RESEARCH ARTICLE

Clinical Ability of Neutrophil–Lymphocyte Ratio in Pregnancy as a Predictor of Preeclampsia

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Abstract

Aim and objective: Preeclampsia is part of the hypertension spectrum that occurs during the pregnancy period, especially when the gestational age is 20 weeks or more. Preeclampsia has a broad impact not only on pregnant women but also on the fetus they contain. It is said that in preeclampsia, there is an increase in inflammatory stimulation and an abnormal immune response so that routine blood values increase. Neutrophil–lymphocyte ratio (NLR) values reported in several studies have risen notably in the incidence of preeclampsia.

Materials and methods: A cross-sectional observational analysis study was conducted on 924 pregnant respondents from January to December 2019 at Cimacan District Hospital, Cianjur. Statistical analysis test of the average difference between the two groups and the prediction test of NLR values was conducted between the healthy pregnant women group of 838 respondents and the group of 86 pregnant women with preeclampsia.

Results: In statistical tests regarding the differences in the mean of the two groups, a significant NLR value was obtained ($p = 0.004$). Then the NLR value was tested again by the receiver-operating characteristic (ROC) curve method, and the results of the area under the curve (AUC) on the variable values were obtained in the form of AUC: 0.595/*p*-value: 0.035.

Conclusion and clinical significance: Despite the differences in the mean NLR in the two groups, however, the NLR of women in predicting the incidence of pregnancy with preeclampsia is very low.

Keywords: Neutrophil–lymphocytes ratio, Preeclampsia, Pregnancy.

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Introduction

Preeclampsia is part of the symptom spectrum of hypertension in which blood pressure is or more than 140/90 mm Hg on two tests within 4 hours of pregnancy over 20 weeks accompanied by proteinuria and new onset of thrombocytopenia, renal insufficiency, impaired hepatic function, pulmonary edema, visual, and brain disorders.[1–5] The clinical presentation of preeclampsia itself has been known since the late 19th century. A researcher stated that preeclampsia is a spectrum of pregnancy toxemia.[6] Preeclampsia remains a major cause of fetomaternal morbidity and mortality.[7,8]

Worldwide, 10% of all pregnancies are complicated by hypertension accompanied by preeclampsia and eclampsia, which are the biggest causes of maternal and prenatal mortality and morbidity.[9] Then other data state that around 2–8% of all pregnancies in the world occur with preeclampsia and are responsible for global maternal mortality as much as 12%.[10,11] Preeclampsia and eclampsia alone are estimated to cause up to 50,000 maternal deaths per year, with variations in frequency based on geographic regions. In industrialized countries, rates of hypertension in pregnancy associated with mortality are higher in African–American women than for Hispanic, American–Indian, Asian, and Pacific Island women.[12] In Indonesia alone, the incidence of death due to preeclampsia is estimated to be around 7–10% of all pregnancies.[8]

Preeclampsia is divided into two categories, namely mild and severe preeclampsia, that can cause adverse effects during pregnancy, both maternal and uterine, such as proteinuria, edema, cesarean delivery, kidney failure, liver failure, coagulopathy, stroke, respiratory distress syndrome, cardiac arrest, and fetal growth restriction, until the death of the mother or the fetus.[13,14] Symptoms that arise in the event of preeclampsia are severe headaches; visual disturbances, such as blurred vision or glare; severe pain under the ribs; vomiting; and swelling of the face, hands, or feet.[15] Several causative factors explain pathological changes in preeclampsia such as mechanisms due to chronic uteroplacental ischemia, immune maladaptation, very-low-density lipoprotein toxicity, genetics, and increased apoptosis or trophoblastic necrosis.[2] One of the best known is the inflammatory stimulation of the abnormal immune response and dysfunction of the endothelium that causes hypertension.[14] Based on the results of previously published publications, deficiency from trophoblastic invasion in the first trimester causes preeclampsia later in pregnancy.[10] Another condition of systemic inflammation in preeclampsia is the

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involvement of the inflammatory response of T-helper 1 (Th1) and T-helper 2 (Th2) cells.[7,16] Then in patients with preeclampsia, it was also found that decidual lymphocytes and peripheral mononuclear blood cells synthesize high enough Th1 cytokines.[7] Involvement and overreactivation of inflammatory cells and immune responses that release inflammatory cytokines and antibodies causing endothelial disorders, such as increased capillary permeability, microvascular thrombosis, and increased vascular tone, are also factors thought to cause preeclampsia.[10,11,17]

Several recognized inflammatory markers can be a marker for the incidence of preeclampsia such as C-reactive protein and mean platelet volume (MPV). Recently, the use of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) obtained from routine complete blood counts is widely used as a marker of a systemic inflammatory response, especially preeclampsia.[1,10,11,16,18,19] In the field of obstetrics, it has been reported that the NLR value is increased in patients with hyperemic gravidarum, gestational diabetes, preeclampsia, intrahepatic cholestasis in pregnancy, HELLP syndrome, (hemolysis, elevated liver enzyme levels, low platelet levels) ectopic pregnancy, preterm labor, and other diseases.[18,20,21] The interpretation of laboratory values such as the result of an increased white blood count is of interest to know more. Pregnancy involves a variety of physiological changes, yielding specific preference values for laboratory testing. Based on the above background, the researcher wanted to know the difference in NLR in the group of normal pregnant patients compared to preeclampsia and also to test how strong the NLR variable was in predicting pregnancy with preeclampsia.

Materials and Methods

The design of this study was in the form of cross-sectional to see differences in the mean age, gravida, and NLR in the normal pregnancy group and pregnancy with preeclampsia. This research was conducted at Cimacan Regional Hospital, Palasari, Kec. Cipanas, Cianjur Regency, West Java in the June to July 2020 period. The sample of this study included all three-trimester pregnant women in Cimacan Regional Hospital in the period from January 2019 to December 2019. The inclusion criteria for these patients were all pregnant patients undergoing labor and surgery at the Cimacan Regional Hospital. The minimum number of necessary samples used in this study was 700 to the sampling method in the form of total sampling. The procedure of this research started as a research ethics study with the "Tarumanagara University Research Ethics Commission," taking care of licensing with the hospital and medical records.

Furthermore, secondary data in the form of medical records were seen in succession to see data in the form of history taking complaints, history of obstetrics, physical examination, and complete blood. The independent variables in this study include age, gravida, and complete blood laboratory parameters, such as hemoglobin, hematocrit, red cell distribution width (RDW), platelets, neutrophils, lymphocytes, leukocytes, MPV, NLR, PLR, and absolute lymphocyte count (ALC). The dependent variables in this study were pregnancy without preeclampsia and preeclampsia. Prior to statistical testing, the normality of the data was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests and variance testing between groups with the Levene test. Data analysis or statistical tests conducted in this study are in the form of the independent t-test to calculate the difference of two averages in the normal data distribution and an alternative test in the form of Mann–Whiney in an abnormal data distribution. When the relationship between the two variables was found to be a significant average difference or p-value <0.05 between the two groups, the variable will be retested for its predictor ability by the receiver-operating characteristic (ROC) test in predicting the incidence of preeclampsia in pregnancy. ROC or area under the curve (AUC) values are said to have good predictor capability if the angle deviation is above 45° and the p-value < 0.05. The accuracy of the test is further divided into five groups: AUC value is 0.90–1.00 is considered excellent, 0.80–0.90 is considered good, 0.70–0.80 is considered sufficient (fair), 0.60–0.70 is considered bad (poor), and 0.50–0.60 is considered fail (fail). When the AUC results are below 0.50, the AUC conversion evaluation uses the conversion method for the formula (1-AUC basis) and views the ability of the variable's accuracy as a predictor parameter.

Results

This study included 924 respondents who met the inclusion criteria with the average age of 29.624 (7.33) years and the mean gravida of 2.57 (1.57). The number of respondents in normal pregnant women was 838 (90.7%) respondents and preeclampsia was 86 (9.3%) respondents (Table 1).

The data normality test results for the independent variables on the dependent variable using the Kolmogorov–Smirnov test obtained abnormal data distribution on all variables (p-value < 0.05). Therefore, the statistical test uses an alternative test in the form of the Mann–Whitney test.

The results of the Mann–Whitney test statistic showed that there were significant mean differences between the pregnancy groups without preeclampsia and pregnancy with preeclampsia on the age variable (p-value: < 0.001), gravida (p-value: 0.003), platelets (p-value: 0.001), lymphocytes (p-value: 0.003), MPV (p-value: 0.002), NLR (p-value: 0.004), and ALC (p-value: 0.006) and no significant mean differences between the pregnancy groups without preeclampsia and pregnancy with preeclampsia on variable hemoglobin (p-value: 0.141), hematocrit (p-value: 0.104), RDW (p-value: 0.081), neutrophils (p-value: 0.077), leukocytes (p-value: 0.172), and PLR (p-value: 0.878) (Table 2).

From the results of statistical tests on the average difference between the two groups, seven variables were obtained, which could be used as a reference to predict the incidence of pregnancy with preeclampsia in the form of age, gravida, platelet, lymphocyte, MPV, NLR, and ALC variables. The seven variables tested again using the ROC curve method. This test is used to test how strong the model of each of these variables is predicting pregnancy with preeclampsia. AUC results on the seven variables obtained in the form of age (AUC: 0.627/p-value: 0.032), gravida (AUC: 0.594/p-value: 0.032), platelets (AUC: 0.390/p-value: 0.034), lymphocytes (AUC: 0.402/p-value: 0.035), MPV (AUC: 0.603/p-value: 0.033), NLR (AUC: 0.595/p-value: 0.035), and ALC (AUC: 0.410/p-value: 0.034) (Fig. 1 and Table 3). From the seven variables, it can seem that although there are differences in the mean age, gravida, platelets, lymphocytes, MPV, NLR, and ALC in both groups, their ability to predict the incidence of pregnancy with preeclampsia is very low.

Discussions

Preeclampsia is a progressive, unpredictable, and incurable disease, and the only current treatment is the termination of pregnancy. Identify preeclampsia as early as possible is essential to monitor the

Table 1: Basic characteristics of respondents

Variable	*N (%)*	*Mean (SD)*	*Med (Min–Max)*
Age	924 (100)	29.6212 (7.33)	29 (13–49)
Gravida		2.57 (1.57)	2 (1–11)
• 1	293 (31.7)		
• 2	219 (23.7)		
• 3–5	369 (39.9)		
• >5	43 (4.7)		
Parturition		1.38 (1.41)	1 (0–8)
• 0	319 (34.5)		
• 1	237 (25.6)		
• 2	184 (19.9)		
• 3–5	172 (18.6)		
• >5	12 (1.2)		
Abortion		0.2 (0.49)	0 (0–4)
• 0	766 (82.9)		
• 1	135 (14.6)		
• 2	17 (1.8)		
• >3	1 (0.1)		
Hypertension		33	Elective LSCS
• Normal	838 (90.7)		
• Preeclampsia	86 (9.3)		
Hemoglobin		11.64 (1.53)	11.9 (4.30–16.60)
Hematocrit		33.94 (4.33)	34.2 (10.20–46.80)
RDW		14.32 (2.20)	13.85 (10.60–42.70)
Platelets		257.57 (67.70)	251 (38–499)
Neutrophil		76.99 (8.36)	76.7 (50–96.2)
Lymphocytes		17.33 (7.94)	17.3 (2–74.70)
Leukocytes		11.97 (4.38)	10.80 (4.60–38.20)
MPV		8.41 (0.93)	8.40 (5.90–11.60)
NLR		6.21 (4.99)	4.46 (1–47.800)
PLR		161.04 (104.41)	138.52 (21.16–2111.76)
ALC		1879.02 (735.40)	1819.5 (170–7021.8)

Table 2: Difference in mean complete laboratory blood parameters between groups with and without preeclampsia

	Disease										
	Without preeclampsia (n =86)					*Preeclampsia*					*p value*
Parameter	*Mean*	*SD*	*Med*	*Min*	*Max*	*Mean*	*SD*	*Med*	*Min*	*Max*	*Min*
Age	29.24	7.25	28.00	13.00	49.00	32.40	7.10	34.00	17.00	46.00	0.000
Gravida	2.52	1.56	2.00	1.00	11.00	3.02	1.63	3.00	1.00	7.00	0.003
Hemoglobin	11.63	1.49	11.80	4.30	16.60	11.80	1.82	12.10	6.20	15.50	0.141
Hematocrit	33.89	4.29	34.15	10.20	46.80	34.45	4.71	35.05	20.20	43.80	0.104
RDW	14.29	2.21	13.80	10.60	42.70	14.59	2.12	14.15	11.30	25.50	0.081
Platelets	260.22	66.30	252.50	63.00	499.00	231.74	75.78	231.50	38.00	428.00	0.001
Neutrophil	76.84	8.26	76.50	50.00	96.20	78.46	9.21	79.60	56.30	94.20	0.077
Lymphocytes	17.55	7.86	17.60	2.00	74.70	15.17	8.42	11.55	3.30	36.20	0.003
MPV	8.38	0.92	8.30	5.90	11.60	8.72	0.98	8.70	6.90	10.80	0.002
Leukocytes	11.91	4.39	10.70	4.60	38.20	12.51	4.32	11.75	6.10	25.70	0.172
NLR	6.07	4.93	4.34	1.00	47.80	7.55	5.44	6.91	1.68	28.55	0.004
ALC	1898.87	733.43	1839.25	170.00	7021.80	1685.55	730.74	1493.80	498.40	3764.80	0.006
PLR	160.99	106.43	138.43	21.16	2111.76	161.58	82.64	139.39	31.71	397.27	0.878

Table 3: AUC parameter of predictors of pregnancy occurrence with preeclampsia

				Asymptotic 95% confidence interval	
Test result variable(s)	*Area*	*Std. error* [a]	*Asymptotic sig.* [b]	*Lower bound*	*Upper bound*
Usia	0.627	0.032	0.000	0.565	0.689
Gravida	0.594	0.032	0.004	0.531	0.658
Trombosit	0.390	0.034	0.001	0.324	0.456
Limfosit	0.402	0.035	0.003	0.333	0.471
MPV	0.603	0.033	0.002	0.538	0.669
NLR	0.595	0.035	0.004	0.526	0.664
ALC	0.410	0.034	0.006	0.342	0.477

The test result variable(s): Usia, gravida, trombosit, limfosit, MPV, NLR, and ALC have at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased; [a]Under the nonparametric assumption; [b]Null hypothesis: true area = 0.5

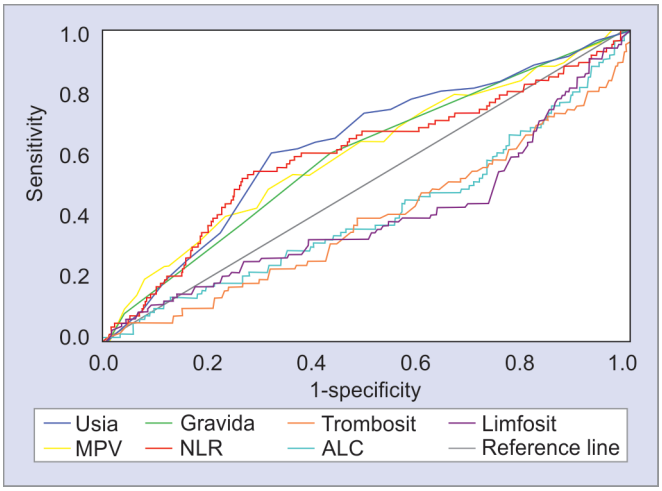

Fig. 1: ROC curve predictor parameters for preeclampsia

clinical condition of the patient and pregnancy so that when giving birth to mothers and children conceived.[22] Serological markers in the incidence of preeclampsia are still limited in health facilities and are not routine to do. A complete blood cell examination is a routine blood test that can be carried out and borne by the state insurance agency "Jaminan Kesehatan Nasional."[23] An increase in NLR is associated with an increase in the risk of cardiovascular events, diabetes mellitus, and mortality in several malignant states. NLR was also previously used as a predictor of complications in pregnancy, but the results were inconsistent. For example, NLR did not find satisfactory results to predict hypertension in pregnancy.[11] However, in other similar studies, it was found that NLR increased in patients with preeclampsia.[24] Nevertheless, further research is needed regarding the predicted value of the incidence of preeclampsia from the use of NLR inflammatory markers.[10]

The results of NLR values describe nonspecific inflammatory mediators as first-line defenses and protective components in inflammation. NLR believed in providing diagnostic and prognostic values.[7] We have involved 924 respondents in making this study. From these results, we found that there were significant mean differences in the NLR variable (p-value < 0.005) between the normal pregnancy group and the pregnancy with preeclampsia (Table 2). A study conducted by Mohammad et al. stated that NLR values were higher in preeclampsia patients compared to normal pregnant patients and increased significantly in the severe preeclampsia (PEB) group ($p = 0.042$).[25] The same results were obtained in a study conducted by Kurtoglu et al. that showed significant NLR results in the group of women with preeclampsia compared to the control group ($p = 0.023$), but when comparing the severity, proteinuria levels, subjective symptoms, and onset of preeclampsia concerning NLR values, there is no difference.[17]

Some studies show that NLR values increase significantly only in cases of preeclampsia, especially severe cases.[17,24] Research Yucel et al. conducted a study that divided the study into three groups between the control group, mild preeclampsia (PER) group, and severe preeclampsia group. Between these groups, no significant results were found in each comparison.[11] The results of research conducted by Serin et al. obtained higher NLR values in the PEB group compared to PER ($p = 0.032$) and a positive correlation between NLR values and proteinuria ($p = 0.013$, $r = 0.319$).[24] These results are supported by the results of a meta-analysis conducted by Kang et al. involving 3982 patients stating that NLR has a higher value in preeclampsia patients, especially PEB.[26] When Widyastiti et al. conducted a study comparing NLR values found differences between normal pregnancies with PEB ($p = 0.000$), and there were also differences between PER and PEB ($p = 0.000$).[8]

Research in India conducted by Gogoi et al. compared NLR values between pregnant women with preeclampsia and the control group of pregnant women with normal tension involving 67 respondents. Their results showed that NLR values were higher in women with preeclampsia than in the control group ($p = 0.001$).[1] In the same country, India, Sachan et al. showed that in women with preeclampsia, NLR values were higher compared to the group of normal pregnant women, even in the early weeks of pregnancy. The ROC curves obtained show significant results of NLR accuracy as a diagnostic value between healthy groups with PER (AUC = 0.75; $p = 0.01$) with a cutoff value >3.35%, sensitivity 52.9%, and specificity 64.5%.[27] A similar study to compare NLR values was also carried out in Indonesia by Prasmusinto et al., involving 134 pregnant women with preeclampsia and 118 normal pregnant women. From this research that has been done, it was found that pregnant women with preeclampsia showed higher NLR values with a mean value of 4.41 [95% confidence interval (CI), 1.41–32.54; $p < 0.001$], but the onset of preeclampsia did not affect the NLR value. In the ROC analysis curve, NLR is an important marker of preeclampsia with a sensitivity value reaching 80.1%

and specificity of 87.3% (95% CI, 0.85–0.93; cutoff value 3.295).[23] Research that takes NLR results in the first trimester of pregnancy as an indicator to predict preeclampsia was conducted by Gezer et al. based on the results of multivariate regression analysis showing NLR values increased in preeclampsia patients compared to the group of normal pregnant women (Odd Ratio, 1.43; 95% CI, 1.21–1.76; p <0.005). AUC results from the ROC curve of 0.716 with a cutoff ≥ of 3.08, with a sensitivity of 74.6%, and a specificity of 70.1%.[10]

Different results obtained in a study conducted by Yavuzan et al., which showed that NLR did not significantly increase in cases of PEB when compared with patients with normal pregnant women.[16] Similar results were also obtained from a population study through a retrospective analysis conducted by Klement et al. with coverage of research respondents up to 11,415 patients. They divided two groups between normal population groups and high-risk pregnant women population, and from these results, they redivided based on the trimester of pregnancy. The results of differences in NLR values based on the time of pregnancy trimester were obtained (p = 0.3, 0.5, and 0.4) in each trimester.[18] In 2019, a meta-analysis study conducted by Zheng et al. to assess the diagnostic picture of preeclampsia using NLR values showed that the diagnostic accuracy of NLR specificity was less satisfactory, and sensitivity is accepted as a diagnostic aid of preeclampsia.[14]

In this research, we have made testing variables to predict pregnancy with preeclampsia using the ROC analysis curve method. The AUC result on NLR variables is 0.595 and p-value is 0.035. Although the NLR variable has a mean difference, the ability to predict the incidence of pregnancy with preeclampsia is very low (Table 3). Our research shows that by using NLR values, the incidence of preeclampsia can be predicted. NLR is an examination that is easy, cheap, and fast to do. Our research is not without limitations; the effects of confounding factors that might obscure the results of this study could be involved, such as body mass index and systemic disease. With the results of this study, clinicians can detect women who are at risk of preeclampsia without symptoms.

Conclusion and Clinical Significance

Data from our study indicate that NLR values can be used to predict the incidence of preeclampsia later in pregnant women. However, it is crucial to know many other factors that also influence the value of the NLR, not only from the state of preeclampsia itself. Because the NLR value is easy, cheap, and fast, it is applied so that the NLR value can be used as a predictor. Future studies with larger samples are expected to be carried out to explore more profound the potential of the NLR value itself to predict the incidence of preeclampsia.

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