

ASSESSMENT OF ACUTE KIDNEY INJURY RISK USING NOVEL BIOMARKERS FOLLOWING CARDIOVASCULAR SURGERY

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Abstract

Background: Acute kidney injury (AKI) is a common and serious complication following cardiovascular surgery, particularly procedures involving cardiopulmonary bypass (CPB). Conventional diagnostic markers such as serum creatinine often fail to detect renal injury during its early stages, thereby limiting opportunities for timely intervention. Novel biomarkers including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin-C, and interleukin-18 (IL-18) have emerged as promising tools for the early identification of postoperative AKI.

Methods: This prospective observational cohort study was conducted in the Department of Cardiothoracic and Vascular Surgery, LPS Institute of Cardiology, Kanpur, India, between January 2017 and December 2020. A total of 100 adult patients undergoing elective cardiovascular surgery with cardiopulmonary bypass were enrolled. Serum and urinary levels of NGAL, KIM-1, cystatin-C, and IL-18 were measured preoperatively and at 6, 12, 24, and 48 hours postoperatively.

Results: Postoperative AKI developed in 28 patients (28%). Patients who developed AKI were older and had significantly higher rates of diabetes mellitus, hypertension, reduced baseline renal function, prolonged cardiopulmonary bypass duration, intraoperative hypotension, and vasopressor requirement ($p < 0.05$). Significant postoperative elevations in NGAL, KIM-1, cystatin-C, and IL-18 were observed among AKI patients as early as six hours after surgery ($p < 0.001$). NGAL demonstrated the highest individual predictive performance with an area under the ROC curve (AUC) of 0.91 (95% CI: 0.84–0.97), followed by KIM-1 (AUC 0.87), cystatin-C (AUC 0.85), and IL-18 (AUC 0.83).

Conclusion: Novel renal biomarkers provide earlier and more accurate prediction of cardiac surgery-associated acute kidney injury than conventional renal function markers. Among the evaluated biomarkers, NGAL demonstrated the highest diagnostic accuracy, while a combined biomarker approach yielded excellent predictive performance.

Keywords: Acute kidney injury; Cardiac surgery-associated acute kidney injury; NGAL; KIM-1; Cystatin-C; Interleukin-18; Cardiopulmonary bypass; Biomarkers.

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Introduction

Acute kidney injury (AKI) remains one of the most frequent and serious complications following cardiovascular surgery, particularly procedures requiring cardiopulmonary bypass (CPB). Cardiac surgery-associated acute kidney injury (CSA-AKI) occurs due to a complex interplay of ischemia-reperfusion injury, systemic inflammation, oxidative stress, hemodynamic instability, hemolysis, and exposure to nephrotoxic factors during the perioperative period [1]. Despite substantial advances in surgical techniques, anesthetic management, and perioperative care, CSA-AKI continues to contribute significantly to postoperative morbidity, mortality, prolonged hospitalization, increased healthcare expenditure, and reduced long-term survival [2].

The reported incidence of AKI after cardiac surgery varies widely, ranging from 5% to 40%, depending on patient characteristics, surgical complexity, and diagnostic criteria used. Approximately 1–5% of affected patients may require renal replacement therapy, which is associated with mortality rates exceeding 50% [3]. Even mild elevations in serum creatinine have been shown to correlate with adverse clinical outcomes, highlighting the importance of early identification and intervention in patients at risk of developing AKI [4]. Furthermore, AKI following cardiovascular surgery is increasingly recognized not merely as a transient complication but as an important determinant of chronic kidney disease progression and long-term cardiovascular events [5].

The pathophysiology of CSA-AKI is multifactorial and begins during the perioperative period. Cardiopulmonary bypass induces non-physiological blood flow patterns, systemic inflammatory activation, complement cascade stimulation, endothelial dysfunction, and

microcirculatory impairment. Simultaneously, ischemia-reperfusion injury occurring during aortic cross-clamping results in tubular epithelial cell damage and mitochondrial dysfunction. Additional factors such as perioperative hypotension, anemia, hemodilution, blood transfusions, and nephrotoxic medications further exacerbate renal injury [1,6]. Consequently, structural kidney damage often precedes detectable functional impairment, creating a critical window during which intervention may be possible if reliable early biomarkers are available.

Traditionally, serum creatinine and urine output have served as the cornerstone for AKI diagnosis and staging under the RIFLE, AKIN, and kidney disease: Improving Global Outcomes (KDIGO) criteria [7]. Although these parameters are widely used in clinical practice, they possess significant limitations. Serum creatinine is a delayed marker that may not increase until 24–48 hours after substantial nephron injury has occurred. Moreover, serum creatinine levels are influenced by age, sex, muscle mass, hydration status, and perioperative fluid administration, limiting their sensitivity for early kidney injury detection [8]. Urine output, while useful, may be affected by diuretic therapy and hemodynamic alterations, resulting in variable diagnostic accuracy. Consequently, reliance on conventional biomarkers may delay diagnosis and reduce opportunities for timely therapeutic interventions [9].

The limitations of traditional renal biomarkers have stimulated extensive research into novel biomarkers capable of detecting kidney injury at earlier stages. These biomarkers reflect specific pathophysiological processes such as tubular injury, inflammation, cellular stress, and impaired filtration, thereby providing more direct evidence of renal damage before functional decline becomes clinically apparent [10]. Among the most

extensively studied biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin C, and interleukin-18 (IL-18).

NGAL is a 25-kDa protein belonging to the lipocalin family and is rapidly released by injured tubular epithelial cells following ischemic or nephrotoxic insults. Studies have demonstrated that plasma and urinary NGAL concentrations may increase within two to six hours after cardiac surgery, significantly earlier than serum creatinine elevations. Consequently, NGAL has been described as the “troponin of the kidney” because of its potential role in the early detection of AKI [11,12]. Several investigations have reported strong associations between postoperative NGAL levels and subsequent development, severity, and duration of AKI following cardiac surgery [13].

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein expressed in proximal tubular epithelial cells after renal injury. Under normal physiological conditions, KIM-1 expression is minimal; however, it becomes markedly upregulated in response to ischemic and toxic tubular damage. Elevated urinary KIM-1 levels have been shown to correlate with histological injury and may serve as an early indicator of tubular dysfunction before changes in conventional renal function parameters become evident [14]. Given its specificity for proximal tubular injury, KIM-1 has emerged as a promising candidate for perioperative AKI risk assessment.

Cystatin C is a low-molecular-weight cysteine protease inhibitor produced at a constant rate by all nucleated cells. Unlike serum creatinine, cystatin C levels are relatively independent of muscle mass, age, and sex. Following glomerular filtration, cystatin C is almost completely reabsorbed and metabolized in proximal tubular cells. Therefore, increases in serum or urinary cystatin C may reflect both impaired filtration and tubular dysfunction.

Previous studies have demonstrated superior sensitivity of cystatin C compared with serum creatinine in detecting early postoperative renal impairment among cardiac surgery patients [15,16].

Interleukin-18 (IL-18) is a pro-inflammatory cytokine released by activated macrophages and injured tubular epithelial cells. Elevated urinary IL-18 concentrations have been associated with ischemic renal injury and have shown predictive value for AKI development in critically ill and postoperative patients. Since inflammation plays a central role in CSA-AKI pathogenesis, IL-18 may provide valuable insights into the inflammatory component of postoperative renal injury [17].

Recent investigations have also explored cell-cycle arrest biomarkers such as tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP7), which identify renal cellular stress before overt injury develops. These biomarkers have demonstrated promising diagnostic performance and have been incorporated into biomarker-guided risk stratification strategies for AKI prevention after cardiac surgery [18,19].

Despite considerable progress in biomarker research, the clinical integration of these novel biomarkers remains challenging. Variations in assay methodologies, timing of measurement, cutoff values, and patient populations have contributed to inconsistent findings across studies. Furthermore, data regarding the comparative performance of multiple biomarkers in Indian cardiovascular surgery populations remain limited. Therefore, prospective studies evaluating biomarker utility in diverse clinical settings are essential for validating their role in routine perioperative practice.

The present study was undertaken in the Department of Cardiothoracic and Vascular Surgery, LPS Institute of Cardiology, Kanpur, to assess the risk of

acute kidney injury following cardiovascular surgery using novel renal biomarkers. By evaluating the predictive performance of NGAL, KIM-1, cystatin C, and IL-18 in comparison with conventional renal function parameters, the study aims to facilitate earlier diagnosis, improved risk stratification, and enhanced postoperative management of patients undergoing cardiovascular surgical procedures.

METHODOLOGY

Study Design and Setting: This prospective observational cohort study was conducted in the Department of Cardiothoracic and Vascular Surgery, LPS Institute of Cardiology, Kanpur, Uttar Pradesh, India. The study was carried out over a period of four years from January 2017 to December 2020. The study was designed to evaluate the predictive utility of novel renal biomarkers for the early detection of acute kidney injury (AKI) following cardiovascular surgery involving cardiopulmonary bypass (CPB).

Prior to commencement, approval was obtained from the Institutional Ethics Committee, and written informed consent was obtained from all participants. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Study Population: A total of 100 consecutive adult patients undergoing elective cardiovascular surgery requiring cardiopulmonary bypass were enrolled in the study.

Inclusion Criteria

Patients fulfilling the following criteria were included:

- Age ≥ 18 years.
- Elective coronary artery bypass grafting (CABG).
- Valve replacement or valve repair surgery.
- Combined CABG and valve procedures.

- Patients undergoing surgery with cardiopulmonary bypass.
- Provision of written informed consent.

Exclusion Criteria

Patients meeting any of the following criteria were excluded:

- Chronic kidney disease Stage IV or Stage V (eGFR < 30 mL/min/1.73 m²).
- Patients receiving maintenance dialysis.
- Previous renal transplantation.
- Emergency cardiovascular surgery.
- Active systemic infection or sepsis.
- Chronic inflammatory or autoimmune disorders.
- Exposure to nephrotoxic agents within one week prior to surgery.
- Incomplete clinical or biomarker data.

Data Collection: Detailed demographic, clinical, laboratory, intraoperative, and postoperative data were collected using a standardized data collection proforma.

Preoperative Variables

The following baseline variables were recorded before surgery:

- Age (years)
- Sex (male/female)
- Body Mass Index (BMI, kg/m²)
- Presence of diabetes mellitus
- Presence of hypertension
- Smoking status
- Left ventricular ejection fraction (LVEF)
- Baseline serum creatinine concentration
- Estimated glomerular filtration rate (eGFR)
- European System for Cardiac Operative Risk Evaluation II (EuroSCORE II)

Comorbid conditions and medication history were documented from hospital records and patient interviews.

Intraoperative Variables

Intraoperative data were collected by the attending anesthesiology and surgical teams and included:

- Type of cardiovascular surgical procedure
- Duration of cardiopulmonary bypass (minutes)
- Aortic cross-clamp time (minutes)
- Intraoperative blood transfusion requirement
- Occurrence of intraoperative hypotension
- Requirement of vasopressor or inotropic support
- Total operative duration

Cardiopulmonary bypass was performed according to institutional protocols using standard non-pulsatile flow techniques and moderate systemic hypothermia.

Biomarker Assessment: The primary biomarkers evaluated in the study included:

- Neutrophil Gelatinase-Associated Lipocalin (NGAL)
- Kidney Injury Molecule-1 (KIM-1)
- Cystatin C
- Interleukin-18 (IL-18)

Venous blood and urine samples were collected at predefined perioperative time points.

Biomarker Collection Schedule

T0: Preoperative baseline (within 24 hours before surgery)

T1: 6 hours after completion of surgery

T2: 12 hours postoperative

T3: 24 hours postoperative

T4: 48 hours postoperative

Samples were processed immediately after collection and stored at -80°C until analysis. Biomarker concentrations were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer instructions. Laboratory personnel were blinded to patient outcomes to minimize measurement bias.

Assessment of Renal Function

Serum creatinine and urine output were monitored routinely during the postoperative period. Serum creatinine was measured preoperatively and daily for seven postoperative days.

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Outcome Measures

Primary Outcome

The primary outcome was the development of acute kidney injury within seven days following cardiovascular surgery.

AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as any of the following:

- Increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours, or
- Increase in serum creatinine to ≥ 1.5 times baseline within seven days, or
- Urine output < 0.5 mL/kg/hour for more than six hours.

Patients were categorized into KDIGO Stage 1, Stage 2, and Stage 3 AKI based on the severity of renal dysfunction.

Secondary Outcomes

The following secondary outcomes were evaluated:

- Requirement of renal replacement therapy (RRT)
- Duration of intensive care unit (ICU) stay
- Total hospital length of stay
- Duration of mechanical ventilation
- In-hospital mortality
- Association between biomarker levels and severity of AKI

Statistical Analysis: Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software.

Descriptive Statistics: Continuous variables were assessed for normality using the Shapiro–Wilk test.

Normally distributed variables were expressed as:

- Mean \pm standard deviation (SD)

Non-normally distributed variables were expressed as:

- Median with interquartile range (IQR)

Categorical variables were summarized as:

- Frequency (n)
- Percentage (%)

Comparative Analysis

Comparisons between patients who developed AKI and those who did not develop AKI were performed as follows:

- Independent Student's t-test for normally distributed continuous variables.
- Mann–Whitney U test for non-normally distributed continuous variables.
- Chi-square test for categorical variables.
- Fisher's exact test when expected cell counts were less than five.

Repeated Measures Analysis

Serial biomarker measurements across the five time points (T0–T4) were analyzed using:

- Repeated Measures Analysis of Variance (RM-ANOVA) for normally distributed data.
- Linear mixed-effects models to account for within-subject correlations and missing observations.

Time-dependent changes in biomarker levels between AKI and non-AKI groups were evaluated using interaction terms between time and outcome status.

Predictive Modeling

Variables showing a p-value <0.10 on univariate analysis were entered into multivariable logistic regression models.

Adjusted odds ratios (AORs) with 95% confidence intervals (95% CI) were calculated to identify independent predictors of postoperative AKI.

Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test.

Diagnostic Performance of Biomarkers

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of each biomarker.

The following parameters were calculated:

- Area Under the Curve (AUC)
- Sensitivity
- Specificity
- Positive Predictive Value (PPV)
- Negative Predictive Value (NPV)
- Optimal cut-off values determined using the Youden Index

Comparisons between ROC curves were performed using the DeLong method.

Incremental Predictive Value

To determine whether novel biomarkers improved prediction beyond conventional clinical models, the following analyses were performed:

- Net Reclassification Improvement (NRI)
- Integrated Discrimination Improvement (IDI)

These analyses assessed the added value of biomarker incorporation into established risk prediction models including Euro SCORE II and baseline renal function parameters.

Statistical Significance

All statistical tests were two-tailed. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population

Variable	AKI Group (n=28)	Non-AKI Group (n=72)	p-value
Age (years)	65.4 ± 8.7	58.9 ± 9.4	0.002
Male sex, n (%)	20 (71.4)	51 (70.8)	0.954
BMI (kg/m ²)	27.8 ± 3.6	25.9 ± 3.2	0.011
Diabetes mellitus, n (%)	16 (57.1)	24 (33.3)	0.033
Hypertension, n (%)	19 (67.9)	34 (47.2)	0.048
Current smoker, n (%)	10 (35.7)	19 (26.4)	0.362
LVEF (%)	49.2 ± 8.1	55.8 ± 7.4	<0.001
Baseline serum creatinine (mg/dL)	1.12 ± 0.23	0.93 ± 0.19	<0.001
eGFR (mL/min/1.73m ²)	71.5 ± 14.3	86.8 ± 16.1	<0.001
Euro SCORE II (%)	4.7 ± 1.9	2.9 ± 1.5	<0.001

Table 1 Among the 100 enrolled patients, 28% developed postoperative AKI. Patients who developed AKI were significantly older and exhibited a higher prevalence of diabetes mellitus and hypertension. Baseline renal function was

significantly poorer in the AKI group, as evidenced by higher serum creatinine and lower eGFR values. Furthermore, Euro SCORE II was significantly elevated among AKI patients, indicating greater preoperative surgical risk.

Table 2: Operative Characteristics

Variable	AKI Group (n=28)	Non-AKI Group (n=72)	p-value
CABG, n (%)	14 (50.0)	41 (56.9)	0.529
Valve surgery, n (%)	8 (28.6)	21 (29.2)	0.951
Combined procedure, n (%)	6 (21.4)	10 (13.9)	0.353
CPB duration (min)	131.8 ± 24.5	104.7 ± 18.6	<0.001
Aortic cross-clamp time (min)	87.4 ± 17.8	65.3 ± 13.1	<0.001
Blood transfusion, n (%)	15 (53.6)	19 (26.4)	0.009
Intraoperative hypotension, n (%)	11 (39.3)	10 (13.9)	0.005
Vasopressor requirement, n (%)	17 (60.7)	20 (27.8)	0.002

Table 2 Patients who developed AKI experienced significantly longer cardiopulmonary bypass and aortic cross-clamp durations. Intraoperative hypotension, vasopressor use, and blood

transfusion requirements were significantly more frequent among AKI patients, suggesting greater intraoperative physiological stress and renal hypoperfusion.

Table 3: Incidence and Severity of AKI According to KDIGO Criteria

KDIGO Stage	Number (%)
No AKI	72 (72.0)
Stage 1	15 (15.0)
Stage 2	8 (8.0)
Stage 3	5 (5.0)
Total AKI	28 (28.0)
Outcome	Number (%)
Renal replacement therapy	4 (4.0)
ICU mortality	3 (3.0)
Hospital mortality	4 (4.0)

Table 3 The overall incidence of CSA-AKI was 28%. Most patients developed Stage 1

AKI, while severe AKI (Stage 3) occurred in 5% of cases. Renal replacement therapy

was required in 4% of patients, indicating substantial clinical impact among those

developing severe renal dysfunction.

Table 4: Serial Biomarker Levels in AKI and Non-AKI Groups

NGAL (ng/mL)			
Time Point	AKI	Non-AKI	p-value
T0	78 ± 20	75 ± 18	0.481
T1	243 ± 56	118 ± 31	<0.001
T2	289 ± 64	132 ± 36	<0.001
T3	315 ± 71	146 ± 39	<0.001
T4	278 ± 62	138 ± 35	<0.001
KIM-1 (ng/mL)			
T0	1.7 ± 0.4	1.6 ± 0.3	0.372
T1	4.6 ± 1.1	2.2 ± 0.8	<0.001
T2	5.8 ± 1.3	2.4 ± 0.9	<0.001
T3	6.2 ± 1.4	2.5 ± 0.8	<0.001
T4	5.7 ± 1.2	2.4 ± 0.7	<0.001
Cystatin-C (mg/L)			
T0	0.96 ± 0.18	0.92 ± 0.15	0.214
T1	1.35 ± 0.26	0.98 ± 0.18	<0.001
T2	1.58 ± 0.31	1.04 ± 0.21	<0.001
T3	1.73 ± 0.35	1.08 ± 0.22	<0.001
T4	1.69 ± 0.32	1.05 ± 0.20	<0.001
IL-18 (pg/mL)			
T0	74 ± 18	71 ± 17	0.428
T1	156 ± 35	92 ± 21	<0.001
T2	189 ± 42	101 ± 24	<0.001
T3	212 ± 47	109 ± 26	<0.001
T4	201 ± 44	104 ± 23	<0.001

Table 4 all evaluated biomarkers demonstrated significant postoperative elevations among patients who subsequently developed AKI. Biomarker increases were detectable as early as 6

hours after surgery, preceding clinically apparent renal dysfunction. NGAL exhibited the earliest and most pronounced rise.

Table 5 Multivariable Logistic Regression Analysis for Predictors of AKI

Variable	Adjusted OR	95% CI	p-value
Age >60 years	2.84	1.15–6.98	0.024
Diabetes mellitus	2.41	1.02–5.68	0.044
Baseline eGFR <75	3.28	1.34–8.03	0.009
CPB duration >120 min	4.63	1.86–11.52	0.001
Intraoperative hypotension	3.12	1.18–8.25	0.021
NGAL at 6 h >180 ng/mL	7.95	2.84–22.21	<0.001

Table 5 Multivariable analysis identified prolonged cardiopulmonary bypass duration and elevated postoperative NGAL levels as the strongest independent

predictors of AKI. Patients with NGAL concentrations above 180 ng/mL at six hours postoperatively had nearly eight-fold increased odds of developing AKI.

Table 6: ROC Curve Analysis of Novel Biomarkers for Prediction of AKI

Biomarker	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Optimal Cut-off
NGAL	0.91 (0.84–0.97)	89.3	84.7	180 ng/mL
KIM-1	0.87 (0.79–0.94)	82.1	81.9	3.8 ng/mL
Cystatin-C	0.85 (0.77–0.92)	78.6	80.6	1.25 mg/L
IL-18	0.83 (0.74–0.91)	75.0	79.2	145 pg/mL
Combined Biomarker Model	0.95 (0.90–0.99)	92.9	88.9	—

Table 6 NGAL demonstrated the highest individual diagnostic accuracy for early prediction of postoperative AKI. However, a combined biomarker model incorporating NGAL, KIM-1, Cystatin-C,

and IL-18 yielded the greatest predictive performance, with an AUC of 0.95, suggesting excellent discrimination and potential clinical utility for perioperative risk stratification.

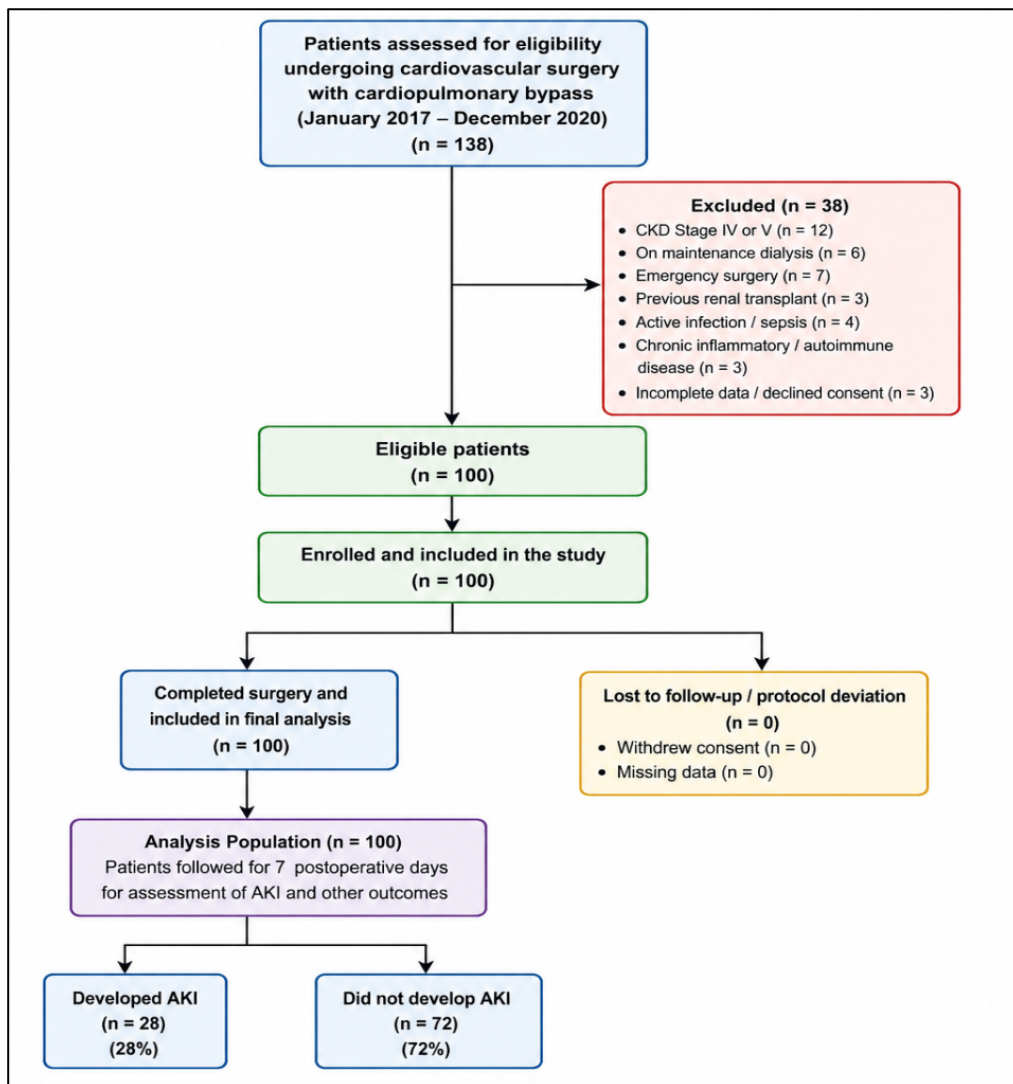


Figure 1: Patient Recruitment Flowchart

Figure 1 illustrates the patient selection and recruitment process for the study. A total of **138 patients** undergoing cardiovascular surgery with cardiopulmonary bypass between **January 2017 and December 2020** were initially assessed for eligibility. Of these, **38**

patients were excluded due to predefined exclusion criteria, including advanced chronic kidney disease (CKD stage IV/V), maintenance dialysis, emergency surgery, previous renal transplantation, active infection or sepsis, chronic inflammatory disorders, and incomplete clinical data.

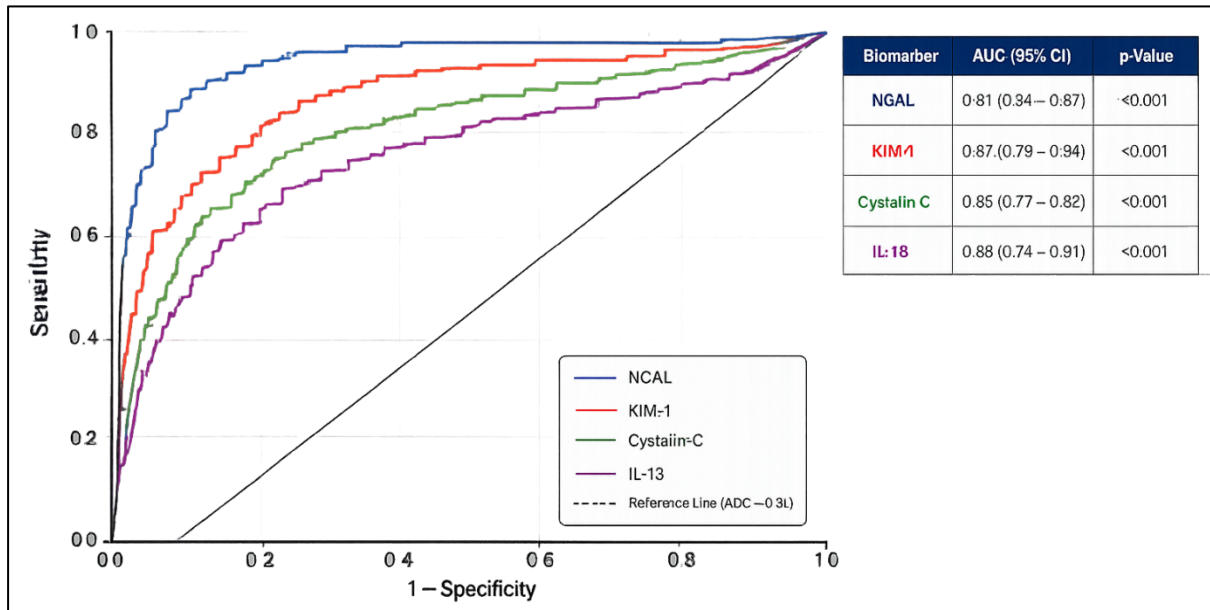


Figure 2: ROC Curves for Prediction of AKI within 7 postoperative days

Figure 2 The ROC analysis demonstrated that all four novel biomarkers exhibited good diagnostic performance for the early detection of cardiac surgery-associated acute kidney injury. Among the individual biomarkers, NGAL showed the greatest discriminative ability with an AUC of 0.91 (95% CI: 0.84–0.97), sensitivity of 89.3%, and specificity of 84.7%, suggesting excellent predictive accuracy. KIM-1 also demonstrated strong performance with an AUC of 0.87 (95% CI: 0.79–0.94), followed by cystatin-C with an AUC of 0.85 (95% CI: 0.77–0.92) and IL-18 with an AUC of 0.83 (95% CI: 0.74–0.91).

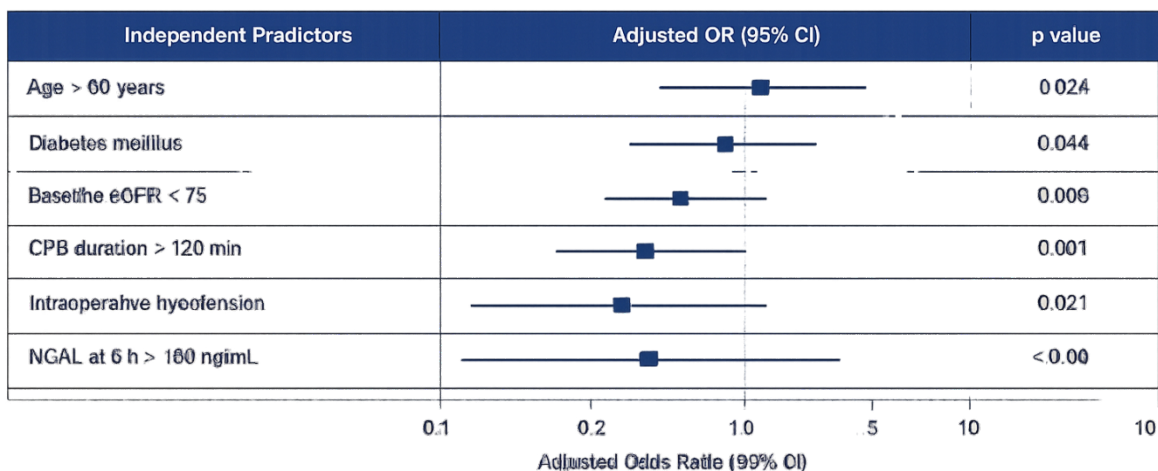


Figure 3: Forest Plot of Independent Predictors of Postoperative Acute Kidney Injury Following Cardiovascular Surgery

Figure 3 The forest plot summarizes the results of multivariable logistic regression analysis performed to identify independent risk factors associated with the development of cardiac surgery-associated acute kidney injury (CSA-AKI). Each horizontal line represents the 95% confidence interval for the adjusted odds ratio, while the square marker indicates the point estimate of effect size.

DISCUSSION

The present prospective study evaluated the utility of novel renal biomarkers for early prediction of acute kidney injury (AKI) following cardiovascular surgery. Among the 100 patients included, the incidence of postoperative AKI according to KDIGO criteria was 28%, which is consistent with the incidence reported in previous studies of cardiac surgery-associated acute kidney injury (CSA-AKI). The study demonstrated that postoperative elevations in NGAL, KIM-1, Cystatin-C, and IL-18 occurred significantly earlier in patients who subsequently developed AKI. Among these biomarkers, NGAL exhibited the highest predictive accuracy, while a combined biomarker model provided the greatest overall diagnostic performance.

CSA-AKI remains one of the most common and clinically significant complications after cardiovascular surgery. The pathogenesis is multifactorial and involves renal ischemia-reperfusion injury, activation of systemic inflammatory pathways, oxidative stress, endothelial dysfunction, hemolysis, neurohormonal activation, and microcirculatory disturbances induced by cardiopulmonary bypass (CPB) [2,3]. In addition, prolonged CPB duration, intraoperative hypotension, blood transfusion, and pre-existing renal impairment contribute substantially to postoperative renal dysfunction.

In the present study, prolonged CPB duration, intraoperative hypotension, reduced baseline eGFR, advanced age, and diabetes mellitus emerged as significant predictors of AKI. These findings are

consistent with the consensus report of the Acute Disease Quality Initiative (ADQI), which identified preoperative renal dysfunction, advanced age, diabetes, prolonged bypass time, and hemodynamic instability as major determinants of CSA-AKI development [2]. Similarly, Rosner and Okusa reported that perioperative renal hypoperfusion and systemic inflammatory activation are key mechanisms responsible for postoperative kidney injury after cardiac surgery [3].

The most important finding of the present study was the excellent diagnostic performance of NGAL. Patients who developed AKI demonstrated significantly elevated NGAL concentrations as early as six hours after surgery, and NGAL emerged as the strongest independent predictor of postoperative AKI in multivariable analysis. ROC analysis revealed an AUC of 0.91, indicating excellent discriminative ability.

These findings closely align with the landmark study by Mishra et al., who first demonstrated that urinary NGAL increased within two hours after pediatric cardiac surgery and predicted AKI with an AUC exceeding 0.95 [11]. Subsequently, Haase-Fielitz et al. reported that plasma NGAL provided earlier identification of AKI than serum creatinine in adult cardiac surgery patients and significantly improved risk stratification [16]. Similarly, Cruz et al. demonstrated that postoperative plasma NGAL levels accurately predicted AKI severity and adverse clinical outcomes following cardiac surgery [12].

The superior performance of NGAL is attributable to its rapid release from injured renal tubular epithelial cells immediately following ischemic and nephrotoxic insults. Unlike serum creatinine, which reflects delayed functional impairment, NGAL directly reflects structural tubular injury, enabling earlier diagnosis and intervention.

Kidney Injury Molecule-1 (KIM-1) also demonstrated strong predictive performance in the present study, with significantly higher postoperative levels observed among AKI patients and an AUC of 0.87. KIM-1 is expressed predominantly in proximal tubular epithelial cells following ischemic injury and serves as a highly specific marker of tubular damage.

Our findings are comparable to those reported by Han et al., who demonstrated that urinary KIM-1 concentrations increased significantly after cardiac surgery among patients who subsequently developed AKI [13]. Similarly, Vaidya et al. identified KIM-1 as a sensitive marker of ischemic tubular injury and reported its potential utility for early diagnosis of postoperative renal dysfunction [20]. The present findings further support the growing evidence that KIM-1 reflects structural kidney injury earlier than conventional renal function markers.

Cystatin-C demonstrated good diagnostic performance with an AUC of 0.85 and significant postoperative elevation among patients who developed AKI. Unlike serum creatinine, cystatin-C is less influenced by muscle mass, age, sex, and nutritional status, making it a potentially more reliable marker of renal function.

These observations are consistent with the study by Koyner et al., who reported that urinary cystatin-C predicted AKI after cardiothoracic surgery significantly earlier than serum creatinine [15]. Similarly, Haase-Fielitz et al. demonstrated that serum cystatin-C identified postoperative renal dysfunction before detectable changes in conventional renal function tests [21]. The present findings therefore reinforce the value of cystatin-C as an early indicator of glomerular dysfunction and evolving kidney injury.

Interleukin-18 (IL-18) demonstrated moderate predictive accuracy in the current study, with significantly elevated levels among AKI patients beginning at

six hours postoperatively. IL-18 is a pro-inflammatory cytokine released by injured tubular cells and activated macrophages during ischemic renal injury.

Parikh et al. demonstrated that urinary IL-18 levels increased significantly after cardiac surgery and predicted AKI approximately 24–48 hours before serum creatinine elevation [17]. Similar observations were reported in critically ill patients, where IL-18 reflected the inflammatory component of acute tubular injury [22]. Although IL-18 exhibited lower predictive performance than NGAL and KIM-1 in the present study, its association with inflammatory renal injury supports its role as part of a multimarker diagnostic strategy.

Although TIMP-2 and IGFBP7 were not directly measured in the present study, these biomarkers deserve consideration because of their increasing importance in perioperative AKI prediction. TIMP-2 and IGFBP7 are markers of cell-cycle arrest and identify renal cellular stress before irreversible injury occurs.

Kashani et al. reported that the product $[TIMP-2] \times [IGFBP7]$ accurately predicted moderate-to-severe AKI in critically ill patients and outperformed several previously studied biomarkers [23]. Subsequent investigations by Meersch et al. demonstrated that biomarker-guided implementation of KDIGO preventive measures significantly reduced postoperative AKI among high-risk cardiac surgery patients identified using $TIMP-2 \times IGFBP7$ testing [24]. These findings suggest that future biomarker panels may incorporate both injury biomarkers and cellular stress markers to improve predictive accuracy.

One of the most important observations from the present study was that all evaluated biomarkers increased significantly before clinically apparent AKI was detected using serum creatinine. This finding highlights a major limitation

of traditional renal monitoring. Serum creatinine is a delayed functional marker and often fails to identify kidney injury until substantial nephron damage has already occurred.

Novel biomarkers provide earlier detection because they directly reflect structural injury, inflammation, or cellular stress. Consequently, biomarker-guided diagnosis enables identification of renal injury during a potentially reversible stage. Similar conclusions have been reported by Devarajan, who emphasized that novel biomarkers have transformed AKI from a delayed functional diagnosis into an early injury-based diagnosis analogous to cardiac troponins in myocardial infarction [25].

The present findings have important clinical implications for perioperative management. Early postoperative measurement of NGAL, KIM-1, and cystatin-C may identify patients at high risk for CSA-AKI before significant deterioration in renal function occurs. Such patients may benefit from intensified hemodynamic optimization, avoidance of nephrotoxic medications, careful fluid management, and closer postoperative surveillance.

The excellent performance of the combined biomarker model (AUC = 0.95) suggests that a multimarker strategy may be more effective than reliance on a single biomarker. Combining markers that reflect different pathophysiological mechanisms—tubular injury, glomerular dysfunction, and inflammation—may improve diagnostic precision and facilitate personalized risk stratification.

The implementation of novel biomarker testing in low- and middle-income countries remains challenging because of assay costs and laboratory infrastructure requirements. However, the economic burden associated with AKI, prolonged ICU stay, dialysis, and postoperative complications often exceeds the cost of

biomarker-based screening. In tertiary cardiac centers performing large numbers of cardiovascular procedures, selective testing of high-risk patients may represent a cost-effective strategy.

Among currently available biomarkers, NGAL appears particularly attractive because of its strong predictive performance, rapid turnaround time, and increasing commercial availability. As assay costs continue to decline, biomarker-guided perioperative monitoring may become increasingly feasible in resource-constrained healthcare settings.

Early identification of patients at risk for AKI provides an opportunity to implement targeted renoprotective interventions before irreversible kidney damage occurs. Such strategies include optimization of intravascular volume, maintenance of adequate renal perfusion pressure, minimization of CPB duration, avoidance of nephrotoxic drugs, glycemic control, and early nephrology consultation.

Recent studies have demonstrated that biomarker-guided implementation of KDIGO care bundles can significantly reduce the incidence and severity of postoperative AKI [24]. Therefore, incorporation of novel biomarkers into routine perioperative protocols may represent an important step toward precision medicine in cardiovascular surgery.

Overall, the findings of the present study support the growing body of evidence that novel renal biomarkers, particularly NGAL, provide earlier and more accurate prediction of CSA-AKI than conventional renal function tests. The use of multimarker approaches may further enhance risk stratification and improve postoperative outcomes through timely implementation of preventive and therapeutic interventions.

CONCLUSION

Acute kidney injury remains a frequent and clinically significant complication following cardiovascular surgery, contributing substantially to postoperative morbidity, prolonged intensive care unit stay, increased healthcare costs, and mortality. In the present study, the incidence of cardiac surgery-associated acute kidney injury (CSA-AKI) was 28%, highlighting the continued burden of postoperative renal complications despite advances in perioperative care.

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