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Original Research Article

# Association between Neutrophil to Lymphocyte Ratio and Post Operative Atrial Fibrillation after Coronary Artery Bypass Graft operation

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**Abstract**

**Background:** Post operative atrial fibrillation (POAF) is associated with cardiovascular outcomes such as stroke, heart failure, and mortality. Neutrophil to lymphocyte ratio (NLR) is one of biomarker of inflammation. The use of cor pulmonary bypass (CPB), surgical trauma and reperfusion injury during cardiac surgery causes inflammation. NLR is suspected to be a biomarker that represents the inflammatory response as a modulator of POAF, but data are still lacking. This study analyzed the association between NLR and POAF after coronary artery bypass graft (CABG) operation.

**Methods:** This was an Observational analytic study, involving patients after the CABG procedure in Kariadi Hospital between June 2022 to September 2023. NLR was assessed in the first three hours after operation. ECG Holter was attained for 96 hours post-CABG procedure.

**Results:** The total subject was 62 patients, consisting of 57 men and 5 women with a mean age of 58,7 ± 6.39 years. Mean postoperative NLR 4.95 ± 2.17 with a median of 4.56 (1.52-11.00). There was a significant association between post-operative NLR with POAF after CABG (p=0.006, OR 4.64, 95%CI 1.50-14.35). High inotropic dose and *β* blocker initiation time less than 45 hours correlate significantly with POAF after CABG (p<0.001, OR 6.94 dan p=0.001, OR 0.17).

**Conclusions:** Postoperative NLR is associated significantly with POAF after CABG.

**Keywords:** *Neutrophil to Lymphocyte Ratio; Post Operative Atrial Fibrillation, coronary artery bypass graft; ECG Holter*

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## INTRODUCTION

Post Operative Atrial Fibrillation (POAF) is defined as new onset atrial fibrillation which occurs after surgery. POAF could develop in cardiac surgery and noncardiac surgery. Prevalence of POAF after Coronary Artery Bypass Graft (CABG) was around 20%.[1] Hence, the prevalence of POAF after CABG in 2021 at Kariadi Hospital Semarang was 55%.

POAF was considered to be a benign and self-limiting complication. Nowadays, it is known to be associated with cardiovascular events, such as stroke, heart failure, and mortality. POAF is also associated with prolonged hospital and intensive care stays. [1,2]

Pathophysiology of POAF after CABG is caused by several factors. Fibrotic substrates which develop chronically added with acute factors that are caused by surgery, propagate atrial fibrillation. Factors that make ideal conditions for AF to occur are defined as the modulator. Inflammation, oxidative stress, and sympathetic nerve activation serve as a modulator of POAF. Inflammation that occurs in cardiac surgery is caused by cardiopulmonary bypass and injury reperfusion.[1,3,4]

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**Table 1**. Baseline Characteristics

| Variable | Description |
|---|---|
| Age (years) | 58.7± 6.39 |
| Sex | |
| Men | 57 (89.1%) |
| Woman | 5 (10.9%) |
| Body Mass Index ($kg/m^2$) | 25.30 ± 3.41<br>24.60 (16.76-34.81) |
| GFR (mL min-1 1.73 $m^2$) | 61.03 ±18.71 |
| ACEI or ARB | |
| yes | 52 (83.8%) |
| no | 10 (16.2%) |
| *β-blocker* | |
| yes | 59 (92.2%) |
| no | 3 (7.8%) |
| *Calcium channel blocker* | |
| yes | 19 (31.7%) |
| no | 43 (69.3%) |
| *Mineral receptor antagonis* | |
| Yes | 26 (41.9%) |
| No | 36 (58.1%) |
| Statin | |
| Yes | 61 (98.3%) |
| No | 1 (1.7%) |
| LV *ejection fraction* (%) | 50.46 ± 10.42 |
| LA diameter (mm) | 36.46 ± 5.39 |
| Amount of SVG *graft* | |
| 2 graft | 22 (25.2%) |
| 3 graft | 33 (53.2%) |
| 4 graft | 7 (11.6%) |
| IABP | |
| Yes | 11 (17.7%) |
| No | 51 (82.3%) |
| Reoperation | |
| Yes | 3(7.8%) |
| No | 59 (92.2%) |
| Aortic cross clamp time (minutes) | 55.29 ± 10.67 |
| Cardiopulmonary Bypass time (minutes) | 67.86 ± 11.75 |
| Post operative Atrial Fibrillation | |
| Yes | 28 (45.2%) |
| No | 34 (54.8%) |
| Total Hospital stay (days) | |
| Mean ± SD | 12.08 ± 4.99 |
| Median (min-max) | 11 (6-31) |
| Total ICCU stay (days) | |
| Mean ± SD | 5.42 ± 2.53 |
| Median (min-max) | 5 (2-14) |
| Total ventilator time (hours) | |
| Mean ± SD | 51.29 ± 52.49 |
| Median (min-max) | 24.5 (12-192) |
| Mortality in hospital | |
| Yes | 9 (14.5%) |
| No | 53 (85.5%) |

GFR: Glomerular Filtration Rate; ACEi: Angiotensin Converting Enzyme inhibitor; ARB: Angiotensin Receptor Blocker; LV : Left ventricle; IABP : Intra Aortic Ballon Pump, ICCU : Intensive Cardiac Care Unit

The neutrophil-to-lymphocyte ratio is a popular inflammation marker associated with cardiovascular disease. NLR is suspected to be a biomarker that represents the inflammatory response as a modulator of POAF, but data are still lacking. In 2019, Study by Weedle showed high preoperative and postoperative NLR associated with POAF after cardiac surgery (CABG and valvular surgery) ($p=0.011$ and $p<0.001$).[5] These studies aimed to assess the association between postoperative NLR with POAF after CABG.

## METHODS

### Study Design and Participants

This was an observational analytic study with a cross-sectional design done in Kariadi Hospital. Patients were enrolled at the Dr. Kariadi General Hospital, Semarang,

Indonesia who were (1) ≥ 18 tahun years of age and (2) underwent elective on pump CPB procedures. Informed consents were obtained before cardiac surgery, patient given detailed information about study and asked for permission. Patient recruitment occurred between June 2022 and September 2023. Exclusion criteria included a history of atrial fibrillation, diagnosed with moderate-severe valvular disease and scheduled for valve replacement, consumed anti-arrhythmic drug class I or III, history of chronic kidney disease, ongoing chemotherapy treatment, history of leukemia, diagnosed with HIV and didn't have complete blood count assessment 0-3 hours after surgery. POAF was evaluated with a Holter ECG 96 hours after surgery.

**Table 2.** Correlation analysis of Postoperative NLR with POAF after CABG

| Variable | POAF after CABG | |
|---|---|---|
| | Coefficient Correlation (r) | p-value |
| **Post operative NLR** | r=0.32 | p=0.01[b*] |

Statistical analysis using Spearman test

### Statistical Analysis

Data were displayed in mean, standard deviation, and percentage. The Kolmogorov-Smirnov test was used to check the normality of the data. Either Pearson or Spearman test was used to analyzed the correlation within the variable. The cut-off value was defined with receiver operating characteristic (ROC) analysis. The numeric variable was converted to a nominal variable and underwent bivariate analyses. The chi-square test was used to analyzed the association between post-operative NLR and POAF after CABG. All statistical analyses were performed using the IBM SPSS software version 26 and a P value of <0.05 was used to ascribe statistical significance.

## RESULTS

A total of 62 subjects met the inclusion criteria. The baseline characteristic of patients is shown in **Table 1**. 57 patients (89.1%) were male. Mean age was 58.7± 6.39 years. Majority of patients had 3 vessel disease (89.1%). Mean left ventricle ejection fraction was 50.46±10.42%. Mean aortic cross-clamp time was 55.29±10.67 minutes and cardiopulmonary bypass time was 67.86±11.75 minutes.

**Table 2** shows the correlation between postoperative NLR with POAF after CABG. There was a positive correlation with weak correlation power between post-operative NLR with POAF after CABG with p=0.01 r=0.32.

**Table 3** shows the cut-off value of post-operative NLR which divides high risk and low risk of developing POAF after CABG. The cut-off value was 4.14 with a sensitivity of 78% and specificity 56%.

**Table 4** shows the association between post-operative NLR and POAF after CABG. There is a significant association between post-operative NLR and POAF after CABG with p=0.006 OR 4.64 95%CI 1.50-14.35.

**Table 5** shows the association between confounding factors and POAF after CABG. Confounding factors analyzed in this study such as Age > 60 years, Hypertension, DM, COPD, LVEF > 40%, LA diameter > 38,5mm, High inotropic dose, and Initiation of $\beta$ blocker < 45 hours. High inotropic dose and Initiation of $\beta$ blocker < 45 hours were significantly associated with POAF after CABG with p=0.000 OR 6.94 95%CI 2.27-21.27 and p=0.001 OR 0.17 95%CI 0.05-0.50.

**Table 4.** Association of postooperative NLR with POAF after CABG

| Association | POAF after CABG | | |
|---|---|---|---|
| | OR | P value | 95% CI |
| Post operative NLR | 4.64 | p=0.006[*] | 1.50-14.35 |

## DISCUSSION

Atrial fibrillation is multifactorial arrythmia that share classical cardiovascular risk factor.[6] Risk factor of atrial fibrillation which chronically overdue in patient, creating fibrotic substrate that maintain atrial fibrillation once triggered. In CABG patients, another risk factors due to surgical procedure and medical management after surgery, such as inflamation, stress oxydative and symphatetic nervous activation, acts as modulator of atrial fibrillation which increase susceptibility of FAPO.[1,3,4]

Confounding preoperative factors that led to the formation of fibrotic substrate were analysed and assessed. These factors included ageing, hypertension, diabetes mellitus, chronic pulmonary obstructive disease, left ventricle ejection fraction, and LA diameter.[7–11] Because the population in this study was younger (mean age 58 years) than in previous studies (mean age 65 years), there was no significant correlation found between ageing and POAF[12]. Furthermore, this study found no evidence of a significant correlation between FAPO and LA diameter. In terms of demographics, the population in this study had a mean LA diameter of 36.46±5.39 mm, which was smaller than the mean LA diameter of 40.09±3.47 mm in another study that demonstrated a significant correlation.[13] There were no significant association between each confounding pre operative factors with POAF after CABG in this study, due to relatively younger and less structural LA remodelling compared to other significant prior studies.[12–15]

**Table 3.** Cut off Post Operative NLR

| Variable | cutoff | AUC | p-value | Sensitivity | Specitifity |
|---|---|---|---|---|---|
| Post operative NLR | 4.14 | 0.684 | 0.012 | 78% | 56% |

**Table 5.** Association of confounding factor with POAF after CABG

| Confounding factor | Description | POAF after CABG | | |
|---|---|---|---|---|
| | | OR | p value | 95% IK |
| Age | | 1.15 | 0.82 | (0.41-3.06) |
| ≥ 60 years | 30 (51.6%) | | | |
| < 60 years | 32 (48.4%) | | | |
| Hypertension | | 3.37 | 0.14 | (0.64-17.75) |
| Yes | 53 (82.8%) | | | |
| No | 9 (17.2%) | | | |
| DM | | 0.56 | 0.26 | (0.20-1.55) |
| Yes | 27 (42.2%) | | | |
| No | 35 (57.8%) | | | |
| COPD | | 1.22 | 0.89 | (0.07-20.47) |
| Yes | 2 (3.1%) | | | |
| No | 60 (96.9%) | | | |
| LVEF > 40% | | 0.95 | 0.94 | (0.28-3.24) |
| ≥40% | 49 (79.7%) | | | |
| <40% | 13 (20.3%) | | | |
| LA Diameter >38.5mm | | 1.59 | 0.38 | (0.57-4.42) |
| ≥ 38.5mm | 25 (42.2%) | | | |
| < 38.5mm | 37 (57.8%) | | | |
| High dose inotropic use | | 6.94 | 0.000* | (2.27-21.27) |
| Yes | 33 (51.6%) | | | |
| No | 29 (40.4%) | | | |
| Initiation of B-blocker <45 hour | | 0.17 | 0.001* | (0.05-0.50) |
| <45hour | 32 (48.4%) | | | |
| >45hour | 30 (51.6) | | | |

CABG procedure triggered inflammation response due to tissue injury, use of *Cardio Pulmonary Bypass* (CPB) and reperfusion injury.[16]. The use of inotropic after surgery and initiation time of $\beta$ blocker affected sympathetic nerve activation. Both mechanism, inflammation and sympathethic nerve activation act as modulator of POAF which enchanced susceptibility of POAF.[2] There were significant association between high dose inotropic use and also $\beta$ blocker initiation time with POAF after CABG (p<0.001 and p=0.001).This study mainly focused to assesed association between postoperative NLR which stands as a marker of inflammation with FAPO after CABG.

NLR is an inflammation biomarker arranged into a ratio of absolute neutrophil count divided by absolute lymphocyte count taken from vein blood. It could describe two kinds of immunity systems, innate immune response and adaptive immune response.[17,18] This study assessed post-operative NLR taken 0-3 hours after surgery.

The mean postoperative NLR was 4.95 ± 2.17 with a median of 4.56 (1.52-11.00). The correlation test of postoperative NLR and POAF after CABG concluded a positive correlation with weak correlation power (p=0.012; r= 0.317). Cut-off value assessed to divide subjects with a high risk of POAF based on postoperative NLR. The ROC analysis concluded 4.14 as a cut-off value, with sensitivity of 78% and specificity of 56%.

Mean postoperative absolute neutrophil count was 9.54 ± 3.95 $10^3$/mL with a median of 8.72 (4.08-22.35) $10^3$/mL. Correlative analysis showed no significant correlation between postoperative neutrophil and POAF after CABG with p=0.09. Despite no significant correlation, it can be seen that the trend of neutrophil increase has occurred 0-3 hours after surgery. The study by Kawahito et al, showed the trend of neutrophil increase started right after the end of CPB, with a peak 12 hours after surgery and decreased gradually after.[19]

Mean post operative absolute lymphocyte count was 2.19 ± 1.05 $10^3$/mL with median 2.01(0.50-5.68) $10^3$/mL. Correlative analysis showed no significant correlation between postoperative lymphocyte and POAF after CABG with p=0.55.

The chi-square test used to assess the association between postoperative NLR and POAF after CABG, concluded a significant association with p=0.006, OR 4.64 dan 95% CI 1.5-14.35. Similar findings were also obtained from a prospective study by Gibson et al, which showed a significant association of postoperative NLR with POAF after CABG with p< 0.001.[12] Weedle et al, also showed a significant correlation of post-operative NLR with POAF after CABG with p=0.03 dan OR 1.04.[5] Postoperative NLR value showed immune response happened when blood was sampled. Postoperative stress was the cause of high immunity response. Production of reactive oxygen species, ongoing hypoperfusion, contact activation with CPB, and tissue injury were causing innate immunity response and increased neutrophil count.[20] The dynamic of adaptive immunity started with transient lymphocytopenia early after surgery. The study by Jankovicova et al, showed nadir point of decreasing lymphocytes happened on the first day after surgery.[21]

The limitation of this study is that there is no evaluation of the activation sympathetic nervous system using actual biomarkers. Also, there is no data about inotropic and

vasoactive drug doses used intraoperatively. The fibrotic substrate also wasn't assessed directly with imaging modality. Lastly, the history of AF only asses by preoperative ECG.

## CONCLUSION

The results of this study demonstrated that the neutrophil-to-lymphocyte ratio is associated with the incidence of POAF after CABG. If it confirmed by further studies, it might be beneficial if we monitor the NLR after CABG to predict POAF event.

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