The relationship of lactic acid, neutrophil lymphocyte ratio and monocyte lymphocyte ratio with the outcomes of coronary arterial disease patients following coronary artery bypass surgery

Cynthia Citradinata,[1*] Nyoman Suci Widyastiti[2]

ABSTRACT

Background: Coronary artery bypass surgery (CABG) is a surgical procedure for coronary arterial disease (CAD). It has a risk of postoperative complication, extending from a long length of stay in the intensive care unit (ICU) to death. CABG needs a long duration of perioperative time, which decreases tissue oxygenation. It causes increased lactic acid production and initiates the secretion of inflammatory factors. Neutrophil/lymphocyte ratio (NLR) and monocyte/lymphocyte ratio (MLR) become inflammatory signs that are caused by the failure of heart microcirculation during the operative procedure. This study aimed to determine the relationship of lactic acid, NLR and MLR with the outcomes of CAD patients following CABG surgery.

Methods: This was a prospective study including 42 CAD patients who had undergone CABG procedure at Dr. Kariadi Hospital Semarang

between December 2017 and July 2018. Lactic acid data were taken using the spectrophotometer method. NLR and MLR were taken by the calculation index. The outcomes data were ICU length of stay (LoS), complications, and death, which were obtained from the medical record. The data were analyzed using bivariate analysis.

Results: There was a significant correlation between lactic acid with ICU LoS (p = 0.001), complication (p = 0.01), and mortality (p = 0.044). There was a significant correlation between NLR with ICU LoS (p = 0.003), complication (p = 0.009), and mortality (p = 0.014). There was a significant correlation between MLR with ICU LoS (p = 0.02), complication (p = 0.027), and mortality (p = 0.017).

Conclusion: There was a significant correlation between lactic acid, NLR dan MLR with the outcomes of CAD patients (ICU LoS, complication and mortality) that have undergone CABG procedure.

[1]Clinical Pathology Specialist Education Program, Department of Clinical Pathology, Faculty of Medicine Diponegoro University, Dr. Kariadi Hospital Semarang
[2]Department of Clinical Pathology, Faculty of Medicine Diponegoro University, Dr. Kariadi Hospital Semarang

*Correspondence to:
Cynthia Citradinata, Clinical Pathology Specialist Education Program, Department of Clinical Pathology, Faculty of Medicine Diponegoro University, Dr. Kariadi Hospital Semarang
cynthiatjitra@gmail.com

BACKGROUND

Coronary Arterial Disease (CAD) is a major health problem in both developed and developing countries. Based on the World Health Organization (WHO) data, heart disease is the number one cause of death in the world. It is estimated that in 2030, about 23.6 million people in the world will die because of cardiovascular disease.[1,2]

Coronary Artery Bypass Surgery (CABG) is surgical procedure for CAD by creating new bypass channels around the narrowed or blocked arteries. Blood vessels that are often used are the internal mammary artery, radial artery, and the saphena magna vein.[3,4] Various risks are associated with CABG, from postoperative complications to death. Complications after CABG that often occur include arrhythmia (30%), acute myocardial infarction (1% - 5%), heart failure (4% - 9%), stroke (2% - 4%) and other complications such as hemothorax, pneumothorax and postoperative wound infections (1%). Coumbe et al. stated that post-cardiac surgery

death rate was 2.6%.[5] Increased complications after cardiac surgery resulted in increased ICU length of stay, and caused variations in healing time from each cardiac surgery and the worst is death.[6,7]

The level of lactic acid should be a concern for cardiac surgery patients. High blood lactic acid levels are associated with poor outcomes. Anderson et al. found that blood lactic acid levels were the earliest known predictors of mortality at the time of measurement as early as 12 hours after intensive treatment.[7] Blood lactic acid levels > 4 mmol / L at 12 hours after admission to intensive care had a positive predictive value for increased mortality. Hyperlactatemia during cardiac surgery is associated with low tissue oxygenation.[7,8]

Neutrophil/lymphocyte ratio (NLR) is an inflammatory marker that is inexpensive and easy to examine, yet it is still rarely studied in cardiac surgery patients, especially those who undergo CABG. Dragu et al. found an increase in the total

number of leukocytes, neutrophils and monocytes and a decrease in lymphocyte count was associated with the outcome of CAD.[9] NLR is known as a sign of an inflammatory response, especially in cardiovascular disease.[10,11] NLR has been studied as a screening tool for the risk of death and the prognosis for malignancy and pulmonary heart surgery.[11,12]

Some studies link monocytes with cardiovascular disease. Monocyte lymphocyte ratio (MLR) is a risk factor for cardiovascular disease and a predictor of the severity of cardiovascular lesions. MLR with a cut-off point of 0.18 has a sensitivity of 69.03% and a specificity of 64.81% in detecting cardiovascular disease. Gibson et al. reported that low lymphocytes were associated with an increased risk of myocardial infarction and death through an analysis of 1030 patients.[10] Xiang et al. stated that increasing MLR was a predictor of outcome in cardiovascular disease.[13]

No previous studies have investigated the link between lactic acid, NLR and MLR with CAD patient outcome following CABG. Therefore, this study aimed to determine the relationship of lactic acid, NLR and MLR with the outcome of CAD patients following CABG surgery.

METHODS

This was a prospective study conducted from December 2017 to July 2018 at Dr. Kariadi General Hospital Semarang. This study involved 42 patients, which consisted of 34 men and eight women who met the inclusion criteria. The inclusion criteria were men and women aged 30 – 80 years who suffered from CAD and underwent CABG surgery. Patients with comorbidities such as malignancy and hematological abnormalities were excluded from this study. Ethical clearance was obtained from the Institution of Ethics for Medical and Health Research, Faculty of Medicine, Diponegoro University, Semarang.

The examination of lactic acid was performed using the spectrophotometer method. NLR and MLR were obtained from index/calculations based on absolute neutrophil, lymphocyte and monocyte data using an automatic hematology analyzer. The measured outcomes in this study were ICU length of stay, postoperative complications including atrial fibrillation, ventricular fibrillation, sinus tachycardia, AV block, non-hemorrhagic stroke, angina pectoris, and postoperative wound pain, and mortality.

Patient characteristics data were presented descriptively using tables. Data normality was tested using the Shapiro-Wilk test because the sample size was less than 50. The Spearman correlation test and Mann Whitney test were used to determine the correlation and the difference between variables when the data were not normally distributed. The independent t-test was used to determine the difference between variables when the data were normally distributed. Statistical analysis was processed using a computer program. Significant p-value was defined as < 0.05 at 95% of confidence interval.

RESULTS

Characteristics of the samples can be seen in Table 1. The subjects consisted of 34 men (81%) and eight women (19%) who were aged 41 to 70 years. As shown in Table 2, 22 subjects experienced postoperative complications.

Table 1   Characteristic of the subjects

Variable	N	%	Mean ± SD	Median (min – max)
Age (years)			58.60 ± 8.63	61 (41 – 70)
Sex				
Male	34	81.0		
Female	8	19.0		
Lactic acid (mmol/L)			3.97 ± 0.86	3.95 (1.7 – 5.69)
NLR			5.50 ± 2.44	5.13 (2.68 – 12.71)
MLR			0.14 ± 0.07	0.125 (0.05 – 0.36)
ICU length of stay (days)			4.40 ± 3.19	3 (3 – 18)
Complications				
Yes	22	52.4		
No	20	47.6		
Death				
Yes	3	7.1		
No	39	92.9		

Table 2   Post CABG complications

Complications	N	Percentage
Atrial fibrilation	4	0.40%
Ventricle fibrilation	6	0.10%
Sinus tachycardia	2	0.04%
AV block	1	0.02%
Non-hemorrhagic stroke	1	0.02%
Angina pectoris	1	0.02%
Postoperative wound pain	3	0.07%

Table 3 Correlation between lactic acid, NLR and MLR with ICU length of stay

Variable	ICU length of stay		Note
	p¶	r	
Lactic acid	0.001*	0.642	Significant, positive, strong
NLR	0.003*	0.453	Significant, positive, moderate
MLR	0.020*	0.359	Significant, positive, moderate

* Significant; ¶ Spearman's correlation test

Table 4 The difference based on complication

Variables	Complication		P
	Yes	No	
Lactic acid	4.28 ± 0.91	3.62 ± 0.67	0.010§*
NLR	5.89 (3.17 – 12.71)	4.22 (2.68 – 9.7)	0.009‡*
MLR	0.16 (0.07 – 0.36)	0.11 (0.05 – 0.20)	0.027‡*

* Significant; § Independent t; ‡ Mann Whitney

Table 5 The difference based on mortality

| Variables	Death		P
	Yes	No	
Lactic acid	4.93 ± 0.19	3.89 ± 0.85	0.044§*
NLR	11.12 (6.46 – 12.71)	4.76 (2.68 – 11.12)	0.014‡*
MLR	0.25 (0.21 – 0.36)	0.12 (0.05 – 0.28)	0.017‡*

* Significant; § Independent t; ‡ Mann Whitney
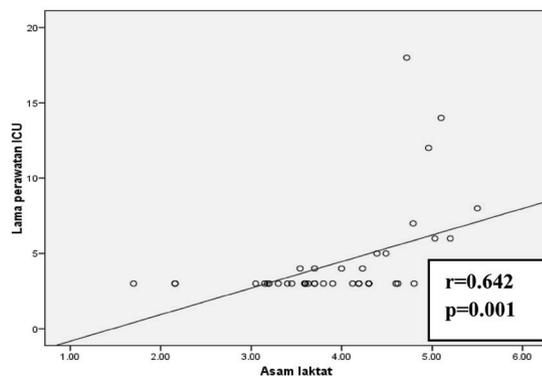
Figure 1 Correlation between lactic acid with ICU length of stay

The result of the analysis showed a significant relationship between lactic acid and ICU length of stay (p = 0.001), with a correlation value of 0.642.

The result of the analysis showed that there was a significant relationship between NLR and ICU length of stay (p = 0.003), with a correlation value of 0.453.

The result of the analysis showed that there was a significant relationship between MLR and ICU length of stay (p = 0.020), with a correlation value of 0.359.
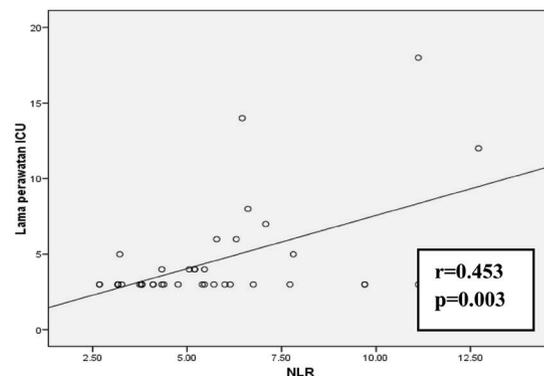
Figure 2 Correlation between NLR with ICU length of stay
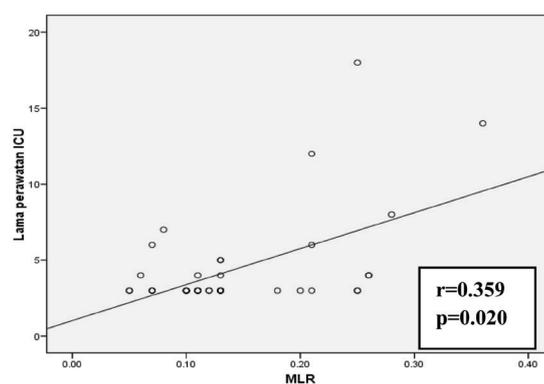
Figure 3 Correlation between MLR with ICU length of stay

DISCUSSION

The subjects consisted of 34 men (81%) and eight women (19%) who were aged 41 to 70 years. Forty-one subjects (97.61%) in this study experienced increased levels of lactate, and one subject (2.38%) had a normal level, with reference values of lactic acid ranging from 0.44 – 2.0 mmol/L. This study found one patient with normal levels of lactic acid; this patient was the youngest among all subjects, where being older is more prone to hypoxia.[7] According to Soe J et al., the mean NLR of all ages was 1.63 (0.76), while the mean MLR was 0.13 (0.68).[14] In this study, the mean NLR was 5.50 ± 2.44 and mean MLR was 0.14 ± 0.07, so it can be concluded that the NLR and MLR in this study were higher than in healthy subjects. The increase in NLR and MLR was associated with the presence of postoperative tissue inflammation.[15] The mean ICU length of stay in this study was 4.40 ± 3.19. The treatment of postoperative patients in the ICU varies depending on whether there are complications or not. According to a study by Almashrafi et al., which included 280 patients, 184 (65.7%) subjects in who were in the ICU for ≤ 96 hours and 96 (34.3%) subjects who stayed in the ICU for > 96 hours were affected by complications.[16]

In this study, 22 subjects experienced complications; the most common was ventricular fibrillation, which was experienced by six patients (0.1%). Mikhael et al. reported that ventricular fibrillation complication in cardiopulmonary bypass procedure could occur in 1-3% of elderly patients.[17] In this study, we found three subjects (7.1%) who died. Alberto et al. stated that of 1,628 patients who underwent CABG, 141 (8.7%) died.[18] It was stated that the risk factors for post-CABG death were age and duration of surgery.[18]

The results of the analysis showed a significant relationship between lactic acid and ICU length of stay (p = 0.001) with a correlation value of 0.642, indicating a strong correlation. Lactic acid levels in subjects with complications (4.28 ± 0.91) were higher than in subjects with no complications (3.62 ± 0.67) and were significantly different (p = 0.010). Also, we found that the levels of lactic acid in subjects who died postoperatively (4.93 ± 0.19) were higher than those who did not (3.89 ± 0.85) and were significantly different (p = 0.044). This is consistent with Anderson et al. who stated that blood lactic acid levels were the predictors of postoperative cardiac surgery at the time of early measurement 12 hours after the admission to intensive care.[7] Hyperlactatemia during cardiopulmonary bypass (CPB) procedures was associated with low tissue oxygenation.[8] Abraham et al. found that lactate concentrations were higher in patients who died than those who lived.[12]

The results of the analysis showed that there was a significant relationship between NLR and ICU length of stay (p = 0.003) with a correlation value of 0.453. The mean NLR in subjects with complication [5.89 (3.17-12.71)] was higher than subjects with no complications [4.22 (2.68 - 9.7)], and the difference was statistically significant (p = 0.010). Additionally, we found that the mean NLR in the subjects who died postoperatively [11.12 (6.46 - 12.71)] was significantly higher than subjects who did not die postoperatively [4.76 (2.68 - 11.12)] (p = 0.014). According to Gibson et al., there was a relationship between increased NLR and inflammatory response and oxidative stress after cardiac surgery.[10] Research by Dragu et al. found an increase in total leukocytes, neutrophils, and monocytes and decreased lymphocyte count associated with outcome in CAD.[9]

The results of the analysis in this study showed that there was a significant relationship between MLR and ICU length of stay (p = 0.020) with a correlation value of 0.359. The MLR mean for subjects with complication [0.16 (0.07 - 0.36)] was significantly higher than subjects with no complications [0.11 (0.05 - 0.20)] (p = 0.027). Also, we found that the MLR mean in subjects who died postoperatively [0.25 (0.21 - 0.36)] was significantly higher than who did not die postoperatively [0.12 (0.05 - 0.28)]. MLR value is obtained from the number of monocytes divided by the number of lymphocytes. Decreased lymphocytes illustrate of the failure of the cardiac microcirculation in the pathogenesis of cardiovascular disease. The high level of monocytes is confirmed as an independent indicator of the risk for cardiovascular disease.[11] Xiang et al. stated that an increase in MLR is a predictor of outcome in cardiovascular disease.[13]

CONCLUSION

There is a significant relationship between lactic acid levels and ICU length of stay, complications, and death in CABG patients. There was a significant relationship between NLR and ICU length of stay, complications, and death in CABG patients. There was a significant relationship between MLR and ICU length of stay, complications, and death in CABG patients.

CONFLICT OF INTEREST

There is no conflict of interest regarding manuscript.

ETHICAL CLEARANCE

This study has been received ethical approval by the Ethics Committee prior study was carried out.

FUNDING

AUTHOR CONTRIBUTION

All authors are contributed equally to the content of study from data preparation, statistical analysis, results, and data synthesis.

REFERENCES

1. World Health Organization. *Cardiovascular diseases*. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/2016 [Accessed June 2016].
2. World Health Organization. The Top 10 Causes of Death. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/. [Accessed May 2014].
3. Libby P, Antman AM, Selwyn AP et al. Vascular disease. In: Longo DL, Fauci AS, Kasper DL et al. (eds.). *Harrisons Principles of Internal Medicine*. 18th ed. New York: The McGraw-Hill Companies; 2012.

4. Yerokun BA, Williams JB, Gaca J, Smith PK, Roe MT. Indications, algorithms, and outcomes for coronary artery bypass surgery in patients with acute coronary syndromes. *Coron Artery Dis*. 2016; 27(4): 319 – 26. DOI: 10.1097/MCA.0000000000000364.

5. Christian WH, Helge M, Jean-Pierre B, Frans van de Wer A. Acute Coronary Syndrome. In: Jhon C, Thomas F L, Patrick WS. (eds.). *Cardiovascular Medicine*. 2nd ed. West Sussex: Blackwell Publishing Ltd; 2009.

6. Hein OV, Birnbaum J, Wernecke K, England M, Konertz W, Spies C. Prolonged intensive care unit stay in cardiac surgery : risk factor and long-term survival. *Ann Thorac Surg*. 2006; 81(3): 880 – 5. DOI: 10.1016/j.athoracsur.2005.09.077.

7. Anderson LW, Holmberg MJ, Doherty M, Khabbaz K, Lerner A, Berg KM, Donnino MW. Postoperative Lactate Levels and Hospital Length of Stay After Cardiac Surgery. *J Cardiothorac Vasc Anesth*. 2015; 29(6): 1454 – 60. DOI: 10.1053/j.jvca.2015.06.007.

8. Ranucci M, Isgro G, Romitti F, Mele S, Biagioli B, Giomarelli P. Anaerobic metabolism during cardiopulmonary bypass: predictive value of carbon dioxide derived parameters. *Ann Thorac Surg*. 2006; 81(6): 2189 – 95. DOI: 10.1016/j.athoracsur.2006.01.025.

9. Dragu R, Khoury S, Zuckerman R, Suleiman M, Mutlak D, Agmon Y et al. Predictive value of white blood cell subtypes for long-term outcome following myocardial infarction. *Atherosclerosis*. 2008; 196(1): 405 – 12. DOI: 10.1016/j.atherosclerosis.2006.11.022.

10. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J*. 2007; 154(5): 995-1002. DOI: 10.1016/j.ahj.2007.06.043.

11. Ji H, Li Y, Fan Z, Zuo B, Jian X, Li L et al. Monocyte/lymphocyte ratio predicts the severity of coronary artery disease: a syntax score assessment. *BMC Cardiovasc Disord*. 2017; 17(1): 90. DOI: 10.1186/s12872-017-0507-4.

12. Abraham BP, Prodhan P, Jaquiss RD, Bhutta AT, Gossett JM, Imamura M et al. Cardiopulmonary bypass flow rate: a risk factor for hyperlactatemia after surgical repair of secundum atrial septal defect in children. *J Thorac Cardiovasc Surg*. 2010; 139(1): 170 – 3. DOI: 10.1016/j.jtcvs.2009.04.060.

13. Xiang F, Chen R, Cao X, Shen B, Liu Z, Tan X et al. Monocyte/lymphocyte ratio as a better predictor of cardiovascular and all-cause mortality in hemodialysis patients: A prospective cohort study. *Hemodial Int*. 2018; 22(1): 82 – 92. DOI: 10.1111/hdi.12549.

14. Lee JS, Kim NY, Na SH, Youn YH, Shin CS. Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. Medicine (Baltimore). 2018; 97(26): e11138. DOI: 10.1097/MD.0000000000011138.

15. 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; 21(2): 139 – 43. DOI: 10.1177/1076029614531449.

16. Almashrafi A , Elmontsri M, Aylin P. Systematic review of factors influencing length of stay in ICU after adult cardiac surgery. *BMC Health Serv Res*. 2016; 16: 318. DOI: 10.1186/s12913-016-1591-3.

17. El-Chami MF, Sawaya FJ, Kilgo P, Stein W 4th, Halkos M, Thourani V et al. Ventricular arrhythmia after cardiac surgery: incidence, predictors, and outcomes. *J Am Coll Cardiol*. 2012; 60(25): 2664 – 71. DOI: 10.1016/j.jacc.2012.08.1011.

18. Santos CA, Oliveira MA, Brandi AC, Botelho PH, Brandi Jde C, Santos MA et al. Risk factors for mortality of patients undergoing coronary artery bypass graft surgery. *Rev Bras Cir Cardiovasc*. 2014; 29(4): 513 – 20. DOI: 10.5935/1678-9741.20140073.