Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Novel Biomarkers of Primary Open-Angle Glaucoma

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Purpose: We aimed to assess the levels of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with primary open-angle glaucoma (POAG) and to compare the NLR and PLR results of patients with POAG and ocular hypertension, as well as in healthy controls.

Patients and Methods: Eighty-four patients with POAG, 94 patients with ocular hypertension, and 80 healthy subjects were enrolled in this retrospective study. Complete ophthalmological examination and complete blood count measurements were performed for all subjects.

Results: There was a significant difference in the NLR ($P = 0.003$) and PLR ($P = 0.049$) between POAG and control groups. In addition, there was a correlation between pattern standard deviation and NLR in the POAG group. The receiver operating characteristics analysis revealed that the value of NLR to distinguish patients with POAG and controls was found to be 0.651. The best cutoff value was 2.1, with a sensitivity of 65% and a specificity of 65%.

Conclusions: Our study for the first time provides evidence that NLR and PLR may be useful as biomarkers in patients with POAG.

Key Words: inflammation, neutrophil-to-lymphocyte ratio, ocular hypertension, platelet-to-lymphocyte ratio, primary open-angle glaucoma

(*J Glaucoma* 2016;25:e815–e820)

Glaucoma is a neurodegenerative disease that leads to progressive optic disc atrophy and visual field defects, and it is usually associated with an elevated intraocular pressure (IOP), which is a known risk factor for disease progression that can result in irreversible blindness.[1] Progressive degeneration of retinal ganglion cells and their axons is the primary cause of glaucomatous visual loss. In glaucoma, aqueous humor drainage through the trabecular meshwork largely determines the IOP, and an elevated IOP is a result of trabecular meshwork resistance to aqueous outflow. Nevertheless, approximately one-third of patients with glaucoma exhibit normal IOP.[2] Moreover, a substantial number of primary open-angle glaucoma (POAG) cases continue to progress despite therapeutically lowered IOP. The culmination of these observations has spurred further research to determine the existence of other possible risk factors for glaucoma.[2] The events that compose the molecular pathogenic mechanisms that are responsible for glaucoma are not yet fully understood, but there is also growing evidence that an autoimmune and inflammatory mechanism is involved in the development and progression of this disease. Recent studies suggest that antibodies against ocular antigens, such as heat-shock proteins, tumor necrosis factor-α, and glycosaminoglycans, are possible neurodegenerative factors in glaucomatous eyes.[3–9] In addition, IgG antibodies against retinal antigens in POAG, normotensive glaucoma, and ocular hypertension (OHT) patients were determined as the evidence of an autoimmune mechanism involved in the development of glaucoma.[10] Significant alterations of serum cytokines are associated with glaucoma, suggesting the possibility that abnormal immune environments contribute to the glaucomatous neuropathy of POAG.[11,12] These studies provide critical data of alterations of different immune mediators measured in blood, aqueous humor, or eye tissues supporting abnormal activity of the immune system, and thus the potential role for inflammation as an initiating or exacerbating etiology in some patients with POAG should be assessed.[13]

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are easy-to-analyze inflammation biomarkers derived from complete blood count (CBC), which have usually been investigated as predictors of prognosis of several cancers, cardiovascular and inflammatory diseases, rheumatoid arthritis, and hepatopancreaticobiliary malignancies in recent studies.[14–18] Although papers from the ophthalmology clinics related to NLR and PLR have a trend of increase and they have rose to prominence as an early biomarker of some ocular diseases such as retinal vein occlusion (RVO), age-related macular degeneration (AMD) and keratoconus, studies investigating the predictive value of these markers in the progression and prognosis of patients with POAG are limited.[19–22] Moreover, there is no consensus on the ideal biomarker to assess the inflammation, which has a crucial role in the development and progression of glaucoma.

Because of the need for an ideal biomarker and considering the role of inflammation in POAG, we aimed to investigate the value of NLR and PLR levels in predicting the diagnosis and prognosis of patients with POAG and OHT as simple and easily accessible indicators of subclinical inflammation.

Received for publication July 3, 2015; accepted January 28, 2016.
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DOI: 10.1097/IJG.0000000000000392

PATIENTS AND METHODS

This retrospective study was approved by the local ethics committee of Gulhane School of Medicine, which was conducted according to the Helsinki II Declaration. The data were obtained from patients' medical records between January 2009 and March 2015.

Study Population

We reviewed 314 patients' files. After the initial assessment of the records, we excluded 21 patients for the lack of visual field records and 35 patients regarding failure to reach CBC results. Finally, 84 patients with POAG, 94 patients with OHT, and 80 age-matched and sex-matched senile cataract patients without glaucoma as controls were enrolled in the study. All patients' complete ophthalmological examination including best-corrected visual acuity, anterior segment and fundus examination, gonioscopic evaluation of the anterior chamber angle, IOP measurement by Goldmann applanation tonometry and automated perimetry (Humphrey Field Analyzer, Carl Zeiss Meditec Inc., Dublin, CA), pattern standard deviation (PSD), and CBC parameters were noted.

POAG was defined as follows: 21 mm Hg or higher IOP, open angles on gonioscopy, typical glaucomatous optic disc damage, and glaucomatous visual field defects with Swedish Interactive Threshold Algorithm Standard strategy, program 24-2 visual field test. Typical glaucomatous visual field loss was characterized by nasal steps, arcuate defects, paracentral scotoma, and temporal wedge constantly confirmed with at least 2 different visual field tests. We defined typical optic disc damage as follows: rim thinning, notching, baring, hemorrhages, and increasing excavation of the optic cup with no pallor. The diagnosis of OHT was made if IOPs were >21 mm Hg on 2 separate occasions, with normal optic disc appearance and no visual field loss using Swedish Interactive Threshold Algorithm Standard strategy, program 24-2. All patients enrolled in the control group had senile cataracts without glaucoma.

Inclusion criteria were as follows: 20/40 or better best-corrected visual acuity, within $\pm$ 5.0 D spherical correction, and $\pm$ 3.0 D cylinder correction. The exclusion criteria were as follows: history of ocular surgery, ocular trauma, ocular manifestations other than glaucoma and cataract, secondary causes of high IOP (eg, pseudoexfoliation, pigment dispersion syndrome, iridocyclitis, trauma), major systemic diseases (diabetes, renal or hepatic disease, hematologic and autoimmune disorders, arteriosclerotic/cardiovascular disease) that could probably affect the NLR and PLR levels, neurological diseases possibly affecting visual field, and any special drug use (eg, iron preparations, chemotherapeutic agents, vitamins, corticosteroids) that could influence the CBC measurements.

Laboratory Assessment

On admission, venous blood samples were obtained from the antecubital vein, and CBC measurements were performed within 2 hours after blood collection with an automated blood cell counter (ABX Pentra 120, Horiba, Japan). Levels of neutrophils, lymphocytes, platelets, red blood cells, and white blood cells were measured as part of the automated CBC. The NLR and PLR were calculated as the ratio of the neutrophils to lymphocytes and that of platelets to lymphocytes.

Statistical Analysis

The Statistical Package for the Social Science version 16.0 software (SPSS, Chicago, IL) was used to conduct the statistical analyses. Anthropometric and biochemical features were categorized as categorical variables or continuous variables. Comparisons between the groups were made using the Student t test or Mann-Whitney U test as appropriate. Categorical variables were compared using the χ^2 test. One-way ANOVA and Kruskal-Wallis variance analysis were used for multigroup comparison of continuous variables. If the differences were significant, pairwise comparisons would be based on the Mann-Whitney U test or Student t test with Bonferroni correction to establish which subgroups were different. Correlation analyses were performed with Pearson's correlations. All of the reported P-values were 2-tailed, and those <0.05 were considered to be statistically significant. Receiver operating characteristic (ROC) analysis was also performed to determine the cutoff threshold and to quantify the accuracy of NLR and PLR. Sensitivity, specificity, and the area under the ROC (AUROC) curve were used for an overall estimation of the accuracy of the classifier.

RESULTS

The comparison of anthropometric and laboratory features of patients with OHT, POAG, and control groups

TABLE 1. Comparison of Demographic and Laboratory Parameters Between 3 Groups

Variables	Control (n = 80)	OHT (n = 94)	POAG (n = 84)	*P*
Age (y)	68 ± 10	68 ± 8	70 ± 10	0.315
Sex (male/female)	39/41	40/54	33/51	0.463
WBC ($10^3/\mu L$)	6.92 ± 1.52	6.63 ± 1.73	6.92 ± 1.62	0.395
Neutrophil ($10^3/\mu L$)	4.09 ± 1.06	4.30 ± 1.36	4.47 ± 1.19	0.137
Lymphocyte ($10^3/\mu L$)	2.11 (0.70)	1.97 (0.70)	1.89 (0.76)	0.189
Platelet ($10^3/\mu L$)	244 (85)	265 (97)	255 (75)	0.200
NLR	1.98 (0.73)[a]	2.12 (0.92)	2.33 (0.90)	**0.005**
PLR	118.5 (64.7)[b]	132.2 (61.3)	136.2 (61.6)	**0.034**

Data are expressed as the mean ± SD, median (interquartile range), or number of cases as appropriate.

P-values were calculated using Student t test, Mann-Whitney U test and χ^2 as appropriate.

N indicates the number of patients; NLR, neutrophil-to-lymphocyte ratio; OHT, ocular hypertension; PLR, platelet-to-lymphocyte ratio; POAG, primary open-angle glaucoma; WBC, white blood cells.

The bold indicate the statistically significant *P* values.

[a] $P = 0.003$ versus POAG.

[b] $P = 0.049$ versus POAG.

is shown in Table 1. The mean age was 68 ± 10 years in the control group (n = 80), 68 ± 8 years in the OHT group (n = 94), and 70 ± 10 years in the POAG group (n = 84) ($P = 0.315$). There were 39 (49%) men in the control group, 40 men (43%) in the OHT group, and 33 men (39%) in the POAG group ($P = 0.463$). A significant difference was found in terms of NLR and PLR levels between 3 groups, with *P*-values of 0.005 and 0.034, respectively. Comparison of the groups with post hoc tests revealed a significant difference between POAG and control groups in terms of NLR ($P = 0.003$) and PLR ($P = 0.049$) (Fig. 1).

Comparison of IOPs and PSD between the 2 groups is shown in Table 2. Mean IOP was 26 ± 4 mm Hg in the OHT group and 29 ± 5 mm Hg in the POAG group ($P = 0.006$). Median PSD of the POAG group was 2.38 (5.34). Correlation analysis revealed significant correlations between PSD and NLR ($P = 0.014$, $r = 0.310$), as well as between mean deviation (MD) and NLR ($P = 0.018$, $r = 0.292$) in the POAG group, as shown in Figure 2. There was no significant correlation between MD and PLR, as well as PSD.

The ROC analyses of the studied variables are shown in Figure 3. According to this, the AUROC value of the NLR to distinguish patients (POAG, n = 84) and senile cataract patients without glaucoma (n = 80) was found to be 0.651. The best cutoff value was 2.1, with a sensitivity of 65% and a specificity of 65% (Fig. 3A). A secondary ROC analysis was also performed to distinguish POAG patients (n = 84) and OHT patients (n = 94). According to this, the AUROC value of NLR to distinguish patients with POAG and OHT was found to be 0.574. The cutoff value was 2.1, with a sensitivity of 65% and a specificity of 52% (Fig. 3B). In addition, the AUROC value of the PLR to distinguish POAG patients from senile cataract patients and OHT patients was 0.608 and 0.526, respectively. Both had a cutoff value of 116 with a sensitivity of 70% and 70% and a specificity of 50% and 36%, respectively (Figs. 3A, B).

TABLE 2. Comparison of IOPs Between the 2 Groups and PSD of the POAG Group

Variables	OHT (n = 94)	POAG (n = 84)	*P*
IOP (mm Hg)	26 ± 4	29 ± 5	**0.006**
PSD	0.97 (1.14)	2.38 (5.34)	**0.005**

Data are expressed as the median (interquartile range).
P-values were calculated using Mann-Whitney *U* test.
The bold indicate the statistically significant *P* values.
IOP indicates intraocular pressure; N, number of patients; OHT, ocular hypertension; POAG, primary open-angle glaucoma; PSD, pattern standard deviation.

DISCUSSION

To the best of our knowledge, this study showed for the first time that patients with POAG have increased NLR and PLR levels compared with controls. In addition, correlation results suggest that there was a positive correlation between PSD, an indicator of glaucomatous visual field defects, and NLR. In addition, ROC analysis showed that the sensitivity of NLR and PLR was >65%, with cutoff values of 2.1 and 116, respectively. However, the specificity of PLR was relatively low (50%) in distinguishing POAG patients from senile cataract patients.

The studies to uncover the exact mechanisms underlying the pathogenesis of POAG are still ongoing. In a study that was aimed to determine C-reactive protein levels in patients with normotensive glaucoma, higher C-reactive protein levels were found to be associated with normotensive glaucoma, and the vascular inflammatory process involved in the etiology of this glaucoma was proposed as a possible mechanism.[23] In another study aiming to assess the proinflammatory cytokine profile of aqueous humor from glaucomatous eyes, increased concentrations of interleukin (IL)-9, IL-10, and IL-12 were determined in patients with POAG compared with the cataract group, and increased levels of these cytokines were claimed to be associated with activation of leukocytes in glaucomatous eyes.[24] As is known, increased tumor necrosis factor-α and IL-10 levels lead to a decrease in the lymphocyte count, as well as lymphocyte dysfunction, while increasing neutrophil function.[25,26] This deems markers such as NLR and PLR worthwhile in the diagnosis and follow-up of diseases accompanied by inflammation. These studies also reveal that chronic subclinical inflammation may constitute the pathophysiological basis for our present findings. In the current study, we found that NLR and PLR levels were significantly higher in the POAG group than in controls, whereas mean NLR and PLR levels were also higher in the OHT group than in controls; however, it was not statistically significant.

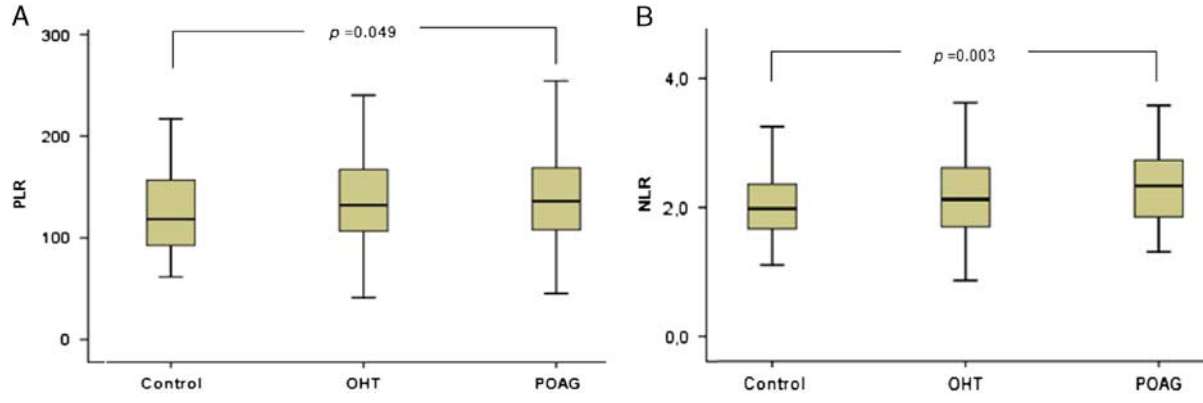

FIGURE 1. A, Comparison of 3 groups in terms of NLR ($P = 0.005$); comparison of control versus POAG ($P = 0.003$). B, Comparison of 3 groups in terms of PLR ($P = 0.034$); comparison of control versus POAG ($P = 0.049$). NLR indicates neutrophil-to-lymphocyte ratio; OHT, ocular hypertension; PLR, platelet-to-lymphocyte ratio; POAG, primary open-angle glaucoma.

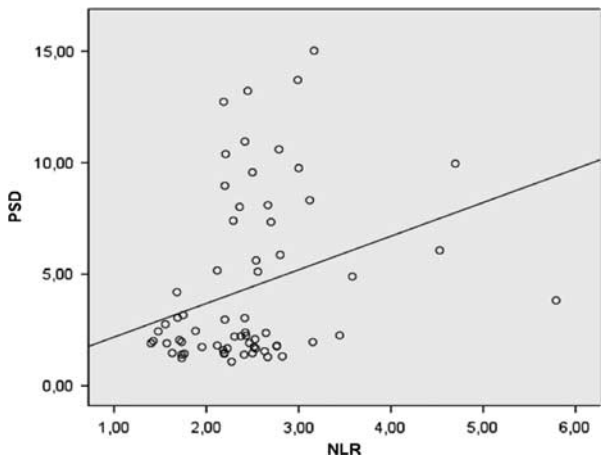

FIGURE 2. Correlation between neutrophil-to-lymphocyte ratio (NLR) and pattern standard deviation (PSD) in the primary open-angle glaucoma group ($P = 0.014$, $r = 0.310$).

As discussed above, alteration of different immune mediators measured in blood, aqueous humor, or eye tissues supports abnormal activity of the immune system in POAG. Nevertheless, it is not clear whether glaucomatous damage induces inflammation markers in the peripheric blood of patients or whether the inflammatory status of the patients induces glaucomatous damage. This issue has not been clarified by the current literature so far. However, the presence and persistence of inflammation is effective on prognosis. Therefore, specific inflammatory markers that can be used widely would be beneficial to follow-up these patients. As given in a recent study evaluating the predictive value of NLR in identifying the risk for RVO, NLR was found to be significantly higher in RVO patients compared with the controls.[19] In another study evaluating NLR in dry and wet AMD, patients with AMD were determined to have higher NLR values compared with controls, and NLR was correlated with disease severity.[20] In keratoconus patients in whom local inflammatory cascades are more prominent, NLR was significantly higher in patients with progressive keratoconus than in the nonprogressive group and controls.[21] In addition, according to 2 different studies performed in the patients with diabetic retinopathy (DR), which is secondary to a systemic metabolic disorder, diabetes mellitus, NLR values were found to be correlated with the presence of DR and DR grades.[22,27] All these findings prove that the prognostic value of NLR in ocular diseases that thought both local and systemic inflammatory cascades have critical roles in the pathophysiology. However, as in other system inflammation processes, the lack of specific inflammatory biomarkers creates a major shortcoming in ocular inflammatory pathologies. However, as we have shown in our study, particularly in risk groups and follow-up cases, a cutoff value of > 2.1 for NLR distinguishes 65% of patients with 65% sensitivity in monitoring disease development. In addition, this cutoff is also valuable to conduct patients to the advanced tests for definite diagnosis. At the same time, especially during the treatment process, we believe that this cutoff value may have a crucial role in determining the limitation of inflammation. Moreover, NLR cutoff value (> 2.1) was found in discrimination of POAG and OHT patients that the role of inflammation in etiopathogenesis is controversial over again with a sensitivity of 65%. However, the specificity of this cutoff value was 52%, and it was lower than that found in the discrimination of POAG and control groups. Nevertheless, when we evaluated PLR to distinguish POAG from OHT and control groups, the PLR cutoff value (> 116) was found with

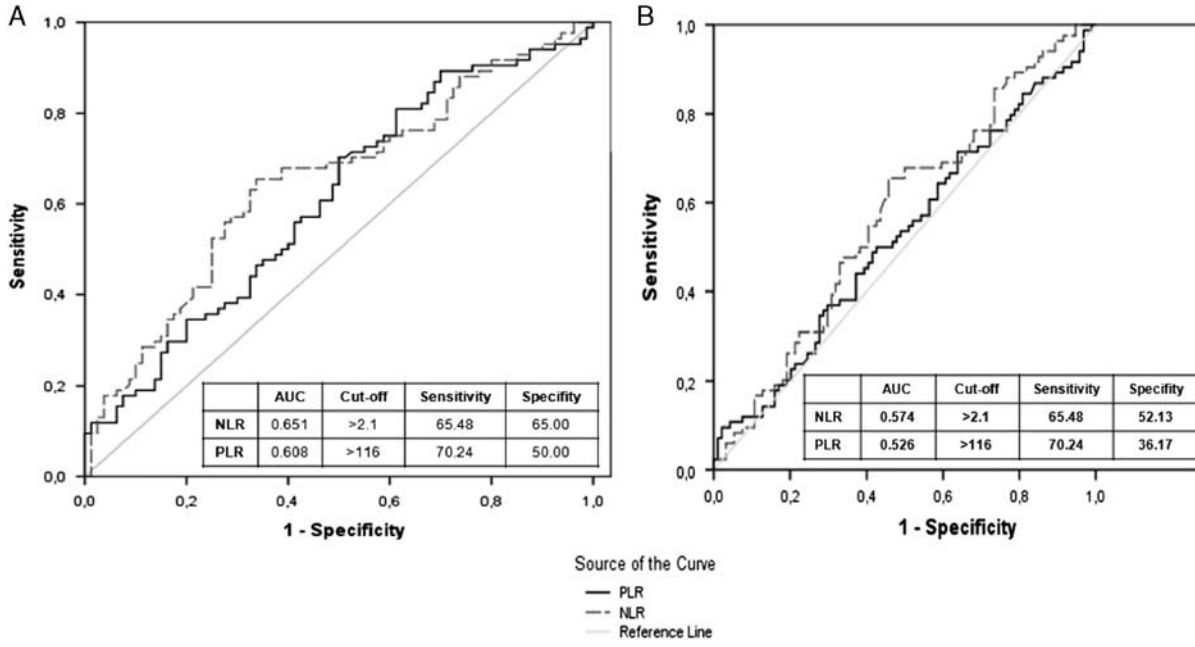

FIGURE 3. Receiver operating characteristics curve analysis for discrimination between (A) controls and primary open-angle glaucoma (POAG), (B) ocular hypertension and POAG. NLR indicates neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

a sensitivity of 70% (for both group) and specificities of 50% and 36%, which were lower than the specificities of NLR. The similar sensitivity levels of NLR and PLR cutoff values to distinguish POAG patients from OHT patients and controls prove the discriminative and prognostic power of these biomarkers once again. This also indicates that NLR and PLR have equivalent value to distinguish the POAG group from the others.

As is known, unlike POAG patients, neurodegeneration does not occur in OHT patients.[28] However, various studies have revealed different levels of IOP increases in OHT and POAG patients.[29] In the current study, a statistically significant difference was found between OHT and POAG groups in terms of IOP. Mean IOP was 26 ± 4 and 29 ± 5 mm Hg in OHT and POAG groups, respectively. We believe that these increased IOP levels probably lead to neurodegenerative conditions, which explain the higher NLR and PLR levels in POAG patients.

Visual field losses in patients with POAG may vary from complete tunnel vision to insensitive levels of losses. The median PSD was 2.38 (5.34) in our POAG patients, which means that typical glaucomatous visual field defects were present; however, the group comprised mild and moderate POAG patients. Therefore, we also believe that the NLR and/or PLR have the ability to predict the prognosis of POAG in earlier stages of the disease. In contrast, there are several studies that evaluated the relationship between visual field loss levels and inflammation in POAG patients. For example, in a study evaluating 40 POAG patients, increase in ET-1 levels was claimed to be related to the progression of both the visual field damage and vascular dysfunction, which was a result of subclinical intraocular inflammation.[30] Furthermore, in another study that aimed to assess visual field and serum cytokine profiles in a similar patient group, POAG patients with severe optic neuropathy as indicated by MD > 12 dB demonstrated significant differences in cytokine profiles from the POAG patients with MD < 12 dB.[12] Thus, we can make the inference that the visual field analysis shows the status of neurodegeneration of the optic nerve, and that it correlates with the inflammatory status in the blood of the POAG patients. Concordantly, we found a positive correlation between NLR and PSD.

The main limitation of our study is the lack of data on proinflammatory cytokines and/or inflammation markers such as C-reactive protein, which possibly have a key role in inflammation processes. Another limitation is the relatively small sample size. The present data should therefore be interpreted with caution and need reconfirmation in a larger cohort. Last, as is known, chronic use of topical antiglaucoma medication is associated with conjunctival and aqueous inflammation.[31] This could be a confounder in the interpretation of our results, and ideally blood samples obtained from newly diagnosed glaucoma patients before commencement of medical therapy would help determine the significance and role of chronic antiglaucoma medication on the detection of NLR and PLR as markers of inflammation.

In conclusion, considering the limited numbers of studies investigating the association between NLR/PLR and ocular diseases in the literature and despite the limitations indicated above, this is the first study evaluating NLR and PLR in patients with OHT and POAG, and this makes the results of our study more meaningful. Our study for the first time provides evidence that PLR and NLR may be useful for predicting the prognosis of POAG patients. These results leadingly may prove the beneficial effects of the value of NLR and PLR to make the diagnosis and to predict the prognosis of patients with POAG. However, larger study populations are needed to improve our knowledge about the mechanisms that have a role in chronic low-grade inflammation in patients with POAG.

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