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Evaluation of progression predictability with systemic inflammatory biomarkers in keratoconus patients

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Abstract

This research aimed to assess the association between keratoconus (KC) progression and systemic inflammation markers. Additionally, we aimed to identify which specific systemic inflammation markers have a predictive effect on the progression of KC. 111 patients, including 69 with stable KC, and 42 with progressive KC were diagnosed and subsequently followed up between 2020-2023 at the Ophthalmology Clinics. This retrospective study also included 52 gender and age-matched healthy individuals who underwent examination at the Ophthalmology department. From the hemogram parameters, neutrophils, lymphocytes, platelets, and monocytes levels were used to calculate the systemic inflammation markers. When the KC patients and the healthy control group were related, significant differences were found in keratometry values (K1, K2, Kmax), astigmatism, central cornea thickness (CCT), and Baiocchi Calossi Versaci (BCV) values. No significant difference was detected when hemogram parameters except for neutrophils and platelets were compared in all groups ($p>0.05$). However, statistically significant differences were detected among the groups in the inflammatory values ($p<0.001$). When the post-hoc analysis of the groups was performed, the progressive KC patients were found to have statistically significant differences from stable KC and control groups in all inflammation parameters ($p<0.001$). However, no notable variation was observed between the stable KC and healthy group ($p>0.05$). Our research revealed a notable correlation between elevated inflammatory biomarkers and keratoconus progression, suggesting they may serve as independent prognostic indicators.

Keywords: Keratoconus, systemic inflammation markers, inflammation

Introduction

Keratoconus (KC) is a corneal disorder that leads to irregular astigmatism, nearsightedness, and diminished vision [1]. It is marked by thinning of the corneal stroma, bulging, and scarring. KC typically affects both eyes and often begins during puberty or early adulthood [2]. The global prevalence of KC has been estimated to range from 0.0004% to 0.27% [3].

The exact pathophysiology of KC remains unclear. There are many proposed mechanisms, but the most important factors in the pathogenesis of the disease are genetic predisposition and environmental factors [4]. Inflammation is an important environmental factor in the pathogenesis of KC. Risk factors such as allergies, ultraviolet exposure, eye trauma, contact lens use, and dry eye syndrome may contribute to the pathogenesis of keratoconus by provoking inflammatory processes [5]. Additionally, increases in ocular and systemic inflammation mediators have been shown in KC patients. A notably elevated tear production of cytokines was detected in KC tears [6]. KC progression is strongly associated with increased inflammation. Notably, chronic eye rubbing and repetitive mechanical trauma are postulated to induce inflammation, significantly contributing to KC progression [7].

Systemic inflammatory markers have been identified as indicators of systemic inflammation response in various research [8-16]. Several of these indicators have been examined across numerous eye diseases associated with systemic inflammation, such as retinal artery and vein occlusion, dry eye, and pseudoexfoliation syndrome [17,18]. Previous studies have found conflicting results concerning the association between KC and widespread inflammatory response. While some studies did not detect a relationship between systemic inflammation markers and KC, some indications found a positive correlation between these markers and KC pathogenesis [2,19]. Although the relationship between KC pathogenesis and systemic inflammation is investigated, to the best of our knowledge, the contribution of

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systemic inflammation to KC progression has not been evaluated. Therefore, we aimed to assess the association between KC progression and systemic inflammation markers. Additionally, we investigated which of systemic inflammation markers have a predictive effect on KC progression.

Material and Methods

A total of 111 patients, including 69 with stable KC, and 42 with progressive KC were diagnosed and subsequently followed up between March 2020-November 2023 at the Ophthalmology Clinics of Aksaray University Training and Research Hospital. This retrospective study also included 52 gender and age-matched control subjects who were examined at the ophthalmology department. Demographic data for the groups were obtained based on medical facility records. The Aksaray University Health Sciences Scientific Research Ethics Committee approved the study in accordance with the Helsinki guidelines (Approval no: SAGETİK02, Date: 21.03.2024).

Patients with any ocular condition besides keratoconus were excluded, as well as those with a prior history of corneal or other eye surgeries, cross-linking, or medical conditions such as diabetes, high blood pressure, cardiovascular or cerebrovascular issues, renal or liver disorders (acute or chronic), infections (local or systemic, acute or chronic), anemia, or cancer. Exclusion criteria also included recent surgeries within the past three months, pregnancy, systemic or ocular allergies (like atopic eye disease or hay fever), steroid or anti-hyperlipidemic medication use, and ongoing anti-inflammatory treatments.

A comprehensive ophthalmologic examination was conducted on all patients included in the study, and their keratometry values (K1, K2, K max), corneal astigmatism, central corneal thickness (CCT), and Baiocchi Calossi Versaci index (BCV) were obtained using the Scheimpflug corneal topography system (Sirius, Costruzioni Strumenti Ophthalmici, Italy). Following clinical and topographic assessments, eyes exhibiting corneal thinning, apical protrusion, and ectasia were classified as KC.

KC patients were followed up regularly at 6-month intervals, and patients with decreased visual acuity, increased keratometry values, tapered CCT, increased astigmatism, and significantly increased BVC values were recorded as progressive KC patients.

Demographic data and hemogram parameters were gathered from hospital records. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), and pan-immune-inflammation value (PIV) were calculated using the following formulas:

$$\text{neutrophils} \div \text{lymphocytes}$$

$$\text{platelets} \div \text{lymphocytes}$$

$$\text{platelets} \times (\text{neutrophils} \div \text{lymphocytes})$$

$$(\text{neutrophils} \times \text{monocyte}) \div \text{lymphocytes}$$

$$(\text{neutrophils} \times \text{platelets} \times \text{monocytes}) \div \text{lymphocytes}$$

Statistical analysis

IBM SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA) statistical software was utilized to analyze group data. Kolmogorov-Smirnov test was used to determine whether the groups were normally distributed. The ANOVA test was used to compare the study groups. Categorical variables were analyzed with the chi-square test. $P<0.05$ was considered statistically significant.

Results

A total of 163 subjects -69 with stable KC, 42 with progressive KC, and 52 with healthy group- with average ages of 31.7±11.3 years, 30.9±11.6, and 29.1±5.1 years, respectively, were included in this study. When the KC patients and the control group were compared, significant differences were found in K1, K2, Kmax, astigmatism, CCT, and BCV values, as expected ($p<0.001$, Table 1). Table 2 displays the hemogram parameters and inflammatory indices. No significant difference was detected when hemogram parameters except for neutrophils and platelets were compared in all groups. ($p>0.05$, Table 2). However, statistically significant differences were detected among the groups in the NLR, PLR, SII, SIRI, and PIV values ($p<0.001$, Table 2). When the post-hoc analysis of the groups was performed, the progressive KC patients were found to have statistically significant differences from stable KC and control groups in all parameters for NLR, PLR, SII, SIRI, and PIV ($p<0.001$). However, no significant difference was found between stable KC and control groups ($p>0.05$).

Table 1. Demographic information of the study and control groups

Parameters		Control (n=52) Mean±SD	Stable KC (n=69) Mean±SD	Progressive KC (n=42) Mean±SD	p*
Gender	Male	33 (63.5%)	32 (46.4%)	17 (40.5%)	0.600
	Female	19 (36.5%)	37 (53.6%)	25 (59.5%)	
Age (year)		29.1±5.1	31.7±11.3	30.9±11.6	0.789
K1		43.1±1.5	45.1±2	46.6±3.2	<0.001
K2		43.8±1.5	48.8±2.9	50.4±3.8	<0.001
Kmax		43.9±1.6	51.5±3.3	53.1±4.2	<0.001
Ast		-0.7±0.4	-3.6±2.3	-3.7±1.7	<0.001
CCT		529.7±36.5	456.7±48.4	440.2±56.4	<0.001
BCV		0.2±0.2	2.6±1.4	3.2±2.2	<0.001

*Chi-square test, Ast: astigmatisma, BCV: Baiocchi Calossi Versaci, CCT: central corneal thickness, K: keratometry, KC: keratoconus, SD: standart deviasion

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Table 2. Comparison of the hemogram parameters of the study and control groups

	Control (n=52) Median (min-max)	Stable KC (n=69) Median (min-max)	Progressive KC (n=42) Median (min-max)	p*
WBC (10^3µL)	7.1 (4.2-10)	7.1 (3-16.5)	7.5 (4.6-15.4)	0.057
NEU (10^3µL)	3.9 (2-5.9)	3.9 (1.2-10.8)	4.9 (2.7-11.3)	0.002
LYM (10^3µL)	2.3 (1.6-4.5)	2.3 (0.9-5.3)	2 (1.1-4.1)	0.074
Mono (10^3µL)	0.4 (0.2-0.6)	0.4 (0.1-0.7)	0.4 (0.2-1)	0.167
HGB (g/dL)	14.7 (9-18)	14.5 (9.3-14.4)	13.9 (11.1-17.6)	0.404
PLT (10^3µL)	258 (81-360)	266 (164-464)	298 (158-418)	0.007
NLR	1.6 (0.6-2.3)	1.5 (0.7-3.9)	2.1 (1.6-5.5)	<0.001
PLR	100.9 (37.8-169.6)	108.2 (53-261.2)	132.6 (61.2-290.2)	<0.001
SII	383.9 (170-682)	430 (131-1408)	599.3 (361-1497)	<0.001
SIRI	0.7 (0.2-1.4)	0.7 (0.2-2.7)	1 (0.4-5.9)	<0.001
PIV	179.4 (30.6-331.8)	175.8 (42-830)	274.5 (101-1198)	<0.001

*ANOVA test NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic inflammatory index (neutrophil x platelet / lymphocyte count), SIRI: systemic inflammatory response index (neutrophil × monocyte / lymphocyte count) and PIV: pan-immune inflammation value (neutrophil × platelet x monocyte / lymphocyte count)

Discussion

We indicate that this is the first study to investigate blood count parameters and inflammation-related markers, such as NLR, PLR, SII, SIRI, and PIV, were analyzed collectively in individuals with stable and progressive keratoconus. Our study shows that, a significant difference was observed between patients with stable KC and patients with progressive KC in terms of hematological indices.

This is the first report to evaluate the role of systemic inflammatory indices to predict the prognosis of KC patients. KC, classically defined as noninflammatory, has recently been associated with chronic inflammation. Disruptions in immune-related homeostasis within the tear film, observed in KC patients, indicate ocular inflammation [20]. Latest researches have been indicated that pro-inflammatory markers, such as Interleukin-6, 1-β, and Interferon-γ, are overexpressed in individuals with KC [4]. Besides these local inflammatory markers, systemic inflammatory markers have also been found to be elevated in KC patients [8,18].

A recent investigation analyzing keratoconus cases uncovered new links between keratoconus and Hashimoto's thyroiditis, as well as inflammatory skin disorders. It also reaffirmed established connections between keratoconus and atopic conditions such as allergic rashes, asthma, bronchial hyperresponsiveness, and allergic rhinitis [21]. These findings suggest that keratoconus is positively correlated with various immune-mediated diseases, supporting the notion that systemic inflammatory responses may play a role in its development. Many studies evaluate whether simple and inexpensive routine hematologic inflammation biomarkers have a role in the development of KC. Oltulu et al. study detected that NLR values considered inflammatory markers were statistically significantly higher in the keratoconus group [2]. However, Bozkurt et al found, that although no significant difference was found between the groups in terms of NLR levels, PLR was significantly higher in the KC group [8]. Elbeyli et al. reported that the inflammatory pathway may play an important role in the pathogenesis of KC disease and found that SII, NLR, and PLR levels were significantly increased in patients with KC [1]. In the present study, there was no difference in NLR, PLR, SII, SIRI, and PIV parameters between stable KC patients and control group patients. However, all parameters were found to be significantly higher in progressive KC patients than in the control group. We believe that the significant differences observed in other studies may be attributed to the lack of distinction between stable and progressive KC, as the entire cohort of KC patients was compared with the control group.

It has been reported that there is a positive correlation between ocular inflammation and progression in KC patients [22,23]. Nichani et al. found that keratoconic eyes with MMP 9 positive tears have been associated with increased disease severity. They found a significantly higher presence of the inflammatory marker in eyes with more severe KC [24]. Our study is the first in this regard and is important in terms of determining a correlation between systemic inflammatory biomarkers and KC progression. In present study, progressive KC patients had significantly higher NLR, PLR, SII, SIRI, and PIV values than both the stable and control groups, indicating that inflammatory biomarkers are important in determining progression. This research is the first report to indicate the prognostic significance of the NLR, PLR, SII, SIRI, and PIV results in patients with KC. This study's key advantage lies in utilizing systemic inflammation markers, known as prognostic indicators, to examine progressive keratoconus.

The important aspect of the study is the use of inflammatory markers in the investigation of advanced KC. The limitation of the current study is in a single-center setting. Further prospective studies with larger sample sizes are needed in the future.

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Conclusion

The current research found that elevated inflammatory biomarkers were significantly linked to patients with progressive keratoconus and may serve as an independent prognostic factor. While these biomarkers solely are not definitive, this research is valuable as it may help predict the likelihood of progressive keratoconus.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The Aksaray University Health Sciences Scientific Research Ethics Committee approved the study in accordance with the Helsinki guidelines (Approval no: SAGETİK02, Date: 21.03.2024).

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