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# Predication of Preeclampsia Severity by NLR and PLR

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**ABSTRACT**

**Background & Objective**: We aimed to assess the Neutrophil Lymphocyte Ratio (NLR) and the Platelet Lymphocyte Ratio (PLR) in pregnant women with Severe Preeclampsia (SPE) compared with Non-Severe Preeclampsia (NSPE) and Non Preeclamptic (NPE) controls to evaluate whether there is an association between these hematologic parameters and severity of preeclampsia (PE).

**Methods:** Demographic data and laboratory results of 148 pregnant women (age range:15-43 years; mean age:30 years), with SPE, NSPE and NPE were retrospectively evaluated in this cohort study during 2019-2021. Three groups were evaluated in terms of demographic characteristics and the hematological parameters of first trimester including Neutrophil, Lymphocyte, Platelet, NLR and PLR. Receiver Operating Characteristic curve (ROC) analysis was also performed to identify the optimal levels of NLR and PLR to predict PE.

**Results**: In the present study, of 148 pregnant women, 47(31.7%) were SPE, 46(~31.1%) were NSPE and the remaining 55 (~37.2%) were NPE. According to the Kolmogorov-Smirnov Test, variables don't have normal distribution between groups ($p<0.05$). According to the Kruskal-Wallis Test, there was not a statistically significant difference between NLR and PLR in these three groups ($p<0.05$); however, the median of PLR in SPE group was higher than the two other groups. In the hematological parameters after Generalized Estimating Equation (GEE) analysis, NLR ($p=0.000$, $\beta=-0.405$) and PLR ($p=0.001$, $\beta=15.5$) levels in the SPE group were higher than the NSPE group. Also NLR ($p=0.000$, $\beta=0.529$) and PLR ($p=0.000$, $\beta=-39.03$) levels in the SPE group were higher than the control group. In the ROC analysis, for both NLR and PLR, the area under the curve was <0.07. The cut-off values of NLR>2.13 and PLR>81 predicted PE between NSPE and NPE groups with the sensitivity of 73% and 60% and specificity of 43% and 48% respectively. The cut-off values of NLR>2.03 and PLR>85 predicted PE between SPE and NSPE groups with the sensitivity of 70% and 60% and the specificity of 27% and 46.7% respectively.

**Conclusion**: NLR and PLR cannot be used as a marker. in predicting of subsequent PE or its severity.

**Keywords:** *PE prediction, Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio*

## 1. INTRODUCTION

Preeclampsia (PE) is a pregnancy-specific hypertensive syndrome with associated impaired maternal systems and organs (1). It is characterized by the onset of hypertension and proteinuria after 20 weeks of gestation (2). In PE, inflammatory and immune reaction imbalance, leads to abnormal immune tolerance and excessive systematic inflammatory response (SIR). Since SIR is suggested to be an important process in PE (3), many researchers have investigated in white blood cell (WBC) counts in order to find out the correlation between WBC counts and PE (4). PLR (Platelet Lymphocyte Ratio) and NLR (Neutrophil Lymphocyte Ratio) are makers of SIR, that can be evaluated automatically during a complete blood count (CBC) for regular obstetric evaluation (5). Hematologic indexes of SIR have been investigated in patients for the prediction of presence and severity of PE with conflicting results (6-11), while others did not (12, 13). Moreover; neutrophil, lymphocyte and platelet number are influenced by geographic location, racial features, nutritional properties and many other factors (14). This study investigated the diagnostic value of PLR and NLR during first trimester for early prediction of PE or its severity in Rasht, Iran.

## 2. MATERIALS AND METHODS

This retrospective cohort study was conducted at the department of obstetrics and gynecology at Alzahra training and research hospital from 15 December 2019 to 10 January 2021. The ethics committee of Guilan university of medical sciences approved the study (IR.GUMS.REC.1399.365).

According to the current guidelines, patient with systolic blood pressure ≥ 140 mmHg or diastolic pressure ≥ 110 mmHg on two occasions at least two hours apart while the patient is on bed rest, define as PE.

The study groups consisted of hospitalized mild to severe preeclamptic patients between 20 to 41 weeks of gestation. Non preeclamptic (NPE) controls were randomly selected among hospitalized patients without PE and or proteinuria, at ≥ 37 weeks of pregnancy during the same period. We matched the three groups for blood pressure and sign and symptoms of PE.

The study was conducted on 148 pregnants (age range: 15-43 years), who were divided into three groups: group 1: 55 NPE pregnants as control group, group 2: 46 non severe preeclamptic (NSPE) women and group 3: 47 severe preeclamptic (SPE) pregnants.

Preeclamptic women were diagnosed and classified into NSPE and SPE according to the criteria recommended by the

American College of Obstetricians and Gynecologists (ACOG).

We used the strict criteria of ACOG for PE definition (15).

The authors excluded cases with chronic hypertension, infectious diseases, diabetes mellitus, cardiovascular or renal or hepatic or thyroid dysfunction, premature rupture of membranes (PROM), history of recurrent abortion or any bad obstetric outcomes and corticosteroid use, malignancy.

We diagnosed PE at≥ 20 weeks of gestation when systolic blood pressure (BP) was > 140/90 mmHg or diastolic BP was > 90 mmHg in at least 2 measurements made 4 hours apart in a pregnant with a previously normal BP or a dipstick reading of 1+ protein and proteinuria (≥ 300mg/24-hour).

CBC values were measured using an automated machinery.

Neutrophil, Lymphocyte and Platelet counts were extracted from patients' medical records. We calculated the NLR by dividing the neutrophil count by the lymphocyte count and calculated the PLR by dividing the platelet count by the lymphocyte count.

**Statistical analysis:**

The data were statistically analyzed with SPSS software, version 20 (Chicago, Illinois). Mea soured variables are presented as mean ± SD, and categorical variables are presented as numbers and percentages. The Kolmogorov-Smirnov test was used to determine if the numerical data matched the normality distribution. We used the Independent t-test to compare the normality distributed data. Mann-Whitney u test and Kruskal-Wallis were used to compare the qualitative variables. The chi-square test used to compare the qualitative variables. We also used Fisher's exact test and the regression analyze with the Generalized Estimating Equation (GEE). Receiver Operating Characteristic (ROC) curve was used to evaluate the cut off, sensitivity and specificity values. $P < 0.05$ was considered as the significant level.

**Ethical considerations:**

Before data collection, the researchers informed the participants about the objectives of the research and started the study after obtaining written consent from participants.

## 3. RESULTS

According to the inclusion criteria, 183 patients were included in the study, and of those, 35 women had incomplete data. Data from 148 patients in three groups of SPE (n=47, 31.7%), NSPE (n=46, 31.1%) and control group (n=55, 37.2%) were evaluated and analyzed. Patient's baseline demographic features are shown in table1.

In terms of education, 69 (52.3%) participants had a diploma {including 30 (60%), 21(51.2%) 18 (43.9%) in control NSPE and SPE groups respectively. Most participants (n=91, 74.6%) were rural women {(n=29, 69%) from the control group, (n=32, 84.2%) from the NSPE group and (n=30, 71.4%) from the SPE group}00.

Before analyzing the data, the variables were examined for normal distribution in the study groups using the Kolmogorov-Smirnov test, and the distribution of the data was not normal ($P < 0.05$). Hence, in order to compare the three groups in a univariate analysis, the Kruskal-Wallis nonparametric test for quantitative variables was used (table 2).

In the hematological parameters after GEE analysis, NLR (p=0.000, β=-0.405) and PLR (p=0.001, β=15.5) levels in the SPE group were higher than the NSPE group. Also NLR (p=0.000, β=0.529) and PLR (p=0.000, β=-39.03) levels in the SPE group were higher than the control group. In the ROC analysis, for both NLR and PLR, the area under curve was <0.07. The cut-off values NLR>2.13 and PLR>81 predicted PE between NSPE and NPE groups, with the sensitivity of 73% and 60% and specificity of 43% and 48% respectively. The cut-off values of NLR>2.03 and PLR>85 predicted PE between SPE and NSPE groups with the sensitivity of 70% and 60% and the specificity of 27% and 46.7% respectively. The predictive value of PE based on PLR and NLR was weak in three groups as compared to each other (Table 3).

**Table1: Demographic information of the study groups**

| Quantity factors | SPE (n=47) | NSPE (n=46) | NPE (n=55) | Total (n=148) | *P-value |
|---|---|---|---|---|---|
| | Mean ± SD (median) | Mean ± SD (median) | Mean ± SD (median) | Mean ± SD (median) | |
| Age (year) | 31.5± 5.6 (29) | 6.3 ±30.3 (29) | 27.8± 6.3 (32) | 30± 6.3 | 0.015 |

| | | | | | |
|---|---|---|---|---|---|
| **Gestational age (week)** | 31.4± 5.2 (39) | 37.4± 0.95 (37) | 38.6± 1.1 (35) | 36.7± 3.6 (57) | 0.0001 |
| **Height (cm)** | 160.5± 6.3 (160) | 159.8± 6.4 (159) | 161.4± 5.1 (160) | 160.1±5.8 | 0.288 |
| **Weight (kg)** | 75.2± 14.8 (72) | 75.2± 15.1 (74) | 72.7± 14.8 (75) | 74.3±14.8 | 0.577 |
| **BMI (kg/m$^2$)** | 29.2± 5.4 (27.4) | 29.4± 5. 5 (28.8) | 27.9± 5.8 (28.3) | 28.8±5.6 | 0.259 |

SPE = Severe preeclampsia, NSPE = Non Severe preeclampsia,NPE=Non preeclamptic, BMI: Body Mass index

* Kruskal-Wallis

**Table 2: The Comparison of NLR & PRL between 3 groups**

| **Variables** | **SPE(n=47)** | **NSPE (n=46)** | **normotensive(n=55)** | **Chi-square** | ***P-value** |
|---|---|---|---|---|---|
| | **Mean± SD (median)** | **Mean± SD (median)** | **Mean± SD (median)** | | |
| NLR | 2.8±1.08 (2.5) | 2.7± 0.89 (2.6) | 2.5±0.98 (2.4) | 2.01 | 0.365 |
| PLR | 102.9±40.8 (97.7) | 104.1±56.8 (93.3) | 86.1±27.4 (82.8) | 4.8 | 0.089 |

SPE: Severe preeclampsia, NSPE: Non Severe preeclampsia, NLR: Neutrophil Lymphocyte Ratio, PRL: Platelet Lymphocyte Ratio

* Kruskal-Wallis

**Table 3: Area under the curve (AUC) for variables of the study.**

| Area Under the Curve | | | | | | |
|---|---|---|---|---|---|---|
| **Groups** | **Variable** | **Area** | **Std. Error[a]** | **P-value** | **CI 95%** | |
| | | | | | **Lower Bound** | **Upper Bound** |
| SPE & normotensive | NLR | 0.568 | 0.058 | 0.254 | 0.454 | 0.682 |
| | PLR | 0.617 | 0.085 | 0.049 | 0.503 | 0.730 |
| NSPE & normotensive | NLR | 0.580 | 0.087 | 0.173 | 0.467 | 0.692 |
| | PLR | 0.604 | 0.057 | 0.077 | 0.491 | 0.716 |
| SPE & NSPE | NLR | 0.484 | 0.062 | 0.802 | 0.363 | 0.606 |
| | PLR | 0.506 | 0.062 | 0.927 | 0.384 | 0.628 |
| PE & normotensive | NLR | 0.574 | 0.051 | 0.140 | 0.474 | 0.674 |
| | PLR | 0.610 | 0.048 | 0.028 | 0.516 | 0.704 |

SPE: Severe preeclampsia, NSPE: Non Severe preeclampsia, NLR: Neutrophil Lymphocyte Ratio, PRL: Platelet Lymphocyte Ratio

## 4. DISCUSSION

Worldwide, about 76000 maternal deaths per year are associated with PE (16). Unfortunately, there is no simple, reliable and accepted evaluation for early prediction or diagnosis of PE.

Because of the central role of SIR in the pathogenesis of PE (17, 18). It is necessary to find predictive screening indicators for early identification of SPE before the appearance of the syndrome (19).

Various biomarkers have attracted interest for their potential profit in prediction of PE as early as the first trimester (17, 18).

NLR is a good, easy available effective and reliable biomarker in conditions with low-grade systemic inflammatory conditions (20, 21).

In PE, the endothelial dysfunction will active neutrophil to make further damage (22).

NLR and PLR are haematological parameters, which are cheaply and easily obtained by calculation after CBC testing and are widely used in the diagnosis of many SIR and in the prediction of early pregnancy loss (23).

Oğlak et al showed that NLR and PLR are useful markers in the prediction of PE (8).

The present study revealed no statistically significant difference between patients with SPE , NSPE and NPE regarding NLR and PLR and this is in agreement with the study of Kholeif et al (7) Singgih et al (12), Yücel et al (24) and Sweed et al (13).

Yavuzcan et al showed that NLR was statisticaly significant higher in SPE pregnants in comparison to NPE pregnants and not statistically significant between SPE patients in comparison to NPE (25). The findings of our study suggest that NLR and PLR in the first trimester of pregnancy are weak predictors of subsequent PE.

In contrast to present results, a meta- analysis found that NLR is a useful marker for prediction of PE and its severity (4).

Ye et al found that PLR has an acceptable moderate accuracy but limited sensitivity, for the diagnosis of PE (6).

Prasetyo et al showed NLR can be used as screening tools for PE in the first trimester (9).

Aslan et al suggested that third trimester NLR is associated with fetal loss in patients with SPE (26).

Toptas et al found that NLR had no significant difference between PE patients with SPE and NSPE degrees but a significant higher difference in PE than with NPE (27).

Serin et al showed that NLR had a significant high difference in PE compared to the NPE pregnants and NLR was significantly higher in the SPE cases than NSPE. Therefore NLR could predict the severity of the disease (28).

Hong-Biao et al (29), Oğlak et al (8),Gezer et al (30) found that PLR may be useful in predicting PE.

According to a metaanalysis NLR significantly elevates in PE, especially in SPE (4). The findings of another meta-analysis, support that PLR has a low sensitivity and misdioagnostic rate, moderate diagnostic value and high specificity in the second and third trimesters of PE. Therefor PLR has a good diagnostic efficacy (6).

The difference between ours results and the recent studies may be attributed to the contradictions and number of cases. Some studies (27, 28, 31, 32) using ACOG recommendation (15) included proteinuria, fetal growth restriction (FGR), and oligohydramnios as criteria to classify SPE which the present authors omitted in this study.

It was suggested that PLR is associated with many inflammatory conditions, but the association of PLR and PE has somewhat limited data yet (1, 16).

Kholeif et al demonstrated that there was a statistically significant difference between the NPE and SPE cases and between the NSPE and SPE cases but PLR had no statistically significant difference between the NPE and NSPE cases (7).

Yücel et al showed that PLR, was lower in the SPE cases than in the NPE cases and with a NPE pregnant females with a statistical significance (25). The reason may be because the study showed no statistical significant difference with regards to platelet count between SPE patients and healthy pregnant controls.

NLR didn't differ between SPE, NSPE and NPE women, so it cannot be used as a marker for prediction of PE or it's severity.

It was proposed that PLR was a more sensitive marker of systemic inflammation in various conditions. Although association of PLR with inflammation and numerous disease was reported, there are limited data evaluating the association of PLR and PE (7).

## 5. CONCLUSIONS

Our study found that due to low sensitivity and specificity of NLR and PLR, the percentage of these marker has no predictive value in PE. Our study found that, despite the differences in the mean NLR and PLR in the three groups and although the percentage of this factors increased in PE, due to its low sensitivity and specifitcy, it has no predictive value and these markers cannot be used as a marker in predicting the incidence of subsequent PE.

In contrast to the present results, despite the differences in the mean NLR and PLR in the three groups, however, the NLR and PLR in the first trimester are weak biomarkers in predicting the incidence of subsequent PE. Additional large-scale prospective studies are needed to validate the potential use of NLR and PLR alone or in combination with other markers such as PE biomarkers and to identify potential factors that may affect the accuracy of these markers for PE detection.

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