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Procalcitonin as a Predictor of Acute Kidney Injury Following Cardiopulmonary Bypass

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Abstract **Original Research Article**

Background: Renal dysfunction following cardiac surgery involving cardiopulmonary bypass is associated with considerable morbidity and mortality. Procalcitonin has demonstrated effectiveness as a biomarker for guiding the initiation and duration of antibiotic therapy in patients admitted to intensive care units. This study aimed to assess procalcitonin as a predictor of acute kidney injury following cardiopulmonary bypass. ***Methods:*** This prospective observational study was conducted at the Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2021 to December 2023. A total of 40 patients who underwent elective cardiopulmonary bypass surgery were enrolled purposively. Data were analyzed using SPSS version 23.0. ***Results:*** Postoperatively, 37.5% of patients experienced acute kidney injury (AKI), with 86.7% classified as stage 1 and 13.3% as stage 2 AKI. A significant association was observed between the development of AKI and elevated postoperative procalcitonin levels ($p < 0.05$), indicating that higher procalcitonin levels correlate with an increased risk of AKI. Receiver Operating Characteristic (ROC) analysis of procalcitonin levels for AKI diagnosis revealed an Area Under the Curve (AUC) of 0.860 (95% CI: 0.725–0.995). A procalcitonin cutoff value of ≥4 ng/ml demonstrated 80% sensitivity and 92% specificity. ***Conclusion:*** The increased serum procalcitonin levels on 1st post-operative day can predict acute kidney injury in patients undergoing cardiac surgery with cardiopulmonary bypass.

Keywords: Acute kidney injury, AKI, Cardiopulmonary bypass, Procalcitonin, Predictor, Renal dysfunction.

INTRODUCTION

Acute kidney injury (AKI) is a common and serious complication following cardiac surgery, affecting up to 30% of patients undergoing such procedures, with approximately 2% requiring dialysis [1]. Patients who develop AKI experience higher rates of morbidity and mortality compared to those with preserved renal function. Furthermore, AKI contributes to prolonged intensive care unit (ICU) and hospital stays, increased risk of infection, and higher healthcare costs. As a result, AKI is a critical complication closely associated with cardiac surgery utilizing cardiopulmonary bypass (CPB) [2]. CPB, a technique of extracorporeal circulation, provides circulatory and respiratory support while managing body temperature to enable cardiac and great vessel surgeries. The first successful use of CPB in human cardiac surgery was performed by John Gibbon in 1952 for the repair of an atrial septal defect. The safe execution of cardiopulmonary bypass (CPB) relies on a collaborative effort among the surgeon, perfusionist, and anesthesiologist. Significant advancements in cardiac surgery have been made possible through the development of CPB [3]. The pathogenesis of acute kidney injury (AKI) following CPB is highly complex and influenced by multiple factors [4]. CPB triggers a systemic inflammatory response that disrupts normal physiological processes. This inflammatory reaction, often referred to as the "whole-body inflammatory response," is associated with bleeding, thrombotic events, substantial fluid shifts, and activation of cellular and hormonal defense mechanisms [5]. Additionally, blood product transfusions directly contribute to systemic inflammation. Systemic inflammatory response syndrome (SIRS) following cardiac surgery appears to play a central role in the development of AKI and significantly impacts patient outcomes [6,7]. Cardiopulmonary bypass (CPB) triggers an inflammatory response, which is reflected in the alterations of acute-phase mediators. Procalcitonin, a 116-amino acid peptide primarily secreted by thyroid parafollicular cells as a precursor to calcitonin, plays a significant role in this context. During inflammatory responses, procalcitonin is synthesized in various organs, including the liver, lungs, kidneys, intestines, and numerous other tissues [8,9]. Its production is stimulated by gram-negative bacterial endotoxins or proinflammatory cytokines. Notably, in severe bacterial infections and sepsis, plasma procalcitonin levels, predominantly derived from human peripheral blood mononuclear cells and regulated by bacterial lipopolysaccharides and sepsis-related cytokines, can surge up to 10,000-fold, ranging from 1 to 1000 ng/mL [10]. The kinetics of procalcitonin reveal a peak concentration of approximately 12–16 hours following the initial stimulus, with a half-life of 20–24 hours [11]. Procalcitonin has been successfully used as guidance for the initiation and duration of antibiotic therapy in patients with infections and to discontinue antibiotic therapy in intensive care unit (ICU) patients, being able to reduce antibiotic use as compared with standard therapy. However, the value of procalcitonin assessment in this situation is not clear. Renal dysfunction decreases procalcitonin elimination, and some studies observed no variation or just a small increase of procalcitonin plasma levels in patients with AKI. A more recent study has shown a marked increase in procalcitonin in 67 patients with postoperative renal dysfunction, either with or without infection [12].

METHODOLOGY

This prospective observational study was conducted in the Department of Cardiac Surgery at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from January 2021 to December 2023. The study included 40 patients who underwent elective cardiac surgery with cardiopulmonary bypass (CPB). Inclusion criteria encompassed patients scheduled for elective cardiac surgery requiring CPB. Conversely, the exclusion criteria ruled out those undergoing planned off-pump surgery, urgent cardiac procedures, redo surgeries, or patients with a history of prior cardiac surgery. Additional exclusions included patients with cardiac failure during preoperative evaluation, a left ventricular ejection fraction of <30% preoperatively, known bleeding disorders, hepatic impairment, impaired renal function at admission (indicative of acute kidney injury), or those unwilling to participate. Data on clinical profiles and demographic characteristics were collected. Serum creatinine and procalcitonin levels were measured one day before surgery and on the first postoperative day. Serum creatinine was reassessed on the third postoperative day. Postoperative monitoring of all patients was conducted in the intensive care unit (ICU). Ethical approval for the study was obtained from the relevant hospital committee, and data analysis was performed using SPSS version 23.0. p-value, >0.05 was considered not to be significant.

RESULT

The study revealed that 32.5% of patients were aged between 53 and 63 years, followed by 30% aged 42 to 52 years, 25% aged 64 to 74 years, 7.5% aged 31 to 41 years, and only 5% aged between 20 and 30 years. The mean age of the participants was 55.17 ± 10.50 years. Among the study population, 65% were male, while 35% were female. These differences were not statistically significant. It showed that preoperatively mean PCT was 0.43±0.34 ng/ml and mean S. Creatinine was 1.2±0.08 mg/dl. The findings were statistically not significant (p>0.05). Among 40 patients, 37.5% developed AKI, 5% developed pneumonia, 5% had wound infection and 2.5% patient died. Among those who developed AKI, 86.7% had stage 1 of AKI, 13.3% had stage 2 and no patient developed stage 3 AKI. As the distribution of post-operative variables in the study population, it was observed that AKI was significantly associated with 1st post-operative day high procalcitonin level. It was found that the ROC analysis of PCT level in the diagnosis of AKI found an AUC of 0.860 (95% CI 0.725- 0.995). A cut-off value of ≥ 4 ng/ml showed 80% sensitivity and 92% specificity. Among 15 cases of AKI, PCT (cut-off value ≥ 4 ng/ml) could detect 12 cases as AKI, and among 25 patients with no AKI, PCT level could detect 23 cases as no AKI. In the current study, a cut-off value of PCT ≥4 ng/ml showed sensitivity, specificity, PPV, NPV, and accuracy as 80%, 92%, 85.71%, 88.46%, and 87.50% accordingly.

Table 1: Demographic status of patients (N=40)

Variable	n	%	p-value
^{a}**Age (Years)**			
20-30 Yrs.	2	5	0.59^{ns}
31-41 Yrs.	3	7.5	0.321^{ns}
42-52 Yrs.	12	30	0.12^{ns}
53-63 Yrs.	13	32.5	0.02^{s}
64-74 Yrs.	10	25	0.086^{ns}
Mean ± SD	55.17±10.50		
^{b} **Gender**			
Male	26	65	0.249^{ns}
Female	14	35	0.42^{ns}

Table 2: Distribution of preoperative variables (N=40)

Variables	Mean ± SD	p-value
Serum Procalcitonin (ng/ml)	0.43±0.34	0.06^{ns}
Serum Creatinine (mg/dl)	1.2±0.08	0.559^{ns}

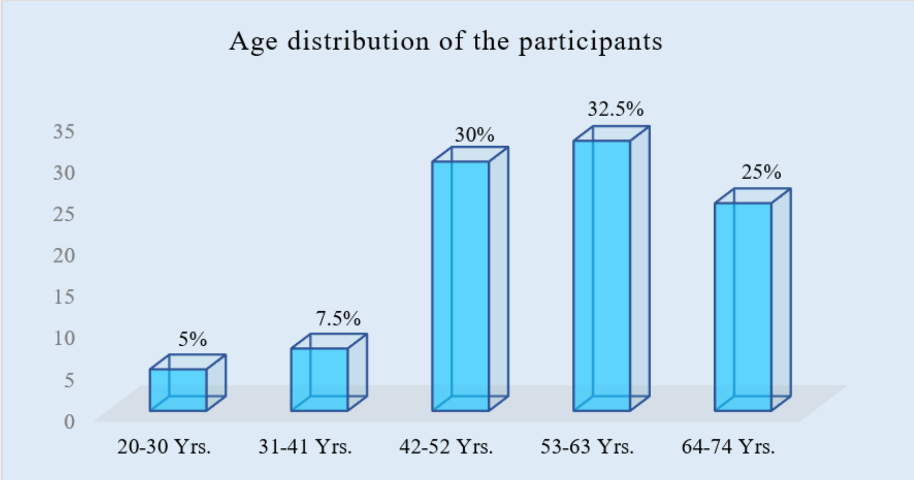

Figure I: Column chart showed age wise *patients* distribution (N=40)

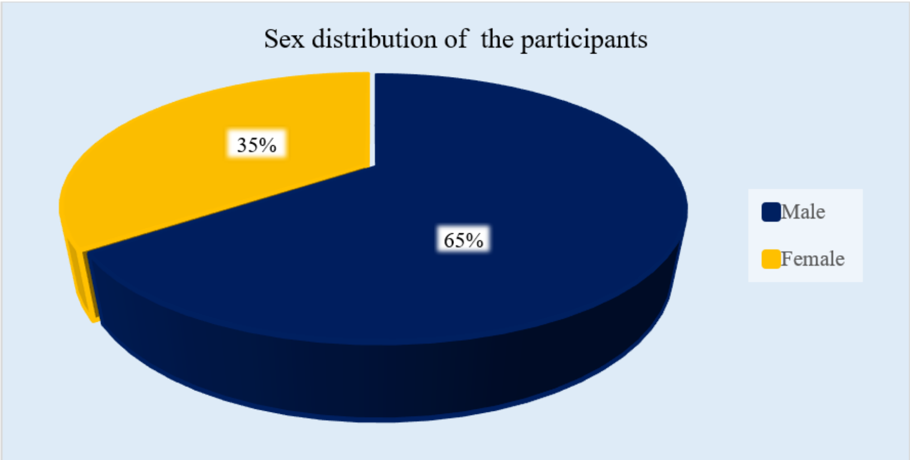

Figure II: Pie chart showed gender wise *patients* distribution (N=40)

Table 3: Distribution of AKI Stage (N=40)

Outcome	**n**	**%**
AKI	15	37.50%
Stage 1	13	86.70%
Stage 2	2	13.30%
Stage 3	0	0%

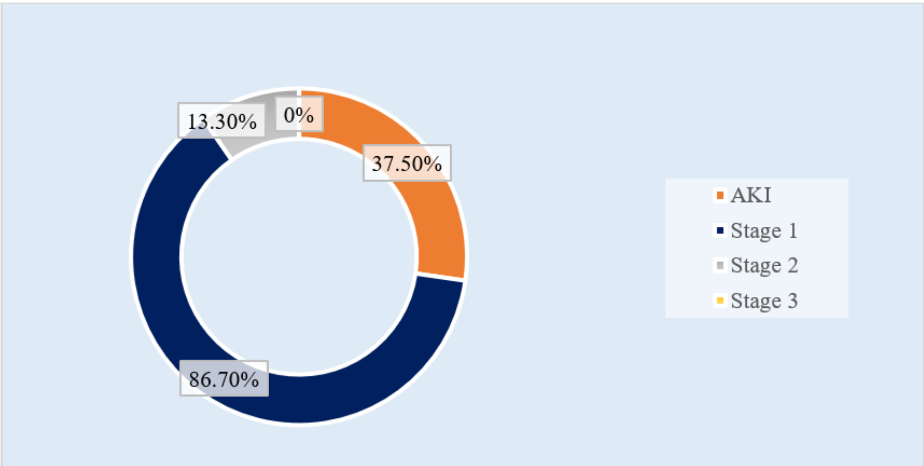

Figure III: Ring chart showed AKI stage wise *patients* distribution (N=40)

Table 4: Distribution of post-operative variables (N=40)

Variables	AKI (n=15)	Non-AKI (n=25)	P value
	Mean± SD		
[a] Procalcitonin			
1st POD	6.37 ± 2.08	2.16 ± 1.09	<0.01s
[b] S. Creatinine			
1st POD	2.3 ± 0.08	1.12 ± 0.16	0.028s
3rd POD	3.4 ± 0.017	1.04 ± 0.08	

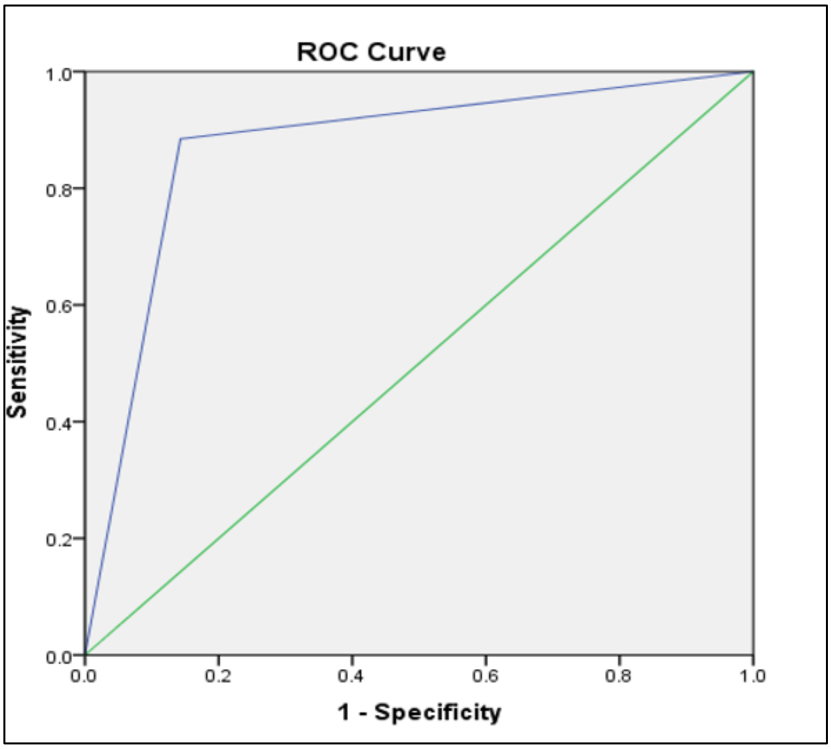

Figure IV: ROC curve analysis of PCT level in the diagnosis of AKI

Table 5: Cross-tabulation of AKI with PCT level based on derived cut-off value (N=40)

PCT level (ng/ml)	AKI	No AKI	Total
≥4	True Positive	False Positive	All patient (TP+FP)
	12	2	14
<4	False Negative	True Negative	All patients (FN+TN)
	3	23	26
All patients			
	with AKI (TP+FN)	without AKI (FP+TN)	40
	15	15	

Table 6: Diagnostic accuracy of PCT for detection of AKI (N=40)

Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
≥4 ng/ml	80	92	85.71	88.46	87.5

DISCUSSION

In our study, a total of 40 patients were included. Among them, 32.5% were aged between 53 and 63 years, 30% were between 42 and 52 years, 25% were between 64 and 74 years, 7.5% were between 31 and 41 years, and only 5% were between 20 and 30 years. The mean age of the patients was 55.17 ± 10.50 years (SD). This study found that the incidence of acute kidney injury (AKI) was more prevalent in older age groups (p=0.02). In a previous study, the mean age of 440 patients was 67 ± 11 years (SD) [13]. Another study by K. Chun *et al.*, reported a mean age of 60.3 ± 17.1 years (SD) among 790 patients [14]. All studies concluded that AKI incidence is higher in older individuals. In our study, 65% of the participants were male and 35% were female, with a male predominance, consistent with the demographic profile in this country. A similar finding was observed in a study by Heredia-Rodriguez *et al.*, [13]. In this study, the majority of patients (66.6%) were male. It was observed that 37.5% of the patients developed acute kidney injury (AKI) after cardiac surgery, which is consistent with a previous study by Chun *et al.*, where 33.7% of 790 patients developed AKI [14]. In another study by Kurtul *et al.*, AKI was observed in 96 patients (11.8%). Among the patients with AKI in this study, 86.7% had stage 1, 13.3% had stage 2, and no patients had stage 3 AKI. This is in contrast to a study by S. Schopka *et al.*, where 8.8% had stage 1, 9.8% had stage 2, and 6.1% had stage 3 AKI [15]. Additionally, this study found that the mean serum creatinine was 1.2 ± 0.08 mg/dl preoperatively, 1.6 ± 0.027 mg/dl on the first postoperative day, and 1.9 ± 0.9 mg/dl on the third postoperative day. A similar finding was observed in a previous study, where serum creatinine levels were significantly higher in patients with AKI after cardiac surgery on day 3 [13]. In this study, the mean procalcitonin (PCT) level was 0.43 ± 0.34 ng/ml preoperatively and increased to 3.74 ± 2.55 ng/ml on the first postoperative day. A previous study reported mean PCT levels on the first postoperative day ranging from 4.4 ± 4.8 ng/ml to 12.8 ± 17.3 ng/ml [16]. Another study by Loebe et al. observed PCT levels rising to 4.2 ± 16.3 ng/ml (ranging from 0.02 to 266.97 ng/ml) 24 hours after cardiac surgery [17]. In the current study, AKI was significantly associated with higher PCT levels on the first postoperative day, with a higher PCT level correlating with an increased frequency of AKI (P value <0.01). Receiver Operating Characteristic (ROC) analysis of PCT levels in diagnosing AKI revealed an Area Under the Curve (AUC) of 0.860 (95% CI 0.725-0.995). A PCT cut-off value of ≥4 ng/ml demonstrated sensitivity of 80%, specificity of 92%, positive predictive value (PPV) of 85.71%, negative predictive value (NPV) of 88.46%, and accuracy of 87.50%. These findings are consistent with a previous study that found procalcitonin (PCT) showed the largest Area Under the Curve (AUC) of 0.85 (95% CI 0.79—0.90) and the highest relative risk (RR 12.17; 95% CI 5.26—28.16; P<0.001) [18]. Similarly, Klingele *et al.*, found that PCT levels were significantly elevated in patients with delayed complications, including AKI, in both univariate and multivariate analyses. ROC analysis revealed high accuracy for PCT in predicting delayed complications, with an optimal cutoff value of 2.95 ng/ml, an AUC of 0.90, a sensitivity of 73%, and specificity of 97%. Patients with PCT levels above 2.95 ng/ml on the first postoperative day had a markedly increased risk of delayed complications [16]. In another study, Adhamik *et al.*, observed the AUC for PCT as a predictor of postoperative complications at four time points: 0.56, 0.61, 0.85, and 0.94, respectively. For a cutoff value of 0.15 ng/ml measured before and during surgery, the PPV/NPV values were 23/86% and 67/82%. For a cutoff value of 2.0 ng/ml measured on the first and second postoperative days, the PPV/NPV values were 100/93% and 100/87% [19]. A study by Kurtul *et al.*, also identified a cutoff value for PCT of 0.065 mg/L for predicting AKI, with an AUC of 0.779 (95% CI 0.730-0.828; P<0.001), sensitivity of 72%, and specificity of 70% [20]. The major finding in our study was that high PCT levels on the first postoperative day were associated with a higher incidence of AKI following cardiopulmonary bypass surgery.

LIMITATION OF THE STUDY

This study has several limitations. It evaluated a small patient population and was conducted over a limited period. Additionally, the study was carried out at a single center in Bangladesh, meaning that the sample represents only a small fraction of patients undergoing elective cardiac surgery with cardiopulmonary bypass. Consequently, the findings may not be generalizable to a larger or more diverse patient population.

CONCLUSION & RECOMMENDATION

An increased serum procalcitonin level on the first post-operative day can serve as a predictive marker for acute kidney injury (AKI) in patients undergoing cardiac surgery with cardiopulmonary bypass. This suggests that serum procalcitonin levels on the first post-operative day could be used as a screening tool to identify patients at higher risk for developing AKI following surgery. To further validate these findings, multi-center, larger prospective studies are needed.

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