

RESEARCH

Correlation of Neutrophil Lymphocyte Ratio (NLR) Values with Severe Preeclampsia, HELLP Syndrome, and Eclampsia

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Abstract

Background: Preeclampsia (PE) is the leading cause of maternal and fetal morbidity and mortality. The disease is characterized by hypertension ($\geq 140/90$ mmHg), proteinuria, thrombocytopenia, renal failure, neurological complications, liver involvement, and fetal growth retardation. HELLP syndrome is a variant of preeclampsia that causes an increase in liver enzymes and a low platelet count. Eclampsia is the heaviest complication of preeclampsia. Neutrophil lymphocyte ratio (NLR) is part of the leukocyte type count examination which is an easy, available examination parameter and can be used as an index of the severity of systemic inflammation. This study aimed to determine the relationship of neutrophil-lymphocyte ratio (NLR) values with severe Preeclampsia, HELLP syndrome, and eclampsia.

Method: This research is a comparative analytical study with a case control study approach. This research was conducted from April-November 2022. This study was conducted at the emergency room (ER) and inpatient department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Andalas – RSUP Dr. M. Djamil Padang. The study sample was part of the population that met the inclusion and exclusion criteria. The study required 108 samples, namely 27 from the severe preeclampsia group, 27 from the eclampsia group, 27 from the HELLP syndrome group, and 27 from the control group. Bivariate statistical analysis using Independent T-Test. Samples were taken by the method of consecutive sampling. The data were analyzed at a 95% confidence interval, if obtained p value < 0.05 then there is a significant relationship. The Data was analyzed by the SPSS computer program.

Results: The results of this study obtained neutrophil-lymphocyte ratio in eclampsia has the highest average value compared with HELLP syndrome, severe preeclampsia, and control. While HELLP syndrome has a higher mean value than severe preeclampsia and control and subsequently severe preeclampsia also has a higher mean value NLR than control. This study found a significant relationship between neutrophil-lymphocyte ratio (NLR) with severe Preeclampsia, HELLP syndrome, and eclampsia (all p values = 0.000).

Conclusion: This study proves that neutrophil-lymphocyte ratio (NLR) has a significant relationship with severe Preeclampsia, HELLP syndrome, and eclampsia so further research can develop this study by analyzing other factors that affect preeclampsia. For clinicians can make this study as a reference in monitoring the progression of inflammation that occurs in severe preeclampsia, HELLP syndrome, and eclampsia.

Keywords: *Neutrophil-lymphocyte ratio (NLR), preeclampsia, HELLP syndrome, eclampsia*

INTRODUCTION

Preeclampsia (PE) is the leading cause of maternal and fetal morbidity and mortality. Preeclampsia affects 5-8% of all pregnancies. The disease is characterized by hypertension ($\geq 140/90$ mmHg), proteinuria, thrombocytopenia, renal failure, neurological complications, liver involvement and fetal growth retardation.^[1,2] Preeclampsia is a pregnancy-related hypertensive disorder that occurs in 2-8% of pregnancy complications. Preeclampsia causes 9-26% of maternal deaths in low-income countries. Hypertensive disorders due to pregnancy are one of the causes of maternal morbidity and mortality worldwide. By the middle of this century, the incidence of preeclampsia and maternal mortality had decreased in developed countries. Although in developing countries, the incidence of preeclampsia and maternal mortality remains high. Based on a meta-analysis, the global incidence of preeclampsia is 4.6%. Research by Wang et al, showed South Asia had the highest incidence of hypertensive disease due to pregnancy in 2019. Southeast Asia had an incidence of Pregnancy-Induced Hypertension of 14.79: 10,000 in 2019. The incidence of preeclampsia in Indonesia is 128,273/year or about 5.3% and is the second highest cause of maternal mortality after bleeding from all pregnancies, occurring about 3-8% of pregnancies with preeclampsia^[3,4]

Epidemiological research related to the prevalence of preeclampsia in West Sumatra is still small. Based on data from Putra & Basyi (2022) taken from the data recap of preeclampsia pregnant women at Dr M Djamil Padang hospital from July 2020 to July 2021, it shows that most of the distribution of preeclampsia patients by age occurs at the age of 20-35 years with 119 (66.1%) cases, for the distribution of preeclampsia based on parity mostly occurs in multipara with 100 (55.6%) cases.^[5]

Preeclampsia represents a complex obstetric condition characterized by hypertension and proteinuria at ≥ 20 weeks of gestation or can be diagnosed with hypertension along with other diagnostic criteria involving multiple organ targets. Preeclampsia is one of the leading causes of maternal and fetal death and morbidity with long-term effects on maternal and fetal health. Preeclampsia causes activation of immunological factors such as stimulation of systemic inflammation that leads to increased neutrophil levels, platelet activation and endothelial dysfunction. HELLP syndrome is a variant of preeclampsia that causes an increase in liver enzymes and a low platelet count. HELLP syndrome is thought to have a stronger inflammatory reaction. Eclampsia is the heaviest complication of preeclampsia. Eclampsia is thought to be associated with systemic inflammatory processes and causes neuroinflammation in the brain. The neuroinflammation that occurs can lower the threshold for the occurrence of seizures.^[5,6]

Neutrophil-lymphocyte ratio (NLR) is part of the leukocyte type count examination which is an easy, available examination parameter and can be used as an index of the severity of systemic inflammation. Systemic inflammation due to immunological factors or excessive inflammatory response is characterized by an increase in the neutrophil-lymphocyte ratio (NLR). Neutrophils themselves serve as a defense against microbial invasion or phagocytosis. These cells play an important role in the diagnosis of inflammation and infection. While lymphocytes are part of the leukocytes that move to the inflammatory area. Lymphocytes are also an important source of immunoglobulins in the body's cellular immune response. Lymphocytes have a role to fight infections caused by viruses or bacteria.^[7,8]

NLR values obtained by calculating the ratio of neutrophils and lymphocytes, is a new marker of systemic inflammation. NLR has been extensively studied for the prediction of the incidence of major heart disease among patients with stable coronary artery disease, acute myocardial infarction, acute pulmonary embolism, and hypertension. NLR and other hematological indices have an influence on the occurrence of systemic inflammation and have been investigated in patients with preeclampsia.^[7,8]

Research conducted by Wang et al (2019) has investigated the value of systemic immune inflammatory indices, namely neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) to identify and evaluate preeclampsia patients. In this study, it was found that the differential leukocyte count was significantly altered in preeclampsia patients because preeclampsia patients had significantly higher MLR and NLR values than control women with normal pregnancies.⁹

Serin et al (2016) conducted a study on the use of maternal neutrophil lymphocyte ratio (NLR) to assess the severity of preeclampsia, eclampsia or the severity of proteinuria. Based on the results of a study by Serin et al (2016), a very high neutrophil-lymphocyte ratio was determined in patients with preeclampsia compared to those who were healthy pregnant. In addition, NLR was found to be significantly higher in the severe preeclampsia group compared to the mild preeclampsia group indicating that NLR can determine the severity of preeclampsia.^[10,11] However, there is also a different study conducted by Toptas et al (2016) in which it was found that NLR values were not related to the severity of PE. But data on the importance of NLR in PE is insufficient and further research is needed to elucidate the importance of NLR in PE.^[12]

Based on the results of the above study, the researchers were interested in conducting research on the relationship of neutrophil lymphocyte ratio (NLR) with the incidence of preeclampsia. The incidence of preeclampsia to be investigated in this study will be divided into uncomplicated Preeclampsia, HELLP syndrome and eclampsia and assessed whether there are differences in the neutrophil lymphocyte ratio (NLR) values of each of them.

METHOD

This research is comparative analytical research with a case control study approach. This research was conducted from April 2022-November 2022. This study was conducted in the Emergency Room (ER) and inpatient Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Andalas – RSUP Dr. M. Djamil Padang. The population in this study was all pregnant women who came to the obstetrics department at RSUP M. Djamil Padang. The study sample is the part of the population that meets the inclusion and exclusion criteria, as follows:

a. Inclusion Criteria

1. Pregnant women who experience severe Preeclampsia, HELLP syndrome, or eclampsia at RSUP Dr. M. Djamil.
2. Pregnancy with a single fetus
3. Willing to follow research



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b. Control Inclusion Criteria

1. Pregnant women without severe Preeclampsia, HELLP syndrome, or eclampsia at RSUP Dr. M. Djamil
2. Pregnancy with a single fetus
3. Willing to follow research

c. Exclusion Criteria

1. Pregnant women with a history of malignancy
2. Pregnant women with a history of infectious diseases
3. Pregnant women with a history of premature rupture of membranes
4. Pregnant women with a history of cardiovascular disease
5. Pregnant women with a history of diabetes mellitus

Determination of the sample size in the study was calculated statistically using the Formula Lemeshow (1997) obtained 108 samples, namely 27 from the group of severe preeclampsia, 27 from the eclampsia group, 27 from the HELLP syndrome group and 27 from the control group. Samples were taken by the method of consecutive sampling. Researchers conducted a study of pregnant women diagnosed with severe Preeclampsia, HELLP syndrome or eclampsia at RSUP Dr. M. Djamil Padang. Previously, informed consent was done by filling out the approval sheet and then blood was taken to determine the ratio of neutrophils and lymphocytes.

Univariate analysis is used to see the distribution of data of each variable and then presented in Tabular Form. The Data consist of sample characteristics presented in frequency distribution tables and values of neutrophil-lymphocyte ratio (NLR) in severe preeclampsia, HELLP syndrome, eclampsia, and control in the form of mean, median, and standard deviation/minimal-maximal ranges. The normality of the distribution of the study sample was tested with Shapiro-Wilk. To determine the comparison of NLR values in severe preeclampsia, HELLP syndrome, and eclampsia with the control group performed bivariate statistical analysis using Independent T-Test. If the data is not normally distributed then the non-parametric test, Mann-Whitney U Test is an alternative. The data were analyzed at a 95% confidence interval, if obtained p value < 0.05 then there is a significant relationship. The Data was analyzed by the SPSS computer program. Multivariate analysis is used to determine the exposure together of several factors that affect the value of NLR. The statistical test used is linear Regression. The final conclusion on the multivariate test as follows:

- a. All variables that enter the model or qualify for candidate selection are variables that have an influence on the dependent variable, p value < 0.05 .
- b. The variable with the largest OR in the multivariate final model, being the one that most dominantly affects the dependent variable.

The study was conducted after the research subjects were given information and a statement of consent stating voluntarily to sign the agreement to follow the study. After this study received research approval (ethical clearance) from the Ethics Committee of Health Research, Faculty of Medicine, Universitas Andalas/RSUP M. Djamil Padang.

RESULTS

Research has been conducted on respondents who experience preeclampsia to determine the relationship of neutrophil lymphocyte ratio (NLR) with severe Preeclampsia, HELLP syndrome and eclampsia. Characteristics of research respondents can be seen in **Table 1.1** below:

Table 1.1 Characteristic of Responden

Characteristic	Group Mean±SD, f(%)			
	Severe Preeclampsia	Eclampsia	HELLP Syndrom	Control
Age (year)	32,2±4,2	27,1±7,9	30,3±6,4	33,8±5,23
Parit				
Primigravid	2(7,4)	15(55,6)	7(25,9)	1(3,7)
Multigravid	25(92,6)	12(44,4)	20(74,1)	26(96,3)
Gestational Age				
≥37 weeks	7 (26)	8 (30)	8 (30)	17 (63)
<37 weeks	20 (74)	19 (70)	19 (70)	10 (37)
NLR	6,0±4,9	11,4±7,7	7,0±3,8	4,2±1,7

Based on Table 1.1 it can be seen that patients with eclampsia have the youngest mean age and the control group has the oldest mean age. The primigravid group was more prevalent in eclampsia patients than the severe preeclampsia, HELLP syndrome, and control groups. Regarding gestational age, the pathological group had approximately the same proportion of childbirth at 37 weeks, namely in HELLP syndrome and eclampsia of 70% and severe preeclampsia of 74%, while this is very contrary to normal pregnancy which has a proportion of childbirth of 37 weeks of 37%. NLR values were found to be highest in the eclampsia group, followed by HELLP syndrome, severe preeclampsia, and controls.

Research conducted by Grum et al. (2017) found that primigravida or nulliparous is a risk factor for the occurrence of preeclampsia and/or eclampsia. Preeclampsia is generally considered a disease of the first pregnancy caused by immunological incompetence between fetoplacental and maternal tissues. The results of this study differ from those studies due to the number of samples obtained in this study in general in the pathological group and the control

group, more multigravides were found in accordance with the research conducted by Syahputra et al (2019).^[13] However, although the primigravida group was not found as much as in the Grum et al (2017) study, in this study the eclampsia group had more primigravida respondents than the control group (55% vs. 44%).

Neha et al (2016) found that a small age of 20 years is one of the risk factors for the incidence of preeclampsia. Factors influencing the development of preeclampsia before the age of 20 may be due to the invasion of early trophoblasts and the reaction of the mother's body. Failure of trophoblast invasion leads to maladaptation of the spiralis arterioles associated with the cause of preeclampsia.^[14]

Based on gestational age, the proportion of preterm pregnancies (<37 weeks) was not much different between Preeclampsia, HELLP syndrome, and eclampsia, but compared to the control group, the proportion of preterm pregnancies (<37 weeks) was much higher. This shows that the incidence of preeclampsia often occurs in pregnancies with a smaller gestational age which results in more frequent terminations at that age to save the mother and baby by research conducted by Aulia et al. (2020) where pathological conditions of pregnancy such as severe Preeclampsia, HELLP syndrome, and eclampsia are associated with preterm labor.^[15]

NLR values in the incidence of preeclampsia can be seen in **Table 1.2** below.

Table 1.2 NLR Values in Severe Preeclampsia, HELLP Syndrome, and Eclampsia

GROUP	NLR			
	Mean	Min - Max	Median	SD
Severe eclampsia	6,0	1,8-23,5	4,2	4,9
HELLP syndrome	7,0	1,1-15,0	6,2	3,8
Eclampsia	11,4	2,5-31,4	6,9	7,7
Control	4,2	2,1-8,9	3,8	1,7

Based on Table 1.2, it can be seen that eclampsia has the highest average value compared to HELLP syndrome and severe preeclampsia, which is 11.4 ± 7.7 with the smallest NLR being 2.5 and the largest is 31.4. The lowest NLR value was found in the control group with an average of 4.2, a minimum NLR of 2.1, and a maximum of 8.9 where the min-max value when compared to the entire pathological group was still smaller.

Based on the results of this study, eclampsia has the highest average value compared to HELLP syndrome, severe preeclampsia and control. While HELLP syndrome has a higher mean value than severe preeclampsia and control and subsequently severe preeclampsia also has a higher mean value NLR than control. This shows that eclampsia has a more severe inflammatory reaction than preeclampsia / severe preeclampsia and HELLP syndrome. HELLP syndrome is part of hypertension in pregnancy, but compared to preeclampsia, the inflammatory reaction is stronger and the immune system attacks the liver and the coagulation cascade.^[16] The research by Gogoi et al. (2017) in India found a higher NLR value in preeclampsia patients compared to controls, which was 6.8 ± 7.6 . Sachan et al. (2017) in their research on 543 pregnant women in India also found in preeclampsia found NLR values above

normal with the cut-off obtained from the ROC curve is >3.35 while in severe preeclampsia found a higher cut-off is >3.42. In this study, NLR was measured at 13-20 weeks of gestation. [17,18]

Correlation of neutrophil lymphocyte ratio (NLR) values with severe Preeclampsia, HELLP syndrome, eclampsia **Table 1.3** below.

Table 1.3 Correlation of Neutrophil-Lymphocyte Ratio (NLR) Values with Severe Preeclampsia, HELLP Syndrome, Eclampsia

Group	n	NLR		*P-value
		Mean ± SD	Median	
Severe Preeclampsia	27	6,0±4,9	4,2	0,000
Control	27	4,2±1,7	3,8	
HELLP Syndrome	27	7,0±3,8	6,2	0,000
Control	27	4,2±1,7	3,8	
Eclampsia	27	11,4±7,7	6,9	0,000
Control	27	4,2±1,7	3,8	

* *Mann-Whitney U Test*

Based on **Table 1.3**, there is a relationship between NLR and severe preeclampsia (p value 0.000) where the NLR average is higher in the group of severe preeclampsia than the control (6.0±4.9 vs. 4.2±1.7). **Table 1.3** also found a relationship between NLR with HELLP syndrome (p value 0.000) with the mean NLR HELLP syndrome is 7.0±3.8 higher than the control group (NLR 4.2±1.7). In also found a relationship between NLR with eclampsia (p value 0.000) with NLR eclampsia mean is 11.4±7.7 which is higher than the control group (NLR 4.2±1.7).

There is a significant association of neutrophil-lymphocyte ratio (NLR) values with severe preeclampsia. A similar study was conducted by Yavuzcan et al. (2014) who found that NLR was higher in preeclampsia women compared to controls. Wang et al. (2019) have also investigated the value of systemic immune-inflammatory indices, namely neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) to identify and evaluate the prognosis of preeclampsia patients. In this study, it was found that the differential leukocyte count was significantly altered in preeclampsia patients, as preeclampsia patients had significantly higher MLR and NLR values than women with normal pregnancies. Higher NLR values have better diagnostic performance in differentiating the severity of preeclampsia. Patients with higher NLR values were at higher risk in the study population. Higher NLR and MLR values were significantly associated with severe maternal morbidity, adverse neonatal outcomes, and preterm labor. NLR and MLR offer clinical assessment indicators, evaluation of disease severity, and more effective evaluation of preeclampsia prognosis.^[11,19]

Early identification of preeclampsia events is beneficial for close clinical monitoring of patients and can safely prolong pregnancy through effective treatments. Circulating leukocytes in the mother are activated during pregnancy and subsequently activated in preeclampsia. These activated leukocytes are responsible for the vascular dysfunction associated with preeclampsia. NLR is considered a marker for predicting the presence and severity of preeclampsia.^[19,20]

Based on the results of this study, eclampsia has the highest average value compared to HELLP syndrome, severe preeclampsia and control. While HELLP syndrome has a higher mean value than severe preeclampsia and control and subsequently severe preeclampsia also has a higher mean value NLR than control. This shows that eclampsia has a more severe inflammatory reaction than preeclampsia / severe preeclampsia and HELLP syndrome. HELLP syndrome is part of hypertension in pregnancy, but compared to preeclampsia, the inflammatory reaction is stronger and the immune system attacks the liver and the coagulation cascade.^[16,21]

In this study found a significant relationship between NLR and eclampsia where the average NLR was found to be higher than the control group. This is in accordance with research by Banda et al. (2016) who found neutrophils in eclampsia women were significantly higher with lower CD3+ and CD4+ T cells. Eclampsia is a major neurological complication of preeclampsia defined as episodes of seizures or other signs of altered consciousness that occur in preeclampsia and cannot be attributed to a preexisting neurological condition.^[21,22]

The significant differences found in the subset of T lymphocytes in the peripheral blood of pregnant women with eclampsia in this study could be due to the immunosuppressive effect of placental products such as pregnancy-specific beta-1 glycoprotein, progesterone or human chorionic gonadotrophin. Pregnancy is associated with inflammatory processes that can lead to increased expression of cell adhesion molecules (CAMs) that facilitate the extravasation of leukocytes to the tissue site where the activation of the immune system occurs.^[22]

Multivariate analysis of this study by including 3 models of severe Preeclampsia, HELLP syndrome and eclampsia can be seen in **Table 1.4** below.

Table 1.4. Multivariate analysis of the incidence of severe Preeclampsia, HELLP syndrome, and eclampsia on NLR values

Group	p-value	Odd Ratio	CI 95%	
			Lower	Upper
Severe preeclampsia	0,019	1,800	18,778	41,629
HELLP syndrome	0,048	2,763	17,815	40,666
Eclampsia	0,000	7,144	13,434	36,285

***Linier Regression**

Based on Table 1.4, it was found that all three groups had a significant relationship with NLR with the highest OR obtained in eclampsia followed by HELLP syndrome and severe preeclampsia. In eclampsia, there is a 7 times higher risk of experiencing an increase in NLR than in normal pregnancy.

In this study, the highest NLR was found in the eclampsia group which indicates eclampsia has the most effect on NLR values. Further analysis with logistic regression also found the strongest relationship between eclampsia and NLR with a risk of 7 times compared to normal pregnancy in line with NLR results obtained the highest compared to the other two pathological groups.

This is supported by the research of Khamis et al. (2020) who found the fact that the more severe the Preeclampsia, the higher the NLR level also indicates a higher excessive immune response.^[21,23]

A different thing was discovered by Kholief et al. (2018) in 105 pregnant women with gestational age ≥ 34 weeks in Egypt where it was stated that NLR did not differ between control patients and patients with preeclampsia incidence or severity. In this study mentioned platelet / lymphocyte ratio (PLR), and C-reactive protein (CRP) are more sensitive in predicting the incidence and severity of preeclampsia. This study used a case control study design and only included patients with mild and severe preeclampsia without including patients with HELLP syndrome and eclampsia so that this could be the cause of differences in study results. In addition, the measurement time of laboratory values that are not the same as the study can also be the cause of differences in the results of the study.^[24]

Kurtoglu et al. (2014) also found NLR not significantly associated with increased severity of the incidence of preeclampsia although in the study said NLR can be used to predict the incidence of preeclampsia. In this study, the differences in the study were caused by samples that were included only from mild and severe preeclampsia so that the same as Kholief's findings, the results found did not show significant differences because the HELLP syndrome and eclampsia samples were not included in the study.^[25]

CONCLUSION

Based on the characteristics of the sample in this study found in the eclampsia group found the smallest average age, the proportion of primigravida are also more and the highest levels of NLR. Preterm pregnancy was found more often in the pathological group than in the control group. Mean NLR values were found to be highest in the eclampsia group, followed by HELLP syndrome, severe preeclampsia, and controls. There is a significant association of NLR values with severe Preeclampsia, HELLP syndrome, and eclampsia. Eclampsia was found to be the pathological condition that most affected NLR with a significantly higher risk than HELLP syndrome and severe preeclampsia.

This study proves that neutrophil-lymphocyte ratio (NLR) has a significant relationship with severe Preeclampsia, HELLP syndrome, and eclampsia so further research can develop this study by analyzing other factors that affect preeclampsia. For clinicians can make this study as a reference in monitoring the progression of inflammation that occurs in severe preeclampsia, HELLP syndrome, and eclampsia.

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