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CLINICAL STUDY

Systemic inflammation in both open-angle and angle-closure glaucoma: role of platelet-to-lymphocyte ratio

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ABSTRACT
AIM: To analyse the effect of systemic inflammatory status in patients with primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) by calculating platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR).
METHODS: This retrospective case-control study included 200 patients with POAG, 22 patients with PACG and 100 healthy subjects. The participants' white-blood-cell, lymphocyte, neutrophil, and platelet counts were recorded from previous blood assays. NLR and PLR were calculated manually. Results were compared among the groups.
RESULTS: Both the POAG and PACG groups had higher platelet counts and PLR values than the control group (p=0.001 and p=0.001; respectively). The difference in NLR between POAG, PACG and control groups was not statistically significant (p=0.076). The POAG group had higher NLR values than the control (p=0.035).
CONCLUSION: Both the POAG and the PACG groups exhibited higher platelet and PLR levels than the control. These results indicate a potential role of systemic inflammation in the pathogenesis of POAG and PACG *(Tab. 4, Fig. 1, Ref. 35)*. Text in PDF *www.elis.sk*
KEY WORDS: neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte-ratio; primary open-angle glaucoma; primary angle-closure glaucoma; systemic inflammation.

Introduction

Glaucoma is thought to be amongst the major causes of irreversible blindness worldwide and it is composed of groups of progressive optic neuropathies (1–3). While high intraocular pressure (IOP) is a well-known treatable risk factor, discussion remains regarding the exact mechanism of both primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) (3–5). Notably, vascular dysfunction, autoimmune processes, impaired systemic oxidation/anti-oxidation balance and inflammatory pathways are blamed as underlying molecular mechanisms (6–11). Therefore, there could be a role of systemic inflammation in the etiopathogenesis of glaucoma.

One of the most inexpensive and simplest ways to evaluate systemic inflammation is the calculation of platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) (12). These parameters are obtained from a complete blood count (CBC) and have widely been used as predictors in the prognosis of several systemic diseases (13–18). It has also been noted that favourable outcomes could be achieved by using both PLR and NLR in ocular pathologies (19–22). However, there are few existing studies in the literature that have compared both PLR and NLR in glaucoma patients (23–25).

In this present study, our purpose was to evaluate whether there is an effect of systemic inflammation by comparing the values of PLR and NLR between the patients with any types of glaucoma (POAG and/or PACG) and healthy subjects.

Patients and methods

Study population

This was a retrospective case-control study performed at the Dicle University Department of Ophthalmology in Diyarbakir, Turkey. Digital medical records between January 2010 and February 2019 were used to obtain the research data. The Dicle University Review Board approved the methodology. The study adhered to the Declaration of Helsinki for clinical research.

The patients were all followed up in the Department of Glaucoma. A total of 306 patients' files were searched. We excluded 54 patients for the lack of detailed ophthalmological examination data, while 30 additional patients were excluded for the absence of CBC results. Finally, 200 patients with POAG, 22 patients with PACG and 100 gender-matched subjects who were otherwise healthy were enrolled in the study as controls. Controls were individuals who were arranged for routine cataract surgery and their CBC was obtained during preoperative laboratory assessments (Fig. 1).

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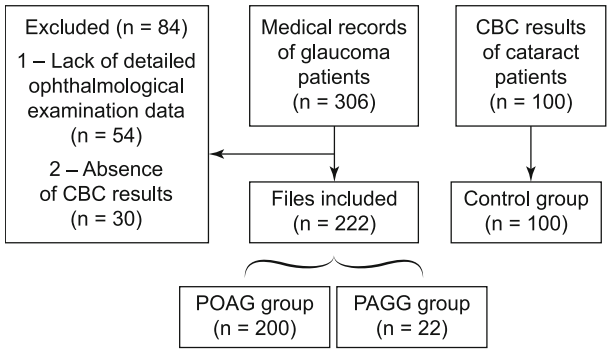

Fig. 1. Flow of inclusion criteria.

A detailed ophthalmological examination was performed, including best corrected visual acuity (BCVA) measurements with Snellen charts, anterior and posterior segments evaluation by slit-lamp biomicroscopy and IOP measurements using a Goldmann applanation tonometer (Haag-Streit Inc., Köniz, Switzerland). In our glaucoma department, if we diagnose a patient for any type of glaucoma, we routinely perform a complete blood analysis, including CBC, biochemistry and hepatitis markers from all the patients on the same day.

Clinical evaluation of glaucoma

POAG was diagnosed if the anterior chamber angle was open on the gonioscopy with glaucoma-related optic neuropathy (GON), IOP of > 21 mmHg and glaucoma-related visual field defect (GVFD).

PACG was defined as follows: the angle is occludable and/or the peripheral iris is capable of obstructing the angle on gonioscopy, GON, and GVFD and an IOP of > 21mm Hg (26).

GON was defined as an increase in optic cup excavation, neuro-retinal rim thinning, notching, haemorrhages on optic disc head, or cup/disc ratio (CDR) asymmetry among the eyes (27, 28).

In the Department of Glaucoma, a Humphrey Field Analyser was used to perform visual field tests (VFTs) (Carl Zeiss Meditec Inc., Dublin, CA). VFTs were completed using the Swedish Interactive Threshold Algorithm (SITA) Standard strategy, programme 30-2. Typical GVFDs were identified if at least in two reliably performed consecutive tests (SITA, 30-2 VFTs) in an individual have an abnormal glaucoma hemifield test or pattern standard deviation. Abnormal VFTs met a minimum one of the following three criteria: ≥ 3 nearby points with $p < 0.05$ or greater loss; ≥ 2 adherent points with $p < 0.01$ or greater loss; or a 10 dB dissimilarity across the nasal horizontal midline in ≥ 2 adjacent locations compared to perimeter-defined gender-matched normal values (26).

Blood sampling

The antecubital vein was used to obtain the blood samples, and the measurements were done at the Biochemistry Department on the day of the diagnosis was made. The values of red blood cells (RBC), white blood cells (WBC), neutrophils, lymphocytes and platelets were measured in CBC tests (BC-6800, Mindray, Shenzhen, China). PLR and NLR were calculated manually.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 20.0 version was used for statistical analysis on a Windows-based PC. In our study, 'median (min-max)' and 'percentage (%)' were used among the descriptive statistics. The Kolmogorov–Smirnov test was used to evaluate the distribution of variables. Quantitative values were compared between three groups with the Kruskal-Wallis test. Mann-Whitney U test was used for further pairwise comparisons. The χ^2 test was used for comparing the qualitative variables. A p-value ≤ 0.05 was accepted as statistically significant.

Results

Table 1 presents the anthropometric details and CBC results of patients in the POAG, PACG, and control groups. The median age was 70 (40–85) years in the POAG group (n = 200), 57 (42–89) years in the PACG group (n = 22), and 67 (41–86) years in the control group (n = 100) ($p = 0.001$). There were 49 (49 %) men in the control group, 92 men (46 %) in the POAG group, and 7 men (32 %) in the PACG group ($p = 0.342$). The PACG group was younger than the POAG and control groups ($p < 0.05$).

The difference in WBC, neutrophils, lymphocytes and NLR between POAG, PACG and control groups was not statistically significant ($p = 0.237$, $p = 0.249$, $p = 0.089$ and $p = 0.076$, respectively). A significant difference was found in terms of PLT and PLR levels between three groups ($p < 0.001$ and $p < 0.001$, respectively).

We also compared the results between pairs of groups as follows: POAG and controls; PACG and controls; POAG and PACG. The values of platelets, NLR and PLR were significantly higher in the POAG group than in the control group ($p = 0.025$; $p = 0.035$ and $p < 0.001$, respectively). PLR and platelets were significantly higher in the PACG group than in the control group ($p = 0.023$; $p = 0.041$, respectively). Moreover, there were no differences in NLR or PLR between POAG and PACG ($p = 0.869$ and $p = 0.559$, respectively). The PACG group was significantly younger than the POAG group ($p = 0.002$).

Tab. 1. Comparison of demographic and laboratory parameters between three groups

Variables	POAG (n=200)	PACG (n=22)	Control (n=100)	p
Age (y)	70 (40–85)	57 (42–89)	67 (41–86)	0.001*
Sex (male/female)	92/108	7/15	49/51	0.342
WBC (10^3/mL)	6.40 (4–15)	7.06 (4.77–8.25)	6.66 (4.57–9.81)	0.237
Neutrophil (10^3/mL)	3.81 (2.03–11.00)	4.25 (2.51–6)	4.03 (2.09–7.60)	0.249
Lymphocyte (10^3/mL)	1.80 (0.61–3.88)	1.87 (1.04–2.96)	1.96 (0.83–2.13)	0.089
Platelet (10^3/mL)	261 (121–520)	256.50 (204–329)	234.50 (106–359)	0.001*
NLR	2.19 (0.79–13.23)	2.27 (1.39–3.88)	2.08 (0.20–6.73)	0.076
PLR	147.77 (61.63–412.9)	139.63 (82–269.2)	109.95 (12.30–304.8)	0.001*

Data are expressed as the median (min–max) or number of cases as appropriate. p-values were calculated using Kruskal-Wallis, Mann-Whitney U test and $\chi 2$ as appropriate. n=the number of patients; POAG, primary open angle glaucoma; PACG, primary angle closure glaucoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; WBC, white blood cells. *$p < 0.05$

Tab. 2. Comparison of NLR and PLR between POAG and control.

Variables	POAG (n=200)	Control (n=100)	p
NLR	2.19 (0.79–13.23)	2.08 (0.20–6.73)	0.035*
PLR	147.77 (61.63–412.9)	109.95 (12.30–304.8)	0.001*

POAG – primary open angle glaucoma; NLR – neutrophil–to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; * $p < 0.05$

Tab. 3. Comparison of NLR and PLR between PACG and control.

Variables	PACG (n=22)	Control (n=100)	p
NLR	2.27 (1.39–3.88)	2.08 (0.20–6.73)	0.100
PLR	139.63 (82–269.2)	109.95 (12.30–304.8)	0.023*

PACG – primary angle closure glaucoma; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; * $p < 0.05$

Tab. 4. Comparison of NLR and PLR between POAG and PACG.

Variables	POAG (n=200)	PACG (n=22)	p
NLR	2.19 (0.79–13.23)	2.27 (1.39–3.88)	0.869
PLR	147.77 (61.63–412.9)	139.63 (82–269.2)	0.559

POAG – primary open angle glaucoma; PACG – primary angle closure glaucoma; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio

Discussion

We found that platelets and PLR levels were significantly higher in both the POAG and PACG groups than in the control group, whereas NLR levels were significantly higher only when comparing the POAG and control groups. NLR levels were also higher in the PACG group when compared to the control group; however, this difference was not statistically significant.

Neutrophils, lymphocytes and platelets are easily determined by a CBC assay. These blood cells serve a significant role in the control of inflammation. The systemic inflammation is associated with alterations in the quantity and composition of circulating blood cells such as thrombocytosis, lymphopenia and neutrophilia (29). Since NLR and PLR are calculated manually from neutrophils, lymphocytes and platelet levels, they are supposed to be worthwhile in the management of diseases related to inflammation.

NLR and PLR values were not widely being used in ocular diseases until their positive role in determining the severity of certain diseases was demonstrated. For instance, Karaca et al demonstrated that the NLR value was capable of predicting keratoconus progression in patients (30). Furthermore, Huang et al evaluated serum cytokine levels in patients with POAG and claimed that higher cytokines were associated with optic neuropathy in POAG (31).

However, relatively few studies have evaluated NLR and PLR in patients with glaucoma. Similar to our results, Ozgonul et al observed higher levels of NLR and PLR in the POAG group than in the control group (25). Moreover, Li et al demonstrated that NLR values were higher in patients with PACG than in controls (32). In agreement with Li's findings, we also observed higher NLR values in the PACG group when compared to the control group; however, our findings did not reach the significance level.

Platelets are blood cells that initiate the release of inflammatory mediators by interacting with endothelial cells and leukocytes. In the process of inflammation, megakaryocytic proliferation and relative thrombocytosis occur. Moreover, increased platelet counts may be more likely to form platelet-rich vascular thrombi on atherosclerotic plaques in the coronary artery and/or peripheral arterial tree (33). PLR has been found to be an independent indicator of adverse medical conditions such as tissue ischemia in patients with acute myocardial infarction (34). One of the possible molecular mechanisms for POAG is thought to be ischemia in the optic nerve. Furthermore, chronic circulatory impairment in the optic nerve head (ONH) causes irreversible damage to the retinal ganglion cells (6, 35). In our study, according to the finding of higher platelets and PLR values in the POAG and PACG groups, we suggest that platelets may play a role in both initiating inflammation and micro-plaque formation, thereby altering the blood supply of ONH.

The main limitation of this study is the lack of data on patients' history of medicine intake, co-morbidities, inflammation markers and/or inflammatory cytokines (e.g., CRP, MCP-1). The study design is another limitation since it is a retrospective and single-centre study. Moreover, the lack of measurements from Doppler ultrasonography and fundus fluorescein angiographic findings evaluating the presence of any abnormalities in vascular structures associated with the optic nerve represents another limitation.

In conclusion, higher serum platelets and PLR levels indicate that systemic inflammatory responses may be involved in both POAG and PACG pathogenesis. The use of systemic anti-inflammatory as well as anti-coagulant agents in glaucoma patients should be further investigated while managing glaucomatous optic neuropathies.

Learning points

- This is the first clinical study evaluating the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in both the primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) in a single study.
- The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inexpensive biomarkers obtained from complete blood count.
- It is found that PLT and PLR levels were significantly higher in both the POAG and PACG groups than in the control group,
- Vascular dysfunction that causes ischemia in the optic nerve is one of the major causes for the development and progression of glaucoma. Similarly, the higher levels of platelets and PLR may also indicate that systemic inflammation may play a role in the pathogenesis of POAG and PACG.
- This study adds new insight to the possible mechanisms of glaucoma.
- Future studies should be planned for the affectivity of anti-inflammatory as well as anti-coagulant treatment strategies in glaucoma patients

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