

Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as inflammation markers in patients with papilledema due to idiopathic intracranial hypertension

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Purpose: The aim of this study was to investigate the role of inflammation in the pathogenesis of idiopathic intracranial hypertension (IIH) using the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as inflammation markers. **Methods:** The files of 33 IIH patients and 33 controls were screened for this retrospective study. For each patient, the NLR and PLR values were calculated using a single fasting blood sample. For both eyes, papilledema (PE) grades, best-corrected visual acuity (BCVA), retinal nerve fiber layer thickness (RNFLT), and ganglion cell layer thickness (GCLT) measurements were recorded along with the demographic data, including body mass index (BMI), and complete neurological and ophthalmological findings. Comparisons between the two groups and between the IIH patients with and without PE were made. The associations of NLR and PLR with all other parameters were analyzed independently from age, gender, and BMI. **Results:** NLR and PLR were higher in patients with IIH than controls ($P < 0.05$). They were also higher in patients with PE ($P < 0.05$) in the IIH group. NLR and PLR were found to be associated with BCVA ($P < 0.001$ and $P = 0.023$, respectively), global RNFLT ($P = 0.004$ and 0.012 , respectively), RNFLT of the temporal quadrant ($P < 0.001$ and $P = 0.042$, respectively) and PE grade ($P < 0.001$ and $P = 0.035$, respectively). **Conclusion:** The NLR and PLR values and their associations with BCVA, RNFLT, and PE support the hypothesis that inflammation is a very important component of the pathogenesis of IIH.

Key words: Idiopathic intracranial hypertension, inflammation, papilledema, retinal nerve fiber layer thickness

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by increased intracranial pressure (ICP). IIH is strongly associated with female gender and obesity. The most common symptoms of this disorder are headache, neck pain, pulsatile tinnitus, visual loss, and diplopia.^[1-4] IIH was once accepted as a benign disorder; however, significant comorbidities, such as vision loss and chronic headache causing reduced quality of life suggest otherwise.^[5,6] The pathogenesis of IIH remains unclear but there are three possible mechanisms that could alter the cerebrospinal fluid (CSF) physiology: CSF hypersecretion, CSF outflow obstruction, and increased venous sinus pressure. Researchers have also considered that metabolic and hormonal factors^[7-9] and genetics^[10] could play significant roles in the pathogenesis of IIH, as well as inflammation. There are several studies that found evidence of low-grade inflammation's role in IIH, especially in obese females.^[11] And, researchers suggested that some pro-inflammatory adipokines may be used as prognostic markers in IIH.^[12]

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Currently, the modified and revised Dandy criteria are used for the diagnosis of IIH,^[13,14] papilledema (PE) is a diagnostic hallmark. The Frisén scale is utilized for grading PE, and visual field (VF) testing and optical coherence tomography (OCT) are very important tests for the diagnosis and follow-up of patients.^[6,15] Peripapillary OCT has been widely used for the diagnosis of PE and plays an important role in decisions concerning treatment. The associations between the retinal nerve fiber layer thickness (RNFLT) and ICP have been presented in previous studies.^[15,16]

Research has shown that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are useful inflammatory markers for many systemic and ocular chronic diseases, and they are associated with the prognosis of various disorders.^[17-19] Many inflammatory markers and pro-inflammatory cytokines such as IL-1 β , IL-8, TNF α , INF γ , IL-4, IL-10, IL-12, and IL-17 have been found to be associated with IIH^[12,20-23] but to the best of our knowledge, to date, NLR and PLR have not been evaluated in terms of

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their relationship with IIH. Therefore, this study aimed to investigate the associations of NLR and PLR with PE and RNFLT measurements in patients with IIH.

Methods

This retrospective observational study was carried out in accordance with the principles of the Declaration of Helsinki after obtaining the approval of the Non-Interventional Clinical Research Ethics Committee of Dışkapi Yildirim Beyazıt Training and Research Hospital. The files of the IIH patients that presented to the outpatient clinic of Dışkapi Yildirim Beyazıt Training and Research Hospital Neurology Department and were referred to the Ophthalmology Department for consultation between February 2018 and February 2020 were screened.

The patients over 18 years old, who were diagnosed with IIH in accordance with the Friedman *et al.*'s revised diagnosis criteria^[14] [Table 1], and had complete neurological and ophthalmological examinations were included in this study as the patient group. Other sex, age, and body mass index (BMI) matched individuals who presented with a headache complaint and scanned for IIH in the neurology and ophthalmology clinics, and therefore had all the recorded data we need for this study, but received a diagnosis of tension-type headache were included as the control group. Excluded from the study were patients with a refractive error greater than ± 3 D, those with ocular pathologies (cataract, glaucoma, corneal and retinal diseases, or ocular surgery history), those with neurological disorders other than IIH or tension-type headache, those with BMI greater than 30 kg/m² (obesity itself is a reason of low-grade chronic inflammation^[24]), those with systemic diseases and those using systemic drugs that could cause changes in the ocular and neurological physiology and ICP (diabetes mellitus, connective tissue diseases, autoimmune diseases, isotretin, and minocycline use). The patients who had received any treatment prior to the first examination and those that did not

attend the second visit were also excluded from the study. The participants were stratified into the IIH and control groups based on the results of all parameters.

Clinical data

The demographic data of all participants were recorded. In the neurology department, the findings of brain magnetic resonance imaging (MRI, Table 1 and Fig. 1) and magnetic resonance venography (MRV) with contrast undertaken for differential diagnosis, the results of complete blood count (CBC) analysis, and BMI were recorded. Before lumbar puncture, which was done using bedside surface landmark technique, and one month after starting treatment, all the patients were referred to the ophthalmology clinic for PE screening. For the treatment, acetazolamide 1 to 3 g per day was used for the patients with mild visual loss, furosemide (20–40 mg) was used when acetazolamide was not tolerated. If the acetazolamide and furosemide fail, topiramate (1,5–3,0 mg/kg/day) was used for the treatment. For the patients with severe or progressive visual loss, optic nerve sheath decompression or shunt surgeries along with high-dose intravenous steroids were considered.^[25] All the participants' complete ophthalmological examination data, including Log-MAR-converted best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp biomicroscopy and non-dilated funduscopy findings along with the results of visual field testing (Humphrey Field Analyzer II, Carl Zeiss Meditec) and RNFLT analyses (Avanti SD-OCT, RTVue, Optovue Inc., Fremont, California) of both eyes were recorded at two visits. In addition, for the patients with PE, the Frisén scale was used for grading.^[26,27]

RNFLT and GCLT measurement

A RTVue XR 100°CT (software v6.1, Optovue Inc., Fremont, CA, USA) device was used in the analysis of RNFLT. This device generates 70,000 A-scan per second using a light source of 840 nm wavelength. While performing the RNFLT measurements, after the confocal scanner focusing on the

Table 1: Diagnostic criteria of IIH

1. Required for diagnosis of IIH.
 - a- Papilledema
 - b- Normal neurologic examination except for cranial nerve abnormalities.
 - c- Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used.
 - d- Normal CSF composition
 - e- Elevated lumbar puncture opening pressure (>250 mm CSF in adults and >280 mm CSF in children [>250 mm CSF if the child is not sedated and not obese]) in a properly performed lumbar puncture
2. Diagnosis of IIH without papilledema.
 - a- In the absence of papilledema, a diagnosis of IIH can be made if b-e from above are satisfied, and in addition the patient has a unilateral or bilateral abducens nerve palsy
 - b- In the absence of papilledema or sixth nerve palsy, a diagnosis of IIH can be suggested but not made if b-e from above are satisfied, and in addition at least 3 of the following neuroimaging criteria are satisfied:
 - i. Empty sella
 - ii. Flattening of the posterior aspect of the globe
 - iii. Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
 - iv. Transverse venous sinus stenosis

Adapted from the 2013 revised diagnostic criteria.^[14] IIH; idiopathic intracranial hypertension, MRI; magnetic resonance imaging, CT; computerized tomography, CSF; cerebrospinal fluid

optical disc (OD) created the ophthalmoscope image, a circle of 3.45 mm in diameter centering the OD was placed, and a series of images were obtained at high resolution. The mean RNFLT was automatically calculated using the embedded software. For each case, the global RNFLT and the RNFLT values of the superior, nasal, inferior, and temporal quadrants were recorded. The mean ganglion cell layer thickness (GCLT) was also determined from the analyses.

Laboratory testing

Fasting venous blood samples were collected from all the participants. CBC measurements were performed on an automated hematology analyzer (Sysmex Corporation, Kobe 651-0073, Japan). The NLR values were calculated by dividing the neutrophil count by the lymphocyte count, and the PLR values with the same method using the platelet count instead of neutrophil count.

Statistical analyses

Quantitative variables were described as mean and standard deviation (SD), and qualitative variables as percentages. Power calculation was not executed as the study was exploratory. The individuals with missing data were excluded from the analyses. The Shapiro-Wilk test was used to determine whether the sample came from a normally distributed population. According to the results of the normality test, Student's *t* test or Mann-Whitney U test was used to compare the IIH patients and controls in terms of the NLR and PLR values, and the paired *t* test or related-samples Wilcoxon signed-rank test was conducted for the comparison of the results of the BCVA, PE grade, RNFLT, and GCLT between the first and second visits. To explain the inter-eye effects within

the same individual, a single age-, gender- and BMI-corrected generalized estimating equation (GEE) model with a working correlation matrix "independent" was created for each eye parameter (BCVA, PE grade, RNFLT, and GCLT values) as a dependent variable, and the group of the individual was taken as the main effect (ordinal factor). GEE models were also used to check the independent associations of NLR and PLR with the same eye parameters. The GEE results were obtained with regression coefficient (B) and 95% Wald confidence interval (CI) values.

All statistical analyses were performed using SPSS v. 21 (SPSS, Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

Demographic features and clinical data

Eighty eyes of 40 IIH patients and 66 eyes of 33 controls were screened for this study. Of those 80 eyes, 24 eyes had grade 1 PE, 20 had grade 2, 15 had grade 3, and 11 had grade 4, while 10 eyes did not have any PE (grade 0). Control subjects had not been referred to the ophthalmology clinics for PE screening for the second visit after they were diagnosed as tension-type headache. Therefore, control subjects did not have the second visit's data. Seven patients (14 eyes) from the IIH group were excluded because they did not meet the inclusion criteria (due to a refractive error greater than ± 3 D in one, glaucoma in one, autoimmune diseases in two, diabetes mellitus in two, and missing follow-up visit in one). All 33 IIH patients had fulfilled the diagnosis criteria. Thirty (60 eyes) of those 33 had PE. Remaining 3 patients (6 eyes) did not have PE, they had fulfilled the diagnostic criteria due to having abducens nerve palsy at least in one eye. All the patients received medical therapy for the treatment, surgery (optic nerve sheath decompression) was considered for only one patient; however, the patient did not consent to surgery. The groups were similar in terms of age, gender, and BMI. Medical histories of the study subjects were not remarkable. The demographic data and clinical characteristics of the study subjects are presented in Table 2.

There was a significant decrease in the PE grade of the patients at the second visit ($P < 0.001$, paired *t* test). There was also a decrease in the Log-MAR-converted BCVA; however, the difference between the first- and second-visit BCVA values was not significant ($P = 0.147$, paired *t* test).

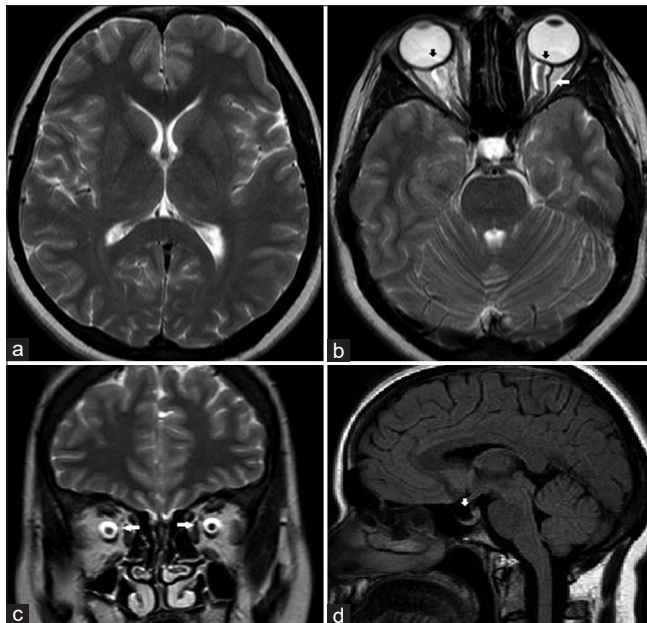


Figure 1: Magnetic resonance images of the brain of an idiopathic intracranial hypertension patient with a grade 4 papilledema. Narrowing of the bilateral third and lateral ventricles in axial T2-weighted image (a), distension of the perioptic subarachnoid space with bilateral optic nerve tortuosity which was more clear at the left (white arrow), and bilateral scleral flattening at the posterior pole of the globe (black arrows) (b), bilateral distension of the perioptic subarachnoid space in coronal T2-weighted image (white arrows) (c), moderate expansion of the sella and decrease in adenohypophysis height (white arrow) (d)

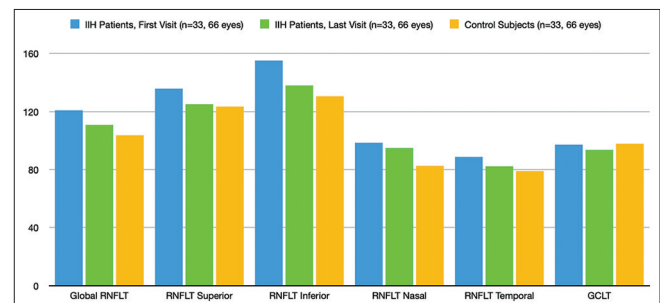


Figure 2: The graphical illustration of the OCT measurements of the study groups. IIH: idiopathic intracranial hypertension, RNFLT; retinal nerve fiber layer thickness, SD; standard deviation, GCLT; ganglion cell layer thickness

The CSF sample contents' distribution was completely normal for all of the IIH patients and no oligoclonal band was observed in CSF samples.

RNFLT and GCLT analyses

The RNFLT and GCLT values of the patients and controls are given in Table 3 and Fig. 2. At the first visit, the global RNFLT and the RNFLT of all quadrants were significantly greater in the IIH group than in the control subjects ($P < 0.05$, GEE). The difference in the GCLT between the groups was not significant ($P = 0.791$, GEE). For the IIH group, the RNFLT values were thinner at the second visit compared to the first measurements; however, the decrease in RNFLT was not significant enough for the nasal and temporal quadrants ($P = 0.064$ and 0.054 , respectively, paired t test). GCLT was also significantly thinner at the second visit compared to the first measurements ($P = 0.004$, paired t test).

Laboratory findings

The neutrophil, platelet, and lymphocyte counts and the NLR and PLR values derived from these counts are presented

in Table 4. All of the parameters investigated, except the lymphocyte count significantly differed between the two groups ($P = 0.099$, Mann-Whitney U test). None of the study subjects had leukocytosis. The NLR and PLR values were greater in the IIH group than in the control group ($P = 0.001$ and 0.016 , respectively, Student's t test).

Associations of NLR and PLR

Greater NLR and PLR values were found to be associated with worse visual acuity (greater Log-MAR-converted BCVA) at the first visit ($B = 1.149$, 95% Wald CI = $0.631/1.668$, $P < 0.001$ for NLR and $B = 23.681$, 95% Wald CI = $0.007/50.368$, $P = 0.049$ for PLR, GEE); however, these two parameters did not have any association with the BCVA obtained at the second visit ($P = 0.055$ for NLR and 0.132 for PLR, GEE).

The NLR and PLR values were found to be associated with the presence of PE in the IIH group ($B = 0.570$, 95% Wald CI = $0.226/0.914$, $P = 0.001$ for NLR and $B = 22.658$, 95% Wald CI = $3.129/42.188$, $P = 0.023$ for PLR, GEE). Both values were also

Table 2: Demographic data and clinical characteristics of the study groups

	IIH Group (n=33, 66 eyes)	Control Group (n=33, 66 eyes)	P
Age (years±SD)	35.03±11.02	36.74±9.90	0.457*
Female (n/%)	29/88%	28/85%	0.783**
BMI (kg/m ² ±SD)	25.9±3.4	26.1±3.6	0.373*
BCVA, first visit (LogMAR±SD)	0.167±0.353	0.0±0.0	0.006***
BCVA, second visit (LogMAR±SD)	0.145±0.263	n/a	-
PE, first visit (eyes/%)	52/78.7%	0/0%	<0.001***
PE, second visit (eyes/%)	34/51.1%	n/a	-
PE grade, first visit (mean/range)	1.53/0-4	0/0-0	<0.001***
PE grade, second visit (mean/range)	0.70/0-4	n/a	-

IIH; idiopathic intracranial hypertension, SD; standard deviation, BMI; body mass index, BCVA; best-corrected visual acuity, PE; papilledema, n/a; not applicable.

*The results of Student's t test, **The results of the Pearson Chi-square test, ***The results of the generalized estimating equations

Table 3: The RNFLT and GCLT measurements of the study groups

	IIH Group, First Visit (n=33, 66 eyes)	IIH Group, Second Visit (n=33, 66 eyes)	Control Group (n=33, 66 eyes)	P*/P**
Global RNFLT (μm±SD)	120.97±30.42	110.74±27.03	103.63±8.83	0.001/0.006
RNFLT Superior (μm±SD)	135.76±36.94	125.07±33.33	123.58±13.15	0.041/0.009
RNFLT Inferior (μm±SD)	155.32±42.26	137.96±27.68	130.64±17.85	0.001/0.001
RNFLT Nasal (μm±SD)	98.45±39.89	94.95±36.64	82.55±11.31	0.019/0.064
RNFLT Temporal (μm±SD)	88.71±27.51	82.12±26.69	78.95±10.87	0.034/0.054
GCLT (μm±SD)	97.13±12.88	93.71±11.25	97.73±5.00	0.791/0.004

IIH; idiopathic intracranial hypertension, RNFLT; retinal nerve fiber layer thickness, SD; standard deviation, GCLT; ganglion cell layer thickness. *The results of the generalized estimating equation models, comparison of the IIH patients with the controls. **The results of the paired t tests, comparison of the first visit to the second visit

Table 4: The CBC results of the study groups

	IIH Group (n=33)	Control Group (n=33)	P
Neutrophil (10 ² /μL)	5.06±1.47	4.21±1.40	0.002*
Platelet (10 ² /μL)	314.77±87.64	262.75±11.44	<0.001*
Lymphocyte (10 ² /μL)	2.45±0.55	2.29±0.49	0.099*
NLR	2.16±0.73	1.82±0.38	0.001**
PLR	133.47±38.43	118.48±28.20	0.016**

CBC; complete blood count IIH; idiopathic intracranial hypertension. *The results of the Mann-Whitney U test. **The results of Student's t test

associated with the grading of PE [Table 5]. Greater NLR and PLR values were associated with more severe PEs ($B = 0.273$, 95% Wald CI = 0.154/0.392, $P < 0.001$ for NLR and $B = 10.378$, 95% Wald CI = 0.048/20.804, $P = 0.035$ for PLR, GEE), and the strongest association was observed for grade 4 PE ($B = 1.594$, 95% Wald CI = 1.445/1.743, $P < 0.001$ for NLR and $B = 58.597$, 95% Wald CI = 1.971/127.165, $P = 0.003$ for PLR).

There was no association between the GCLT of both visits with NLR and PLR. (first visit's GCLT; $P = 0.126$ for NLR and 0.232 for PLR, second visit's GCLT; $P = 0.074$ and 0.093, respectively.) The associations between the NLR and PLR values and RNFLT measurements of the first and second visits are presented in Tables 6 and 7, respectively. According to the GEE results the strongest associations found with the temporal RNFLT (for the first visit's temporal RNFLT: $B = 0.008$, 95% Wald CI = 0.004/0.013, $P < 0.001$ for NLR and $B = 0.240$, 95% Wald CI = 0.017/0.497, $P = 0.042$ for PLR, for the second visit: $B = 0.010$, 95% Wald CI = 0.003/0.017, $P = 0.004$ for NLR and $B = 0.499$, 95% Wald CI = -0.001/1.060, $P = 0.048$ for PLR, GEE). The associations of NLR were stronger with all the investigated parameters than those of PLR.

Discussion

The purpose of this retrospective observational study was to investigate NLR and PLR as inflammation markers. Platelets and neutrophils are mediators of inflammatory responses, and NLR and PLR can be simply calculated by dividing the neutrophil and platelet counts by the lymphocyte count. In this study, the results showed that the neutrophil and platelet counts, NLR, and PLR, which are inflammatory markers obtained from a simple CBC test, were increased in patients with IIH.

The role of inflammation in the pathogenesis of IIH has been previously investigated in many studies.^[11,12,20-23,28,29] Sinclair *et al.* found that the CSF leptin levels were significantly higher in patients with IIH compared to the age-, gender- and BMI-matched controls.^[23] Dhungana *et al.* also found elevated leptin levels in the CSF along with the IL-1 α and CCL2 chemokine levels.^[29] Lample *et al.* reported similar findings in the blood serum samples.^[21] Leptin is an adipokine, which is believed to stimulate the release of pro-inflammatory cytokines.^[30] However, leptin is mainly raised in patients with obesity, therefore, these studies did not give any information about the role of inflammation in patients with IIH but without obesity. Samancı *et al.* showed significant increase in the serum IL-1 β , and decrease in the IL-8 and TNF α levels and suggested that their regulation played a very important role in IIH prognosis.^[12] Altlokka-Uzun *et al.* found oligoclonal bands (OCB) in the CSF of 30% of the patients with IIH. They showed that the frequency of vision loss was significantly higher in OCB(+) cases. In the same study, TNF α , INF γ , IL-4, IL-10, IL-12, and IL-17 were found to be highly elevated in the serum samples.^[20] IL-17, which is known to have increased levels in CSF of patients with many inflammatory and infectious diseases,^[31-34] was found elevated in CSF along with the IL-2 in Edward *et al.*'s study.^[22] Da *et al.* showed that both T-cell-dependent and T-cell-independent humoral immunity were present in CSF in patients with IIH. Also there are several case reports in which IIH presented with a systemic inflammatory disease. Komura *et al.* reported a systemic lupus erythematosus patient presenting with IIH

Table 5: The associations of the NLR and PLR values with the first visit's PE grades

	PE grades	B	95% Wald CI	P*
NLR	Grade 4	1.594	1.445/1.743	<0.001
	Grade 3	1.095	0.152/1.854	0.024
	Grade 2	0.403	-0.003/0.809	0.052
	Grade 1	0.339	-0.139/0.816	0.164
PLR	Grade 4	58.597	1.971/127.165	0.003
	Grade 3	18.153	0.998/55.064	0.027
	Grade 2	12.674	-3.476/38.824	0.091
	Grade 1	5.421	-6.534/27.377	0.234

PE; papil edema, NLR; neutrophil-to-lymphocyte ratio, PLR; platelet-to-lymphocyte ratio, CI; confidence integral. *The results of the generalized estimating equation models

Table 6: The associations of the NLR and PLR values with the first-visit RNFLT measurements

		B	95% Wald CI	P*
NLR	Global RNFLT	0.010	0.003/0.016	0.004
	RNFLT Superior	0.005	-0.001/0.011	0.084
	RNFLT Inferior	0.006	0.001/0.010	0.010
	RNFLT Nasal	0.004	0.000/0.009	0.072
	RNFLT Temporal	0.008	0.004/0.013	<0.001
PLR	Global RNFLT	0.569	0.123/1.015	0.012
	RNFLT Superior	0.157	-0.098/0.516	0.063
	RNFLT Inferior	0.191	-0.091/0.473	0.185
	RNFLT Nasal	0.273	-0.013/0.558	0.072
	RNFLT Temporal	0.240	0.017/0.497	0.042

NLR; neutrophil-to-lymphocyte ratio, PLR; platelet-to-lymphocyte ratio, RNFLT; retinal nerve fiber layer thickness, CI; confidence interval. *The results of the generalized estimating equation models

Table 7: The associations of the NLR and PLR values with the second-visit RNFLT measurements

		B	95% Wald CI	P*
NLR	Global RNFLT	0.009	-0.007/0.014	0.522
	RNFLT Superior	0.003	-0.002/0.020	0.101
	RNFLT Inferior	0.007	-0.004/0.018	0.193
	RNFLT Nasal	0.007	-0.001/0.015	0.076
	RNFLT Temporal	0.010	0.003/0.017	0.004
PLR	Global RNFLT	0.554	-0.002/1.110	0.051
	RNFLT Superior	0.384	-0.072/0.840	0.099
	RNFLT Inferior	0.502	-0.029/1.033	0.064
	RNFLT Nasal	0.381	-0.032/0.798	0.071
	RNFLT Temporal	0.499	-0.001/1.060	0.048

NLR; neutrophil-to-lymphocyte ratio, PLR; platelet-to-lymphocyte ratio, RNFLT; retinal nerve fiber layer thickness, CI; confidence interval. *The results of the generalized estimating equation models

and elevated IL-6 levels in the CSF.^[35] Zhao *et al.* similarly reported a IIH patient with Guillain-Barré syndrome.^[36] All of these studies indicate that inflammation plays an important role in the pathogenesis of IIH.

There are also many studies that investigated and confirmed that NLR and PLR were inflammation markers in many chronic conditions such as systemic lupus erythematosus, Takayasu's arteritis, cardiovascular disorders and intrahepatic cholangiocarcinoma, and ocular diseases such as non-arteritic anterior ischemic optic neuropathy, primary open-angle glaucoma, keratoconus and high axial myopia.^[17-19,37-42] However, to our knowledge, the present study is the first that explored the relationship of inflammation with IIH pathogenesis using NLR and PLR values. Both NLR and PLR values were found to be higher in patients with IIH compared to the age-, gender- and BMI-matched controls, and they were also higher in IIH patients with PE than those without PE. It is known that PE is a hallmark for the diagnosis of IIH and very important for monitoring the disease and measuring the effectiveness of the therapeutic strategy. To monitor the changes in PE, the measurement of RNFLT and optic nerve head volume have paramount importance.^[15,43,44] Our results revealed that NLR and PLR were associated with the grade of PE and RNFLT, especially that of the temporal quadrant, suggesting that inflammation was related to the severity of IIH. This is further supported by the association of these two inflammation markers with BCVA.

Another important finding of the present study is that GCLT of the second visit was significantly thinner than the GCLT of the first visit and of the control subjects. Despite this significance we did not find any association between the GCLT of both visit with NLR and PLR. Therefore, we did not use GCLT in further analyses for its prognostic value for the IIH patients, as the study's main aim is to investigate the inflammation theory. Further studies are needed to examine the GCLT for its prognostic value in the IIH patients.

This study has several limitations. The first concerns the retrospective design. As a result, the dates of ocular examination, blood sample collection and lumbar puncture were not the same for some of the participants. For 11 patients, ocular examinations, OCT measurements and blood sample collection had been done one day before the lumbar puncture procedure. The differences in the time of these tests, even for one day, could have caused possible fluctuations in the parameters investigated, such as thickening or thinning of the RNFL. Also we did not have dilated fundus examination reports of the study participants as a result of the retrospective design, therefore, we could have missed potential retinal disorders. Secondly, we did not investigate the associations of NLR and PLR with CSF opening pressure. ICP measurements were not recorded as exact values, all the CSF data for IIH patients were ">250 mmH₂O" in patients' files. It is known that PE grade and ICP are correlated, and we found that PE grade was associated with NLR and PLR [Table 5]. The presence of an association between these two inflammation markers and ICP could support the hypothesis that they are also related to the severity of IIH.

Conclusion

In conclusion, NLR and PLR, inflammation markers that are easily obtained, were higher in patients with IIH, which supports the theory that inflammation plays an important role in the pathogenesis of this disorder. Further studies with

prospective designs are needed to investigate the associations of NLR and PLR with other inflammatory and pro-inflammatory cytokines and chemokines in both serum and CSF in order to confirm the inflammation theory in IIH.

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