# Association Between Neutrophil to Lymphocyte Ratio and Left Ventricle Global Longitudinal Strain in Acute Myocardial Infarction

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## ABSTRACT

**Background:** High neutrophil to lymphocyte ratio (NLR) is independently associated with lower EF, in hospital complications, and higher mortality rates in acute myocardial infarction (AMI). Global longitudinal strain (GLS) measurement after AMI demonstrated specific benefit compared with LVEF in evaluation of the extent of post MI left ventricular myocardial injury. The aim of this study wasto determine the association between NLR and left ventricular GLS in AMIpatients.

**Methods:** An analytic observational study was conducted on August-December 2017 to patients who admited to Dr. Moewardi General Hospital which diagnosed STEMI or NSTEMI. Blood examination and transthoracic echocardiography were performed. They were divided into two groups according to GLS measurement  result, GLS>-13.8% and GLS≤-13.8%. The cut-off value of NLR to predict GLS>-13.8%was determined by ROC curve analysis. Bivariate and multivariate analysis to assess whether high NLR was associated with GLS>-13.8% were performed.

**Results:** As many as 57 patients were included in this study, 24 patients (mean age 56,21±9,43) in GLS ≤-13.8% group and 33 patients (mean age 56.67±8.24) in GLS >-13.8%. NLR was significantly higher in GLS>-13.8% group 6.06 (5.36-6.86) compare 4.20 (3.49-5.04),in GLS≤-13.8%, p=0.001. The cut-off value of NLR was 4.69. The bivariate analysis showed that NLR>4.69 associated with GLS>-13.8%, OR 2.70 (CI 95% 1.41-5.17, p=0.001). Multivariate analysis shown that higher NLR have more probability to develop GLS>-13.8%, OR 8.53 (CI 95% 2.38-30.60, p<0.001).**Conclusion:** There is an association between NLR and left ventricular GLS in AMI  patients. AMI patients with high NLR are more likely to have worse GLS.

**Keywords:** neutrophil to lymphocyte ratio; global longitudinal strain; acute myocardial infarction.

## INTISARI

**Latar Belakang:** Rasio neutrofil terhadap limfosit (RNL) yang tinggi berhubungan dengan rendahnya *left ventricular ejection fraction* (LVEF) pada pasien infark miokard akut (IMA). Pengukuran *global longitudinal strain* (GLS) paska IMA memberikan informasi tambahan mengenai luas area infark. Tujuan dari penelitian ini untuk mengetahui hubungan antara RNL dengan GLS ventrikel kiri pasien IMA.

**Metode:** Penelitian ini merupakan penelitian observasional analitik, dilakukan pada bulan Agustus-Desember 2017 terhadap pasien IMA baik dengan elevasi segmen ST (IMA EST) maupun tanpa elevasi segmen ST (IMA non EST) yang datang ke Rumah Sakit Dr Moewardi. Pemeriksaan darah dan ekokardiografi transtorakal dilakukan pada semua pasien. Pasien dibagi dalam dua kelompok berdasarkan hasil GLS, yaitu GLS >-13,8% dan GLS ≤-13,8%. Nilai titik potong untuk memprediksi GLS>-13,8% ditentukan berdasarkan analisis kurva ROC. Analisis bivariat dan multivariat dilakukan untuk menilai apakah RNL tinggi berhubungan dengan terjadinya GLS>-13,8%.

**Hasil:** Sebanyak 57 pasien diikutsertakan pada penelitian ini, terdapat 24 pasien (rerata usia 56,21±9,43 tahun) kelompok GLS ≤-13,8% dan 33 pasien (rerata usia 56,67±8,24 tahun)

kelompok GLS>-13,8%.  Rerata RNL lebih tinggi pada kelompok GLS>-13,8% yaitu 6,06 (5,36-6.86) dibandingkan kelompok GLS ≤-13,8% sebesar 4,20 (3,49-5,04), p=0,001. Nilai titik potong RNL adalah 4,69. Analisis bivariat menunjukan RNL>4,69 berhubungan dengan GLS>-13,8% dengan rasio odds (OR) 2,70 (interval kepercayaan (IK)  95% 1,41-5,17, p=0,001). Analisis multivariat menunjukan RNL tinggi memiliki kemungkinan untuk terjadi GLS >-13,8% dengan OR 8,53 (IK 95% 2,38-30.60, p<0,001).
**Simpulan:** Terdapat hubungan antara RNL dengan GLS ventrikel kiri pada pasien dengan IMA. Pasien IMA dengan RNL tinggi memiliki kemungkinan untuk terjadinya GLS yang lebih buruk.

## INTRODUCTION

Acute myocardial infarction (AMI) is the most severe manifestation of coronary heart disease, which accounts for the deaths of more than 2.4 million people in the United States, more than 4 million deaths in Europe and North Asia, and accounts for more than one third of deaths in developed countries annually.[1] AMI is a condition of myocardial necrosis due to unstable ischemic syndrome. AMI, with or without ST segment elevation (STEMI or NSTEMI), is a cardiac emergency, with significant potential for morbidity and mortality.[2]

Necrotic cells release danger signals, activate non-specific immune pathways, and trigger a strong inflammatory response. The inflammatory signals promote the interaction of attachment between leukocytes and endothelial cells, thus causing neutrophil and monocyte extravasation.[3] Neutrophils are an important component of non-specific immunity. They infiltrate coronary plaque and infarcted myocardium, and mediate tissue damage by releasing matrix degrading enzymes and reactive oxygen species.[4] Recently, the ratio of neutrophils to lymphocytes (NLR) has been known to be an independent predictor of mortality and myocardial infarction in CHD patients, exceeding the predicted ability of total number of leukocytes and neutrophils.[5] In AMI patients, high NLR is associated with low left ventricular ejection fraction (LVEF).[6]

Assessing the size and distribution of infarct areas after revascularization therapy may help for better clinical interventions. Conventional echocardiography studies provide a quick overview of the general condition of myocardium, but LVEF poor to detects earlier and minimal pathological changes.[7] Echocardiography is widely available and can be done in acute conditions, so this modality becomes the first choice in assessing risk stratification after AMI.[8] The GLS measurements after AMI show specific benefits over the LVEF evaluation of information on the infarction area.[9] Poor GLS in AMI patients is associated with extensive infarction and LVEF, predicts left ventricular changes, clinical events and responses to reperfusion strategies.[10] This study aims to determine the relationship between the NLR and left ventricular GLS on the patients with AMI.

## METHODS

This was an analytic observational study. The subjects were STEMI and NSTEMI patients who underwent treatment at Intensive Cardiovascular Care Unit of RSUD Dr. Moewardi, Surakarta, Central Java. The samples were taken consecutively from August to December 2017. The inclusion criteria in this study were: the patients with AMI (based on chest pain complaints accompanied by elevated cardiac enzyme with either ST-segment elevation or without ST-segment elevation, onset of chest pain ≤ 24 h, and willing to be the subjects of the study). The exclusion criteria for this study were: patients with previous history of acute coronary syndrome or chronic heart failure, patients with valvular heart disease, and patients with atrial fibrillation, echocardiography result not feasible for GLS analysis, patients with chronic renal failure, liver cirrhosis, chronic inflammatory disease or malignancy, patients with acute infection or sepsis, or the patients with acute stroke.

The blood sampling for NLR test was performed when the patients entered the Emergency Department of Dr Moewardi Hospital. The blood samples for NLR test were taken from the antecubital vein. The blood samples obtained were put into EDTA tube and then centrifuged and put into the automatic blood cell counting device BC-5800 Auto Haematology Analyzer (Mindray, Shenzen, China). The

total number of leukocytes and differential counting, including the number of neutrophils and lymphocyte were analyzed with an automatic blood cell counting device in the clinical pathology laboratory of RS Dr Moewardi. NLR was calculated by dividing the number of neutrophils with lymphocytes. Other routine laboratory tests were also performed, and the blood sampling was done before treatment.

      The echocardiography test was performed on 24-48 hours of hospitalization. GLS was examined using the automated function imaging (AFI) technique that available in the Vivid S6 Cardiovascular Ultrasound System (GE Healthcare, Wisconsin, USA) echocardiography software, based on 2-dimensional longitudinal strain imaging. The longitudinal strains were defined as physiological changes of the length of the region of interest (ROI) from the end of diastole to the end of systole. During this period, the longitudinal strainswere negative because of the shortening of the ROI. The GLS test results were expressed in software as GLPSS-Avg which reflected the overall systolic peak of each left ventricular segment.[11] After the GLS valueswere obtained, the samples were grouped into two: GLS≤-13.8% and GLS> -13.8%.[12]

      The data obtained were analyzed statistically using SPSS 22.0 software. The continuous characteristic data were tested using Kolmogorov-Smirnov normality test followed by the mean difference test using independent T-test. If the data were not normally distributed, then the data transformation was continued with the mean difference test using independent T-test. If the data remained not normally distributed, then to test whether there wereany differences, thedifference test was performed using Mann Whitney test using median value. To test whether there were any significant differences between the two groups of categorical samples, a nonparametric comparative test using Chi-Square was performed; if the requirements

were not met, there would be done Fischer exact test. Receiver-operating characteristics (ROC) curve analysis wasconducted to determine the NLR cutoff point toward the GLS. The variables showing statistical differences between the two groups with p <0.25 were included in the multivariate analysis.

## RESULTS

      As many as 57 patients with AMI were included in this study, then they were divided into two groups, i.e. GLS≤-13.8% group and GLS >-13.8% group. Demographically, there was no significant difference between the two groups. In the GLS≤ -13.8% group there were of 19 male and 5 female with the mean age of 56.21 ± 9.43 years old, and there were 28 male and 7 female with the mean age of 56.67 ± 8,24 years old in GLS> -13.8% group. From table 1 it is identified that GLS group of> -13.8% there were more patients suffering from STEMI (30; 90.9%) than in the GLS group ≤ -13.8% (14; 58.3%) with p = 0.004 . The number of neutrophils in the GLS group> -13.8% ($9.45 \pm 2.87 \times 10^3/mm^3$) was higher than in the GLS group ≤ -13.8% ($8.31 \pm 3.23 \times 10^3/mm^3$) but this difference was statistically not significant (p = 0.167). The number of lymphocytes of GLS group> -13.8% ($1.54 \pm 0.47 \times 10^3/mm^3$) was lower than in the GLS group ≤ -13.8% ($1.96 \pm 0.75 \times 10^3/mm^3$) with p = 0.017. LVEF was lower in the GLS group> -13.8% by 43.85 ±7.10% compared with the GLS group ≤-13.8% of 51.29 ± 6.14% with p <0.001>.

      T-independent test was performed to identify the mean difference of NLR value between GLS group> -13.8% and GLS group ≤-13.8%. The independent T-test from logaritmic transformation data showed that the geometric average value ofNLR in the GLS > -13.8% group was 6.06 (95% CI 5.36-6.86) which was higher when compared with the GLS ≤-13.8% group 4.20 (95% CI 3,49-5,04). This difference is statistically significant,with p value = 0.001 (table 2).

**Table 1. Basic Characteristics of Subjects Based on GLS value**

| Parameters | GLS ≤-13,8% (n=24) | GLS>-13,8% (n=33) | p |
|---|---|---|---|
| **Demography** | | | |
| Sex | | | |
|    Male n, (%) | 19 (79.2) | 28 (78.8) | 0.972 |
|    Female n, (%) | 5 (20.8) | 7 (21.2) | |
| Age | 56.21±9.43 | 56.67±8.24 | 0.846 |
| **Risk factors, n (%)** | | | |
| Diabetes Mellitus | 8 (30.3) | 10 (33.3) | 0.808 |
| Hipertension | 10 (41.7) | 17 (51.5) | 0.462 |
| Active Smokers | 15 (62.5) | 17 (51.5) | 0.409 |
| Dislipidemia | 8 (33.3) | 9 (27.3) | 0.621 |
| **Clinical Conditions** | | | |
| Body mass index (kg/m$^2$) | 23.87±3.21 | 24.01±3.28 | 0.871 |
| Onset (hour) | 5.92 (4.53-7.74) | 5.86 (4.53-7.57) | 0.958 |
| Killip Class II-IV | 10 (30.3) | 3 (12.5) | 0.114 |
| STEMI, n (%) | 14 (58.3) | 30 (90.9) | 0.004 |
| **Laboratory Parameters** | | | |
| Hemoglobin (g/dL)** | 13.80(11.40-15.70) | 13.70(10.30-17.10) | 0.740 |
| Erythrocyte(x10$^6$/µL) | 4.80±0.59 | 4.82±0.65 | 0.904 |
| Leucocyte (x10$^3$/ µL) | 11.14±3.65 | 11.75±3.21 | 0.504 |
| Neutrophil (x10$^3$/ µL) | 8.31±3.23 | 9.45±2.87 | 0.167 |
| Lymphocyte (x10$^3$/ µL) | 1.96±0.75 | 1.54±0.47 | 0.017 |
| Glucose(mg/dL) ** | 131.50 (93-359) | 156.00 (85-429) | 0.109 |
| Creatinine (mg/dL) * | 0.92 (0.81-1.06) | 1.00 (0.88-1.14) | 0.414 |
| Ureum(mg/dL) | 29.71±9.22 | 33.79±12.02 | 0.170 |
| **Echocardiographic  Parameters** | | | |
| GLS (%)** | -14.3(-18.4 – (-13.9)) | -9.8 (-13.4 – (-7.3)) | <0.001 |
| LVEF (Simpson) (%) | 51.29±6.14 | 43.85±7.10 | <0.001 |
| **Therapy** | | | |
| Fibrinolytics | 12 (50.0) | 19 (54.5) | 0.571 |

*Geometric mean: means (confidence interval 95%).
** The data are not normally distributed and can not be transformed, the data are presented in median (minimum-maximum) and the analysis with Mann-Whintey U test.

**Table 2. Comparison of the means of NLR values between GLS groups**

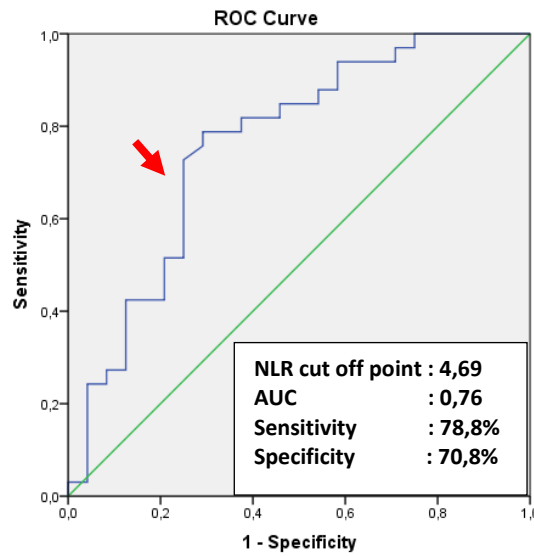| Parameters | n | mean (95% CI) | Value of p |
|---|---|---|---|
| GLS ≤-13.8% | 24 | 4.20 (3.49-5.04) | 0.001 |
| GLS >-13.8% | 33 | 6.06 (5.36-6.86) | |

Figure 1. ROC analysis curve of NLR on GLS >-13,8%.

**Table 3. Bivariate analysis of several variables with GLS**

| Variable | GLS ≤-13,8% (n=24), n(%) | GLS >-13,8%, (n=33), n(%) | OR (95% CI) | p value |
|---|---|---|---|---|
| Age (years) | | | | 0.948 |
| > 65 | 6 (25.0) | 8(24.2) | 0.98 (0.58-1.65) | |
| ≤ 65 | 18 (75.0) | 25(75.8) | | |
| BMI (kg/m$^2$) | | | | 0.738 |
| ≤ 25 | 7 (29.2) | 11 (33.3) | 1.08 (0.68-1.71) | |
| > 25 | 17 (70.8) | 22 (66.7) | | |
| Killip Class | | | | 0.114 |
| I | 21 (87.5) | 23 (69.7) | 1.47 (0.98-2.22) | |
| II-IV | 3 (12.5) | 10 (30.3) | | |
| Type of AMI | | | | 0.004 |
| STEMI | 14 (58.3) | 30 (90.9) | 2.96 (1.07-8.14) | |
| NSTEMI | 10 (41.7) | 3 (9.1) | | |
| Fibrinolytic | | | | 0.571 |
| Yes | 12 (50.0) | 19 (57.6) | 1.14 (0.72-1.79) | |
| No | 12 (50.0) | 14 (42.4) | | |
| NLR | | | | <0.001 |
| >4.69 | 7 (29.2) | 26 (78.8) | 2.70 (1.41-5.17) | |
| ≤4.69 | 17 (70.8) | 7 (21.2) | | |
| Hiperglycemia | | | | 0.206 |
| Yes | 6 (25.0) | 18 (54.5) | 1.35 (0.88-2.06) | |
| No | 18 (75.0) | 15 (45.5) | | |
| LVEF | | | | 0.009 |
| < 50% | 10 (41.7) | 25 (75.8) | 1.96 (1.09-3.55) | |
| ≥ 50% | 14 (58.3) | 8 (24.2) | | |

**Table 4. Multivariate analysis of several variables with GLS**

|  | Coefficient | p value | OR (95% CI) |
|---|---|---|---|
| LVEF <50% | 1.392 | 0.035 | 4.02(1.10-14.69) |
| NLR >4.69 | 2.144 | 0.001 | 8.53 (2.38-30.60) |
| Constanta | -1.686 |  |  |

The ROC analysis was performed to obtain the NLR cutoff point to predict the prognosis of GLS value> -13.8%. The optimal NLR cutoff point was 4.69, as a predictor of GLS>-13.8% with sensitivity 78.8% and specificity70.8%. The value of area under the curve (AUC) was 0.76 (95% CI 0.63-0.89; p = 0.001) **(**figure 1).

The result of the bivariate analysis showed that patients in GLS >-13,8% group had higher proporiton of NLR >4.69 (n= 26 vs. 7, 78.8% vs.29.2%, p <0.001) with OR 2.70 (95% CI 1.41-5.17). Patients in GLS >-13.8% group also had higher proportion for STEMI and LVEF < 50% **(**table 3**).**

Multivariate analysis using logistic regression in this study was conducted for Killip class, type of AMI, hyperglycemia, NLR value, and LVEF variables.The logistic regression analysis showed that only LVEF <50% and NLR >4.69 were associated with GLS >-13.8%. LVEF <50% had an odds ratio (OR) value of 4.02 with 95% CI 1.10-14.69 with p value = 0.035. NLR >4.69 had OR 8.53 with 95% CI 2,38-30-60 with p value = 0.001 ( table 4).

## DISCUSSIONS

This study showed that the meanNLR in AMI patients with GLS> -13.8% was higher compared with AMI patients with GLS ≤-13.8% with mean with mean 4.20 (3.49-5.04) vs 6.06 (5.36-6.86), with p = 0.001. In this study, the AMI patients were grouped according to the level of GLS with a cutoff point of -13.8% in accordance with Eek et al.,[12] 2010 study, which states that GLS > -13.8% is associated with an area of infarction > 12%. The study by Miller et al. (1995) shows the area of infarction > 12% is associated with higher mortality rate in short-term observations.[13]

Patients with high NLR (NLR >4.96) have worse GLS compared with low NLR (NLR ≤ 4.96).These results are similar with another study conducted on 72 patients with anterior STEMI undergoing PPCI,

indicating the patients with NLR ≥ 6.37 have higher average of infarct ratios compare with low NLR group < 6.37.[13] A similar study was conducted on 538 patients with STEMI, showing STEMI patients undergoing PPCI with NLR ≥ 6.5 have a lower average LVEF of 46 ± 8% when compared to the NLR group < 6.5 of 49 ± 8% p <0.001.[6]

An NLR is a cheap and widely available parameter, in almost emergency care. NLR has been studied as a prognostic marker of AMI.[14] NLR has a better predictability than the total number of leukocytes and neutrophil as the prognostic parameters of cardiovascular disease.[15] NLR is a ratio of two pathways of the immune system, the neutrophil which have responsible for nonspecific inflammation, and lymphopenia which is a marker of poor health and physiological stress.[16]

Neutrophils release inflammatory mediators and regulate tissue inflammation. An increase in the number of neutrophils is associated with an acute inflammatory response due to tissue injury or a necrosis. In the AMI condition, neutrophil recruitment aims as a necrotizing myocardial cleansing system.[17] However, some maladaptive processes may occur, and become the main contributors in poor clinical outcomes such as: infarction expansion, post-infarction heart failure, epicardial and microvascular perfusion disorders, and post-infarction death. Some of the causes of these maladaptive processes have been formulated, including intravascular blockages, reperfusion lesions, oxidative stress, plaque damage due to neutrophil infiltration, and increased neutrophil-thrombocyte adhesion.[5,17]

In an acute condition, lymphopenia is a common condition as a result of elevated levels of cortisol. Lymphopenia in critical inflammatory conditions may result from increased apoptosis of lymphocytes. Under the condition of lymphopenia, clearance of apoptotic cells is imperfect due to poor phagocytosis, leading to the release

of proinflammatory cytokines. In the AMI condition, it is known that lymphopenia is associated with low LVEF and serious myocardial damage.[18] Taken together, the high NLR reflects an increase in acute inflammation and physiological stress, leading to maladaptive responses in the acute phase of AMI.[17]

There were several weaknesses in this study, such as no observation of the location of infarction or angiography evaluation, so wecould notidentifiy artery-related infarction, in which it may be related to GLS. Not all subjects received revascularisation therapy; only some of patients those have STEMI who get pharmacological revascularisation therapy so we not yet known how is the influence of the revascularisation therapy on the values of GLS.

## CONCLUSION

There is anassociation between NLR and left ventricular GLS in AMI patients, where high NLR is associated with worse GLS. High NLR is an independent risk factor for the worse GLS in the AMI patients.

## ACKNOWLEDGEMENTS

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