ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2024;8(2): 113-119
DOI: 10.29058/mjwbs.1485822

The Relationship Between Platelet Indices, Hormonal Status, and Insulin Resistance in Adolescents with Polycystic Ovary Syndrome: A Retrospective Case-Control Study

Polikistik Over Sendromlu Adölesanlarda Trombosit İndeksleri, Hormonal Durum ve İnsülin Direnci Arasındaki İlişki: Retrospektif Bir Vaka-Kontrol Çalışması

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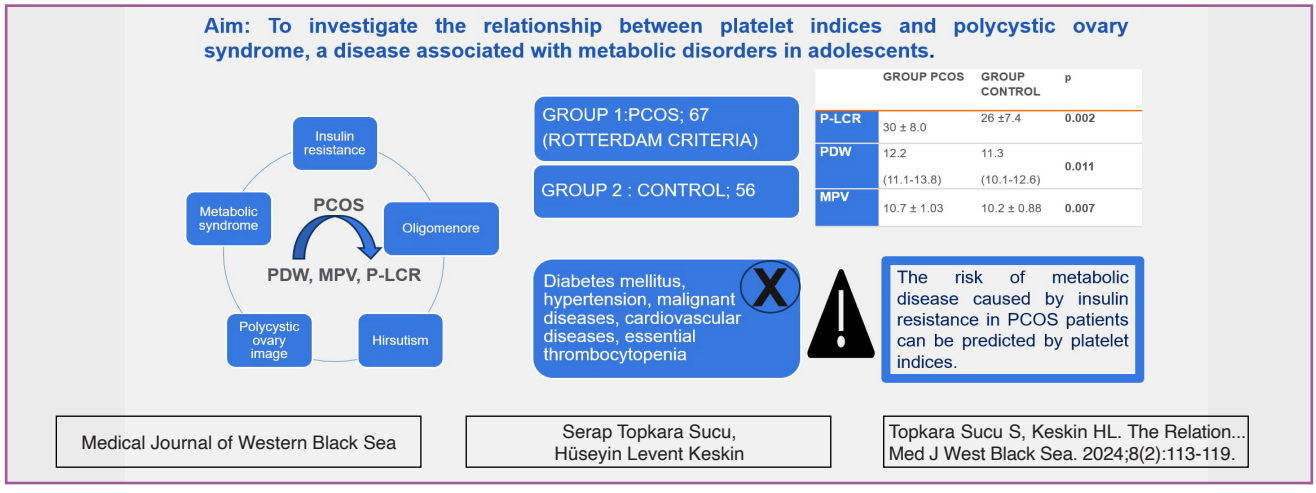
Cite this article as: *Topkara Sucu S and Keskin HL. The relationship between platelet indices, hormonal status, and insulin resistance in adolescents with polycystic ovary syndrome: a retrospective case-control study. Med J West Black Sea. 2024;8(2):113-119.*

GRAPHICAL ABSTRACT



ABSTRACT

Aim: The study investigated the relation between polycystic ovary syndrome, a disease caused by inflammation and insulin resistance associated with metabolic disorders, and platelet indices, which provide information about platelet activity.

Material and Methods: Patients with oligoovulation, hyperandrogenemia, or clinical signs of hyperandrogenism (hirsutism, acne, etc.) and polycystic appearance with ≥ 20 small follicles ≥ 2~ 9 mm in diameter in both ovaries on ultrasound according to the newly updated Rotterdam criteria formed PCOS group. As a control group, adolescents with similar age groups and body mass index (BMI) values were selected who presented to the clinic due to non-PCOS symptoms (vaginitis, dysmenorrhea, cystitis), whose complete blood count was checked in a hormone test and who did not meet the Rotterdam criteria.

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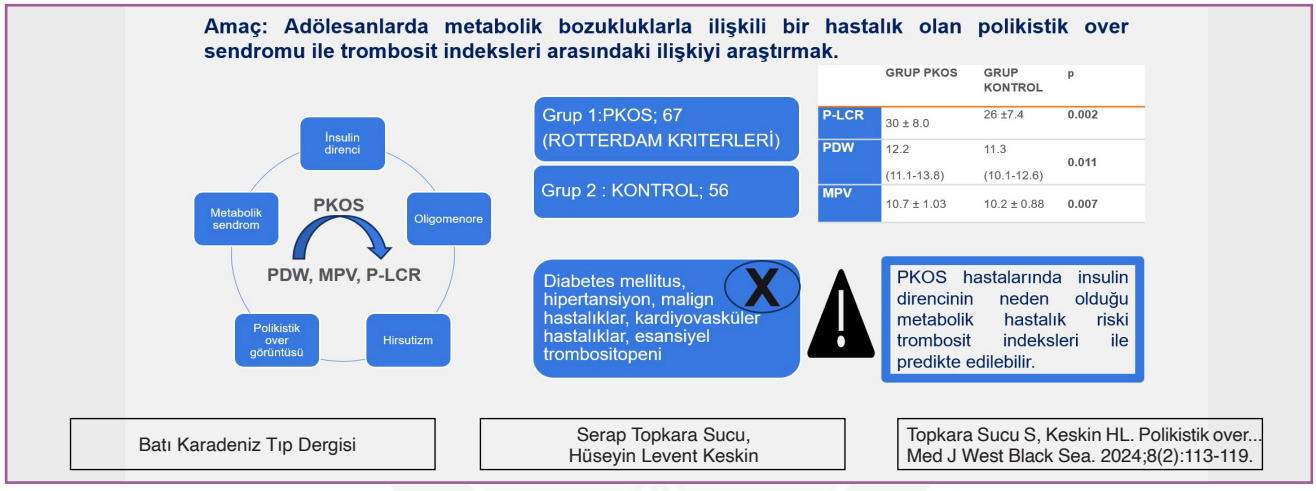
Platelet indices found in routine blood count parameters were analyzed between the two groups. In addition, the relation between these indices and hormone status and insulin resistance in PCOS patients was analyzed. Patients with diabetes mellitus, high blood pressure, malignant diseases, cardiovascular diseases, essential thrombocytopenia, or other blood diseases as well as patients taking medication are excluded.

Results: In the study of 123 patients, there was no statistical result between the groups about age and body mass index (p:>0.05). The hemogram parameters were compared between the groups. Hemogram parameters such as P-LCR (p: 0.002), PDW (p: 0.011), and MPV (p: 0.007), which indicate platelet activity, were statistically higher in the PCOS group. When analyzing the data of PCOS patients, it was found that platelet indices were higher in the group with high insulin resistance (p: <0.005). When analyzing the hormonal status, only the blood prolactin level correlated positively with the values of P-LCR (r: 0.223, p: 0.017), PDW (r: 0.214, p: 0.022), and MPV (r: 0.213, p: 0.023).

Conclusion: Analyzing platelet indices on routine blood counts in polycystic ovary syndrome, informing patients of their predisposition to metabolic diseases, and making the necessary referrals will contribute to the treatment and follow-up of polycystic ovary syndrome. These tests, which can be easily performed in any center, should be used in standard practice.

Keywords: Blood platelets, metabolic syndrome, polycystic ovary syndrome

GRAFİKSEL ÖZET



ÖZ

Amaç: Bu çalışmanın amacı, adölesanlarda metabolik bozukluklarla ilişkili, inflamasyon ve insülin direncinin neden olduğu bir hastalık olan polikistik over sendromu (PKOS) ile trombosit aktivitesi hakkında bilgi veren trombosit indeksleri arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Oligoovulasyon, hiperandrojenemi veya hiperandrojenizmin klinik bulguları (hirşutizm, akne vb.) ve yeni güncellenen Rotterdam kriterlerine göre ultrasonda her iki overde ≥ 20 küçük folikül ≥ 2~ 9 mm çapında polikistik görünümü olan hastalar polikistik over sendromu tanısı ile çalışmaya dahil edildi ve PKOS grubunu oluşturdu. Kliniğe PKOS dışı nedenlerle (vajinit, dismenore, sistit) başvuran, hormon testi sırasında tam kan sayımına bakılan ve Rotterdam kriterlerini karşılamayan benzer yaş grupları ve vücut kütle indeksi (VKİ) değerlerine sahip hastalar kontrol grubu olarak seçildi.

Rutin kan sayımı parametrelerinde bulunan trombosit indeksleri iki grup arasında analiz edilmiştir. Ayrıca, PKOS hastalarında bu indeksler ile hormonal durum ve insülin direnci arasındaki ilişki analiz edilmiştir. Diabetes mellitus, hipertansiyon, malign hastalıklar, kardiyovasküler hastalıklar, esansiyel trombositopeni veya diğer kan hastalıkları olan hastalar ve ilaç kullanan hastalar çalışma dışı bırakıldı.

Bulgular: Çalışmaya dahil edilmiş olan 123 hastadan 67 tanesi polikistik over sendromu tanısı alarak vaka grubunu, geri kalan 56 hasta kontrol grubunu oluşturmuştur. Gruplar arası yaş ve vücut kütle indeksi açısından istatistiksel fark bulunmamaktadır (p: >0,05). Gruplar arasında tam kan sayımı parametreleri karşılaştırıldığında, trombosit aktivitesini gösteren trombosit büyük hücre oranı (p: 0,002), trombosit dağılım genişliği (p: 0,011) ve ortalama trombosit hacmi (p: 0,007) polikistik over sendromu grubunda istatistiksel anlamlı olarak daha fazla bulunmuştur. Polikistik over sendromu hastalarının verileri incelendiğinde insulin direnci yüksek olan grupta trombosit indeksleri daha yüksek bulunmuştur (p: <0,005). Hormonal durumu analiz ettiğimizde, sadece kandaki prolaktin seviyesi P-LCR (r: 0,223, p: 0,017), PDW (r: 0,214, p: 0,022) ve MPV (r: 0,213, p: 0,023) değerleriyle pozitif korelasyon göstermektedir.

Sonuç: Polikistik over sendromu hastalarının rutin kan sayımlarında mevcut olan trombosit indekslerini inceleyip hastalara metabolik hastalıklara yatkınlık konusunda bilgi vermek ve gerekli yönlendirmeleri yapmak hastalığının tedavisi ve takibine katkı sağlayacaktır. Her merkezde bakılması kolay olan bu tetkikler güncel pratikte kullanım alanı almalıdır.

Anahtar Sözcükler: Metabolik sendrom, polikistik over sendromu, trombosit

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent hormonal disorder affecting around 6-10% of women during their reproductive years (1). According to the Rotterdam diagnostic criteria, the presence of polycystic ovaries detected by ultrasound, along with clinical and/or biochemical hyperandrogenism and oligo-ovulation, is required for diagnosis. PCOS is diagnosed when at least two of the three features are present. The cause of PCOS is not yet found and the disease is characterized by diverse and complicated clinical manifestations (2).

Current research suggests that the etiology of PCOS is multifactorial. Genetic predisposition, inflammatory reactions, low-grade chronic inflammation in the body, possibly reactive oxygen species (ROS), overexposure to embryonic androgens, an unhealthy lifestyle, and hormonal imbalances are involved in etiopathogenesis (3-7).

PCOS is associated with metabolic disorders caused by inflammation and insulin resistance. Inflammation and insulin resistance may cause vascular endothelial damage and dysfunction, followed by platelet activation. Studies have shown that this condition is critical to the pathophysiology of cardiovascular disease (CVD) and type 2 diabetes (8,9).

Platelet large cell ratio (P-LCR), platelet distribution width (PDW) and mean platelet volume (MPV) are inexpensive and easy-to-measure parameters obtained from whole blood cells in daily clinical practice. They serve as effective markers for platelet activity. Recent studies suggest that platelet indices are associated with vascular and cardiac disease in type 2 diabetes mellitus (10,11). In a study conducted in PCOS patients, MPV was found to be higher than in the control group and it was suggested that this was probably related to insulin (12). In the literature, platelet indices such as P-LCR and PDW have not been extensively studied in PCOS.

We analyzed the relation between platelet indices (P-LCR, PDW, and MPV) in routine blood parameters and PCOS.

MATERIAL and METHODS

This retrospective study was conducted between January 2023 and January 2024. Patients with oligo-ovulation, hyperandrogenemia or clinical signs of hyperandrogenism (hirsutism, acne, etc.) and polycystic appearance with ≥ 20 small follicles with a diameter of ≥ 2~ 9 mm on ultrasound in both ovaries according to the newly updated Rotterdam criteria formed the case group (13). Patients with similar age groups and body mass index (BMI) who presented to the clinic with problems other than PCOS (vaginitis, dysmenorrhea, cystitis) and underwent hormone testing and complete blood tests were selected as the control group. Patients with diabetes mellitus, hypertension, malignant diseases, cardiovascular diseases, essential thrombocytopenia, or other blood diseases as well as patients who were taking medication were excluded.

Blood samples for blood cell count (CBC) were taken during outpatient clinic visits in BD Vacutainer K2E tubes containing anticoagulants. The hormone profiles of the patients were analyzed in follicular phase (2-5 days) of the menstrual cycle. The levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, total testosterone, free testosterone, 17-OH progesterone, dehydroepiandrosterone sulfate (DHEAS), and thyroid-stimulating hormone (TSH) were analyzed, as well as hemoglobin, white blood cells, neutrophils, lymphocytes, monocytes, platelets, P-LCR, PDW, MPV and immature granulocytes (Ig). The platelet indices are included in the CBC parameters. Insulin resistance was determined using the formula Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) fasting insulin (mIU/L) x fasting glucose (mg/dL) /405 (14).

Statistical Analysis

RStudio was used for the statistical analysis. Normally distributed variables were calculated using Kolmogrov-Simirnov and Shapiro-Wilk tests and presented with the mean values and standard deviations of the variables. The t-test for independent samples was used to compare these parameters between groups. Descriptive methods were used in the study to examine non-normally distributed numerical data. Measures such as averages and quartiles (Q1-Q3) were used and Mann-Whitney U tests were performed. The Spearman test was used to calculate correlations and relationships between variables that are not regularly distributed. The Pearson test was used to assess the correlation between variables with a parametric distribution. A p-value below 0.05 was considered statistically significant.

RESULTS

The study included a total of 123 patients. Group I comprised 67 participants who had been diagnosed with PCOS, while Group II comprised 56 patients who served as a control group. No significant difference was found between the groups in terms of BMI and age. Both groups had an average age of 18 years and an average BMI within the normal range of 18.5-24.9 kg/m^2. Group I had statistically higher blood levels of estradiol, LH, total testosterone, free testosterone, and 17-hydroxyprogesterone compared to group II ($p<0.05$). There was no significant differences in the blood levels of FSH, DHEAS, TSH, and prolactin between the groups, as shown in Table 1.

The analysis of the blood count data showed that the PCOS group had statistically higher values for P-LCR, PDW, and MPV compared to the other groups. No differences were observed between the groups for the other blood count parameters (Table 2).

Table 1: Demographic characteristics and hormone levels of the patients included in the study.

Characteristics*	Group PCOS (n= 67)	Group Control (n=56)	*p***
Age (years)	18 (17-19)	18 (16-19)	0.470
BMI (kg/m^2)	22.6 (19.6-24.7)	20.6 (18.8-24.4)	0.123
Estradiol (pg/mL)	44 (35-65)	32 (21-49)	**<0.001**
FSH (mIU/ml)	5.47 (4.29-6.29)	5.74 (4.76-6.91)	0.234
LH (mIU/ml)	9.14 (6.85-14.18)	5.83 (4.04-7.10)	**<0.001**
Total testosterone (ng/dL)	34 (20-51)	22 (14-32)	**0.001**
Free testosterone (ng/dL)	2.37 (1.44-3.30)	1.50 (0.95-2.43)	**0.031**
DHEAS (μg/dL)	275 (163-355)	216 (155-332)	0.361
TSH (mIU/L)	2.11 (1.32-2.87)	1.90 (1.30-2.87)	0.714
Prolactin (ng/mL)	18.4 (12.5-24.1)	17.4 (13.6-25.4)	0.969
17-hydroxyprogesterone (ng/L)	0.41 (0.30-0.60)	0.27 (0.18-0.40)	**<0.001**

BMI: body mass index, **FSH:** follicle-stimulating hormone, **LH:** Luteinizing hormone, **DHEAS:** Dehydroepiandrosterone sulfate, **TSH:** thyroid stimulating hormone. A p-value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

*Data are expressed as median and quartiles (Q1-Q3) according to statistical analyses. **Mann Whitney U Test.

Table 2: Blood cell parameters of the patients included in the study.

Blood cell parameters*	Group PCOS (n=67)	Group Control (n=56)	*p*
Hb (g/dl)	13.5 (12.8-14.1)	13.4 (12.7-14.2)	0.646**
WBC (10^3/µL)	7.08 (5.80-9.00)	7.49 (6.23-8.53)	0.847**
Neutrophils (10^3/µL)	3.68 (3.00-5.13)	4.03 (3.30-5.04)	0.430**
Lymphocytes (10^3/µL)	2.38 (2.02-2.71)	2.40 (2.02-2.95)	0.699**
Monocytes (10^3/µL)	0.54 (0.42-0.71)	0.56 (0.44-0.65)	0.491**
Platelets (10^3/µL)	299 ± 67.5	320 ± 61.3	0.079***
P-LCR (%)	30 ± 8.0	26 ±7.4	**0.002*****
PDW (fL)	12.2 (11.1-13.8)	11.3 (10.1-12.6)	**0.011****
MPV (fL)	10.7 ± 1.03	10.2 ± 0.88	**0.007*****
Ig (%)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.239**

Hb: Hemoglobine, **WBC:** White blood cell, **P-LCR:** Platelet-large cell ratio, **PDW:** Platelet distribution width, **MPV:** Mean platelet volüme, **Ig:** Immature granulocytes. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

*Data are expressed as mean±SD or median and quartiles (Q1-Q3) where appropriate according to statistical analyses. **Mann Whitney U Tes. ***Student's t-test.

The patients diagnosed with PCOS were divided into two groups based on their insulin resistance. The group with higher HOMA-IR had elevated blood insulin levels and increased P-LCR, PDW, and MPV compared to those without insulin resistance. There was no statistically significant difference between these two groups in terms of BMI, fasting blood glucose (FBG), and age (Table 3).

When analyzing the correlation of platelet-derived hemogram parameters with BMI, FBG, blood insulin levels, and HOMA-IR values, neither BMI nor insulin has a statistically significant relationship with platelet-derived hemogram parameters. There is a positive correlation between FBG and platelet-derived hemogram parameters. (P-LCR, r:0.328, p:0.007; PDW, r:0.339, p:0.005; MPV, r:0.309, p:0.012) There is a positive correlation between HOMA-IR and both P-LCR and MPV (r:0.294, p:0.017 and r:0.286, p:0.020). Platelet-derived hemogram parameters increase with increasing FBG. P-LCR and MPV increase with an increase in HOMA-IR. In the correlation analysis of the platelet-derived hemogram parameters with the hormone levels of the participants in the groups, none of the hormone levels except prolactin was found a statistically significant relationship. The prolactin level in the blood correlates positively with the values of P-LCR (r: 0.223, p: 0.017), PDW (r: 0.214, p: 0.022), and MPV (r: 0.213, p: 0.023) (Table 4).

Table 3: Demographic characteristics, fasting blood glucose, insulin blood levels, and platelet-derived hemogram parameters of the PCOS group.

Parameters*	HOMA-IR>2.5 (n=26)	HOMA-IR≤2.5 (n=41)	*p*
Age (years)	18 (17-19)	18 (17-19)	0.455**
BMI (kg/m^2)	22.6 (19.6-26.6)	22.1 (19.6-24.7)	0.711**
FBG (mg/dL)	88±11.2	83±10.8	0.064***
Insulin (mIU/L)	14.4 (13.0-21.4)	10.6 (8.5-12.1)	**<0.001****
P-LCR (%)	34±7.4	28±7.3	**<0.001*****
PDW (fL)	13.1±1.99	11.9±1.94	**0.022*****
MPV (fL)	11.1±1.05	10.4±0.92	**0.004*****

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, **BMI:** Body-mass index, **FBG:** Fasting blood glucose, **P-LCR:** Platelet-large cell ratio, **PDW:** Platelet distribution width, **MPV:** Mean platelet volüme. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold. *Data are expressed as mean±SD or median and quartiles (Q1-Q3) according to statistical analyses. **Mann Whitney U Test. ***Student's t-test.

Table 4: Correlation analysis of diabetes-related parameters with platelet derived hemogram parameters in PCOS patients.

Diabetes-related parameters		P-LCR	PDW	MPV
BMI (kg/m^2)	r	0.119	0.144	0.106
	p	0.342*	0.246*	0.396*
FBG (mg/dL)	r	0.328	0.339	0.309
	p	**0.007****	**0.005****	**0.012****
Insulin (mIU/L)	r	0.117	0.020	0.137
	p	0.350*	0.874*	0.272*
HOMA-IR	r	0.294	0.207	0.286
	p	**0.017***	0.095*	**0.020***
Estradiol	r	0.157	0.081	0.116
	p	0.089*	0.378*	0.207*
FSH	r	0.114	0.167	0.099
	p	0.216*	0.069*	0.282*
LH	r	-0.031	0.005	-0.012
	p	0.740*	0.957*	0.894*
Total testosterone	r	0.102	0.127	0.069
	p	0.311*	0.205*	0.490*
Free testosterone	r	0.043	0.048	0.062
	p	0.673*	0.634*	0.538*
DHEAS	r	0.081	0.180	0.038
	p	0.422*	0.072*	0.706*
TSH	r	0.106	0.041	0.085
	p	0.252*	0.659*	0.357*
Prolactin	r	0.223	0.214	0.213
	p	**0.017***	**0.022***	**0.023***
17-hydroxyprogesterone	r	0.016	0.002	0.029
	p	0.873*	0.983*	0.777*

BMI: Body-mass index, **FBG:** Fasting blood glucose, **HOMA-IR:** Homeostatic Model Assessment for Insulin Resistance, **P-LCR:** Platelet-large cell ratio, **PDW:** Platelet distribution width, **MPV:** Mean platelet volüme, **FSH:** Follicle stimulating hormone, **LH:** Luteinizing hormone, **DHEAS:** Dehydroepiandrosterone sulfate, **TSH:** Thyroid stimulating hormone. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

* Spearman test; ** Pearson test.

DISCUSSION

Polycystic ovary syndrome is an endocrinopathy associated with reproductive abnormalities, marked insulin resistance, increased risk of type 2 diabetes, dyslipidemia, coronary heart disease, and cerebrovascular morbidity. Studies have reported that metabolic syndrome, obesity, insulin resistance, and hyperlipidemia are observed, is common in PCOS patients compared to controls (15,16).

Platelets are small, nucleated cells, and the number of them is measured by the platelet count (PLT) (17). MPV index is a helpful tool for figuring out the size of these platelets. Large platelets aggregate and react more than little platelets (18,19). MPV has an impact on mortality in vascular pathology, especially in patients with acute coronary syndrome (20, 21).

In our study, MPV, PDW, and P-LCR were found to be higher among the platelet indices in the PCOS group. In a systemic meta-analysis, Li et al. investigated the relationship between MPV levels and PCOS and found that patients with PCOS had significantly higher MPV levels than women without PCOS, which could be related to insulin resistance (12).

In contrast, Doğan et al. found that MPV levels of non-obese women with and without PCOS were similar and that insulin resistance had no effect on MPV values, and that PCOS patients with high androgen levels had low MPV values (22).

Yang et al. in China examined the platelet parameters of adults with metabolic syndrome and found no association between MPV and P-LCR, but PDW was found to be higher in individuals with metabolic syndrome (23).

We calculated insulin resistance using the HOMA-IR test and found that platelet indices increase in PCOS patients with high HOMA-IR. In an Indian study, platelet indices were used to assess cardiovascular risk in premenopau-

sal patients with metabolic syndrome. Platelet indices were significantly positively correlated with HbA1C, FBG, total cholesterol, and triglycerides and negatively correlated with high-density lipoprotein (24). Similarly, Buch et al. analyzed platelet volume indices to predict diabetes complications and found higher MPV and PDW values in diabetic patients with complications and showed that there was no association between P-LCR and diabetes complications (25). These studies and our results demonstrate the association between increased insulin resistance, platelet activity, and thrombogenic events.

When we compared platelet indices and hormone status in PCOS patients in our study, only a statistical correlation with prolactin was found among the indices. Yılmaz et al. studied the relationship between MPV and prolactin in PCOS patients and found that MPV levels increased with increasing prolactin levels, similar to our study. Thus, the study suggests that in women with PCOS, high PRL levels may increase the risk of atherothrombotic events through platelet activation. In our study, we found no correlation between other hormone levels and platelet indices. Ozay and Ozay. investigated inflammatory markers in PCOS patients and found no correlation between androstenedione, DHEAS, free testosterone PDW, and MPV (26,27).

Although studies show an increase in MPV in patients with PCOS, no study in the literature examines all platelet indices in PCOS. Our study adds to the literature as it is the first to investigate the relationship between all platelet indices and both insulin resistance and hormonal status, particularly in adolescent patients with PCOS. It should be noted that our study has some limitations. The limitations of the study include the fact that it was a retrospective study at a single center and that other metabolic syndrome criteria such as waist circumference or lipid profile were not recorded in the patient files.

In conclusion, there is an association between PCOS and cardiovascular disease, hypertension, diabetes mellitus, and atherosclerosis. Platelet indices are elevated in CVD, DM, and atherosclerosis. Screening platelet indices in routine blood tests of adolescents with PCOS, especially those with insulin resistance, educating patients about their predisposition to metabolic diseases, and referring them to the appropriate services will help in the management and follow-up of PCOS disorders. These tests, which can be easily performed in any center, should be used in common practice. However, further prospective studies are needed to confirm our findings.

Acknowledgment

None.

Author Contributions

Concept, Constructing hypothesis or idea of research and/or article: **Serap Topkara Sucu,** Design and planning methodology to reach the conclusions: **Serap Topkara Sucu,** Data Taking responsibility for patient/follow-up, collection of biological data materials, data management, and collection or reporting, execution of the processing experiments: **Serap Topkara Sucu,** Taking responsibility for logical analyses interpretation and conclusion of the results / Analysis or Interpretation: **Serap Topkara Sucu, Hüseyin Levent Keskin,** Literatüre review for the study: **Serap Topkara Sucu,** Writing: **Serap Topkara Sucu / Hüseyin Levent Keskin,** Approval: **Hüseyin Levent Keskin.**

Conflicts of Interest

The authors have no conflict of interest in this study.

Financial Support

There was no financial support in our study.

Ethical Approval

The study was conducted in accordance with the rules of the Declaration of Helsinki and approved by the Ethics Committee of Ankara Etlik City Hospital (Date: 24 April 2024-AESH-BADEK-2024-340).

Review Process

Extremely and externally peer-reviewed.

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