

## Analysis of Pre-and Post-operative Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio in Acute Kidney Injury After Coronary Artery Bypass Grafting Surgery

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### ABSTRACT

Acute Kidney Injury (AKI) remains a common complication of post-operative Coronary Artery Bypass Grafting (CABG) related to high morbidity and mortality. Systemic inflammation has been known as a part of the pathogenesis of acute kidney injury. This study aimed to analyze the Neutrophil Lymphocyte (N/L) ratio and Platelet Lymphocyte (P/L) ratio in post-operative AKI. This research was a retrospective study involving 76 patients who underwent CABG surgery in Dr. Wahidin Sudirohusodo Central Hospital, Makassar, between January 2015 and May 2019. The diagnosis of AKI was based on Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria. The N/L ratio and P/L ratio were calculated respectively as a neutrophil count ratio to lymphocyte count and platelet count to lymphocyte count. Twenty-five (32.9%) patients developed AKI in the first 48 hours of the post-operative period. There was no difference in pre-operative N/L ratio and the P/L ratio between AKI and non-AKI groups ( $p > 0.05$ ). Both ratios increased after surgery and were significantly different between the two groups with higher mean ratio in non-AKI ( $16.93 \pm 9.16$  vs.  $21.86 \pm 11.13$ ,  $p=0.040$  and  $239,24 \pm 184,36$  vs.  $314,49 \pm 143,73$ ,  $p=0.011$ ). Both pre-operative and post-operative N/L ratio and P/L ratio could not distinguish AKI after CABG.

**Keywords:** Coronary artery bypass grafting, acute kidney injury, neutrophil-lymphocyte ratio, platelet lymphocyte ratio

### INTRODUCTION

Coronary Artery Bypass Grafting (CABG) is a surgical procedure to create new blood vessels across stenotic coronary arteries.<sup>1</sup> This action aims to increase blood flow to the heart and has been the definitive therapy for Coronary Heart Disease (CHD) for the last few years.<sup>1-3</sup> Since its introduction in the 1950s to date, CABG has made various advances, especially in terms of surgical techniques, to minimize surgical complications and improve quality of life.<sup>1,2</sup>

Acute Kidney Injury (AKI) is a complication that remains frequent after CABG surgery, with 1-30% incidence. Despite its reversibility within a few days to a few weeks, the reported morbidity and mortality are relatively high.<sup>1,2,4-6</sup> It was reported that there is approximately 1-1.5% dialysis after surgery. The MMR mortality rate is in the range of 7-38%.<sup>1,2,5</sup> A study by Lassnigg *et al.* proved that the 30-day mortality after cardiac surgery reached 32.5% at  $> 0.5$  mg/dL increase of creatinine concentration compared to the previous concentration.<sup>7</sup>

The inflammatory process has long been known to play a role in the pathogenesis of AKI in addition to impaired renal perfusion, ischemia-reperfusion injury, and increased oxidative stress.<sup>8,9</sup> Clinical and laboratory studies have reported that inflammation occurs in ischemia-reperfusion injury, and AKI coincides with this systemic inflammatory response.<sup>10</sup> Also, most of the patients are elderly with various risk factors that can trigger AKI and the potential to develop chronic renal failure.<sup>9</sup>

The N/L and P/L ratio are known as markers of systemic inflammation. Both tests are relatively simple, inexpensive, and the results can be obtained from a complete blood count.<sup>11,12</sup> Neutrophils cause a destructive inflammatory reaction, while lymphocytes represent an immune response. In conditions of ongoing inflammation, the number of lymphocytes may decrease due to increased apoptosis of lymphocytes. Besides, these inflammatory conditions lead to an increased serial proliferation of megakaryocyte and relative thrombocytosis.<sup>13</sup>

The study conducted by Yilmaz *et al.* showed that the N/L ratio was superior to C-Reactive Protein (CRP) and leukocytes in predicting the incidence of AKI in patients with severe sepsis.<sup>14</sup> Research by Ho *et al.* specifically proved that an increase in the N/L ratio was proportional to AKI risk after cardiac surgery.<sup>10</sup> Parlar and Saskin showed that increased N/L ratio and P/L ratio were associated with the incidence of AKI after CABG surgery.<sup>15</sup>

Based on the description, the authors aimed to analyze the N/L ratio and the P/L ratio as markers of inflammation in patients with AKI after CABG surgery to provide scientific information about these two ratios to AKI.

## METHODS

This study was conducted retrospectively with the aim to analyze the N/L ratio and the P/L ratio before and after CABG surgery on the incidence of AKI. Medical record data of patients who underwent CABG surgery between January 2015-May 2019 at Dr. Wahidin Sudirohusodo, Makassar, were used. A total of 76 out of 140 patients met the inclusion criteria, such as patients with complete laboratory data and serum creatinine concentrations < 1.5 mg/dL before surgery. Contrastingly, patients without any history of cardiac surgery, other heart diseases, end-stage renal failure, history of dialysis, malignancy, autoimmune disease, or acute infection were excluded.

Acute kidney injury diagnosis was based on the KDIGO 2012 criteria, such as an increase in serum creatinine  $\geq 0.3$  mg/dL within 48 hours, an increase in serum creatinine  $\geq 1.5$  times compared to the previous concentration in 7 days, or urine volume 0.5 mL/kg/hr within 6 hours. The KDIGO criteria classify AKI into three degrees based on the severity. Grade 1 is characterized by an increase in serum creatinine  $\geq 0.3$  mg/dL within 48 hours of the previous concentration or an increase in serum creatinine  $\geq 1.5$  times compared to the last concentration. An increase in serum creatinine 2-2.9 times compared to the previous level is classified as grade 2 and grade 3. Grade 4 comprises the rise in serum creatinine over  $\geq 3$  times than the last concentration or serum creatinine  $\geq$  increase 4.0 mg/dL or initialization of Renal Replacement Therapy (RRT).<sup>16</sup>

Baseline characteristics of patients in this study consisted of age, gender, and history of diseases such as Diabetes Mellitus (DM), hypertension, and dyslipidemia. Laboratory data, including urea,

creatinine, leukocytes, platelets, lymphocytes, and neutrophils before and after CABG surgery were used. The N/L ratio was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. The P/L ratio was obtained by dividing the absolute platelet count by the absolute lymphocyte count.

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Data were analyzed the Statistical Package for the Social Science (SPSS). Categorical data were expressed in percentage, and the Chi-Square test was used for comparison. The quantitative data were expressed as mean  $\pm$  Standard Deviation (SD), and their comparisons were determined using the T-test and the Mann-Whitney U test. P-value < 0.05 was significantly different.

## RESULTS AND DISCUSSIONS

A total of 25 patients (32.9%) had AKI after CABG surgery with grade 1 AKI as the most common grade, and it was found in 19 patients (76%) (Table 1). The characteristics of patients before surgery can be seen in Table 2. Gender, age, and history had no effect on the incidence of AKI after surgery ( $p > 0.05$ ). Laboratory parameters, especially the N/L ratio and the P/L ratio before surgery, were not significantly different between the AKI and non-AKI group ( $1.86 \pm 0.93$  to  $2.17 \pm 1.52$ ,  $p = 0.631$  and  $112,76 \pm 46.99$  vs.  $118,02 \pm 46.14$ ,  $p = 0.525$ ).

**Table 1.** Distribution of patients according to KDIGO 2012 criteria

Group	Patient (n=76)	Percentage (%)
<b>AKI</b>	25	32.9
Degree 1	19	76
Degree 2	4	16
Degree 3	2	8
<b>Non-AKI</b>	51	67.1

The laboratory parameters after surgery can be seen in Table 3. An increase of several laboratory parameters was found in both groups after surgery except for platelets and lymphocytes. There was no significant difference in platelets' mean between both groups ( $164.8 \pm 42.60$  against  $168,69 \pm 42.71$ ,  $p = 0.761$ ). Contrastingly, there was a significant difference in the mean of lymphocytes between both groups ( $1.19 \pm 0.91$  against  $0.71 \pm 0.49$ ,  $p = 0.003$ ). There was a significant difference of N/L ratio and the

**Table 2.** Characteristics of patients before CABG surgery

Parameter	AKI (n=25)	Non-AKI (n=51)	p-value
<b>Gender</b>			1.000
Male	22 (88%)	45 (88.2%)	
Female	3 (12%)	6 (11.8%)	
Diabetes mellitus	6 (24%)	9 (17.6%)	0.549
Hypertension	6 (24%)	10 (19.6%)	0.887
Dyslipidemia	1 (4%)	2 (3.9%)	1.000
Age	57.92±8.07	60.37±8.08	0.218
Ureum (mg/dL)	30±7.92	27.22±8.49	0.143
Creatinine (mg/dL)	1±0.23	0.98±0.20	0.721
Leukocytes (10 <sup>3</sup> /uL)	7.42±1.27	7.67±1.68	0.650
Platelet (10 <sup>3</sup> /uL)	253,84±74.06	248,43±84.29	0.442
Lymphocytes (10 <sup>3</sup> /uL)	2.44±0.82	2.26±0.71	0.413
Neutrophils (10 <sup>3</sup> /uL)	3.96±0.91	4.26±1.44	0.539
N/L ratio	1.86±0.93	2.17±1.52	0.631
P/L ratio	112,76±46.99	118,02±46.14	0.525

**Table 3.** Laboratory data of patients after CABG surgery

Parameter	AKI (n=25)	Non-AKI (n=51)	p-value
Ureum (mg/dL)	60.60±28.55	37.82±12.72	0.000 *
Creatinine (mg/dL)	1.85±0.61	1.03±0.21	0.000 *
Leukocytes (10 <sup>3</sup> /uL)	15.25±4.39	13.58±4.04	0.102
Platelet (10 <sup>3</sup> /uL)	164.8±42.60	168,69±42.71	0.761
Lymphocytes (10 <sup>3</sup> /uL)	1.19±0.91	0.71±0.49	0.003 *
Neutrophils (10 <sup>3</sup> /uL)	13.26±3.66	12±3.52	0.140
N/L ratio	16.93±9.16	21.86±11.13	0.040 *
P/L ratio	239,24±184,36	314,49±143,73	0.011 *

P/L ratio between both group but with a higher mean ratio in the non-AKI group (16.93±9.16 to 21.86±11.13, p=0.040 and 239,24±184,36 against 314,49±143,73, p=0.011).

This retrospective study involved 76 patients who underwent CABG surgery and recorded 25 patients (32.9%) who developed AKI after surgery. The results of this study were similar to previous studies and other references.<sup>1,2,5,17,18</sup> Grade 1 AKI was the most common grade in this study, found in 19 patients (76%). This condition was further investigated by Lassnigg *et al.* in cardiac surgery patients with elevated serum creatinine ≤ 0.5 mg/dL and > 0.5 mg/dL, which showed 30-day mortality of 2.77 and 18.64 times higher compared to those without an increase in serum creatinine.<sup>7</sup>

Risk factors and inflammatory markers such as the N/L ratio and the P/L ratio were identified in this study as measures to predict AKI incidence after CABG surgery. This study's risk factors were age, gender, and history of DM, hypertension, and hyperlipidemia, which tended to develop AKI

compared to non-AKI.<sup>1,5,17,18</sup> It was different from the results of this study and research by Parlar and Saskin, which showed no relationship between these risk factors and the incidence of AKI after CABG surgery.<sup>15</sup>

There was no significant difference in N/L ratio and the P/L ratio before surgery in the AKI and non-AKI groups. Research by Ho *et al.* proved that the N/L ratio before surgery did not act as a predictor of AKI after cardiac surgery.<sup>10</sup> Research by Hakan and Huseyin suggested that the increase in the N/L ratio and the P/L ratio before surgery, respectively, with a median ratio of 3.3 and 154.5, was associated with AKI incidence CABG surgery.<sup>15</sup> Silberman *et al.*, in their study, stated that an N/L ratio ≥ 2.6 before surgery led to an increase in the incidence of AKI after cardiac surgery.<sup>19</sup>

Several laboratory parameters but not platelets and lymphocytes have been shown to increase after surgery. Increased N/L ratio and P/L ratio are always followed by lymphopenia due to systemic inflammation. The release of several immunologic

inhibitory mediators can provide immunosuppressive effects resulting in impaired lymphocyte function.<sup>20</sup> Median 7.9 (4.5-10.2) for the N/L ratio and 156.6 (108.2-198.9) for the P/L ratio, according to a study by Hakan and Huseyin, were associated with the incidence of AKI after CABG surgery.<sup>10</sup>

The mean of both ratios after CABG surgery was higher in the non-AKI group and significantly different from the AKI group. A relatively high incidence of complications involving a systemic inflammatory process other than AKI after CABG surgery is Atrial Fibrillation (AF) (20-50%).<sup>1,21,22</sup> Research conducted by Gungor *et al.* showed that an increase in the P/L ratio ( $152.8 \pm 82.2$ ) before surgery had a higher risk of AF after CABG surgery.<sup>21</sup> The parameter N/L ratio  $\geq 2.6$  increases the incidence of AF after cardiac surgery, according to the study by Silberman *et al.*<sup>20</sup> Also, an increase in the N/L ratio and the P/L ratio can be triggered by a series of inflammatory reactions due to surgical procedures.<sup>23</sup>

## CONCLUSIONS AND SUGGESTIONS

The N/L ratio and the P/L ratio could not distinguish the incidence of AKI after CABG. Further studies with consideration of other complications such as AF that can affect N/L and P/L ratio were needed.

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