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The role of inflammatory biomarkers in predicting primary acquired nasolacrimal duct obstruction and postoperative recurrence

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ABSTRACT

This study aims to determine the relationship between systemic inflammatory biomarkers and primary acquired nasolacrimal duct obstruction and to evaluate whether they can be used as indicators in determining the risk of recurrence after dacryocystorhinostomy. This retrospective, comparative case series was conducted with 57 primary acquired nasolacrimal duct obstruction patients and 58 age- and gender-matched controls. All subjects underwent a complete ophthalmologic examination and complete blood count measurements. The mean neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index were significantly higher in patients with primary acquired nasolacrimal duct obstruction (p = 0.005, p = 0.01, and p = 0.003, respectively). In recurrent patients, the neutrophil-to-lymphocyte ratio was significantly higher than in those who did not develop a recurrence (p = 0.029). The area under the curve was determined as 0.775 (p = 0.029) for the neutrophil-to-lymphocyte ratio in predicting recurrence. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index levels were significantly higher in patients with primary acquired nasolacrimal duct obstruction compared to healthy controls. The neutrophil-to-lymphocyte ratio might be used as a simple and inexpensive indicator for predicting recurrence in patients with primary acquired nasolacrimal duct obstruction.

Keywords: inflammation, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, primary acquired nasolacrimal duct obstruction, systemic immune-inflammation index

Abbreviations:
PANDO: primary acquired nasolacrimal duct obstruction
DCR: dacryocystorhinostomy
NLR: neutrophil-to-lymphocyte ratio
PLR: platelet-to-lymphocyte ratio
SII: systemic immune-inflammation index
CBC: complete blood count

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INTRODUCTION

Primary acquired nasolacrimal duct obstruction (PANDO) is a common ophthalmologic problem of the lacrimal passages that causes epiphora.[1] PANDO is characterized by idiopathic inflammation and fibrosis, resulting in partial stenosis or complete occlusion of the nasolacrimal duct.[2,3] Many factors have been suggested that trigger the inflammation in PANDO, such as infection in the conjunctiva, sinusitis, and nasal pathway diseases.[1,3] Although the main etiological factors causing PANDO remain unknown, it is recognized that chronic inflammation has a prominent role in its pathogenesis.[2-4] Dacryocystorhinostomy (DCR), which is based on the creation of an alternative pathway for drainage of tears between the lacrimal sac and nasal cavity, is considered the gold standard treatment for PANDO.[5]

Recently, white blood cells, neutrophil, monocyte, platelet, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been proposed as indicators of subclinical systemic inflammation.[6] These simple and inexpensive methods for assessing inflammation have been used as predictors of several ocular diseases, including dry eye,[7] retinal vein occlusion,[8] neovascular glaucoma,[6] diabetic retinopathy,[9] and age-related macular degeneration.[10]

The systemic immune-inflammation index (SII) is a novel inflammatory biomarker that has been proposed as a prognostic indicator in various diseases, such as cancer,[11] stroke,[12] cardiovascular diseases,[13,14] and systemic inflammatory disorders.[15] Tang et al[16] suggested that NLR and SII might serve as inflammatory predictors in primary open-angle glaucoma patients. Ozcan et al[17] reported that the SII is superior to other inflammatory biomarkers in dry eye patients. Atum and Alagöz[18] reported higher NLR and lower mean platelet volume levels in PANDO patients compared to healthy controls and suggested that NLR and mean platelet volume counts were associated with PANDO.

Based on this knowledge, it has been hypothesized that there might be a relationship between subclinical systemic inflammation and the development of PANDO. Therefore, this study aims to determine the relationship of inflammatory biomarkers, including NLR, PLR, and SII, with PANDO and to evaluate whether they can be used as indicators in determining the risk of recurrence after DCR.

MATERIALS AND METHODS

This retrospective, comparative case series was conducted with 115 participants in the Ophthalmology Department of the Trakya University School of Medicine. This study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the institutional Human Research and Ethics Committee (Approval code: TÜTF-GOBAEK 2022/55). Written informed consent was obtained from all participants before enrollment.

The study group consisted of 57 patients who underwent DCR surgery because of the established diagnosis of PANDO. Fifty-eight healthy individuals who were admitted to the ophthalmology outpatient clinic for a routine ophthalmological examination were included in the control group. In both the study and control groups, participants who had a medical history of disorders influencing inflammatory biomarkers, such as diabetes mellitus, cardiovascular diseases, arterial hypertension, chronic obstructive lung disease, hyperthyroidism, hypothyroidism, anemia, malignancies, renal dysfunction, liver dysfunction, hematologic or autoimmune disorders, and chronic systemic inflammatory diseases, or those who had a history of prior ocular surgery, ocular inflammation, age-related macular degeneration, retinal occlusive disease, or glaucoma were excluded. Patients who were taking anti-inflammatory therapies were also excluded.

Demographic data, such as age and sex, were noted from the medical records of all patients. White blood cell, lymphocyte, neutrophil, platelet, and mean platelet volume values were recorded from the complete blood count (CBC). The CBC parameters of each participant were measured by the fluorescent flow cytometry method using the Sysmex XE-2100 (Sysmex Corporation, Kobe, Japan) automated hematology system. The counts of white blood cells, neutrophils, lymphocytes, monocytes, platelets, and mean platelet volume were measured as part of the automated CBC. The NLR and PLR were calculated as the ratios of neutrophil-to-lymphocyte and platelet-to-lymphocyte, respectively. SII was calculated as platelet count x (neutrophil/lymphocyte).

All surgeries were performed by the same surgeon (RG). The patients in the study group were divided into two subgroups according to the presence or absence of postoperative recurrence. Postoperative recurrence or DCR failure is defined as recurrent epiphora and the observation of insufficient anatomical patency with lacrimal irrigation.

Statistical analysis was performed using IBM SPSS Statistics 20 (SPSS Inc, Chicago, IL, USA) for Windows. Parametric data were presented as mean ± standard deviation, and categorical data were presented as percentages. The Kolmogorov–Smirnov test was used to assess data normality, and an independent t-test was performed to compare variables between the study group and healthy subjects when data normality was assumed. A Mann–Whitney U test was performed if the normal distribution was rejected. Chi-square was used for the comparison of categorical variables between the two groups. Receiver operator characteristic curve analyses were performed to determine the optimal cut-off points of SII, NLR, and PLR for the discrimination of PANDO patients from healthy individuals and recurrent cases from nonrecurrent patients. The areas under the curves were calculated for each parameter as measures of the accuracy of the tests. Statistical significance was considered as $p < 0.05$.

RESULTS

One hundred and fifteen individuals were included in the study. The study group consisted of 57 patients, and the control group consisted of 58 healthy individuals. The mean age was 60.8 ± 12.9 years (range 30–88) in the study group and 60.7 ± 9.0 years (range 43–87) in the control group. There were 9 males (15.8%) and 48 females (84.2%) in the study group and 9 males (15.5%) and 49 females (84.5%) in the control group. There were no significant differences between the two groups in terms of age and gender ($p = 0.948$ and $p = 0.968$, respectively). DCR failure was observed in six patients (10.5%).

The laboratory characteristics and p-values of the patients and the control group are shown in Table 1. Although no statistically significant differences were observed between the two groups in terms of white blood cell, neutrophil, lymphocyte, platelet, and mean platelet volume values ($p > 0.05$, independent sample t-test), NLR, PLR, and SII values were found to be statistically significantly higher in the study group compared to the control group (independent sample t-test, $p = 0.005$, $p = 0.01$, and $p = 0.003$, respectively).

A receiver operator characteristic curve analysis was used to determine the predictive values of NLR, PLR, and SII (Fig. 1). The calculated areas under the curves and optimal cut-off values for each parameter are shown in Table 2. According to the receiver operator characteristic curve analysis, the areas under the curves of NLR, PLR, and SII were 0.638 ($p = 0.011$), 0.616 ($p = 0.032$), and 0.626 ($p = 0.02$), respectively. The optimal cut-off value of NLR to predict PANDO was > 1.66, with a sensitivity of 61% and a specificity of 55% (95% confidence interval: 0.538–0.739). The optimal cut-off value of PLR to predict PANDO was > 106.46, with a sensitivity of 61% and a specificity of 55% (95% confidence interval: 0.512–0.720). The

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Table 1 The meanWBC, neutrophil, lymphocyte, platelet, NLR, PLR, MPV, and SII values of the study and control groups

	Study group (N=57)		Control group (N=58)		p-value
	mean ± SD	Min – Max	mean ± SD	Min – Max	
WBC	2.3 ± 0.8	4.6 – 10.8	2.3 ± 0.5	4.6 – 9.1	0.591
Neutrophil	1.9 ± 0.6	0.7 – 3.7	1.7 ± 0.5	1.0 – 3,1	0.077
Lymphosit	2.3 ± 0.8	1.0 – 6.0	2.4 ± 0.4	1.6 – 3.5	0.389
Platelet	254.6 ± 58.2	122 – 379	242.1 ± 41.8	130 – 327	0.188
MPV	9.5 ± 1.2	7.2 – 12.4	9.3 ± 1.1	7.2 – 11.4	0.273
NLR	1.9 ± 0.6	0.6 – 3.7	1.7 ± 0.4	1.0 – 2.9	0.005*
PLR	121.7 ± 45.3	45 – 310	104.4 ± 21.5	62.8 – 143.9	0.01*
SII	487.7 ± 199.4	175.5 – 1147.0	396.9 ± 112.2	207.8 – 660.5	0.003*

N: number of participiants
WBC: white blood cell
MPV: mean platelet volume
NLR: neutrophil to lymphocyte ratio
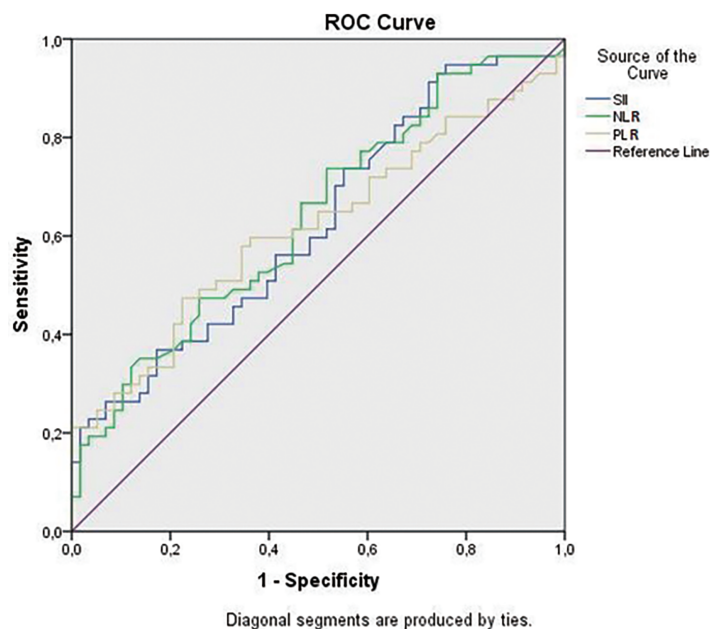PLR: platelet to lymphocyte ratio
SII: systemic immune inflammation index
SD: standard deviation
Min: minimum
Max: maximum
*: statistical significance

Fig. 1 Receiver operator characteristic curve analysis
Receiver operator characteristic curve (ROC) of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) for the prediction of primary acquired nasolacrimal duct obstruction (PANDO).

Table 2 The AUC, optimal cutoff, sensitivity, and specificity values of NLR, PLR, and SII levels obtained from ROC analysis

Variable	AUC	95% CI	P value	Cutoff value	Sensitivity %	Specificity %
Study (N=57) vs control (N=58) groups						
NLR	0.638	0.538–0.739	0.011	1.66	61	55
PLR	0.616	0.512–0.720	0.032	106.46	61	55
SII	0.626	0.524–0.727	0.02	394.95	60	52
Recurrent vs non-recurrent groups						
NLR	0.775	0.573–0.976	0.029	2.06	83	70

AUC: area under the curve
NLR: neutrophil to lymphocyte ratio
PLR: platelet to lymphocyte ratio
SII: systemic immune inflammation index
ROC: receiver operator characteristic
CI: confidence interval
N: number of participiants

optimal cut-off value of SII to predict PANDO was > 394.95, with a sensitivity of 60% and a specificity of 52% (95% confidence interval: 0.524–0.727).

Six patients developed recurrence after surgery. The mean surgery duration was 84.22 ± 3.93 minutes in the recurrent group and 81.28 ± 5.37 minutes in the nonrecurrent group. There was no significant difference between the two groups in terms of surgery duration (p = 0.09). In six patients who developed recurrence after surgery, the NLR was significantly higher than in those who did not (Mann–Whitney U test, p = 0.029). Although the PLR and SII values were found to be higher in cases with recurrence, the difference was not statistically significant (Mann–Whitney U test, p = 0.263 and p = 0.16, respectively). Detailed information about the groups is shown in Table 3. According to the receiver operator characteristic curve analysis (Fig. 2), the area under the NLR curves was 0.775 (p = 0.029). The corresponding optimal cut-off value of NLR to predict postoperative recurrence was identified as 2.06, with a sensitivity of 83% and specificity of 70% (95% confidence interval: 0.573–0.976).

DISCUSSION

The CBC is an inexpensive, reproducible, and reliable method that provides an evaluation of the abnormalities in the hematopoietic and immune systems.[16] It has been suggested that some biomarkers obtained from a CBC, such as NLR, PLR, and SII, are indicative of subclinical systemic inflammation.[6,11,13] Recently, these inflammatory biomarkers have been shown to have predictive and prognostic importance in various eye diseases such as glaucoma,[16] central retinal artery occlusion,[19] retinal vein occlusion,[20] and keratoconus.[21] Although the exact pathogenesis of PANDO remains unclear, it is known that inflammation plays a prominent role.[22] Considering the inflammatory nature of PANDO, systemic inflammatory biomarkers may help predict both the development of PANDO and the risk of recurrence after surgery.

In the present study, it was found that NLR, PLR, and SII levels in patients with PANDO were higher than in healthy subjects. Atum and Alagöz[18] reported higher NLR levels in PANDO

Table 3 The mean WBC, neutrophil, lymphocyte, platelet, NLR, PLR, MPV, and SII values of patients with and without postoperative recurrence

	Recurrent (N=6)		Non-recurrent (N=51)		p-value
	mean ± SD	Min – Max	mean ± SD	Min – Max	
WBC	7.4 ± 2.0	5.0 – 10.7	7.0 ± 1.3	4.6 – 10.8	0.815
Neutrophil	2.5 ± 0.7	1.6 – 3.2	1.8 ± 0.6	0.6 – 3.7	0.156
Lymphosit	1.9 ± 0.4	1.4 – 2.5	2.3 ± 0.8	1.0 – 6.0	0.152
Platelet	244.8 ± 43.2	181 – 295	255.7 ± 59.9	122 – 379	0.675
MPV	9.1 ± 1.0	8.0 – 10.5	9.5 ± 1.2	7.2 – 12.4	0.422
NLR	2.5 ± 0.7	1.6 – 3.2	1.8 ± 0.6	0.6 – 3.7	0.029*
PLR	136.3 ± 45.2	72.4 – 196.7	119.9 ± 45.5	45.0 – 310.0	0.277
SII	632.2 ± 249.6	346.9 – 904.7	470.7 ± 188.4	175.5 – 1147.0	0.168

N: number of participiants
WBC: white blood cell
MPV: mean platelet volume
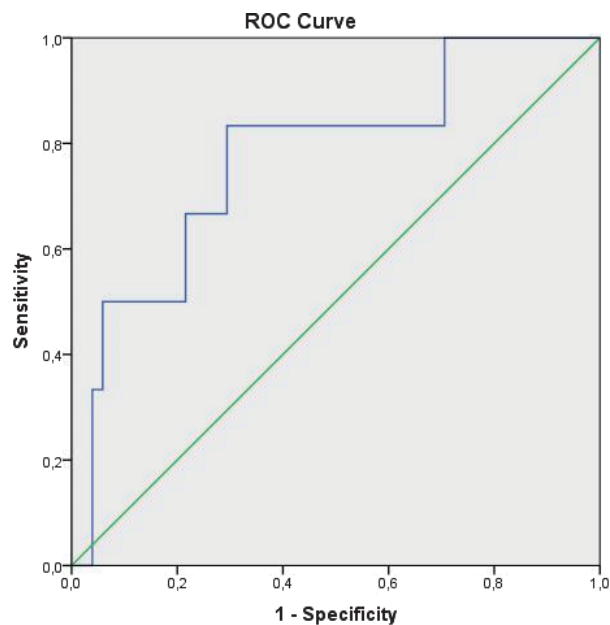NLR: neutrophil to lymphocyte ratio
PLR: platelet to lymphocyte ratio
SII: systemic immune inflammation index
SD: standard deviation
Min: minimum
Max: maximum
*: statistical significance

Fig. 2 Receiver operator characteristic curve analysis (ROC) of neutrophil-to-lymphocyte ratio (NLR) in recurrent cases (green line: reference line)
Receiver operator characteristic curve (ROC) of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) for the prediction of recurrence after surgery.

patients compared to the control group, similar to our results, but they found no significant difference in PLR levels between the two groups. However, SII levels were not included, and the inflammatory biomarkers in recurrent cases and the relationship of these biomarkers with recurrence were not evaluated in their study.

Chronic inflammation signs have been shown in biopsy specimens of the lacrimal sac obtained during DCR in patients with PANDO. Linberg and McCormick[23] reported 16 cases of PANDO seen with clinical chronic dacryocystitis, and they observed that in 14 of the 16 cases, a biopsy of the nasolacrimal duct revealed active chronic inflammation along the narrowed nasolacrimal duct in early cases. They observed fibrosis and fibrous obstruction of the nasolacrimal duct in intermediate and late cases. They suggested that the obliteration of the nasolacrimal duct by inflammatory infiltrates and edema leads to PANDO and chronic dacryocystitis. Makselis et al[3] evaluated histopathologic specimens of patients with nasolacrimal duct obstruction and reported chronic nongranulomatous inflammation in 70.5% of the cases. They suggested that chronic nongranulomatous inflammation is the most common histological finding in cases of nasolacrimal duct obstruction. Based on this knowledge, considering the role of inflammation in the pathogenesis of PANDO, it can be suggested that systemic subclinical inflammation may trigger inflammation in the nasolacrimal duct, play a role in disease pathogenesis, and affect the course of the disease and treatment success. In line with the results of the present study, higher NLR, PLR, and SII levels, which are accepted as indicators of subclinical systemic inflammation, may be indicative of the risk of PANDO development.

Amin et al[24] found chronic nonspecific inflammation in the lacrimal sac biopsies of 33 patients with nasolacrimal duct obstruction and emphasized that nonspecific inflammation-causing fibrosis was the most common cause in these cases. They also evaluated the severity of inflammation in the lacrimal sac of all specimens by the clinical inflammation score, which is obtained by examining the inflammatory cell infiltration density, fibrosis, and capillary proliferation. Patients were divided into three groups—mild, moderate, and severe inflammation—according to clinical inflammation scores. When the unsatisfactory surgical outcome was evaluated according to the clinical inflammation score, it was 0% in the mild group, 7.7% in the moderate group, and 40% in the severe inflammatory group. In the same study, an increase in fibrosis density was observed in two patients who underwent revision DCR. Although the rate of unsatisfactory surgical outcomes was higher in the severe group, they could not find a significant relationship between inflammatory infiltration, fibrosis, capillary proliferation, and surgical success. In another study by Çiftçi et al,[25] a significant increase in fibrosis density was observed in recurrent cases, and it was suggested that fibrosis-related changes were predominantly responsible for recurrence. A wound-healing response occurs as a result of tissue damage caused by various reasons, such as surgery, mechanical damage, infection, and autoimmune inflammation. As a result of this healing response, damaged cells are replaced by restructuring the extracellular matrix. The wound-healing response includes hemostasis, inflammation, activation, and proliferation of collagen-producing cells, tissue remodeling, and resolution. If the resolution phase is not completed, this process turns into abnormal extracellular matrix deposition, resulting in tissue fibrosis. Eventually, the abnormal wound-healing process progresses to chronic inflammation in which tissue destruction and regeneration occur simultaneously, resulting in tissue fibrosis.[26] Considering the relationship between DCR recurrence and lacrimal sac fibrosis, which is suggested in the literature by biopsy results, the abnormal chronic inflammation process that develops in the postoperative period may be one of the causative factors for recurrence. Systemic inflammation biomarkers may be proposed as indicators of inflammation that develops in the postoperative period. In the present study, it was observed that the NLR was at higher levels in recurrent cases than in those without recurrence. Patients with higher levels of inflammatory biomarkers may develop more fibrosis,

with a stronger inflammatory response. Therefore, the NLR may be used to determine the risk of recurrence in PANDO patients before DCR surgery.

The failure rates for DCR have been reported to be between 6% and 14%. Various methods have been proposed to reduce failure rates.[27] In line with the results of the present study, in cases with high NLR (cut-off value: 2.06) values in the preoperative period, ophthalmologists and otolaryngologists might be aware of the risk of postoperative recurrence. In these cases, precautions such as opening a sufficient osteotomy size,[28] silicone intubation,[29] intraoperative mitomycin-c application,[30] suturing the lacrimal sac to the nasal mucosa,[31] and lacrimal irrigation during the follow-up period[32] can be applied to reduce recurrence.

The main limitations of this study are its retrospective nature and relatively small sample size. More comprehensive studies, including larger numbers of recurrent cases, will better emphasize the importance of systemic inflammatory biomarkers in detecting the recurrence of DCR. Another important limitation is the lack of biopsy examinations. Evaluation of the correlation between inflammatory changes in biopsy specimens and systemic inflammatory biomarkers may help to better explain the relationship between them.

Overall, this is the first study to evaluate the relationship between DCR recurrence and inflammatory biomarkers. In conclusion, NLR, PLR, and SII levels were significantly higher in PANDO patients than in healthy controls. NLR levels were significantly elevated in recurrent cases. The NLR may be used as a simple, inexpensive, and reliable indicator for predicting DCR failure in PANDO patients. More comprehensive studies, including biopsy specimens and serum inflammatory biomarkers, may highlight the relationship between systemic inflammation and PANDO. Further investigations, including more patients, are needed to better understand the possible role of serum NLR levels in the failure of DCR.

CONFLICT OF INTEREST

The authors declare that they have no conflicting interests.

FUNDING

REFERENCES

1   Ohtomo K, Ueta T, Toyama T, Nagahara M. Predisposing factors for primary acquired nasolacrimal duct obstruction. *Graefes Arch Clin Exp Ophthalmol*. 2013;251(7):1835–1839. doi:10.1007/s00417-013-2288-5.
2   Kashkouli MB, Sadeghipour A, Kaghazkanani R, Bayat A, Pakdel F, Aghai GH. Pathogenesis of primary acquired nasolacrimal duct obstruction. *Orbit*. 2010;29(1):11–15. doi:10.3109/01676830903207828.
3   Makselis A, Petroska D, Kadziauskiene A, et al. Acquired nasolacrimal duct obstruction: clinical and histological findings of 275 cases. *BMC Ophthalmol*. 2022;22(1):12. doi:10.1186/s12886-021-02185-x.
4   Gul A, Aslan K, Karli R, Ariturk N, Can E. A possible cause of nasolacrimal duct obstruction: narrow angle between inferior turbinate and upper part of the medial wall of the maxillary sinus. *Curr Eye Res*. 2016;41(6):729–733. doi:10.3109/02713683.2015.1052520.
5   Ghasemi H, Asghari Asl S, Yarmohammadi ME, Jafari F, Izadi P. External dacryocystorhinostomy; success rate and causes of failure in endoscopic and pathologic evaluations. *Iran J Pathol*. 2017;12(3):189–194.
6   Zhang A, Ning L, Han J, et al. Neutrophil-to-lymphocyte ratio as a potential biomarker of neovascular glaucoma. *Ocul Immunol Inflamm*. 2021;29(2):417–424. doi:10.1080/09273948.2019.1677916.
7   Sekeryapan B, Uzun F, Buyuktarakci S, Bulut A, Oner V. Neutrophil-to-lymphocyte ratio increases in

patients with dry eye. *Cornea.* 2016;35(7):983–986. doi:10.1097/ICO.0000000000000872.

8   Dursun A, Ozturk S, Yucel H, et al. Association of neutrophil/lymphocyte ratio and retinal vein occlusion. *Eur J Ophthalmol.* 2015;25(4):343–346. doi:10.5301/ejo.5000570.

9   Ulu SM, Dogan M, Ahsen A, et al. Neutrophil-to-lymphocyte ratio as a quick and reliable predictive marker to diagnose the severity of diabetic retinopathy. *Diabetes Technol Ther.* 2013;15(11):942–947. doi:10.1089/dia.2013.0097.

10 Ilhan N, Daglioglu MC, Ilhan O, et al. Assessment of neutrophil/lymphocyte ratio in patients with age-related macular degeneration. *Ocul Immunol Inflamm.* 2015;23(4):287–290. doi:10.3109/09273948.2014.921715.

11 Zhou Y, Dai M, Zhang Z. Prognostic significance of the systemic immune-inflammation index (SII) in patients with small cell lung cancer: A meta-analysis. *Front Oncol.* 2022;12:814727. doi:10.3389/fonc.2022.814727.

12 Chen PY, Chen GC, Hsiao CL, et al. Comparison of clinical features, immune-inflammatory markers, and outcomes between patients with acute in-hospital and out-of-hospital ischemic stroke. *J Inflamm Res.* 2022;15:881–895. doi:10.2147/JIR.S342830.

13 Luo Y, Zhang J, Liu T, et al. The systemic-immune-inflammation index predicts the recurrence of atrial fibrillation after cryomaze concomitant with mitral valve surgery. *BMC Cardiovasc Disord.* 2022;22(1):45. doi:10.1186/s12872-022-02494-z.

14 Esenboğa K, Kurtul A, Yamantürk YY, Akbulut İM, Tutar DE. Comparison of systemic immune-inflammation index levels in patients with isolated coronary artery ectasia versus patients with obstructive coronary artery disease and normal coronary angiogram. *Scand J Clin Lab Invest.* 2022;82(2):132–137. doi:10.1080/00365513.2022.2034034.

15 Pakoz ZB, Ustaoglu M, Vatansever S, Yuksel ES, Topal F. Serum immune-inflammation index assessment in the patients with ulcerative colitis. *Gastroenterol Res Pract.* 2022;2022:9987214. doi:10.1155/2022/9987214.

16 Tang B, Li S, Han J, Cao W, Sun X. Associations between blood cell profiles and primary open-angle glaucoma: a retrospective case-control study. *Ophthalmic Res.* 2020;63(4):413–422. doi:10.1159/000504450.

17 Ozarslan Ozcan D, Kurtul BE, Ozcan SC, Elbeyli A. Increased systemic immune-inflammation index levels in patients with dry eye disease. *Ocul Immunol Inflamm.* 2022;30(3):588–592. doi:10.1080/09273948.2020.1821899.

18 Atum M, Alagöz G. Blood cell ratios in patients with primary acquired nasolacrimal duct obstruction. *Ophthalmol J.* 2020;5:76–80. doi:10.5603/OJ.2020.0017.

19 Elbeyli A, Kurtul BE, Ozcan DO, Ozcan SC, Dogan E. Assessment of red cell distribution width, platelet/lymphocyte ratio, systemic immune-inflammation index, and neutrophil/lymphocyte ratio values in patients with central retinal artery occlusion. *Ocul Immunol Inflamm.* 2022;30(7–8):1940–1944. doi:10.1080/09273948.2021.1976219.

20 Zuo W, Chen T, Song J, Ai M. Assessment of systemic immune-inflammation index levels in patients with retinal vein occlusion. *Ocul Immunol Inflamm.* 2022;1–5. doi:10.1080/09273948.2022.2032199.

21 Elbeyli A, Kurtul BE. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio levels are associated with keratoconus. *Indian J Ophthalmol.* 2021;69(7):1725–1729. doi:10.4103/ijo.IJO_3011_20.

22 DeAngelis D, Hurwitz J, Oestreicher J, Howarth D. The pathogenesis and treatment of lacrimal obstruction : The value of lacrimal sac and bone analysis. *Orbit.* 2001;20(3):163–172. doi:10.1076/orbi.20.3.163.2626.

23 Linberg JV, McCormick SA. Primary acquired nasolacrimal duct obstruction. A clinicopathologic report and biopsy technique. *Ophthalmology.* 1986;93(8):1055–1063. doi:10.1016/s0161-6420(86)33620-0.

24 Amin RM, Hussein FA, Idriss HF, Hanafy NF, Abdallah DM. Pathological, immunohistochemical and microbiologicalal analysis of lacrimal sac biopsies in patients with chronic dacrocystitis. *Int J Ophthalmol.* 2013;6(6):817–826. doi:10.3980/j.issn.2222-3959.2013.06.14.

25 Ciftci F, Erşanli D, Civelek L, Baloglu H, Karadayi K, Güngör A. Histopathologic changes in the lacrimal sac of dacryocystorhinostomy patients with and without silicone intubation. *Ophthalmic Plast Reconstr Surg.* 2005;21(1):59–64. doi:10.1097/01.iop.0000148408.51615.fe.

26 Fernández-Colino A, Iop L, Ventura Ferreira MS, Mela P. Fibrosis in tissue engineering and regenerative medicine: treat or trigger? *Adv Drug Deliv Rev.* 2019;146:17–36. doi:10.1016/j.addr.2019.07.007.

27 Leong SC, Macewen CJ, White PS. A systematic review of outcomes after dacryocystorhinostomy in adults. *Am J Rhinol Allergy.* 2010;24(1):81–90. doi:10.2500/ajra.2010.24.3393.

28 Onerci M, Orhan M, Ogretmenoğlu O, Irkeç M. Long-term results and reasons for failure of intranasal endoscopic dacryocystorhinostomy. *Acta Otolaryngol.* 2000;120(2):319–322. doi:10.1080/000164800750001170.

29 Apaydin KC, Fisenk F, Karayalcin B, Akar Y, Saka O. Endoscopic transnasal dacryocystorhinostomy and bicanalicular silicone tube intubation. *Ophthalmologica.* 2004;218(5):306–311. doi:10.1159/000079471.

30 Qian Z, Zhang Y, Fan X. Clinical outcomes of dacryocystorhinostomy with or without intraoperative use of mitomycin C: a systematic review and meta-analysis. *J Ocul Pharmacol Ther.* 2014;30(8):615–624. doi:10.1089/jop.2013.0230.

31 Tsirbas A, Wormald PJ. Endonasal dacryocystorhinostomy with mucosal flaps. *Am J Ophthalmol.* 2003;135(1):76–83. doi:10.1016/s0002-9394(02)01830-5.

32 Ha TS, Na KS, Chi NC. Effectiveness of washing nasolacrimal duct as an additional therapy after dacryocystorhinostomy. *J Korean Ophthalmol Soc.* 2000;41(11):2308–2312.