Diagnostic Accuracy of Urinary Kidney Injury Molecule-1 in Early Diagnosis of Acute Kidney Injury in Cardiopulmonary Bypass Patients

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Abstract

Objective: To assess diagnostic accuracy of KIM-1 as compared to serum creatinine in patients undergoing cardiopulmonary bypass for diagnosis of acute kidney injury.

Material and Methods: This is a comparative cross-sectional study and was conducted in the Biochemistry & Chemical Pathology department of Shaikh Zayed Hospital Lahore over the course of one year. The study received approval from the organization's ethical committee (Letter No. SZMC/IRB/Internal/0059/2021). A total of 190 patients who met the inclusion criteria were included in the study. Blood samples for serum creatinine and urine samples for KIM-1 were collected pre-operatively, 3hrs and 24hrs after surgery. Quantitative analysis of serum creatinine and urinary KIM-1 were done. Reports were evaluated and levels were recorded. Data was analyzed by SPSS 25.0.

Results: Out of 190 patients, 26(13.7%) developed AKI after cardiopulmonary bypass diagnosed by high serum creatinine. Serum creatinine started to rise in the patients after 24hrs of surgery whereas urinary KIM-1 showed increased in level 3hrs after surgery. Sensitivity of KIM-1 at 3hrs in patients who developed AKI was found to be 92.3% and specificity was 87.2% with diagnostic accuracy of 87.9%.

Conclusion: From the findings, it can be concluded that urinary KIM-1 may be used as an early diagnostic marker of AKI, since it showed an increase within 3hrs post-surgery while serum creatinine level remained normal during that time and started to rise after 24hours.

Keywords: Serum Creatinine, Urinary KIM-1, Acute Kidney Injury, Cardiopulmonary Bypass

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Introduction

A cute kidney injury is a commonly encountered issue during cardiac surgery that often leads to fatal outcomes.¹ AKI is primarily characterized by an increase in levels of serum creatinine in the blood and a decrease in urine output.² A research study carried

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out in Pakistan reveals that the prevalence of postoperative acute kidney injury is approximately 8.2%, with a mortality rate of nearly 34.5%.³ The cause of acute kidney injury related to cardiac surgery is very complex and involves various aspects of the disease's pathophysiology.⁴ Several studies indicate that various factors such as age, diabetes, chronic kidney disease, cardiac surgeries, and high blood pressure, are linked to the likelihood of developing this condition.⁵ The existing research indicates that the development of AKI in patients is caused by the activation of specific inflammatory substances and by induction of hemodilution. Other factor includes cardiogenic hypotension, older age, higher body mass index and high cardiopulmonary bypass time.⁶

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AKI is more commonly found in patients who exhibit the predisposing factors.7 Serum creatinine concentration is a reliable test for diagnosing acute kidney injury. It is considered the best method, but it can sometimes lead to a delay in diagnosis due to sluggish kinetics of serum creatinine after the injury and higher dependency on muscle mass.8 When there is enough renal reserve, the levels of serum creatinine may not change even if there is acute damage to the tubules. In such cases, the sensitivity of serum creatinine as an indicator is low.9 KIM-1, on the other hand, is seen as a potential marker for early detection of AKI. Research has demonstrated that KIM-1 levels can quickly rise after damage to the renal tubules.¹⁰ KIM-1 is a specific type of glycoprotein that extends across the cell membrane and has sugar molecules attached to it.11 Studies have demonstrated that the levels of KIM-1 can rise significantly within a few hours of kidney injury, indicating its potential as a reliable indicator for early detection.¹² Xie's metaanalysis revealed that the levels of uKIM-1 can start to increase as early as 2-8hours after the injury, making it a valuable marker for early diagnosis.¹³ The reason for conducting the study is to compare the levels of KIM-1 with serum creatinine in patients undergoing cardiac surgery for detection of AKI. KIM-1 levels are expected to rise early in blood and urine (within 12hrs) as compared to serum creatinine. Hence, KIM-1 may act as an early diagnostic marker for acute kidney injury.

Material and Methods

After approval of IRB Shaikh Zayed hospital (letter number SZMC/IRB/Internal/0059/2021) and Punjab Institute of Cardiology samples were collected from Punjab Institute of Cardiology, Lahore. One hundred and ninety patients were enrolled in this comparative cross-sectional study. Adult patients of both genders and of age 30-60 years with normal renal functions undergoing cardiopulmonary bypass were included. Patients with pre-existing chronic kidney disease, acute kidney disease, diabetic nephropathy and glomerulonephritis were excluded from the study. Non- probability convenient sampling method was used. Demographic information including name, age, gender and general physical examination were recorded. For serum creatinine estimation 4ml of blood was drawn from the patient pre-operatively and after 3hrs and 24hrs of surgery. After blood clotting in the tube, serum was separated by centrifugation and stored at -20 Celsius. To determine the level of urinary KIM-1 15ml of urine was collected without any preservative and centrifuged for about 20mins and then specimen were stored at -20 degree Celsius. Quantitative analysis of urinary KIM-1 was carried out by using sandwich enzyme linked immunosorbent assay by Human KIM-1 ELISA Kit (E-EL-H6029) United States and serum creatinine was estimated by using Jaffe's method on HumaStar 200. Levels of analytes were noted after running quality control followed by reports assessment. The data was analyzed using SPSS 25.0. Based on serum creatinine level, patients were divided into two groups AKI and Non-AKI and the comparison of creatinine and KIM-1 values between these groups was made using independent sample t-test at each follow up time. If p-value was ≤ 0.05 the results were considered statistically significant.

Results

The study comprised a sample size of 190 patients undergoing cardiopulmonary bypass. The mean age of the patients was 49.5±10.0 years. There were 118(62.1%) males and 72(37.9%) females. In this study based on serum creatinine levels at 24hrs 164(86.3%) patients out of 190 did not develop acute kidney injury while 26(13.7%) patients developed AKI after undergoing cardiopulmonary bypass (fig 1.1). Due to non-normal data Mann-Whitney U-test was used to compare the serum creatinine levels between AKI and non-AKI patients. The findings showed that there was no noticeable disparity in the average levels of serum creatinine between patients who developed AKI and those who did not at 3hours level. However, the median serum creatinine levels were significantly higher after 24hrs in AKI patients as compared to non-AKI patients (table 1.). The findings showed that median levels of uKIM-1 in AKI patients were significantly higher both at 3hrs and 24hrs after surgery (table 1.2). The sensitivity, specificity, Positive Predictive Value, Negative Predictive Value and diagnostic accuracy of KIM-1 at 3hrs were 92.3%, 87.2%, 53.3%, 98.6% and 87.9% respectively taking actual status of injury by creatinine level at 24hrs as reference (table 1.3). The area under curve (AUC) of uKIM-1 levels after 3hrs

and 24hrs was 0.927 with Cl of 0.845 - 1.008 (p-value < 0.001) and 0.983 with Confidence Interval(CI) of 0.962 - 1.00(p-value < 0.001) respectively which shows that uKIM-1 level is reliable marker for diagnosis of AKI in patients after cardiopulmonary bypass (fig 1.2)



Figure-1.1: Incidence of AKI in Patients after Cardiopulmonary Bypass.

Table 1.1: Comparison of S. Creatinine levels between

 AKI and non-AKI patients

Interval	Group	Median (IQR)	p-value ^a
	•	mg/dl	
3 hours	AKI	1.05 (0.90 – 1.13)	0.064
	Non-AKI	1.00 (0.90 - 1.10)	0.004
24 hours	AKI	4.10 (3.00 - 4.63)	<0.001*
	Non-AKI	1.00 (0.90 - 1.10)	~0.001

Table 1.2: Comparison of urinary KIM-1 levels between

 AKI and non-AKI patients

Interval	Group	Median (IQR)	p-value ^a
		pg/ml	
3 hours	AKI	429.0 (340.1 - 850.1)	<0.001*
	Non-AKI	135.0 (110.0 - 167.0)	<0.001
24 hours	AKI	1035.0 (489.5 - 1582.5)	<0.001*
	Non-AKI	167.0 (124.0 - 220.8)	<0.001

Table 1.3: Predictive measures for KIM-1 level at 3 hours

 with 95% CI.

Measure	Value %	95% Confidence Interval
Sensitivity	92.3	75.9 – 97.9
Specificity	87.2	81.2 - 91.5
Positive Predictive value	53.3	39.1 - 67.1
Negative Predictive value	98.6	95.1 - 99.6
Accuracy	87.9	82.5 - 91.8



Figure-1.2: Area under the ROC Curve at 3hours and 24hours after Cardiopulmonary bypass.

Discussion

Cardiopulmonary bypass is a surgical technique that temporarily assumes the function of the heart and lungs in order to maintain a constant supply of blood and oxygen in the patient's body.¹¹ Although cardiopulmonary bypass is commonly employed, it carries various risks such as acute kidney injury, stroke, and platelet dysfunction.¹⁴ Currently, serum creatinine levels are widely accepted as the primary method for diagnosing acute kidney injury, but it is necessary to explore alternative markers. This research was conducted to determine the effectiveness of uKIM-1 as an early indicator of AKI in cardiopulmonary bypass patients, with creatinine being used as the benchmark. The research was carried out on 190 patients who were undergoing cardiopulmonary bypass. Out of 190, 14 males developed AKI, while 12 females also developed AKI. The study conducted by Temraz indicates that gender and age do not play a role in the development of AKI after cardiac surgery.¹⁵ In the present research, it was observed that 26 patients developed acute kidney injury following surgery, as indicated by an increase in serum creatinine levels after 24hours, in contrast to patients who did not develop AKI (fig 1.1). Recent research has demonstrated that patients who developed AKI after surgery and show elevated levels of serum creatinine 48hours after the injury experience a notable increase in mortality rates.¹⁶ In our study 26 patients developed AKI after surgery. A

study conducted by Zhang et al in 2023 showed similar results that serum creatinine level raised at 24hrs after surgery in patients who developed AKI after undergoing cardiopulmonary bypass.¹⁷ It was noticed that the levels of uKIM-1 began to increase earlier after the surgery, specifically at the 3hour mark, in 26 patients. The comparison between the two groups is given in the table 1.5. In a study conducted by Eslami in 2021, urinary samples were collected at various time. The study found that uKIM-1 showed statistical significance in the AKI group when compared to serum creatinine levels, which remained within normal range during the early postoperative period.¹⁸ The uKIM-1 marker shows potential in detecting early kidney injury because it is released in urine immediately after proximal tubular injury occurs.¹⁹ The diagnostic accuracy and ROC curve were created to assess the uKIM-1 level. The AUC value, which was 0.927, was obtained 3hours after surgery (fig1.2). This AUC value, along with the sensitivity and specificity, suggest that uKIM-1 could potentially serve as a dependable marker for early detection of AKI. A recent study by Geng et al in 2021 examined patients who underwent cardiac surgery and found similar results that the sensitivity of KIM-1 in diagnosing AKI was 0.74, while the specificity was 0.84. The study also reported an AUC value of 0.62.²⁰

Conclusion

The study was conducted on adult patients undergoing cardiopulmonary bypass. The findings suggested that uKIM-1 can potentially serve as an indicator for acute kidney injury at the early stages, as it showed an increase within 3hours after the bypass procedure, even though serum creatinine levels remained normal at that time. However, the serum creatinine levels began to rise after 24hours.

None

None

Conflict of Interest	
Funding Source	

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Authors Contribution

- AJ, TN: Conceptualization of Project
- AJ, SH, MK: Data Collection
- AJ, SH, MK: Literature Search
- AJ, TN: Statistical Analysis
- AJ, TN: Drafting, Revision
- AJ: Writing of Manuscript