Analysis Of Cardiopulmonary Bypass Duration Towards Neutrofil Limfosite Ratio On Patients After Coronary Artery Bypass Grafting In Cardiac Surgical Intensive Care Unit At Adam Malik Hospital Medan

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DOI: 10.29322/IJSRP.11.05.2021.p11357
http://dx.doi.org/10.29322/IJSRP.11.05.2021.p11357

***Abstract*- Background:** The aim of this study was to investigate the prognostic role of the neutrophil to lymphocyte ratio (NLR) in patients undergoing Coronary Artery Bypass Grafting (CABG) with cardiopulmonary bypass (CPB).

Methods: A retrospective cohort study of 91 patients who underwent CABG with CPB in the Cardiac Surgical ICU , Haji Adam Malik Hospital, Medan from January 2019 to December 2019 was conducted. All perioperative clinical data, including CPB time, Aortic cross clamp (AOX) time, neutrophil count, lymphocyte count, were collected retrospectively. Retrospective study was performed to compared NLR in patients with prolonged CPB Time. The prognostic value of NLR and its association duration of intensive care unit (ICU) stay were analyzed.

Results: Leucocytes count, NLR, and CRP were significantly increased post-operative compared with pre-operative ($p < 0.05$). The increased post-operative levels of NLR were significantly associated with prolonged CPB time ($p < 0.05$). Strong correlation (r: 0.505) between CPB time and NLR were reported. The increased post-operative levels of NLR were also significantly associated with prolonged post-operative cardiac ICU stay ($p < 0.05$).

Conclusion: Increased post-operative NLR followed by cardiac surgery with prolong CPB time in CABG patients was associated with a longer duration of an ICU stay.

***Index Terms*-** CABG, Cardiopulmonary Bypass, Neutrophil Lymphocyte Ratio, ICU stay

I. Introduction

Open heart surgery is a type of surgery with a large amount of trauma, which requires a period known as the Extra Corporal Circulation (CPB) or the Cardiopulmonary Bypass (CPB). In carrying out the process of circulation outside the body, a machine is used, namely a heart-lung bypass machine.[1]

One of the detrimental effects of using a cardiac bypass machine is contact between the blood and various foreign objects or biomaterials from the cardiac-pulmonary machine circuit (ie: cannulae, oxygenators, tubing, etc.). This condition results in activation of the cellular components of the blood, namely: erythrocytes, vascular endothelium, leukocytes, neutrophils, monocytes, platelets and the coagulation system and non-cellular (humoral) components of blood, namely inflammatory mediators and the complement system, all of which can trigger the systemic inflammatory response syndrome (SIRS).

Tissue trauma, endotoxemia, and blood-to-surface contact with the CPB circuit are thought to initiate a systemic inflammatory response following cardiac surgery. Pro-inflammatory and anti-inflammatory mediators have been shown to play an important role in the incidence of SIRS, these mediators include: Tumor Necrosis Factor α (TNF-α), Interleukin Iβ (IL-Iβ), Interleukin -6 (IL-6), Platelet Activating Factor (PAF), while the anti-inflammatory mediators include Interleukin-10 (IL10).[2]

Apart from contact of the blood with the inner lining of the heart-lung machine circuit, other causes of SIRS in open-heart surgery are: Ischemic reperfusion injury, endotoxin, and surgical trauma. Although it has a relatively small effect on the onset of SIRS compared to blood contact with the inner lining of the heart-lung machine circuit, ischemic reperfusion injury, endotoxin and surgical trauma, conditions such as hypothermia, relative anemia, administration of heparin during external circulation and administration of protamine after circulation. terminated outside the body can cause SIRS to arise, therefore SIRS can still occur even though circulation outside the body has been stopped.[3]

This results in the activation of an inflammatory process, including the release of cytokines. The release of these cytokines will result in an increase in CRP levels in hepatocyte cells in the liver, and become the initial stage of the inflammatory process which is responsible for damage to tissues and organs. This symptom is usually known as SIRS. Increased circulating levels of CRP are a sign of SIRS.[4]

Apart from being caused by the use of a CPB machine, the incidence of SIRS in open heart surgery can also be caused by ischemia reperfusion injury. Ischemia reperfusion injury is associated with an acute inflammatory response mediated by cytokines, chemokines, and adhesion molecules such as neutrophils, monocytes and other inflammatory cells that can result in cardiac muscle ischemia.[5]

The lymphocyte neutrophil ratio is a combination of inflammatory markers, neutrophils as a marker of nonspecific inflammatory reactions and lymphocytes as a marker of regulatory pathways, integrating the two roles of leukocyte subtypes with their respective pathways into one predictor factor that can be applied to patients undergoing CABG. Unlike other inflammatory markers, RNL is also an inexpensive and widely available test providing an affordable option.[6]

The duration of aortic cross clamp (AOX) and CPB is a predictor of immediate postoperative morbidity and mortality in open heart surgery. The lack of research on the duration of CPB and AOX on morbidity and mortality makes it difficult to determine the exact duration that can affect morbidity and mortality. Nissinen et al (2009) reported 3280 adult patients who underwent open heart surgery of varying complexity. As a result, a cardiac surgery procedure with a CPB duration of more than 240 minutes and AOX 150 is a predictor of worsening in cardiac surgery patients which is characterized by an increase in patient mortality within 30 days.

Shultz et al (2016). examined 30-day mortality as associated AOX duration in 202 people who underwent open-heart surgery. The results showed that patients with AOX duration greater than 300 minutes had a lower 30-day survival rate. The mean cross clamp time in this study was 346 ± 45 minutes, and the total time for CPB was 421 ± 70 minutes. In addition, this study also explains that the incidence of postoperative complications is quite large. The incidence of bleeding and stroke were 6.4% and 4.0%, respectively. The incidence of postoperative atrial fibrillation was reported to be 53%. While AKI was experienced by 10.4% of total postoperative patients.[2,3]

Prolonged cross clamp time is significantly associated with poor clinical outcomes in patients undergoing cardiac surgery in both low-risk and high-risk patients. These complications include death in hospital, prolonged length of stay, prolonged mechanical ventilation, side effects of blood transfusions, and complications in the kidney. This effect was similar in the low-risk and high-risk groups of patients. Prolonged cross clamp time decreases cardiac function due to ischemia, decreases postoperative cardiac output, increases the risk of re-surgery, and increases the risk of lung and gastrointestinal infections, thereby increasing mortality after coronary bypass surgery. In this study, the CPB time mortality rate in the group of patients who died CPB ≥ 120 minutes 46.7% greater than the CPB <120 minutes 5.9%.[7]

After multivariate adjustment, RNL was significantly an independent predictor of mortality (HR for increase per unit of RNL was 1.05, 95% CI 1.01-1.10, p = 0.008). This study concluded that preoperative RNL increase was an independent predictor of long-term mortality after CABG.[8]

II. METHODS

This research is a descriptive analysis study using a cross-sectional study design carried out for 12 months, namely in January - December 2019 at the Cardiac Surgical Intensive Care Unit At Adam Malik Hospital Medan. The sample obtained in this study amounted to 91 people according to the calculation of the number of samples, inclusion and exclusion criteria. The research subjects were taken by looking at the patient's medical records that met the inclusion criteria. The data collected included: sample characteristics: age, gender, comorbidities including the following; diabetes, dyslipidemia, hyperuricemia, hypertension, chronic renal failure Supporting examination data related to CHD and comorbidities. CPB duration is the length of the patient's circulation. flow through cardiopulmonary bypass during surgery Duration of aortic cross clamp is the duration of the aorta clamped with aortic clamp to isolate blood flow to the heart The RNL value was obtained when the patient first performed perioperative examination and after CABG surgery, and the day the patient moved from the Cardiac Surgical Intensive Care Unit.

III. RESULTS

This research involves 57 subjects who met the inclusion criteria. The characteristics of this study were displayed on the table below.

4.1 Characteristic of Research Sample

Variable	Value
Age, Mean (±SD)	56,6 (±5,8)
Gender, n (%)	
Male	81 (89,0%)
Female	10 (11,0%)
Number of graft, n (%)	
1	2 (2.2%)
2	4(4.4%)
3	30 (33%)
4	53 (58.2%)
6	2 (2.2%)
Duration of *CPB* (minute), mean (±SD)	123,55 (± 22,85)
Duration of AOX (minute), mean (±SD)	95,3 (±16,6)
Duration of ICU stay (day), mean (±SD)	2 (±1,6)
Laboratory preoperative	
Haemoglobin (g/ dL) (±SD)	13,23 (± 1,94)
Haematocrit (%) (±SD)	39,18 (± 5.70)
Leukocyte (/µL) (±SD)	8301 (± 2111)
Platelet (/µL) (±SD)	247054 (55311)

NLR Preoperative, mean (±SD)	2,38 (±1,39)
TOTAL	**91 sample**

Based on Table 4.1 above, it can be seen that the average age of the sample is 56.6 (± 5.8) years. Based on gender, it was found that 81 samples (89%) were male and 10 samples (11.0%) were female. Based on the duration of CPB, the patients had a mean duration of 123.55 (± 22.85) minutes. Based on AOX duration, patients had a mean duration of 93.5 (± 16.6) minutes. Based on the length of stay in the ICU, the mean patient was treated for 2 (± 1.6) days. Preoperative laboratory values showed that the patient's mean hemoglobin was 13.23 (± 1.94) g / dL, hematocrit 39.18 (± 5.70)%, leukocytes 8301 (± 2111) / µL, and platelets 247054 (55311) / µL. Based on the NLR value, the sample with a mean preoperative NLR value was 2.2 (± 0.9).

4.2 Perioperative Leukocyte Value

Leukocyte Perioperative	**Value**	**p-value**
Leukocyte Preoperative(/µL) (±SD)	8301 (± 2111)	0,000
Leukocyte Postoperative (/µL) (±SD)	16723 (± 6006)	
Leukocyte Out ICU (/µL) (±SD)	17385 (± 5232)	0.000
TOTAL	**91 sample**	

*Paired T-test

Table 4.2 shows the difference in the average number of leukocytes preoperative with postoperative and at the time of discharge from the ICU. The table above shows the preoperative leukocytes with a value of 8301 (± 2111). There was a significant difference between the value of preoperative leukocytes and postoperative leukocytes with a value of 16723 (± 6006) ($p < 0.05$).

4.3 Perioperative Lymphocyte Ratio Neutrophil Value

Leukocyte Perioperative	**Value**	**p-value**
NLR Preoperative (±SD)	2,38 (±1,39)	
NLR Postoperative (±SD)	5.58 (± 5.51)	0,000
NLR Out ICU (±SD)	16.49 (± 9.77)	0.000
TOTAL	**91 sample**	

*Paired T-test

Table 4.3 shows a significant difference in the mean value of preoperative and postoperative NLR and at the time of discharge from the ICU. The table above shows the preoperative NLR with a value of 2.38 (± 1.39). There was a significant difference between the preoperative NLR and the postoperative NLR with a value of 5.58 (± 5.51) ($p < 0.05$). A significant difference was also seen in the NLR value at ICU discharge with a value of 16.49 (± 9.77) ($p < 0.05$).

4.4 Relationship of CPB with NLR

Karakteristik	**Mean (±SD)**	***p-value***
***NLR* Paska Operasi**		
CPB 90-120	3,67 (±1,58)	0,002
CPB >120	7,21 (±6,99)	
***NLR* Out ICU**		
CPB 90-120	15,63 (±10,06)	0,441
CPB >120	17,22 (±9,55)	

T-Test Independent

From this table, it is shown that the study sample who underwent CPB with postoperative NLR assessment at 90-120 minutes had a mean value of 3.6 (SD 1.58) and patients who underwent CPB at> 120 minutes with postoperative NLR assessment with a sample size 49 had a mean value of 7.2 (SD 6.99). If assessed by independent T-test, it can be concluded that there are significant differences in these two data groups, (p = 0.002). The NLR of post-ICU patients who underwent CPB at 90-120 minutes had a mean of 15.6 (SD 10.06), and post-ICU NLR patients who underwent CPB at> 120 minutes with a sample size of 49 out of a total of 91 samples, had a mean of 17.2 (SD 9.5), and it was concluded that there was no significant difference between these two data groups (p = 0.441).

4.5 The relationship between AOX duration and NLR value

	NLR value	
	Postoperative	**Out ICU**
Duration of AOX (minute)		
60-90 (n=35)	**3,49 ± 1,36**	**17,03 ± 10,45**
>90 (n=56)	**6,88 ± 6,64**	**16,14 ± 9,4**
p-value	**0,004**	**0,677**

T-Test Independent

Based on the table above, it is known that the relationship between AOX duration of 90 minutes with the postoperative NLR value and the ICU discharge NLR value. By using the independent T-test, it was found that there was a difference in the mean postoperative NLR value in samples undergoing AOX 60-90 minutes, namely 3.49 ± 1.36 and samples undergoing AOX> 90 minutes, namely 6.88 ± 6.64 with p value = 0.004. So, statistically there is a significant difference between the two ($p < 0.05$). Meanwhile, the mean ICU discharge NLR value between samples undergoing AOX for 60-90 minutes (17.03 ± 10.45) and samples undergoing AOX> 90 minutes (16.14 ± 9.4) obtained p value = 0.677. So, statistically there was no significant difference between the NLR value of ICU discharge in the samples who underwent AOX 60-90 minutes and> 90 minutes ($p < 0.05$).

4.6 Correlation of CPB, AOX, and NLR values

	***CPB*, (r)**	**p-value**
***NLR* Postoperative**	**0,505**	**0,001**
***NLR* Out ICU**	**0,121**	**0,253**
	AOX, (r)	
***NLR* Postoperative**	**0,367**	**0,001**
***NLR* Out ICU**	**0,090**	**0,399**

Pearson Correlation

From Table 4.6, CPB duration has a significant correlation with postoperative NLR (p = 0.001), and CPB duration is considered to have a strong correlation with postoperative NLR (r = 0.505). However, duration of CPB was not significantly associated with ICU discharge NLR (p = 0.253).

For the AOX value, based on the Pearson test, it can be seen that AOX has a significant relationship with the postoperative NLR value (p = 0.001), and has a positive correlation (r = 0.367). AOX and ICU discharge NLR values had no significant relationship (p = 0.399).

4.7 Correlation of ICU Duration and NLR Value

	NLR Postoperative (r)	**p-value**
Duratiof of ICU stay	**0.337**	**0,013**

Spearman Correlation

Based on the table above, it shows the correlation between the duration of the ICU with the postoperative NLR value and ICU discharge using the Spearman correlation. There was a positive correlation between ICU duration and postoperative NLR value (r = 0.337) which was statistically significant.

IV. CONCLUSIONS

1. There is a significant relationship between the neutrophil lymphocyte ratio value and the duration of cardiopulmonary bypass on patients after coronary artery bypass grafting in Cardiac Surgical Intensive Care Unit At Adam Malik Hospital Medan.

2. The duration of cardiopulmonary bypass has a strong positive correlation with the increase in the value of the postoperative lymphocyte neutrophil ratio in patients after Coronary Artery Bypass Grafting who are admitted to the Cardiac Surgical Intensive Care Unit at Adam Malik Hospital Medan

3. The postoperative lymphocyte neutrophil ratio value has a positive correlation with the duration of ICU stay in patients after Coronary Artery Bypass Grafting who are admitted to the Cardiac Surgical Intensive Care Unit at Adam Malik Hospital Medan.

REFERENCES

[1] Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11:55-9.

[2] Gomar FS, Quilis CP, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med. 2016;4(13):256.2. Tyroler HA. Coronary heart disease epidemiology in the 21st century. Epidemiol Rev. 2000;22(1):7–13.3.

[3] Katseni K, Chalkias A, Kotsis T, Dafnios N, Arapoglou V, Kaparos G, dkk. The effect of perioperatif ischemia and reperfusion on multiorgan dysfunction following abdominal aortic aneurysm repair. Biomed Res Int. 2015;2015:1–11.22.

[4] Cislaghi F, Condemi AM, Corona A. Predictors of prolonged mechanical ventilation in a cohort of 3,269 CABG patients. Minerva Anestesiol. 2007;73:615–21.15.

[5] Ascione R, Lloyd C, Underwood M, et al, Inflammatory Response After Coronary Revascularization With or Without Cardiopulmonary Bypass. The Society of Thoracic Surgeon, Elsevier. 2000.

[6] Kounis NG, Soufras GD, Tsigkas G, Hahalis G. White Blood Cell Counts, Leukocyte Ratios, and Eosinophils as Inflammatory Markers in Patients With Coronary Artery Disease. Clin Appl Thromb Hemost. 2015 Mar;21(2)

[7] Santos CA, Oliviera MA, Brandi C. Risk factors for mortality of patients undergoing coronary artery bypass graft surgery. Rev Bras Cir Cardiovasc. 2014;29(4):513–20.4.

[8] Santos CA, Oliviera MA, Brandi C. Risk factors for mortality of patients undergoing coronary artery bypass graft surgery. Rev Bras Cir Cardiovasc. 2014;29(4):513–20.4.

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