The Role of Neutrophil-Lymphocyte Ratio (NLR) as a Predictor of Successful Thrombolysis in Patients with STEMI at RSUP Dr. Sardjito

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ABSTRACT

Background. Coronary atherosclerosis is a major cause of ST-elevation acute myocardial infarction (STEMI). Many factors influence the pathophysiology of atherosclerosis formation, and one of the most important is inflammation. Neutrophils have an important role in the progression and instability of atherosclerotic plaques that lead to acute coronary syndromes, while lymphopenia is caused by an increase in endogenous cortisol that occurs during acute stress in acute coronary syndromes. The neutrophil-lymphocyte ratio (NLR) is a combination of inflammatory markers, integrating the two roles of leukocyte subtypes with their respective pathways into one predictor factor that can be applied to the outcome stratification of patients with STEMI undergoing thrombolytic therapy.

Objectives. To identify the role of NLR as a predictor of successful thrombolysis in patients with STEMI and knowing the NLR cut-off point that can act as a predictor of successful thrombolysis in patients with STEMI.

Method. This study was a retrospective cohort study. The research subjects were patients who were first diagnosed with STEMI in the ER/ICCU Dr. Sardjito Hospital and who met the inclusion and exclusion criteria, from January 1, 2016, to November 30, 2020. The independent variable in this study was the NLR at admission. The dependent variable in this study was the success of thrombolysis. Characteristic data in this study are presented in the form of categorical data. Bivariate statistical analysis with Chi-Square test. The prognostic value for success of thrombolysis was analyzed using the Receiver Operating Characteristic curve to determine the NLR limit value, followed by calculating the Relative Risk (RR). Variables having $p<0.25$ were continued in multivariate analysis.

Result. A total of 162 subjects met the inclusion and exclusion criteria. Overall, the success of thrombolysis was 81.5%. NLR values are in the range of 6 to 13 with a median value of 6.38. ROC NLR analysis on the success of thrombolysis obtained a cut-off of 10.16 fL. From the bivariate analysis for all possible predictors, 6 predictors had logistical significance ($p<0.25$) namely NLR, gender, age, BMI, onset, and Killip. From multivariate analysis, statistically significant independent predictors of thrombolysis success were NLR ($p=0.007$, OR 3.44), onset ($p=0.003$, OR 4.13), and Killip ($p=0.009$, OR 6.76).

Conclusion. A low NLR can be used as a predictor of successful thrombolysis in STEMI patients at RSUP Dr. Sardjito, with 3.44 times higher compared to the high NLR.

Keywords. *STEMI, Neutrophil-Lymphocyte Ratio, Thrombolysis*

ABSTRAK

Latar Belakang. *Penyakit arteri koroner dan infark miokard akut merupakan salah satu penyebab utama morbiditas dan mortalitas pada populasi di dunia. Aterosklerosis koroner merupakan penyebab utama terjadinya ST elevasi infark miokard akut (STEMI). Banyak faktor yang mempengaruhi patofisiologi pembentukan aterosklerosis, salah satu yang terpenting adalah inflamasi. Netrofil memiliki peranan yang penting pada progresifitas dan instabilitas plak aterosklerosis, sementara limfopenia diakibatkan oleh peningkatan kortisol endogen yang terjadi selama stress akut. Rasio netrofil-limfosit (RNL) merupakan kombinasi dari penanda inflamasi, mengintegrasikan dua peran subtipe leukosit dengan jalurnya masing-masing menjadi satu faktor prediktor yang dapat diaplikasikan untuk stratifikasi luaran pasien dengan STEMI yang menjalani terapi trombolisis.*

Tujuan. *Mengetahui peran RNL sebagai prediktor keberhasilan trombolisis pada pasien dengan STEMI dan mengetahui titik potong RNL yang dapat berperan sebagai prediktor keberhasilan trombolisis pada pasien dengan STEMI.*

Metode. *Penelitian ini merupakan penelitian kohort retrospektif. Subjek penelitian adalah pasien yang pertama kali terdiagnosis STEMI di UGD/ICCU RSUP Dr. Sardjito yang memenuhi kriteria inklusi dan eksklusi, sejak 1 Januari 2016 sampai 30 November 2020. Variabel bebas pada penelitian ini adalah RNL saat admisi. Variabel terikat pada penelitian ini adalah keberhasilan trombolisis. Data karakteristik pada penelitian ini disajikan dalam bentuk data kategori. Analisis statistik bivariat dengan uji Chi-Square. Nilai prognosis terhadap keberhasilan dianalisis menggunakan kurva* Receiver Operating Characteristic *untuk menentukan nilai batas nilai RNL, dilanjutkan dengan menghitung* Relative Risk *(RR). Variabel yang memiliki* p *<0,25 dilanjutkan dalam analisis multivariat.*

Hasil. *Sebanyak 162 subjek memenuhi kriteria inklusi dan eksklusi. Secara keseluruhan keberhasilan trombolisis sebanyak 81,5%, dengan rata-rata kegagalan trombolisis sebesar 18,5%. Nilai RNL berada pada rentang 6 hingga 13 (tidak terdistribusi normal) dengan nilai median 6,38. Analisis ROC RNL terhadap keberhasilan trombolisis diperoleh titik potong 10,16 fL. Analisis statistik bivariat dengan uji Chi-Square menunjukkan subyek dengan RNL rendah (<10,16 fL) lebih banyak mengalami keberhasilan trombolisis yaitu 105 pasien (86,8%), dibandingkan RNL tinggi yaitu 27 pasien (65,9%) (*p*=0,003, RR 1,32). Dari analisis bivariat untuk semua kemungkinan prediktor terdapat 6 prediktor yang memiliki nilai bermakna logistik (*p*<0,25) yaitu RNL, jenis kelamin, usia, IMT, onset, dan killip untuk dilakukan analisis multivariat. Dari analisis multivariat, faktor prediktor independen yang bermakna secara statistik terhadap keberhasilan trombolisis adalah RNL (*p*=0,007, OR 3.44), onset (*p*=0,003, OR 4,13), dan Killip (*p*=0,009, OR 6,76).*

Kesimpulan. *RNL yang rendah dapat digunakan sebagai prediktor keberhasilan trombolisis pada pasien STEMI di RSUP Dr. Sardjito, dengan keberhasilan 3.44 kali lebih tinggi dibanding RNL yang tinggi.*

Kata kunci. STEMI, Rasio Neutrofil Limfosit, trombolisis

INTRODUCTION

Coronary artery disease and acute myocardial infarction are some of the leading causes of morbidity and mortality in the world's population. Coronary atherosclerosis is a major cause of ST elevation acute myocardial infarction (STEMI). Many factors influence the pathophysiology of atherosclerosis formation, and one of the most important is inflammation. The inflammatory process underlying atherosclerosis has a role in causing plaque instability. This process also affects the formation of thrombus which exacerbates the erosion of atherosclerotic plaques, causing acute myocardial infarction.[1]

The total leukocyte count as a marker of acute and chronic inflammation has become the focus of research in the last two decades and the results show that the total leukocyte count is not only a risk factor for cardiovascular disease but also a prognostic factor.[2] Leukocytes are the main inflammatory mediators and play a role in the response to an injury. From a follow-up study, it was found that neutrophils affect

infarct healing adaptation, formation of leukocyte-platelet aggregation and are associated with reperfusion injury in acute coronary syndrome patients, while monocytes and lymphocytes influence plaque in coronary arteries.[3]

Neutrophils have an important role in the progression and instability of atherosclerotic plaques that lead to acute coronary syndromes, while lymphopenia in acute coronary syndromes is caused by an increase in endogenous cortisol that occurs during acute stress acute coronary syndromes. The neutrophil-lymphocyte ratio is a combination of inflammatory markers, neutrophils as markers of non-specific inflammatory reactions, and lymphocytes as regulatory pathway markers, integrating the two roles of leukocyte subtypes with their respective pathways into one predictor factor that can be applied to the outcome stratification of patients with acute coronary syndrome undergoing thrombolytic therapy.

METHODS

This study is a retrospective cohort study. This research was conducted at the Installation of Medical Records RSUP Dr. Sardjito Yogyakarta. Data collection was carried out in December 2020 – January 2021. The sample in this study was the medical record data of patients who were first diagnosed with STEMI in the ER/ICCU Dr. Sardjito Hospital and who met the inclusion and exclusion criteria, from January 1, 2016, to November 30, 2020.

Inclusion criteria included patients aged 18 years or older, who were admitted through the emergency department and treated at the ICCU of Dr. Sardjito Hospital and diagnosed with STEMI for the first time who were upright based on the 2015 PERKI Clinical Practice Guidelines and received thrombolytic therapy using t-PA thrombolytic drugs or intravenous streptokinase according to the regimen and data on the neutrophil lymphocyte ratio examination are available at the beginning of the diagnosis of STEMI.

The sample size was calculated by the study sample size formula using the Power and Sample Size Calculation version 3.0 software for independent dichotomy data using two proportions.[4] This formula was used in a cohort study aimed at finding the relationship between the RNL score and the success of thrombolysis in hospitalization. Based on the calculation of the formula, each group obtained n of 81 subjects so the minimum number of samples in this study was 162 subjects.

The variables of this study consisted of the dependent variable and the independent variable. The dependent variable in this study was the success of thrombolysis (defined as the presence of at least two of the subsequent criteria at 2 hours after thrombolytic treatment: 1) significant relief of pain (a 5-

point reduction on a 1 to 10 subjective scale), 2) ≥50% reduction of sum of ST segment elevation, and () abrupt initial increase of creatine kinase levels, as stated in the medical records). The independent variable in this study was NLR at admission. Confounding variables are variables related to independent variables and dependent variables. The confounding variables in this study were age, gender, nutritional status, severity of STEMI, comorbidities (DM, hypertension, heart failure, smoking, stroke, COPD), and medications that have been given.

Characteristic data in this study are presented in the form of categorical data with numbers or percentages, numerical data with mean and SD (standard deviation) or median (minimum-maximum value). Bivariate statistical analysis with Chi-Square test with categorical variables of 2 unpaired groups. The prognostic value for success was analyzed using the Receiver Operating Characteristic curve to determine the limit value of the RNL value, followed by calculating the Relative Risk (RR) to determine the magnitude of the risk among STEMI patients with low and high RNL values. The results are said to be statistically significant if $p<0.05$ with 95% confidence interval and RR > 1. Variables that have $p <$ 0.25 were continued in multivariate analysis with logistic regression and said to be statistically significant if $p<0.05$ with 95% confidence interval and RR > 1.

This research has received ethical approval from the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University - RSUP Dr Sardjito number KE/FK/0820/EC/2020. All medical record data used will be kept confidential.

RESULTS AND DISCUSSIONS

During the 2 months research period (December 2020 to January 2021) medical records have been successfully studied for 4 years (1 January 2016 – 30 November 2020). A total of 162 subjects met the inclusion and exclusion criteria (Figure 1).

The number of male research subjects was 88.9%, with a mean age of 55.2 (± 10.8) years, with the highest proportion <65 years, namely 131 subjects and 19.1% of subjects aged > 65 years. A total of 53.7% (87 subjects) had overweight and obese nutritional status (BMI 23 kg/m2). Smoking status was divided into 2 categories, namely the group had smoked with a percentage of 75.3% and the non-smoking group was 24.7%. The most comorbid was DM as much as 85.2% (138 subjects) followed by dyslipidemia and hypertension as much as 74.1% and 56.8%, respectively.

There 79% used a fibrinolytic agent in the form of alteplase and 21% used a streptokinase agent. Most location of infarct is anterior as much as 56.2%. With the most

Killip degrees, Killip I was 93.8%. Overall, the success of thrombolysis was 81.5%, with an average thrombolysis failure of 18.5%. NLR values are in the range of 6 to 13 (not normally distributed) with a median value of 6.38 (Table 1).
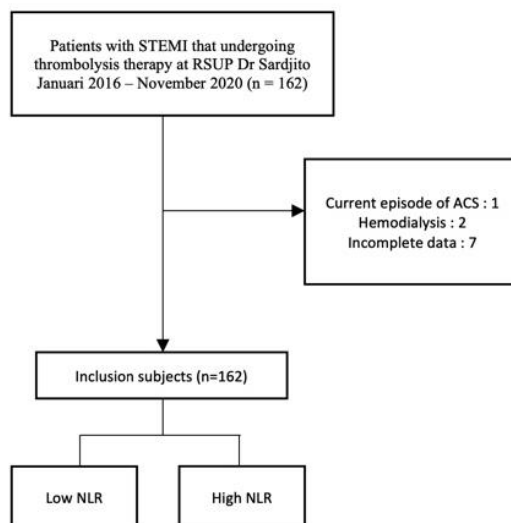

Figure 1. Research flow

Table 1. Baseline characteristics

Subject Characteristic		N	%
Gender	Male	144	88.9%
	Female	18	11.1%
Age		55.2 ± 10/8	
	≥65 years	31	19.1%
	<65 years	131	80.9%
BMI	Normal	75	46.3%
	Overweight	39	24.1%
	Obese	48	29.6%
DM	No	138	85.2%
	Yes	24	14.8%
Hypertension	No	92	56.8%
	Yes	70	43.2%
Dyslipidemia	No	120	74.1%
	Yes	42	25.9%
Smoking	No	40	24.7%
	Yes	122	75.3%
Thrombolytic agents	Alteplase	128	79.0%
	Streptokinase	34	21.0%
Onset	<4 hours	86	53.1%
	4-6 hours	76	46.9%
Infarct Location	Non anterior	71	43.8%
	Anterior	91	56.2%
Killip	I	152	93.8%
	II	10	6.2%
Outcome	Successful	132	81.5%
	Failed	30	18.5%
NLR		6.38 (0.67– 27.72)	

The next step is to determine the limit value of the NLR value to success, which is analyzed using the Receiver Operating Characteristic (ROC) curve. ROC NLR analysis on the success of thrombolysis obtained a cut-off of 10.16 fL then the NLR was divided into low NLR if <10.16 fL and high if >10.16 fL (Figure 2).
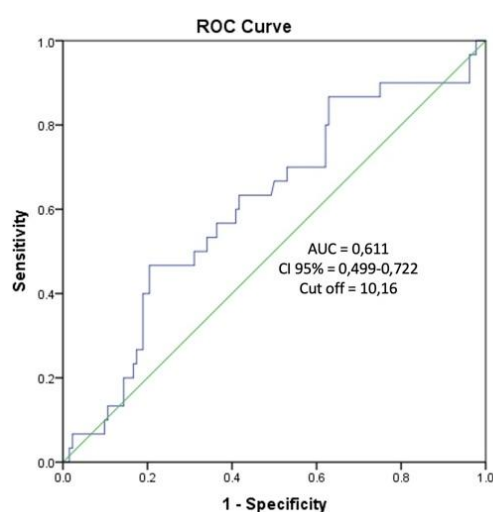

Figure 2. ROC Curve

This was followed by bivariate statistical analysis with the Chi-Square test with category 2 unpaired group variables and continued with calculating the Relative Risk (RR) to determine the magnitude of thrombolysis success among STEMI patients with low NLR values and high NLR values (Table 2). Patients with low NLR (<10.16 fL) experienced more successful thrombolysis, namely 105 patients (86.8%), this was more than high NLR, 27 patients (65.9%) with a significant difference p=0.003 (p<0.05).

In a previous study of the neutrophil to lymphocyte ratio, a high NLR value (>3) could be an independent predictor of the degree of cardiovascular disease and also a predictor of poor clinical outcome in a cohort study of a heterogeneous number of patients undergoing angiography.[5]

In patients with acute coronary syndromes with NLR > 9.10, there was a greater risk of death compared to the groups with the lowest NLR (8.5% vs. 1.8% in treatment) and (11.5% vs. 2.5% at 6 months). A study on the prognosis of patients with acute coronary syndromes with various NLR values found that the higher the NLR (>4.5) the higher the mortality (11%) compared to the NLR <1.5 (2.4%).[6]

Several other studies have attempted to obtain the NLR cut-off point in predicting outcomes. A study conducted in a tertiary care center in the USA found that the NLR cut-off point of 7.4 as a predictor of short-term (≤ 30 days) and long-term (≤ 2 years) mortality in STEMI patients undergoing revascularization.[2] So far, there has been no research that looks for optimal cut points in ACS patients treated in Indonesia, and with variations in the inflammatory response based on genomic differences in each race and ethnicity, a separate study is needed for each population.[7]

Table 2. Bivariate analysis

		Outcome				*p*	RR	CI 95%
		Successful		Failed				
		N	%	N	%			
NLR	<10.16 fL	105	86.8%	16	13.2%	0.003*	1.32	1.05-1.66
	>10.16 fL	27	65.9%	14	34.1%			

In this study, patients with low NLR (<10.16 fL) significantly had more successful thrombolysis than patients with high NLR (105 patients vs 27 patients, *p*=0.003). The RR value is 1.32, which means that patients with low NLR have a 1.32 times higher chance of successful thrombolysis compared to high NLR, so the lower the neutrophil-lymphocyte ratio value at admission, the higher the success of thrombolysis in STEMI patients.

The ratio of neutrophil to lymphocyte is a sign of the balance between neutrophils and lymphocytes in the body which is an indicator of systemic inflammation. Increased inflammation in STEMI patients is associated with extensive atheroma and associated inflammatory and thrombotic pathways as previously described. Neutrophils can contribute to the pathology of arterial and venous thrombosis or immunothrombosis by secreting neutrophil extracellular traps (NETs) and NET secretion is a major contributor to thrombogenesis in pathological conditions such as sepsis and malignancy.[8]

Table 3. Bivariate analysis based on outcome

Variables		Outcome				*P*	RR	CI 95%
		Successful		Failed				
		N	%	N	%			
Gender	Male	120	83.3%	24	16.7%	0.107$	1.25	0.89-1.75
	Female	12	66.7%	6	33.3%			
Age	≥65 years	23	74.2%	8	25.8%	0.245	0.892	0.72-1.11
	<65 years	109	83.2%	22	16.8%			
BMI	Normal	59	78.7%	16	21.3%			
	Overweight	31	79.5%	8	20.5%	0.212	0.89	0.77-1.05
	Obese	42	87.5%	6	12.5%	0.312	0.91	0.75-1.10
Thrombolysis agents	Alteplase	109	85.2%	19	14.8%	0.019*	1.26	0.99-1.61
	Streptokinase	23	67.6%	11	32.4%			
Onset	<4 hours	77	89.5%	9	10.5%	0.005*	1.24	1.06-1.45
	4-6 hours	55	72.4%	21	27.6%			
Killip	I	128	84.2%	24	15.8%	0.003*$	2.11	0.98-4.51
	II	4	40.0%	6	60.0%			
DM	No	112	81.2%	26	18.8%	1.000$	0.97	0.80-1.18
	Yes	20	83.3%	4	16.7%			
Hypertension	No	77	83.7%	15	16.3%	0.406	1.06	0.92-1.24
	Yes	55	78.6%	15	21.4%			
Dyslipidemia	No	98	81.7%	22	18.3%	0.918	1.01	0.85-1.19
	Yes	34	81.0%	8	19.0%			
Smoking	No	31	77.5%	9	22.5%	0.455	0.94	0.78-1.13
	Yes	101	82.8%	21	17.2%			

Bivariate analysis showed that the predictor factors that influenced the success of thrombolysis were Killip (p= 0.003) (Table 3). Several previous studies have shown a relationship between the success of thrombolysis and the onset (window period or pain to fibrinolytic), for example, a 2015 study examined the factors that influence the success of thrombolysis, namely the time window period of 0 to 4 hours since symptom onset has a higher success rate ($p<0.01$) compared after 4 hours, patients with higher Killip had a higher rate of thrombolytic failure ($p<0.05$).[9] From the bivariate analysis for all possible predictors, 6 predictors had logistical significance ($p<0.25$) namely NLR, gender, age, BMI, onset, and Killip for multivariate analysis.

Table 4. Multivariate Analysis of Variables on Successful Thrombolysis

		p	OR	CI 95%
NLR	<10.16	0.007*	3.44	1.39 – 8.49
	>10.16			
Age	< 65 years	0.686	0.79	0.25 – 2.45
	> 65 years			
Gender	Male	0.122	2.70	0.77 – 9.51
	Female			
BMI	Normal	0.427	0.63	0.20 – 1.98
	Overweight	0.227	0.46	0.13 – 1.61
	Obese			
Killip	I	0.009*	6.76	1.59 – 28.65
	II			
Onset	< 4 hours	0.003*	2.90	1.61-10.61
	4-6 hours			

Multivariate analysis with logistic regression obtained the following results showed in Table 4. The independent predictor factor which was statistically significant for the successful thrombolysis was NLR (p=0.007, OR 3.44, CI 1.39 - 8.49), this means that patients with low NLR had a 3.44 times higher chance of successful thrombolysis compared to high NLR. Patients who underwent thrombolysis less than 4 hours from the onset of pain (p=0.003, OR 4.13, CI 1.61-10.61) had a 4.13 times higher chance of successful thrombolysis than those who underwent thrombolysis more than 4 hours. Time window period, patients who underwent thrombolysis within 0-4 hours of symptom onset had a higher success rate than those who were more than 4 hours ($p<0.01$). Patients with higher Killip had a high failure rate ($p<0.05$).[7]

The results in this study are in accordance with previous studies, where patients with Killip I (p=0.009, OR 6.76, CI 1.59 -28.65), had a 6.76 times higher chance of successful thrombolysis than those with Killip II. In previous studies, it was stated that the factors that influence the success of

thrombolysis include gender, age > 75 years, renal insufficiency, and heart failure. Killip IV could not predict thrombolysis failure (p=0.609; 0.33; 0.081; 0.459). Anemia, diabetes, high blood pressure, and use of inotropic agents at admission were predictors of thrombolytic failure (p=0.03; 0.007; 0.002; <0.001).

Thrombolysis in less than 4 hours was also a predictor of successful thrombolysis (p<0.001). In a multivariate analysis, hypertension and inotropic drug use were the two independent factors of thrombolytic failure. In this study, age, gender, diabetes, hypertension, dyslipidemia, and smoking were not predictors of thrombolysis success as in previous studies, where the results obtained were not significantly significant on these variables.

This study has limitations, related to the retrospective cohort design, causing the data to be collected only from medical records, thereby reducing the completeness of information.

CONCLUSION

This study concludes that a low neutrophil-lymphocyte ratio (NLR) can be used as a predictor of successful thrombolysis in STEMI patients at Dr. Sardjito Hospital, with 3.44 times success compared to the high NLR.

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