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ORIGINAL ARTICLE

Modified Complete Blood Count Indices as Predicting Markers of Preeclampsia from Gestational Hypertension: Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, and Platelet to Neutrophil Ratio

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SUMMARY

Background: **To evaluate modified complete blood count (CBC) indices as a predicting marker of preeclampsia (PE) from gestational hypertension (GH), we analyzed the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and platelet to neutrophil ratio (PNR). PNR was a newly designed index in this study based on results of PE patients having a tendency toward higher neutrophil count and lower platelet count compared to normal pregnant women in previous studies.**
Methods: **We recruited 86 normal pregnant women, 33 patients with GH and 68 patients with PE. Subjects with any history of membrane rupture, infection, or multiple pregnancies were excluded. PNR, NLR, and PLR values including other CBC indices were statistically analyzed.**
Results: **NLR value of PE patients was significantly higher than GH patients ($p = 0.011$). PNR value was the most statistically significant index separating patients with PE and GH ($p < 0.001$). PLR value was lower in patients with PE compared to GH; however, statistical significance was low.**
Conclusions: **NLR as well as PNR is a useful index to help predicting progression from GH to PE. Further studies are required to evaluate the full extent of utility of PNR as a predictive index in PE patients.**
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INTRODUCTION

Complete blood count (CBC) is one of the routine laboratory tests for evaluation of disease status. The parameters such as neutrophils, lymphocytes, and platelets of the CBC exhibit changes related to infection and inflammation [1]. Also, modified CBC indices calculated by the ratios of each CBC parameter have been presented as markers for various infection or inflammatory diseases by increasing the extent of these changes of count. Among them, neutrophil to lymphocyte ratio (NLR) has been demonstrated as a marker of systemic inflamma-

tion and a useful marker in predicting vascular diseases or adverse outcomes of several malignancies [2,3]. Platelet to lymphocyte ratio (PLR) is also a sensitive marker of systemic inflammation and a prognostic factor in some malignancies such as breast cancer and colorectal cancers [4]. These indexes provide clinically relevant information by showing the changes in the distribution of hematologic cells according to pathologic conditions.

Recently, NLR and PLR values have been reported to be associated with the prediction of preeclampsia (PE) or PE with severe features in studies comparing normal pregnancy and PE [5-9]. PE can be diagnosed when gestational hypertension (GH), characterized by hypertension that first occurred after 20 weeks of gestation, is accompanied by proteinuria or end-organ dysfunction associated with hypertension [10]. Although PE and GH have pregnancy-induced hypertension as the main axis of the diagnosis, their progress and prognosis are very different. While GH has a relatively benign course of pregnancy and favorable outcome, PE is a major course of maternal and perinatal morbidity and mortality [11, 12]. Despite the uncertainty whether GH and PE are diseases in a single pathologic spectrum or distinct pathologies, about 10 - 50% of pregnant women diagnosed with GH at the initial stage suffer progression to PE [12-15]. There has been a clinical demand for predictive factors associated with these progressive changes [14, 15]. However, there were no studies evaluating NLR and PLR in PE and GH patients.

The previous studies regarding CBC changes of PE patients showed the tendency of higher neutrophil count and lower platelet count compared to healthy pregnancy [16-18]. In this regard, we first designed the platelet to neutrophil ratio (PNR) to maximize these differences in this study. We evaluated the NLR, PLR, and PNR value as a predicting marker of the progression from GH to PE by comparing the PE patients with the GH patients as well as with normal pregnancy women (NP).

MATERIALS AND METHODS

We conducted a retrospective analysis of demographic data and the results of laboratory tests of 188 pregnant women who were admitted to our hospital between January 2007 and December 2016. The study comprised 86 healthy pregnant women, 33 pregnant women with GH, and 68 with PE. The diagnosis of GH and PE was made according to the recommendation of ACOG 2013, and the severity of PE was not distinguished. GH was defined as new-onset hypertension (either a systolic blood pressure (BP) of 140 mm Hg or higher or a diastolic BP of 90 mm Hg or higher on at least two occasions at least 4 hours apart) after 20 weeks of gestation without evidence of proteinuria. PE is characterized by gestational hypertension with development of proteinuria (protein $\geq$ 300 mg per 24 hours urine collection or protein/creatinine ratio $\geq$ 0.3). Patients with thrombocytopenia (platelet count < 100,000/μL), impaired liver function (alanine transaminase or aspartate aminotransferase up to twice the normal concentration), renal insufficiency (serum creatinine $\geq$ 1.1 mg/dL), pulmonary edema, or symptoms suggesting cerebral involvement such as headache or visual disturbances were diagnosed as PE despite the absence of proteinuria. The exclusion criteria were as follows: chronic hypertension, diabetes mellitus, nephropathy, heart disease, malignancy, abnormal thyroid function tests, membrane rupture or infection.

The age, gestational age, fetal birth weight, and 1st and 5th minute Apgar scores were compared among the three groups. The CBC with differential count was performed using blood samples collected before delivery. NLR, PLR, and PNR values were derived from CBC data.

SPSS software (v.20; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The data were presented as numbers (percentages) or means ± standard deviations. Continuous variables were analyzed using the Mann-Whitney *U* test for two groups and the Kruskal-Wallis test for three groups. Pearson's Chi-square test was employed for categorical variables. The comparison of receiver-operator curve (ROC) between NLR, PLR, and PNR for PE was performed using MedCalc for Windows, version 11.0 (MedCalc software, Ostend, Belgium).

RESULTS

The demographic characteristics between PE, GH, and NP groups were presented in Table 1. The PE group had higher maternal age and percentage of primipara and shorter gestational period than that of GH and NP groups. GH and NP groups showed similar fetal birth weight and Apgar scores at 1 and 5 minutes after birth, whereas the PE group had lower fetal birth weight and Apgar scores.

The CBC indices including NLR, PLR, and PNR between GH and NP groups did not show statistically significant differences (Table 2). However, the PE group had higher white blood cells (WBC) and neutrophils and lower platelet counts than the other two groups ($p = 0.005$, 0.004, and 0.007, respectively). The lymphocyte counts in the three groups were similar. In addition, the PE group showed significantly higher NLR than GH and NP group (6.2 ± 4.9, 4.2 ± 2.3, and 4.3 ± 1.6, respectively). The PNR was statistically significantly lower in PE than GH and NP (24.7 ± 13.2, 36.3 ± 12.2, and 32.3 ± 11.9, respectively). However, the PLR had weak significance only in the comparison between PE and GH, although statistical power was not strong (119.3 ± 52.8 and 138.6 ± 50.9, respectively). The comparison of NLR, PLR, and PNR between GH and NP showed no statistical significance.

The ROC curves for NLR, PLR, and PNR in PE and GH groups were compared (Figure 1). PNR had the

Table 1. The comparison of demographic characteristics between preeclampsia, gestational hypertension, and normal pregnancy groups.

	PE (n = 68)	GH (n = 33)	NP (n = 86)	p
Age (years)	33.3 ± 4.8 *	30.3 ± 5.4	32.2 ± 3.7	0.010
GA (week)	35.3 ± 3.2	37.8 ± 1.7	39.8 ± 1.0	0.000
Primipara	64.7%	30.3%	60.5%	0.003
FBW (g)	2,154.1 ± 680.1	3,035.5 ± 659.8	3,311.6 ± 405.6	0.000
APG_1	6.9 ± 1.5	7.7 ± 0.9	7.9 ± 0.3	0.000
APG_5	8.4 ± 1.0	8.9 ± 0.6	9.0 ± 0.2	0.000

Abbreviations: PE - preeclampsia, GH - gestational hypertension, NP - normal pregnancy, GA - gestational age, FBW - fetal birth weight, APG_1 - Apgar score at 1 minute after birth, APG_5 - Apgar score at 5 minutes after birth. * - Data are expressed as means ± standard deviations.

Table 2. The comparison of CBC indices including NLR, PLR, and PNR between preeclampsia, gestational hypertension, and normal pregnancy groups.

	PE (n = 68)	GH (n = 33)	NP (n = 86)	p		
				PE:GH	PE:NP	GH:NP
Hemoglobin (g/dL)	12.4 ± 1.5 *	12.1 ± 1.4	12.0 ± 1.5	0.465	0.484	0.819
WBC (10^3/μL)	11,543.2 ± 2457.4	9,253.9 ± 2305.3	9,590.2 ± 2194.1	0.005	0.005	0.383
Platelet (10^3/μL)	189.8 ± 65.4	230.3 ± 64.3	212. 7 ± 46.1	0.005	0.007	0.204
Neutrophil (10^3/μL)	9,158.7 ± 4,235.7	6,775.3 ± 2,266.6	7,137.9 ± 2,045.9	0.003	0.004	0.233
Lymphocyte (10^3/μL)	1,723.7 ± 582.2	1,765.7 ± 457.4	1,744.5 ± 380. 5	0.434	0.357	0.799
NLR	6.2 ± 4.9	4.2 ± 2.3	4.3 ± 1.6	0.014	0.013	0.289
PLR	119.3 ± 52.8	138.6 ± 50.9	126.8 ± 36.0	0.044	0.070	0.296
PNR	24.7 ± 13.2	36.3 ± 12.2	32.3 ± 11.9	0.000	0.000	0.056

Abbreviations: WBC - white blood cells, PE - preeclampsia, GH - gestational hypertension, NP - normal pregnancy, NLR - neutrophil to lymphocyte ratio, PLR - platelet to lymphocyte ratio, PNR - platelet to neutrophil ratio. * - Data are expressed as means ± standard deviations.

highest area under the curve (AUC) value among indices derived from the CBC (PNR; 0.755, NLR; 0.652, and PLR; 0.624) with statistical significance. NLR and PLR had lower AUC values than that of original the CBC parameters such as WBC, neutrophils, and platelet count (AUC value; 0.674, 0.683, and 0.672, respectively, and data not shown in the figure). The AUC values of PNR were higher than those of the original CBC parameters despite low statistical significance.

DISCUSSION

Higher NLR values in PE patients or PE patients with severe features have been demonstrated in several studies comparing healthy non-pregnant or normal pregnancies [5-7]. This is due to an increase of WBC in PE compared with normal pregnancy and a higher elevation of neutrophil count than other parameters [19,20]. The infiltration of these neutrophils to systemic vascular tissue induces the release of reactive oxygen species, which enhances vascular reactivity and constriction in PE [21,22]. This is suggested as an important mechanism for hypertension in PE [23-25].

In this study, NLR values of the PE group were higher than those of the GH or NP group, with both groups showing similar NLR values. These results are related to the different mechanisms of hypertension between PE and GH in several respects [26]. PE patients have high systemic vascular resistance and low cardiac output, whereas GH patients maintain systemic vascular resistance as low as normal pregnancy and progressively increase cardiac output in hemodynamic studies [27,28]. The neutrophil-mediated systemic vascular resistance is less likely to contribute to GH.

Although the PLR value is a systemic inflammation

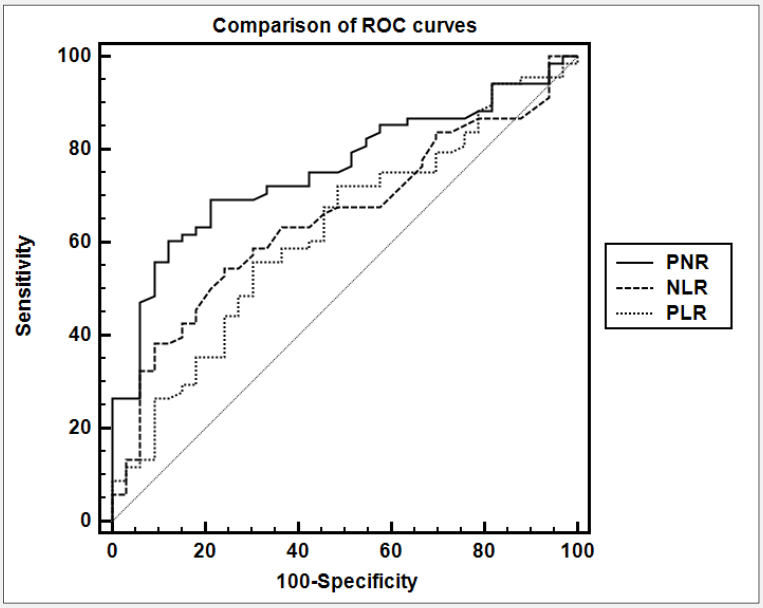

Figure 1. Receiver operating characteristic (ROC) curves for NLR, PLR, and PNR in preeclampsia and gestational hypertension groups.

The area under the curves (AUC) for PNR, NLR, and PLR in preeclampsia and gestational hypertension groups were 0.755 (95% CI: 0.660 - 0.835), 0.652 (95% CI: 0.550 - 0.744), and 0.624 (95% CI: 0.522 - 0.719). (Abbreviations: PNR - platelet to neutrophil ratio, NLR - neutrophil to lymphocyte ratio, PLR - platelet to lymphocyte ratio; CI - confidence interval).

marker that has been evaluated as a prognostic predictor of various diseases, data associated to PE are limited. PLR values of PE patients show significantly lower values than those of NP or only a lower tendency without statistical significance [8,9]. In this study, PLR values of the PE group were significantly lower than those of the GH group, but the statistical power was low. Meanwhile, the platelet count itself of PE patients was significantly lower than that of NP or non-pregnant controls in several studies [8,18,29]. The circulating platelet count of PE is lowered due to endothelial injury, which increases platelet turnover and mean platelet volume [18,30,31]. PE groups of this study had lower platelet counts than GH or NP groups. The statistical significance of platelet count was higher than PLR.

PNR value was applied as a new index based on results of higher neutrophil and lower platelet count compared to NP or non-pregnant controls reported in many studies [8,18-20,29-31]. The PNR value of the PE group was significantly lower than that of the GH or NP groups. The statistical significance of the PNR was stronger than the original CBC parameter or other derived indices such as NLR or PLR. Also, the AUC value of PNR to detect PE in PE and GH groups was highest. When comparing with the PE group without severe features (systolic BP $\geq$ 160 mmHg, diastolic BP $\geq$ 110 mmHg, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, and new-onset cerebral or visual disturbances) (35 among 86 PE patients) and the GH group, PNR had the highest statistical significance (p-value of NLR, PLR, and PNR; 0.012, 0.496, and 0.002, respectively, data not shown).

CONCLUSION

As far as we know, the present study, for the first time, evaluated the clinical usefulness of indices derived from CBCs such as NLR, PLR, and PNR as markers for predicting progression from GH to PE. In this study, NLR as well as PNR is an index that may be useful for predicting progression to PE from GH or NP. The limitation of our study was the small subject size. This availability of PNR and NLR should be evaluated for more PE and GH patients. In addition, PNR is difficult to use as a general marker of systemic inflammatory status because it is based on the specific CBC changes of PE. Both PNR and NLR had statistical significance in comparison to GH and PE patients. Especially PNR has shown the potential as a more sensitive and useful marker in predicting progression from GH to PE in the current study. These findings imply that NLR as well as

PNR indexes derived from the differential counts of CBCs can help predict the progression from GH to PE. Further studies are required to evaluate the full extent of the utility of PNR and NLR as a predictive index of progression from GH to PE on larger population.

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Declaration of Interest:
All authors declare that they have no conflicts of interest.

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