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Risk factors for pterygium recurrence based on a retrospective study of 196 patients

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Pterygium is considered as important clinical problem due to its special characteristics such as high incidence, multi-factorial disorder and high recurrence rate. The purpose of this study is to identify the postoperative recurrence rate of pterygium and examine the association between systemic inflammation and the type of pterygium and pterygium recurrence. From January 2017 to January 2018, a total of 196 pterygium patients who received surgery were included in this study. Demographic and clinical data were available and extracted from the ongoing clinic records and interviews. Kaplan–Meier analysis was used to evaluate recurrence over time, univariate analysis and logistic regression analysis were applied to identify the variables that may affect the recurrence after pterygium surgery. All enrolled patients were routinely followed up for average of 24.78 ± 6.08 months, among them, 15 patients (7.65%) presented with recurrence following resection surgery. Multivariate analysis showed that recurrence was significantly associated with neutrophil to lymphocyte ratio (NLR) (odds ratio [OR] 4.35, 95% confidence interval [CI], 1.14–16.61, $P = 0.03$) and pterygium grade (OR: 6.08, 95% CI, 1.52–24.31, $P = 0.01$) . The postoperative recurrence rate of recurrent pterygium was 7.65%. The preoperative NLR and pterygium grade were significantly associated with recurrence. This study brings potential future benefits to patients selection outcome prediction and improving long-term care strategies.

Keywords Pterygium, Recurrence, Risk factors, Neutrophil to lymphocyte ratio (NLR)

Pterygium is a common conjunctival degenerative change and these fibrovascular tissues can extend into the cornea by direct wing-shaped growth. Song Peige et al[1] reported that the prevalence of pterygium in China was 9.84% in people aged 15–84 years. While pterygium can be clinically asymptomatic, patients may present with foreign body sensation, redness or tearing. When a pterygium not only enlarges, but intrudes in a wing-shaped manner onto the cornea, visual impairment may result from astigmatism, partial or full pupil occlusion, or even diplopia may be induced by limited ocular motility. Although studies have indicated that inflammatory factors, anti-apoptotic and immunological mechanisms are implicated in the pathogenesis of pterygium, the mechanism underlying it, remains poorly understood. Long-term ultraviolet (UV) exposure is considered to be the most significant aetiological risk factor for pterygium[2,3], several others, including systemic and local inflammation, have also been reported to influence the development and progression of pterygium[4–6]. Moreover, more intensive inflammation is also noted during the excision recurrence pterygium surgery.

The surgical treatment for pterygium has had variations over the past several years. Excision and leaving a bare sclera were the most widely performed previously, but, unfortunately, ended with recurrence in up to 88% of the cases. Since then, various surgical methods such as excision combined with conjunctival autografting, amniotic membrane transplantation and mitomycin C injection have been used[7,8]. However, pterygium recurrence remains a significant problem in every single described procedure, arising the need of considering new prognostic factors. Due to the development of microscopic technique in recent years, the recurrence rate of pterygium may be overestimated.

Although tumor necrosis factor-α (TNF-α), interleukin- 6 (IL-6) and intercellular cell adhesion molecule (ICAM) is most commonly used as a conventional examination to monitor the progression of systemic inflammation[9], there are limited by their expense and their difficulty to obtain data in pterygium patients;

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by contrast, the use of complete blood count (CBC) and biochemical analyses to determine the presence of systemic inflammation benefits from cheap and routine test. Moreover, newly identified biomarkers of systemic inflammation can be directly calculated by neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) with those data[10,11]. Although studies have shown relationships between PLR and pterygium[12], there is a knowledge gap regarding biomarkers of systemic inflammation, disease severity and outcome of pterygium surgery.

This study aimed to analyze the recurrence rate of conjunctival autografting alone over a long follow-up period. Moreover, this study also examined the association between systemic inflammation and the type of pterygium and pterygium recurrence. We expect these analyses to update the recurrence rate of pterygium and to yield information that will help to prevent pterygium recurrence.

Materials and methods

Study participants and procedures

This was a longitudinal, retrospective and observational study of 196 participants treated for pterygium in Xiamen, Fujian, China. All the participants were inpatients of the Zhongshan hospital of Xiamen university from January 2017 to January 2018. And we had access to information that could identify individual participants during or after data collection. The study group was composed of patients (1) who were diagnosed with pterygium according to the International Classification of Diseases, 10th version (ICD-10); and (2) who underwent surgical treatment; (3) Recurrence pterygium were who had received one or more pterygium surgeries prior to the study. The patients were excluded (1) if the follow-up time was less than 6 months; (2) if the patient did not receive surgical treatment; (3) had been using Glucocorticoids or Nonsteroidal anti-inflammatory drugs; (4) was diagnosed with ocular surface disorders including keratitis, corneal degeneration, corneal dystrophy; (5) if the patient had a history of ocular surface injury, or any ocular surface surgery. Recurrence was defined as fibrovascular regrowth extending beyond the limbus, confirmed by slit-lamp examination. The study was approved by the ethics committees of Zhongshan Hospital of Xiamen University (XMZSYY-AF-SC-12–03) and was conducted with strict adherence to the tenets of the Declaration of Helsinki (Edinburgh, 2000). Informed consent was obtained from all study participants or from their legal guardians in the study.

Data collection

Electronic medical records were abstracted for clinical variables of possible prognostic significance. These variables included basic demographic information (age, gender), clinical characteristics of pterygium (pterygium location, grade, and laboratory examination [white blood cell (WBC) count, neutrophil count, lymphocyte count, hemoglobin (Hb), platelet count (PLT)]). Moreover, clinical comorbid conditions, including hypertension, diabetes mellitus were recorded. The pterygium location was classified as either nasal or temporal or bilateral. Pterygium were graded for severity (T1 to T3) based on the visibility of the underlying episcleral blood vessels[13]. The grading was defined as follows: T1 (atrophic) refers to a thin, transparent pterygium with visible underlying episcleral vessels; T2 (intermediate) represents a moderately thickened pterygium with partially obscured episcleral vessels; and T3 (fleshy) indicates a thick, opaque pterygium that completely covers the underlying episcleral vessels. Blood samples were collected from an antecubital vein by standard venipuncture, and blood cell counts were performed in a certified laboratory. NLR was defined as dividing the number of neutrophils by the number of lymphocytes and PLR was the number of neutrophils by the number of lymphocytes.

Surgical technique

Topical anesthesia was performed with proparacaine 0.5% and local injection in the body of the pterygium with lidocaine 2% with a 30-gauge needle. Using forceps and Westcott scissors, the pterygium was resected from the semilunar fold towards the limbus. Subsequently, subconjunctival Tenon tissue was excised to expose the bare sclera. When necessary, diathermy was used to coagulate the bleeding points on the sclera. Afterward, a corneal scraper was used to smooth the involved part of the cornea. Then, the matching size of the superior bulbar conjunctiva was dissected using scissors and forceps and was delivered carefully to cover the bare sclera. The conjunctival autograft was finally sutured with interrupted 8–0 absorbable sutures. No bandage contact lens was used after surgery.

Postoperative period

Tobramycin-dexamethasone eye drop was used for the first 2 weeks, four times a day, then tapering the dose for 4 weeks following relief from ocular inflammatory reaction during the follow-up period. When the patient presented to our clinic for follow-up, a careful and comprehensive eye examination was administered. After slit-lamp examination, anterior segment color photography was taken.

Statistical analysis

The summary statistics for normally distributed variables (such as age) were given as the mean and standard deviation. For non-normally distributed variables, we used the median with interquartile range (25th and 75th percentiles). Categorical variables were expressed by ratios and percentages. Chi square and independent t tests were applied to analyze the demographic characteristics of our patients. Categorical variables of various eye conditions are presented as proportions, and numerical variables are presented as means and standard deviations. The Kaplan–Meier method was employed to analyze recurrence rates over time. A stepwise binary logistic regression was employed to identify key variables associated with surgical outcomes. Following this, a multiple logistic regression analysis, was conducted to control for these covariates, ensuring that identified associations were independent of these demographic factors. Odds ratios with 95% confidence intervals were calculated to quantify the strength of each association. NLR was defined as the ratio of neutrophils to lymphocytes; hence, we excluded WBC and neutrophil (Neut) counts from the regression analysis. Similarly, PLR was calculated by dividing the platelet count by the lymphocyte count, so platelet and lymphocyte variables were also excluded to avoid collinearity. All statistical tests were performed using R statistical software (http://www.r-project.org) for Macs and findings were considered statistically significant at $P < 0.05$.

Results

Baseline clinical characteristics

A total of 212 subjects were initially evaluated for inclusion in the study. After applying the inclusion and exclusion criteria, 16 subjects were excluded due to loss to follow-up, prior ocular surgeries, and other reasons. Consequently, 196 subjects were included in the final analysis. The baseline demographics and clinical characteristics of the 196 pterygium patients are detailed in Table 1. The age range was from 24 to 83 years with a mean age of 56.66 ± 11.25 years. There were 134 women (68.37%). The presence of hypertension was 20.41% and diabetic was 6.63% of the patients.

In terms of pterygium type, 83.16% (n = 163) of the cases were primary pterygium, while 16.84% (n = 33) were recurrent. Among the primary pterygium 5 were bilateral and 158 were nasal pterygium. The number of previous surgeries was 1.10 ± 0.30 in recurrent pterygium. Furthermore, pterygium severity was categorized into three grades: Grade 1 represented 55.61%, Grade 2 comprised 33.67%, and Grade 3 represented the most severe cases, accounting for 10.71% (Table 1).

Incidence of pterygium recurrence

Figure 1 demonstrates the cumulative probability of pterygium recurrence over a mean follow-up period of 24.78 ± 6.08 months. The overall recurrence rate was 7.65%, with a recurrence rate of 6.13% in the primary pterygium group and 15.15% in the recurrent pterygium group. The average time to recurrence was 8.87 ± 5.15 months, indicating that most recurrences occurred within the first year after surgery.

Biomarkers and recurrence

The analysis of laboratory biomarkers between cure and relapse groups showed significant differences. The WBC count was notably higher in the relapse group (6.85 [6.32; 8.30]) than in the cure group (6.08 [5.26; 6.90]), with a p-value of 0.011. Similarly, neutrophils were elevated in the relapse group (4.77 [4.00; 6.08] vs. 3.64 [2.87; 4.40]), showing high significance ($P = 0.001$). NLR levels were also significantly higher in the relapse group (3.14 [2.62; 3.92]) compared to the cure group (1.98 [1.52; 2.43], $P < 0.001$). Other markers, including Hb, PLT, hematocrit (Hct), and PLR, showed no significant differences, with P-values from 0.164 to 0.831 (Table 2).

Factors association with pterygium relapse

In the univariate logistic regression analysis, NLR (Odds Ratio [OR]: 4.32, 95% Confidence Interval [CI]: 1.18–15.83, $P = 0.027$), Grade 3 (OR:6.50, 95% CI:[1.69-24.99], $P = 0.006$) were significantly associated with relapse after pterygium resection. Similary, in multivariate regression analysis, NLR (OR=4.35, 95% CI: [1.14-16.61, $P =$

	All N = 196
Age	56.66 (11.25)
Gender	
Female	134 (68.37%)
Male	62 (31.63%)
Hypertension	40 (20.41%)
Diabetes	13 (6.63%)
Type:	
Primary	163 (83.16%)
Recurrent	33 (16.84%)
Grade:	
T1	109 (55.61%)
T2	66 (33.67%)
T3	21 (10.71%)
Follow-up time	24.78 (6.08)
Previous number of surgeries	1.10 (0.30)
Surgical result	
Cure	181 (92.35%)
Recurrence	15 (7.65%)

Table 1. Demographics characteristic of pteryium patients. T1 (atrophic): Thin, transparent pterygium with visible underlying episcleral vessels. T2 (intermediate): Moderately thickened pterygium with partially obscured episcleral vessels. T3 (fleshy): Thick, opaque pterygium completely covering the underlying episcleral vessels.

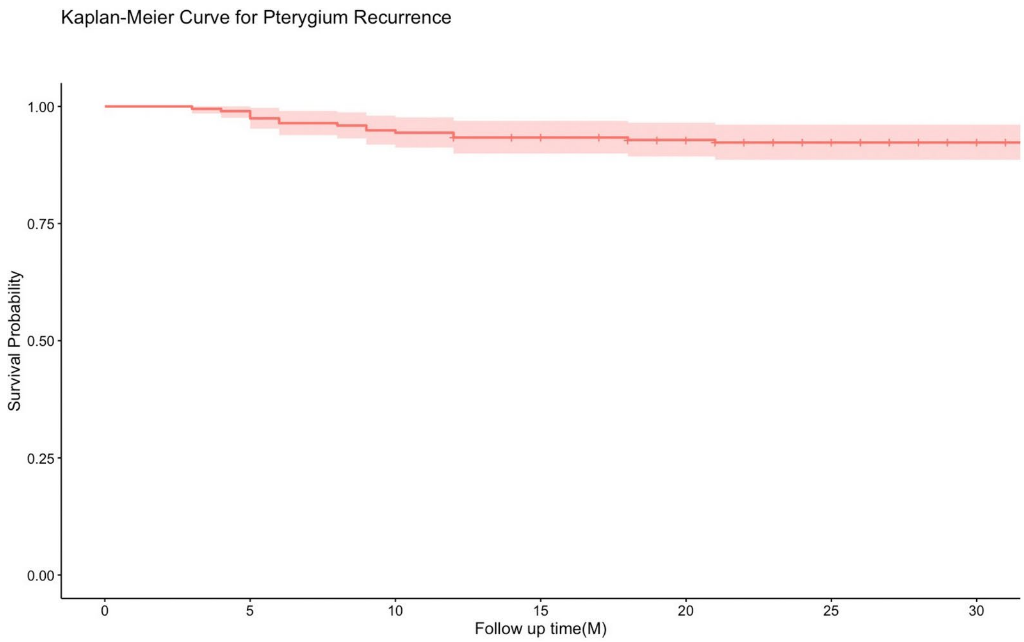

Fig. 1. This Kaplan–Meier curve illustrates the cumulative probability of overall pterygium recurrence over time in 196 eyes, with a mean follow-up period of 24.78 ± 6.08 months. The overall recurrence rate was 7.65%. The average time to recurrence was 8.87 ± 5.15 months.

	All N = 196	Cure N = 181	Relapse N = 15	P-values
WBC	6.14 [5.27;6.97]	6.08 [5.26;6.90]	6.85 [6.32;8.30]	0.011
Neut	3.73 [2.95;4.52]	3.64 [2.87;4.40]	4.77 [4.00;6.08]	0.001
Lymph	1.82 [1.49;2.22]	1.84 [1.50;2.22]	1.64 [1.26;2.42]	0.400
Hb	136.52 (12.95)	136.62 (12.89)	135.33 (14.03)	0.736
PLT	239.98 (54.78)	241.50 (54.97)	221.60 (50.54)	0.164
Hct	40.70 [38.70;43.20]	40.70 [38.80;43.20]	41.40 [38.55;43.05]	0.925
MPV	10.00 [9.50;10.53]	10.00 [9.50;10.50]	10.30 [9.65;11.05]	0.279
PDW	11.20 [10.20;12.60]	11.10 [10.20;12.60]	11.70 [10.20;13.20]	0.383
RDWSD	40.70 [39.10;42.60]	40.70 [39.10;42.40]	41.30 [38.70;43.40]	0.831
RDWCV	12.40 [12.00;13.00]	12.50 [12.00;13.00]	12.20 [12.05;12.95]	0.567
NLR	2.01 [1.56;2.57]	1.98 [1.52;2.43]	3.14 [2.62;3.92]	< 0.001
PLR	133.05 [103.78;164.96]	132.63 [103.85;164.88]	135.01 [103.09;155.08]	0.807

Table 2. Laboratory biomarker-related variables by pterygium result classification. WBC: White blood cell count; Neut: Neutrophil count; Lymph: Lymphocyte count; Hb: Hemoglobin; PLT: Platelet count; Hct: Hematocrit; MPV: Mean platelet volume; PDW: Platelet distribution width; RDWSD: Red cell distribution width—SD; RDWCV: Red cell distribution width—CV; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

0.032]), Grade 3 (OR = 6.08, 95% CI:[1.52-24.31, P = 0.011]) remained significantly associated with recurrence, In contrast, age, sex, type, PLR, mean platelet volume (MPV), platelet distribution width (PDW) showed no significant association in either model. Further details are provided in Table 3.

Discussion

The findings of this study revealed that the preoperative NLR ratio and pterygium grade is predictor of relapse in patients with pterygium.. Furthermore, it can be readily extracted using routine blood test results. Various surgical methods such as excision combined with conjunctival autografting, amniotic membrane transplantation and mitomycin C injection have been used, However, pterygium recurrence remains a challenging problem in every single described procedure. The overall recurrence rate in our study was found to be 7.65%, 6.13% in primary pterygium group and 15.15% in recurrence pterygium group with an average follow-up time of 24.78 ± 6.08 months. The technique of conjunctival autografting has been shown effective in pterygium in terms

		OR (Univariable)	OR (Multivariable)
Age	Mean ± SD	1.04 (0.99–1.09, $P=0.133$)	
Gender	Female		
	Male	1.09 (0.36–3.33, $P=0.883$)	
Type	Primary		
	Recurrence	2.73 (0.87–8.60, $P=0.086$)	
Grade	T1		
	T2	1.70 (0.47–6.13, $P=0.414$)	1.27 (0.34–4.71, $P=0.717$)
	T3	6.50 (1.69–24.99, $P=0.006$)	6.08 (1.52–24.31, $P=0.011$)
NLR	< 2.01		
	≥ 2.01	4.32 (1.18–15.83, $P=0.027$)	4.35 (1.14–16.61, $P=0.032$)
PLR	< 133.05		
	≥ 133.05	1.55 (0.53–4.54, $P=0.423$)	
MPV	< 10		
	≥ 10	1.66 (0.57–4.85, $P=0.356$)	
PDW	< 11.2		
	≥ 11.2	2.21 (0.73–6.72, $P=0.163$)	

Table 3. Univariate and multivariate analysis of prognostic factors for pterygium recurrence. NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MPV: Mean platelet volume; PDW: Platelet distribution width.

of low recurrence rate, a procedure first described Kenyon et al. in 1998[14]. As an overview of the recurrence rate ranged from 5 to 39% following conjunctival autografting[15–17]. Our result is close to what has been shown by Kocamis et al., who reported a recurrence rate of 8% over an average follow-up time of 4.5 months[18]. This is lower to what has been reported from study conducted in the United States by Varssano et al. with a similar mean follow-up period (34.4 months) to that in our study (24.7 months), recurrence rates was 11.4%[17]. In current study, we assume that we observed lower recurrence rate due to surgical skills and experience. We removed the pterygium from the semilunar fold towards the limbus that means the size of the resected pterygium was larger, which we believe will result in better appearance and decrease of recurrence rate. Moreover, the variation in recurrence rates is mainly due to areas and populations differences, which indicate the existence of considerable systemic inflammatory variation.

Thus, it is necessary to identify novel risk factors for recurrence. To the best of our knowledge, this is the first study to investigate an association between pre-operative NLR and prognosis in pterygium. Our findings add valuable insight into the predictive potential of the systemic inflammatory response on the surgery outcomes of pterygium.

There are numerous studies postulating that local inflammatory cells and cytokines contribute to the pathogenesis of pterygium. Tekelioglu Yavuz et al[19] reported the levels of T-lymphocyte infiltration and inflammatory markers was increased in pterygium tissue. Another study by Zidi et al[5] reported that NOS2, NF-κB and Bcl2 local inflammation play an important role in tissue damage and enhanced cellular proliferation, which lead to the pathogenesis of pterygium. Previous studies[12] have reported that MPV was significantly lower and PLR was significantly higher in pterygium patients than in healthy subjects, and inverse correlation between MPV and the pterygium classification groups, which hinted the association between the systemic inflammatory and pathogenesis of pterygium. Belviranli et al[20] reported increased NLR in patients with pterygium may be an indicator of systemic inflammation. However, in existing studies that compared pterygium patients with normal individuals, none showed the association between the systemic inflammatory and prognosis of pterygium.

Given the association between inflammatory and pathogenesis of pterygium, we hypothesized that the systemic inflammatory may affect the prognosis of pterygium. Thus, we sought to define prognostic factors associated with recurrence in a single-institution study of patients with pterygium. In our study, both univariate and multivariate analyses indicated a significant association between NLR and pterygium relapse, establishing NLR as a risk factor for recurrence.

The mechanisms underlying the association between high NLR and high recurrence rate remain largely unknown so far. Neutrophils play an important role in innate immunity, which that can produce chemokines, cytokines, vascular endothelial growth factor to reinforce the initial line of immune system. Likewise, lymphocytes are a type of adaptive immunity cell that can control particular immune responses. The increase in NLR is resulting from both neutrophilia and lymphopenia. So we assume that neutrophils and lymphocytes may interact with each other, which amplify the immune response's amplitude.

Our results demonstrate that NLR is associated with recurrence in patients with pterygium, which indicate that the immune system play an important role in this disease. It might be possible to identify patients who are at high risk of recurrence after the surgery. Therefore, we recommend further aggressive treatment in perioperative period in patients with high NLR.

Our study has limitations that must be considered. First, certain characteristics could not be evaluated or controlled for due to limitations of retrospective chart review. Second, the sample size (196 pterygium patients) may have been insufficient, and a study with larger sample size could be used to further validate the findings. Third, there was no defined cutoff value for NLR, further larger scale studies should be performed to determine an optimal cutoff value for NLR. Nevertheless, our study is valuable as we found that an elevated NLR was significantly associated with recurrence in patients with pterygium.

In conclusion, our findings indicate that NLR may be clinically applicable and useful as an independent prognostic marker for patients with pterygium recurrence. This study brings potential future benefits to patients selection, outcome prediction and improving long-term care strategies.

Data availability

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [SK.C], [MX. Z], [YS. L], [QX. L], [YL. S], and [TY. X]. The first draft of the manuscript was written by [SK.C], and [LY. T]. All authors read and approved the final manuscript.

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Declarations

Competing interests
This study did not receive any industrial support. The authors have no competing interests to declare regarding this study.

Ethical approval and consent to participate
The study methods and protocols were approved by the Medical Ethics Committee of the Zhongshan Hospital of Xiamen University (Fujian, China) and followed the principles of the Declaration of Helsinki. All subjects were notified of the objectives and content of the study and latent risks, and then provided written informed consent to participate.

Additional information
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