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# Predictive value of inflammatory and hematological data in diabetic and non-diabetic retinopathy

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**Abstract. – OBJECTIVE: The current study aimed at investigating the predictive role of inflammatory, hematological and biochemical parameters in diabetic and non-diabetic retinopathy.**

**MATERIALS AND METHODS: The cross-sectional study was conducted between June 2019 and September 2020. We included patients with diabetic retinopathy (proliferative DR=14, non-proliferative DR=16), patients with non-diabetic retinopathy (n=30), patients with Type 2 Diabetes Mellitus (T2DM) without retinopathy (n=30) and control group (n=30). Demographic, hematological, and biochemical parameters of the participants were examined.**

**RESULTS: Participants' age and duration of diabetes mellitus were higher in proliferative and non-proliferative DR groups than patients with T2DM without retinopathy ($p$<0.001). There were significantly difference in terms of BMI ($p$<0.001), HbA1c ($p$<0.001), glucose ($p$<0.001), LDL ($p$<0.001), AST ($p$=0.001), hemoglobin ($p$<0.001), urea ($p$<0.001), creatinine ($p$<0.001), lymphocyte ($p$=0.001), and neutrophil ($p$=0.002) levels between groups. IL-6 levels were higher in proliferative DR, non-proliferative DR, and non-diabetic retinopathy groups than the control group. TNF-α levels were higher in proliferative DR and non-diabetic retinopathy groups than the control group. The NLR and PLR median values were significantly higher in the proliferative DR group than in other groups ($p$<0.001).**

**CONCLUSIONS: The current study showed that IL-6 and TNF-α levels are elevated in diabetic and non-diabetic retinopathy. In addition, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) median levels are higher in proliferative diabetic retinopathy than other groups. These findings support the inflammatory process may be accelerating the development of retinopathy.**

*Key Words:*
Diabetes mellitus, Retinopathy, Neutrophil/lymphocyte ratio, Platelet/lymphocyte ratio.

## Introduction

Chronic hyperglycemia in DM can cause microvascular complications as well as long-term damage and dysfunction in various organs and systems of the body[1].

Diabetic retinopathy is one of the most common complications of diabetes mellitus. Also, diabetic retinopathy is the most common cause of preventable blindness today. The pathogenesis of blindness due to diabetic retinopathy is that hyperglycemia causes vascular damage, leading to anatomical and functional disorders in retinal neurons and glial cells[2]. Diabetic retinopathy, based on the presence or absence of vitreous lesion, can broadly be classified into: Non-proliferative (NPDR) or Proliferative (PDR) retinopathy. While the damage is limited to the retina in NPDR, the lesion has progressed to the vitreous in PDR. In addition, diabetic ischemic maculopathy describes retinal microvascular degeneration within the macular region which can also result in loss of central visual acuity[3,4]. All of these endpoints are associated with poor glycemic control and prolonged disease duration. Early diagnosis of diabetic retinopathy is of great importance in preventing irreversible vision loss, but current screening methods are insufficient to identify the majority of high-risk patients[5].

NLR, PLR and platelet indices are easy-to-reach and low-cost parameters that can be easily studied in all laboratory settings, and they have been shown to be associated with many medical conditions and pathologies[6-8]. Studies[9,10] have shown that there is a relationship between metabolic and endocrinological diseases and these hematological indices and rates. Inflammation plays a role in the process that can be associated with many chronic diseases that we may think of, and it is one of these diseases in diabetes[11].

Inflammation marker NLR significantly increases in prediabetic and diabetic patients. PLR signifi-



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cantly decreases in prediabetes and early stages of diabetes but increases in later stages. NLR and PLR values may be reliable predictive markers in prediabetes and diabetes mellitus[12].

Type 2 diabetes is a chronic inflammatory disease. Diabetes is known to cause end-organ damage after prolonged exposure to inflammation, but no study has previously been conducted to compare the extent to which hematological markers are affected in diabetic retinopathy and non-diabetic retinopathy. We aimed to investigate the levels of hematological markers (NLR and PLR) in routine hemogram tests, which are easily accessible and cheap in patients with diabetic and non-diabetic retinopathy, and their possible roles in the early diagnosis and detection of DR.

## Materials and Methods

### Study Design and Sampling

This cross-sectional study was performed at department of Endocrinology and Ophthalmology clinics between June 2019 and September 2020. A total of 120 participants were enrolled in the study. The study population consisted of four groups. Group 1 (diabetic retinopathy [Proliferative DR n=14] and [non- proliferative DR, n=16]], group 2 (non-diabetic retinopathy n=30), group 3 (T2DM without retinopathy) and group 4 (control group without T2DM and retinopathy). T2DM was diagnosed by an endocrinologist according to the American Diabetes Association guidelines. Participants aged 40-75 years old were defined as eligible for the study. T2DM was diagnosed based on either the fasting plasma glucose (FPG) of ≥126 mg/dL (7.0 mmol/L) or 2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT or glycated hemoglobin (HbA1c) ≥ 6.5% (48 mmol/mol), or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)[13].

Diagnosis of DR was made based on clinical features observed during comprehensive eye examination by ophthalmologist and these patients were included in the DR group. Initially, patients were evaluated by the endocrinologist for the diagnosis of T2DM, and the diagnosis of T2DM was confirmed by the endocrinologist. Diagnosis of DR and classification of DR were confirmed according to the international clinical diabetic retinopathy and diabetic macular edema disease severity scales by two ophthalmologists[14]. The diagnosis of non-DR was made by the ophthalmologist based on the clinical features observed during the comprehensive eye examination. These patients had retinopathy but had not diabetes mellitus. This group consisted of patients without diabetes mellitus in the etiology of retinopathy. Firstly, the diagnosis of diabetes mellitus in patients was ruled out by the endocrinologist. Diagnosis of non-DR was confirmed by two ophthalmologists taking into account absence of DR diagnostic criteria. Another study group was defined as T2DM group. These patients were diabetic patients but there was any retinopathy. Diagnosis of T2DM was confirmed by endocrinologist, in addition, two ophthalmologists confirmed no signs of retinopathy in patients. The control group consisted of healthy volunteers who did not report diabetes mellitus, retinopathy and any chronic disease. It was confirmed by the endocrinologist and ophthalmologist that the participants in the control group did not have diabetes mellitus and retinopathy.

Exclusion criteria included any other ocular diseases, pregnancy and lactation, cognitive impairments, autoimmune diseases, systemic infection, terminal illness, malignancy, another type of diabetes than T2DM, steroid treatment and metabolic and endocrine diseases which can affect glucose metabolism. This cross-sectional study was approved by the Noninvasive Ethics Committee of the Fırat University (Date: 22.11.2018 No: 2018:19/8). The study was performed in accordance with the rules of the Helsinki Declaration. Written consent was obtained from all participants in the study.

### Data Collection

Sociodemographic characteristics, such as "age, gender, weight, height", were recorded. Body mass index (BMI) was calculated using the conventional Quetelet formula (BMI= kg/m$^2$). Overnight, fasting venous blood samples were collected. Biochemical parameters such as "glucose, HbA1c, lipids, AST, ALT, urea, creatinine" were performed in the laboratories of the Fırat University, Faculty of Medicine, Hospital.

Five-milliliter blood (5 mL) sample was obtained for analyses of IL-6, TNF-α and CRP. These samples were centrifuged at 5°C at 4,000 rpm and were stored at -80°C for further analyses. These analyzes were carried out by a medical biochemist at the medical biochemistry department of Fırat University. Serum CRP, IL-6 and TNF-alpha levels were measured by enzyme linked-immunosorbent assay (ELISA) method.

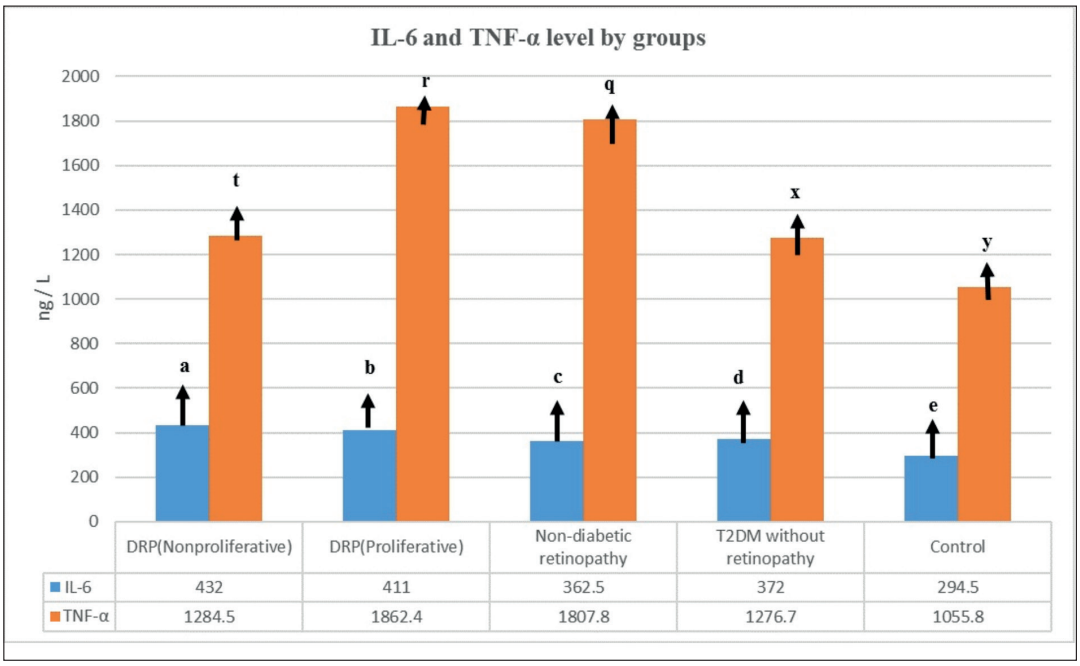


**Figure 1.** Comparison of IL-6 and TNF-α levels between groups. (IL-6 comparison: a-d: $p$=0.044; a-e: $p$ <0.001; b-e: $p$ =0.004; c-e: $p$ =0.028) (TNF-**α** comparison: t-q: $p$ =0.006; q-x: $p$ <0.001; q-y: $p$ <0.001; r-x: $p$ =0.008; r-y: $p$ =0.008).

Hematological parameters, such as "white blood cell, hemoglobin, neutrophil, lymphocyte, platelet" were obtained from hemogram analysis. Neutrophil lymphocyte ratio (NLR) was defined as "Neutrophil count/Lymphocyte count" and platelet lymphocyte ratio (PLR) was defined as "platelet count/Lymphocyte count"

### *Statistical Analysis*

We used IBM SPSS 22 package program for statistical analysis. Shapiro-Wilk test was used for to determinate the distribution of data. The continuous variables showed as mean± SD or Median (quarter 1 quarter 3) by distribution. Kruskal-Wallis test or One-Way Anova Test was used for statistical analysis according to the distribution of data. Bonferroni test was used for post hoc analysis. The p value <0.05 considered statistically significant.

## Results

There was no statistically significant difference in the age of onset of diabetes between the groups ($p$=0.211). Age of participants and duration of diabetes mellitus were higher in PDR and NPDR groups than patients with T2DM without retinopathy ($p$<0.001). Demographic features of diabetic patients showed in Table I.

There were significantly difference in terms of BMI ($p$<0.001), HbA1C ($p$<0.001), glucose ($p$<0.001), LDL ($p$<0.001), AST ($p$=0.001), hemoglobin ($p$<0.001), urea ($p$<0.001), creatinine

**Table I.** Demographic features of diabetic patients.

| Variables | Proliferative DR (n=14) | Nonproliferative DR (n=16) | T2DM without retinopathy (n=30) | *p*-value |
|---|---|---|---|---|
| Age | 60.86±4.70 | 61.44±6.25 | 56.15±10.03 | ***<0.001*** |
| Age of onset (year) | 48.82±3.91 | 50.74±4.24 | 49.62±5.67 | 0.211 |
| Duration of DM (year) | 15.63±2.67 | 13.26±3.64 | 7.81±1.37 | ***<0.001*** |
| Gender (female/male) | 8/6 | 9/7 | 18/12 | |

DRP: diabetic retinopathy; T2DM: type 2 diabetes mellitus.

**Table II.** Comparison some demographic, hematological and biochemical parameters by groups.

| Variables | Non-proliferative DR | Proliferative DR | Non-diabetic retinopathy | T2DM without retinopathy | Control | *p*-value |
|---|---|---|---|---|---|---|
| Age (years) | 61.44±6.25 | 60.86±4.70 | 60.67±8.51 | 56.15±10.03 | 43.10±7.82 | ***<0.001*** |
| BMI (kg/m$^{2)}$ | 28.9 (25.5-31.0) | 28.0 (25.0-30.0) | 27.0 (26.0-28.8) | 30.0 (28.0-31.0) | 26.5 (23.0-29.0) | ***<0.001*** |
| HbA1c (%) | 9.9 (7.5-11.8) | 9.0 (9.2-11.0) | 5.7 (5.3-5.8) | 9.7 (6.0-12.7) | 5.2 (4.8-5.7) | ***<0.001*** |
| Glucose (mg/dl) | 180.0 (132.0-235.0) | 167.0 (116.0-310.0) | 90.5 (84.3-101.5) | 169.5 (121.0-208.0) | 86.0 (81.0-97.0) | ***<0.001*** |
| Total Chol. (mg/dl) | 189.0 (148.0-227.0) | 181.0 (138.0-203.0) | 175.0 (130.5-175.0) | 181.0 (163.3-214.0) | 183.5 (165.0-205.8) | 0.270 |
| LDL (mg/dl) | 100.0 (95.0-134.0) | 120.0 (54.8-138.0) | 93.5 (76.8-116.0) | 131.0 (102.0-157.0) | 107.0 (96.0-123.8) | ***<0.001*** |
| TG (mg/dl) | 158.0 (109.0-289.5) | 136.0 (105.0-153.0) | 121.0 (103.0-164.5) | 148.0 (110.8-190.0) | 113.0 (81.0-175.0) | 0.060 |
| VLDL (mg/dl) | 31.0 (21.5-62.5) | 27.0 (21.0-30.6) | 25.0 (18.0-37.5) | 28.8 (23.0-38.8) | 26.0 (16.0-45.0) | 0.263 |
| AST (mg/dl) | 16.5 (15.0-17.5) | 19.0 (15.0-23.0) | 24.0 (16.8-28.0) | 19.0 (17.0-25.3) | 19.0 (17.0-23.8) | ***0.001*** |
| ALT (mg/dl) | 18.0 (14.5-25.5) | 20.0 (14.0-27.0) | 21.0 (14.0-34.0) | 25.5 (14.5-33.5) | 18.0 (14.0-30.0) | 0.316 |
| Hb (g/dl) | 13.17±1.69 | 12.72±1.91 | 12.97±2.14 | 13.78±1.78 | 15.01±1.14 | ***<0.001*** |
| Plt (x10$^{9}$/L) | 268.3 (190.0-357.0) | 275.0 (195.0-338.0) | 226.0 (187.0-251.0) | 244.0 (208.3-349.0) | 231.0 (215.0-251.0) | 0.071 |
| Ure (mg/dl) | 46.0 (34.0-56.0) | 48.0 (31.0-52.0) | 42.5 (34.0-63.3) | 32.0 (26.0-39.0) | 30.0 (26.0-32.5) | ***<0.001*** |
| Creatinine (mg/dl) | 1.09 (0.82-1.30) | 0.8 (0.71-1.40) | 1.03 (0.85-1.53) | 0.77 (0.66-0.94) | 0.86 (0.75-0.89) | ***<0.001*** |
| Lymphocyte (x10$^{9}$/L) | 1900.0 (1320.0-2820.0) | 1450.0 (1080-1630) | 1900.0 (1190.0-2200.0) | 2270.0 (1697.5-2877.5) | 2160.0 (1885.0-2330.0) | ***0.001*** |
| Neutrophil (x10$^{9}$/L) | 4970.0 (3950.0-6070.0) | 4310.0 (3610.0-6530.0) | 3530.0 (3272.5-4207.5) | 4150.0 (3840.0-4560.0) | 3430.0 (2840.0-4330.0) | ***0.002*** |

BMI: body mass index; LDL: low density lipoprotein; VLDL: very low-density lipoprotein; TG: triglyceride; Hb: hemoglobin; Plt: platelet.

($p$<0.001), lymphocyte ($p$=0.001), and neutrophil ($p$=0.002) levels between groups. Some demographic, hematological and biochemical features are presented in Table II.

IL-6 levels were higher in proliferative DRP, non-proliferative DRP, and non-diabetic retinopathy groups than the control group. TNF-α levels were higher in proliferative DRP and non-diabetic retinopathy groups than the control group (Figure 1).

The distribution of inflammatory parameters by groups were shown in Table III.

The NLR and PLR median values were significantly higher in proliferative DRP group than other groups ($p$<0.001).

## Discussion

Chronic inflammation, which has an important role in the initiation and progression of T2DM, induces micro and macrovascular complications in patients with T2DM[12]. As a result of the data obtained, it has been shown that leukocytes in the blood cause complications in patients with T2DM. NLR and PLR are two parameters that are accepted as new markers of systemic inflammatory response, and they consist of the formation of different subgroups of leukocytes in the blood[15]. Many studies[12,16] have shown evidence confirming their association with T2DM. DR has a process with an increase in inflammatory cytokines, and treatments given to prevent the inflammatory response may delay the formation and progression of DR[17-19]. In this study, we provided DR risk classification in type 2 diabetic patients with a simple blood test.

There was a significant difference in the data we obtained in mean CRP, NLR, and PLR in five groups. CRP level was higher in proliferative DR groups than the control group. NLR level was statistically significantly higher in the other groups when compared to the control group. When the other 4 groups except the control group were evaluated within themselves, the highest NLR level was found in the group with proliferative retinopathy. The highest PLR level among the groups was found in the proliferative DR and non-proliferative DR groups, and statistical significance was found only between the other 4 groups and the control group. In this study, we confirmed that the levels of NLR and PLR were higher in the PDR group. Studies[20,12] have proven that PLR and NLR are simple and usable parameters associated with diabetes and its complications.

Similar to the studies conducted in our study, it showed that increasing NLR levels significantly increased the risk of DR. High NLR may be the result of a large number of neutrophils attached to the vascular endothelial cells secondary to inflammation, causing endothelial damage[21,22]. Therefore, NLR can be a guide for demonstrating microvascular inflammation in DR patients.

Studies[23,24,25] have shown that PLR is closely related to macrovascular and microvascular complications that occur in the later stages of diabetes. However, one study did not find a significant relationship between PLR and DR[23]. In our study, as a continuous variable, PLR was found to be quite high in the proliferative DR group compared to the other groups, and based on this, we can conclude that the PLR value is highly correlated with the progression of diabetic retinopathy in diabetic patients. Many previous studies[26,27] have proven that platelets play an important role in the immunoinflammatory response, which supports our study. Increased PLR might represent the relatively active inflammatory response of platelets among DR patients. Although the studies and our study show that the PLR value can be a good predictor of progression in DR patients, more comprehensive multicenter studies are needed.

IL-6 levels were higher in proliferative DRP, non-proliferative DRP, and non-diabetic retinopathy groups than the control group. TNF-α levels were higher in proliferative DRP and non-diabetic retinopathy groups than the control group. In our study, when we compare the diabetic and non-diabetic retinopathy groups with the healthy control group, the platelet count was found to be statistically significantly higher in the retinopathy groups.

The current study showed that platelet counts and PLR are elevated in diabetic retinopathy. Previous studies demonstrated that higher platelet counts and PLR are associated with diabetic complications. The current study's data were consistent with previous literature. These findings may contribute to the prevention and delay of diabetic complications.

## Conclusions

The current study showed that IL-6 and TNF-α levels are elevated in diabetic and non-diabetic retinopathy. In addition, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) median levels are higher in proliferative diabet-

**Table III.** Comparison of inflammatory parameters by groups.

| Variables | Non-proliferative DR | Proliferative DR | Non-diabetic retinopathy | T2DM without retinopathy | Control | *p*-value* |
|---|---|---|---|---|---|---|
| CRP | 4.21 (3.13-11.30)[1] | 4.00 (3.01-7.64)[5] | 6.01 (3.27-3.50)[2] | 3.20 (3.04-8.84)[3] | 3.44 (3.14-5.14)[4] | 0.110 |
| NLR | 2.67 (1.97-3.19)[1] | 2.93 (2.67-6.05) | 2.40 (1.64-3.14)[2] | 1.71 (1.37-2.19)[3] | 1.66 (1.16-2.00)[4] | ***<0.001*** |
| PLR | 137.04 (110.78-178.11)[1] | 221.71 (167.59-305.88) | 114.71 (102.85-134.44) | 111.66 (85.91-141.81) | 114.10 (93.04-129.96) | ***<0.001*** |

| Multiple comparison (CRP) *p*-value | | Multiple comparison (NLR) *p*-value | | Multiple comparison (PLR) *p*-value | |
|---|---|---|---|---|---|
| 1-2: *p*>0.99<br>1-3: *p*>0.99<br>1-4: *p*=0.270<br>1-5: *p*>0.99<br>2-3: *p*=0.179 | 2-4: ***p=0.023***<br>2-5: *p*>0.99<br>3-4: *p*>0.99<br>3-5: *p*=0.685<br>4-5: *p*=0.99 | 1-2: *p*>0.99<br>1-3: *p*>0.99<br>1-4: *p*=0.281<br>1-5: ***p=0.020***<br>2-3: p>0.99 | 2-4: *p*=0.562<br>2-5: ***p=0.002***<br>3-4: *p*>0.99<br>3-5: ***p<0.001***<br>4-5: ***p<0.001*** | 1-2: *p*>0.99<br>1-3: *p*>0.99<br>1-4: *p*>0.99<br>1-5: ***p<0.001***<br>2-3: *p*>0.99 | 2-4: *p*>0.99<br>2-5: ***p<0.001***<br>3-4: *p*>0.99<br>3-5: ***p<0.001***<br>4-5: ***p<0.001*** |

ic retinopathy than other groups. These findings support the inflammatory process may be accelerating the development of retinopathy.

### Conflicts of Interest
The authors declare no conflicts of interest.

### Ethical Approval
A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of Fırat University (Number:19-8, Date: 22/11/2018).

### Patient Consent
Written informed consents were obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Authors' Contribution
HA: Data collection, design, Led and conceived the project, and authored the manuscript. EO: Data collection, compiling, and discussion. BY: Contributed to collecting and analysis data, discussion. DD: Contributed to collecting and analysis data. ED: Contributed to collecting, statistics and analysis data.

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