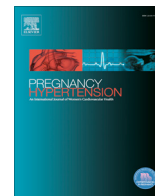


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Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume, red cell distribution width and plateletcrit in preeclampsia



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ABSTRACT

Introduction and aim: Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width (RDW) and plateletcrit (PCT) have all been recognized as systemic inflammatory response (SIR) markers. Our aim was to evaluate changes in NLR, PLR, RDW, MPV and PCT in preeclampsia and their use in predicting the severity of PE.

Study design: This retrospective cohort study included 219 patients. Of them, 27 had mild PE, 82 had severe PE, and 110 were healthy, normotensive pregnant patients.

Results: There were no significant differences in NLR between the groups ($p = 0.423$). Both PLR and PCT were lower in the patients with severe PE than in the control group, and these differences showed a statistical significance ($p = 0.007$ and $p < 0.001$). On the other hand, both RDW and MPV were statistically higher in the patients with severe PE compared to the control group ($p = 0.011$ and $p < 0.001$). ROC analyzes were used to examine the ability of markers to predict those with severe PE from those with mild PE. Areas under the curve for NLR, PLR and RDW were not statistically significant ($p = 0.636$, 0.104 and 0.36 , respectively). For MPV and PCT, the values of area under the curve were 0.641 and 0.712 , respectively, and the p values for these parameters statistically differed ($p = 0.028$, $p = 0.001$).

Conclusion: MPV or PCT may be clinical useful markers in the prediction of severe PE. Further, prospective multicenter studies are warranted to better reveal the association between SIR markers and PE.

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1. Introduction

Preeclampsia (PE) is still one of the leading causes of maternal-fetal morbidity and mortality, affecting approximately 2–8% of all pregnancies worldwide [1].

Despite no known definitive cause for PE, it is likely to be related to a number of factors. Studies have suggested that hyper-reactivation of inflammatory cells and immunologic responses of neutrophils and lymphocytes take place by releasing inflammatory cytokines and autoantibodies leading to endothelial dysfunction [2]. The clinical manifestations of PE are associated with generalized endothelial dysfunction, which causes vasoconstriction and end-organ ischemia [3].

The changes in the values of hematological parameters including, neutrophil-lymphocyte ratio (NLR, platelet-lymphocyte ratio

(PLR), red cell distribution width (RDW), mean platelet volume (MPV), and plateletcrit (PCT) are known as systemic inflammatory response (SIR) markers [4]. These markers have been separately investigated in patients with PE in previous studies. Whereas some researchers found these markers to be helpful in predicting the presence or severity of the disease [5–8], others did not [9–11].

In this study, we aimed to evaluate changes in NLR, PLR, RDW, MPV, PCT in preeclampsia and their use in predicting its severity. To the best of our knowledge, our investigation, for the first time, brought these markers together in one study.

2. Material and methods

This retrospective cohort study with prospectively collected data enrolled 219 pregnant women who were admitted to the delivery unit of a tertiary research and training hospital between March 2016 and July 2016. The local ethics committee approved the study and all participants signed an informed consent form.

The participants were stratified into three groups; mild PE ($n = 27$) and severe PE ($n = 82$) as study groups, and healthy-

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normotensive pregnant women (n = 110) as a control group, who were randomly selected from among patients hospitalized for labour during the latent phase in the same hospital in the same period. They had no evidence of preeclampsia and its clinical or laboratory findings.

PE was diagnosed based on the recently revised criteria of the American College of Obstetrics and Gynaecology in 2013 [12]: (i) Blood pressure ≥ 140 mmHg systolic or 90 mmHg diastolic on two occasions at least 4 h apart after 20 weeks of gestation with a previously normal blood pressure or blood pressure ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic and (ii) proteinuria (Protein/creatinine ratio ≥ 0.3 or dipstick reading of 1+) or (iii) in the absence of proteinuria, new-onset hypertension with the new onset of any of the following: Thrombocytopenia (Platelet count $\leq 100,000$ /microliter), renal insufficiency (Serum creatinine concentrations ≥ 1.1 mg/dl, elevated blood concentrations of liver transaminases to twice normal concentration, pulmonary oedema, cerebral or visual symptoms.

Severity of the disease was assigned according to the same reference [12]. The diagnosis was severe PE when a patient had one or more of the following criteria; blood pressure or blood pressure ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic, thrombocytopenia, renal insufficiency, elevated liver transaminases, pulmonary edema, cerebral and visual symptoms.

Exclusion criteria used were as follows; chronic systemic disease during pregnancy such as diabetes mellitus, nephropathy, renal or hepatic dysfunction, active local or systemic infection, chorioamnionitis, or any medication such as corticosteroids prior to admission that related to inflammatory condition of patient.

Serum samples for complete blood count with differentials including neutrophil leukocyte, platelets, RDW, MPV, PCT, and urine samples were obtained at the admission of the patients to the emergency department, before the initiation of any medical treatment such as magnesium sulphate or antenatal corticosteroids. Venous blood samples were drawn into EDTA samples tubes (5 mL). All samples were processed within 2 h after venipuncture, using an automatic blood cell counter.

Data analysis was performed by using SPSS for Mac OS version 21 (SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to analyze the distribution of the data. Variables are given as mean \pm standard deviation or median (minimum-maximum). Non-parametric tests were performed to compare data within between two groups (Mann-Whitney Test) and within three groups (Kruskal-Wallis Test). In PE group, receiver operating characteristic (ROC) curves were performed and the area under curve (AUC) was calculated for each marker. The sensitivity, specificity and odds ratio were calculated according to the cut-off point determined by ROC curves.

3. Results

The comparisons of demographic characteristics between the groups were shown in Table 1. There were no statistically significant differences between the three groups in terms of median age, gravida, and parity. As expected, group with severe PE had higher diastolic and systolic blood pressure levels compared to groups with mild PE ($p < 0.001$) or healthy controls ($p < 0.001$).

There was no a statistically significant difference in NLR between the groups ($p = 0.901$). Both PLR and PCT were lower in the patients with severe PE than in the control group, and these differences showed a statistical significance ($p = 0.007$ and $p < 0.001$). On the other hand, both RDW and MPV were statistically higher in the patients with severe PE compared to the control group ($p = 0.011$ and $p < 0.001$) (Table 2).

The performances of all parameters to identify severe preeclamptic women within women with PE were measured in ROC curve: the values of AUC for NLR, PLR and RDW were not statistically significant ($p = 0.636$, 0.104 and 0.36 , respectively). For MPV and PCT, AUC values were 0.641 and 0.712 , and the p values for these parameters were also statistically significant ($p = 0.028$ and $p = 0.001$). The best cut-off value for MPV was 8.04 with a sensitivity of 74.39% , a specificity of 33.33% , a PPV of 77.22% , a NPV of 30% , and an accuracy of 86.11% . The best cut-off value for PCT was 0.25 with a sensitivity of 80.49% , a specificity of 22.22% , a PPV of 75.86% , a NPV of 27.27% , and an accuracy of 79.82% (Table 3).

4. Discussion

PE is a hypertensive, multisystem disorder which has unclear aetiology, as yet. Earlier studies have suggested several factors including activation of inflammatory cells and immunologic responses in which neutrophils, lymphocytes, and thrombocytes participate by releasing inflammatory cytokines and auto-antibodies [2,13]. Recent studies showed that SIR markers, obtained from complete blood count in peripheral blood, such as NLR, PLR, RDW, MPV and PCT have prognostic and predictive values in various benign and malignant diseases including coronary artery disease, inflammatory diseases, PE and gynaecologic or gastrointestinal malignancies [14–17].

There is one study regarding the incidence of preeclampsia in Turkey. Kumtepe et al. diagnosed 242 preeclamptic women within 196,273 births during five year-period (0.12%) [18]. The relatively high incidence of the preeclampsia ($109/3812$, 2.86%) in the present study could be due to the following characteristics of our hospital: It is the biggest tertiary hospital in the region with around twenty-two thousand deliveries each year. In addition, patients with preeclampsia who needs intensive care, are referred to our hospital from all around Istanbul, being the biggest city of Turkey with nearly 15 million residents.

Maternal circulating leukocytes are activated in pregnancy and further activated in PE [19]. Otherwise these activated leukocytes could be responsible for the vascular dysfunction associated with PE [20]. NLR and PLR were thought to be markers for predicting the presence and severity of PE, however, conflicting results have been reported to date: Yavuzcan et al. found that NLR were higher in preeclamptic women compared to controls. Nonetheless, there was no statistically significant difference [5]. These results were consistent with the results of our study. Several authors demonstrated that NLR in preeclamptic women were significantly higher than those in the controls: Serin et al. found that NLR could predict the severity of the disease [21], Kirbas et al. found NLR useful for predicting PE and its severity in the first trimester [9]. The results of Akil et al.'s study suggested that the increase in NLR with increasing severity of PE may represent an independent predictor for the severity of disease [22]. PLR were studied in two studies: Kirbas et al. found lower PLR in mild PE group compared to controls, but the difference was not statistically significant [9]. Surprisingly, PLR were higher in severe PE group compared to mild PE group and healthy pregnant controls. This study was performed in the first trimester; so, we thought that, early evaluation could cause this discrepancy. According to Yavuzcan et al., PLR were lower in severe PE group compared to controls without being statistically significance [5]. In our study, PLR significantly decreased from control group to severe PE group.

The RDW is a readily available hematologic index, that shows a variation in erythrocyte volume called as anisocytosis. Although, the exact mechanism behind this is not known, high-RDW levels are believed to reflect increased inflammation [23]. The relationship between RDW and PE was studied in several studies: Abdul-

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