Original Article / Özgün Araştırma

Erythrocyte Indices in Patients with Preeclampsia

Preeklamptik Hastalarda Eritrosit İndeksleri

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Abstract

Objective: The purpose of study was to investigate erythrocyte indices in patients with preeclampsia.

Materials and Methods: The study population consisted of 102 patients with preeclampsia (49 mild, 53 severe preeclampsia) and 98 control pregnant patients. For the entire study population, red blood cell indices, including baseline mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and red blood cell (RBC) were measured by using an automatic blood counter.

Results: In the preeclampsia group, the median RDW was 15% (13.8-16.57), whereas in the control group it was 13.9% (13-15.6) ($p<0.01$). On the other hand, the mean MCV value was 80.42±7.86 (fL) in preeclampsia group and 83.88±2.31 (fL) in control group ($p=0.003$). Besides, the mean MCHC value was 33.66±1.71 (g/dL) in preeclampsia group and 33.09±1.48 (g/dL) in control group ($p=0.012$). However MCH and RBC values were not statistically different between the groups. ($p>0.05$) Moreover, subgroup analysis revealed that RDW levels were significantly increased in preeclampsia subjects than in mild preeclampsia patients (15.4% (13.9-17.45) vs 14.3% (13.7-15.7), $p=0.031$), MCV levels were decreased (78.81±7.91 (fL) vs 82.16± 7.43 (fL), $p=0.03$), RBC values were increased (4.16 (3.79-4.85)x(10^{12}/L) vs 3.82 (3.45-4.34)x(10^{12}/L), ($p=0.006$)) in patients with severe preeclampsia when compared to the patients with mild preeclampsia. In the receiver operator characteristic (ROC) analysis of subjects with and without preeclampsia, RDW and MCV showed high predictive values ($p<0.01$). Besides, in ROC analysis of preeclampsia patients with different severities, RDW and RBC showed the ideal predictive values ($p=0.006$, $p=0.031$, respectively).

Conclusion: Our study results revealed that among the red blood cell indices, only increased RDW values were associated with both the presence and the severity of preeclampsia.

Özet

Amaç: Bu çalışmanın amacı preeklampsi tanısı konmuş hastalarda eritrosit indekslerini araştırmaktır.

Gereç ve Yöntemler: Bu çalışmaya 102 preeklampsi (49 hafif ve 53 şiddetli preeklampsi olmak üzere) ve 98 kontrol hastası dahil edilmiştir. Tüm çalışma grubunda eritrosit indeksleri olan ortalama korpuskular hacim (MCV), ortalama korpuskular hemoglobin (MCH), ortalama korpuskular hemoglobin konsantrasyonu (MCHC), eritrosit sayımı ve eritrosit dağılım genişliği değerleri otomatik kan sayım cihazı ile ölçüldü.

Key words
Preeclampsia, red blood cell indices, RDW

Anahtar kelimeler
Preeklampsi, eritrosit indeksleri, RDW

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Bulgular: Preeklampsi grubunda, medyan RDW %15 (13,8-16,57), ortalama MCV değeri 80,42±7,86 (fL), ortalama MCHC değeri 33,66±1,71 (g/dL) ve kontrol grubunda medyan RDW %13,9 (13-15,6), ortalama MCV değeri 83,88±2,31 (fL), ortalama MCHC değeri 33,09±1,48 (g/dL) idi (sırasıyla p<0,01, p=0,003, p=0,012). Fakat preeklampsi ve kontrol grubunda MCH and RBC değerleri arasında fark saptanmadı (p>0,05). Preeklampsi grubunda subgroup analizi yapıldığında, hafif preeklampsi grubuna göre, ciddi preeklampsi grubunda artmış RDW değerleri (% 15,4 (13,9-17,45) vs %14,3 (13,7-15,7), p=0,031), azalmış MCV değerleri (78,81±7,91 (fL) vs 82,16±7,43 (fL), p=0,03), artmış RBC değerleri (4,16 (3,79-4,85)x(10^{12}/L) vs 3,82 (3,45-4,34)x(10^{12}/L), (p=0,006) saptandı. Preeklampsi ve kontrol grubu hastalarının Receiver operatör karakteristik (ROK) analizi sonuçlarına göre eritrosit sayımı ve eritrosit dağılım genişliğinin hastalığı tespit etmede yüksek prediktif değerleri saptandı (p<0,01). Ayrıca ROK analiz sonuçlarına göre, hafif ve ciddi preeklampsili hastalarda RDW ve RBC değerleri hastalığın ciddiyetini belirlemede ideal prediktif değerlere sahip idi (p=0,006, p=0,031).
Sonuç: Eritrosit indeksleri arasında artmış RDW değerleri hem preeklampsi tanısı, hem de hastalığın ciddiyeti ile ilişkilidir.

Introduction

Hypertensive disorders complicating pregnancy are responsible for a high incidence of maternal deaths (1). Preeclampsia is a disorder of pregnancy characterized by hypertension with a blood pressure of ≥140/90 mmHg and proteinuria with ≥300 mg/24 h urine or ≥2+ dipstick after 20th week of gestation (2). It is seen in 3-7% of pregnancies. It is one of the major causes of mortality during pregnancy with hemorrhage and thromboembolism (3). It has been determined that 18% of maternal deaths occur due to preeclampsia (4). If the disease begins before 34 weeks of gestation, it is early and if it starts after 34 weeks, it is late preeclampsia (5).

In the literature, there have been many theories about preeclampsia. First, defective trophoblast invasion was claimed to cause preeclampsia (6). Another theory about preeclampsia was changes in immune system of pregnant women causing increased inflammatory response. According to the second theory, increased inflammatory response leads to wrong placentation, increased capillary permeability, microvascular thrombosis, and increased vascular tonus (6,7).

Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and red blood cell (RBC) are known as the red blood cell indices. MCV defines the size of the red blood cells. MCH determines the amount of hemoglobin per red blood cell. MCHC indicates the amount of hemoglobin per unit volume (8). RDW is an indicator of red cell size variation called anisocytosis. It reflects early changes in red blood cells. All these parameters are important for detecting and investigating anemia (9). They are usually evaluated in a fully automated hematology analyzer, as part of the complete blood count. In the literature, it has been shown that RDW was higher in prehypertension. Prehypertension was described as slightly elevated blood pressure which would likely turn into high blood pressure (hypertension) in non-pregnant people if lifestyle changes like eating healthier and starting to exercise were not done (10). Furthermore, the association between RDW values and non-cardiac and cardiac mortality in patients with cardiovascular and thrombotic disorders, diabetic ketoacidosis, acute and chronic heart failure, coronary artery disease, and stroke has been investigated (11,12). However in the literature, there have been limited data on the relationship between red blood cell indices, including RDW, and preeclampsia. In the present study, we aimed to investigate the association between preeclampsia and red blood cell indices.

Materials and Methods

The present study was approved by the local ethics committee of Adnan Menderes University Faculty of Medicine, where the study was conducted. The study population consisted of 102 patients with preeclampsia who were diagnosed between January 2013-2015 and 98 gestational age-matched control participants. The gestational stage of each subject was determined by ultrasonography using the fetal crown-rump length during the 10th to 12th week of gestation. Of the patients with preeclampsia, 49 had mild and 53 had severe preeclampsia. Preeclampsia was diagnosed based on the practice bulletin on the diagnosis and management of preeclampsia and eclampsia developed by the American College of Obstetricians and Gynecologists in 2002 (13); a systolic blood pressure (BP) ≥140 mmHg on more than two readings taken 6 hours apart, a diastolic BP ≥90 mmHg and detectable urinary protein (>1 + by

dipstick or 0.3 g/24 hour and more) after 20 weeks of gestation. Measured BP should be previously normal. Clinical definition of severe preeclampsia (if any) was as follows: a BP of ≥160 mmHg/110 mmHg, with either a urine dipstick showing 3+ or 4+ in a random urine analysis or a proteinuria greater than 5 g over 24 hours and manifestations of multiple organ damage or dysfunction like pulmonary edema, headache, oliguria or fetal growth restriction. Mild preeclampsia was defined as new onset of blood pressure ≥140/90 mmHg on more than two readings taken 6 hours apart, combined with proteinuria ≥0.3 g/24 hours after 20 weeks of gestation, but not meeting the standards for severe preeclampsia. Patients with chronic hypertension, infectious diseases diagnosed during pregnancy, polyhydramnios, active labor, premature rupture of membrane, anemia, inflammatory diseases, and kidney diseases were excluded from the study. Control group included all healthy women with a singleton gestation and a normal obstetric history. The control group had blood pressures less than 140/90 mmHg, or no proteinuria. They also had no sign of any gestational complication or fetal distress. Pregnant women in the control group all delivered congenitally healthy, full-term live births. Written informed consent was received from all participant and their families.

All participants underwent blood collection before birth via antecubital vein puncture. The red blood cell indices were measured as part of the automated complete blood count using a Mindray BC 6800 analyzer (M68 LH LYSE, Shenzhen, China).

The Kolmogorov-Smirnov test was used to assess the normality of numeric variables. For the numeric variables that were normally distributed, comparison between the two groups was made by independent sample t-test and descriptive statistics are presented as mean ± standard deviation. For the numeric variables that were not normally distributed, comparison between the two groups was made by the Mann-Whitney U test and descriptive statistics are presented as median (25-75 percentiles). To analyze the categorical data, a chi-square test was used and descriptive statistics are presented as frequency (%). Spearman's correlation coefficient was used for qualitative data and Pearson's correlation coefficient for quantitative data. Receiver operator characteristic (ROC) curve analysis and calculation of the area under the curve (AUC) were performed. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) statistical software for Windows (Version 18.0). A p value of less than 0.05 was regarded as statistically significant.

Results

A total of 200 patients (mean age: 29.77±5.62 ranged from 18 to 43) were included in the study. In the preeclampsia group, the median RDW was 15% (13.8-16.57), whereas in the control group it was 13.9% (13-15.6) ($p<0.01$). On the other hand, the mean MCV value was 80.42±7.86 (fL) in preeclampsia group and 83.88±2.31 (fL) in control group ($p=0.003$). Besides, the mean MCHC value was 33.66±1.71 (g/dL) in preeclampsia group and 33.09±1.48 (g/dL) in control group ($p=0.012$). However, MCH and RBC values were not statistically different between the groups ($p>0.05$). The baseline characteristics of the patients with preeclampsia and without preeclampsia are summarized in Table 1.

Of the women with preeclampsia, 53 patients (52%) had severe preeclampsia. In addition, subgroup analysis revealed that the RDW levels were higher in patients with severe preeclampsia ($p=0.031$) (Figure 1). On the other hand, the mean MCV value was 78.81±7.91 (fL) in severe preeclampsia group and 82.16±7.43 (fL) in mild preeclampsia group ($p=0.03$). In severe preeclampsia group, RBC was 4.16 (3.79-4.85)x(10^{12}/L) and it was 3.82 (3.45-4.34)x(10^{12}/L) in mild preeclampsia group ($p=0.006$). However, MCHC and MCH values were not statistically different between the groups ($p>0.05$) (Table 2).

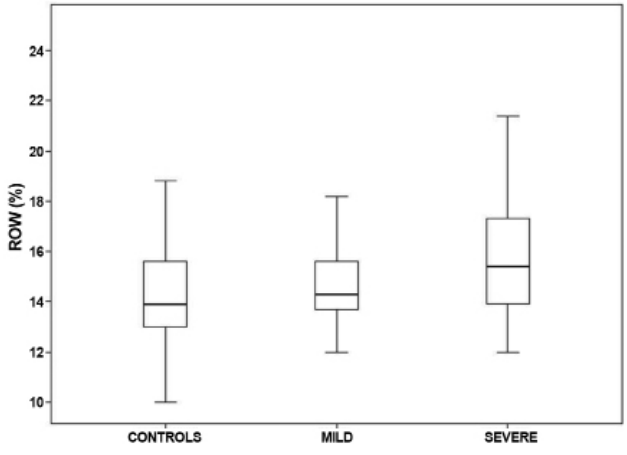

Figure 1. Comparison of red cell distribution width levels in the mild preeclampsia, severe preeclampsia and controls

Analysis of ROC curves for blood parameters and red blood cell indices for predicting the onset of preeclampsia and the severity of preeclampsia

The ROC analysis of AST, ALT, Crea, Alb, Hgb, Hct, WBC, PLT, MCV, MCHC, RBC, and RDW was performed in all subjects of all groups. Of these parameters; AST, Crea, Alb, also MCV, MCHC and RDW were considered to be possible predictors of preeclampsia ($p<0.01$, $p=0.032$, $p<0.01$, $p<0.01$, $p=0.005$ and $p<0.01$, respectively) (Table 3) (Figure 2).

The ROC analysis of AST, ALT, Crea, Alb, Hgb, Hct, WBC, PLT, MCV, MCHC, RBC, and RDW was performed in subjects in only preeclampsia group. Of these parameters; AST, Alb and also RBC and RDW were considered to be possible predictors of severity of preeclampsia ($p=0.004$, $p=0.001$, $p=0.006$ and $p=0.031$, respectively) (Table 4) (Figure 3).

Discussion

In present study, RDW was found to be higher in preeclampsia and severe preeclampsia group compared to controls. In addition, our study results revealed that among the red blood cell indices, only RDW levels were associated with both the presence

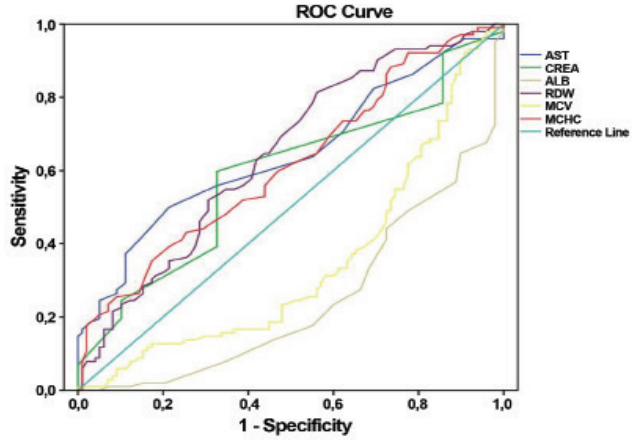

Figure 2. Receiver operator characteristic curves for aspartate aminotransferase, creatinin, albumin, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin concentration for predicting preeclampsia

Table 1. Baseline characteristics of pregnant women with preeclampsia and patients in control group

Variables	Controls (n=98) (Mean ± SD/Median)	Preeclampsia (n=102) (Mean ± SD/Median)	p
Age (years)	28.55±4.91	30.94±6.02	0.020
Gestational age (weeks)	37.04±1.42	37.03±0.94	>0.05
Nulliparity (%)	25 (25.5%)	41 (40.2%)	0.027
C-S1 (%)	53 (54.1%)	85 (83.3%)	<0.01
Birth weight (gr)	3191.58±522.05	2537.54±939.69	<0.01
AST[3]	17 (14-18)	18.5 (15-26.25)	<0.01
ALT[4]	13 (11-15)	13 (10-20)	>0.05
Crea[5]	0.6 (0.6-0.7)	0.63 (0.60-0.70)	0.028
Alb[6]	3.81±0.56	3.26±0.57	<0.01
Hgb[7] (g/dl)	11.15±1.29	10.95±1.91	>0.05
Hct[8] (%)	34 (31.27-36.2)	34.2 (31.07-37.85)	>0.05
PLT[9] ($\times10^9$/L)	217.97±73.61	223.77±85.80	>0.05
WBC[10] ($\times10^9$/L)	10500 (8945-12175)	10500 (9145-12725)	>0.05
RDW[11] (%)	13.9 (13-15.6)	15 (13.8-16.57)	<0.01
MCV[12] (fL)	83.88±2.31	80.42±7.86	0.003
MCHC[13] (g/dL)	33.09±1.48	33.66±1.71	0.012
MCH[14] (pg)	28.6 (24.9-30.4)	28.15 (25.5-30.82)	>0.05
RBC[15] (10^{12}/L)	3.94 (3.69-4.34)	3.94 (3.63-4.64)	>0.05

C-S[1]: Cesarean section, NVB[2]: Normal vaginal birth, AST[3]: Aspartate aminotransferase, ALT[4]: Alanin Aminotransferase, Crea[5]: Creatinin, Alb[6]: Albumin, Hgb[7]: Hemoglobin, Hct[8]: Hematocrit, Plt[9]: Platelet, WBC[10]: White blood cell, RDW[11]: Red cell distribution width , MCV[12]: Mean corpuscular volume, MCHC[13]: Mean corpuscular hemoglobin concentration, MCH[14]: Mean corpuscular hemoglobin, RBC[15]: Red blood cell

and the severity of preeclampsia. In the literature, there have been one study from Sudan (14) and one study from Turkey (15) that investigated the relationship of RDW width with preeclampsia. The study from Sudan including 65 patients in study and 65 in control groups found that RDW levels were not associated with the presence or severity of preeclampsia (14), but the study from Turkey determined higher levels of RDW in patients with preeclampsia (15).

RDW is routinely examined with the complete blood count test that showing the heterogeneity in erythrocyte size. Recent studies have reported the

Table 2. Baseline characteristics of pregnant women with mild and severe preeclampsia

Variables	Mild preeclampsia (n=49) (Mean ± SD/Median)	Severe preeclampsia (n=53) (Mean ± SD/Median)	p
Age (years)	31.81±5.56	30.13±6.36	>0.05
Gestational age (weeks)	37.04±2.38	33.32±4.37	<0.01
Nulliparity (%)	18 (36.7%)	23 (43.4%)	>0.05
C-S[1] (%)	35 (71.4%)	50 (94.3%)	0.002
Birth weight (gr)	3124.79±678.89	2034.90±846.34	<0.01
AST[3]	17 (14.5-20.5)	19 (16-36)	0.004
ALT[4]	13 (9-19)	13 (11-22)	>0.05
Crea[5]	0.62 (0.6-0.7)	0.65 (0.6-0.75)	>0.05
Alb[6]	3.45±0.55	3.08±0.53	0.001
Hgb[7] (g/dl)	11.20±1.89	10.71±1.91	>0.05
Hct[8] (%)	34 (30.4-37.1)	34.8 (31.4-38.5)	>0.05
PLT[9] ($\times 10^9$/L)	227.81±63.14	220.03±102.91	>0.05
WBC[10] ($\times 10^9$/L)	10500 (8645-12400)	10500 (9375-13905)	>0.05
RDW[11] (%)	14.3 (13.7-15.7)	15.4 (13.9-17.45)	0.031
MCV[12] (fL)	82.16±7.43	78.81±7.91	0.03
MCHC[13] (g/dL)	33.94±1.32	33.41±1.98	>0.05
MCH[14] (pg)	28.10 (25.7-31)	28.3 (24.75-30.6)	>0.05
RBC[15] (10^{12}/L)	3.82 (3.45-4.34)	4.16 (3.79-4.85)	0.006

C-S[1]: Cesarean section, NVB[2]: Normal vaginal birth, AST[3]: Aspartate aminotransferase, ALT[4]: Alanin aminotransferase, Crea[5]: Creatinin, Alb[6]: Albumin, Hgb[7]: Hemoglobin, Hct[8]: Hematocrit, Plt[9]: Platelet, WBC[10]: White blood cell, RDW[11]: Red cell distribution width, MCV[12]: Mean corpuscular volume, MCHC[13]: Mean corpuscular hemoglobin concentration, MCH[14]: Mean corpuscular hemoglobin, RBC[15]: Red blood cell

Table 3. Receiver operator characteristic analysis for aspartate aminotransferase, creatinin, albumin, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin concentration for predicting preeclampsia

	Area Under Curve						
Test result variable	Area	Cut off value	Sensitivity-specificity (%)	Standard error	p value	95% Cls	
						Lower bound	Upper bound
AST[1] (U/L)	0.643	>18	50-78.57%	0.039	<0.01	0.567	0.720
Crea[2] (mg/dl)	0.588	>0.6	59.80-67.35%	0.041	0.032	0.508	0.667
Alb[3] (g/dL)	0.753	≤0.36	72.55-66.33%	0.034	<0.01	0.687	0.819
MCV[4] (fL)	0.654	≤84.4	74.51-56.12%	0.039	<0.01	0.577	0.731
MCHC[5] (g/dL)	0.615	>34.3	35.29-82.65%	0.039	<0.01	0.537	0.692
RDW[6] (%)	0.645	>13.6	81.37-43.88%	0.039	<0.01	0.569	0.722

AST[1]: Aspartate aminotransferase, Crea[2]: Creatinin, Alb[3]: Albumin, MCV[4]: Mean corpuscular volume, MCHC[5]: Mean corpuscular hemoglobin concentration, RDW[6]: Red cell distribution width

association between high RDW levels and increased mortality (16) in patients with cardiovascular disease (17), brain vascular disease (18), septicemia (19), chronic obstructive pulmonary disease (20), and hepatitis B (21). Besides, the activity of inflammatory bowel disease (22) as well as pulmonary functions (23) has also been reported to be associated with RDW values (24). RDW has been recently determined to be associated with hypertension and it was an indicator of poor prognosis in heart failure and acute myocardial infarction (10,25,26). Although the mechanism of the relationship between hypertension and RDW was not clearly understood, increased inflammation was the most reasonable theory (27).

In the literature, there is only limited data on the influence of normal pregnancy on RDW. Between 16 and 34 weeks of gestation, it is stable (27), but between 34 weeks of gestation and the onset of labor, high RDW values have been reported (28).

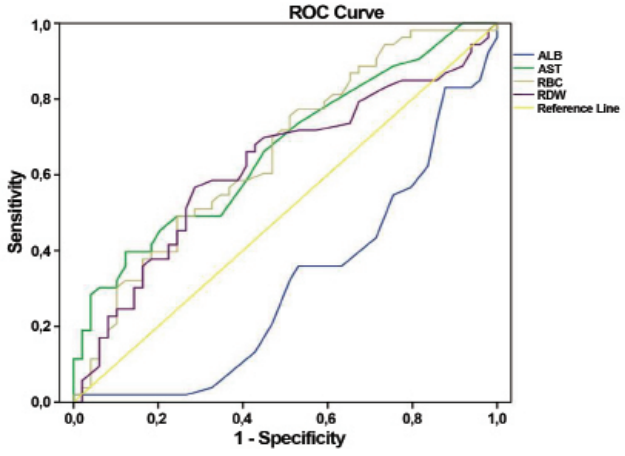

Figure 3. Receiver operator characteristic curves for aspartate aminotransferase, albumin, red blood cell, red cell distribution width for predicting severity of preeclampsia

Similar to the relationship of inflammation with increased RDW values in hypertensive non-pregnant women, inflammatory theory has been also blamed for increased RDW values preeclamptic women. In a study by Kurt et al. (15), a positive correlation between high-sensitivity C-reactive protein and increased RDW levels was determined in preeclamptic women.

In preeclamptic women, another issue supporting inflammatory theory was increased levels of lactoferrin due to neutrophil activation (29). Besides, in a study performed in rats, proteinuria and preeclampsia developed after giving endotoxin after 14th day of pregnancy (30). That condition has also shown that any inflammatory reaction during implantation and placentation might cause preeclampsia during pregnancy (5). Therefore, placental hypoxia due to inflammation leads to increased stimulation of erythropoiesis (31). Immature erythrocytes enter the circulation (32). As these erythrocytes have poor repair mechanisms, they may be destroyed by any minor event causing damage. In preeclampsia, increased inflammatory process also causes the destruction of red blood cells by reaction with oxygen radicals and proteolytic enzymes. After this destruction, the levels of some catabolic products, such as erythrocyte membrane band 3 protein, increase (33-35). Besides, tissue hypoxia-induced erythropoietin secretion stimulates bone marrow (36). In the literature, increased erythropoietin also was determined in patients with preeclampsia (37). Increased erythropoietin levels supported that inflammation induced hypoxia in in preeclampsia. So inflammatory theory, placental hypoxia, red blood cell destruction and defective erythropoisesis might help us explain the high RDW values indicating different size of erythrocytes in preeclampsia. Especially increased

Table 4. Receiver operator characteristic curves for aspartate aminotransferase, albumin, red blood cell, red cell distribution width for predicting severity of preeclampsia

Area Under Curve							
Test result variable	Area	Cut off value	Sensitivity-specificity (%)	Standard error	p value	95% CIs	
						Lower bound	Upper bound
AST[1] (U/L)	0.665	>25	39.62-87.76%	0.053	0.004	0.561	0.769
Alb[2] (g/dL)	0.689	≤3.6	86.79-42.86%	0.053	0.001	0.586	0.792
RBC[3] (1012/L)	0.659	>4.23	49.06-75.51%	0.054	0.006	0.553	0.765
RDW[4] (%)	0.624	>15.2	56.60-71.42%	0.056	0.031	0.514	0.734

AST[1]: Aspartate aminotransferase, Alb[2]: Albumin, RBC[3]: Red blood cell, RDW[4]: Red cell distribution width

RDW values have predictive value for diagnosing preeclampsia including severe and mild types.

Another red blood cell index is MCV. In pregnancy, MCV value has been found to increase about 3-5 (fL) (38). In the present study, MCV was determined to be lower in preeclampsia and severe preeclampsia groups in contrast to the literature (39). In another study, it was found that there was no difference in MCV values between preeclamptic women and controls (40). In the present study, in addition to decreased values of MCV, unchanged MCH and RBC values in patients with preeclampsia might be due to unsatisfactory iron replacement therapy. In addition, the study population was living in the western part of Turkey in which vegetable nutrition is common. As we know, nutritional status (e.g. iron, folate, and vitamin B12 deficiency) and eating habits (41,42) may affect red blood cell indices. Thus, one limitation of our study is not to investigate iron, folate and vitamin B12 levels in the participants due to financial constraints.

Consistent with the literature, no significant difference was found in Hgb, Hct, WBC, PLT, RBC, and MCH levels between patients with preeclampsia and controls (37,40). In contrast to the literature, we did not observe any increase in Hct and any decrease in PLT, especially in severe form of preeclampsia, despite we expected to see (14,43). Conflicting results may be mainly due to the small number of subjects in severe and mild preeclampsia groups. We have also determined that AST, ALT, and creatinin levels were higher and albumin levels were lower in patients with preeclampsia, and especially, AST levels were higher, albumin levels were lower in severe preeclampsia group. It may be explained by damage to the renal and hepatic systems confirmed by a significant increase in blood markers (40). In the present study, especially lower albumin levels had predictive values for preeclampsia and severe preeclampsia together with increased RDW levels.

In conclusion, complete blood count test, including especially RDW, is an easy, inexpensive, routinely reported investigation, which might allow the acquisition of significant diagnostic and prognostic information in patients with preeclampsia and to determine the severity of preeclampsia. However, results of our study should be confirmed by multicentre studies including larger number of cases in addition to controlling nutritional status of participants by measuring iron, folate and vitamin B12 levels.

Ethics Committee Approval: The study were approved by the Adnan Menderes University Local Ethics Committee. Informed Consent: Consent form was filled out by all participants. Concept: Selda Demircan Sezer, Sümeyra Nergiz Avcıoğlu, Design: Sümeyra Nergiz Avcıoğlu, Hasan Yüksel, Data Collection or Processing: Sümeyra Nergiz Avcıoğlu, Sündüz Özlem Altınkaya, Analysis or Interpretation: İmran Kurt Ömürlü, Hasan Yüksel, Mert Küçük, Literature Search: Sümeyra Nergiz Avcıoğlu, Selda Demircan Sezer, Writing: Sümeyra Nergiz Avcıoğlu, Peer-review: Internal peer-reviewed. Conflict of Interest: No conflict of interest was declared by the authors. Financial Disclosure: The authors declared that this study has received no financial support.

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