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NEUTROPHIL TO LYMPHOCYTE RATIO AS A PREDICTOR OF ACUTE KIDNEY INJURY IN PATIENTS UNDERGOING CARDIAC SURGERY: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Incidence of postoperative renal dysfunction in patients undergoing cardiac surgery has been reported to be 13-43%. Early prediction and vigilance can help the clinician take precautionary measures. Laboratory predictors include C-Reactive Protein, Plasma and urinary Neutrophil gelatinase associated lipocalin, Preoperative serum albumin level, Neutrophil - Lymphocyte Ratio etc. The focus of this study was to find if there is an association of the Neutrophil- Lymphocyte Ratio with Acute Kidney Injury in patients undergoing on-pump cardiac surgery. Also studied is the association between NL Ratio and the incidence of postoperative atrial fibrillation, pneumonia, sternotomy wound complications and duration of postoperative mechanical ventilation.

Methods & Results: This study analyzed 142 patients who underwent cardiac surgery with cardiopulmonary bypass. As per the KDIGO criteria, 15% developed acute kidney injury. Cardiopulmonary bypass and cross clamp times were similar in patients with and without renal injury. Preoperative Neutrophil to Lymphocyte Ratio was not an accurate predictor.

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Postoperative Day 1 Ratio had a sensitivity of 85.71% but relatively low specificity at 36.44%. The Positive Predictive Value was 19.35% while the Negative Predictive Value was 93.48%. Postoperative Day 2 Ratio had a sensitivity of 66.67% , specificity of 52.54%, Positive Predictive Value of 20.00% and a Negative Predictive Value of 89.86%.
Conclusion: While the Neutrophil Lymphocyte Ratio shows promise as a potential diagnostic tool forAKI given its high sensitivity and Negative Predictive Value , its specificity and overall discriminatory ability need to be improved for reliable clinical use.

Keywords: Neutrophil Lymphocyte Ratio, Cardiac Surgery, Cardiopulmonary Bypass, Acute Kidney Injury

INTRODUCTION

Patients at increased risk of renal injury after cardiopulmonary bypass include those with diabetes, hypertension, preoperative renal impairment, reduced ejection fraction, advanced age, prolonged cardiopulmonary bypass (CPB) time[1] etc. Other factors that play a role include ischemia–reperfusion injury, inflammation, oxidative stress and hemodynamic instability.[2] A routinely performed low-cost reliable predictor of Acute Kidney Injury (AKI) that shows changes earlier than decreased urine volume and elevated serum creatinine is highly desirable. A predictor with high sensitivity and specificity enables the clinician to take precautionary measures and intervene timely. Novel cell cycle arrest biomarkers such as urinary IGFBP7 and TIMP2 have shown promising laboratory results in predicting cardiac surgery associated AKI but need costly equipment. Other predictors include C-Reactive Protein (CRP)[3,4] creatinine kinase-MB,[5,6] Plasma and urinary Neutrophil gelatinase associated lipocalin (NGAL)[7] Preoperative serum albumin [8,9,10] and the Neutrophil to Lymphocyte ratio (NLR) [11,12]

NLR a routinely performed low-cost laboratory investigation has sparked interest as an inflammatory biomarker. It has been found to have prognostic significance in multiple surgical disciplines.[13,14,15] . While elevated neutrophils represent non-specific inflammation, decreased lymphocytes are associated with poorer general health, increased physiological stress and depressed immune response. Thus, NLR integrates these two opposite immune pathways. [16,17]

Pre-existing physiological stress due to underlying co-morbidities favors lymphopenia and could cause a dysregulated immune response to cardiac surgery.[18] Pro-oxidants & prothrombotic substances released due to cardiopulmonary bypass cause endothelial dysfunction and platelet aggregation, leading to neutrophilia.[19] While there are many studies that have found a co-relation between raised NLR and AKI after cardiac surgery, there are varied findings as far as the time of investigation is concerned. Some meta-analysis found that only postoperative and not preoperative NLR was associated with AKI.[18] Others found elevated preoperative NLR to be predictive of AKI.[20]. Yet some other studies found postoperative Day 2 NLR but not postoperative Day 1 to correlate with AKI [21,22,23,24]

Perioperative NLR has also been used to predict poor outcomes other than AKI in patients undergoing cardiac surgery. These include Postoperative atrial fibrillation (POAF)[24,25] increased incidence of pneumonia, re-explorations and prolonged hospital stay. The primary objective of this study was to find if there was an association of NLR with AKI in patients undergoing on-pump cardiac surgery. We co-related the preoperative, postoperative day1 & postoperative day2 NLR with AKI using the Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI.[26] The secondary objectives were to study if there was an association between NLR and the incidence of POAF, pneumonia, duration of postoperative mechanical ventilation, sternotomy wound complications and duration of stay in the intensive care unit (ICU).

Method: This prospective observational study was conducted after approval of the protocol from the Institutional Ethics and Research committee in a tertiary care centre. (ECARP/2023/197). Written informed consent was taken from patients for documentation of data and its use for research and publication. Patients of both genders, above 18years of age, undergoing cardiac surgery with cardiopulmonary bypass were included. Those below 18 yr and patients with pre-existing renal dysfunction and atrial fibrillation were excluded. The preoperative investigations of the patient scheduled for surgery were reviewed a day prior. Data collected and recorded included: Age, Gender, BMI, Comorbid illnesses and Type of surgery (CABG or Valve Replacement). Investigations recorded were: Complete blood count, Liver function tests, Renal function tests, Xray, ECG and 2D Echo.

No change in the conduct of anaesthesia or surgery was made for the purpose of the study. Duration of Ischemia (Aortic Cross Clamp time) and Total cardiopulmonary bypass time was noted. As per our institution protocol, patients were mechanically ventilated in the intensive care unit until deemed fit for weaning and extubation. Total duration of mechanical ventilation was recorded. The Chest Xray films and patients' clinical status was daily evaluated for evidence of pneumonia. Postoperative Atrial fibrillation if any was noted. Diagnosis of Acute Kidney Injury (if present) was made according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines i.e change in serum creatinine levels (≥ 0.3 mg/dL within 48 h or ≥ 50% within 7 days) or urine output volume less than 0.5 mL/kg/hour for > 6 hours.[26]

M_2 = Mean of the outcome variable in the group without acute kidney injury i.e., group B (6.7)
α= 0.05 Error Statistical Analysis:
were therefore taken as reference values to derive the sample size of this study. The sample size was calculated using the following formula,

$$n = [Z_{1-\alpha/2} + Z_{1-\beta}]^2 \times \frac{(S.D._1)^2 + (S.D._2)^2}{(M_1 - M_2)^2}$$

where, n = Sample size

$S.D._1$ = Standard deviation of the outcome variable in the group with acute kidney injury i.e., group A (5.4)

$S.D._2$ = Standard deviation of the outcome variable in the group without acute kidney injury i.e., group B (5.1)

M_1 = Mean of the outcome variable in the group with acute kidney injury i. In a study on "The neutrophil to lymphocyte ratio and serum albumin as predictors of acute kidney injury

after coronary artery bypass grafting" by Masashi Ishikawa et al.[27] the NLR in patients without AKI (6.7 + 5.1) and in those with AKI (9.7 + 5.4) was found to be significantly different ($p < 0.001$). These values e., group A (9.7)

β= Power 95%

$Z_{1-\alpha/2}$= 1.96 at a 95% Confidence interval

$Z_{1-\beta}$= 1.28 at 90% power

Putting the values = $n_1 = n_2 = \frac{[1.96 + 1.28]^2 \times [5.4]^2 + [5.1]^2}{[9.7-6.7]^2}$

$= \frac{[3.24]^2 \times [29.16 + 26.01]}{[3]^2}$

$\frac{10.5 \times 55.17}{9}$

= 64.36 + 6.43 (10% dropout)

= 70.8

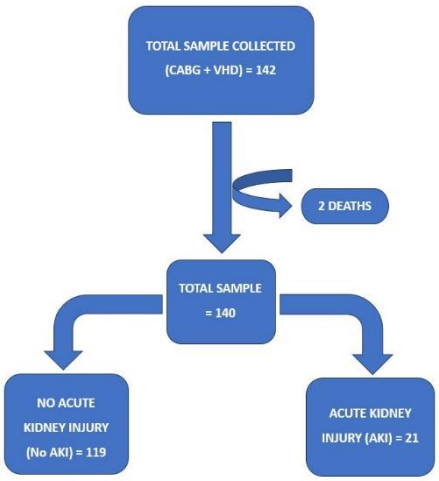
$n = n_1 = n_2 = 71$

Therefore, we took a total sample size of 142 for this study. Quantitative data i.e age, weight, height, BMI, blood investigations, duration of mechanical ventilation and ICU stay is represented using mean and standard deviation. Qualitative data i.e comorbidities and complications is represented using frequency and percentage. To compare the change in the parameter at two different time intervals, an unpaired t-test (for parametric data) and Mann-Whitney U-test (for non-parametric data) is used. The normal distribution of data is assessed by using the Shapiro-Wilk test. Chi-square /Fishers exact test is used to determine the association for the categorical outcome. P-value≤ 0.05 is considered significant.

OBSERVATION AND RESULTS

Of the total 140 patients that were enrolled in this study, 21 (15.00%) developed AKI. **Fig 1** depicts the data selection approach. The demographic features of patients with and without AKI are summarized in **Table 1**. The patients who developed AKI had a higher mean age of 59.8±11 years versus 53.4 ± 11.6 years. Out of the total 140 patients, 98 were male and 42 were female. Among the male patients, 83 did not develop AKI while 15 did. Among the female patients, 36 did not develop AKI and 6 did. **Fig1: The process of data selection**

The associated comorbidities are presented in **Table 2.** There were no statistically significant differences in pre-operative TLC, BUN, creatinine and serum albumin between patients with and without AKI as shown in **Table 3.** There were no statistically significant differences observed in the duration of cardiopulmonary bypass, cross-clamp, mechanical ventilation and incidence of postoperative atrial fibrillation. Patients who suffered AKI had a longer ICU stay. **Table 4.** There was an association between NLR and AKI on postoperative days 1 and 2 but not the preoperative levels. **Table 5.** The sensitivity of NLR was found to be 85.71%, indicating its ability to correctly identify 85.71% of patients with AKI. However, its specificity was



relatively low at 36.44%, suggesting a higher rate of false positives. The positive predictive value (PPV) was 19.35%, indicating the probability of AKI when the NLR is raised, while the negative predictive value (NPV) was 93.48%, indicating the probability of not having AKI when the NLR is not elevated. The area under the curve (AUC) was 0.597, **(Fig 2**) indicating poor to fair discriminatory ability of the NLR on postoperative day 1. The postoperative Day 2 NLR showed a sensitivity of 66.67% , specificity of 52.54% , PPV of 20.00% and NPV of 89.86%. The (AUC) value of 0.607 (**Fig 3**) indicates moderate discriminatory ability. **Table 6.**

On postoperative day-1, there were no patients diagnosed with Pneumonia, 2 cases were recorded on days 2, 3, and 4, and none on day 5**.(Fig 4)**

Characteristics	AKI	No AKI
Age(y)	59.8±11	53.4±11.6
Sex-male	15	83
Sex-female	6	36

BMI (kg/m2)		
<18.5 (underweight)	0	12
18.5 - 22.9 (normal)	7	45
23-24.9 (overweight)	5	26
>25(obesity)	9	36

Table 1. Demographic features of patients who developed AKI versus those who did not.

AKI-acute kidney injury BMI-body mass index

Comorbidities	AKI	No AKI
DM	0.7%	6.4%
DM +Hypertension	2.1%	5.7%
DM+Hypothyroidism	8.6%	30%

Table 2. Comorbidities in patients with and without AKI DM-diabetes mellitus

Preoperative laboratory Values	AKI Mean± SD	No AKI Mean ± SD	p value
Total WBC / cu mm	8462 ± 2474	7554 ± 2531	P=0.131
Preop BUN mg/dL	15.4 ± 4.37	15.4 ± 3.31	p=0.633
Preop Serum Creatinine(mg/dl)	1.1 ±0.3	1.0±0.6	p=0.754
Preop serum albumin g/dL	3.65±0.367	3.59± 0.333	p=0.446

Table 3. Comparison of preoperative laboratory investigations BUN-blood urea nitrogen

Perioperative variables	AKI Mean ± SD	No AKI Mean ± SD	p value
Cross-clamp time(min)	78.8±27.3	77.7±18.6	p=0.864
Cardiopulmonary bypass(min)	113±28.7	111±31.1	p=0.939
POAF	8	6	p=0.786

Mean duration of mechanical ventilation(h)	12.7 ± 1.9	10.7 ± 2.8	p=0.138
Duration of ICU stay(h)	131±35.8	124± 11.7	p=0.002
Sternal Wound Complications	Nil	Nil	

Table 4. Comparison of perioperative variables POAF- Postoperative Atrial Fibrillation ICU Intensive Care Unit

NLR	AKI Mean ± SD	NO AKI Mean ± SD	P value Mean ± SD
Pre-operative	4.03 ± 3.82	3.63 ± 2.18	0.496
Post-op d1	19.9 ± 11.7	16.4 ± 6.32	0.043
Post-op d 2	20.8 ± 10	17.4 ± 6.32	0.041

Table 5: Neutrophil to Lymphocyte Ratio in Patients with and without AKI

AKI- Acute Kidney Injury NLR Neutrophil Lymphocyte Ratio

NLR	Postoperative D1-NLR	Postoperative D2-NLR
Sensitivity (%)	85.71%	66.67 %
Specificity (%)	36.44%	52.54 %
PPV (%)	19.35%	20.00 %
NPV (%)	93.48%	89.86 %
AUC	0.597	0.607

Table 6. Validity and Reliability of NLR in the Diagnosis of AKI

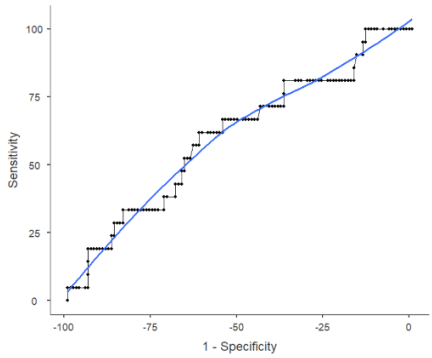


Fig2. Postoperative D1

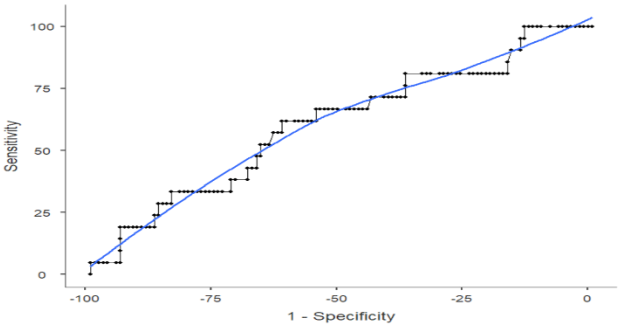
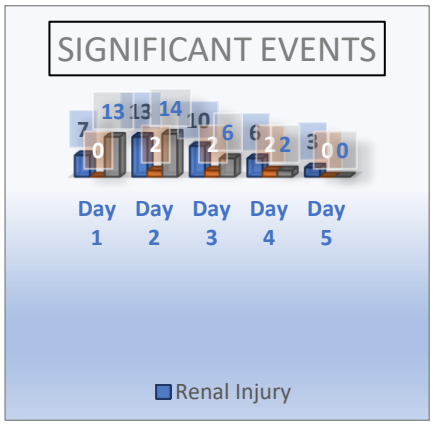


Fig 3. Postoperative D2

Data figure of the Area Under the curve

Fig 4. Postoperative complications



Discussion

The findings of our study revealed that Preoperative NLR was not an accurate predictor of Acute Kidney Injury following Cardiac surgery on CPB.

Postoperative Day 1 NLR had a sensitivity of 85.71% indicating its ability to correctly identify 85.71% of patients with AKI. but with a relatively low specificity at 36.44%. The Positive Predictive Value (PPV) was 19.35% while the Negative Predictive Value was 93.48% indicating the probability of not having AKI when the NLR is low. The Area Under the Curve (AUC) was 59.7%s indicating poor to fair discriminatory ability of the NLR in distinguishing patients with and without AKI on postoperative Day 1. Postoperative Day 2 NLR demonstrated a sensitivity of 66.67% , specificity of 52.54%, PPV of 20.00% and a NPV of 89.86%. The AUC value of 60.7% indicates moderate discriminatory ability.

These findings suggest that while the NLR shows promise as a potential diagnostic tool for AKI, particularly given its high sensitivity and NPV, its specificity and overall discriminatory ability need to be improved for reliable clinical use.

Out of the total cohort of 140 patients, 21 (15.00%) developed AKI postoperatively, whereas121 (85.00%) did not . A retrospective observational study by Kim et al in 590 patients found the postoperative AKI rate to be 28.1%[11] while Benedetto U reported an incidence of 40%[28] Difference in incidence can be attributed to several factors like heterogenous cohorts, difference in cardiopulmonary bypass times in various studies and also variation in criteria used to define AKI eg AKIN, RIFLE, KIDGO [29] etc. We used the KIDGO criteria to identify patients of AKI. In our study amongst those who developed AKI, only one patient had KDIGO stage II. The others did not progress beyond stage I and none of the patients needed renal replacement therapy. With off-pump CABG too, Yu Ruiming et al found a prevalence of 20.95 % in a retrospective study of 420 patients [30] The mean age of patients who did not develop AKI was 53.4 ± 11.6 years while those who experienced AKI had a higher mean age of 59.8 ± 11 years. Other studies [18,23] have also found that patients with AKI were often older than those who did not have drop in renal function.

There was a higher incidence of AKI amongst males as compared to females in this study. Wang Y et al in their single center retrospective study concluded that there was no gender difference in AKI frequency in patients less than 60 versus those more than 60 years old post-cardiac surgery, yet women display increased AKI severity and extended intubation duration.[31]

In this study, out of the 45 patients with a BMI greater than 25, nine had AKI while 36 did not. In the overweight category, 5 had AKI while 26 did not. There are numerous studies that have shown BMI to be an independent risk factor for AKI after cardiac surgery.[31,32] In the group that did not develop AKI, there were 6.4% without any comorbidities. Amongst those who suffered AKI, only 1.4% did not have any comorbidities. Patients without kidney injury also had comorbidities like diabetes (6.4%), DM with thyroid disorders (30%), and DM with hypertension (5.7%). The comorbidities among patients who developed AKI were DM (0.7%), DM with thyroid disorders (8.6%) and DM with HTN (2.1%). Tumer et al found that the presence of Subclinical hypothyroidism seems to be associated with an increased incidence of AKI and increased requirement for RRT after cardiac surgery.[33]

Guangquing Z et al found no significant difference between the two groups in terms of age, gender, or comorbidities, including diabetes, hypertension, atrial fibrillation, myocardial

infarction, cerebrovascular disease and heart failure.[34] Wang et al in their study concluded that diabetics were at increased risk of AKI after CABG independent of baseline renal or cardiac function. [35]Those on insulin treatment were associated with an increased rate and severity of AKI compared with those on oral hypoglycemic agents. This study did not classify diabetic patients based on their treatment regime.

There were no statistically significant difference in pre-operative Total leucocyte count , BUN, creatinine and albumin levels between patients with and without AKI. The serum albumin protects renal function by maintaining the oncotic pressure, which augments the intravascular volume[36] maintains renal perfusion, and improves glomerular filtration. [37] In patients with hypoalbuminemia, the glycocalyx might be compromised, leading to the loss of oncotic pressure gradients and barrier function, the fluid leakage into the tissue, and the microvascular flow alterations.[38] Ishikawa M et al proved that albumin with a cutoff value of 3.8 was a valuable predictor of early but not late AKI in isolated On-Pump CABG. [27]A similar study by Findik O et al showed that low preoperative serum albumin levels result in severe acute kidney injury and increase the rate of renal replacement therapy and mortality. [10]

This study did not find statistically significant difference in the preoperative NLR between patients who did and did not develop AKI. However significant differences in NLR levels were observed on postoperative day 1 and day 2 , suggesting a potential association between elevated NLR and the development of AKI. However, the increase in total counts in the postoperative period was present in both groups.

Although many studies state that an elevated NLR prior to cardiac surgery is associated with decreased survival.[18,39,40] there is no consensus on the threshold value for NLR. While some previous studies took a preoperative NLR of 2.65 as raised,[29] this study considered a ratio greater than 3.5 as elevated. Wheatley et al considered a threshold for elevated preoperative NLR between 2.51 and 3.4 [20] whereas Guangqing Z [41]et al found the significant increase in the incidence of AKI with the preoperative NLR > 3.09 after adjusting for confounding factors. Specifically, neutrophil infiltration is implicated in reperfusion injury through both direct toxic effects on the myocardium and vascular endothelium and leucocyte plugging in the microvasculature. Lymphopenia is a sign of the general state of immunosuppression, and diminished immune system function adversely affects survival.[42] A multivariate analysis by Weedle et al concluded that Preoperative NLR was not significantly associated with AKI. Day 1 NLR

showed a trend towards association while Day 2 NLR was significantly associated with postoperative AKI.[18]

Research by Usta S[31] revealed that the values of NLR obtained during the post cardiotomy period and on the first postoperative day are independent predictors of in-hospital AKI. NLR values were calculated in preoperative, postoperative days 1, 3 and 7 by Parlar [29] who found postoperative Day-1 values to independently predict AKI. Systematic review and meta-analysis by Wheatley J [20] including data from more than 10,000 patients, identified that preoperative elevation of the NLR is predictive of both postoperative AKI and the requirement for Renal replacement therapy. Thus, there is not a clear consensus regarding the actual time when NLR can be considered to have a definitive predictive value.

Axtell A [43]et al found that the risk of postoperative renal failure rises continuously with time on bypass, particularly among those with preoperative impairment. For those with estimated Glomerular filtration rate <30ml/min/1.73m2, the risk rises exponentially and much less so for those with eGFR>60ml/min/1.73m2. Incidence of Renal failure was more common in patients undergoing Combined valve & CABG operations, likely due to the higher mean CPB time. Cross clamp time is also a risk factor for renal dysfunction since it is associated with ischemic reperfusion damage. Serraino G et al found that 51 minutes of cross clamp was the best value which discriminates patients with and without AKI while it was 91minutes for CPB.[44]

In this study, patients with AKI had a mean duration on cardiopulmonary bypass of 113±28.7 minutes while those without AKI had a mean duration of 111±31.1min. Patients without AKI had a mean cross clamp time duration of 78.8±27.3 min while those who suffered AKI had a mean cross clamp duration of 77.7±18.6 min. There was no statistically significant difference with respect to CPB duration and cross clamp times. This was probably because it being a prospective study, number of patients who had AKI were not enough to draw a valid conclusion. Barbu M et al concluded that longer CPB times, longer aortic cross clamp time, and lower nadir hematocrit during CPB were independently associated with AKI after cardiac surgery.[45] A nadir Hematocrit limit of ≥ 26% has been identified to minimize the risk of AKI in cardiac surgery.[46] This study did not analyze hematocrit values .

Postoperative events like atrial fibrillation, Pneumonia and Sternal wound complications were documented. Pneumonia cases were absent on day 1 , two cases recorded on days 2, 3, and 4, and none on day 5. There was only one patient who was re-explored for surgical bleeding, with successful outcome. Two patients

with low cardiac output syndrome died within eight hours of surgery. None of the 140 patients had sternal wound complications. Patients who developed AKI had a significantly longer duration of ICU stay. Postoperative atrial fibrillation (POAF) is one of the most common complications after cardiac surgery, with a reported incidence varying between 15–40% after coronary artery bypass grafting, 33–49% after valve surgery and 33–67% after combined valve surgery and CABG. This study did not classify patients as per their cardiac procedure but included all on Cardiopulmonary Bypass. Liu et al found that the odds of developing POAF was 42% higher in individuals with an elevated preoperative NLR compared to those without, whereas elevated postoperative NLR was not a statistically significant predictor.[18]Weedle et al(26) observed that use of patients cut-off points allows for patients to be stratified into high and low risk groups for development of POAF. Using a cutoff point of 8, they found that preop NLR predicted POAF with a sensitivity of 6.2 and a specificity of 98.87%. Using a cutoff point of 26.526.25, postoperative day 1 NLR predicted POAF with a sensitivity of 15.76% and a specificity of 90.71%. Using a cutoff point of 10, day 2 NLR predicted POAF with a sensitivity of 33.33% and a specificity of 80.49%. (26) . In this study, amongst the 14 patients who developed POAF, nine had preoperative NLR less than 3.5 while five patients had a NLR greater than 3.5. All the patients irrespective of AKI had elevated NLR on Day 1 and Day 2 postoperatively. We were not able to identify a particular cutoff value of Ratio for occurrence of POAF.

Limitations: This study was planned as prospective to avoid selection bias that is inherent to retrospective studies. However given the limited time frame for data collection and analysis of results, we were unable to have equal number of patients who developed Acute Kidney Injury versus those who did not. Also, in a study like this, confounding variables are plenty. There is a lot of interplay between comorbidities, cardiac surgery and factors affecting cardiopulmonary bypass. Hence these results cannot be extrapolated. A longer study period would be desirable for conclusive results.

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