Assessment of the Neutrophil Lymphocyte Ratio and Mean Platelet Volume in Pregnancy

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A B S T R A C T

Background: Hypertension in pregnancy is a common complication that affects maternal and fetal morbidity and mortality. The use of inflammatory markers is widely used as a predictor of the incidence of hypertension in pregnancy, especially preeclampsia. Neutrophil-lymphocyte ratio and mean platelet volume values are believed to predict the incidence of hypertension in pregnancy. This study was aimed to determine the neutrophil-lymphocyte rate and mean platelet volume as a predictor of hypertension in pregnancy. **Methods:** This research is an analytic observational study using secondary data from medical records. The data were taken from the Cimacan Regional Hospital from January to December 2019. The variables were then tested statistically to see the difference in the mean. If there are significant results, the predictor's ability will be tested again with the ROC curve test. **Results:** The results of statistical tests between the normotensive pregnancy group and pregnancy with hypertension showed that the mean difference was significant in the neutrophil-lymphocyte ratio variable with a p-value of 0.004 and mean platelet value with a p-value of 0.005. Then the ratios were tested again by the ROC Curve method. The AUC of neutrophil-lymphocyte ratio results was 0.562 (p-value 0.022) and mean platelet value (AUC: 0.560 / p-value: 0.022). **Conclusion:** The ability of neutrophil-lymphocyte ratio and mean platelet value to predict pregnancy with hypertension was meagre.

1. Introduction

Hypertensive disorders in pregnancy are one of the crucial problems in the world of health, where 10% of total pregnancies worldwide have complications of hypertension with preeclampsia and eclampsia being the leading causes of maternal and perinatal morbidity and mortality. [1,2] Hypertension is defined when the systolic blood pressure is ≥ 140 mmHg and or systolic blood pressure ≥ 90 mmHg.

The classification of hypertension that occurs in pregnancy is divided into chronic hypertension, gestational hypertension (GHT), and superimposed preeclampsia (PE). [3] Chronic hypertension refers to hypertension that has occurred at ≤ 20 weeks of gestation. GHT was defined as hypertension at gestational age ≥ 20 weeks without preeclampsia

symptoms and returning to normal ≤ 12 weeks after delivery in women who were previously normotensive. PE is hypertension accompanied by proteinuria (excretion of ≥ 300 mg of protein per day), which occurs at ≥ 20 weeks of gestation or nearing termination and returns to regular ≤ 12 weeks after delivery. Superimposed PE is an occurrence of proteinuria that happens when gestational age ≥ 20 weeks is accompanied by chronic hypertension that has when gestational age <20 weeks and before pregnancy, or hypertension and or proteinuria at gestational age ≥ 20 weeks in patients with chronic hypertension with proteinuria at the time. gestational age <20 weeks or GHT accompanied by kidney disease with proteinuria at gestational age <20 weeks and before pregnancy. [1,3,4]

PE is the most common occurrence of hypertension

in pregnancy and involves a multisystem.[5] PE itself occurs in 5-7% of all pregnancies.[2] The aetiology and pathogenesis of PE are multifactorial.[6] Some of the events that occur in PE are characterized by poor placentation, placental ischemia, abnormal remodelling of spiral arteries, oxidative stress between mother and child, angiogenic imbalance in maternal circulation accompanied by endothelial and multi-organ damage.[7] PE then causes activation of immunological factors such as stimulation of systemic inflammation of an abnormal immune response, increased levels of neutrophils, activation of platelets and endothelial dysfunction.[8,9] Several studies have shown similar results, namely an association between PE in pregnant women and increased platelet levels.[10-14] PE patients also found a high enough peripheral lymphocyte count.[15] The use of neutrophil/lymphocyte ratio (NLR) and mean platelet volume ratio (MPV) as markers of systemic inflammation, especially in PE, is often used in recent times.[16-20]

PE is an important problem to observe and affects almost all pregnancies around the world. Many modalities are used to detect PE, but none can be done effectively in terms of price, time and convenience. The use of inflammatory markers, such as routine blood, presents a challenge in predicting the incidence of PE in the future. In addition to the use of NLR, MPV values are also an indicator of platelet activation sensitivity and are routinely used in reporting through routine blood tests.[11,12] Therefore, in this study, we tried to include the entire spectrum of hypertensive disease during pregnancy and investigated whether there was a relationship between the incidence of hypertension in pregnancy with the parameters of NLR and MPV.

2. Method

The design of this study is an observational analytic study to see the differences in the mean age, gravida, and NLR in the normotensive pregnancy group and pregnancy with hypertension (both chronic hypertension, gestational hypertension and preeclampsia). This research was conducted at Cimacan Regional Hospital, Cianjur, West Java from June to July 2020. The research data were taken from the medical records of patients who met the inclusion criteria, namely all pregnant patients at Cimacan Regional Hospital identified with gestational hypertension, chronic hypertension, PE, overlapping PE with chronic hypertension, pregnancy without hypertension, impending eclampsia and eclampsia which was confirmed by physical examination and supporting examinations, and recorded in medical records. The study exclusion criteria were patients with a history of systemic diseases such as kidney, diabetes, sepsis, liver, respiratory and incomplete medical records.

The minimum sample used in this study was 765 samples with the sampling method in the form of total sampling. Furthermore, secondary data in the form of medical records were seen in a row to view data in the way of complaint history, obstetric history, physical examination and complete blood count. The independent variables in this study included age, gravida, and full blood laboratory parameters such as haemoglobin, hematocrit, RDW, platelets, neutrophils, lymphocytes, leukocytes, MPV, NLR, PLR, and ALC. The dependent variables in this study were pregnancy without hypertension (normotension) and pregnancy with hypertension (chronic hypertension, gestational, PE overlapping with chronic hypertension, PE, impending eclampsia and eclampsia). All procedures in this study has been approved by Ethical Committee of Faculty of Medicine, Universitas Tarumanegara, Indonesia.

Before statistical testing is carried out, the data is first tested for normality using the Kolmogorov-Smirnov and Shapiro Wilk tests and variance testing between groups using the Levene Test. Data analysis or statistical tests carried out in this study are in the form of the Independent T-Test to calculate the difference between the two means on normal data distribution and an alternative test in the way of Mann-Whiney on abnormal data distribution. If the relationship between the two variables shows a significant mean difference or p-value <0.05 between the two groups, then the variable will be tested again for its predictor ability with

the ROC test in predicting the incidence of hypertension in pregnancy. The ROC or AUC value is said to have a predictor ability good is if the angle deviation is above 45 degrees and the p-value <0.05. The accuracy value of the test is further divided into five groups where the AUC value of 0.90 - 1.00 is considered excellent, 0.80 - 0.90 is deemed to be fair, 0.70 - 0.80 is considered to be sufficient, 0.60 - 0.70 is supposed to below, and 0.50 - 0.60 is deemed to fail. If the AUC result is below 0.50, the AUC conversion assessment uses the conversion method for the formula (1-AUC basis) and the accuracy of the variable is seen as a predictor parameter

3. Result

This study included 924 respondents who met the inclusion criteria with a mean age of 29.624 (7.28) years and a mean gravida of 2.57 (1.57). The number of respondents without hypertension was 678 (73.3%) respondents, chronic hypertension was 27 (2.9%) respondents, gestational hypertension was 134 (14.5%) respondents, mild preeclampsia was 16 (1.7%) respondents, severe preeclampsia were 60 (6.5%) respondents, impending eclampsia were 5 (0.5%), and superimposed were 4 (0.4%) respondents (Table 1).

The results of the data normality test for the independent variables on the dependent variable using the Kolmogorov Smirnov test showed that the distribution of data was not normal for all variables (p-value <0.05). Therefore, the statistical analysis used an alternative analysis in the form of the Mann Whitney test.

The results of the *Mann Whitney* Test statistical test showed that there was a significant difference between the groups of pregnancy with hypertension and pregnancy with hypertension on the variable age (p-value: <0.001), gravida (p-value: <0.001), lymphocytes (p-value: 0.003), MPV (p-value: 0.005), NLR (p-value: 0.004), and ALC (p-value: 0.002), and there were no significant mean differences between the groups of pregnancy with hypertension and pregnancies with hypertension on the variable hemoglobin (p-value: 0.666), hematocrit (p-value: 0.571), RDW (p-value: 0.696), platelets (p-value: 0.066), neutrophils (p-value: 0.123), leukocytes (p-value: 0.495), and PLR (p-value: 0.146) **(Table 2).**

From the results of statistical tests regarding the mean difference between the two groups, it was found that six variables could be used as a reference to predict the incidence of pregnancy with hypertension, namely variables of age, gravida, lymphocytes, MPV, NLR, and ALC. The six variables were tested again using the ROC Curve method. This test used to test how strong the model of each of these variables is in predicting pregnancy with hypertension. The AUC results on the six variables obtained results in the form of age (AUC: 0.663 / p-value: 0.020), gravida (AUC: 0.651 / p-value: 0.020), lymphocytes (AUC: 0.436 / p-value: 0.022), MPV (AUC: 0.560 / p-value: 0.022), NLR (AUC: 0.562 / p-value: 0.022) and ALC (AUC: 0.434 / p-value: 0.022) **(Figure 1 and Table 3).**

Of the six variables, it can be seen that although there are differences in the mean age, gravida, lymphocytes, MPV, NLR, and ALC in the two groups, their ability to predict the incidence of pregnancy with hypertension is deficient.

Table 1. Basic characteristics of respondents

Variable	N (%)	Mean (SD)	Med (Min-Max)
Age	924 (100%)	29.62 (7.28)	29 (13-49)
Gravida		2.57 (1.57)	2 (1 – 11)
• 1	293 (31.7%)		
• 2	219 (23.7%)		
• 3-5	369 (39.9%)		
• More than 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%)		
• More than 5	12 (1.2%)		
Abortion		0.2 (0.49)	0 (0 – 4)
• 0	766 (82.9%)		
• 1	135 (14.6%)		
• 2	17(1.8%)		
• More than 3	1 (0.1%)		
Hypertension			
• Normal	678 (73.4%)		
• Chronic hypetension	27 (2.9%)		
• Gestational hypertension	134 (14.5%)		
• Mild preeclampsia	16 (1.7%)		
• Severe preeclapmsia	60 (6.5%)		
• Impending eclampsia	5 (0.5%)		
• Superimposed preeclampsia	4 (0.4%)		
Haemoglobin		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. The difference in mean complete laboratory blood parameters between normotensive pregnancy groups and pregnancy with hypertension

Parameter	Disease										p-value
	Normotensive Pregnancy (n = 678)					Pregnancy with Hypertension (n = 246)					
	Mean	SD	Med	Min	Max	Mean	SD	Med	Min	Max	
Age	28.52	6.98	27.00	13.00	49.00	32.63	7.27	34.00	17.00	49.00	0.000
Gravida	2.35	1.46	2.00	1.00	9.00	3.17	1.69	3.00	1.00	11.00	0.000
Haemoglobin	11.63	1.51	11.80	4.30	15.50	11.69	1.57	11.90	6.20	16.60	0.666
Hematocrit	33.89	4.36	34.10	10.20	46.30	34.08	4.28	34.50	20.20	46.80	0.571
RDW	14.37	2.33	13.80	10.90	42.70	14.17	1.78	13.90	10.60	25.50	0.696
Platelets	260.41	66.85	252.00	63.00	499.00	249.79	69.51	248.00	38.00	498.00	0.066
Neutrophil	76.79	8.08	76.40	50.00	96.20	77.54	9.08	78.40	50.40	94.20	0.123
Lymphocytes	17.73	7.78	17.90	2.00	74.70	16.25	8.29	14.60	3.20	42.10	0.003

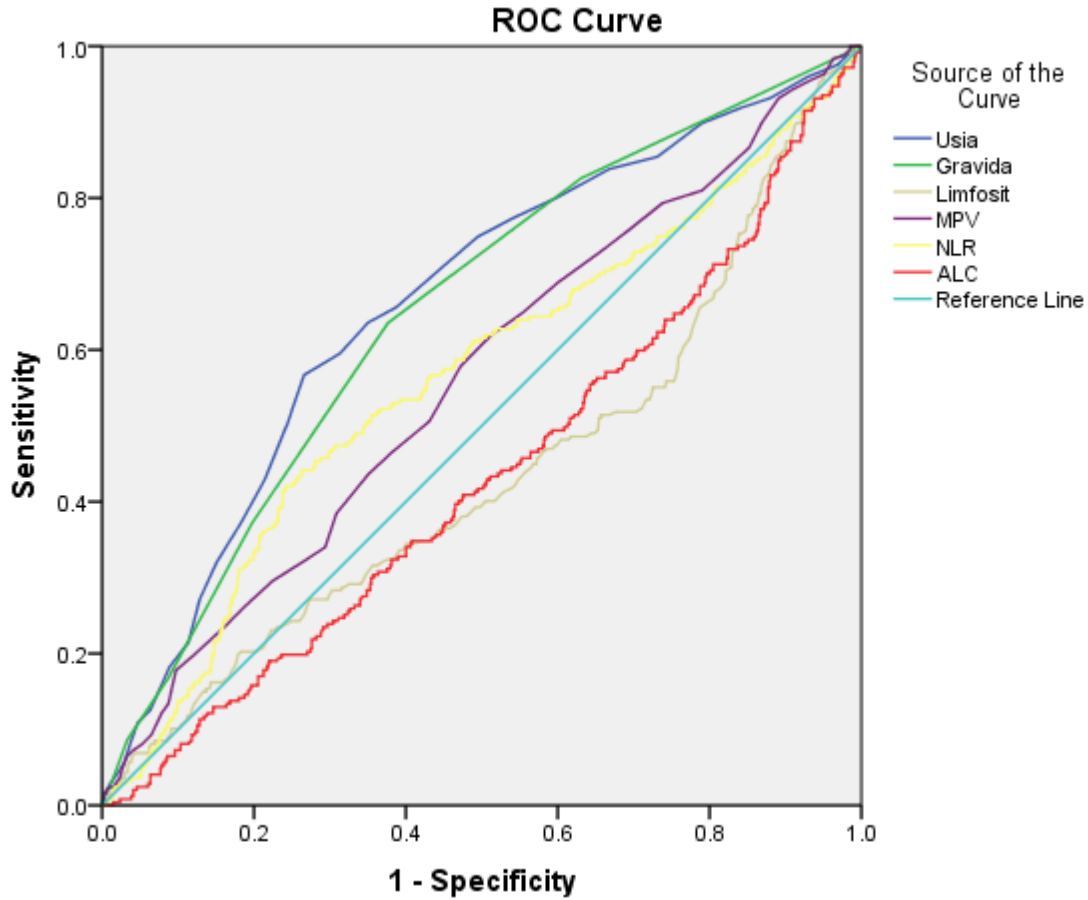|											
MPV	8.35	0.91	8.30	5.90	11.60	8.56	0.97	8.50	6.50	11.50	0.005
Leukocytes	11.94	4.44	10.70	4.60	38.20	12.05	4.22	10.90	5.60	32.10	0.495
NLR	6.01	5.04	4.27	1.00	47.80	6.75	4.84	5.47	1.20	28.59	0.004
ALC	1925.92	748.41	1852.50	170.00	7021.80	1750.48	683.61	1683.00	453.60	3764.80	0.002
PLR	158.91	110.38	137.60	21.16	2111.76	166.88	85.86	144.19	31.71	527.72	0.146

Figure 1. ROC curve predictor parameters for pregnancy with hypertension

Table 3. Area under curve (AUC) parameter of predictors of pregnancy with hypertension

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig. [b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Age	0.663	0.020	0.000	0.623	0.703
Pregnancy	0.651	0.020	0.000	0.611	0.691
Lymphocyte	0.436	0.022	0.003	0.392	0.480
MPV	0.560	0.022	0.005	0.518	0.602
NLR	0.562	0.022	0.004	0.519	0.606

ALC	0.434	0.022	0.002	0.391	0.476

The test result variable(s): Usia, Gravida, Limfosit, MPV, NLR, ALC has at least one tie between the positive actual state group and the negative virtual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

4. Discussion

Pregnancy is a physiological process but can lead to hypertension in pregnant women who were previously normotensive or gaining weight in women who already have hypertension. Identification of clinical signs and effective treatment is of great importance in determining the outcome of pregnancy.[5] In this study, we tried to see the ability of routine blood test modalities such as NLR and MPV as predictors of hypertension due to pregnancy. A total of 924 respondents were involved in this study. From these results, we found that there was a significant mean difference in the NLR variable (p-value = 0.004) between the normotensive pregnancy group and pregnancy accompanied by hypertension (table 2).

Research conducted by Mohammad et al. showed that the maternal NLR value was higher in the PE patient group compared to the normal pregnancy group (p value> 0.0003).[21] A similar study was conducted by Kurtoglu et al. where the NLR value in the PE group was significantly higher than the normal group (p-value = 0.023) and the area under the receiver operating characteristic (ROC) was also found to be statistically significant (p-value = 0.023).[22] Gogoi et al. in India conducted a study involving 67 respondents who compared the NLR value between pregnant women with PE, and the normotension group was obtained (p-value = 0.001).[17] A study in the same country conducted by Sachan et al. found that the group of women with PE had higher NLR values than the group of normotensive pregnant women. Their study's ROC curve showed a significant NLR value as a diagnostic value between the normal group with mild mild PE (area under the curve [AUC] = 0.75, p = 0.01) with a cutoff value> 3.35%, 52.9% sensitivity and 64.5% specificity.(23) A similar study was carried out in Indonesia involving 134 pregnant women with PE and 118 normotensive pregnant women by Prasmusinto et al. It was found that pregnant women with PE showed a higher NLR value with a mean value of 4.41 41 (95% CI 1.41-32.54, p <0.001). On the ROC analysis curve, the sensitivity value of NLR as a marker of preeclampsia reached 80.1% and specificity 87.3% (95% CI 0.85-0.93, cutoff point value 3.295).[24]

Different results showed that the NLR value did not have a statistical significance value in the case of PE compared to the normal group of women in the study conducted by Yavuzan et al. (p-value 0.721).[25] Meta-analysis study in 2019 led by Zheng et al. to assess the diagnostic features of PE using the NLR value, showed that the accuracy of the diagnostic specificity is less significant but in terms of sensitivity it can be accepted as a diagnostic tool for PE.[8]

In addition to the NLR values that have been described, several other studies have shown differences in cytokines and coagulation profiles in pregnant women with hypertension compared with normotensive pregnant women. Some of these studies suggest the presence of platelet values that may predict disease progression and may help in the prognosis of the disease.[26] In our study, there was a significant mean difference in the MPV variable (p-value = 0.005) between the normotensive pregnancy group and pregnancy accompanied by hypertension **(table 2).**

Research conducted by Reddy et al. (2019) showed that MPV values were higher in the severe PE group compared to PE alone and compared to normotensive pregnancies (11.67 [1.4] vs 8.07 [0.8], p <0.001, and 10.14 [1] vs 8.07 [0.8], p <0.001). The AUC of the study's ROC curve also shows that the MPV value has a significant diagnostic value, where the MPV AUC value (AUC = 0.78%, 95 confidence intervals [0.719 -

0.842], the cutoff point value> 10.95 with a sensitivity of 80% and a specificity of 75%.[14] Similar results were also found by Vilchez et al. who compared the group of pregnant women with PE with the group of normotensive pregnant women where the MPV value was highest in the PE group, especially at the time of admission compared to the first visit or intrapartum (11.3 ± 1.3 vvs10.1 ± 0.8 fL, p = 0.002). For the study's ROC curve, the MPV value in the late-onset PE group, an AUC value of 0.7 with a sensitivity of 85.5% and a specificity of 28.3%.[27] A meta-analysis study conducted by Bellos et al. in 2018 involving 14,614 women from 50 studies. A total of 7,905 pregnant women suffering from PE obtained a higher MPV value with a mean difference of 1.04 and a 95% confidence interval [0.76 - 1.32].[10] However, from the research above that has been described above, there are several studies that also show different results. In a study conducted by Iqbal et al., which showed that the MPV value between groups of pregnant women with hypertension and proteinuria compared with normotensive pregnant women did not show significant results (p = 0.142).[5] Similar results were also obtained by Gameti et al. where the MPV value in pregnant women in the final trimester did not have statistically significant value with the ANOVA test between the PE group and the normal group (p> 0.05).[20]

In this study, the variable test results to predict pregnancy with hypertension using the ROC analysis curve method, the AUC results were obtained on the NLR variable, namely (AUC: 0.562 / p-value = 0.022) and MPV (AUC: 0.560 / p-value: 0.022). Although there are differences in the mean between the NLR and MPV variables, their ability to predict the incidence of hypertension in pregnancies with pregnancy with normotension is meagre **(Table 3).**

5. Conclusion

The NLR and MPV values had significant mean differences between the group of normotensive pregnant women and those with hypertension. However, its ability to predict the incidence of hypertension with pregnancy needs further research.

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