

Association between neutrophil to lymphocyte ratio on admission and grace mortality risk score among acute myocardial infarction patient at BRSUD Tabanan in 2017

P G E A Suyasa^{1,2}

¹Cardiovascular Department BRSU of Tabanan Hospital, Bali, Indonesia

²Universitas Warmadewa, Bali, Indonesia

*dexthey@gmail.com

Abstract. Myocardial infarction has become the leading cause of more than 80% of death from cardiovascular disease worldwide. Since inflammation plays a significant role in myocardial ischemia, neutrophil to lymphocyte ratio is an independent predictor of acute coronary syndrome. The study objective was to evaluate the association between neutrophil to lymphocyte ratio and GRACE mortality risk score among acute myocardial infarction patients at BRSUD Tabanan in 2017. A retrospective study based on the medical record of ACS patient during 2017 was conducted at BRSU Tabanan on March 2018. Of 103 ACS patients enrolled to the study, 84% was male whose the mean age was 58.95 ± 12.25 years. The mean ratio of neutrophil and lymphocyte was 3.96 ± 2.95 . Majority of the samples, 57 (55.3%) has low GRACE risk score. There is a positive correlation between the NLR ratio and GRACE score ($r=0,388$; $p<0,05$). In conclusion NLR may be a useful surrogate marker in predicting an increase of GRACE risk mortality score of acute myocardial infarction patients.

1. Introduction

Coronary Heart Disease (CHD) is a condition caused by an inadequate supply of blood and oxygen to the myocardium, resulting in an imbalance between blood needs and supply. This condition can lead to myocardial disturbance ranging from *reversible* myocardial ischemia to *irreversible* myocardial death or myocardial infarction marked by increased cardiac biomarkers post attack [1,2].

As well known, atherosclerosis is an important mechanism in myocardial infarction and the role of inflammation in the process of initiation, progression and plaque de-stabilization in atherosclerosis has been well studied. White blood cell (WBC) and its sub-type are one of the inflammatory markers that have been studied for a long time in cardiovascular disease. Relative neutrophilia and lymphopenia were a potential condition as a predictor of mortality and recurrence in patients with myocardial infarction. The ratio of neutrophils and lymphocyte (NLR) is a combination of two independent markers above which is simple and non-specific to predict the inflammatory state in patients with myocardial infarction as well as predictors of mortality and morbidity [2,3].



Global Registry of Acute Coronary Events (GRACE) risk score is a validated scoring system used in patients with acute coronary syndrome (ACS) to predict mortality in hospital. This study studied how the role of NLR as a non-specific and independent laboratory biomarkers in predicting the morbidity and mortality of patient with myocardial infarction when associated with GRACE mortality risk score [4]. The study aim was to evaluate the association of NLR ratio and GRACE mortality risk score among acute infarction patients.

2. Material and methods

This is an observational analytic study with *cross-sectional* study design. This study was conducted in BRSUD Tabanan in March 2018 employing patient medical records. Samples were taken using total sampling methods, i.e. patients who came to Tabanan Hospital Emergency Medical Services (EMS) from January 1, 2017 until December 31, 2017 diagnosed with Acute Myocardial Infarction (AMI). Samples were obtained using computerized systems that had been integrated with the patients diagnosis using keywords; "acute myocardial infarction" then patient medical records can be obtained. The diagnosis of AMI is obtained based on the criteria of the European Society of Cardiology (ESC) which includes a significant increase in cardiac biomarker with at least one of; symptoms of ischemia, changes in ST segments as well as new or considered new T waves or new onset LBBB, and progression of pathological Q waves on ECG. The IMA spectrum includes both STEMI and NSTEMI [5].

Patient's demographic data and data on the variables to be studied were recorded after being obtained through the patient's medical records. Data on variables to be studied include complete blood count value (WBC, neutrophil, lymphocyte) which performed first time at the admission and data that determined GRACE mortality risk score. NLR is calculated based on neutrophil to lymphocyte count ratio. GRACE scores include; age, heart rate, systolic blood pressure, creatinine, cardiac arrest upon arrival, ST segment deviation on ECG, cardiac enzyme abnormalities and killip class. The GRACE score was calculated using the MDCalc application, which was later obtained numerical values and classified as low (<108), intermediate (108-140) and high (>140) [6].

Exclusion criteria includes; leukocytosis or current inflammatory condition of another reasons than AMI that may interfere with high or low NLR output to GRACE score; patients with acute infections, cancer, hematological disorders, systemic inflammatory conditions (SIRS), immune mediated disease or autoimmune disorders, chronic kidney disease and chronic liver disease [6]. We checked patient medical reports whether they had a history of certain medical condition above and current inflammatory condition.

2.1 Statistical analytic

Statistical analysis was performed using SPSS software version 17.0 (SPSS Inc., Illinois). Categorical variables are presented in table, in percentage form while numerical variables are presented in the table in the mean $\pm$ standard deviation. Variables distribution based independent variable category is also presented. Normality and homogeneity tests were performed on independent variables using *Kolmogorov-Smirnov* test and *Levene* test. To assess the magnitude of the correlation between 2 variables, Pearson's correlation test was performed. Comparative test to measure the average of NLR in GRACE score group is done using one way ANNOVA if eligible. If the results are significant, post-hoc test performed.

3. Results

From 107 samples with AMI, 103 samples met the inclusion criteria. From the total sample, more than half (84.5%) were men with a mean sample age 58.95 ± 12.28 years. The average ratio of neutrophil and lymphocyte was 3.96 ± 2.95 . Based on GRACE risk score, 57 (55.3%) samples with low GRACE risk score, 24 (23.3%) samples with intermediate GRACE risk score, and 22 (21.4%) samples with high GRACE risk score. Variables distribution based on GRACE risk score classification can be seen in table 1.

Table 1. Variable distribution based on GRACE score classification (N=103).

Variable	GRACE score		
	Low	Intermediate	High
Age	52,25 ± 7,71	62,42 ± 9,16	72,55 ± 12,35
Men (%)	48 (84,2)	20 (83,3)	19 (86,4)
NLR	3,18 ± 2,73	4,53 ± 2,58	5,33 ± 3,32

From the normality test results using Kolmogorov-Simonov, p value obtained = 0.239 ($p > 0.05$), which mean the average data of NLR based on GRACE score has a normal distribution. The result of homogeneity test using Levene test showed p value = 0,126 ($p > 0,05$) this means the value of NLR based on GRACE score has homogeneous variation, bivariate test can be continued using parametric test using Pearson's correlation test (Table 2).

Table 2. Bivariate test results between NLR and GRACE score using pearson correlation Test (N=103).

Variable	GRACE score			R	P
	Low	Intermediate	High		
NLR	3,18 ± 2,73	4,53 ± 2,58	5,33 ± 3,32	0,388	0.000

From Pearson correlation test, there was a weak positive correlation between NLR value and GRACE risk score ($r=0,388$; $p<0,05$). This positive correlation means increasing value of NLR will be followed by an increase in GRACE score.

In this study, one-way ANOVA test was performed to compare mean of NLR value in GRACE score group classification (low, intermediate, and high). This test showed that there was a significant difference of NLR mean in GRACE score group {F (2,100) = 5,215, $p=0,007$ } (Table 3).

Table 3. Bivariate test results between NLR and GRACE score using one way ANOVA test (N=103).

NLR	Df	F	p value
Between Groups	2	5,215	0.007
Within Groups	100		
Total	102		

This significant result is a requirement to perform post hoc test. Using smallest real difference (BNT), it was found that there was a significant difference of NLR mean between low and high GRACE score group. { $p=0,003$; 95% CI = -3,556 – (-0,736)}.

4. Discussion

White blood cells play an important role in the underlying inflammatory process of atherosclerosis. Neutrophils the first leucocytes to be found in damaged myocardial area have a role in acute plaque disruption and blockage due to thrombus. Neutrophils were secreted by bone marrow in response to acute inflammatory process. Activated neutrophils exacerbate inflammatory response through secretion of inflammatory mediators and *reactive oxygen species* (ROS). This causing additional tissue damage and exacerbate infarct size by area.

Meanwhile lymphocytes also appear in early plaque formation but have a positive manner in contrary to neutrophils respectively. They infiltrating injured myocardial area and play a significant role in healing process during infarction [7]. Both of this leucocyte sub-type are associated with acute stress condition related to immunity in patients with acute coronary syndrome, which is mediated by cortisol hormone

secretion [7,8,9]. Neutrophilia and lymphopenia was associated with the severity or increased mortality related to AMI.

NLR, a ratio of 2 independent markers above has the best prognostication value in AMI patients compared with other routine hematologic parameters in predicting future cardiovascular events and their severity [7,9]. GRACE score, a validated scoring system, is used to assess mortality risk in AMI patients. The magnitude of GRACE score is proportional to increase risk of mortality in AMI patients [4]. NLR literature suggest this biomarkers may be used as an additional independent predictor in addition to the GRACE score in predicting output in AMI patients [5,8].

This study shows that there is a relation between NLR value and GRACE score. Bivariate analysis using Pearson correlation test shows there is a weak positive correlation between NLR value and GRACE score classification. This result is consistent with theory that WBC plays a vital role in acute atherosclerosis in myocardial infarct manifestations. The higher WBC are also associated with poor outcomes in AMI [7]. Poor outcomes in AMI patients, can be predicted using GRACE scores so that higher WBC are presented in NLR value, proportional with higher GRACE score stratification or value [8].

From comparison test using one-way ANOVA, there is significant mean difference of NLR in GRACE group. Post hoc test show us the significant results is in *low* and *high* GRACE group. From those results we can conclude in this study the significant results according to NLR value in GRACE score group can be divided into 2, low and high. The current study finding is concordance with another study result in which NLR served as an independent all mortality (in-hospital and 6 months mortality rate) risk due to acute coronary syndrome [10].

Several study result also support this study finding particularly in acute myocardial infarction with elevated serum creatinine level in which the diagnostic value of troponin I is affected by renal insufficiency [11], NLR in combination with C-reactive protein [12], combine useful of Platelet to Lymphocyte ratio and NLR [13]. In addition, the using of NLR is not only in AMI mortality risk but also another cardiovascular events [14]. The NLR also implemented in predicting of adverse clinical outcome of patients with severe calcific aortic stenosis [15].

There is several limitations on this study and should be assessed in future studies. This include there is does not rule out the possibility of false positive results or increasing NLR value in any condition non-related to AMI. Regardless of the exclusion criteria made based on patient medical history and brief finding of acute inflammatory state other than AMI, other more specific supporting examination is needs to rule out those circumstances in future study. Other supporting studies with larger samples also need in future to re-assess the power of correlation result and the stratification of GRACE scores based on NLR value due to significance results on comparison test only exist in low and high groups.

5. Conclusion

In this study, there was an increase in NLR value proportional to the higher GRACE stratification risk score and there was a significant difference between NLR values and GRACE groups. NLR would be an independent, simple, inexpensive and accurate new early predictor of the increasing value of GRACE scores in AMI patients.

References

- [1] P Ramrakha, J Hill 2006 *Oxford Handbook of Cardiology: Coronary Artery Disease* 1st ed USA (Oxford University Press)
- [2] E M Antman, E Braunwald 2012 In P Libby, R O Bonow, D L Mann and D P Zipes, *Braunwald's heart disease: a textbook of cardiovascular Edisi ke-9*. Philadelphia: (Elsevier Sunders)
- [3] U Gul, S Hussain, and R Munir et al 2017 *J College Phy Surg* **27** 1 p4

- [4] Perhimpunan dokter spesialis kardio vaskular indonesia. *Jurnal Kardiologi Indonesia* 2015
- [5] *European Society of Cardiology* 2012 33:2551
- [6] R C Oncel, M Ucar and M S Karakas et al 2015 *Clin Appl Thrombo/Hemost* **21** 4 p383-388
- [7] E Yalcinkaya, U C Yuksel and M Celik et al 2014 *Arq Bras Cardiol*
- [8] J He, J Li and Y Wang et al 2014 *Int J Clin Exp Pathol* **7** 7 4045
- [9] A Korkmaz, A Yildiz and H Gunes et al 2015 *Clin Appl Thrombo/Hemost* **21** 7 p667
- [10] R Bajari, S Tak 2017 *Indian Heart Journal* **69** S46
- [11] A Nalbant, H Cinemre and T Kaya et al 2016 *Pak J Med Sci* **32** 1 p106
- [12] H C Shin, J S Jang and H Y Jin et al 2017 *Korean Circ J* **47** 3 p338
- [13] K I Cho, S H Han and G B Sigh 2015 *Plos One* **10** 7 e0133934
- [14] M Verdoia, A Schaffer and L Barbieri et al 2016 *Neth Heart J* **24** 7-8 p462
- [15] K I Cho, S H Cho and A Y Her et al 2016 *Plos One* **11** 8 e0161530