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# Effects of systemic isotretinoin treatment on hemogram, biochemical parameters, and inflammatory markers

## *Sistemik izotretinoin tedavisinin hemogram, biyokimyasal parametreler ve enflamatuvar belirteçler üzerine etkisi*

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### Abstract

**Background and Design:** Isotretinoin, a vitamin A derivative, is widely used to treat moderate and severe acne. Although the effect of systemic isotretinoin treatment on hemogram parameters has been demonstrated, the results are still controversial. In the present study, we investigated the effect of isotretinoin on biochemical parameters, hemogram, and inflammatory markers in the Black Sea Region.
**Materials and Methods:** Medical data of 300 patients with moderate and severe acne vulgaris who received systemic isotretinoin treatment for at least three months were analyzed retrospectively. Hemogram parameters, serum creatinine levels, liver transaminase levels, serum lipid levels, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and monocyte/high-density lipoprotein (HDL) ratios were evaluated before and three months after the treatment.
**Results:** A significant decrease was found in leukocyte count, red blood cell count, neutrophil count, monocyte count, HDL levels, and NLR after three months of treatment compared to the baseline. A significant increase was found in platelet count, plateletcrit (PCT), platelet distribution width (PDW), red cell distribution width, hematocrit, mean erythrocyte hemoglobin, total cholesterol, low-density lipoprotein, triglyceride, and aspartate aminotransferase levels.
**Conclusion:** According to our results, isotretinoin can affect several hemogram and biochemical parameters. In addition, this article is the only article demonstrating a decrease in monocyte count and an increase in PDW and PCT levels after the treatment of isotretinoin in the literature.
**Keywords:** Acne vulgaris, hemogram, inflammatory markers, isotretinoin

### Öz

**Amaç:** İzotretinoin, orta ve şiddetli akne tedavisinde kullanılan A vitamini türevi bir ilaçtır. Sistemik izotretinoin tedavisinin hemogram parametreleri üzerine etkisi gösterilmiş olmasına rağmen sonuçlar halen tartışmalıdır. Bu çalışmada Karadeniz Bölgesi'nde izotretinoin tedavisinin hemogram, biyokimyasal parametreler ve enflamatuvar belirteçler üzerine etkisini araştırdık.
**Gereç ve Yöntem:** Orta ve şiddetli akne vulgarisi olan ve en az üç ay süreyle sistemik izotretinoin tedavisi alan 300 hastanın dosyaları geriye dönük olarak incelendi. Tedavi öncesi ve tedaviden 3 ay sonraki hemogram parametreleri, serum kreatinin düzeyleri, karaciğer transaminaz düzeyleri, serum lipid düzeyleri, nötrofil/lenfosit oranı (NLO), monosit/yüksek yoğunluklu lipoprotein (HDL) oranları ve trombosit/lenfosit oranı değerlendirildi.
**Bulgular:** Üç aylık tedaviden sonra lökosit sayısı, kırmızı kan hücresi sayısı, nötrofil sayısı, monosit sayısı, HDL seviyeleri ve NLO'da başlangıca göre anlamlı bir azalma bulundu. Trombosit sayısı (PCT), trombosit dağılım genişliği (PDW), eritrosit dağılım genişliği, plateletkrit, hematokrit, ortalama eritrosit hemoglobini, total kolesterol, düşük yoğunluklu lipoprotein, trigliserit ve aspartat aminotransferaz düzeylerinde anlamlı artış bulundu.
**Sonuç:** Sonuçlarımıza göre izotretinoin birçok hemogram ve biyokimyasal parametreyi etkileyebilmektedir. Bu çalışma, literatürde izotretinoin tedavisi sonrası monosit sayısında azalma ve PDW ve PCT düzeylerinde artış gösterilen tek makaledir.
**Anahtar Kelimeler:** Akne vulgaris, hemogram, enflamatuvar belirteçler, isotretinoin

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## Introduction

Acne is a chronic inflammatory disease of the pilosebaceous unit, which is more common in adolescents. Acne commonly appears on the face, back, and trunk skin. Severe acne is an important entity because it often results in acne scars[1]. Isotretinoin (13-cis retinoic acid), a vitamin A derivative, is used for the treatment of moderate to severe acne. It exerts its effect by binding to intracellular retinoic acid receptors (RAR). Isotretinoin is the only drug that affects all stages of acne. It reduces sebum secretion and inhibits inflammation, keratinization, and bacterial growth by inhibiting androgens in sebaceous glands[2].

Dry mucous membranes, lips, and skin are the most common side effects of isotretinoin. Elevated total cholesterol, triglyceride, and liver enzyme levels are the most commonly reported laboratory findings following isotretinoin therapy[1].

The effect of systemic isotretinoin treatment on hemogram parameters has been reported[3-11]. However, the results are still controversial. Thus, we aimed to investigate the effects of isotretinoin treatment on hemogram, biochemical parameters, and inflammatory markers in the Black Sea Region.

## Materials and Methods

Medical records of patients evaluated for acne vulgaris at the Dermatology Outpatient Clinic of Giresun Training and Research Hospital affiliated with the Giresun University between September 6, 2021, and May 31, 2022, were retrospectively reviewed after obtaining approval from the Ethics Committee (permission was obtained from University of Health Sciences Türkiye, Kanuni Training and Research Hospital (approval number: 2022/51, date: 26.09.2022).

The medical records of 2,500 patients referred to the outpatient clinic diagnosed with acne and received systemic isotretinoin treatment for at least three months due to moderate and severe acne vulgaris were reviewed, of whom 537 patients were treated with systemic isotretinoin treatment. Patients with missing data, concomitant infectious and inflammatory diseases, liver disease, and chronic kidney disease, as well as those taking drugs affecting hemogram and biochemical parameters were excluded from the study. Finally, 300 patients who met the inclusion and exclusion criteria were included in the present study (Figure 1).

Hemogram parameters and serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and triglyceride levels, neutrophil-to-lymphocyte ratio (NLR), monocyte/high-density lipoprotein (MHR) ratio, and platelet-to-lymphocyte ratio (PLR) were recorded before and three months after the treatment.

### Statistical analysis

Data were analyzed using SPSS 25 software. The Kolmogorov-Smirnov test first checked the normal distribution of data, and in descriptive statistics, mean ± standard deviation (SD) and median (minimum-maximum) were used to express data with and without normal distribution, respectively. A paired sample t-test was used for normally distributed parameters, and Wilcoxon signed-rank test was used for non-normally distributed parameters to compare hematological and biochemical values at baseline and three months after the treatment. A p-value less than 0.05 was considered statistically significant.

## Results

The study population comprised 300 patients, including 79 males (26.3%) and 221 females (73.7%). The mean age of the patients was 21.9±4.55 years (range: 13-42 years).

A statistically significant decrease was found in the number of white blood cells (WBCs), red blood cells (RBCs), neutrophils, monocytes, NLR values, and HDL levels after three months of treatment compared to the baseline. In contrast, a significant increase was found in red cell distribution width-coefficient of variation (RDW-CW), red cell distribution width-standard deviation (RDW-SD), platelet count, platelet distribution width (PDW), plateletcrit (PCT), and total cholesterol, LDL, triglyceride, and AST, hematocrit (HCT), and mean erythrocyte hemoglobin (MCH) levels. There was no significant difference in MHR and PLR values as inflammatory markers after three months of treatment compared to the baseline (Table 1).

## Discussion

Various drugs may affect the complete blood count parameters. The effects of isotretinoin on hematological parameters has been reported in the literature; however, the results are inconsistent[3-11]. Thus, we evaluated the effect of isotretinoin on hematological parameters and detected some changes in our samples three months after initiating isotretinoin therapy.

Although mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) concentration values were comparable, we found a significant decrease in RBCs and an increase in HCT, MCH, and RDW values in the erythrocyte series.

RDW is an important parameter that shows the heterogeneity in the erythrocyte volume as the degree of anisocytosis. However, it

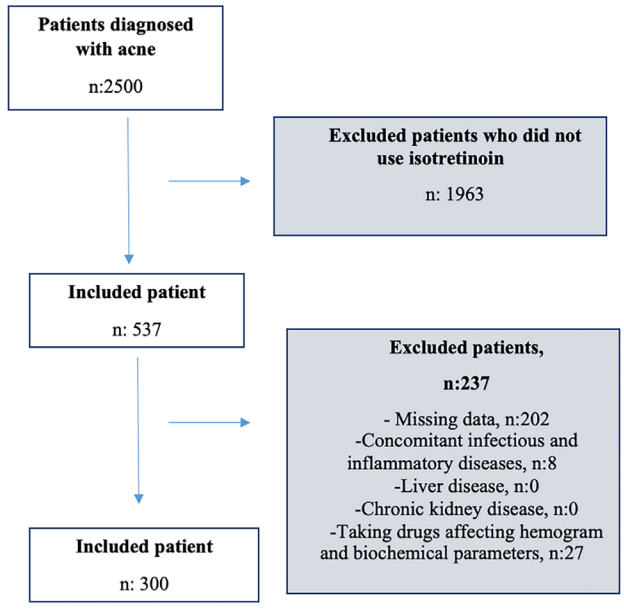


**Figure 1.** Study flow chart

has been shown that increased RDW values may be associated with cardiovascular diseases like acute myocardial infarction, symptomatic chronic heart failure, and ischemic stroke. It has also recently been used as an essential marker for the prognosis of these diseases[12]. In addition, RDW is associated with inflammatory diseases, such as Behçet's and Crohn's diseases[9,13]. Inflammatory diseases, such as inflammatory bowel disease and sacroiliitis, have been reported as adverse effects following isotretinoin treatment[14,15], suggesting that isotretinoin can increase inflammation by some mechanisms that are not known yet[7]. Thus, the observed increase in RDW values during isotretinoin treatment may be due to the inflammatory effect of isotretinoin. However, Seçkin et al.[9] found a significant decrease in RDW values three months after isotretinoin treatment compared to the baseline. Contrary to our interpretation, the authors commented that acne is an inflammatory disease and isotretinoin possibly caused a significant decrease in RDW values due to its anti-inflammatory effect.

In our study, we observed a significant increase in platelet count, PDW, and PCT values three months after isotretinoin therapy, but no change was observed in mean platelet volume and platelet larger cell ratio (P-LCR) values. PDW measures variability in platelet size and indicates platelet anisocytosis. PDW increases in conditions where platelet production increases. PCT is the ratio of total platelet volume to total blood volume. PCT increases when platelet count and/or platelet volume increases. P-LCR is an indicator of large circulating platelets (>12 fL)[16].

Both thrombocytopenia and thrombocytosis have been associated with isotretinoin[17,18]. We found three studies using a similar methodology, in which a significant increase was reported in platelet counts three

**Table 1. Serum parameters before and three months after isotretinoin treatment**

| Parameters | n | Before isotretinoin treatment* | 3rd month of isotretinoin treatment* | Normal ranges | p-value | Statistical method |
|---|---|---|---|---|---|---|
| Hemoglobin (g/dL) | 300 | 13.59±1.54 | 13.52±1.52 | 12-16 | 0.06 | Paired t-test |
| RBC ($10^{12}$/L) | 300 | 4.68 (3.79-5.92) | 4.65 (3.64-5.84) | 4-5.2 | **0.048** | Wilcoxon test |
| HCT (%) | 300 | 39.9 (28.2-52.5) | 40 (28.1-50.1) | 36-46 | **0.01** | Wilcoxon test |
| MCV (fL) | 300 | 86.45 (67.1-98.7) | 86.1 (64.8-97.4) | 80-96 | 0.333 | Wilcoxon test |
| MCH (pg) | 300 | 29.05 (20.5-34.3) | 29.1 (20-32.8) | 26-34 | **0.018** | Wilcoxon test |
| MCHC (g/dL) | 300 | 33.6 (29.9-35.8) | 33.6 (30.3-35.7) | 31-37 | 0.632 | Wilcoxon test |
| RDW-CW (%) | 300 | 13 (12-19.9) | 13.2 (11.9-20.3) | 11-16 | **<0.001** | Wilcoxon test |
| RDW-SD (fL) | 300 | 40.6 (35.8-54.3) | 41.05 (34.9-57.7) | 35-56 | **<0.001** | Wilcoxon test |
| WBC ($10^6$/L) | 300 | 7155 (3530-13010) | 7065 (3,880-12,590) | 4,000-11,000 | **0.001** | Wilcoxon test |
| Neutrophil count ($10^6$/L) | 300 | 4210 (1570-10400) | 4060 (1,730-8,800) | 2,000-7,000 | **<0.001** | Wilcoxon test |
| Lymphocyte count ($10^6$/L) | 300 | 2225 (930-4770) | 2235 (1,140-8,000) | 800-4,000 | 0.051 | Wilcoxon test |
| Monocyte count ($10^6$/L) | 300 | 435 (200-1090) | 420 (200-870) | 120-1,200 | **0.02** | Wilcoxon test |
| Eosinophil count ($10^6$/L) | 300 | 110 (0-2340) | 110 (10-4150) | 20-500 | 0.639 | Wilcoxon test |
| Bazophil count ($10^6$/L) | 300 | 30 (0-110) | 30 (10-120) | 0-100 | 0.388 | Wilcoxon test |
| Platelet count ($10^6$/L) | 300 | 271.000 (152.000-474.000) | 276.000 (152,000-447,000) | 150,000-400,000 | **0.002** | Wilcoxon test |
| MPV (fL) | 300 | 9.4 (7.6-12.6) | 9.4 (7.6-13.7) | 6.5-12 | 0.338 | Wilcoxon test |
| PCT [10 (GSD)] | 300 | 0.254 (0.152-0.436) | 0.262 (0.157-0.469) | 0.108-0.232 | **0.001** | Wilcoxon test |
| PDW [10 (GSD)] | 300 | 16 (15.2-17.3) | 16.1 (13.1-16.9) | 15-17 | **0.014** | Wilcoxon test |
| P-LCR (%) | 286 | 22.8 (30.7-43.6) | 23.1 (11.1-49.8) | 11-45 | 0.101 | Wilcoxon test |
| NLR | 300 | 1.90 (0.7-6.73) | 1.76 (0.27-5.54) | | **<0.001** | Wilcoxon test |
| PLR | 300 | 119.06 (49.84-303.94) | 122.01 (30.03-318.18) | | 0.639 | Wilcoxon test |
| MHR | 300 | 7.92 (1.6-35.16) | 7.96 (2.87-41.77) | | 0.251 | Wilcoxon test |
| Total cholesterol (mg/dL) | 300 | 155 (98-252) | 168.5 (105-267) | 0-200 | **<0.001** | Wilcoxon test |
| HDL (mg/dL) | 300 | 54.5 (27-125) | 51.5 (17-115) | 45-65 | **<0.001** | Wilcoxon test |
| LDL (mg/dL) | 296 | 84 (26-146) | 97 (43-184) | 0-130 | **<0.001** | Wilcoxon test |
| Triglyceride (mg/dL) | 300 | 72.5 (25-286) | 89 (23-734) | 0-200 | **<0.001** | Wilcoxon test |
| ALT (U/L) | 300 | 12 (5-56) | 13 (4-93) | 0-33 | 0.617 | Wilcoxon test |
| AST (U/L) | 300 | 17 (7-80) | 19 (10-75) | 0-32 | **<0.001** | Wilcoxon test |
| Serum creatinine (mg/dL) | 298 | 0.68 (0.37-1.51) | 0.68 (0.27-1.11) | 0.5-0.9 | 0.705 | Wilcoxon test |

*In descriptive statistics, mean ± standard deviation was used for normally distributed data, and median (minimum-maximum) was used for non-normally distributed data. RBC: Red blood cell, HCT: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW-CV: Red cell distribution width-coefficient of variation, RDW-SD: Red cell distribution width-standard deviation, WBC: White blood cell count, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet large cell ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MHR: Monocyte/HDL ratio, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

**Table 2. Comparative results of the literature**

| Laboratory parameters (units) | Our study 2022 | Karadag et al.[5] | Özuğuz et al.[8] | Ataseven and Ugur Bilgin[3] | Seçkin et al.[9] | Tamer et al.[10] | Önder and Ozturk[7] | Kutlu[11] | Metin and Turan[6] | Cosansu et al.[4] |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients | 300 | 70 | 67 | 110 | 112 | 70 | 116 | 89 | 244 | 156 |
| Hemoglobin (g/dL) | ↔ | ↔ | ↓ | ↔ | ↑ | ↔ | | ↔ | ↔ | |
| RBC ($10^{12}$/L) | ↓ | | ↓ | | | ↔ | | | | |
| HCT (%) | ↑ | ↔ | | ↔ | | ↔ | | | | |
| MCV (fL) | ↔ | | ↓ | | | ↔ | | | | |
| MCH (pg) | ↑ | | | | | ↑ | | | | |
| MCHC (g/dL) | ↔ | | | | | ↔ | | | | |
| RDW-CW (%) | ↑ | | | | ↓ | ↔ | | | | |
| RDW-SD (fL) | ↑ | | | | | | | | | |
| WBC ($10^6$/L) | ↓ | ↔ | | ↔ | ↔ | ↓ | ↔ | ↔ | ↔ | |
| Neutrophil count ($10^6$/L) | ↓ | | ↔ | | | ↔ | ↓ | ↔ | ↓ | ↓ |
| Lymphocyte count ($10^6$/L) | ↔ | | ↔ | | | ↓ | ↔ | ↑ | ↑ | ↔ |
| Monocyte count ($10^6$/L) | ↓ | | ↑ | | | ↔ | ↔ | ↔ | ↔ | ↔ |
| Eosinophil count ($10^6$/L) | ↔ | | ↔ | | | ↔ | | ↓ | | |
| Bazophil count ($10^6$/L) | ↔ | | ↔ | | | ↔ | | ↔ | | |
| Platelet count ($10^6$/L) | ↑ | ↑ | ↔ | ↓ | ↑ | ↔ | ↔ | ↔ | ↔ | ↑ |
| MPV (fL) | ↔ | ↔ | | ↓ | ↔ | ↓ | ↑ | ↓ | ↔ | |
| PCT [10 (GSD)] | ↑ | | ↓ | | | | ↔ | ↔ | ↔ | |
| PDW [10 (GSD)] | ↑ | | | | | | ↔ | | | |
| P-LCR (%) | ↔ | | | | | | | | | |
| NLR | ↓ | | ↔ | | ↔ | ↔ | ↔ | ↓ | ↓ | ↓ |
| PLR | ↔ | | | | ↔ | ↑ | ↔ | ↓ | ↔ | ↔ |
| MHR | ↔ | | | | | | ↑ | ↑ | ↑ | |
| Total cholesterol (mg/dL) | ↑ | | | | | ↑ | ↑ | ↑ | ↑ | ↑ |
| HDL (mg/dL) | ↓ | | | | | ↑ | ↓ | ↓ | ↓ | ↔ |
| LDL (mg/dL) | ↑ | | | | | ↑ | ↑ | ↑ | ↑ | ↑ |
| Triglyceride (mg/dL) | ↑ | | | | | ↑ | ↑ | ↑ | ↑ | ↑ |
| ALT (U/L) | ↔ | | | | | ↔ | | ↔ | ↔ | ↑ |
| AST (U/L) | ↑ | | | | | ↔ | | ↑ | ↔ | ↑ |
| Serum creatinine (mg/dL) | ↔ | | | | | ↔ | | ↔ | ↔ | ↔ |

↑: Significant increase, ↓: Significant decrease, ↔: No difference (between 0 and 3rd month of the treatment). RBC: Red blood cell, HCT: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW-CV: Red cell distribution width-coefficient of variation, RDW-SD: Red cell distribution width-standard deviation, WBC: White blood cell count, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet large cell ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MHR: Monocyte/HDL ratio, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

months after isotretinoin therapy[4,5,9]. Ataseven and Ugur Bilgin[3] observed a significant decrease in platelet count three months after isotretinoin therapy.

To our knowledge, the present study is the first to report a significant increase in PDW and PCT values. In contrast to our results, Özuğuz et al.[8] reported a decrease in PDW values three months after isotretinoin therapy compared to the baseline.

Platelets also play a role in inflammation. Platelet count, PCT, and PDW values have been reported as possible prognostic biomarkers in inflammatory bowel disease, thromboembolic events, cardiovascular diseases, and some cancers[16,19]. Tang et al.[19] demonstrated an increase in platelet count and PCT values in the active period of Crohn's disease. Retinoic acid receptor (RAR) alfa and RAR beta are found in the bone marrow. These receptors cause an increase in stem cells in the myeloid series in the bone marrow. Positive effects of isotretinoin on bone marrow stem cell proliferation, cell cycle progression, cellular differentiation, and cell survival have also been demonstrated. Thus, isotretinoin can also treat myelodysplastic syndrome[18,20]. Although there is no evidence to explain the mechanism of increased platelet count, PDW, and PCT values, we hypothesized that it could be associated with the two mechanisms mentioned above.

In the present study, we recorded a significant decrease in WBCs, neutrophils, and monocytes. Agranulocytosis related to isotretinoin has been reported in the literature[21]. However, the underlying mechanism has not been fully understood. Although we did not detect agranulocytosis in our study population, a significant decrease was found in the number of neutrophils compared to the baseline.

We did not notice a study reporting a decrease in monocytes. Peripheral blood monocytes express toll-like receptor 2 (TLR2). The expression of monocytic TLR2 is decreased in patients with acne receiving isotretinoin treatment, and the immunomodulatory effects of isotretinoin can be realized through monocytic TLR2[22]. The decrease in monocyte counts detected in our study can be explained by the mechanism mentioned above.

We detected a significant decrease in NLR values, one of the systemic inflammatory markers, but we did not detect any changes in MHR and PLR values. Similar to our results, some studies have found a decrease in NLR values[4,6,11]. These studies have reported NLR level as a possible inflammatory marker in patients using isotretinoin. Isotretinoin exerts its anti-inflammatory effect by inhibiting neutrophil and monocyte chemotaxis by decreasing TLR2 expression on monocytes and neutrophils[23]. Karadag et al.[24] reported that tumor necrosis factor alpha, interleukin-4 (IL-4), IL-17, and interferon-gamma levels, as inflammatory cytokines were significantly higher in acne patients compared to the control group, and a significant decrease was observed in their levels after isotretinoin treatment.

In the present study, we detected an increase in platelet count, as well as PDW, PCT, and RDW values, which are used as inflammatory markers in various diseases. However, we found a decrease in NLR and the number of WBCs, neutrophils, and monocytes, which are also indicators of inflammation. These findings suggest that isotretinoin may have both inflammatory and anti-inflammatory effects. A similar study by Kutlu[11] concluded that while isotretinoin has an anti-inflammatory effect on the pilosebaceous unit, it may have an inflammatory effect on the endovascular system.

We detected an increase in total cholesterol, LDL, and triglyceride levels, whereas, among biochemical parameters, a significant decrease was detected in HDL levels, consistent with other studies in literature[6,7,11]. In our study, the increase in AST levels without changing the ALT levels may be due to the effect of isotretinoin on muscle enzymes[11]. The comparative results of the studies are summarized in Table 2.

### Study Limitations

We acknowledge some limitations in the present study. All clinical information of the patients could not be accessed due to its retrospective nature. Also, it was impossible to examine any changes in the blood parameters of the patients except at the baseline and three months after the treatment. Finally, due to the study's retrospective nature, the relationship between laboratory findings and the clinical characteristics of the patients could not be compared.

## Conclusion

Isotretinoin has several effects on hemogram and biochemical parameters. This is the first article to demonstrate a significant decrease in monocyte count and an increase in PDW and PCT levels. However, the results of the studies are still controversial. New prospective studies with larger sample sizes are needed to clarify which laboratory changes may occur in which groups of patients. And the impact of the laboratory findings after the treatment of isotretinoin should be investigated by further clinical studies.

### Ethics

**Ethics Committee Approval:** The approval of the University of Health Sciences Türkiye, Kanuni Training and Research Hospital Ethics Committee was received (approval number: 2022/51, date: 26.09.2022).

**Informed Consent:** Because of the retrospective nature of the study informed consent was not prepared.

### Authorship Contributions

Surgical and Medical Practices: I.D.O., S.K., Concept: I.D.O., Design: I.D.O., Data Collection or Processing: I.D.O., S.K., Analysis or Interpretation: I.D.O., Literature Search: I.D.O., Writing: I.D.O.

**Conflict of Interest:** The authors declared that they have no conflict of interest.

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