Preeclampsia (PE) is characterized by new-onset hypertension after 20 weeks of gestation with proteinuria and/or end-organ dysfunction. The clinical manifestations differ depending on a wide range of microangiopathies in target organs, including the brain, liver, kidney, and placenta. PE appears in nearly 4-6% of all pregnancies and is usually 1.5 to 2-times higher in first pregnancies. The placenta plays a crucial role in the pathogenesis. In this pathogenesis, a number of etiologies have been defined, including genetic, immunologic, and environmental. An excessive reaction to encounters with paternal and/or fetal antigens forms the basis for those immunologic factors that cause abnormal placentation. Nulliparous women who change partners between pregnancies, who have long gestational intervals, who use barrier contraception, and who are pregnant through intracytoplasmic sperm injection, are less exposed to paternal antigens and have a higher risk of developing PE. The presence of these risk factors inspired this study.

Eosinophils, neutrophils, and basophils are white blood cells (WBC) of granulocytic lineage. The physiologic function of eosinophil and basophils remain a mystery although they are most likely involved in the immune response to infection, tumor surveillance, remodeling of tissue, and interactions of other immune cells. Eosinophils and basophils are mostly elevated in parasitic, helminth, allergic diseases, drug reactions, solid tumors, adrenal insufficiency, and vari-
ous autoimmune diseases. In the literature, eosinophil-basophil ratio (EBR), eosinophil-lymphocyte ratio (ELR), and basophil-lymphocyte ratio (BLR) have been studied, mostly in allergic diseases. Some studies found that ELR was significantly lower in patients with nasal polyposis. Some studies in the literature found significantly higher EBRs in patients with chronic rhinosinusitis, nasal polyps, and asthma. Although ELR, BLR, and EBR have not been examined in studies on patients with PE, variables such as eosinophils, basophils, and lymphocytes have been examined. Conflicting results have been found in the literature, and the number of eosinophils has been shown to decrease in patients with hypertension, and further decrease as disease severity increases. In these diseases, glucocorticoid release or use has been claimed to cause eosinophil apoptosis. In this study, we aimed to investigate these markers in PE.

**MATERIAL AND METHODS**

This is a retrospective, case-control study conducted at the department of obstetrics and gynecology in a university hospital. The local ethics committee approved the study (2018/201, 30/05/2018, Selcuk University Local Ethics Committee). The study was performed in accordance with the principles of the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

The case and control group patients were selected among the patients admitted to the hospital between January 1st, 2016, and January 1st, 2018. A total of 162 patients were included in the study; 81 patients who experienced PE formed the study group, and 81 age-matched patients without PE constituted the control group. In the PE group, 40 patients had mild PE and 41 patients had severe PE. The control group was randomly selected from patients without PE and systemic disease, who were in their third trimester, and being followed up and treated in our hospital.

Inclusion criteria: Being aged 18-45 years, not having a known systemic disease, not having a known allergic disease, and singleton pregnancy. The diagnosis and severity criteria for PE were based on the criteria cited by the American College of Obstetrics and Gynecology in 2019. The exclusion criteria were having systemic diseases (e.g. diabetes, chronic hypertension), known active infection, and current medication use. Serum samples for complete blood count tests were collected on the early admission of patients to the hospital before the initiation of any medical treatment.

**STATISTICAL ANALYSIS**

The SPSS version 22 (SPSS Inc., Chicago, IL) software package was used for data analysis. The Kolmogorov-Smirnov test, histogram, and Q-Q plots were used to analyze the distribution of the data. Variables are given as mean (±standard deviation) or median (minimum-maximum). Non-parametric tests (Mann-Whitney U test, Kruskal-Wallis test) and parametric tests [independent sample t-test, one-way analysis of variance (ANOVA)] were performed to compare data. The Mann-Whitney U and Tukey post hoc tests were used for multiple comparisons. Receiver operating characteristic (ROC) curve analysis was conducted to identify the optimal cut-off values of BLR and EBR. p<0.05 was considered statistically significant.

The required sample size was calculated using the G*Power software version 3.1.9.2 (*Heinrich Heine Universität; Düsseldorf; Germany) for the independent sample t-test, the α-error probability at 0.05, power (1-β error probability) at 0.80%, and effect size (d) at 0.45. The total number of 158 participants (79 in each group) were needed to achieve a statistically acceptable figure. To allow for dropouts, the sample size was increased to 162 patients.

**RESULTS**

Comparisons of demographic variables and laboratory data between the control and PE groups are shown in Table 1. No statistical differences were found between the two groups in terms of age, gravidity, parity, lymphocytes, eosinophils, and ELR (p=0.201, 0.735, 0.214, 0.841, 0.410, and 0.302, respectively). EBR was lower in the PE group than in the control group (p=0.033). Basophil (p=0.049) and BLR (p=0.029) values were higher in the PE group than in the control group.
Comparisons of laboratory data among the three groups are shown in Table 2. There were significant differences between the three groups in terms of median age (p=0.021). There were no differences between the groups in terms of age, gravidity, parity, lymphocytes, eosinophils, basophils, and BLR (p=0.239, 0.445, 0.373, 0.869, 0.128, 0.070, and 0.052, respectively). EBR (p=0.010) and ELR (p=0.039) were significantly different among the groups. As PE severity increased, EBR decreased, and ELR increased gradually.

The ROC curve analysis was used to examine the performance of the EBR and ELR values in predicting PE. The ROC analysis results of EBR and BLR are shown in Table 3 and Figure 1. The ROC analysis results of EBR was found as sensitivity 51.90% and specificity 69.1% [area under the curve (AUC): 0.597, 95% confidence interval (CI): 0.51-0.68], and BLR was found as sensitivity 62.85% and specificity 59.78% (AUC: 0.600, 95% CI: 0.51-0.69).

### DISCUSSION

PE is a multi-systemic progressive disease caused by placental and maternal vascular dysfunction, and always resolves after delivery of the placenta. Even though most affected pregnancies deliver nearly at full term with no adverse maternal and fetal outcomes, these pregnancies are at increased risk for maternal or fetal mortality and morbidity. In addition,
women with PE are at increased risk for future cardiovascular disease.

As epidemiological data and pathophysiologic mechanisms show that the main pathology is in the placenta in PE. The defect that may occur during the 2-stage formation of the placenta causes PE. The fact that PE occurs in pregnancies after oocyte donation and happens after a sperm exposure for a short time suggest that excessive response to foreign antigens may also be a key or side pathway in the etiology of PE. When looking at the pathogenesis of allergic diseases, an inflammatory cascade is formed in allergic substance-susceptible people after allergen exposure, secreted by mast cells, immunoglobulin (Ig)-E, histamine, basophils, lymphocytes, various prostaglandins, and leukotrienes. Allergens adhere to IgE and then attach to receptors in mast cells and basophil cells, which is the mechanism that initiates pathogenesis. After allergic reactions begin, mast cells amplify such reactions by releasing vasoactive agents, cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin (IL)-1 to IL-6, and IL-13. Tissue eosinophilia is characteristic of allergic diseases. Eosinophils secrete a plethora of cytokines including IL-3, IL-4, IL-5, IL-10, and GM-CSF. Eosinophils release oxygen radicals and proteins such as eosinophil cationic protein, and eosinophil peroxidases. These have been shown to be associated with epithelial injury and desquamation, subepithelial fibrosis, and hyper-responsiveness. Basophils contribute to the allergic reaction by secreting histamine, like mast cells. Allergy and PE can use common cytokines and prostaglandins in the inflammation stage. We aimed to investigate whether there was a relationship between PE and allergy. We also investigated whether there was a relationship between allergy markers and PE severity. We were only able to use basophil and eosinophil values in our study because used complete blood count results.

Basophils that represent about 0.5% to 1% of leukocytes have a crucial role in the immune system. Basophils can release IL-4, whether or not in a IgE-dependent manner, in response to a variety of stimuli. IL-4 promotes the differentiation of CD4+ T cells into Th2 cells. In addition, IL-4 increases the level of eosinophils by increasing the release of CCL11 (known as eosinophil chemotactic protein). Basophils and eosinophils play important roles in various host defense mechanisms, but they also act as harmful effectors in allergic disorders. Basophils and eosinophils have also been investigated in other diseases. Studies on patients with PE with basophil and eosinophil counts are also available. Basophil and eosinophil counts are increased in allergic diseases. There are different results in studies that investigated the patients with PE. In some studies, the eosinophil counts were found to be low in patients with PE. In another study, both eosinophils and basophils were found to be high in the PE group. In our study, the eosinophil counts were similar in both groups, whereas basophil counts in patients with PE were significantly higher.

Eosinophils and basophils were found to vary in patients with PE, whereas lymphocyte counts were not variable. Evaluation of these markers may not be appropriate due to hemodilution in normal pregnancy and hemoconcentration in PE. The ratio of these markers to each other is used to diagnose diseases. ELR, BLR, and EBR have mostly been investigated in allergy and other diseases. In studies by Kara et al., and Yenigun et al., ELR and BLR were found to be higher in allergic disease groups. In the literature, there are no studies of ELR, BLR, and EBR in PE groups. In our study, EBR was significantly lower and BLR was significantly higher in the PE group. When comparing the control group with the mild-severe PE group, EBR and ELR were found to be significantly different between the groups. As
PE severity increased, EBR decreased, and ELR increased gradually. When the data were analyzed, it was observed that basophil counts were higher than eosinophil. The mean lymphocyte counts appeared to be similar in both groups. We can say that the increase between the groups in EBR and ELR was due to the increase in basophilia in patients with PE compared with eosinophils. There are conflicting results related to eosinophil and basophil changes in patients with PE. It was claimed that the decrease in the number of eosinophils was associated with apoptosis caused by cortisol released into the circulation. However, there are insufficient data to explain the basophil change.

The limitations of this study are its retrospective design, the collection of data from a single center and the relatively small population, lack of allergy markers such as mast cells, IgE levels, and clear allergy history of the patients with PE. The strength of the study is that this subject has never been investigated before and PE severity subgroups were also examined.

**CONCLUSION**

As shown in our study, allergy-related mechanisms may also play a role in the pathogenesis of PE. If this relationship is shown more clearly, the treatment strategies used in allergic diseases may be considered in the prevention and treatment of PE in the future.

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**Conflict of Interest**

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

**Authorship Contributions**

**Idea/Concept:** Ersin Çintesun, Feyza Nur İncuesu Çintesun, Huriye Ezveci; **Design:** Ersin Çintesun, Feyza Nur İncuesu Çintesun; **Control/Supervision:** Fikret Akyürek, Çetin Çelik; **Data Collection and/or Processing:** Huriye Ezveci, Denizhan Bayramoğlu, Çetin Çelik; **Analysis and/or Interpretation:** Ersin Çintesun, Feyza Nur İncuesu Çintesun, Huriye Ezveci, Denizhan Bayramoğlu, Fikret Akyürek, Çetin Çelik; **Literature Review:** Ersin Çintesun, Huriye Ezveci, Fikret Akyürek, Denizhan Bayramoğlu, Çetin Çelik; **Writing the Article:** Ersin Çintesun; **Critical Review:** Ersin Çintesun, Denizhan Bayramoğlu, Çetin Çelik; **References and Fundings:** Feyza Nur İncuesu Çintesun, Huriye Ezveci; **Materials:** Ersin Çintesun, Çetin Çelik.

**REFERENCES**

1. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA. 2002;286(24):3183-6. [Crossref] [PubMed]
11. Ackerman SJ, Bochner BS. Mechanisms of eosinophilia in the pathogenesis of hypereosinophilic disorders. Immunol Allergy Clin North Am. 2007;27(3):357-75. [Crossref] [PubMed] [PMC]
12. Kara A, Guven M, Yilmaz MS, Demir D, Elden H. Are neutrophil, platelet and eosinophil-to-lymphocyte ratio and red blood cell distribution width can be used for nasal polyposis? Eur Arch Otorhinolaryngol. 2018;275(2):409-13. [Crossref] [PubMed]


