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High first-trimester neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are indicators for early diagnosis of preeclampsia

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ABSTRACT

Objectives: The aim of our study is to determine whether first-trimester neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) would be useful as new predictors of subsequent preeclampsia.

Material and methods: Medical records of women with preeclampsia and healthy controls from a tertiary referral center were retrospectively evaluated. The two groups were compared in terms of clinical characteristics and first-trimester levels of hemoglobin, leukocyte, neutrophil, lymphocyte, platelet, NLR and PLR. Receiver operating characteristic curve (ROC) analysis was performed to identify the optimal NLR and PLR levels predicting preeclampsia.

Results: Neutrophil ($p < 0.001$), platelet ($p < 0.001$), NLR ($p < 0.001$) and PLR ($p < 0.001$) levels were significantly elevated, whereas hemoglobin concentration ($p = 0.003$) was significantly lower in the group with preeclampsia as compared to the control group. On multivariate regression analysis, NLR (OR 1.43; 95% CI 1.21–1.76; $p = 0.005$) and PLR (OR 1.38; 95% CI 1.15–1.63; $p = 0.008$) were the most powerful predictive variables. The area under the ROC was 0.716 and 0.705 for NLR and PLR, respectively. The cut-off values of NLR ≥ 3.08 and PLR ≥ 126.8 predicted preeclampsia with the sensitivity of 74.6% and 71.8% and specificity of 70.1% and 72.4%, respectively.

Conclusions: High NLR and PLR during the first trimester are independent predictors of subsequent preeclampsia.

Key words: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, preeclampsia

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INTRODUCTION

Preeclampsia is characterized by a new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive pregnant woman [1]. It is one of the most common complications of pregnancy, affecting 3–5% of all pregnant women and is responsible for 12% of the global maternal mortality [1]. Numerous etiological factors have been proposed to explain the pathological changes in preeclampsia. According to previous publications, deficient trophoblastic invasion in the first trimester results in preeclampsia later in pregnancy. The altered immune response of a gravid woman, causing excessive maternal inflammation and poor placentation, leading to increased capillary permeability, micro-vascular thrombosis, and increased vascular tone, has been among the proposed mechanisms [2, 3].

Recently, elevated neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have generated significant interest as systemic inflammatory response markers in various clinical circumstances. Elevated NLR is associated with increased cardiovascular risk and mortality in some malignancies [4]. PLR is assumed to show increased platelet activation which leads to initiation and progression of atherosclerosis [4]. However, the predictive value of NLR and PLR in the early diagnosis of preeclampsia remains unclear.

Therefore, the aim of our study was to assess the diagnostic value of NLR and PLR, as well as neutrophil, lymphocyte and platelet counts during the first trimester of gestation to predict the subsequent development of preeclampsia.

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MATERIAL AND METHODS

Our retrospective study included 209 pregnant women diagnosed with preeclampsia and 221 normotensive pregnant controls, presenting at the Department of Perinatology between January 2013 and April 2015. Local Ethics Committee approved of the study. The diagnosis of preeclampsia was made in accordance with the American College of Obstetrics and Gynecology criteria [5]. All preeclamptic patients were diagnosed between 22 to 40 weeks of gestation. The control group consisted of pregnant women who gave birth to children between 38 to 41 weeks, appropriate for gestational age, without any history of complications throughout the pregnancy. First-trimester (7–14 weeks) complete blood cell counts (CBC) were obtained in all patients. Patients with systemic diseases, history of hematopoietic system disorders, malignancies, acute or chronic inflammatory diseases, and those who were on any medication which could have affected the CBC results were excluded from the study.

The following clinical data were collected from patient medical reports: maternal age, parity, abortus, body mass index, type of conception, smoking habit, gestational age at the time of diagnosis, fetal gender, gestational age at delivery, type of delivery, gender, birth weight and percentile of the newborn and first-trimester CBC. CBC was performed in the first trimester at our center using a Coulter LH 750 device (Beckman Coulter, Brea, CA, USA). When more than one CBC result was available, the result of the date which is closest to 7 weeks of gestation was recorded for statistical analysis. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and PLR was defined as the absolute platelet count divided by the lymphocyte count. Percentile of the fetal weight was calculated by the Hadlock formula and fetal weight < 5 percentile was accepted as small for gestational age [6].

The study group was assessed for the presence of preeclampsia and their first-trimester inflammation markers. Statistical analyses were performed using SPSS (SPSS for Windows version 20.0, Chicago, Illinois, USA). Chi-square analysis was used to analyze categorical variables, Student's t-test was used for normally distributed variables and the Mann-Whitney U-test was used for non-normally distributed variables. Relative risks with 95% confidence intervals (CIs) were calculated. A p-value of < 0.05 was considered as statistically significant. A receiver operating characteristic (ROC) curve was used to evaluate the cut-off, sensitivity, and specificity values.

RESULTS

Clinical characteristics of the preeclamptic and control groups are presented in Table 1. Gestational age at delivery ($p < 0.001$), birthweight ($p < 0.001$), and birth percentile ($p < 0.001$) were significantly lower and the cesarean section rate ($p < 0.001$) was significantly higher in the preeclamptic group as compared to healthy controls. Among serum markers, hemoglobin levels ($p = 0.003$) were significantly lower and the values of neutrophil ($p < 0.001$), platelet ($p < 0.001$), NLR ($p < 0.001$), and PLR ($p < 0.001$) were significantly higher in the group with preeclampsia as compared to the control group.

In multivariate analysis, NLR and PLR remained the most powerful predictors ($p = 0.005$ and $p = 0.008$, respectively) (Table 2). ROC curve analysis suggested that NLR (area under the curve [AUC] = 0.716; 95% CI 0.666–0.766; $p < 0.001$) and PLR (AUC = 0.705; 95% CI 0.656–0.754; $p < 0.001$) had the highest AUC in predicting preeclampsia (Table 3 and Figure 1). The optimum cut-off points for NLR and PLR were 3.08 (sensitivity: 74.6%, specificity: 74.6%) and 126.8 (sensitivity:71.8%, specificity:72.4%), respectively.

DISCUSSION

Current evidence suggests that a vascular endothelial multisystem disorder which leads to microvascular thrombosis induced by platelets, increased capillary permeability, increased vascular tone and hypertension, contributes to the pathogenesis of preeclampsia [3]. Altered immune response, excessive maternal inflammation, and immune maladaptation are also among the proposed etiological factors [2]. Sacks et al., demonstrated a massive influx of proinflammatory macrophages and a natural killer in human decidua in the first trimester as early as 4 weeks of gestation [7]. The results of their research prompted us to believe that initiation of preeclampsia might be predicted by assessing the values of NLR and PLR, which are systemic inflammatory markers in the first trimester of pregnancy.

Various studies have shown white blood cell subtypes to be associated with cardiovascular diseases. Neutrophils are reported to have a role in atherogenesis and atherothrombosis [8]. Neutrophils also play an important role in the inflammatory processes. They are the first blood cells responding to inflammation [4]. Kurt et al., reported higher neutrophil counts in preeclamptic patients, implying the presence of an increased inflammatory state [9]. Our findings are consistent with their results as we detected the mean neutrophil count in the first trimester to be significantly higher in the group with preeclampsia.

Troeger el al., reported that increased erythropoietic stimulation associated with placental hypoxia can be detected in preeclamptic patients [10]. This tissue hypoxia causes secretion of erythropoietin and stimulates bone marrow, resulting in increased megakaryocyte and platelet counts [11]. Activated platelets and neutrophils pass through the intervillous space and cause endothelial dysfunction [1]. It was hypothesized that activation of platelets during trophoblast invasion in early pregnancy can differ between in

Table 1. Clinical characteristics of the study group

Parameters	Preeclampsia group (n = 209)	Normotensive group (n = 221)	P value
Maternal age (years)†	26.6 ± 6	25.8 ± 4.9	0.15
Nulliparity	136	128	0.138
Parity	1.34 ± 0.7	1.48 ± 0.9	0.11
Abortus	36	26	0.131
BMI at enrollment†	25.7 ± 3.7	25.2 ± 4.1	0.526
Conception by IVF	8	6	0.593
Smoker	11	5	0.128
Gestational age at diagnosis (weeks)†	34.08 ± 3.96	N/A	N/A
Female to male ratio	95/104 (0.91)	108/103 (1.05)	0.104
Gestational age at delivery (weeks)†	35.8 ± 3.02	39.37 ± 1.16	< 0.001
Birth weight [g]†	2371 ± 790	2950 ± 768	< 0.001
Birth percentile	23.32 ± 28.22	40.44 ± 25.66	< 0.001
Cesarean delivery rate (%)	128	81	< 0.001
Hemoglobin	10.9 ± 1.8	11.5 ± 1.9	0.003
Leukocyte	11.1 ± 2.3	10.7 ± 2.3	0.105
Neutrophils [10^3/mm^{-3}]†	7.3 ± 2	5.9 ± 1.5	< 0.001
Lymphocytes [10^3/mm^{-3}]†	2.07 ± 0.63	2.19 ± 0.92	0.095
Platelets [10^3/mm^{-3}]†	270.1 ± 59.8	229.9 ± 60.2	< 0.001
NLR†	3.8 ± 1.5	3.1 ± 1.3	< 0.001
PLR†	141.9 ± 50.8	118.5 ± 47.2	< 0.001

† Values are expressed as mean ± standard deviation or n (%) unless otherwise specified; BMI — body mass index; IVF — *in-vitro* fertilization; N/A — not available; NLR — neutrophil to lymphocyte ratio; PLR — platelet to lymphocyte ratio

Table 2. Significant predictors of preeclampsia in multivariate regression analysis

Markers	Odds ratio	95% CI	P value
Hemoglobin	0.95	0.87–1.21	0.242
Neutrophil	1.24	0.98–2.14)	0.096
Platelet	1.18	0.95–1.87	0.105
NLR	1.43	1.21–1.76	0.005
PLR	1.38	1.15–1.63	0.008

CI — confidence interval; NLR — neutrophil to lymphocyte ratio; PLR — platelet to lymphocyte ratio

preeclamptic and healthy individuals [2]. Altered platelet reactivity was detected in preeclampsia and suggested as an early marker for the disease [12]. Similar to our study, Tzur et al., reported high first-trimester platelet counts in preeclamptic patients [13].

High NLR and PLR have been found to be associated with increased inflammation. These markers were studied as new predictors for various illnesses. Higher platelet count is also associated with adverse cardiovascular outcomes in cardiac diseases, and high PLR value is used as a marker for long term mortality [14]. The results of our study on preeclampsia are in agreement with other studies, suggesting that elevated NLR and PLR are available markers for predicting vascular events which are associated with increased inflammation [15]. In a previous paper, high PLR and NLR were reported in non-dipper hypertensive patients, which is associated with end-organ damage and cardiovascular mortality [16]. As endothelial pathology and end-organ damage are common features of non-dipper hypertension and preeclampsia, PLR and NLR were also found to be elevated in our study. Contrary to our study, Kurt et al., reported that NLR was not significantly different between preeclampsia and control groups, although the neutrophil count was significantly higher in the group with preeclampsia [9]. However, recently NLR has been reported to be significantly higher in preeclamptic patients in two publications supporting our results [17, 18]. The ROC analysis of our study showed the NLR value of 3.08 or higher, with the sensitivity of 74.6%, specificity of 70.1% and a PLR value of 126.8 or higher, with the sensitivity of 71.8%, specificity of 72.4% to predict preeclampsia. Therefore, the use of these markers in clinical practice seems adequate.

Our study is not without limitations, e.g. the effect of unidentified confounding factors due to retrospective design. We are of the opinion that some missing data such as autoimmune diseases, antiphospholipid syndrome, and

Table 3. Prognostic values of optimum cut-offs for first trimester NLR and PLR in predicting preeclampsia

Markers	AUC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR^+ (95% CI)	LR^- (95% CI)	Cut-off value
NLR	0.716 (0.666–0.766)	74.6 (68.2–80.4)	70.1 (63.6–76.1)	70.3 (63.8–76.2)	74.5 (68–80.3)	2.5 (2–3.1)	0.4 (0.3–0.5)	3.08
PLR	0.705 (0.656–0.754)	71.8 (65.1–77.8)	72.4 (66–78.2)	71.1 (64.5–77.1)	73.1 (66.7–78.8)	2.6 (2.1–3.3)	0.4 (0.3–0.5)	126.8

AUC — area under curve; CI — confidence interval; LR^+ — positive likelihood ratio; LR^- — negative likelihood ratio; NLR — neutrophil to lymphocyte ratio; NPV — negative predictive value; PLR — platelet to lymphocyte ratio; PPV — positive predictive value

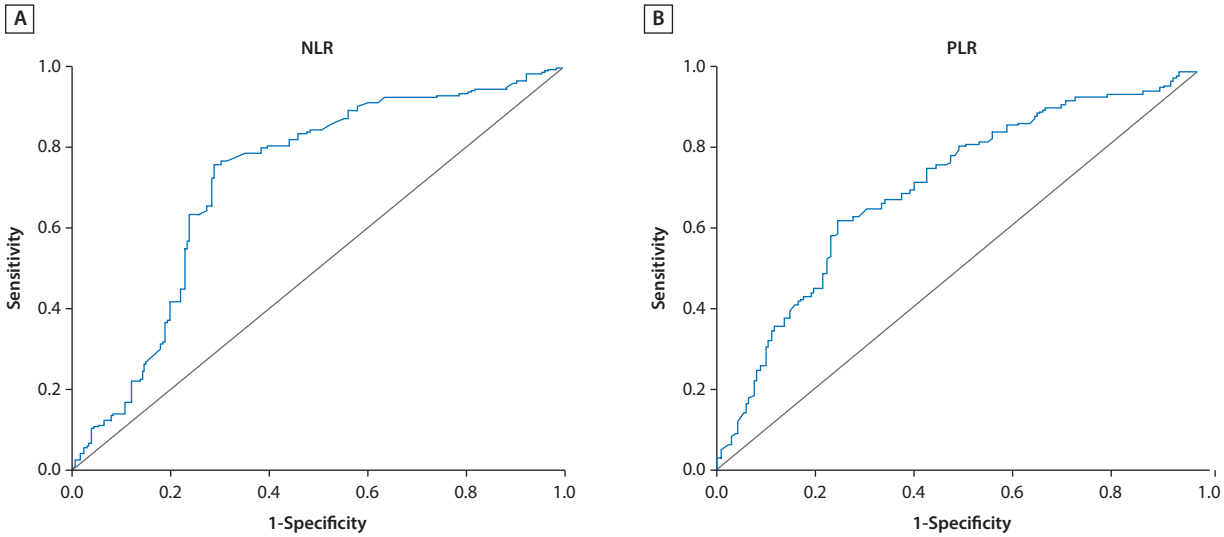

Figure 1. Receiver operating characteristic curves for neutrophil to lymphocyte ratio (NLR) (**A**) and platelet to lymphocyte ratio (PLR) (**B**) used to make the clinical decision regarding preeclampsia. The areas under the receiver operating characteristic curve (ROC) were 0.716 and 0.705, respectively

short interpregnancy interval could also confound the effects. However, this potential selection bias was likely to be reduced by excluding some of the strongest risk factors including age, parity, body mass index, and systemic illnesses.

CONCLUSIONS

Our data revealed that both, NLR and PLR in the first trimester of pregnancy could be used for the early diagnosis of preeclampsia. NLR and PLR are inexpensive, rapid and easily applicable tests for determining the pregnancies at risk for preeclampsia. Our study can provide useful basic information for clinical practice in detecting asymptomatic women at increased risk for preeclampsia. Thus, it is also suggested that pregnant women with high NLR and PLR during the first trimester of pregnancy should be monitored closely for signs of preeclampsia such as hypertension and proteinuria.

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