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ORIGINAL ARTICLE

Urinary Kidney Injury Molecule-1 (Kim-1) As an Early Predictor of Acute Kidney Injury After Cardiopulmonary Bypass

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ABSTRACT

Background: Acute Kidney Injury (AKI) is a common complication post-cardiac surgery, influenced by factors like reduced renal blood flow during CPB and inflammatory mediators damaging renal tubular epithelium. This study aimed to evaluates urinary Kidney Injury Molecule 1 (KIM-1) as an early predictor of acute kidney injury in open heart patients after Post-Cardiopulmonary Bypass.

Methods: This was an observational follow up prospective cohort study design was done in the clinical pathology and Cardiothoracic Surgery Departments at Zagazig University for one year, where the enrolled 48 cardiac patients who had undergone open heart surgery with cardiopulmonary bypass and fulfilled the inclusion and exclusion criteria of the study, were laboratory investigation, Kidney function tests (BUN and creatinine). An enzyme-linked immunoassay (ELISA) kit was used to determine urinary KIM-1, and KDIGO-guided postoperative monitoring was conducted to check for acute kidney injury.

Results: A cutoff value of ≥916.64 for KIM-1 at 3 hours postoperatively showed high sensitivity (94.7%) and specificity (93.1%) for predicting AKI. Similarly, KIM-1 ≥944.697 at 24 hours postoperatively had a sensitivity of 100% and specificity of 86.2%. AKI incidence correlated significantly with CPB duration and cross-clamp time but showed no significant association with demographic factors or comorbidities.

Conclusion The findings suggest that KIM-1 is a promising early biomarker for AKI detection post-CPB surgery.

Keywords: Kidney Injury Molecule-1; Cardiopulmonary Bypass; Acute Kidney Injury.

INTRODUCTION

A frequent consequence of heart surgery is renal injury, which can have serious repercussions for the patient's prognosis, length of stay in the intensive care unit, and expense of therapy [1]. Low renal blood flow during cardiopulmonary bypass (CPB) may cause renal failure, and a number of proinflammatory mediators, including interleukins, TNFα, and other metabolites, can cause membrane damage to the renal tubular epithelium. The pathogenesis appears to be multifactorial [2].

Less invasive techniques can reduce the incidence of post-surgical AKI, but they are not always appropriate because cardiac surgery is still the primary and only treatment for many disorders, including complex operations, valvular heart diseases, and severe coronary artery disease. As a result, it is critical to implement techniques that assist clinicians in preventing or early diagnosis of AKI. Risk factors for AKI, poor outcomes, death, and post-cardiopulmonary bypass (CPB) include the following: wide pulse pressure, obesity,

preprocedural chronic renal illness, old age, specific comorbidities, and specific drug regimens [3].

The definition of acute kidney damage (AKI) used in several research varied from 7.7% to 28.1% in patients having heart surgery[4].

Postoperative AKI is tightly associated with important intraoperative variables, such as the length and usage of CPB [5]. Postoperative measures to increase cardiac output, avoid medications that cause the renal artery to contract, provide a sufficient amount of crystalloid infusion, and alkalize urine [6].

In order to prevent additional kidney damage and enhance patient outcomes, it is crucial to detect AKI as soon as possible following cardiac procedures [7].

The most commonly used and accepted clinical standard for the definition and diagnosis of AKI today was proposed by AKIN (acute kidney injury network), RIFLE (risk, injury, failure, loss, and ESRD), and KDIGO (Kidney Disease Improving Global Outcomes). Traditionally, this standard relied on a rise in serum creatinine or a fall in urine output[8].

The current gold standard for diagnosing AKI is serum creatinine. Serum creatinine, however, has demonstrated some limitations as a marker to identify AKI, which has an impact on the prognosis and early detection of the condition. [9]. Only after 50% of the renal cells have died can serum creatinine be found. Until a steady state is achieved, it does not provide an accurate representation of renal function. Serum creatinine levels can lag behind changes in GFR by a few days and are comparatively insensitive to slight changes in GFR [10].

Unfortunately, serum creatinine was unable to accurately reflect the timing and type of renal injury because of its low sensitivity and specificity as well as its 48–72 hour time requirements. Furthermore, a few other variables, including age and acute and chronic renal failure, also had an impact on serum creatinine [11]. According to these research, there is an urgent need for more precise and effective methods of diagnosing AKI [12].

AKI was successfully diagnosed using the new urine biomarker KIM-1. The growing evidence that KIM-1 outperformed other markers in the early identification of AKI, particularly within 24 hours, far before blood creatinine increased, has made it possible to deploy prevention or therapy methods at a very early stage of AKI [13].

Kidney injury molecule 1 (KIM-1), also known as T-cell immunoglobulin mucin 1 (TIM-1), is a transmembrane glycoprotein mostly expressed by renal proximal tubular cells[1]. After proximal tubular damage, the extracellular domain of KIM-1 is seen in the urine after being broken down by matrix metalloproteinases.

KIM-1 has a unique role in kidney injury and immunological diseases through a range of molecular targets. KIM-1 affects atopic disorders, immunological tolerance, autoimmune disease, and Hepatitis A virus (HAV) infections. Urine KIM-1 level is closely associated with kidney tissue damage, and kidney tissue level is closely associated with urine KIM-1 level. Within hours of kidney injury, the concentration of kidney injury molecule 1 (KIM-1) rises noticeably, making it a viable marker for early AKI identification [1]. Normal kidneys have modest KIM-1 expression, whereas after AKI, proximal tubule cells exhibit markedly elevated KIM-1 expression [14]. In addition to being an early indicator of acute kidney injury (AKI), KIM-1 may also be useful in forecasting the long-term course of renal disease [15].

In open heart patients following cardiopulmonary bypass (CPB), the purpose of this study was to assess urinary Kidney Injury Molecule 1 (KIM-1) as an early predictor of acute kidney injury.

METHODS

This was an observational follow-up prospective cohort study design was done in the clinical pathology and Cardiothoracic Surgery Departments at Zagazig University for one year from the first of December 2023 to the end of December 2024, the present study

enrolled 48 patients, they were divided into 2 groups: Group (I): non-AKI groups include 29 patients, divided into 15 female and 14 males, their ages range from 40 to 70 years old, Group (II): The AKI group includes 19 patients, divided into 9 female and 10 male patients, their ages range from 42 to 66 years old.

Inclusion criteria included patients accepted to participate in the study, individuals of both sexes who are over the age of eighteen (adult patients) and cardiopulmonary bypass patients undergoing open heart surgery. Patients who refused to take part in the trial and those who were elderly were among the exclusion criteria. < 18 years or ≥80 years of age. Patients with pre-existing chronic kidney disease requiring hemodialysis, Patients with preoperative renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m2), as well as those who have had AKI within the previous three months Vaidya and Aeddula [16], patients with previous kidney transplants, patients on the current use of nephrotoxic drugs like diuretics, NSAIDs, cyclophosphamide, and methotrexate, patients with severe postoperative bleeding, need reoperation, and Death within 48 hours after the operation.

After each subject had agreed to participate, the researcher started the interview with each subject using data collection tools. The study was approved by Zagazig university local ethics commission (ZU-IRB # 16915-October-2023). The study follows the Helsinki Declaration, which is the World Medical Association's guideline of ethics for research involving human subjects. The study work was done three days per week, over three stages (preoperative, intraoperative, and postoperative stages), where each patient included in this study was subjected to the following:

Pre-operative stage:

All study subjects were subjected to full history-taking as well as full clinical examination and radiological investigations, included Plain chest x-ray, pelvic-abdominal ultrasonography, Echocardiography, and CT chest. Routine hematologic investigations included Complete blood picture (CBC) by Sysmex XN1000 cell counter (Siemens Japan), Prothrombin time & concentration, partial thromboplastin time and INR by Sysmex CS-2500 (Siemens Japan), Kidney function tests (BUN and creatinine) were performed by chemistry autoanalyzer Cobas 8000 (Roche Diagnostics Germany), Estimated GFR to detect chronic kidney disease (CKD) stages effectively by Cockcroft Gault equation (creatinine clearance = [(140 - age) * weight] / (72 * serum creatinine). The determination of urinary KIM-1 was done using an enzyme-linked immunoassay (ELISA) kit–Human KIM-1 ELISA Kit (catalog No.DLR-Kim1-Hu, EDL2024013127) supplied by Dldevelop company-China **[17].**

Sampling:

Blood sample: Three ml of venous blood was withdrawn under aseptic conditions from the patient three hours after the operation. After being separated by centrifugation for 15 minutes at 3000 RPM, the serum was stored in aliquots at -20°C.

Urine sample: Prior to surgery, urinary KIM-1, 10 milliliters of mid-flow urine samples were collected in disposable urine cups without preservatives at the same time as blood collection and three hours and one day after surgery. After centrifuging urine samples for 20 minutes at 2000–3000 rpm, the supernatant was stored at -20°C until KIM-1 analysis.

Intra-operative stage:

Surgical procedure: All surgeries were performed through a midline sternotomy. Heparin 400 IU/kg was administered intravenously. CPB was initiated when the activated clotting time (ACT) exceeded 480 seconds. Extracorporeal circulation was performed using a Sorin Inspire adult membrane oxygenator (Sorin Group, LivaNova USA Inc.,14401 West 65th Way, Arvada, CO 80004-3599) and Sarns 8000 perfusion pump (Terumo Cardiovascular Systems Corporation, 6200 Jackson Road, Ann Arbor MI 48103-9586). No pulsatile perfusion was maintained at

a flow rate of 2.2–2.4 L/m2/ min. The bypass circuit was primed using 1 L Crystalloid, 3 mg/kg 10% mannitol, and 10,000 IU heparin. Hematocrit was maintained at 20% to 25% (if needed, packed red cells were added).

The mean arterial pressure (MAP) stayed in the 40–60 mmHg range during CPB. Acid-base control was achieved using the alpha-stat method.

Every patient was cooled to either normothermic CPB or a nasopharyngeal temperature of 28°C (hypothermic). Depending on the indications and surgical preferences, myocardial protection during aortic cross-clamp was accomplished by either antegrade cold blood cardioplegia that occurs intermittently at 4°C,

warm blood cardioplegia, crystalloid cardioplegia, or custodiol cardioplegia. Rewarming was started ten minutes before the aortic cross-clamp was released. 37 °C was used to reheat the patients. Protamine sulfate injections (1–1.3 mg for every 100 IU of heparin) were used to reverse heparinization. Once the patients' hemodynamics stabilized, they were taken off of CPB. Following surgery, patients were transferred to the cardiac intensive care unit**[18].**

Clinical data related to the surgical procedure and cardiopulmonary bypass was collected, including CPB duration, aortic cross-clamp time, and perioperative hemodynamic parameters for all the included patients.

Post-operative stage:

Postoperative follow up during the period of hospital stay and until complete recovery of the patient including Clinical examination, chest X-ray, routine laboratory investigations (CBC, CRP, ESR, coagulation profile), Data was gathered on postoperative fluid intake, blood product transfusions, urine output per hour, inotropes and vasoconstrictors given over the course of 48 hours, the need for renal replacement therapy during that time or during hospitalization, the time to extubation, the duration of the intensive care unit and hospital stay, complications, and mortality.

Following surgery, all pre-operative laboratory tests were repeated in the postoperative phase. Blood samples were taken for serum creatinine measurements three and forty-eight hours after surgery, urine output was measured, and In the intensive care unit (ICU), urine samples were collected twice for KIM-1 measurement three and twenty-four hours following surgery.

The KDIGO criteria for diagnosing acute kidney damage (AKI), which include (i) an increase in serum creatinine (SCr) of more than 0.3 mg/dl within 48 hours, were used to assess and grade the severity of AKI. (ii) A known or assumed increase in SCr during the preceding seven days that is greater than 1.5 times the baseline SCr. (iii) For six hours, the volume of urine should not exceed 0.5 ml/kg/h [8]. This thesis investigated Kidney Injury Molecule-1 (KIM-1) as a possible early predictor of acute kidney injury (AKI) following cardiopulmonary bypass (CPB) surgery.

Statistical Analysis:

The collected data was statistically reported and analyzed using the Statistical Package for Social Science (SPSS). While numbers and percentages were used to represent categorical data, the mean and standard deviation were used to represent continuous data. Appropriate significance tests were applied. In this work, 0.05 was the acceptable level of significance.

RESULTS

Forty-eight patients with ages ranging from 43 to 66 with a mean age of 50.5 years were included in this study. The ratio of males to females was 1:1. Approximately 36% of patients smoked, 29.6% were from cities, and 62.5% had CABG. Comorbid diabetes and hypertension prevailed in 47.9% and 39.6%, respectively. No patient died by the end of the study. Mean CPB duration was 97.19 minutes and mean cross-clamp time was 67.71 minutes. Length of ICU stay ranged from 0.5 to 4 days, with a median 1 day. Postoperative length of hospital stay ranged from 6 to 18 days with mean 9.87 days. Concerning incidence of AKI, 19 patients (39.6%) had developed AKI.

Among them, 47.4% and 42.1% of them had KDIGO staging 2 and 3, respectively.

There was a statistically significant relationship between AKI and left ventricular ejection fraction (LVEF), cross-clamp time, and CPB duration. Left ventricular ejection fraction was significantly lower among patients with AKI, while both cross-clamp time and CPB duration were significantly higher (Table 1).

AKI and either hemoglobin, preoperative creatinine, or BUN had a statistically insignificant relationship. There was a statistically significant relationship between AKI and postoperative creatinine and BUN. Within each group, there was a significant change in BUN, creatinine, and hemoglobin, as shown in Table 2.

Table 3 showed that there was a statistically non-significant relationship between AKI and urine output preoperatively or 3 hours postoperatively. However, there was a statistically significant difference between AKI and urine output at 48 hours postoperatively. Within each group, there was a significant change in urine output at each time point compared to the preceding value.

Table 4 showed that there was a statistically non-significant relationship between AKI and KIM-1 prior to surgery. However, three and twenty-four hours after surgery, there was a statistically significant correlation between AKI and KIM-1, with greater levels associated with AKI. Within the AKI group, there was a significant increase in KIM-1 at 3 hours postoperatively compared to the preoperative value, and also at 24 hours postoperatively compared to the preoperative value. Within the non-AKI group, there was no statistically significant change in KIM-1 at either 3 or 24 hours postoperatively compared to the preoperative value. Regarding KIM-1 levels at 24 hours postoperatively compared to 3 hours postoperatively, the AKI group showed a non-significant change.

Higher KIM-1 levels three hours postoperatively significantly and independently increased the risk of AKI by 1.006-fold, as shown in Table 5.

Table 6 showed that the best cutoff of KIM-1 at three hours postoperatively for diagnosing AKI was ≥916.64, with an area under the curve of 0.95, 94.7% sensitivity, and 93.1% specificity. The positive and negative predictive values were 90% and 96.4%, respectively, with an overall accuracy of 93.8%. The best cutoff of KIM-1 at 24 hours postoperatively for diagnosing AKI was ≥944.697, with 100% sensitivity, 86.2% specificity, and an area under the curve of 0.972. The positive and negative predictive values were 82.6% and 100%, respectively.

Table 7 showed a statistically significant positive correlation between KIM-1 levels at three hours postoperatively and cross-clamp time, CPB duration, ICU stay, creatinine, and BUN. Similarly, there was a statistically significant positive correlation between KIM-1 levels at 24 hours postoperatively and cross-clamp time, CPB duration, ICU stay, length of stay (LOS), creatinine, and BUN.

Table 1: Comparison between the studied groups regarding cardiac surgical data:

	Group I No AKI	Group II AKI	χ^2	P
	N=29 (%)	N=19 (%)		
	Mean ± SD	Mean ± SD	T	P
Postoperative LOS / days	7.43 ± 1.08	13.58 ± 2.14	-11.575	<0.001**
ICU stay/days	0.71 ± 0.25	3.03 ± 0.81	-12.143	<0.001**
Operation:				
CABG	19 (55.2%)	11 (57.9%)		
AVR	2 (6.9%)	1 (5.3%)	0.47	0.79
MVR	8 (27.6%)	7 (36.8%)		
LVEF (%)	60.86 ± 4.13	52.84 ± 5.82	5.587	<0.001**
Cross clamp time/min	58.62± 14.93	81.58 ± 14.44	-5.276	<0.001**
CPB duration/min	85.86± 18.85	114.47± 19.36	-5.008	<0.001**

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant
t independent sample t-test, LOS: Length of Stay, ICU: intensive care unit, CABG**:** coronary artery bypass graft, MVR: CPB stands for cardiopulmonary bypass, LVEF for left ventricular ejection fraction, AVR for aortic valve replacement, and mitral valve replacement.

Table 2: Comparison between the studied groups regarding laboratory data:

	Group I No AKI	Group II AKI	T	P
	Mean ± SD	Mean ± SD		
Hemoglobin preoperative	12.61 ± 1.24	12.55 ± 1.09	0.18	0.858
Hemoglobin post-operative	11.01 ± 1.15	11.17 ± 1.18	-0.467	0.643
Creatinine preoperative	0.51 ± 0.18	0.55 ± 0.17	-0.638	0.257
Creatinine postoperative 3h	0.54±0.22	0.59±0.25	-0.729	0.47
Creatinine postoperative 48h	0.95 ± 0.17	1.59 ± 0.2	-11.653	<0.001**
p¥	<0.001**	<0.001**		
BUN pre	16.36 ± 2.07	17.01 ± 2.38	-1.004	0.321
BUN post	19.55 ± 1.66	30.81 ± 5.5	-8.671	<0.001**
p¥	<0.001**	<0.001**		

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant χ^2Chi square test t independent sample t-test ¥P for paired sample t-test ∞p for Wilcoxon signed rank test
BUN: blood urea nitrogen

Table 3: Comparison between the studied groups regarding urine output:

Urine output /ml/kg/h	Group I No AKI	Group II AKI	T	P
	Mean ± SD	Mean ± SD		
Pre-operative	1.057 ± 0.301	1.059 ± 0.439	−0.017	0.988
3h after the operation	3.67 ± 1.02	3.53 ± 1.43	0.713	0.369
48h after the operation	1.840 ± 0.537	0.402 ± 0.275	5.775	<0.001
P1	<0.001**	<0.001**		
P2	<0.001**	0.002*		
P3	<0.001**	<0.001**		

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant t independent sample t-test p1 for paired sample t-test between preoperative value and 3 hours postoperative level p2 for paired sample t-test between 3 and 48 hours postoperative level p3 for paired sample t-test between preoperative value and 48 hours postoperative level .

Table 4: Comparison between the studied groups regarding KIM-1 pre and postoperatively:

KIM-1 pg/ml	Group I No AKI	Group II AKI	Z	P
	Median (IQR)	Median (IQR)		
Pre operative	474.04 (184.38 – 514.95)	484.45 (229.93 – 550.09)	0.285	0.776
3 hours after	534.12 (117.11 – 624.28)	1422.56 (1261.14 – 1884.73)	5.229	<0.001**
24 hours after	603.25 (210.12 – 735.93)	1563.52 (972.16 – 1934.31)	5.482	<0.001**
P1	0.34	<0.001**		
P2	0.27	0.809		
P3	0.08	<0.001**		

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant t independent sample t-test p1 for Wilcoxon signed rank test between preoperative value and 3 hours postoperative level p2 for Wilcoxon signed rank test between 3 and 24 hours postoperative level p3 for Wilcoxon signed rank test between preoperative value and 24 hours postoperative level

Table 5: Multivariate regression analysis of predictors of AKI

	B	P	AOR	95% C.I.	
				Lower	Upper
KIM1 3 hours after surgery	0.006	<0.001**	1.006	1.003	1.009

AOR adjusted odds ratio CI Confidence interval **p≤0.001 is statistically highly significant

Table 6: Performance of KIM-1 3 and 24 hours after surgery in prediction of AKI among studied patients:

	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
3 hours	≥916.64	0.95	94.7%	93.1%	90%	96.4%	93.8%	<0.001**
24 hours	≥944.697	0.972	100%	86.2%	82.6%	100%	91.7%	<0.001**

PPV positive predictive value NPV negative predictive value AUC area under curve
**p≤0.001 is statistically highly significant

Table 7: Correlation between KIM-1 and baseline data, ICU and hospital stay pre and postoperatively among studied patients:

	Preoperative KIM-1		KIM-1 after 3 hours		KIM-1 after 24 hours	
	R	P	R	P	R	P
Cross clamp time	0.078	0.596	**0.456**	**0.001****	**0.593**	**<0.001****
CBP duration	0.046	0.755	**0.485**	**<0.001****	**0.598**	**<0.001****
ICU stay (day)	-0.035	0.815	**0.746**	**<0.001****	**0.695**	**<0.001****
LOS (day)	0.028	0.851	**0.621**	**<0.001****	**0.682**	**<0.001****
Creatinine (mg/dl)	0.123	0.406	**0.643**	**<0.001****	**0.633**	**<0.001****
BUN (mg/dl)	0.049	0.739	**0.646**	**<0.001****	**0.572**	**<0.001****

r Spearman rank correlation coefficient **p≤0.001 is statistically highly significant *p<0.05 is statistically significant
LOS: Length of Stay, ICU: intensive care unit, CPB: cardiopulmonary bypass, BUN: blood urea nitrogen.

DISCUSSION

Following heart surgery, acute kidney injury is a frustrating complication that raises the risk of death and morbidity, puts patients at risk for a longer hospital stay, necessitates more care, and raises postoperative care expenses [19].

Through prompt therapies, early identification and prediction of AKI can enhance patient outcomes [7].

Therefore, in order to enable the prompt initiation of treatment, sensitive biochemical indicators for the early diagnosis of acute renal injury are required [20].

Serum creatinine is currently the standard test used to identify AKI. Serum creatinine, however, has demonstrated some limitations as a marker to identify AKI, which has an impact on the prognosis and early detection of the condition [9]. Only after 50% of the renal cells have died can serum creatinine be found. Until a steady state is achieved, it does not provide an accurate representation of renal function. Serum creatinine levels can lag behind changes in GFR by a few days and are comparatively insensitive to slight changes in GFR [10].

As a result, it prevents acute renal injury from being detected early. The site and degree of glomerular or tubular injury, as well as the time and type of renal insult, cannot be distinguished by the change in serum creatinine [21].

In open heart patients following CPB, this study assesses urine KIM-1 as an early indicator of acute kidney injury.

This study included 48 participants with ages ranging from 43 to 66 years, with a mean age of 50.5 years; the male to female ratio was 1:1. They divided into two factions. Group I consists of non-AKI groups, while Group II consists of AKI groups. taking into account the KDIGO criteria for diagnosing AKI. Among the patients who experienced acute kidney injury (AKI), 19 patients (39.6%) acquired AKI after surgery; 47.4% were classified as KDIGO stage 2 and 42.1% as stage 3. This outcome is

consistent with that of Oshita et al. [22], who found that the incidence of AKI among their patients who underwent cardiopulmonary bypass surgery varied between 20% and 40%.

According to this study, the development of acute kidney damage (AKI) after cardiopulmonary bypass (CPB) was not significantly impacted by either hypertension or diabetic mellitus (DM). These outcomes are in line with research by Zhang et al. [23], who found no evidence of a significant correlation between AKI and hypertension in this particular setting. However, Khonsha et al. [24] found a substantial correlation between DM and an elevated risk of AKI following CPB, presenting contradictory findings. Variations in study populations, management procedures, or other unquantifiable confounding factors could be the cause of these disparate findings.

There is a statistically significant correlation between AKI and the duration of hospitalization or postoperative critical care unit admission. This demonstrates how acute kidney injury (AKI) and prolonged hospital and intensive care unit (ICU) stays following surgery are closely related. The necessity for more diagnostic testing, prolonged medical supervision, therapy modifications, or even rehabilitation may be the cause of this protracted stay. Additionally, Federspiel et al. [25] demonstrate that AKI is linked to worse outcomes, such as longer length of stay in the intensive care unit.

In our study, we found a statistically significant relationship between the duration of CPB and the development of postoperative AKI. During cardiac surgery, CPB is utilized to temporarily replace the heart and lungs.

A meta-analysis of nine different studies with 12,466 people undergoing CPB was conducted by Kumar et al. [26]. Of them, 756 patients (6.06%) experienced AKI-CPB. In seven of nine studies, the mean CPB periods of the AKI-CPB cohort were statistically longer than those of the control group (cohort without AKI). They concluded that a higher probability of developing AKI-CPB, which has a substantial effect on overall mortality, is associated with longer CPB periods. The fixed-effects model showed an absolute mean difference in CPB time of 25.65 minutes, while the random-effects model showed a difference of 23.18 minutes. The current investigation found a statistically significant correlation between cross-clamp time and the development of AKI. When performing coronary artery bypass grafting or other cardiac procedures, cardiac surgeons must undertake aortic cross-clamping, which is represented by the cross-clamp time during CPB surgery. Our results align with those of Karim et al. [27], who showed a statistically significant correlation between the incidence of AKI and a longer cross-clamp period.

AKI and left ventricular ejection fraction, a measurement of the heart's capacity to pump blood more precisely, the proportion of blood pushed out of the left ventricle with each contraction have a statistically significant association in our investigation.

Cardiac output and renal blood flow are intricately linked. A decrease in LVEF can result in reduced cardiac output, compromising renal perfusion. This reduced perfusion can contribute to the development of AKI, especially in the setting of perioperative stress during cardiac surgery[28].

Palomba et al. [29] have demonstrated a link between a decreased LVEF and an increased risk of AKI after heart surgery. For instance, patients with pre-existing cardiac dysfunction (reflected by lower LVEF) may already have compromised renal perfusion, making them more susceptible to AKI triggered by factors like CPB, inflammation, and hemodynamic instability.

Similar to the findings of Leaf et al. [30], who observed similar hemoglobin levels regardless of AKI development, we did not find a significant link between hemoglobin levels and the incidence of AKI post-CPB. Low hemoglobin concentration is linked to a higher incidence of CPB-associated AKI, in contradiction to Fischer et al. [31]. Since circulating free iron-mediated nephrotoxicity with hemolysis and free hemoglobin are likely

to cause AKI in patients having cardiac surgery with CPB, strategies that increase the hemoglobin concentration such as the cautious use of red blood cell (RBC) transfusion are advised. The discrepancy between your study and Fischer et al. [31] regarding the relationship between hemoglobin levels and AKI post-CPB may stem from several factors, possibly due to conservative RBC transfusion protocols that minimized nephrotoxic risks associated with hemolysis and free hemoglobin, Fischer et al. [31] reported a higher incidence of AKI with low hemoglobin levels, likely due to more frequent transfusions or less stringent management of anemia. Additionally, differences in patient populations, comorbidities, CPB duration, and perfusion strategies could also explain the divergent findings.

In both the AKI group and the non-AKI group, our study discovered a non-significant rise in the creatinine level three hours and a statistically significant increase in the median serum creatinine level 48 hours following the procedure. These results are consistent with those of Wen et al. [32] and Marakala [33], who noted that in instances related to heart surgery, alterations in serum creatinine usually take place 48 hours after the start of operation.

These findings also supported the findings of Han et al. [33] and Mishra et al. [34], who came to the conclusion that, in the case of AKI linked to heart surgery, alterations in serum creatinine happen late in the course of the disease, usually up to 48 hours after surgery begins.

Urine production rose significantly in both groups three hours after surgery in our trial, but there was no statistically significant difference between the AKI and non-AKI groups. This early postoperative polyuria likely reflects aggressive intraoperative fluid administration and the physiological response to cardiopulmonary bypass (CPB), which temporarily increases urine output due to hemodilution and altered tubular handling of solutes. The absence of substantial variations implies that urine production in the early postoperative period is not a good predictor of the onset of AKI. As stressed by Khreba et al. [5], it is crucial to remember that this rise in urine production should not be mistaken for a positive clinical indicator.

A marked reduction in urine output was observed in the AKI group 48 hours postoperative compared to the non-AKI group, with a statistically significant difference, raising greater concerns about renal perfusion and function in these patients. This marked decrease in the AKI group could be attributed to multiple factors, including impaired renal recovery, fluid balance alterations, and possible complications related to acute kidney injury. In the non-AKI group, the decrease in urine output might reflect a normal response to fluid redistribution and postoperative changes in physiology. These findings align with observations reported by Katabi et al. [35] who found that decreased urine output during CPB is predictive of renal complications, with urine output <0.5 mL/kg/h over a 6- to 48-hour period after the intervention being particularly indicative.

Preoperative urine KIM-1 levels and the development of AKI did not significantly correlate in this investigation, suggesting that baseline KIM-1 levels may not be a good predictor of AKI risk in patients having cardiopulmonary bypass. Nonetheless, postoperative urine KIM-1 levels were considerably greater in those who had AKI at 3 and 24 hours, suggesting that it may be used in this situation as an early indicator of renal impairment. These results are in line with a research by Khreba et al. [5], which found that the AKI group had a considerably higher urine KIM-1 level three hours after surgery than the non-AKI group. Additionally, in his prospective pilot investigation for the early diagnosis of AKI in people after heart surgery, Liangos et al. [36] discovered that Urinary KIM-1 showed the best diagnostic performance two hours after CPB.

Among the AKI group of our patients, there is a significant increase in KIM-1 3 hours postoperative compared to preoperative value and between 24 hours postoperative compared to preoperative value. The 3-hour postoperative

increase in KIM-1 indicates that AKI may begin to develop very early in the postoperative period, potentially within hours after surgery. This early rise in KIM-1 is consistent with its role as a sensitive early biomarker for kidney injury. It allows clinicians to detect AKI before more traditional markers, such as serum creatinine, show significant changes. The 24-hour postoperative increase further underscores the progression of renal injury over time. This gradual rise in KIM-1 levels may reflect ongoing damage to the renal tubular cells in response to ischemia, nephrotoxins, or hemodynamic fluctuations during and after CPB. Also, our finding shows that there is no statistically significant change in KIM-1 levels in the non-AKI group at both 3 hours and 24 hours postoperative compared to preoperative values suggesting that in these patients, kidney function remained stable. This finding is in concordance with other studies, such as Zhang et al. [23], which revealed that urinary KIM-1 levels in patients without acute kidney injury (AKI) did not significantly change between the preoperative and postoperative periods; however, urine KIM-1 levels in patients with AKI increased by 40% at two hours postoperatively and more than doubled at twenty-four hours postoperatively.

Moreover, the current study revealed that higher urinary KIM-1 three hours postoperatively was considered to be a significantly independent risk of AKI by 1.006 folds our result goes with Han et al. [33] They conducted a prospective study in which urine KIM-1 was tested at various intervals throughout the first 24 hours after heart surgery in 90 patients. According to the study, patients who had AKI had higher levels of KIM-1, which suggests that it could be used as an early biomarker for the identification of AKI.

Urinary KIM-1's cutoff values and diagnostic performance in our investigation at three and twenty-four hours after surgery offer important new information about its possible function as an early indicator of AKI following CPB surgery. Three hours after surgery, a urine KIM-1 level of ≥916.64 pg/mL showed a high degree of discriminative ability, with an area under the curve (AUC) of 0.95, a sensitivity of 94.7%, and a specificity of 93.1%. While the positive predictive value (PPV) of 90% suggests a significant risk of AKI in people with elevated KIM-1 levels, the negative predictive value (NPV) of 96.4% shows that it is dependable in ruling out AKI. The 93.8% overall diagnosis accuracy highlights how reliable KIM-1 is in this context as an early indicator of AKI.

Similarly, Khreba et al. [5] reported found the urine KIM-1 tested three hours after surgery had a sensitivity of 48%, specificity of 94%, and AUC of 0.715 at a threshold value of 1.9 ng/mL.

The differences in cutoff values and diagnostic performance between studies may be attributed to variations in patient populations, AKI definitions, and assay methodologies.

At 24 hours postoperatively, a urinary KIM-1 level of ≥944.697 pg/mL demonstrated 100% sensitivity but slightly lower specificity (86.2%), resulting in an excellent AUC of 0.972. The positive predictive value (PPV) of 82.6% indicates a high likelihood of true positives, while the negative predictive value (NPV) of 100% highlights the reliability of a normal KIM-1 level in ruling out AKI. The overall accuracy remained high at 91.7%, reinforcing the strong diagnostic potential of KIM-1 at this later time point.

Moreover, Shao et al. [37] investigated the utility of urinary KIM-1 for AKI diagnosis after CPB and reported a sensitivity of 74% and specificity of 86%. Similarly, Ghaheh et al. [38] found that at a cutoff point of 14.8 ng/mL, KIM-1 demonstrated 84% sensitivity and 89% specificity.

There are a number of reasons for the variation in urine KIM-1 cutoff values, sensitivity, and specificity amongst studies. First, differences in patient demographics, including age, pre-existing renal function, and comorbidities, may have an effect on baseline and postoperative KIM-1 levels. Second, differences in diagnostic performance may result from differing AKI definitions based on various criteria, such as the

KDIGO, RIFLE, or AKIN classifications. Third, assay methodologies differ across studies, as KIM-1 can be measured using various immunoassays with different sensitivities and detection limits. Additionally, the timing of KIM-1 measurement plays a crucial role; while early postoperative levels reflect acute tubular stress, later measurements may capture established renal injury, leading to differences in reported diagnostic accuracy. Finally, perioperative factors such as CPB duration, fluid management, and use of nephrotoxic agents may influence KIM-1 expression and contribute to the observed variability. These elements emphasize the necessity of multicenter validation and uniform methodologies to establish more universally applicable cutoff values for urinary KIM-1 in AKI diagnosis after CPB.

There are statistically significant positive correlations between KIM-1 levels at different postoperative time points (3 hours and 24 hours) and some intraoperative parameters specifically, the associations with cross-clamp time and CPB duration indicating that longer ischemic times during surgery may contribute to greater kidney injury, as reflected by elevated KIM-1 levels. This was in agreement with Elmedany et al. [39] who found a positive correlation between longer cross-clamp times (mean of 60.9 minutes) and longer CPB times the development of AKI. Furthermore, as urine KIM-1 levels were considerably greater in patients who experienced renal impairment, there was a positive correlation between them with the start of AKI.

Discussing the correlations between ICU stay and LOS suggests that elevated KIM-1 levels are associated with prolonged recovery periods, likely due to the severity of kidney injury incurred during surgery. This correlation supports the hypothesis that KIM-1 reflects renal tubular damage and dysfunction, possibly contributing to prolonged hospital stays and increased resource utilization. Also, Wajda et al. [40] observed a positive correlation between urinary KIM-1 and the length of hospital stay.

The significant positive correlations between KIM-1 levels at 3 hours and 24 hours postoperatively with postoperative creatinine and blood urea nitrogen (BUN) levels highlight important insights into kidney function and injury following cardiopulmonary bypass (CPB) surgeries.

Given the established pathophysiological function of KIM-1 in responding to renal injury, the strong positive correlations with KIM-1 imply that higher KIM-1 levels indicate more tubular injury and dysfunction. Urinary KIM-1, creatinine, and BUN are positively correlated, according Peng et al. [41] and Elsawy et al. [42].

It is known that KIM-1 is an early indicator of kidney damage, especially acute tubular injury. KIM-1 may be a sensitive marker of continuing or imminent kidney damage soon after CPB surgery, according to the correlations seen at 3 and 24 hours postoperatively. This early detection could facilitate timely intervention strategies to mitigate further renal damage and improve patient outcome.

CONCLUSION

The study showed that in individuals undergoing cardiopulmonary bypass (CPB), urine KIM-1 levels were a significant early predictor of acute kidney injury (AKI). The development of AKI was substantially correlated with elevated KIM-1 levels at three and twenty-four hours postoperatively.

Recommendations:

Future research on AKI following CPB should aim for a larger sample size to increase statistical power and better identify potential links between comorbidities with AKI. Expanding the sample size would help control for confounding variables and offer more comprehensive insights, ultimately contributing to more accurate conclusions and improved clinical management strategies.

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