



Renal Restrictive Index (RRI) Versus Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) for early prediction of acute kidney injury (AKI) in adults undergoing elective cardiac surgeries with cardiopulmonary bypass: A prospective randomized observational study

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ABSTRACT

Background: Acute kidney injury (AKI) complicates most cardiac surgery patients. This study assessed the accuracy of urine neutrophil gelatinase-associated lipocalin (uNGAL) and Renal Resistive Index (RRI) to early predict (AKI) after cardiopulmonary bypass (CPB).

Methods: This work enrolled 57 cases of elective cardiac surgery with CPB. Urinary NGAL and RRI were measured preoperatively and at 1, 6 and 24 h postoperatively. The primary outcome was AKI, defined by Acute Kidney Injury Network Classification (AKIN) System. The secondary aim was to assess the diagnostic accuracy, cut-off point of uNGAL and RRI, and their relation with AKI severity.

Results: AKI developed in 22 patients (38.5%), with 2 cases required dialysis. Mean uNGAL significantly increased by 10 folds at 1h and 15 folds at 6h postoperatively. As regard uNGAL, the 1 h diagnostic accuracy was 94.8%, The area under the curve (AUC) was 0.888, using a cut-off value of 194.3 ng/ml. The 6 h diagnostic accuracy was 96.5%, AUC was 0.995 at a cut-off value 67.1 ng/ml. The 1 and 6 h uNGAL were unrelated to AKI severity. As regard RRI, AKI patients had significantly higher 1 h and 6 h RRI. The diagnostic accuracy at 1 h was 93.0%, AUC was 0.991, using a cut-off value of 0.72. The diagnostic accuracy at 6 h was 94.8%, AUC 0.995 at a cut-off value of 0.71. Values of RRI were significantly related only to severe cases requiring dialysis.

Conclusion: Urinary NGAL and RRI are early accurate indicators of AKI. High RRI can predict dialysis-requirement.

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1. Introduction

The accumulation of experience in the discipline of cardiac surgeries has improved patient outcomes significantly; yet, cardiac surgery associated acute kidney injury (CSA-AKI) is a common post-operative complication that has a poor prognosis. The incidence of CSA-AKI varies widely among different studies, ranging from 3% to 30%. For patients undergoing cardiac surgery, even mild AKI, is linked to increased short-and long-term morbidity and death [1].

The conventional criteria for AKI diagnosis are based on increased serum creatinine (s.Cr) or reduced urinary output. Now, various studies are searching for new techniques to predict and early detect CSA-AKI because these conventional markers are unreliable, delayed and can be altered by a variety of events throughout the postoperative period [2].

One approach is to measure some serum or urine biomarkers and correlate them with the development of AKI. However, the daily bed-side use of these

biomarkers is limited, mainly by their cost. Among these newer biomarkers, the urinary Neutrophil Gelatinase Associated Lipocalin (uNGAL) seems to be promising in the early detection of AKI. The expression of NGAL is up-regulated immediately following renal injury, making it attributed as a direct biomarker.

Another potential marker, that is rapidly gaining ground as a screening tool for AKI, is the renal resistive index (RRI) via transabdominal ultrasonography. The utility of RRI depends on the fact that renal vasoconstriction is an early manifestation of AKI, which can be detected through measuring alterations in blood flow profile of the intrarenal arcuate or interlobar arteries by renal Doppler [3,4].

The current randomized observational study aims to detect AKI occurrence as defined by the Acute Kidney Injury Network Classification (AKIN) System. The study also investigates the accuracy and cut-off values of uNGAL and RRI for AKI detection and correlates their values with AKI severity.

2. Patients and Methods

Agreement of the Ethics Committee of the Faculty of Medicine (IRB-NO: 00012098 -FWA-NO: 00018699) and a written informed consent from all the patients were obtained. Our study was carried out in Cardio-thoracic unit at Main University Hospital, Alexandria on 57 adult male and female patients, aged between 18 and 75 years, American Society of Anaesthesiologists (ASA) physical status II–III, undergoing elective cardiac surgery using cardiopulmonary bypass. Patients should have at least one of the known risk factors for AKI: Age > 60 yr, arteritis defined by severe lower limb arteriopathy, carotid stenosis >50% or diabetes, preoperative intra-aortic balloon pump, peripheral vascular disease, or on regular to one of the following drug ACE inhibitors, ARBs or NSAIDs. The study was carried out between June 2020 and August 2021.

A minimal sample size of 52 was calculated using MedCalc version 16.4.3 Program to detect an area under the curve (AUC) of 0.95 and 0.91, respectively, for using uNGAL and RRI to early predict AKI, using conventional receiver-operating characteristic (ROC) curve analysis with a significance level (α) of 0.05 and 80% power [5].

The exclusion criteria were: Chronic renal disease with Creatinine Clearance (Cr.CL) < 30 ml.min, renal artery stenosis, dialysis dependency, renal transplantation, severe liver dysfunction, mono-kidney, non-sinus cardiac rhythm, emergent surgery, endocarditis, nephrotoxic treatment as aminoglycosides and metformin, off-pump cardiac surgery and ejection fraction <35%.

Patients evaluated by history taking, clinical examination, routine and required investigations, cardiac and pulmonary medicine assessment on the day before surgery. All preoperative medications were continued until the morning of surgery.

Immediately preoperatively, blood and urine samples were taken for basal values of blood urea (mg/dl), serum creatinine (mg/dl) and basal urinary uNGAL. Renal Doppler was done to record basal RRI.

Anaesthesia and CBP management were standardized for all patients. The use of vasopressor (adrenaline) or inotrope (dopamine) to facilitate weaning of CBP was judged by the haemodynamic state of the patient (mean arterial blood pressure, heart rate), cardiac contractility (by TEE), and the ECHO findings done preoperatively.

In the postoperative ICU, the management was standardized for all patients with the avoidance of nephrotoxic agents and NSAIDs. All vital signs, haemodynamics, inotropes, and vasopressors were continuously assessed. Bleeding per chest tubes and RBC transfusion were recorded. The duration of anaesthesia, surgery, bypass and cross-clamp time were all recorded, as well as the duration of mechanical ventilation and ICU stay.

Renal impairment was assessed by the AKIN system at 1, 6, 24, 48 and 72 h postoperatively and, accordingly, patients were classified into AKI group and Non-AKI group. The AKI group was further classified by AKIN into stage 1, 2 or 3.

Urinary NGAL was measured via a commercial ELISA kit (Quantikine ELISA Human Lipocalin-2/NGAL Immunoassay. R&D Systems. Minneapolis, MN, USA) preoperatively and at 1, 6 and 24 hours postoperatively.

The renal resistive index was measured by two independently trained sonographers using a transparietal 5 MHz pulsed-wave Doppler probe (Sonosite M9). Basal RRI value was measured preoperatively and then postoperatively within 1 h of ICU admission and after stabilization of hemodynamics and adjusting the ventilation without PEEP to obtain a PaCO₂ of 35–40 mmHg to standardize renal blood flow. RRI was measured again at 6 and 24 hours postoperatively. After visualizing the kidney and checking for renal abnormalities, an arcuate or interlobar artery was localized and three successive Doppler measurements at different positions in the kidney (high, middle and low) were performed 3 times in each kidney. The median value of each section was used, and the three median values of each kidney are averaged. $RRI = (\text{peak systolic velocity} - \text{end diastolic velocity}) / (\text{peak systolic velocity})$. Normal values are reported between 0.60 and 0.70 [6].

3. Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov–Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

4. Results

Sixty-five subjects were assessed to participate in this study. Of those, 60 patients were enrolled, with 5 patients excluded for not meeting the inclusion criteria. Three dropouts happened along the course of the study. A total of 57 participants completed the study period (Figure 1). During the study period, 22 patients developed AKI according to AKIN criteria. By the end of the 72 h, nine patients had stage I AKI, nine patients had stage II AKI, and one patient had stage III AKI, while the renal function had recovered in three patients who had AKI in the first two days.

The age of the studied patients was significantly higher in the AKI group, while they were perfectly matched regarding sex and BMI. Regarding the co-

Flow chart of the patients

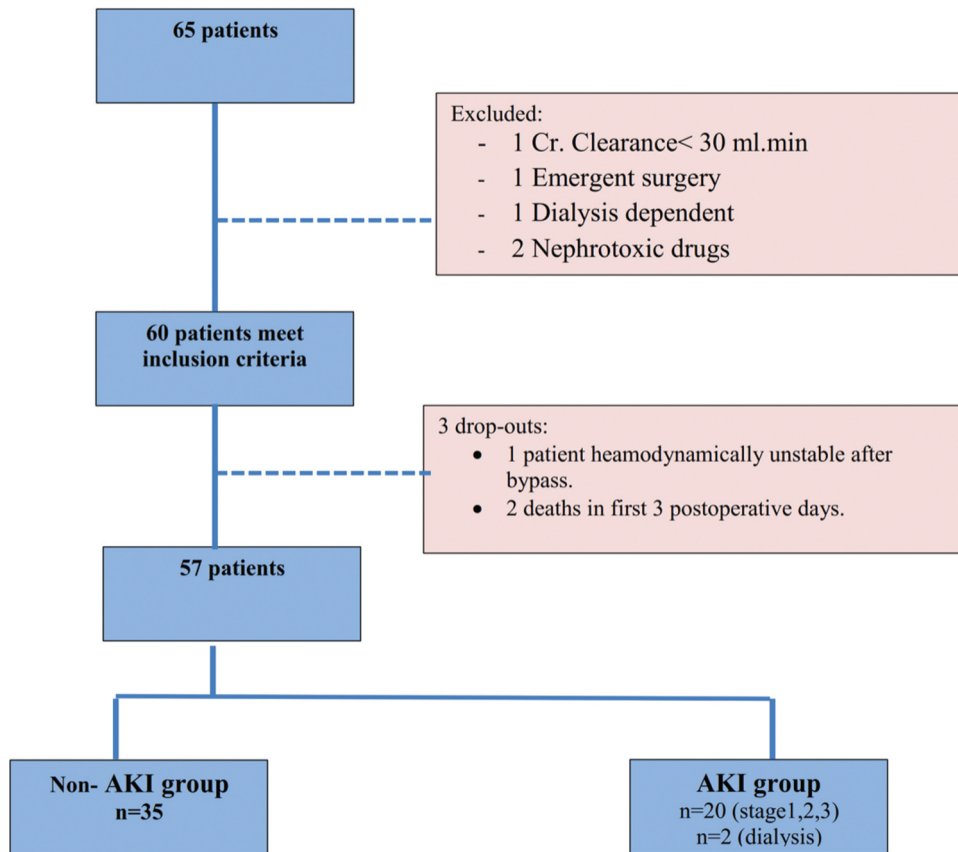


Figure 1. Flow chart of the patients.

morbidities, AKI patients showed a significantly higher incidence of hypertension and peripheral vascular disease besides having a significantly lower preoperative (Cr.Cl).

The type of surgery was not related to AKI occurrence except for combined valve-CABG surgeries, in which AKI incidence was significantly higher. Additionally, the duration of anesthesia, surgery, bypass, and cross clamp time were significantly higher in the AKI group. The incidence of bleeding and RBC transfusion was significantly higher in the AKI group, as well. There was no significant difference in the dose of vasopressors and inotropes between the AKI and Non-AKI group. (Table 1)

Postoperatively, creatinine did not significantly increase in the AKI group until the second postoperative day and remained significantly higher on the third post-operative day. (Figure 2)

The mean uNGAL measurements at baseline were significantly higher in the AKI group. Postoperatively, the uNGAL further increased in a significant manner in subjects who subsequently developed AKI, with a 10-fold increase at 1 h and a 15-fold increase at the 6 h, before it declined to only twofold by the end of the first postoperative day. On the other hand, the Non-AKI

group showed a small increase in uNGAL at the first postoperative hour, which started to decline at 6 and 24 hours (Figure 3).

The ROC curves for uNGAL were generated and the AUCs were calculated. For 1 h uNGAL, sensitivity and specificity were 86.4 and 100 at a cutoff of >194.3 ng/ml, with an AUC of 0.888 for the prediction of AKI. For 6 h, the sensitivity and specificity of uNGAL were optimal, (95.5 and 97.1, respectively) at >67.1 ng/ml cutoff, with an AUC of 0.995 for the prediction of AKI. The accuracy of uNGAL was 94.8% and 96.5% for 1 h and 6 h uNGAL, respectively (Figure 4).

One and six hour uNGAL values were neither related to AKI severity nor dialysis-requirement.

As regards RRI, the values from the left and right kidneys were averaged because there was no significant difference between the left and right. No significant difference was found in preoperative RRI values. However, values of RRI significantly increased in AKI subjects at 1 and 6 h postoperatively (Figure 5).

The ROC curves for RRI were generated, and the AUCs calculated. For 1 h RRI, sensitivity and specificity were 81.8 and 100 at a 0.72 cutoff value, with

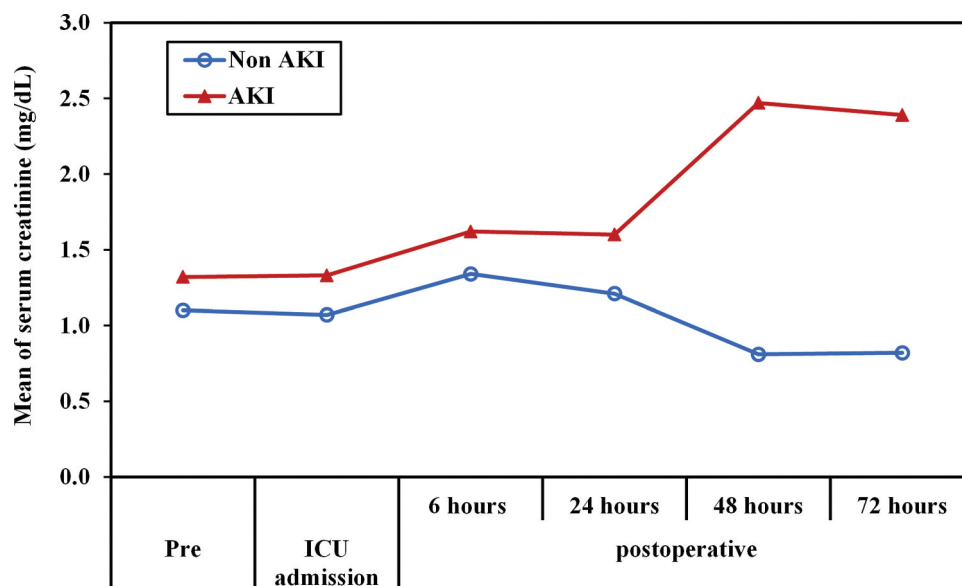
Table 1. Comparison between the two studied groups according to different parameters.

	Presented as	Non AKI (n = 35)	AKI (n = 22)	Test of Sig.	p
Age	Mean \pm SD.	55.51 \pm 10.48	64.0 \pm 10.47	t = 2.978*	0.004*
Sex					
Male	No. (%)	26 (61.9%)	16 (38.09%)	$\chi^2 =$ 0.017	0.897
Female		9 (60.0%)	6 (40.0%)		
Type of surgery					
CABG	No. (%)	21 (70.0%)	9 (30.0%)	$\chi^2 = 1.975$ $\chi^2 = 0.004$ $\chi^2 = 5.663^*$	FE p = 0.184 FE p = 1.000 FE p = 0.027*
Valve		13 (61.9%)	8 (38.0%)		
Comb		1 (16.6%)	5 (83.33%)		
Risk factor for AKI					
DM					
Non-diabetic	No. (%)	5 (14.3%)	0 (0.0%)	$\chi^2 =$ 5.047	0.071
Non-insulin dependent		23 (65.7%)	13 (59.1%)		
Insulin dependent		7 (20.0%)	9 (40.9%)		
Hypertension				$\chi^2 = 4.628^*$	0.031*
Peripheral vascular disease				$\chi^2 = 5.663^*$	FE p = 0.027*
Cr. Clearance	Median (Min. – Max.)	89.30(40.70–188.2)	97.40(44.80–165.6)	U = 231.0*	0.012*
Recent angiography	No. (%)	0 (0.0%)	6 (27.3%)	$\chi^2 = 10.668^*$ $\chi^2 = 5.047^*$	FE p = 0.002* FE p = 0.035*
NSAID		3 (8.6%)	7 (31.8%)		
ACE/ ARBS		13 (37.1%)	14 (63.6%)	$\chi^2 = 3.803$	0.062
EF					
>50%		28 (80.0%)	9 (40.9%)	$\chi^2 = 9.063^*$	0.003*
35–50%		7 (20.0%)	13 (59.1%)		
Cross clamp time	Median (Min. – Max.)	80.0(45.0–165.0)	92.5(45.0–139.0)	U = 211.50*	0.004*
RBCs transfusion	No. (%)	8 (22.9%)	14 (63.6%)	$\chi^2 = 9.479^*$	0.002*
Intropes/vasopressor					
Adrenaline dose (μg/kg/min)	Mean \pm SD.	0.05 \pm 0.02	0.06 \pm .02	t = 1.327	0.191
Dopamine dose (μg/kg/min)	Mean \pm SD.	5.20 \pm 1.45	4.77 \pm 1.74	t = 1.001	0.321
Outcome					
ICU days	Median (Min. – Max.)	4.0(0.0–5.0)	7.0(3.0–27.0)	U = 37.0*	<0.001*
Dialysis	No. (%)	0 (0.0%)	2 (9.1%)	$\chi^2 = 3.298$	FE p = 0.145

 χ^2 : Chi square test FE: Fisher Exact

t: Student t-test U: Mann Whitney test

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$ **Figure 2.** Comparison between the two studied groups according to serum creatinine.

an AUC of 0.991 for the prediction of AKI. For 6 h RRI, sensitivity and specificity were optimal (86.4 and 100, respectively) at a 0.71 cutoff value, with an AUC of 0.995 for the prediction of AKI. RRI values were not related to AKI severity but were significantly related to dialysis-requiring cases. (Figure 6)

5. Discussion

Many studies have investigated the utility of uNGAL and RRI to early predict CSA-AKI [7]. However, the optimal measuring time and cut-off value are still questionable [8]. This observational

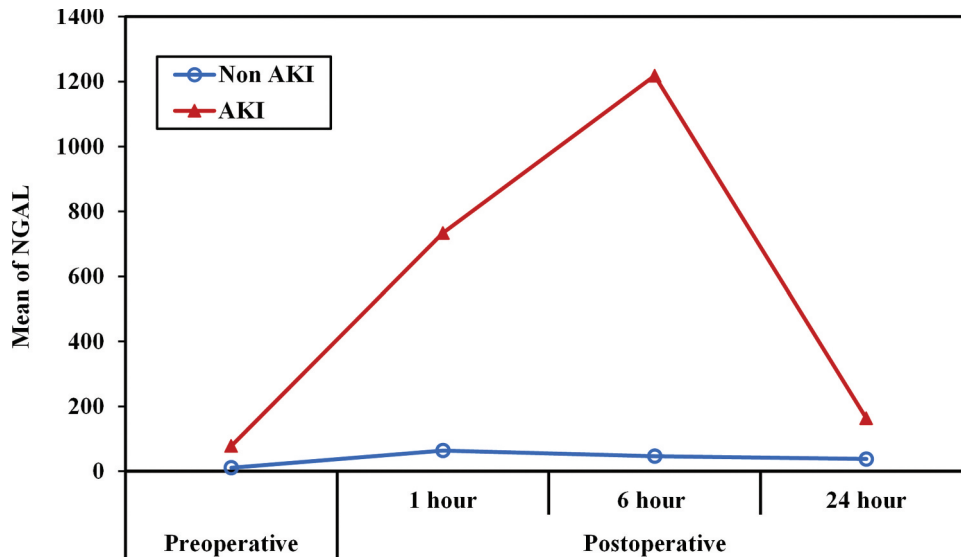


Figure 3. Comparison between the two studied groups according to NGAL.

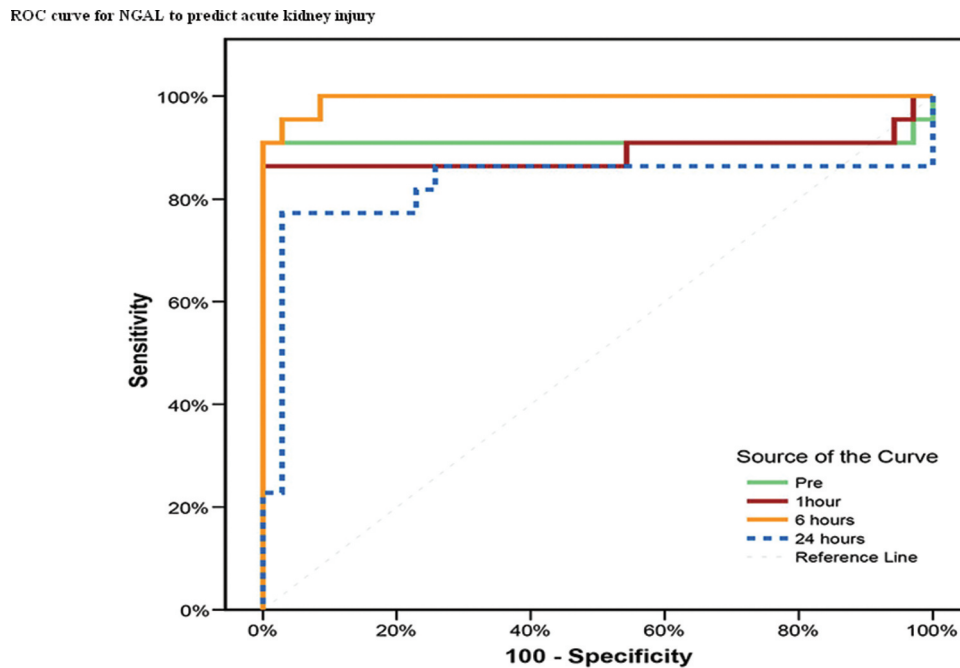


Figure 4. ROC curve for NGAL to predict acute kidney injury.

study assessed uNGAL and RRI to identify their accuracy and cut-off values at the first and sixth postoperative hours.

In the current study, the AKI incidence was 38.5%, of whom 3.5% required dialysis. This incidence was higher than the results of the multicenter studies, in which the incidence ranged between 3 and 30% with 3% of cases requiring dialysis [1]. Our higher incidence might be explained by the higher mean age of our studied population. Moreover, the preoperative Cr.Cl was significantly lower in the AKI group, making them more predisposed to develop postoperative AKI. Additionally, combined valve-CABG surgeries represented 10.5% of our cases, which consequently led to

longer durations of surgery, cross clamp and bypass time as well as a higher incidence of bleeding and packed RBCs transfusion. All the previously mentioned factors increased the hazard of AKI and made it more apparent in our study.

Although our randomly studied population had significantly higher preoperative s.Cr in the AKI group, the postoperative levels did not further increase on the first day. On the second postoperative day, the significant rise in s.Cr started to occur in the AKI group and remained significantly higher till the third day (Table 2).

Similarly, the increase in s.Cr was delayed 2 to 3 days after CPB in Bennet et al and Mishra et al studies; although they included patients with homogenous

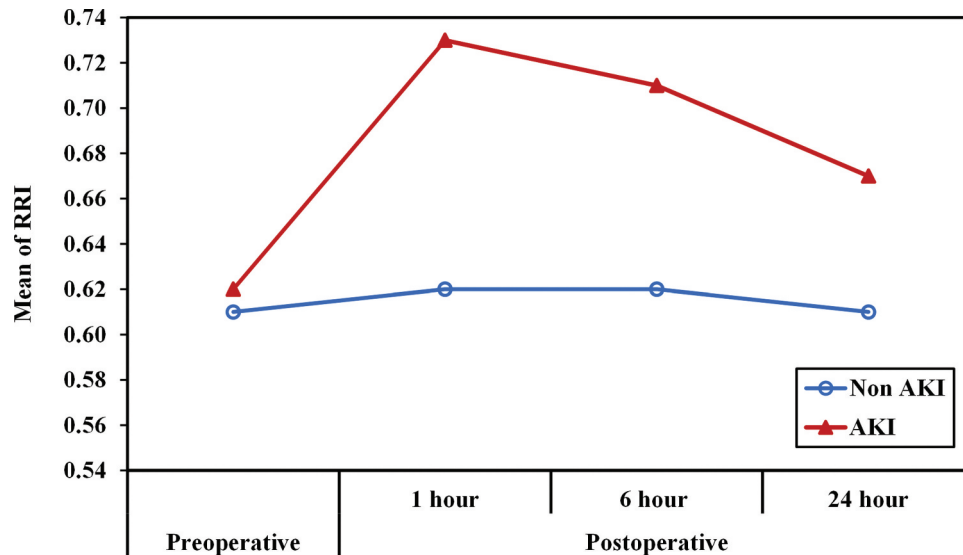


Figure 5. Comparison between the two studied groups according to RRI.

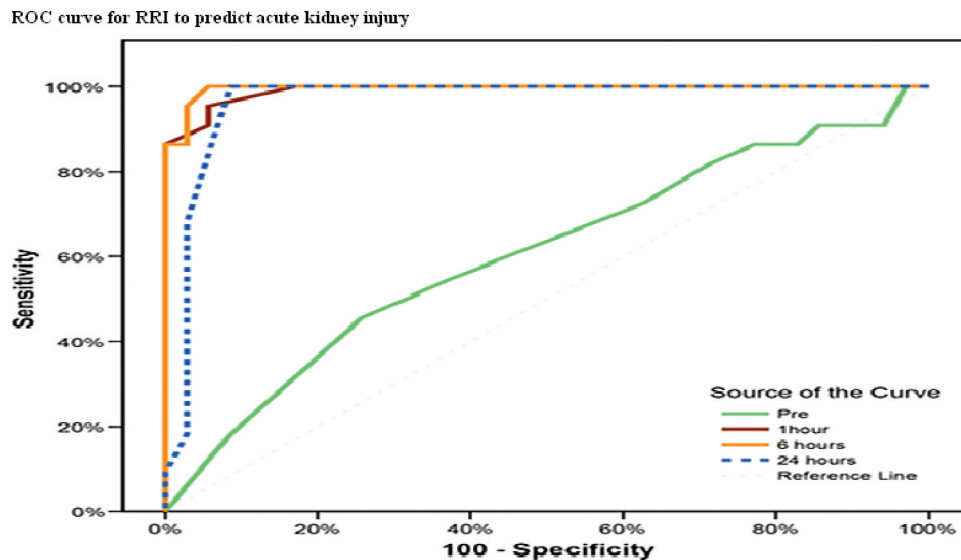


Figure 6. ROC curve for RRI to predict acute kidney injury.

preoperative creatinine clearance [9,10]. On the other hand, Bossard et al. showed that s.Cr peaked significantly in AKI patients during the first postoperative day [11]. This early rise of creatinine can be a result of patients' demographics that showed a significantly higher mean age, a higher incidence of arteritis, and EuroScore. Moreover, Bossards' results showed significantly higher diuretic consumption, blood transfusion, and very long bypass durations in patients that developed AKI.

As regard uNGAL, the current study concluded that it is an accurate, sensitive and specific marker of CSA-AKI. Although our preoperative mean uNAGL values were significantly higher in AKI, we found that uNGAL is still capable of predicting occurrence of AKI as early as 1 h postoperatively by 10-fold increase; however, the best accuracy is achieved 6 h postoperatively with

15-fold increase (Table 2). Our results failed to prove that uNGAL level is a discriminator of severity or dialysis requirement.

The observation that our AKI group had already had a significantly higher preoperative uNGAL could be a result of doing diagnostic coronary angiography for 6 AKI patients in the preoperative period. Additionally, seven AKI patients used NSAID regularly in the preoperative period.

Our findings were parallel to Mishra et al. and Sanker et al. results [10,12], who confirmed that uNGAL is an excellent early predictor of AKI with high sensitivity and specificity. However, they did not investigate the relationship between uNGAL values and AKI severity.

In contrast to our results, Bennet et al. could relate uNGAL's level to AKI severity. This is perhaps because Bennet's has included children with no previous

Table 2. Comparison between the two studied groups according to serum creatinine, uNGAL and RRI.

	Non AKI (n = 35)	AKI (n = 22)	P
Serum creatinine (mg/dL)	Mean ± SD	Mean ± SD	
Preoperative	1.10 ± 0.23	1.32 ± 0.37	0.010*
1 hour postoperative	1.07 ± 0.22	1.33 ± 0.49	0.065
6 hours postoperative	1.34 ± 0.20	1.62 ± 0.62	0.067
24 hours postoperative	1.21 ± 0.36	1.60 ± 0.83	0.051
48 hours postoperative	0.81 ± 0.22	2.47 ± 1.02	<0.001*
72 hours postoperative	0.82 ± 0.22	2.39 ± 1.0	<0.001*
uNGAL (ng/ml)	Mean ± SD	Mean ± SD	
Preoperative	11.07 ± 1.87	77.98 ± 46.04	<0.001*
1 hour postoperative	63.96 ± 35.45	733.41 ± 295.83	<0.001*
6 hour postoperative	46.60 ± 37.98	1218.05 ± 409.72	<0.001*
24 hour postoperative	37.79 ± 29.53	163.15 ± 113.30	<0.001*
RRI	Mean ± SD	Mean ± SD	
Preoperative	0.61 ± 0.03	0.62 ± 0.03	0.255
1 hour postoperative	0.62 ± 0.04	0.73 ± 0.03	<0.001*
6 hour postoperative	0.62 ± 0.03	0.71 ± 0.02	<0.001*
24 hour postoperative	0.61 ± 0.03	0.67 ± 0.02	<0.001*

SD: Standard deviation

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

comorbidities and had homogenous preoperative uNGAL values between the AKI and Non-AKI groups [9].

Most previous studies that tested RRI as a predictor of AKI were performed on ICU patients with shock and sepsis [13–15]. However, some studies have recently conducted to determine whether RRI would act similarly in the postoperative setting of cardiac surgery.

The current study found that RRI is an early predictor of AKI. RRI appeared to have the capability to predict severe cases requiring dialysis.

In agreement with our results, a systemic meta-analysis conducted by Bellos et al. concluded that RRI is a useful marker with fair performance in the prediction of postoperative acute kidney injury after major surgery [16].

Similarly, Qin et al. proved that RRI can accurately predict AKI, with maximal RRI reached at 6 h postoperatively [17]. Furthermore, Bossard found that immediate RRI not only predicted AKI occurrence, but also anticipated its severity [11]. This is perhaps because they had a larger sample size, studied an older age group and had more severe cases that required dialysis, while we had only two cases, which is a very small number to make significant percentage.

On the other hand, Regolisti et al., who compared the value of measuring RRI by transoesophageal Doppler versus transparietal Doppler, found that immediate post-operative RRI had limited predictive performance value for determining which patients would develop AKI. However, Regolisti's study showed a higher mean age and defined the occurrence of AKI according to KIDGO criteria, which relies on sCr as a sole agent to define AKI [18].

6. Conclusion

Urinary neutrophil gelatinase-associated lipocalin (NGAL) and Renal Resistive Index (RRI) are helpful to early predict (AKI) after cardiopulmonary bypass (CPB).

7. Limitations

This study was limited by small sample size, small number of severe renal injury and short follow-up duration.

Abbreviations

AKI: Acute Kidney Injury; CSA-AKI: Cardiac Surgery Associated AKI; uNGAL: Urinary Neutrophil Gelatinase-Associated Lipocalin; RRI: Renal Resistive Index; CBP: Cardiopulmonary Bypass; s.Cr: Serum Creatinine; Cr.Cl: Creatinine Clearance; AUC: Area under the curve; ROC: Conventional receiver-operating characteristic curve.

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Disclosure statement

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