis and monitoring of AKI. Established diagnostic criteria, such as those outlined in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, rely on SCr measurements. SCr closely correlates with glomerular filtration rate, a pivotal indicator of kidney function. Notably, elevated SCr levels signify compromised kidney function, serving as an early indicator of kidney dysfunction. While SCr possesses several limitations, including delayed responsiveness to acute changes in kidney function, it continues to be integral to AKI evaluation.

Monitoring urine output is fundamental in assessing kidney function, as alterations in UO offer early indications of kidney dysfunction. Early AKI detection is vital for timely intervention and improved patient outcomes. Urine output evaluation, complemented by other biomarkers and clinical data, provides valuable insights into the underlying causes of AKI. However, it is essential to recognize that changes in UO can stem from factors unrelated to kidney dysfunction, such as diuretic use or excessive fluid intake. Thus, it is considered alongside other clinical parameters for a comprehensive kidney function assessment.



The nature of the surgical procedure significantly influences the risk of AKI. Emergency surgeries, characterized by hemodynamic instability, inadequate fluid resuscitation, and a lack of preoperative optimization, carry a heightened risk of AKI development. Understanding the surgical type is crucial for identifying high-risk patients and tailoring interventions accordingly.

Several medications possess nephrotoxic potential and can induce or exacerbate AKI. Aminoglycosides, NSAIDs, ACE inhibitors, ARBs, and others fall into this category. Managing these medications, particularly in patients with compromised kidney function, is imperative. Recognizing contributing factors and considering medication adjustments in at-risk patients are vital steps in mitigating drug-induced AKI. Recent studies have underscored the risks associated with specific medications, emphasizing the need for vigilant medication management in clinical practice.

Clinical biomarkers, in conjunction with an understanding of patient-specific factors and surgical risk factors, play an indispensable role in the early detection, risk assessment, and management of AKI among surgical patients. These biomarkers, such as NT-proBNP, KIM-1, SCr, and UO, offer valuable insights into kidney function and injury. Additionally, identifying risk factors related to surgical procedures and medications is pivotal for patient safety and tailored intervention strategies. By leveraging these tools and insights, healthcare providers can enhance patient care, reduce the burden of AKI-related complications, and ultimately improve surgical outcomes. Further research in this field holds the potential to refine risk prediction models and intervention strategies, advancing the management of AKI in surgical settings.

## 5. Conclusions

The conclusion drawn from the review is that AKI in surgical patients is a complex and multifactorial condition influenced by various risk factors. Risk factors such as drug induced-AKI, low urine output, and the type of surgery performed were identified as significant contributors to AKI risk. Additionally, certain clinical biomarkers, including NGAL, NT-proBNP, KIM-1 and CRP, emerged as promising indicators for early detection and prediction of AKI. These findings emphasize the importance of closely monitoring high-risk patients and utilizing clinical biomarkers to identify and manage AKI in the perioperative period effectively. Implementing preventive strategies and early intervention based on identified risk factors and biomarkers may lead to improved patient outcomes and reduced morbidity associated with AKI in surgical patients. However, further research and validation of these findings are warranted to enhance our understanding of AKI and optimize patient care in surgical setting.

## References

- [1] Liu, Kathleen D., Stuart L. Goldstein, Anitha Vijayan, Chirag R. Parikh, Kianoush Kashani, Mark D. Okusa, Anupam Agarwal, and Jorge Cerdá. "AKI! Now initiative: recommendations for awareness, recognition, and management of AKI." *Clinical Journal of the American Society of Nephrology* 15, no. 12 (2020): 1838-1847. <https://doi.org/10.2215/CJN.15611219>
- [2] Oates, Thomas, and Shabbir Moochhala. "Recognition and management of acute kidney injury." *Prescriber* 28, no. 4 (2017): 17-21. <https://doi.org/10.1002/psb.1556>
- [3] Wahba, Ola, Kawthar Hefny Mohamed, Roshdy Abdel Aziz El Khayat, and Ali Maher El Assal. "Acute kidney injury after prolonged neurosurgical operations." *Egyptian Journal of Anaesthesia* 37, no. 1 (2021): 440-444. <https://doi.org/10.1080/11101849.2021.1975438>
- [4] Aitken, E., C. Carruthers, L. Gall, L. Kerr, C. Geddes, and D. Kingsmore. "Acute kidney injury: outcomes and quality of care." *QJM: An International Journal of Medicine* 106, no. 4 (2013): 323-332. <https://doi.org/10.1093/qjmed/hcs237>
- [5] Hobson, Charles, Girish Singhanian, and Azra Bihorac. "Acute kidney injury in the surgical patient." *Critical care clinics* 31, no. 4 (2015): 705-723. <https://doi.org/10.1016/j.ccc.2015.06.007>

- [6] Wang, Henry E., Paul Muntner, Glenn M. Chertow, and David G. Warnock. "Acute kidney injury and mortality in hospitalized patients." *American journal of nephrology* 35, no. 4 (2012): 349-355. <https://doi.org/10.1159/000337487>
- [7] Lei, Victor J., ThaiBinh Luong, Eric Shan, Xinwei Chen, Mark D. Neuman, Nwamaka D. Eneanya, Daniel E. Polsky et al. "Risk stratification for postoperative acute kidney injury in major noncardiac surgery using preoperative and intraoperative data." *JAMA network open* 2, no. 12 (2019): e1916921-e1916921. <https://doi.org/10.1001/jamanetworkopen.2019.16921>
- [8] Boyer, N, J Eldridge, J R Prowle, and L G Forni. 2022. "Postoperative Acute Kidney Injury." <https://www.scopus.com/inward/record.uri?eid=2-s2.0-85140064863&doi=10.2215%2FCJN.16541221&partnerID=40&md5=afa614924c57b508ecaf03121df4bbb6>.
- [9] Allinovi, Marco, Francesco Sessa, Gianluca Villa, Andrea Cocci, Samantha Innocenti, Maria Zanazzi, Lorenzo Tofani et al. "Novel biomarkers for early detection of acute kidney injury and prediction of long-term kidney function decline after partial nephrectomy." *Biomedicines* 11, no. 4 (2023): 1046. <https://doi.org/10.3390/biomedicines11041046>
- [10] National Institute for Health and Care Excellence. 2019. "Acute Kidney Injury: Prevention, Detection and Management." *NICE Guideline*, no. December: 1–26. <https://www.nice.org.uk/guidance/ng148%0Ahttps://www.nice.org.uk/guidance/ng148/chapter/Recommendations>.
- [11] Ronco, Claudio, Rinaldo Bellomo, and John A. Kellum. "Acute kidney injury." *The Lancet* 394, no. 10212 (2019): 1949-1964. [https://doi.org/10.1016/S0140-6736\(19\)32563-2](https://doi.org/10.1016/S0140-6736(19)32563-2)
- [12] Lewington, Andrew JP, Jorge Cerdá, and Ravindra L. Mehta. "Raising awareness of acute kidney injury: a global perspective of a silent killer." *Kidney international* 84, no. 3 (2013): 457-467. <https://doi.org/10.1038/ki.2013.153>
- [13] McBride, William T., Mary Jo Kurth, Gavin McLean, Anna Domanska, John V. Lamont, Daniel Maguire, Joanne Watt et al. "Stratifying risk of acute kidney injury in pre and post cardiac surgery patients using a novel biomarker-based algorithm and clinical risk score." *Scientific Reports* 9, no. 1 (2019): 16963. <https://doi.org/10.1038/s41598-019-53349-1>
- [14] Guenancia, Charles, Abdelkader Kahli, Gabriel Laurent, Olivier Hachet, Ghislain Malapert, Sandrine Grosjean, Claude Girard, Catherine Vergely, and Olivier Bouchot. "Pre-operative growth differentiation factor 15 as a novel biomarker of acute kidney injury after cardiac bypass surgery." *International journal of cardiology* 197 (2015): 66-71. <https://doi.org/10.1016/j.ijcard.2015.06.012>
- [15] Verwijmeren, Lisa, Madeleen Bosma, Lisette M. Vernooij, Esther M. Linde, Ineke M. Dijkstra, Edgar J. Daeter, Eric PA Van Dongen, Wilton A. Van Klei, and Peter G. Noordzij. "Associations between preoperative biomarkers and cardiac surgery-associated acute kidney injury in elderly patients: a cohort study." *Anesthesia & Analgesia* 133, no. 3 (2021): 570-577. <https://doi.org/10.1213/ANE.0000000000005650>
- [16] Yu, Ying, Chenning Li, Shuainan Zhu, Lin Jin, Yan Hu, Xiaomin Ling, Changhong Miao, and Kefang Guo. "Diagnosis, pathophysiology and preventive strategies for cardiac surgery-associated acute kidney injury: a narrative review." *European Journal of Medical Research* 28, no. 1 (2023): 45. <https://doi.org/10.1186/s40001-023-00990-2>
- [17] Fan, Rui, Wei Qin, Hao Zhang, Lichun Guan, Wuwei Wang, Jian Li, Wen Chen, Fuhua Huang, Hang Zhang, and Xin Chen. "Machine learning in the prediction of cardiac surgery associated acute kidney injury with early postoperative biomarkers." *Frontiers in Surgery* 10 (2023): 1048431. <https://doi.org/10.3389/fsurg.2023.1048431>
- [18] Zhao, Bing-Cheng, Pei-Pei Zhuang, Shao-Hui Lei, Shi-Da Qiu, Xiao Yang, Cai Li, Wei-Feng Liu, and Ke-Xuan Liu. "Pre-operative N-terminal pro-B-type natriuretic peptide for prediction of acute kidney injury after noncardiac surgery: a retrospective cohort study." *European Journal of Anaesthesiology | EJA* 38, no. 6 (2021): 591-599. <https://doi.org/10.1097/EJA.0000000000001495>
- [19] Karmakova, T. A., N. S. Sergeeva, K. Yu Kanukoev, B. Ya Alekseev, and A. D. Kaprin. "Kidney injury molecule 1 (KIM-1): a multifunctional glycoprotein and biological marker." *Современные технологии в медицине* 13, no. 3 (eng) (2021): 64-78. <https://doi.org/10.17691/stm2021.13.3.08>
- [20] Vasquez-Rios, George, Dennis G. Moledina, Yaqi Jia, Eric McArthur, Sherry G. Mansour, Heather Thiessen-Philbrook, Michael G. Shlipak et al. "Pre-operative kidney biomarkers and risks for death, cardiovascular and chronic kidney disease events after cardiac surgery: the TRIBE-AKI study." *Journal of Cardiothoracic Surgery* 17, no. 1 (2022): 338. <https://doi.org/10.1186/s13019-022-02066-4>
- [21] Göger, Yunus Emre, Mehmet Serkan Özkent, Cemile Topçu, Ahmet Atıcı, Mehmet Giray Sönmez, Mehmet Balasar, and Mehmet Gürbilek. "Can urinary KIM-1 and NGAL predict management endoscopic surgery in acute unilateral obstructive stone disease? Results from a prospective cohort study." *Urologia Internationalis* 106, no. 5 (2022): 446-454. <https://doi.org/10.1159/000517883>

- [22] Tan, Dan, Liang Zhao, Wei Peng, Fang-Hao Wu, Guo-Bin Zhang, Bo Yang, and Wen-Qian Huo. "Value of urine IL-8, NGAL and KIM-1 for the early diagnosis of acute kidney injury in patients with ureteroscopic lithotripsy related urosepsis." *Chinese Journal of Traumatology* 25, no. 01 (2022): 27-31. <https://doi.org/10.1016/j.cjtee.2021.10.001>
- [23] Jin, Jifu, Jiarui Xu, Sujuan Xu, Jiachang Hu, Wuhua Jiang, Bo Shen, Chunsheng Wang, Jie Teng, and Xiaoqiang Ding. "Hemodilution is associated with underestimation of serum creatinine in cardiac surgery patients: a retrospective analysis." *BMC Cardiovascular Disorders* 21 (2021): 1-7. <https://doi.org/10.1186/s12872-021-01879-w>
- [24] Gameiro, Joana, Inês Duarte, Filipe Marques, José Agapito Fonseca, Sofia Jorge, Rosário Rosa, and José António Lopes. "Transient and persistent AKI and outcomes in patients undergoing major abdominal surgery." *Nephron* 144, no. 5 (2020): 236-244. <https://doi.org/10.1159/000506397>
- [25] De Guglielmo, Wendy, Jean Michel Rebibou, Serge Aho, Thomas Rogier, Gilles Nuemi, Claude Girard, Eric Steinmetz, and Mathieu Legendre. "Pre-Operative Factors Associated with the Occurrence of Acute Kidney Injury in Patients Aged 65 Years and Over Undergoing Non-Ambulatory Non-Cardiac Surgery." In *Healthcare*, vol. 10, no. 3, p. 558. MDPI, 2022. <https://doi.org/10.3390/healthcare10030558>
- [26] Arnaoutakis, George J., Takuya Ogami, Himanshu J. Patel, Chih-Wen Pai, Elise M. Woznicki, Derek R. Brinster, Bradley G. Leshnower et al. "Acute kidney injury in patients undergoing surgery for type A acute aortic dissection." *The Annals of Thoracic Surgery* 115, no. 4 (2023): 879-885. <https://doi.org/10.1016/j.athoracsur.2022.10.037>
- [27] Patel, Hiten D., Phillip M. Pierorazio, Michael H. Johnson, Ritu Sharma, Emmanuel Iyoha, Mohamad E. Allaf, Eric B. Bass, and Stephen M. Sozio. "Renal functional outcomes after surgery, ablation, and active surveillance of localized renal tumors: a systematic review and meta-analysis." *Clinical Journal of the American Society of Nephrology* 12, no. 7 (2017): 1057-1069. <https://doi.org/10.2215/CJN.11941116>
- [28] Jia, Hui-Miao, Yue Zheng, Li-Feng Huang, Xin Xin, Wen-Liang Ma, Yi-Jia Jiang, Xi Zheng, Shu-Yan Guo, and Wen-Xiong Li. "Derivation and validation of plasma endostatin for predicting renal recovery from acute kidney injury: a prospective validation study." *Critical Care* 22 (2018): 1-10. <https://doi.org/10.1186/s13054-018-2232-5>
- [29] Mustafayeva, Aynur, Meliha Orhon Ergün, and Seniyye Ülgen Zengin. "The Role of Neutrophil Gelatinase-associated Lipocalin as a Predictive Biomarker of Acute Kidney Injury in Patients Undergoing Major Abdominal Surgery." *Medical Journal of Bakirkoy* 18, no. 2 (2022). <https://doi.org/10.4274/BMJ.galenos.2022.2021.12-17>
- [30] Allinovi, Marco, Francesco Sessa, Gianluca Villa, Andrea Cocci, Samantha Innocenti, Maria Zanazzi, Lorenzo Tofani et al. "Novel biomarkers for early detection of acute kidney injury and prediction of long-term kidney function decline after partial nephrectomy." *Biomedicines* 11, no. 4 (2023): 1046. <https://doi.org/10.3390/biomedicines11041046>
- [31] Nie, Xin, Bin Wu, Yong He, Xunbei Huang, Zhongqiu Dai, Qiang Miao, Haolan Song et al. "Serum procalcitonin predicts development of acute kidney injury in patients with suspected infection." *Clinical Chemistry and Laboratory Medicine (CCLM)* 51, no. 8 (2013): 1655-1661. <https://doi.org/10.1515/cclm-2012-0822>
- [32] Mihajlovic, Dunja, Snezana Brkic, Arsen Uvelin, Biljana Draskovic, and Vladimir Vrsajkov. "Use of presepsin and procalcitonin for prediction of SeptiFast results in critically ill patients." *Journal of Critical Care* 40 (2017): 197-201. <https://doi.org/10.1016/j.jcrc.2017.04.008>
- [33] Xu, Zhihua, Shuo Chen, Yunxia Feng, and Xue Gong. "Value of procalcitonin as a potential biomarker in predicting acute kidney injury in patients with bee stings." *Zhonghua wei Zhong Bing ji jiu yi xue* 34, no. 8 (2022): 848-852.
- [34] Uğurlu, Esat Taylan, and Mehmet Tercan. "The role of biomarkers in the early diagnosis of acute kidney injury associated with acute pancreatitis: Evidence from 582 cases." *Ulusal travma ve acil cerrahi dergisi= Turkish journal of trauma & emergency surgery: TJTES* 29, no. 1 (2022): 81-93. <https://doi.org/10.14744/tjtes.2022.60879>
- [35] Puckett, Jevon R., John W. Pickering, Suetonia C. Palmer, John L. McCall, Michal T. Kluger, Janak De Zoysa, Zoltan H. Endre, and Mattias Soop. "Low versus standard urine output targets in patients undergoing major abdominal surgery: a randomized noninferiority trial." (2017): 874-881. <https://doi.org/10.1097/SLA.0000000000002044>
- [36] Joosten, Alexandre, Brigitte Ickx, Zakaria Mokthari, Luc Van Obbergh, Valerio Lucidi, Vincent Collange, Salima Naili et al. "Mild increases in plasma creatinine after intermediate to high-risk abdominal surgery are associated with long-term renal injury." *BMC anesthesiology* 21, no. 1 (2021): 135. <https://doi.org/10.1186/s12871-021-01353-2>
- [37] Goldani, João Carlos, José Antônio Poloni, Fabiano Klaus, Roger Kist, Larissa Sgaria Pacheco, and Elizete Keitel. "Urine microscopy as a biomarker of Acute Kidney Injury following cardiac surgery with cardiopulmonary bypass." *Brazilian Journal of Nephrology* 42 (2019): 18-23. <https://doi.org/10.1590/2175-8239-jbn-2018-0133>
- [38] Obata, Yumi, Atsuko Kamijo-Ikemori, Daisuke Ichikawa, Takeshi Sugaya, Kenjiro Kimura, Yugo Shibagaki, and Takeshi Tateda. "Clinical usefulness of urinary liver-type fatty-acid-binding protein as a perioperative marker of acute kidney injury in patients undergoing endovascular or open-abdominal aortic aneurysm repair." *Journal of anesthesia* 30 (2016): 89-99. <https://doi.org/10.1007/s00540-015-2095-8>
- [39] Goren, O., and I. Matot. "Perioperative acute kidney injury." *BJA: British Journal of Anaesthesia* 115, no. suppl\_2 (2015): ii3-ii14. <https://doi.org/10.1093/bja/aev380>

- [40] Vaara, Suvi T., Ilkka Parviainen, Ville Pettilä, Sara Nisula, Outi Inkinen, Ari Uusaro, Raili Laru-Sompa et al. "Association of oliguria with the development of acute kidney injury in the critically ill." *Kidney international* 89, no. 1 (2016): 200-208. <https://doi.org/10.1038/ki.2015.269>
- [41] Grieshaber, Philippe, Sina Möller, Borros Arneht, Peter Roth, Bernd Niemann, Harald Renz, and Andreas Böning. "Predicting cardiac surgery-associated acute kidney injury using a combination of clinical risk scores and urinary biomarkers." *The Thoracic and cardiovascular surgeon* 68, no. 05 (2020): 389-400. <https://doi.org/10.1055/s-0039-1678565>
- [42] Canet, Emmanuel, and Rinaldo Bellomo. "Perioperative renal protection." *Current opinion in critical care* 24, no. 6 (2018): 568-574. <https://doi.org/10.1097/MCC.0000000000000560>
- [43] Hu, Linhui, Lu Gao, Danqing Zhang, Yating Hou, Lin Ling He, Huidan Zhang, Yufan Liang, Jing Xu, and Chunbo Chen. "The incidence, risk factors and outcomes of acute kidney injury in critically ill patients undergoing emergency surgery: a prospective observational study." *BMC nephrology* 23, no. 1 (2022): 42. <https://doi.org/10.1186/s12882-022-02675-0>
- [44] Schiefer, Judith, Martin H. Bernardi, Paul Lichtenegger, Gerhard Schak, Louis Atallah, Robin Ristl, Dariga Ramazanov, and Peter Faybik. "Incidence and outcomes of AKI in postoperative patients admitted to ICU using full KDIGO criteria—a cohort study." *Journal of Clinical Anesthesia* 89 (2023): 111156. <https://doi.org/10.1016/j.jclinane.2023.111156>
- [45] Rossouw, E., and S. Chetty. "Acute kidney injury after major non-cardiac surgery: Incidence and risk factors." *South African Medical Journal* 113, no. 3 (2023): 135-140. <https://doi.org/10.7196/SAMJ.2023.v113i3.16783>
- [46] Perazella, Mark A. "Renal vulnerability to drug toxicity." *Clinical Journal of the American Society of Nephrology* 4, no. 7 (2009): 1275-1283. <https://doi.org/10.2215/CJN.02050309>
- [47] Perazella, Mark A., and Randy L. Luciano. "Review of select causes of drug-induced AKI." *Expert Review of Clinical Pharmacology* 8, no. 4 (2015): 367-371. <https://doi.org/10.1586/17512433.2015.1045489>
- [48] Moore, Peter K., Raymond K. Hsu, and Kathleen D. Liu. "Management of acute kidney injury: core curriculum 2018." *American Journal of Kidney Diseases* 72, no. 1 (2018): 136-148. <https://doi.org/10.1053/j.ajkd.2017.11.021>
- [49] Thomas, Laure, Christine Le Beller, Thierry Trenque, Joëlle Michot, Marie Zenut, Emmanuel Letavernier, Nicolas Mongardon, and Dominique Vodovar. "Amoxicillin-induced crystal nephropathy: A nationwide French pharmacovigilance databases study." *British Journal of Clinical Pharmacology* 86, no. 11 (2020): 2256-2265. <https://doi.org/10.1111/bcp.14328>
- [50] Liang, Chun-An, Yi-Chia Su, Shyh-Jer Lin, and Tsung-Hsien Tsai. "Risk factors for acute kidney injury after high-dose methotrexate therapy: a single-center study and narrative review." *European Journal of Clinical Pharmacology* 79, no. 6 (2023): 789-800. <https://doi.org/10.1007/s00228-023-03491-7>
- [51] Zainudheen, Amith, Ian A. Scott, and Xenia Caney. "Association of renin angiotensin antagonists with adverse perioperative events in patients undergoing elective orthopaedic surgery: a case-control study." *Internal Medicine Journal* 47, no. 9 (2017): 999-1005. <https://doi.org/10.1111/imj.13487>