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Comparison of neutrophil lymphocyte ratio (NLR), mean platelet volume (MPV) and platelet lymphocyte ratio (PLR) in preeclampsia and normotensive pregnancies

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ABSTRACT

The study aimed to compare the NLR (neutrophil lymphocyte ratio), MPV (mean platelet volume), and PLR (platelet lymphocyte ratio) values in preeclampsia and normotensive pregnancies. This was a retrospective case-control study using medical records of pregnancies between January 1, – December 31, 2019. A total 31 pregnancies with preeclampsia who met the inclusion and exclusion criteria were involved in the study. As control, 31 normotensive pregnancies recruited by simple random sampling were used. The data were presented as mean ± standard deviation (SD) and analyzed by using SPSS program. Receiver operating characteristic (ROC) curve were used to determine the optimal cut-off point for predicting preeclampsia. The NLR and MPV values of patients with preeclampsia were significantly higher compare to normotensive pregnancy ($p<0.001$). Whereas, the PLR value of both groups was not significantly different ($p>0.245$). The result of AUC analysis showed that the NLR and MPV have AUC values of 0.758 (95%CI:0.637-0.878; p=0.000) and 0.903 (95%CI:0.816-0.989; p=0.000), respectively. Further analysis showed that the optimal cut-off point for NLR was 4.0 (sensitivity of 64.5% and a specificity of 71.0%) and for MPV was 7.55 (sensitivity of 87.1% and specificity of 80.0%). In conclusion, the NLR and MPV values are significantly higher in preeclampsia. However, the MPV value has a better predictive value than NLR for preeclampsia.

ABSTRAK

Penelitian ini bertujuan membandingkan nilai NLR (*neutrophil lymphocyte ratio*), MPV (*mean platelet volume*), dan PLR (*platelet lymphocyte ratio*) pada preeklampsia dan kehamilan normal. Penelitian kasus-kontrol retropektif ini menggunakan data rekam medis kehamilan antara 1 Januari – 31 Desember 2019. Total 31 kehamilan dengan preeklampsia yang memenuhi kriteria inklusi dan eksklusi terlibat dalam penelitian. Sebagai kontrol adalah 31 kehamilan normal yang direkrut secara sampel acak sederhana. Data disajikan sebagai rerata ± deviasi standar (SD) dan dianalisis dengan program SPSS. Kurva ROC digunakan untuk menentukan nilai *cut-off* optimal untuk memprediksi preeklampsia. Nilai NLR dan MPV pasien preeklampsia lebih tinggi secara nyata dibandingkan dengan kehamilan normal ($p<0,005$). Sedangkan nilai PLR kedua kelompok tidak berbeda secara nyata ($p>0,005$). Hasil perhitungan AUC menunjukkan NLR dan MPV berturut-turut mempunyai nilai AUC 0,758 (95%CI:0,637-0,878; p=0,000) dan 0,903 (95%CI:0,816-0,989; p=0,000). Analisis lanjutan menunjukkan nilai *cut-off* optimal untuk NLR adalah 4,0 (sensitivitas 64,5% dan spesifisitas 71,0%) dan untuk MPV adalah 7,55 (sensitivitas 87,1% dan spesifisitas 80,0%). Dapat disimpulkan, nilai NLR dan MPV secara nyata lebih tinggi pada preeklampsia. Namun demikian, nilai MPV mempunyai nilai prediksi lebih baik dibandingkan NLR untuk memprediksi preeklampsia.

Keywords:
preeclampsia;
normotensive pregnancy;
NLR;
MPV;
PLR

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INTRODUCTION

Maternal mortality rate (MMR) is the quality indicator of health services in a region. World Health Organization (WHO) reported that MMR in developing countries reached 462 compared to developed countries 11 per 100,000 live births.[1] Haemorrhage, hypertension in pregnancy, and sepsis are the causes of more than 50% of maternal deaths worldwide. In Indonesia MMR is still not successful yet to reach the MDG's target.[2,3] Meanwhile, MMR in North Maluku 2019 reached 47 per 29,195 live births, and based on the health profile in Central Halmahera Regency, the MMR reached 118/100,000 live births.[3,4]

Preeclampsia is a term of hypertension in pregnancy that remains a serious problem due to its high level of complexity. It is not only affecting the mother during pregnancy and childbirth, but also causing postpartum problems due to endothelial dysfunction in various organs, and affecting the survival of neonatal outcome. In Indonesia, the incidence of preeclampsia is 128,273/ year (5.3%).[5-7] A meta-analysis reported that the risk of hypertension (RR, 3.7; 95% CI 2.70-5.05), ischemic heart disease (RR, 2.16; 95% CI 1.86-2.52), stroke (RR, 1.81; 95% CI 1.45-2.27) and venous thromboembolism (RR, 1.79; 95% CI 1.37-2.33) of women with preeclampsia increase.[6] Furthermore, WHO reported that proportions of stillbirths (6.4% vs 1.9%), low birth weight (34.2% vs 10.6%), low Apgar score at birth (7.9% vs 2.6%), neonatal complications (20.6% vs 5.3%), and pre-term birth (30.89 vs 7.10%) of the preeclamptic women are more frequent compared to those without preeclampsia/ eclampsia. Whereas, neonates with low birth weight are at risk for metabolic diseases in adults. [5,8]

The cause of preeclampsia has not been fully understood, yet. One of the factors associated with preeclampsia is the inflammatory process. Placental dysfunction and hypoxia that occurred in preeclampsia lead to activation of immunological responses, including increased neutrophil counts, thrombocyte activation, and systemic inflammation process. Hyper-reactivation of inflammatory cells, immunological responses of neutrophils, and lymphocytes are taking place by releasing inflammatory cytokines and autoantibodies which impacting an endothelial dysfunction.[11-14] The changes in the hematological parameters level including, NLR, MPV, and PLR are known as a marker of the systemic inflammatory response in preeclampsia.[9-11] However, some studies showed the different results.

Cintesun *et al.*[9] reported that there is no significantly difference in NLR and PLR levels between healthy pregnancy and preeclampsia ($p > 0.05$), but MPV level is lower in the preeclampsia group ($p<0.001$). Mannaerts *et al.*[10] reported that MPV level significantly elevated in the preeclampsia compared to the control groups ($p<0.006$). Further analysis revealed an optimal cut-off point of 8.15 (sensitivity 66.7%, specificity 56.3%) for predicting preeclampsia. In contrast, NLR and PLR could not be used as marker for predicting preeclampsia. In another study by Syahputra *et al.*[11] reported that the NLR level is significantly higher in preeclampsia compared to normal pregnancy ($p=0.001$). However, there is no a significant difference in MPV and PLR levels values of both preeclampsia and normal pregnancy ($p>0.05$). Although some of those markers have been carried out in many previous research studies in preeclampsia patients, the results is not conclusive.[9,11]

Comprehensive management of preeclampsia requires advance laboratory equipment's and intensive care facilities which are still two major obstacles in Indonesia.[11] A simpler and easier examination method to predict preeclampsia therefore is needed. This

study aimed to compare the values of NLR, MPV, and PLR in preeclampsia and normotensive pregnancy at the Weda General Hospital, Central of Halmahera Regency, North Maluku.

MATERIALS AND METHODS

Subjects

It was a case-control study with a retrospective approach involving 31 patients with preeclampsia as cases group, and 31 normotensive pregnancies as the control group. Subjects was obtained by simple random sampling at the Weda General Hospital, Central of Halmahera Regency, North Maluku for the period of January 1 to December 31, 2019. The protocol of the study was approved by the Medical Research Ethic Committee, Faculty of Medicine, University of Trisakti, Jakarta.

Procedure

Preeclampsia was diagnosed in accordance with the National Guideline of Medical Care (*Pedoman Nasional Pelayanan Kedokteran*/PNPK) POGI 2016, as follow hypertension (SBP of ≥140 mmHg, or DBP of ≥90 mmHg, that occurs after 20-wk pregnancy in a woman with previously normal BP), and proteinuria (measured as 300mg/24-h urine specimen or >1+ with urine dipstick), if proteinuria cannot be obtained, one of the symptoms and signs can be used to diagnose preeclampsia i.e. thrombocytopenia (<100.000/mL), renal insufficiency (creatinine serum >1.1mg/dL or increase creatinine serum in the patient without any other renal diseases), impaired liver functions (elevated transaminases, right upper quadrant or epigastric abdominal pain), pulmonary edema, neurological complications (stroke, headache, visual disturbance), or signs of utero-placental dysfunction (oligohydramnios, fetal growth restriction (FGR), absent or reversed diastolic velocity). The distinction between the severe or mild preeclampsia was not made. Women with HELLP syndrome were also considered to have preeclampsia since HELLP syndrome was a more serious condition in the same spectrum of this disorder.

All demographic and laboratory data of subjects were obtained through a review of all available medical records for the period of 1 January - 31 December 2019 in Weda General Hospital, Central of Halmahera Regency, North Maluku. The maternal nutritional status of the subject was measured based on WHO BMI Classification-2020. The gestational age categories following ACOG-2017b. The NLR, MPV, and PLR levels were determined by manually counting from the CBC of blood laboratory levels of the subjects. The blood samples were taken at the time of admission before any medical treatment such as magnesium sulfate or induction/augmentation of labor. All blood samples were processed using the same automatic blood cell analyzer.

The inclusion criteria of cases group were diagnosis of preeclampsia, singleton fetus, no comorbidities or history of other comorbidities (diabetes mellitus, chronic hypertension, kidney disease, infection during pregnancy), did not have premature rupture of membranes, and did not have a history of malignancy. The inclusion criteria of control group were normal pregnancy, >37 wk of gestational age, singleton fetus, have no comorbidities or history of other comorbidities (diabetes mellitus, chronic hypertension, kidney disease, infection during pregnancy), have no premature rupture of membranes, have no history of malignancy. The exclusion criteria both for cases and control group were incomplete medical records, medical records of subjects who have been referred out of Weda General Hospital, Central of Halmahera Regency, North Maluku.

Statistical analysis

Data analysis were conducted by using the SPSS program. Kolmogorov-Smirnov normality test, bivariate analysis using independent t-test, Mann-Whitney, and Fischer exact with CI; 95% were used. The ROC-curve model gets tested to find the AUC (area under curve) value in predicting the parameters of the maternal preeclampsia sample was used.

RESULTS

A total of 62 subjects consisted of 31 patients with preeclampsia as case group and 31 normotensive pregnancies as control group were involved in this study. No significantly different in the characteristics of subjects ($p>0.05$) was observed between case group and control group (TABLE 1).

TABLE 1. Characteristics of the subject and Chi-square test

Variable	Preeclampsia [n (%)]	Normotensive [n (%)]	p
Gravida			
• Primi-gravid	11 (17.7)	9 (14.5)	0.587
• Multi-gravid	20 (32.3)	22 (35.5)	
Gestational age			
• Pre-term	4 (6.5)	0 (0)	
• Aterm	20 (32.3)	26 (41.9)	0.077
• Post-term	7 (11.3)	5 (8.1)	
Maternal nutritional status			
• Overweight	22 (35.5)	22 (35.5)	1.000
• Normal	9 (14.5)	9 (14.5)	

TABLE 1 describes the characteristics subject of the preeclampsia and normotensive pregnancy groups based on the level of gravida i.e. primigravida preeclampsia 11 (17.7%), multi-gravida preeclampsia 20 (32.3%), primigravida normotensive 9 (14.5%), and multi-gravida normotensive 22 (35.5%). Based on gestational age i.e. pre-term preeclampsia 4 (6.5%), aterm preeclampsia 20 (32.3%), post-term preeclampsia 7 (11.3%), pre-term normotensive 0 (0%), aterm normotensive 26 (41.9%), and post-term normotensive 5 (8.1%). Normal nutrition status for preeclampsia 9 (14.5%), overweight preeclampsia 22 (35.5%), normal nutrition in normotensive 9 (14.5%), and overweight normotensive pregnancy 22 (35.5%). The Chi-square test found that it was not significantly associated between the variables of gravida level, gestational age, and maternal nutritional status with the incidence of preeclampsia ($p>0.05$).

A significantly different in NLR and MPV values between patients with preeclampsia and normotensive pregnancy groups ($p<0.01$) was observed, whereas no significantly different in PLR ($p=0.245$) was observed (TABLE 2).

TABLE 2. The laboratory parameters values between the normotensive and preeclampsia groups.

Variable	Normotensive (mean ± SD)	Preeclampsia (mean ± SD)	p
Maternal age (yrs)	28.83 ± 5.568	30.677 ± 7.444	0.245
NLR	3.403 ± 0.975	5.911 ± 3.663	<0.001
MPV (fL)	6.887 ± 0.902	8.225 ± 0.935	<0.001
PLR	126.19 ± 46.09	138.73 ± 48.62	0.245

No significant difference in the NLR (p=0.792), PLR (p=0.780) and MPV (p=0.964) values between normal nutritional status and overweight were observed (TABLE 3). No significant difference in NLR (p=0.792), PLR (p=0.780) and MPV (p=0.169) values based on gestational groups were also observed (TABLE 4).

TABLE 3. The laboratory parameters value between normal nutritional status and overweight groups.

Variable	Normal (mean ± SD)	Overweight (mean ± SD)	p
NLR	4.801 ± 3.049	4.598 ± 2.933	0.792[a]
MPV (fL)	7.566 ± 1.142	7.552 ± 1.143	0.964[b]
PLR	129.29 ± 38.21	133.76 ± 51.04	0.780[a]

[a]: Mann-whitney; [b]: independent t-test

TABLE 4. The differences of mean laboratory parameters value between aterm and preterm / post-term groups.

Variable	Aterm (mean ± SD)	Preterm &/ post-term (mean ± SD)	p
NLR	4.63 ± 3.15	4.71 ± 2.33	0.792[a]
MPV (fL)	7.43 ± 1.10	7.89 ± 1.20	0.169[b]
PLR	131.14 ± 50.25	136.25 ± 39.31	0.780[a]

*a; Mann-Whitney, b; independent sample t-test

The area under ROC-curve model analysis of the NLR, MPV, and PLR was used to determine the predictive value of preeclampsia in pregnancy (FIGURE 1). The result showed that the AUC value of NLR, MPV and PLR were 0.758 (95%CI:0.637-0.878; p=0.000), 0.903 (95%CI:0.816-0.989; p=0.000) and 0.586 (95%CI: 0.441-0.731; p=0.245), respectively (TABLE 5). Further analysis showed that the optimal cut-off point for NLR was 4.0 with a sensitivity of 64.5% and a specificity of 71.0% (OR=3.8; 95% CI:1.33-10.94; p=0.011) and for MPV was 7.55 with a sensitivity of 87.1% and specificity of 80.0% (OR 28.1; 95% CI:7.09-111.47; p<0.001) (TABLE 6). These results indicate that the NLR-positive (>4.0) value and MPV-positive value (>7.6) are significantly associated with the preeclampsia incidence with the OR of 3.8 and 28.1, respectively.

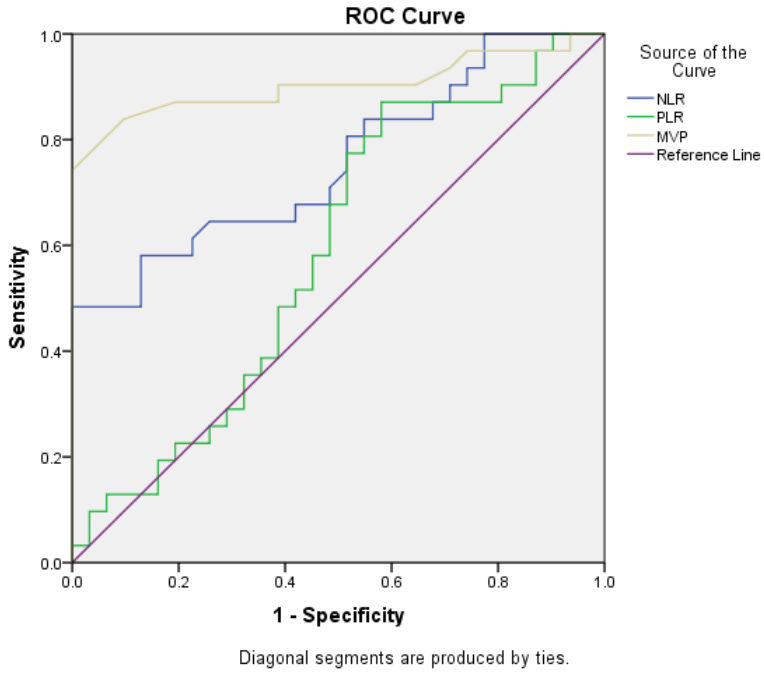

Figure 1. ROC-curve predictor preeclampsia.

TABLE 5. Area under curve (AUC) predictors for preeclampsia

Variable	Area	Standard Error	Sig	95% CI	
				Lower bound	Upper bound
NLR	0.758	0.061	0.000	0.637	0.878
MPV	0.903	0.044	0.000	0.816	0.989
PLR	0.586	0.074	0.245	0.441	0.731

TABLE 6. The result of the area under ROC-curve analysis, cut-off value, sensitivity, specificity and Chi-square test of NLR and MPV

Variable	AUC	p[a]	Cut-off value	Sensitivity (%)	Specificity (%)	p[b]
NLR	0.758	<0.001	4.00	64.5	71.0	0.011 [OR 3.8; 95% CI:1.33-10.94]
MPV	0.903	<0.001	7.55	87.1	80.0	<0.001 [OR 28.1; 95% CI:7.09-111.47]

*[a]; area under ROC-curve analysis, [b]; Chi-square

DISCUSSION

Preeclampsia occurs in 2-8% of pregnancies globally and causes disorder in several organ systems. However, the pathogenesis of preeclampsia is not clear yet.[10-12] The presence of activating factors from inflammatory cells (neutrophils, lymphocytes, platelets) that participate in the releasing of inflammatory cytokines and autoantibody reactions are associated with preeclampsia. Until now, termination of pregnancy is considered appropriate treatment.[11-14] It

makes predictive value and preventive measures essential to avoid maternal and fetal risks.[10,11] Changes in the value of hematological parameters, such as NLR, PLR, and MPV which are known as systemic inflammatory responses in preeclampsia have been studied. However, the results are still inconclusive.[12-16]

The NLR value is representing non-specific inflammatory mediators as the first-line defense and protective components of inflammation.[17,18] It has received more attention in providing predictive value in several diseases such as cancer and cardiovascular disease in recent years. Therefore, the NLR is considered as a provider of diagnostic and prognostic value in preeclampsia.[18-22]

Mannaerts *et al.*[10] reported that patients with preeclampsia have NLR value higher than normotensive pregnancies, although it is not significantly different. In contrast, some studies reported that the NLR value of patients with preeclampsia is significantly different compare with normotensive pregnancies.[18,21] Kang *et al.*[19] also reported that the NLR value is higher in patients with preeclampsia, especially in severe preeclampsia, compared to normotensive pregnancies. Therefore, NLR value might be a useful laboratory marker for clinical prediction and severity evaluation of preeclampsia.[19]

The cut-off value for NLR in predicting preeclampsia have been proposed by some authors. Singhal *et al.*[20] found that the NLR has a cutt-off value of ≥ 4.86 with a sensitivity of 68.6% and a specificity of 80.0% in predicting preeclampsia. Prasetyo *et al.*[22] found that the NLR is associated with preeclampsia with cut-off values between 3.5-5.6 in different sensitivity and specificity. In this study, it was found a cut-off value of 4.0 with a sensitivity of 64.5% and specificity of 71%.

In preeclampsia, neutrophil activation occurs while circulating in the intervillous space due to exposure with oxidized lipids secreted by the placenta.[11,13,14,18] Neutrophils from women with preeclampsia expressed more cyclooxygenase-2 than pregnancies without preeclampsia or in women who were not pregnant.[20,21] However, the mechanism behind this modulation of the immune system has not been elucidated. Another study showed that neutrophil activation occurs in the hypoxic placental circulation so that it infiltrates the systemic vascular tissue in women with preeclampsia which causes vascular inflammation.[11,20,21]

In a previous study, it was reported that all classes of leukocytes were activated in the maternal circulation of preeclampsia, but only neutrophil has significantly infiltrated the systemic vasculature. In the same study, it was found that the number of neutrophils in blood vessels was three times more than in lymphocytes. There are also research results that show an increase in the number of neutrophils up to 2.5 times at gestational age above 30 wk, and increases higher in patients with preeclampsia.[14,20,21]

A high MPV value indicates the number of young platelet cells in the circulation. The MPV value is an indicator of platelet activation, where platelet activity increases in pregnancy caused by the inflammatory process due to endothelial damage. The MPV in patients with preeclampsia was reported to be higher than in normotensive pregnancies.[10,11,16,18,23,25] The MPV was also reported increase as the severity of preeclampsia progressed.[25] The cut-off value for MPV in predicting preeclampsia have been also proposed by some authors. Mannaerts *et al.*[10] found that the MPV has a cutt-off value of 8.15 with a sensitivity of 66.7% and a specificity of 56.3% in predicting preeclampsia of pregnancies before 20 wk and 3rd trimester, whereas Yucel *et al.*[16] found a

cut-off value of 8.04 with a sensitivity of 74.39% and specificity of 33.33%.

Mean platelet volume is considered to reflect the inflammatory state. Its value is elevated in chronic inflammatory disease. In addition, a high MPV value is an independent risk factor for hypertension and a marker of poor prognosis for cardiovascular disease.[10,11,16,18] The high MPV in preeclampsia is caused by hypertension. The MPV increases or decreases depending on the severity of the inflammation. A higher MPV values in hypertensive patients with target organ damage compared to hypertension without target organ damage was observed. [16,21,23,24]

Platelet-lymphocyte ratio was obtained by dividing the number of platelets by the absolute lymphocyte value.[16] Several studies have been conducted to compare the PLR value between patients with preeclampsia and normal pregnancy with varied results. In this study, the PLR value in normotensive pregnancy was higher than patients with preeclampsia, although it was not significantly different (p=0.245). This result is similar with studies conducted by some authors.[11,21] In contrast, Yucel *et al.*[16] reported that the PLR value in patients with preeclampsia is significantly lower than in normal pregnancies. In addition, Kim *et al.*[21] also reported that the PLR values in patients with preeclampsia and severe preeclampsia are lower than in normal pregnancies. Whereas, Toptas *et al.*[26] reported that the PLR value in patients with severe preeclampsia is higher in the normal pregnancy and the patients with preeclampsia. Although, it was not significantly different.

The PLR value explains the correlation with platelet levels. It is associated with immune surveillance and major regulation of the cytokine-independent immune response. The interaction of endothelial cells and platelets in preeclampsia causes the release of inflammatory substances that induce leukocyte adhesion and migration. While platelet as a component of the PLR value decreased in preeclampsia due to the increased of clearance caused by the activation of the coagulation process that there is adhesion to the activated or damaged endothelium and the clearance of platelets through the reticuloendothelial system. In various diseases such as myocardial infarction, limb ischemia, kidney failure, and epithelial ovarian carcinoma, PLR value has correlation and prognostic values.[16,18,25,26] In this study, we have found that there was a slight difference in the mean PLR value, perhaps due to the small number of research samples.

Recent studies showed that systemic inflammatory response markers, such as NLR, PLR, and MPV have prognostic and predictive values in various benign and malignant diseases including coronary artery disease, inflammatory diseases, gynecologic or gastrointestinal malignancies, and preeclampsia. Mortality and morbidity in preeclampsia have significantly encouraged the examination which has a predictive value that could be conducted early in pregnancy to assess the development of preeclampsia, so the evaluation and preventive measures can be carried out.[9,10,16,26]

Cintesun *et al.*[9] reported that only the MPV has provided an higher predictive value for preeclampsia among the three hematological parameters i.e. NLR, MPV, and PLR. Mannaerts *et al.*[10] reported that MPV of pregnancies with preeclampsia before 20 wk and 3rd trimester is significantly higher than those normal pregnancies with optimal cut-off point of 8.15 (sensitivity 66.7% and specificity 56.3%) and 3.92 (sensitivity 84.4% and specificity 69.4%), respectively for predicting preeclampsia. Yucel *et al.*[16] also reported that MPV is significantly higher in patients with severe preeclampsia with cut-off point of 8.04 (sensitivity of 74.39% and specificity of 33.33%), whereas NLR

and PLR have no significantly value for predicting preeclampsia. A prospective case-control study in pregnancies more than 20 wk by Thalor *et al.*[23] concluded that MPV is reliable for predicting and early diagnosis of preeclampsia.

A meta-analysis conducted by Zeng *et al.*[18] reported that the diagnostic accuracy of NLR has unsatisfactory specificity but acceptable sensitivity for predicting preeclampsia. Whereas, another meta-analysis conducted by Kang *et al.*[19] concluded that NLR can be used as a laboratory marker for clinical prediction and severity of preeclampsia, with NLR values higher than in normal pregnancies. In addition, a systematic review conducted by Prasetyo *et al.*[22] concluded that there is a relationship between NLR and preeclampsia with a various cut-off point values between 3.5 – 5.6 in differences in sensitivity and specificity.

In this study, the AUC of NLR was 0.758 (95%CI:0.637-0.878; p=0.000) and the optimal cut-off point was 4.0 (sensitivity of 64.5% and specificity of 71.0%), whereas the AUC of MPV was 0.903 (95%CI: 0.816-0.989; p=0.000) and the optimal cut-off point was 7.55 (sensitivity of 87.1% and specificity of 80.0%). The AUC of PLR was 0.586 (95%CI: 0.441-0.731; p=0.245) (TABLE 5 and 6). The MPV had higher predictive value than NLR for predicting preeclampsia, meanwhile the PLR parameters were not significant in predicting preeclampsia.

CONCLUSION

In conclusion, the NLR and MPV are significantly higher in preeclampsia than in normotensive pregnancies. However, the PLR is not significantly difference in preeclampsia compared to that in normotensive pregnancies. In addition, the MPV has a better predictive value for preeclampsia than NLR. Further large-scale studies are required to validate the potential of MPV alone or in combination with NLR as predictor for preeclampsia.

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