

Hypoalbuminaemia and Blood Urea Nitrogen/Creatinine Ratio as Early Markers of Acute Kidney Injury in Postoperative Cardiac Patients- A Prospective Study

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ABSTRACT

Introduction: Postoperative Acute Kidney Injury (AKI) occurs as the consequence of intraoperative risk factors associated with cardiac surgery. Biochemical monitoring of patients undergoing cardiac surgery enables early detection of AKI. Serum albumin and Blood Urea Nitrogen (BUN): creatinine ratio serves as a simple tool for identifying increased risk of AKI.

Aim: To determine serum albumin and the BUN: creatinine ratio as a predictive tool for AKI risk in patients undergoing cardiac surgery.

Materials and Methods: The present prospective observational study was conducted at Cardio Thoracic super specialty unit of SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India, between July 2020 to March 2021. A total of 30 patients undergoing coronary artery bypass grafting in the age group between 40 to 70 years with normal serum creatinine levels were included. Preoperative and postoperative parameters such as urea, creatinine, total protein, serum albumin, BUN: creatinine ratio and estimated Glomerular Filtration Rate (eGFR) were calculated. Data were analysed statistically by Analysis

of Variance (ANOVA) and Student's t-test. A p-value <0.05 was considered statistically significant.

Results: In present study, 24 (80%) were males and 6 (20%) were females. The mean age of the male and female patients was 57±0.72 years and 55.3±0.81 years, respectively. Mean BUN: creatinine ratio was decreased on day 1 (16±0.78) and day 3 (8.19±0.87) postoperative phase as compared to preoperative day (14±0.63). Compared with preoperative albumin (3.65±0.1 g/dL), hypoalbuminaemia was found on first and third postoperative day, (3.07±0.05 and 3.04±0.05 g/dL) respectively. With Receiver Operating Characteristic (ROC) curve analysis, Area Under the Curve (AUC) for albumin and BUN: creatinine ratio was 0.72 and 0.67 which revealed the diagnostic sensitivity of 86% and 78% respectively. On day 3 postoperative eGFR fell by 12.5%, indicating a danger of kidney injury.

Conclusion: Hypoalbuminaemia and BUN: Creatinine ratio are simple biochemical tools to predict AKI in postoperative phase after cardiac surgery.

Keywords: Biochemical tools, Coronary artery bypass grafting, Renal injury

INTRODUCTION

Acute Kidney Injury (AKI) is defined as an abrupt decrease in kidney function, which encompasses both structural damage and loss of function [1]. AKI results as a consequence of sepsis, ischaemia, nephrotoxicity that challenges clinical decision. AKI is frequently asymptomatic and diagnosed until hospitalised patients' biochemical monitoring reveals an increase in blood urea and serum creatinine values [2].

In India, the incidence of AKI was 17.3 cases among 1000 persons. The prevalence of AKI in critically ill patients admitted in intensive care units with sepsis is more than 40% and the incidence of mortality is 15-60% [3]. According to the National Institute for Health and Care Excellence guidelines the criteria for assessing AKI in the patients during postoperative phase are (i) rise of serum creatinine of 0.29 mg/dL within 48 hours (ii) 25% fall in eGFR within 7 days [4]. Urine albumin creatinine excretion has been recommended a reliable marker for early detection of renal impairment and diffuse endothelial dysfunction and can be used to identify people who are at higher risk [5]. Any patients undergoing open heart surgery will have to stay in the intensive care unit after the cardiac surgery for 3 to 4 days and total length of stay in the hospital is approximately 7 to 10 days. It was observed that patients admitted for longer duration of stay have enhanced risk of AKI with associated complex renal outcome [6].

The main function of circulating albumin is to maintain the plasma oncotic pressure. The prime important function of albumin is to protect renal function by elevating oncotic pressure. In fact

continued renal blood perfusion favours the continuation of renal perfusion and facilitates maintaining the glomerular filtration [7]. The BUN/creatinine ratio is the ratio of two serum laboratory values, BUN and serum creatinine. Interpretation of BUN:creatinine reflects acute prerenal failure when BUN/Creatinine ratio > 20:1; and acute renal failure when BUN/creatinine ratio <20:1 [8]. Kidney's filtration rate called as GFR, shows how well the kidneys are filtering. Most of the studies were retrospective analysis of the data that had utilised albumin cut-off value of 4 g/dL to predict survival rate [9], ventilation support [10] and overall mortality [11]. In this research study, so as to predict AKI in postoperative phase, cut-off value of albumin levels and BUN:creatinine ratio was evaluated which are simple tool to identify the patients who need better postoperative care after cardiac surgery.

In this context, serum albumin levels and BUN:creatinine ratio were used as tools to predict the risk of early renal impairment in critically ill patients [12]. Thus simple available tool is the need of the hour for early prediction of renal AKI thereby therapeutic plan is initiated and risk or progression of AKI is monitored. The aim of present study was to evaluate the diagnostic performance of serum albumin and BUN:creatinine ratio as markers of AKI in patients undergoing cardiac surgery.

MATERIALS AND METHODS

The present prospective study was conducted at Cardio Thoracic super specialty unit of the SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India, from July 2020 to

March 2021. The study protocol was followed in accordance with the approval of the Institutional Ethics Committee (IEC) (IEC NO-1884/IEC/2019). The research protocol was described to the participants and the study commenced with the informed written consent.

Inclusion criteria: Patients aged between 40-70 years, admitted for Coronary artery Bypass Grafting and patients with serum creatinine value <1.3 mg/dL [13], with history of diabetes, hypertension or both were included.

Exclusion criteria: Patients with chronic renal failure or serum creatinine >1.3 mg/dL and liver diseases were excluded.

Sample size calculation: Sample size was calculated based on the albumin levels in AKI (3.6; 0.47) g/dL and non AKI patients (4.1; 0.48 g/dL) from previous study [14].

$$(Z_{1-\alpha/2} + Z_{1-\beta})^2 (SD1 + SD2)^2 / (m1 - m2)^2$$

Total 30 participants were considered by the above formula. Participants were recruited by convenient sampling technique.

Data collection: Preoperative baseline details of all the patients such as age, Body Mass Index (BMI), and history of diabetes and hypertension, previous incidence of myocardial infarction and use of any medications were noted in the documentation sheet on the day of admission.

The routine biochemical investigations were done preoperatively followed by cardiac surgery then postoperatively on day 1 and day 3 (third postoperative day reflects the exact postoperative phase compared to first postoperative that reflects the stress after surgery) to monitor the patients. The data was recorded in Ms Excel sheet that included the day of admission, length of stay after surgery, complications and details of discharge.

Venous sample of 3 mL was collected in red color capped vacutainer tubes. The biochemical parameters: blood urea, serum creatinine, total protein, serum albumin, urine albumin creatinine ratio were analysed in the autoanalyser Beckman Coulter AU 480 using dedicated standardised reagents. Spot midstream urine sample was collected in 50 mL sterile urine container to analyse urine albumin creatinine ratio. [Table/Fig-1] shows biochemical test method with normal range in various parameters [15-18].

Parameters	Biochemical test method	Normal reference range
Blood urea [15]	Urease	17-43 mg/dL
BUN [15]	Calculation-urea/2.14	12-20 mg/dL
Creatinine [15]	Modified Jaffe's	Male: 0.9-1.3 mg/dL Female: 0.6-1.1 mg/dL
Albumin [15]	Bromocresol green	3.5-5.2 g/dL
BUN:Cr ratio [16]	Calculation-BUN divided by creatinine in mg/dL	20:1
Urine albumin creatinine ratio [17]	Urine albumin- Pyrogallol red Urine creatinine- Modified Jaffe's	<30 µg/mg of creatinine
eGFR mL/min [18]	Calculation-Cockcroft's formula (Cr Cl: (140-age)×weight (kg)×0.85 (if females)/(serum creatinine×72)	<60 ml/min have impaired renal function Male: 95-115 mL/min Female: 85-110 mL/min

[Table/Fig-1]: Biochemical test method and normal range for laboratory parameters.

The participants were categorised based on urine albumin creatinine ratio to assess the severity of renal dysfunction low <10 µg/mg of creatinine (n=5), medium >10 - <30 µg/mg of creatinine (n=9), high >30 µg/mg of creatinine (n=16). Also based on eGFR the participants were categorised as <60 mL and ≥60 mL/min of eGFR [18].

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) software version 25.0 was utilised for analysis of data. Student's t-test was used to compare the biochemical parameters between the groups. The data was expressed in mean and standard error of mean. ANOVA was utilised for comparison of the data between preoperative and

postoperative data. ROC curve analysis was done to determine the diagnostic performance of the analyte of interest.

RESULTS

Demographic data of 30 patients admitted for coronary artery bypass grafting revealed that 24 (80%) were males and 6 (20%) were females. The mean age of the male and female patients were 57±0.72 years and 55.3±0.81 years, respectively.

Duration of hospital stay was more than 10 days to 2 weeks in 23 (76.67%) participants whereas the duration of hospital stay was below 10 days in 5 (16.67%). Only 2 (6.66%) patients were admitted in the Cardiac intensive care unit for one month duration. Total 24 (80%) participants were diabetic, 2 (6.67) were hypertensive and 4 (13.33%) had both diabetes and hypertension [Table/Fig-2].

Variables	N (%)
Gender	
Male	24 (80)
Female	6 (20)
Age (years)	
41-50	7 (23.33)
51-60	14 (46.67)
61-70	9 (30)
Co-morbidities	
Diabetes	24 (80)
Hypertension	2 (6.67)
Both diabetes and hypertension	4 (13.33)
History of previous myocardial infarction	7 (23.33)
Duration of stay	
Below 10 days	5 (16.67)
Above 10 days-2 weeks	23 (76.67)
One month	2 (6.66)

[Table/Fig-2]: Demographic details of the cardiac patients admitted.

Preoperative BUN (11.83±0.03 mg/dL) was compared with first postoperative phase (14.36±0.06 mg/dL) and third postoperative phase (13.61±1.02 mg/dL), which was not significant statistically (p-value=0.112). Serum creatinine was found to be elevated on first (0.93±0.04 mg/dL) and third (1.63±0.04 mg/dL) postoperative day as compared to preoperative day (0.84±0.03 mg/dL) and this difference was statistically significant (p-value <0.001). BUN:Cr ratio levels decreased on postoperative day 3 (8.19±0.87), in comparison to preoperative day (14±0.63) and first postoperative day (16±0.78) and was found to be statistically significant (p-value <0.001). On comparison with baseline albumin (3.65±0.10 g/dL), third postoperative day albumin level was found to be decreased (3.04±0.05 g/dL) with p-value <0.0001 [Table/Fig-3].

Parameters	Preoperative	First post-operative	Third post-operative	F value	p-value
Blood urea (mg/dL)	25.33±1.67	30.7±2	29.13±2.18	2.25	0.111
BUN (mg/dL)	11.83±0.03	14.36±0.06	13.61±1.02	2.24	0.112
Creatinine (mg/dL)	0.84±0.03	0.93±0.04	1.63±0.04	47.8	<0.001**
BUN:Cr ratio	14±0.63	16±0.78	8.19±0.87	32.43	<0.001**
Albumin (g/dL)	3.65±0.10	3.07±0.05	3.04±0.05	25.179	<0.0001***
eGFR (mL/min)	95.8±5.24	81±4.78	89.8±6.95	50.5	<0.0001***
Urine ACR (µg/mg)	17.5±3.03	35.7±4.04	30.9±4.25	83.8	<0.0001***

[Table/Fig-3]: Comparison of laboratory parameters between preoperative, first and third postoperative period.
BUN: Blood urea nitrogen; BUN:Cr: Blood urea nitrogen/creatinine ratio; eGFR: estimated glomerular filtration rate; uACR: urine albumin creatinine ratio; ANOVA: Analysis-numerical data's are expressed as mean±SEM; *p-value <0.05 - significant
Significant; *Extremely significant

[Table/Fig-4] represents the analysis of biochemical parameters of third postoperative day between the severity categories of urine Albumin Creatinine Ratio (uACR). In the participants with high uACR level the albumin level was decreased (2.8 ± 0.06 g/dL) in comparison to medium (3.17 ± 0.04 g/dL) and low level of uACR (3.4 ± 0.06 g/dL) (p -value < 0.001). BUN:creatinine ratio was also found to be decreased (7.72 ± 0.9) in patients with high uACR level as compared to medium (16 ± 1.53) and low level of uACR (14.83 ± 2.68), p -value < 0.001 .

Parameter	Low (<10 ug/mg of creatinine) (n=5)	Medium (>10- <30 ug/mg of creatinine) (n=9)	High (>30 ug/mg of creatinine) (n=16)	F value	p-value
Blood urea (mg/dL)	21.48±5.1	29.74±4.7	32.39±6.2	6.39	0.014*
BUN (mg/dL)	10.04±3.9	13.9±1.49	15.14±1.32	9.16	<0.001***
Creatinine (mg/dL)	0.65±0.05	0.87±0.05	1.76±0.06	28.4	<0.001***
BUN:Cr ratio	14.83±2.68	16±1.53	7.72±0.9	37.2	<0.001***
Serum albumin g/dL	3.4±0.06	3.17±0.04	2.8±0.06	21.7	<0.001***
eGFR mL/min	93.2±8	85.54±6.6	66.64±7.2	38.78	<0.001***
uACR (µg/mg of creatinine)	5.17±0.63	16.6±1.05	132.6±58.1	7.974	<0.001**

[Table/Fig-4]: Comparison of BUN:Creatinine ratio and serum albumin on 3rd postoperative day between low, medium and high Albumin creatinine ratio. BUN: Blood urea nitrogen; BUN:Cr: Blood urea nitrogen/creatinine ratio; eGFR: estimated glomerular filtration rate by Cockcroft's formula; uACR: urine albumin creatinine ratio ANOVA: Numerical data's are expressed as mean±SEM; * p -value < 0.05 - significant **Significant; ***Extremely significant; Third postoperative day reflects the exact postoperative phase compared to first postoperative that reflects the stress after surgery

Serum albumin level was decreased (3.04 ± 0.05 g/dL) in the participants with eGFR < 60 mL/min in comparison to patients with eGFR ≥ 60 (3.65 ± 0.2 g/dL) (p -value < 0.0001). uACR was found to be elevated (30.9 ± 4.25 g/dL) in the participants with eGFR < 60 mL/min, as compared to patients with eGFR ≥ 60 (17.5 ± 3.03) (p -value=0.006) [Table/Fig-5].

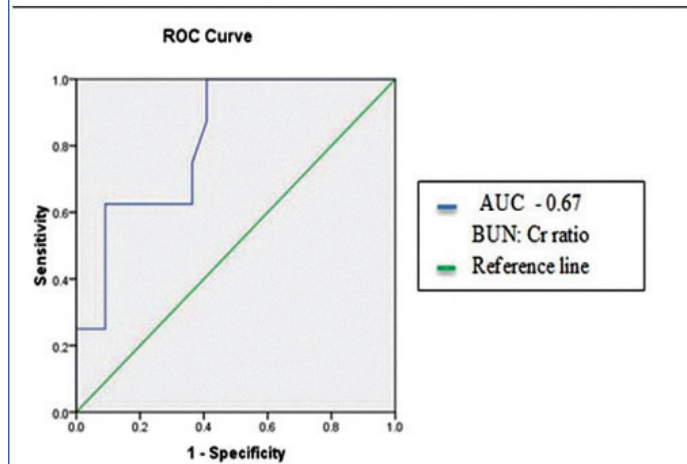
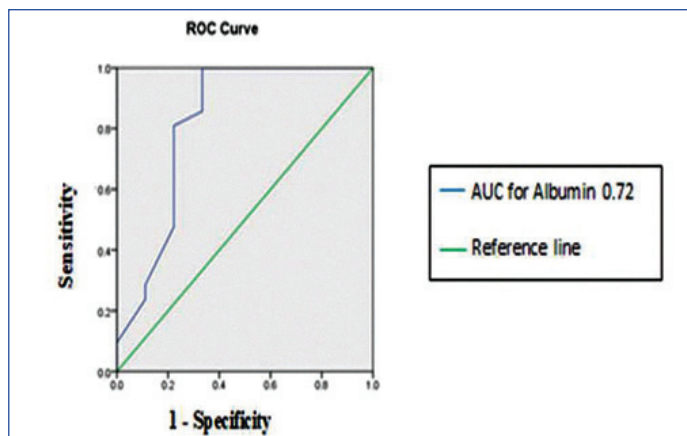
Parameters	eGFR ≥ 60 mL/min	eGFR < 60 mL/min	t value	p-value
Blood urea (mg/dL)	28.4±1.67	31.3±1.98	3.132	0.03*
BUN (mg/dL)	11.08±0.73	14.18±0.8	15.67	0.0001**
Creatinine (mg/dL)	1.60±0.02	1.65±0.02	6.07	0.0001***
BUN:Cr ratio	16.42±3.17	8.1±3.09	33.67	<0.0001***
Serum Albumin (g/dL)	3.65±0.2	3.04±0.05	5.39	<0.0001***
Urine ACR (µg/mg of creatinine)	17.5±3.03	30.9±4.25	-2.57	0.006*

[Table/Fig-5]: Receiver operating characteristics curve analysis of Albumin and BUN: Creatinine ratio with eGFR. * p -value < 0.05 - significant; **Significant; ***Extremely significant

Further diagnostic performance revealed at a cut-off value for albumin of 2.85 g/dL with the area under of curve as 0.72 [Table/Fig-6] had a diagnostic sensitivity of 86%. Whereas BUN: Creatinine ratio at a cut-off value of 12.5 revealed diagnostic sensitivity of 78% [Table/Fig-7].

DISCUSSION

Decreased concentration of serum albumin and BUN:Creatinine ratio have diagnostic importance to identify individuals with AKI risk in cardiac surgery patients. AKI is characterised by abrupt decline in kidney function over a period of hours to days irrespective of the underlying aetiology [19]. Albuminuria is considered as an ideal parameter to assess kidney function expressed as urine albumin creatinine ratio. Infact it is used to monitor the damage caused to renal tubulo interstitial tissue. There are research studies in concordance with this work in support to preoperative hypoalbuminaemia as diagnostic tool in cardiac patients to develop AKI and increased complication rate [20]. The need of the hour is to provide timely and



[Table/Fig-6]: Comparison of Albumin and UACR on day 3 postoperative phase with more than and less than 60 ml/min of eGFR. eGFR-estimated GFR by Cockcroft's formula; uACR (µg/mg of cre)-urine Albumin creatinine ratio in the units of microgram per mg of creatinine, BUN:Cr: Blood urea nitrogen/creatinine ratio Students' t test: Numerical data's are expressed as mean±SEM * p -value < 0.05 - significant; NS: Not significant; **Significant; ***Extremely significant

Markers	Cut-off value	Diagnostic sensitivity (%)	Diagnostic specificity (%)	Area under curve
Serum albumin (g/dL)	2.85	86%	67%	0.72**
BUN : Cr ratio	12.5	78%	60%	0.67**
Receiver's operating characteristics	BUN: Cr - Blood urea nitrogen/creatinine ratio AUC-Area Under Receiver's operating characteristic curve. AUC: (0.9-1.0: very good) (0.8-0.9: good) (0.7-0.8: fair) (0.6-0.7: poor) < 0.5 -no discrimination			

[Table/Fig-7]: Diagnostic performance with ROC analysis.

reliable result that enables potential early interventions to overcome AKI following cardiac surgery.

One of the common postoperative complications is AKI that occurs as the individual is exposed to risk factors during intraoperative period. The prognosis of the patients is determined by the successful follow-up of the patient after cardiac surgery. Patient with AKI are more prone to develop kidney disease and is considered as an adverse outcome after cardiac surgery [21].

This study is a unique prospective study that evaluated BUN:Creatinine ratio and serum albumin as predictor tool of acute kidney injury. This prospective study evaluated serum albumin, BUN: Creatinine ratio, urine ACR and eGFR during (based on Cockcroft's formula) preoperative and postoperative phase in cardiac patients. As the duration of stay of the participants was prolonged especially in the intensive care unit had presented with lowered serum albumin and elevated urine albumin creatinine excretion. The statement is in concordance with the fact that longer hospital stay would increase the risk of AKI and worsened short-term mortality [22]. Most of the diabetic patients got admitted for coronary artery bypass grafting and diabetic patients with hypoalbuminaemia have increased risk to develop postoperative acute kidney injury, thus preoperative serum albumin is an important determinant of morbidity and mortality [23].

Present study evaluated the benefit of the routine biochemical analytes serum albumin, BUN: creatinine ratio to assess the functioning of kidney and estimate GFR. These simple parameters are identified as predictors of AKI. The individuals who have undergone cardiac surgery, the serum albumin levels were found to be lowered on first and third postoperative period.

Plasma proteins have a vital biological function in maintaining the plasma oncotic pressure. Especially in cardiac patients albumin maintains the renal perfusion and rate of glomerular filtration. In a research study conducted during intra-operated patients with albumin infusion undergoing coronary artery bypass grafting found lowered incidence (13.7%) of AKI in patients compared to patients without albumin infusion (25.7%) [24].

Researcher Findik O et al., revealed that diabetic patients with decreased serum albumin levels <3.5 g/dL is considered as an independent risk factor of AKI after isolated Coronary artery bypass grafting [25]. In another study, proteinuria was observed in postoperative period as a result of increased vascular resistance in the microvascular network and decreased coronary flow reserve [26]. Surgical stress was quantitated in a study with serum albumin levels of 3.38 g/dL were correlated with length of stay and postoperative complications. Thus decrease in serum albumin concentration reflects the magnitude of systemic inflammatory response to surgery [27].

It is directly apparent that decreased albumin concentration with increased urine albumin creatinine ratio by 50.9% in the patients who had eGFR rate <60 mL/min on first postoperative day and also on third postoperative period. Urea is the nitrogen containing compound formed in the liver and eliminated by the kidneys. BUN values are elevated in prerenal causes with BUN: creatinine ratio close to 30:1; whereas in renal diseases it is close to 10:1. The diagnostic tool BUN: Creatinine ratio differentiates prerenal and intrinsic renal damage [28].

In the current study BUN:creatinine ratio was decreased in the individuals after cardiac surgery. BUN:creatinine ratio aids to differentiate the aetiology of AKI that directs either prerenal or intrinsic renal damage. It is one of the diagnostic tool for the emergency medicine physician, as studied in this research work was found to be decreased in the individuals with AKI which points to true postoperative AKI.

In a multicentre cohort study conducted in critically ill patients with AKI, the diagnostic performance of fractional excretion of urea was found to be 0.59 with sensitivity of 63% and specificity of 54% with no statistical significance [29]. As a result of impaired proximal tubular function the filtered albumin is not reabsorbed and leads to higher levels of excretion of proteins after the episode of AKI as reflected by lowered glomerular filtration rate [30]. The severity of AKI is related to decrease in estimated glomerular filtration rate which determines the need of dialysis as supported by Atherosclerosis Risk in Community (ARIC) study [31].

ROC curve analysis against serum albumin levels with GFR to determine the risk of AKI revealed that at the cut-off value of 2.85 g/dL the sensitivity, specificity and area under curve for prediction of AKI was found with high significance of 86%, 67% and 0.72, respectively with p-value of <0.001. This current study is in concordance with the retrospective study, where preoperative albumin levels <3.75 g/dL were associated with postoperative stage 3 AKI and hypoalbuminaemia revealed statistical association with risk of AKI [32]. The findings in the current study well matched with a retrospective single centered study that demonstrated early postoperative albumin cut-off of 2.9 g/dL as an independent risk factor for AKI [33].

BUN: Creatinine ratio at the cut-off value of 12.5 is the predictor of AKI with sensitivity and specificity of 78% and 60% respectively, p-value <0.001. Lee EH et al., findings are in concordance with

the fact that hypoalbuminaemia and BUN: Creatinine ratio are ideal tools that predicts the risk of renal dysfunction as revealed in the patients during postoperative phase [34]. In contrast to this study, the retrospective study conducted in patients admitted in the Emergency Department by Manoeuvrier G et al., the BUN:creatinine ratio had area under curve of 0.55 and found no statistical difference [35]. Thus it was not considered as a reliable parameter to differentiate prerenal AKI from intrinsic AKI.

The current study points to the evaluation of the albumin levels that reflects the individuals at risk for AKI and analysis of BUN:creatinine ratio can be considered as a diagnostic tool to determine the prerenal or renal cause of AKI.

Limitation(s)

This research work had certain limitations such as intraoperative analysis of the analytes was not possible, likewise could not carry out follow-up investigations after discharge and advanced biomarkers of AKI were not utilised considering the fact that authors should be able identify the risk in postoperative cardiac patients with the best available simple tools.

CONCLUSION(S)

Preoperative and postoperative hypoalbuminaemia is an independent determinant for development of AKI in patient undergoing cardiac surgery. Thus the risk of AKI during postoperative phase can be identified with monitoring of simple diagnostic analytes such as BUN:creatinine ratio and albumin levels. This study can be further hypothesised with urinary markers and determine the progress of AKI thereby approach to prevention and treatment can be opted.

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