• Clinical Research •

# Hematological inflammation biomarkers in patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma

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## Abstract

● **AIM:** To evaluate complete blood count and biochemical parameters in patients with pseudoexfoliation syndrome (PEXS) and pseudoexfoliation glaucoma (PEXG) and compare the results with healthy controls.

● **METHODS:** Forty-four patients with PEXS, 61 patients with PEXG, and 55 healthy subjects were enrolled in this retrospective study. All systemic and especially pseudoexfoliation-related ophthalmic examination findings of the participants were evaluated. Complete blood count, glucose, creatinine, and serum lipid values were obtained. In line with these data, monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, monocyte-to-high density lipoprotein (HDL) ratio (MHR), and mean platelet volume-to-platelet count ratio were obtained and comparison were made among groups.

● **RESULTS:** Diabetes mellitus and hypertension were significantly more common in the PEXS and PEXG groups than in the control group ($P$=0.021, $P$=0.016, respectively). In the analysis of complete blood count parameters, NLR and MHR values were statistically significantly higher in PEXS and PEXG compared to the control group ($P$=0.037, $P$=0.025, respectively). In addition, glucose, low-density lipoprotein, and triglyceride values were significantly higher in the PEXS and PEXG groups compared to the control group ($P$<0.001, $P$=0.035, $P$<0.001, respectively), and HDL value was significantly lower ($P$=0.031).

● **CONCLUSION:** The hematological inflammation biomarkers we evaluated in our study provide evidence that systemic inflammation and oxidative stress processes play an important role in the pathogenesis of PEXS and PEXG.

● **KEYWORDS:** complete blood count; serum lipid levels; inflammation; oxidative stress; pseudoexfoliation syndrome; pseudoexfoliation glaucoma
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## INTRODUCTION

Pseudoexfoliation syndrome (PEXS) is a disorder of the extracellular matrix that occurs with advancing age, with the accumulation of abnormal extracellular fibrillar material in the anterior segment of the eye, skin, blood vessels, and some internal organs[1]. In addition to being the most common cause of secondary open-angle glaucoma, it also causes ocular problems such as poor pupil dilation, zonule weakness, phacodonesis, crystalline lens subluxation, anterior capsular contraction syndrome, and anterior chamber fibrinoid syndrome[2]. Pseudoexfoliation glaucoma (PEXG) has a more aggressive clinical course than primary open-angle glaucoma[3-4]. In addition, PEXS has been associated with various systemic diseases, especially cardiovascular and cerebrovascular diseases[5-7].

It has been reported that age, race, autoimmune diseases, trauma, and viral infections may be involved in the pathogenesis of PEXS, which progresses with systemic involvement. However, recent studies supporting the role of inflammation and oxidative stress have come to the fore[8-18]. It has been shown that some growth factors and molecules affect these processes. It has been shown that there is an increase in the levels of growth factors (fibroblast growth factor, connective tissue growth factor, transforming growth factor-β-1) and oxidative stress markers (8-isoprostaglandin-F2α) and a decrease in the levels of antioxidative molecules (ascorbic acid)[9-11]. It has been shown that high systemic levels of tumor necrosis factor-α, which is also an inflammatory marker, are associated with PEXG[19]. Its close relationship

with neurodegenerative diseases and cardiovascular disorders, especially Alzheimer's, in which chronic inflammatory processes play a role, also supports the close relationship of PEXS with inflammatory processes[20-21].

In addition to these parameters, complete blood count parameters have recently come to the fore in some studies because they can be more easily obtained as biomarkers of systemic inflammation. High levels of neutrophils, an indicator of inflammation, and the neutrophil-to-lymphocyte ratio (NLR), which combines lymphopenia, an indicator of physiological stress state, is the most studied parameter in this group as a marker of systemic inflammation[22-24]. Platelet-to-lymphocyte ratio (PLR) has also been investigated as an inflammation biomarker in various diseases, especially oncological and cardiovascular diseases[25-26].

In our study, in addition to these parameters, we calculated monocyte-to-lymphocyte ratio (MLR), monocyte-to-high density lipoprotein (HDL) ratio (MHR), mean platelet volume (MPV)-to-platelet count ratios (MPV/PC). It has been shown that these easily obtained laboratory tests can be indicators of inflammation in some systemic diseases, especially cardiovascular diseases, as well as in eye diseases (glaucoma, dry eye, age-related macular degeneration, keratoconus)[27-31]. However, studies revealing the role of inflammation in these processes based on the differences of these markers between PEXS, PEXG, and healthy controls are limited.

The relationship between PEXS and cardiovascular and cerebrovascular diseases has been associated with processes such as decreased antioxidant defense, increased oxidative stress, and lipid oxidation in these patients[32-33]. Additionally, dyslipidemia is a well-known risk factor for systemic vascular diseases[34].

Based on these findings, in our study, we aimed to evaluate inflammatory biomarkers in the light of complete blood count and biochemical data to reveal the role of inflammation in PEXS damage and pathogenesis. Secondary outcomes in this study relate to serum lipid levels involved in oxidative processes in patients with PEXS at risk of systemic vascular disease.

## PARTICIPANTS AND METHODS

**Ethical Approval** In this study, the files of patients who were examined at the Department of Ophthalmology at Gulhane Training and Research Hospital were retrospectively examined. The study was approved by the Local Ethical Committee of the institution with approval number "2023-72" and was conducted in accordance with the principles of the Declaration of Helsinki. Before all procedures, patients were given detailed information about the procedure and their consent was obtained.

Medical records of patients diagnosed with PEXS and PEXG between January 2021 and October 2023 were reviewed. Patients who had a comprehensive ophthalmological examination, whose examination findings were completely recorded, and whose complete blood count and routine biochemistry results could be obtained from the system were included in the study. Forty-four patients diagnosed with PEXS were determined as the 1st group, and 61 patients diagnosed with PEXG were determined as the 2nd group. Fifty-five age and gender matched individuals without PEXS or PEXG were designated as group 3. In addition to the findings of a complete ophthalmological examination of the participants, systemic diseases, especially systemic vascular diseases, and data on their medical history were reported. History of hematological or oncological diseases that will affect blood results, chemotherapy, radiotherapy treatment, infectious disease, history of ocular trauma or surgery (except uncomplicated cataract surgery), inflammatory eye disease, use of an ocular drug other than topical antiglaucomatous, chronic obstructive pulmonary disease, autoimmune disease, current steroid treatment and/or history of steroid use 6mo before admission were determined as exclusion criteria.

The diagnosis of PEXS and PEXG was confirmed by slit lamp biomicroscopy, fundoscopy, gonioscopy, retinal nerve fiber layer thickness analysis, and computerized visual field analysis. After autorefraction (Tonoref III, NIDEK Co., Ltd., Aichi, Japan) measurements of the patients' best-corrected visual acuity examinations were performed using the logarithm of the minimum angle of resolution (logMAR) chart. Slit lamp biomicroscopy and gonioscopy were used to evaluate whether there was typical exfoliative material accumulation in the pupillary border, anterior lens capsule and iridocorneal angle. After pupil dilation was achieved with tropicamide (0.5% tropamide, 5 mL, Bilim Pharmaceuticals, Türkiye), retina and optic nerve head examination was performed. Intraocular pressure (IOP) measurements were performed with a Goldmann applanation tonometer. Visual field assessments were performed with the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA).

Patients with exfoliative material accumulation in the anterior segment, an open anterior chamber angle by gonioscopy, an IOP<21 mm Hg, no glaucomatous optic nerve head changes and normal visual field findings were included in the PEXS group. Patients with exfoliative material accumulation in the anterior segment, an open anterior chamber angle by gonioscopy, an IOP above 21 mm Hg, glaucomatous optic nerve head changes and glaucomatous visual field defects were included in the PEXG group. The control group consisted of participants who had no ocular disease other than refractive error and cataract, no exfoliative accumulation at the pupillary border or in the anterior lens capsule, normal retina and optic disc examination, and IOP<21 mm Hg.

Blood test analyses were performed in the Department of Biochemistry. Complete blood counts and biochemical parameters were obtained from venous blood samples taken from the antecubital vein following at least 8h of fasting. Blood samples were analyzed with an automatic blood cell counter (Sysmex XN-1000, Sysmex Corporation, Kobe, Japan). Red blood cell, white blood cell, neutrophil, monocyte, lymphocyte, and platelet levels were measured. In addition, hemoglobin, MPV, platelet distribution width, red cell distribution width (RDW), and plateletcrit values were obtained. The Sysmex XN-1000 device analyzes blood cell count, white blood cell classification and hemoglobin concentration. It uses semiconductor laser optical detection and flow cytometry for white blood cells and sheath flow direct current detection for red blood cell and platelet counting. For hemoglobin content, sodium lauryl sulfate hemoglobin assay is used for detection[35]. Data including serum lipids [HDL, low-density lipoprotein (LDL), triglyceride (TG) and total cholesterol] were analyzed by a biochemistry analyzer (Cobas e602, Roche Diagnostics GmbH, Mannheim, Germany). With the results of these tests, MLR, NLR, PLR, MHR, and MPV/PC values were calculated.

**Statistical Analysis** Jamovi version 1.6 (computer software, https://www.jamovi.org) was used for statistical analysis. Quantitative variables were defined as mean and standard deviation and qualitative variables as percentages. Power calculation was not required due to the retrospective and exploratory nature of the study. The Shapiro-Wilk test was used to determine whether the sample came from a normally distributed population. The Pearson Chi-square test was used to analyze the gender and systemic comorbidity distribution among the groups. According to the normality test results, the ANOVA or Kruskal-Wallis test was used to compare the age and the blood parameters. Pearson correlation coefficients were calculated to determine the relationship between continuous measurements. A *P* value less than 0.05 was considered significant.

## RESULTS

The files of patients diagnosed with PEXS and PEXG between January 2021 and November 2023 were examined retrospectively. The files of a total of 170 patients were screened. Four patients whose ophthalmological examination findings were not fully recorded, three patients who did not have blood test results, two patients with a history of uveitis, and one patient diagnosed with systemic lupus erythematosus were excluded from the study. As a result, 10 patients were excluded from the study and the data of 160 patients, including 44 patients with PEXS, 61 patients with PEXG, and 55 healthy controls, were analyzed. The mean ages of the PEXS, PEXG, and healthy control groups were 68.4±6.7, 72.4±7.3 and 69.2±6.8, respectively ($P$=0.184). There were 21 (47.7%) men and 23 women (52.3%) in the PEXS group; 32 men (52.4%) and 29 women (47.6%) in the PEXG group; and 28 men (51%) and 27 women (49%) in the control group ($P$=0.225). Diabetes mellitus and hypertension were significantly more common in the PEXS and PEXG groups than in the control group ($P$=0.021, $P$=0.016, respectively). There was no significant difference between the groups in terms of coronary artery diseases and cerebrovascular events. Demographic data and baseline characteristics of the groups were shown in Table 1.

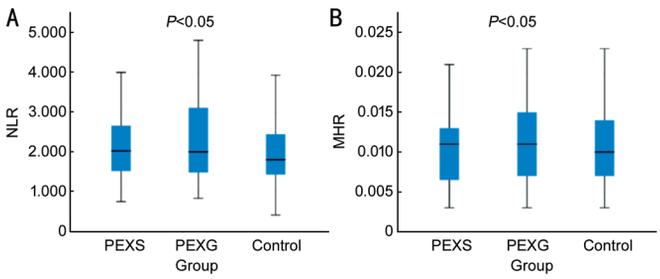


**Figure 1 Boxplot showing the NLR (A) and MHR (B) levels in controls, PEXS and PEXG group** NLR: Neutrophil-to-lymphocyte ratio; MHR: Monocyte-to-high-density lipoprotein ratio; PEXS: Pseudoexfoliation syndrome; PEXG: Pseudoexfoliation glaucoma.

In the analysis of complete blood count parameters, NLR and MHR values were found to be statistically significantly higher in PEXS and PEXG compared to the control group ($P$=0.037, $P$=0.025, respectively; Figure 1). There was no significant difference in terms of other parameters. Comparison of complete blood count results of the groups were shown in Table 2. In addition, glucose, LDL and TG values were significantly higher in the PEXS and PEXG groups compared to the control group ($P$<0.001, $P$=0.035, $P$<0.001, respectively), and HDL value was significantly lower ($P$=0.031). Comparison of biochemical data of the groups were shown in Table 3. A statistically significant positive ($r$=0.313) relationship was found between MLR level and PLR level in the PEXS group ($P$<0.05). Additionally, a statistically significant positive ($r$=0.718) relationship was found between NLR level and PLR level ($P$<0.05). The results of the correlation analysis between inflammatory biomarkers and serum lipid values in the PEXS group were shown in Table 4. In the PEXG group, a statistically significant positive ($r$=0.653, 0.678, 0.541, respectively) relationship was found between the MLR level and NLR, PLR and MHR levels ($P$<0.05). Additionally, a statistically significant positive ($r$=0.653, 0.741, respectively) relationship was found between NLR level and MLR and PLR levels ($P$<0.05). The results of the correlation analysis between inflammatory biomarkers and serum lipid values in the PEXG group were shown in Table 5. In the control group, a statistically significant positive relationship ($r$=0.596, 0.456, 0.447 respectively) was found between the MLR level and NLR, PLR and MHR levels

**Table 1 Baseline characteristics of the groups in the study** *n* (%)

| Variable | Group 1 (PEXS, *n*=44) | Group 2 (PEXG, *n*=61) | Group 3 (Control, *n*=55) | *P* |
|---|---|---|---|---|
| Age, mean±SD (y) | 68.4±6.7 | 72.4±7.3 | 69.2±6.8 | 0.184 |
| Gender (male/female) | 21/23 | 32/29 | 28/27 | 0.225 |
| Diabetes mellitus | 12 (27.2)[a] | 15 (24.5)[a] | 8 (14.5) | 0.021 |
| Hypertension | 27 (61.3)[a] | 31 (50.8)[a] | 14 (25.4) | 0.016 |
| History of coronary artery disease | 3 (6.8) | 5 (8.1) | 2 (3.6) | 0.422 |
| History of cerebrovascular event | 1 (2.2) | 1 (1.6) | 1 (1.8) | 0.523 |

[a]*P*<0.05 versus control group. PEXS: Pseudoexfoliation syndrome; PEXG: Pseudoexfoliation glaucoma; SD: Standard deviation.

**Table 2 Comparison of laboratory parameters among three groups** mean±SD

| Variable | Group 1 (PEXS, *n*=44) | Group 2 (PEXG, *n*=61) | Group 3 (Control, *n*=55) | *P* |
|---|---|---|---|---|
| Mean platelet volume (fL) | 10.05±0.91 | 10.11±1.03 | 10.13±1.02 | 0.539 |
| Platelet distribution width (%) | 11.52±2.04 | 11.62±1.94 | 11.55±1.76 | 0.759 |
| Red cell distribution width (%) | 13.37±1.74 | 13.57±1.57 | 13.55±1.35 | 0.301 |
| Plateletcrit (%) | 0.27±0.02 | 0.24±0.08 | 0.26±0.05 | 0.494 |
| White blood cell ($\times10^3$/μL) | 7.57±2.11 | 7.21±2.01 | 7.33±2.32 | 0.322 |
| Neutrophil count ($\times10^3$/μL) | 4.57±2.22 | 4.38±1.67 | 4.39±1.80 | 0.636 |
| Monocyte count ($\times10^3$/μL) | 0.59±0.28 | 0.57±0.18 | 0.59±0.16 | 0.643 |
| Lymphocyte count ($\times10^3$/μL) | 2.12±0.42 | 2.13±0.65 | 2.16±0.73 | 0.443 |
| Platelet count ($\times10^3$/μL) | 247.03±56.22 | 239.11±59.20 | 244.07±60.21 | 0.956 |
| MLR | 0.34±0.18 | 0.32±0.13 | 0.31±0.73 | 0.542 |
| NLR | 2.57±1.46[a] | 2.62±1.78[a] | 2.01±1.02 | 0.037 |
| PLR | 121.64±49.85 | 120.59±47.41 | 116.37±43.58 | 0.318 |
| MHR | 0.017±0.005[a] | 0.018±0.006[a] | 0.011±0.003 | 0.025 |
| MPV/PC | 0.052±0.013 | 0.057±0.017 | 0.042±0.009 | 0.744 |

[a]*P*<0.05 versus control group. PEXS: Pseudoexfoliation syndrome; PEXG: Pseudoexfoliation glaucoma; SD: Standard deviation; MLR: Monocyte-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MHR: Monocyte-to-high-density lipoprotein ratio; MPV/PC: Mean platelet volume/platelet count ratio.

**Table 3 Comparison of biochemical parameters among three groups** mean±SD

| Variable | Group 1 (PEXS, *n*=44) | Group 2 (PEXG, *n*=61) | Group 3 (Control, *n*=55) | *P* |
|---|---|---|---|---|
| Glucose (mg/dL) | 111.21±42.4[a] | 113.23±39.3[a] | 89.51±7.1 | <0.001 |
| Creatinine (mg/dL) | 0.72±0.20 | 0.73±0.14 | 0.72±0.16 | 0.686 |
| Total cholesterol (mg/dL) | 180.81±41.68 | 177.17±34.61 | 176.32±26.97 | 0.452 |
| LDL (mg/dL) | 117.18±36.77[a] | 117.87±29.98[a] | 95.25±31.78 | 0.035 |
| HDL (mg/dL) | 49.61±10.58[a] | 49.87±13.48[a] | 53.97±15.64 | 0.031 |
| Triglyceride (mg/dL) | 142.36±91.30[a] | 148.1±52.66[a] | 116.1±44.33 | <0.001 |

[a]*P*<0.05 versus control group. PEXS: Pseudoexfoliation syndrome; PEXG: Pseudoexfoliation glaucoma; SD: Standard deviation; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

($P$<0.05). Additionally, a statistically significant positive ($r$=0.596, 0.414, respectively) relationship was found between NLR level and MLR and PLR levels ($P$<0.05). The results of the correlation analysis between inflammatory biomarkers and serum lipid values in the control group were shown in Table 6.

## DISCUSSION

In our study, we evaluated the levels of hematological parameters used as inflammation and oxidative stress markers in PEXS and PEXG patients. Our findings support the relationship between inflammatory markers NLR, MHR and PEXS/PEXG. It also provides evidence for the relationship between PEXS/PEXG and levels of blood lipid parameters that play a role in oxidative-antioxidative processes. The exact pathophysiological mechanism of PEXS is still not clearly revealed, but emphasis is placed on systemic biochemical processes, where oxidative stress and inflammation are at the forefront.

Recently, the results of studies on the role of inflammatory mediators and pathways in PEXS and PEXG have been reported. Yıldırım *et al*[36] stated that there is an increase in interleukin-6 levels in patients with PEXS and that complement pathways may be responsible for the inflammatory processes

**Table 4 Correlation analysis results among inflammatory biomarkers and serum lipid values in the PEXS group**

| Parameters | Coefficient | MLR | NLR | PLR | MHR | MPV/PC | LDL | HDL | TG |
|---|---|---|---|---|---|---|---|---|---|
| MLR | *r* | 1 | 0.286 | 0.313[a] | 0.229 | 0.035 | 0.025 | -0.125 | -0.121 |
| | *P* | - | 0.060 | 0.038 | 0.135 | 0.819 | 0.871 | 0.418 | 0.434 |
| NLR | *r* | 0.286 | 1 | 0.718[a] | 0.067 | 0.147 | -0.004 | -0.110 | -0.153 |
| | *P* | 0.060 | - | 0.000 | 0.665 | 0.339 | 0.981 | 0.476 | 0.322 |
| PLR | *r* | 0.313[a] | 0.718[a] | 1 | -0.136 | -0.383[a] | 0.164 | -0.120 | -0.219 |
| | *P* | 0.038 | 0.000 | - | 0.378 | 0.010 | 0.289 | 0.437 | 0.153 |
| MHR | *r* | 0.229 | 0.067 | -0.136 | 1 | 0.270 | -0.231 | -0.690[a] | -0.061 |
| | *P* | 0.135 | 0.665 | 0.378 | - | 0.077 | 0.131 | 0.000 | 0.692 |
| MPV/PC | *r* | 0.035 | 0.147 | -0.383[a] | 0.270 | 1 | -0.169 | 0.029 | 0.180 |
| | *P* | 0.819 | 0.339 | 0.010 | 0.077 | - | 0.272 | 0.850 | 0.243 |
| LDL | *r* | 0.025 | -0.004 | 0.164 | -0.231 | -0.169 | 1 | 0.010 | 0.156 |
| | *P* | 0.871 | 0.981 | 0.289 | 0.131 | 0.272 | - | 0.949 | 0.313 |
| HDL | *r* | -0.125 | -0.110 | -0.120 | -0.690[a] | 0.029 | 0.010 | 1 | 0.079 |
| | *P* | 0.418 | 0.476 | 0.437 | 0.000 | 0.850 | 0.949 | - | 0.612 |
| TG | *r* | -0.121 | -0.153 | -0.219 | -0.061 | 0.180 | 0.156 | 0.079 | 1 |
| | *P* | 0.434 | 0.322 | 0.153 | 0.692 | 0.243 | 0.313 | 0.612 | - |

*r*: Pearson correlation coefficients; [a]*P*<0.05. PEXS: Pseudoexfoliation syndrome; MLR: Monocyte-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MHR: Monocyte-to-high-density lipoprotein ratio; MPV/PC: Mean platelet volume/platelet count ratio; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride.

**Table 5 Correlation analysis results among inflammatory biomarkers and serum lipid values in the PEXG group**

| Parameters | Coefficient | MLR | NLR | PLR | MHR | MPV/PC | LDL | HDL | TG |
|---|---|---|---|---|---|---|---|---|---|
| MLR | *r* | 1 | 0.653[a] | 0.678[a] | 0.541[a] | -0.018 | 0.055 | -0.047 | 0.157 |
| | *P* | - | 0.000 | 0.000 | 0.000 | 0.893 | 0.674 | 0.720 | 0.227 |
| NLR | *r* | 0.653[a] | 1 | 0.741[a] | 0.108 | 0.014 | 0.023 | 0.035 | -0.176 |
| | *P* | 0.000 | - | 0.000 | 0.405 | 0.913 | 0.861 | 0.787 | 0.175 |
| PLR | *r* | 0.678[a] | 0.741[a] | 1 | 0.086 | -0.215 | 0.013 | 0.066 | -0.054 |
| | *P* | 0.000 | 0.000 | - | 0.510 | 0.097 | 0.919 | 0.613 | 0.681 |
| MHR | *r* | 0.541[a] | 0.108 | 0.086 | 1 | -0.221 | -0.110 | -0.539[a] | 0.408[a] |
| | *P* | 0.000 | 0.405 | 0.510 | - | 0.087 | 0.397 | 0.000 | 0.001 |
| MPV/PC | *r* | -0.018 | 0.014 | -0.215 | -0.221 | 1 | -0.236 | 0.006 | -0.290[a] |
| | *P* | 0.893 | 0.913 | 0.097 | 0.087 | - | 0.068 | 0.963 | 0.023 |
| LDL | *r* | 0.055 | 0.023 | 0.013 | -0.110 | -0.236 | 1 | 0.345[a] | 0.130 |
| | *P* | 0.674 | 0.861 | 0.919 | 0.397 | 0.068 | - | 0.006 | 0.317 |
| HDL | *r* | -0.047 | 0.035 | 0.066 | -0.539[a] | 0.006 | 0.345[a] | 1 | -0.033 |
| | *P* | 0.720 | 0.787 | 0.613 | 0.000 | 0.963 | 0.006 | - | 0.803 |
| TG | *r* | 0.157 | -0.176 | -0.054 | 0.408[a] | -0.290[a] | 0.130 | -0.033 | 1 |
| | *P* | 0.227 | 0.175 | 0.681 | 0.001 | 0.023 | 0.317 | 0.803 | - |

*r*: Pearson correlation coefficients; [a]*P*<0.05. PEXG: Pseudoexfoliation glaucoma; MLR: Monocyte-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MHR: Monocyte-to-high-density lipoprotein ratio; MPV/PC: Mean platelet volume/platelet count ratio; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride.

in PEXS. Okutucu and Arpa[37], in their recent study, revealed decreased levels of the anti-inflammatory mediator semaphorin 3A and increased levels of the inflammatory mediator interleukin-6 in PEXS. They reported that these molecules may play a role in the systemic manifestations of this syndrome, such as inflammation, atherosclerosis, cardiac arrhythmia, and Alzheimer's disease. Cumurcu *et al*[38] stated that the increase in serum alpha-1 antitrypsin levels in patients with PEXS was an indicator of inflammation. Sorkhabi *et al*[39] stated that increased high-sensitivity C-reactive protein and tumor necrosis factor-α levels in PEXS are indicators of inflammation and peripheral endothelial dysfunction and may be a risk factor for ocular and systemic manifestations of PEXS. Türkyılmaz *et al*[40] showed that the serum Chitinase 3-like protein 1

**Table 6 Correlation analysis results among inflammatory biomarkers and serum lipid values in the control group**

| Parameters | Coefficient | MLR | NLR | PLR | MHR | MPV/PC | LDL | HDL | TG |
|---|---|---|---|---|---|---|---|---|---|
| MLR | *r* | 1 | 0.596[a] | 0.456[a] | 0.447[a] | -0.043 | -0.012 | -0.068 | 0.038 |
| | *P* | - | 0.000 | 0.000 | 0.000 | 0.665 | 0.902 | 0.491 | 0.705 |
| NLR | *r* | 0.596[a] | 1 | 0.414[a] | 0.064 | 0.102 | -0.101 | -0.052 | 0.058 |
| | *P* | 0.000 | - | 0.000 | 0.518 | 0.303 | 0.305 | 0.603 | 0.557 |
| PLR | *r* | 0.456[a] | 0.414[a] | 1 | -0.070 | -0.449[a] | 0.009 | 0.098 | -0.104 |
| | *P* | 0.000 | 0.000 | - | 0.482 | 0.000 | 0.931 | 0.321 | 0.295 |
| MHR | *r* | 0.447[a] | 0.064 | -0.070 | 1 | -0.178 | -0.022 | -0.622[a] | 0.396[a] |
| | *P* | 0.000 | 0.518 | 0.482 | - | 0.070 | 0.822 | 0.000 | 0.000 |
| MPV/PC | *r* | -0.043 | 0.102 | -0.449[a] | -0.178 | 1 | -0.094 | -0.038 | -0.087 |
| | *P* | 0.665 | 0.303 | 0.000 | 0.070 | - | 0.342 | 0.703 | 0.380 |
| LDL | *r* | -0.012 | -0.101 | 0.009 | -0.022 | -0.094 | 1 | -0.040 | 0.076 |
| | *P* | 0.902 | 0.305 | 0.931 | 0.822 | 0.342 | - | 0.685 | 0.441 |
| HDL | *r* | -0.068 | -0.052 | 0.098 | -0.622[a] | -0.038 | -0.040 | 1 | -0.418[a] |
| | *P* | 0.491 | 0.603 | 0.321 | 0.000 | 0.703 | 0.685 | - | 0.000 |
| TG | *r* | 0.038 | 0.058 | -0.104 | 0.396[a] | -0.087 | 0.076 | -0.418[a] | 1 |
| | *P* | 0.705 | 0.557 | 0.295 | 0.000 | 0.380 | 0.441 | 0.000 | - |

*r*: Pearson correlation coefficients; [a]*P*<0.05. MLR: Monocyte-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MHR: Monocyte-to-high-density lipoprotein ratio; MPV/PC: Mean platelet volume/platelet count ratio; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride.

(YKL-40) level, which plays a role in systemic inflammation and endothelial dysfunction processes, was significantly higher in the PEXS group than in the control group. Gonen *et al*[41] reported that there was a significant increase in aqueous YKL-40 levels in the PEXS group compared to the control group, but serum YKL-40 levels were similar in both groups.

Hirbo *et al*[42] evaluated the role of inflammatory processes in PEXS by genetically determined gene expression analysis. They showed that gene transcription associated with inflammatory conditions was significant in PEXS. They reported that inflammation pathways play a role in the etiology of PEXS. SarenacVulovic *et al*[43] showed that profibrotic cytokines (transforming growth factor-β, platelet-derived growth factor, epidermal growth factor, insulin-like growth factor, interleukin-8) increased in serum and aqueous in PEXS/PEXG. Okutucu *et al*[44] showed that serum netrin-1 level was significantly lower in PEXS/PEXG patients, similar to diseases whose common pathogenesis is inflammation, such as atherosclerosis and Alzheimer's disease. Based on this, they reported that netrin-1 promises a potential anti-inflammatory role.

Based on neutrophilia, an indicator of inflammation, and lymphopenia, an indicator of physiological stress, NLR is used as a marker of systemic inflammation[24]. Therefore, markers such as NLR and PLR are important in the diagnosis and follow-up of diseases accompanied by inflammation. The prognostic effects of NLR and PLR values have been investigated in various diseases, especially malignancies and cardiovascular diseases[45-46]. In addition to systemic diseases, there are also studies in the literature evaluating the relationship between NLR and eye diseases. Shirvani et al. stated there were significantly higher NLR levels in some eye diseases (keratoconus, glaucoma, pterygium and idiopathic epiretinal membrane) compared to healthy controls. As a result of these findings, they stated that NLR is a valuable marker of systemic inflammation, that it increases significantly in many eye diseases, and that inflammation plays a key role in the pathophysiology of these diseases[27,47].

Ozgonul *et al*[48] found PLR and NLR levels to be significantly higher in primary open-angle glaucoma patients than in the control group. They stated that these parameters may be useful in predicting the prognosis of primary open-angle glaucoma patients. Kurtul *et al*[14] stated that the NLR rate in patients with PEXS and PEXG was significantly increased compared to controls. However, unlike us, they reported that the prevalence of diabetes and hypertension was similar between the groups. Ozgonul *et al*[12] found that NLR levels in PEXS and PEXG were significantly higher than in the control group. They also found a significant difference in PLR values between the control and PEXG groups. They stated that PLR and NLR may be useful in predicting the prognosis of PEXS and progression to PEXG. Recently, Tukenmez Dikmen and Un[49] reported that NLR was significantly higher in patients with PEXS, but PLR did not differ between groups. Recently, the systemic immune-inflammatory index (SII) has been used in studies as an indicator of systemic inflammation[50-54]. SII is calculated by multiplying the neutrophil count by the platelet count and dividing by the lymphocyte count. Tukenmez Dikmen and Un[49] also showed that SII levels were significantly higher

in patients with PEXS. They reported that SII levels may be a supportive parameter for NLR in risk prediction in these patients. Yasar *et al*[55] showed that high calprotectin, an inflammatory marker, increased the risk of glaucoma by 4.36 times in patients with PEXS, and high NLR increased the risk of cardiovascular disease by 3.23 times. Oh *et al*[56] compared the rates of cardiovascular disease and NLR between PEXS and the control group. They reported that the prevalence of cardiovascular disease was higher in the PEXS group, and NLR was higher in the PEX group than in the control group, regardless of cardiovascular comorbidity. Gökçe and Başkan[57] investigated the relationship between NLR and cataract surgery complications. They showed that there was a relationship between cataract surgery complication rates and NLR elevation.

Supporting these results, the findings of our study showed that NLR was significantly higher in the PEXS and PEXG groups than in the control group. These findings suggest that inflammation plays an important role in PEXS and that the NLR can be used as an important indicator of inflammation. In addition, observing the change in NLR values with long-term follow-up of these patients may help predict the progression from PEXS to PEXG. In addition, high NLR seems to be important in terms of its relationship with systemic diseases in which inflammation is important in the pathogenesis, especially atherosclerosis and cardiovascular diseases. In our study, no significant difference was detected in PLR levels among groups. Although some differences were reported in the results of these studies, they reveal evidence for the presence of inflammatory processes in PEXS/PEXG. In addition, they also provides guidance in terms of target molecules for prevention or against progression.

In inflammation, monocytes play an important role in the release of pro-inflammatory and pro-oxidative cytokines[58]. HDL, on the other hand, has anti-inflammatory and antioxidant effects by inhibiting the migration of monocytes and preventing the expression of endothelial adhesion proteins[59]. As a result, MHR emerges as an important marker in inflammatory and oxidative stress situations. Studies have shown that MHR is associated with a number of diseases such as cardiovascular disease, endothelial dysfunction, and chronic kidney disease[60-61]. In addition, studies are showing that MHR is associated with various ocular disorders such as diabetes and diabetes complications, PEXS, glaucoma, branch retinal vein occlusion and central serous chorioretinopathy[62-66]. Yılmaz Tuğan *et al*[67] showed that higher MHR values were associated with increased disease severity and inflammatory activity in patients with Graves' ophthalmopathy. Mirza *et al*[64] showed that MHR was significantly higher in the PEXS and PEXG groups compared to the control group. They stated that MHR may confirm that inflammation is an important factor in the nature of PEXS. They also stated that high MHR values may be useful in elucidating the pathogenesis of PEXS, detecting its progression, and understanding its relationship with accompanying systemic diseases.

Supporting MHR as an indicator of systemic inflammation in PEXS and PEXG, our study showed that MHR was significantly higher in the PEXS and PEXG groups than in the control group. MHR is a parameter that indicates pro-inflammatory and anti-inflammatory balance. Therefore, it is possible to say that it may be a better indicator of systemic inflammation compared to other hematological parameters. Moreover, when compared to other expensive inflammatory markers (tumor necrosis factor-α , interleukin-1, interleukin-6), MHR can be easily calculated by complete blood count analysis. Therefore, it appears as a more practical and cost-effective parameter.

While the association of PEXS with vascular diseases has been established, the underlying mechanisms are not clearly understood. It is known that disorders in lipid metabolism are an important risk factor for systemic vascular diseases[68]. Mastronikolis *et al*[69] showed that in patients with PEX, the oxidant-antioxidant balance in both serum and aqueous shifted towards the oxidants. In addition, many studies have shown that the oxidant-antioxidant balance is altered in the aqueous humor, serum and tissues of patients with PEXS[70-76]. Mastronikolis *et al*[77] stated that the imbalance between antioxidants and oxidants plays an important role in the onset and progression of PEXS. They commented that oxidative stress plays a role in the restructuring of the extraocular matrix and alters the antioxidant system in a way that supports PEXS its progression to PEXG. These studies demonstrate the importance of understanding oxidative stress-mediated pathogenic mechanisms to control and treat PEXS.

High TG, LDL and total cholesterol levels and low HDL cholesterol are important factors that cause vascular calcification[78]. Speckauskas *et al*[79] reported that there was no difference in serum total cholesterol, LDL and TG levels between patients with PEXS and the control group. The same study found no evidence that PEXS increases the risk of ischemic heart disease, hypertension and diabetes. Kurtul *et al*[13] stated that hypertension and diabetes were more common in the PEXS and PEXG group than in the control group, and LDL levels were significantly higher. Türkyılmaz *et al*[40] reported that serum high-sensitivity C-reactive protein, total cholesterol, LDL and TG levels were significantly higher and serum HDL levels were significantly lower in the PEXS group compared to the control group. Erdem and Gok[80] showed that HDL levels were low and TG levels were high in PEXG, and the results were statistically significant. Based

on these results, it was revealed that there is a connection between hematological and atherogenic parameters reflecting cardiovascular risk and that these parameters may be important in the monitoring of PEXS/PEXG and related diseases.

Miyazaki *et al*[81] in their study evaluating 1844 participants aged 50 and over found the prevalence of PEXS to be 3.4%. They reported that hypertension was strongly associated with PEXS in this patient group. Circulating HDL has been shown to be involved in systemic antioxidation and detoxification processes, while TG plays the opposite role[82-83]. In our study, diabetes and hypertension were more common in PEXS and PEXG than in the control group. Additionally, when the PEXS and PEXG groups were compared with the control group, there was a significant difference in LDL, TG and HDL values. It is possible to say that this dyslipidemic situation may be related to systemic vascular diseases, especially diabetes and hypertension. Dyslipidemia causes endothelial dysfunction and prevents the removal of oxidative products, therefore it is known to be closely related to atherogenesis[84].

Bashir *et al*[85] found RDW, an index of change in erythrocyte volume (*i.e*. anisocytosis), to be higher in PEXS/PEXG than in healthy controls. They also reported that RDW levels increased gradually from the control group to the PEXG group. They stated that RDW may be a useful marker in predicting the presence of PEXS and progression to PEXG. It is thought that the increase in inflammatory cytokines in PEXS suppresses the maturation of erythrocytes, causing juvenile erythrocytes to enter the circulation, leading to increased size heterogeneity and, as a result, increased RDW levels[86]. Another explanation is that oxidative stress directly damages erythrocytes and shortens erythrocyte lifespan, resulting in increased RDW levels[87]. In our study, no significant differences were observed among groups in terms of RDW values. However, the cause-effect relationships of these biochemical and molecular pathways strengthen the connection between PEXS/PEXG and oxidative stress and inflammation.

Limitations of our study include its retrospective design, relatively small sample size, and lack of evaluation of other markers and proinflammatory cytokines that play an important role in systemic inflammation. Long-term use of topical anti-glaucomatous drugs causes inflammation in the conjunctiva and aqueous. This should be taken into consideration when interpreting inflammatory parameters. In addition, serum lipid levels may be affected by nutritional habits and some genetic characteristics. It is necessary to consider these variables when interpreting the results. Studies with larger participation and long-term follow-up are needed to predict the progression from PEXS to PEXG. However, it should be kept in mind that all these inflammatory parameters evaluated are not specific to PEXS or PEXG.

In conclusion, the results of our study make important contributions to previous studies. Our study provides evidence that systemic inflammation and oxidative stress processes play important roles in the pathogenesis of PEXS and PEXG. These hematological parameters that we evaluated in the study are easily obtained and cost-effective. We presented evidence that these values have prognostic significance in PEXS and PEXG. Biochemical processes that will shed light on systemic inflammation in patients with PEXS and PEXG should be elucidated, and the relationship between these systemic inflammatory processes and markers and ocular and systemic manifestations should be evaluated. At the same time, it is necessary to be careful in patients with PEXS and PEXG in terms of dyslipidemia and systemic vascular diseases.

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**Availability of Data and Materials:** The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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