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ORIGINAL ARTICLE

# Evaluating lymphocyte-mediated systemic inflammation in patients requiring surgery for pterygium

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## Abstract

**Purpose:** This study aims to evaluate lymphocyte-mediated systemic inflammation by analyzing the level of lymphocyte-to-monocyte ratio (LMR) and other hematological parameters in patients who underwent pterygium surgery.

**Methods:** A retrospective, cross-sectional comparative study. Thirty-five patients underwent pterygium surgery, and 37 age- and sex-matched healthy controls were included. Pre-operative complete blood count parameters of all participants were analyzed. LMR, neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) levels were compared.

**Results:** The mean age was  $56.03 \pm 12.11$  years in the patient group and  $59.84 \pm 6.83$  years in the control group. The lymphocyte count (LY) ( $p=0.009$ ) and LMR were significantly higher in the pterygium group ( $p<0.001$ ). No statistically significant differences were observed in the other hematological parameters between the groups ( $p>0.05$ ). The ROC curve analysis demonstrated that LMR was a more reliable indicator of pterygium than NLR and SII. The AUC was 0.781 for LMR (95% CI, 0.673–0.888;  $p<0.001$ ), was 0.424 (95% CI, 0.291–0.557;  $p=0.267$ ), and 0.443 (95% CI, 0.309–0.577;  $p=0.408$ ) for NLR and SII, respectively. The optimal cutoff value of LMR to predict pterygium patients was  $>4.04$ , with 80.4% sensitivity and 70.3% specificity.

**Conclusion:** The LY and the LMR were found to be significantly elevated in the pterygium group. However, LMR demonstrated relatively lower sensitivity and specificity. Elevated LMR may be a new systemic factor that deserves further evaluation in order to clarify the role of lymphocyte-mediated systemic inflammation in the occurrence of pterygium.

**Keywords:** Clinical tests; immunology; ocular surface surgery; pre-op medical testing; pterygium.

Pterygium is a common disorder characterized by a fibrovascular conjunctival outgrowth onto the corneal surface. It is caused by multiple factors, such as genetic and environmental factors, increasing age, ultraviolet light exposure, human papillomavirus, allergens, and cholesterol metabolism.<sup>[1-4]</sup>

In the pathophysiology of primary pterygium, there is an uncontrollable cellular proliferation of fibrovascular

connecting tissue on the ocular surface resulting from increased systemic and cellular inflammation.<sup>[5]</sup> A range of studies have previously been conducted to determine the role of immunopathological mechanisms in the pathogenesis of pterygia. HLA-DR antigens, mast cells, antigen-presenting cells, intercellular adhesion molecules, and inflammatory T-lymphocyte subpopulations (CD4 and CD8) have been identified in pterygium specimens.



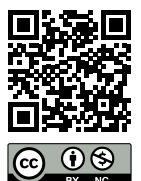
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[6,7] The Receptor for Advanced Glycation Endproducts (RAGE) is a molecule that is expressed in T cells that plays a determinative role in immune responses.<sup>[8]</sup> Upregulated expression of RAGE in vascular endothelial cells has been demonstrated in pterygium.<sup>[9]</sup> Inexpensive and practical tests that can measure the risk of occurrence and recurrence of pterygium, along with local treatment options targeting lymphocytes, will be beneficial in the diagnosis, treatment, and follow-up. In addition to lymphocytes, monocytes represent a category of leukocytes that play an important role in the inflammatory process. In various inflammatory conditions and ocular diseases, an increase in the number of monocytes and inflammation associated with monocyte-macrophages has been observed.<sup>[10,11]</sup> It is evident that studies that investigate the role of monocytes in the pathogenesis of pterygium, in addition to lymphocytes, will be of significant value in facilitating a more profound comprehension of the effect of systemic inflammation in the disease process. Furthermore, such studies will provide new treatment options for the management of the condition.

The hematological indices, such as platelet/lymphocyte ratio (PLR), mean platelet volume, neutrophil/lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII), are easily calculated from whole blood counts and are utilized in various medical fields, including cardiology, oncology, rheumatology, and ophthalmology.<sup>[12-15]</sup> In recent years, these inexpensive, useful, and repeatable indices have provided valuable information on pathophysiology and progression of diseases, risk stratification, and in evaluating the efficacy of treatment. At present, there is a lack of accurate data on the relationship between the development of pterygium and SII and LMR. In order to determine the role of systemic inflammation, especially lymphocytes and monocytes, in the development of pterygium, it may be useful to examine the relationship between LMR, SII, and the occurrence of pterygium. Therefore, this study aims to assess the usefulness of LMR and SII in pterygium occurrence.

## Materials and Methods

This was a retrospective, case-control study. The present study was of a retrospective, case-control nature. Approval for the study was granted by the Ankara Education and Research Hospital Ethics Committee on 9 November 2022, with the decision number E-22-1118. In accordance with the principles of the Helsinki Declaration, informed consent was obtained from all patients during the study period.

## Inclusion and Exclusion Criteria

The study included thirty-five patients diagnosed with primary pterygium who underwent surgery, along with 37 age and sex matched control subjects between January 2020 and December 2022. Inclusion criteria required comprehensive data recording, a thorough ocular examination, and a complete blood count (CBC).

Participants who were pregnant, lactating, had any systemic disease (including diabetes mellitus), showed signs of systemic inflammation such as high fever or elevated white blood cell count, had a history of any infectious disease, underwent ocular surgery other than pterygium or standard cataract surgery, had a history of ocular trauma, used topical or systemic steroids or anti-inflammatory drugs within the past month, or were under 18 years of age were excluded. Moreover, patients with any ocular diseases, including glaucoma, age-related macular degeneration, dry eye disease, and autoimmune diseases or systemic diseases, were excluded from the study.

## Hematological Analysis

Following a 12-h overnight fast, blood samples were extracted from the antecubital vein and transferred into tubes for analysis. The samples were analyzed within 3 hours after sampling using a Sysmex XN 3000 automated hematology analyzer (Kobe, Japan). Lymphocyte counts (LY), neutrophil counts (NEU), platelet counts (PLT), and monocyte counts (MONO) were obtained from the CBCs of participants. LMR and NLR were calculated manually as LMR, NLR, respectively. SII was calculated using the following formula: neutrophilx platelet/lymphocyte. Pterygium patients and healthy controls were compared in terms of these hematologic indices.

## The Classification of Pterygium

Pterygium was graded based on its size from the limbus: Grade 1: 0–2 mm, Grade 2: 2–4 mm, Grade 3: >4 mm. Pterygia larger than 2 mm were selected. Fleshy/opaque pterygia of any size, which are reported to recur frequently, were not operated. According to translucency, which represents its inflammatory activity, pterygium was graded as Grade 1: atrophic, Grade 2: intermediate, and Grade 3: opaque/fleshy.<sup>[16,17]</sup>

## Statistical Analysis

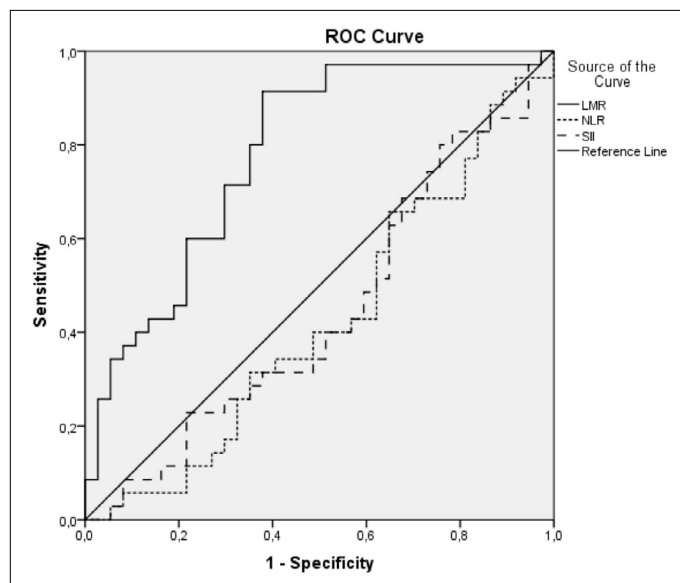
Statistical analysis was performed using IBM SPSS for Windows (version 25.0; IBM Co., Armonk, NY) for each variable; normality was assessed using the Shapiro-Wilk test. T-tests and Mann-Whitney U tests were used to evaluate the statistical differences between the groups. Descriptive statis-

tics were presented as median (minimum-maximum) or mean±SD for continuous variables and frequency (%) for categorical ones. The statistical significance level was set at p≤0.05. Receiver operating characteristic (ROC) analysis was also performed in order to calculate the sensitivity and specificity, the area under the ROC curve (AUROC), and the optimal cut-off values of SII, NLR, and LMR for distinguishing pterygium patients from controls.

### Results

This study included thirty-five patients who underwent pterygium surgery and 37 age- and sex-matched healthy controls. In the pterygium group, 19 (54.2%) patients were male and 16 (45.8%) were female, while in the control group, 19 (51.3%) were male and 18 (48.7%) were female. The mean ages of patients and controls were 56.03±12.11 and 59.84±6.83 years, respectively. LYM (lymphocyte) (p=0.009) count and LMR (p<0.001) were significantly higher in the pterygium group. There was no significant difference between two groups regarding white blood cells (WBC) (p=0.796), NEU (neutrophil) (p=0.120), PLT (platelet) (p=0.990), MON (monocyte) (p=0.133) counts. There was no significant difference in other hematological indices, including SII levels, between groups (Table 1).

In the ROC curve analysis, only LMR showed an AUC of 0.781 (95% CI, 0.673–0.888; p<0.001). The optimal cutoff value of LMR to predict pterygium patients was >4.04, with 80.4% sensitivity and 70.3% specificity (Table 2 and Figure 1 show the results of ROC analysis).



**Fig. 1.** ROC curve of lymphocyte/monocyte ratio, systemic immune inflammation index, and neutrophil/lymphocyte ratio for the prediction of pterygium patients.

**Table 1.** The demographic characteristics and hematological comparisons of patients and controls

Variables	Pterygium group	Controls	P
N, patients	35	37	
Age, years (Mean±SD)	56.03±12.11 (29–81)	59.84±6.83 (49–77)	ns*
Gender M/F	19/16	19/18	ns§
WBC (Mean±SD)	7.47±1.82 (4.64–11.13)	7.58±1.93 (2.99–11.67)	ns*
NEU (Mean±SD)	4.53±1.32 (2.8–8.38)	4.06±1.25 (2.3–7.0)	ns*
<b>LYM (Mean±SD)</b>	<b>2.71±0.81 (1.25–4.68)</b>	<b>2.22±0.7 (1.04–3.71)</b>	<b>0.009*</b>
MONO (Mean±SD)	0.55±0.14 (0.28–0.80)	0.6±0.16 (0.25–0.9)	ns*
PLT (Mean±SD)	260.2±60.15 (140–405)	260.03±59.98 (131–410)	ns*
NLR (Median, min-max)	1.67 (0.87–3.11)	1.80 (0.93–4.18)	ns**
<b>LMR (Mean±SD)</b>	<b>5±1.10 (2.3–7.5)</b>	<b>3.78±1.08 (1.91–6.45)</b>	<b>&lt;0.001*</b>
SII (Median, min-max)	409.46 (198.5–870.65)	468.61 (196.5–1242.5)	ns**

WBC: White blood counts; NEU: Neutrophil counts; LY: Lymphocyte counts; MONO: Monocyte counts; PLT: Platelet counts; NLR: Neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII: Systemic immune-inflammation index; ns: Not significant; §Pearson Chi-Square test was used to generate the P-value; \*T test was used to generate the P-value; \*\*Mann-Whitney U test was used to generate the P-value, P≤0.05 was accepted as statistical significant

**Table 2.** The results of ROC analysis of hematological indices for discriminating the pterygium patients from controls

Hematological indices	AUC (95%)	Cut off	P	Sensitivity (%)	Specificity (%)
LMR	0.781 (0.673–0.888)	4.04	<0.001	80.4	70.3
NLR	0.424 (0.291–0.557)	-	0.267	-	-
SII	0.443 (0.309–0.577)	-	0.408	-	-

NLR: Neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII: Systemic immune-inflammation index.

## Discussion

According to the literature search, the role of lymphocyte-mediated systemic inflammation in the pathogenesis of pterygium has not been previously evaluated. In this study, the first results of LMR in pterygium patients and normal subjects are revealed. The findings of the present study demonstrated that the LY and LMR were elevated in patients with pterygium.

Prior studies evaluating the importance of systemic inflammation and hematological parameters in the pathogenesis of pterygium have indicated an association between pterygium and higher NLR, triglyceride, and higher red cell distribution width but lower high-density lipoprotein levels.<sup>[18-20]</sup> The pathogenesis of pterygium is multifactorial and not fully understood. Histopathological examinations of pterygia specimens in some studies have confirmed increased infiltration of the conjunctiva with B and T lymphocytes.<sup>[6,21]</sup> Similarly, a study analyzed the transcriptional profile and the cellular microenvironment of conjunctival pterygia through RNA sequencing technology revealed that pterygium samples mainly consisted of the enrichment of T cells.<sup>[7]</sup> Previous studies have demonstrated the significant role of local lymphocytic infiltration in the pathologic pathway. In the present study, the LY and the LMR were found to be significantly elevated in the pterygium group. This study is aligned with recent studies indicating that the role of lymphocytes in immunological mechanisms is involved in the pathophysiology of the disease. These findings enhance the knowledge of the immunological mechanisms underlying the pathophysiology of the disease and facilitate the identification of new potential therapeutic targets. Nergiz et al.<sup>[22]</sup> showed that HPV (human papillomavirus) infection may play a role in the development of pterygium and recurrence. However, it was underscored that HPV infection alone might not be adequate, emphasizing the presence of several cofactors in the multi-stage process. The findings not only underscore the complexity of the pathogenic mechanism but also reinforce the association between cell-mediated immunity and the presence of pterygium.

The SII and NLR are novel inflammatory markers used in the diagnosis, prognosis, and management of a range of diseases characterized by chronic inflammation. Contrary to expectations, this study did not find a significant relationship between the presence of pterygium and either SII or NLR level. Gokmen and Gokmen proposed that there may be a correlation between NLR and pterygium, hypothesizing that chronic inflammatory and neovascular

activity in pterygium may result in elevated NLR levels.<sup>[19]</sup> In contrast to their findings, however, no evidence for the relationship between higher NLR and pterygium was detected in the current study. Moreover, probably consistent with the main pathophysiology of the disease, this study showed that LMR could be a better predictor than NLR in identifying patients with pterygium.

The present study comprised patients with primary pterygium; however, further research is required to examine the role of lymphocyte-mediated inflammation in the recurrence of pterygium. In particular, prospective studies including longitudinal analyses of post-operative follow-ups of patients who have undergone surgery and investigating the relationship between recurrence and LY and LMR, will undoubtedly be useful.

Some limitations in this study should be considered. The retrospective design and a relatively small sample size are notable constraints. Moreover, pathological analysis of pterygium specimens in terms of lymphocyte infiltration and the evaluation of peripheral blood lymphocytes were not feasible. A valuable tool for future research could involve classifying subpopulations of lymphocytes, such as B or T lymphocytes, in both peripheral blood and pterygium specimens to uncover connections between increased LMR and lymphocyte subpopulations. Finally, this study is limited by the fact that patients had primary pterygium, and hematological parameters of patients with recurrent pterygium were not analyzed. A comparative analysis of hematological indices in patients with primary and recurrent pterygium could provide insights into the role of LMR in predicting the risk of recurrence following surgical removal.

## Conclusion

Despite its limitations, this study has identified the role of lymphocyte-mediated systemic inflammation in the pathogenesis of pterygium. The evidence indicates that the LY and the LMR may serve as cost-effective and valuable markers for monitoring the incidence of pterygium, particularly in comparison to NLR. Moreover, the relationship between LMR and the presence of pterygium can suggest that LMR may be useful in clinical practice in predicting patients who may develop pterygium or in the clinical follow-up of smaller pterygiums (<2 mm) that do not require surgery. Further prospective studies are required to ascertain the efficacy of the LY and LMR, as well as the optimal cutoff value of the LMR in detecting potential pterygium recurrence and monitoring the effectiveness of local treatment agents.

**Ethics Committee Approval:** The Ankara Education and Research Hospital Ethics Committee granted approval for this study (date: 09.11.2022, number: E-22-1118).

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**Conflict of Interest:** None declared

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