Original Article

Assessing the role of systemic inflammation in the etiopathogenesis of advanced stage keratoconus

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Purpose: It was aimed to compare the levels of inflammation-related parameters, such as neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), in patients with advanced keratoconus (KC) and healthy controls. Also, we evaluated the relationships between these parameters and several corneal topography values used in the KC diagnostic index. **Methods:** Forty patients with advanced and 40 healthy volunteers were included in this study. In the KC group, 20 patients were nonprogressive KC and 20 patients were progressive KC. In all participating individuals, we evaluated detailed ophthalmologic examination findings and complete blood count data, while corneal topographic measurements were also recorded in patients with KC. **Results:** The mean NLR value was 2.3 ± 1.19 in the progressive KC group; nonprogressive KC values were 1.99 ± 1.69 and 1.81 ± 0.72 in the control group. Mean PLR value was 113.24 ± 48.44 in the progressive KC group, nonprogressive KC values were 96.47 ± 31.04 and 104.09 ± 35.14 in the control group. No statistically significant difference was found between patients with progressive KC, nonprogressive KC, and healthy volunteers in terms of mean NLR and PLR values ($P > 0.05$). NLR values were found to demonstrate significant positive correlations with the corneal topography parameters, Symmetry Index front ($r = 0.278$, $P = 0.025$), KC Vertex front ($r = 0.247$, $P = 0.048$), and Baiocchi Calossi Versaci front ($r = 0.273$, $P = 0.028$); there was no significant relationship between corneal topography parameters and PLR values. **Conclusion:** Although there was no significant difference between the progressive KC, nonprogressive KC, and control groups in inflammation parameters such as NLR and PLR, a positive correlation was observed between the NLR value and some corneal topography findings used in the diagnosis of KC. The role of inflammation in the etiology of KC can be better understood by clinical studies and laboratory tests conducted with prospective studies involving a higher number of patients.

Key words: Inflammation, keratoconus, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, sirius corneal topography

Keratoconus (KC) is a bilateral, asymmetric, noninflammatory, progressive corneal ectasia that causes high myopia, astigmatism, and vision loss.[1,2] It typically begins at puberty, progresses and generally stabilizes between 30 and 40 years of age.[3] The prevalence of KC has been reported to be 1/2000; however, it is known to vary according to diagnostic methods and between different studies.[4] The main environmental and demographic factors in the progression of KC include rubbing the eyes, atopy history (hay fever, asthma, urticarial, and eczema), contact lens use, and ultraviolet exposure. Corneal topography systems based on index-based classification principles are used in diagnosis, severity grading, and corneal thickness measurements.[5,6] One of these topography devices, the Sirius system (Costruzione Strumenti Ophthalmici, Florence, Italy), has an anterior segment analysis that combines a 360° rotating Scheimpflug camera and a 22-ring placido-disc approximately 60000 points are examined on both posterior and anterior surface of the cornea with 475 nm blue LED light. The treatment in KC depends on the severity of the disease. Traditionally, glasses in the early stage of the disease, contact lenses in nonsevere cases, and keratoplasty in severe cases are preferred in the treatment. Corneal cross-linking and intracorneal ring segments are alternative surgical methods that can be performed in the treatment of KC.[7] Around 10–20% of cases with KC progress to the final stage necessitating keratoplasty.[7-9]

Although many genetic, biomechanical, and physical causes have been reported, the etiology of KC has not been fully explained. The generally accepted definition of KC is that it is a noninflammatory corneal ectasia; however, recent studies report that proinflammatory factors may play a role in the pathogenesis.[10] In the inflammation observed in the cornea, increased levels of lysosomal proteinases such as cathepsin B-G and other catabolic enzymes, cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6), factors associated with oxidative stress, and eight decreased proteinase inhibitors such as α2-macroglbulin and α1-antiprotease act in a concerted manner leading to proteolytic activity which disrupts the corneal stroma.[11-13] In studies conducted with the tear fluid

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samples of patients with KC, it was observed that IL-6, matrix metalloproteinase-9 (MMP-9), and tumor necrosis factor-α levels were significantly elevated, while immunoglobulin-A and lactoferrin levels were found to be decreased.[10,14,15] The relationship between KC and inflammatory molecules in tear fluid has been extensively studied, but studies exploring relationships between KC and systemic inflammation are rare. In recent years, indices such as neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), erythrocyte distribution width (RDW), and hemoglobin (Hb) have been shown to have been utilized as prognostic markers of systemic inflammation in many systemic diseases, like diabetes mellitus (DM), myocardial infarction, hypertension, cancer, and psoriasis.[16-20]

In the light of these data, the present study investigated the role of systemic inflammation in the etiology of KC by comparing inflammation-sensitive blood marker levels such as PLR and NLR in cases with advanced KC and the control group. In addition, we compared serum PLR and NLR levels in cases with unilateral and bilateral KC. We also sought to determine whether these parameters demonstrated any relationships with corneal topography parameters used in the KC diagnostic index.

Table 1: Comparison of hemogram results in KC and control groups

	KC group (*n*=40) Mean±SD	Control group (*n*=40) Mean±SD	*P*
WBC	8.41±2.76	8.37±2.5	0.912
RBC	5.05±0.63	4.85±0.55	0.085
Hgb	14.11±1.89	13.38±2.04	0.101
RDW	12.69±1.93	14.24±1.25	0.001*
PLT	253.37±71.58	277.3±83.98	0.402
LYM	2.6±0.87	2.82±0.86	0.245
LYM%	32.04±9.61	33.91±10.87	0.825
MONO	0.62±0.33	0.69±0.31	0.289
MONO%	7.12±2.29	8.08±3.47	0.204
NEU	4.97±2.27	4.79±1.7	0.700
NEU%	57.47±10.5	57.09±10.12	0.870
NLR	2.15±1.46	1.81±0.72	0.658
PLR	104.86±41.05	104.09±35.14	0.893

WBC: White blood cell count, RBC: Red blood cell count, Hgb: Hemoglobin, RDW: Red cell distribution width, PLT: Platelet count, LYM: Lymphocyte, MONO: Monocyte, NEU: Neutrophil, NLR: Neutrophil-to-lymphocyte ratio, and PLR: Platelet-to-lymphocyte ratio.

Methods

This study was approved by the Adıyaman University clinical research ethics committee (Date: 07/21/2020 Project No: 2020/7-23), and the study adhered to the research principles in the Declaration of Helsinki. Informed consent was obtained from all participants. Forty patients with advanced KC and 40 healthy volunteers were included in the study. In the KC group, 20 patients were nonprogressive KC (group 1) and 20 patients were progressive KC (group 2). Those who had a habit of smoking and alcohol use, individuals using gas-permeable hard contact lenses, those with a history of ocular disease or surgery, patients who had been diagnosed with atopy or allergic diseases, pregnant subjects, those with any systemic inflammatory disease, and those currently receiving anti-inflammatory treatment were excluded from the study.

Ophthalmological examination of all participants were performed. In the examination, best-corrected visual acuity with Snellen chart, intraocular pressure measurement with Goldmann applanation tonometer, slit-lamp examination, and fundus examination were performed. Additionally, a new-generation noncontact corneal topography (Sirius Costruzione Strumenti Ophthalmic, Florence, Italy) device with placido disc and mobile Scheimpflug camera system was utilized in patients with KC. All corneal topography evaluations were performed by the same qualified technician under scotopic vision without dilating the pupil. The following parameters were recorded in the corneal topography analysis of patients with KC: CCT (central corneal thickness), SimK1 (Simulate K index 1), SimK2 (Simulate K index 2), Thk (thinnest corneal thickness), Slf (Symmetry index front), KVf (KC vertex front), BCVf (Baiocchi Calossi Versaci front), Slb (Symmetry index back), KVb (KC Vertex back), and BCVb (Baiocchi Calossi Versaci back). Advanced stage KC (stage 3–4) diagnoses were made in accordance with the Amsler-Krumeich classification system. According to this classification, patients with the following characteristics are defined to have advanced stage KC: astigmatism value greater than 8 diopters (D) and/or myopia, corneal thickness less than 400 μm, and central keratometry value greater than 53 D.

With regard to complete blood counts (CBC), we only included patients with results that had been obtained within

Table 2: Comparison of hemogram results in nonprogressive kc, progressive kc, and control groups

	Control group (Grup 0)	Nonprogressive KC (Grup 1)	Progressive KC (Grup 2)	*P* (0-1)	*P* (0-2)	*P* (1-2)
WBC	8.37±2.5	8.40±2.6	8.43±2.9	>0.05	>0.05	>0.05
RBC	4.85±0.55	5.07±0.77	2.02±0.46	>0.05	>0.05	>0.05
Hgb	13.38±2.04	13.90±1.98	14.32±1.81	>0.05	>0.05	>0.05
RDW	14.24±1.25	12.71±1.78	12.66±2.11	>0.05	>0.05	>0.05
PLT	277.3±83.98	254,6±76.24	252±68.54	>0.05	>0.05	>0.05
LYM	2.82±0.86	2.79±0.95	2.40±0.74	>0.05	>0.05	>0.05
LYM%	33.91±10.87	34.23±10.04	29.81±8.84	>0.05	>0.05	>0.05
MONO	0.69±0.31	0.58±0.21	0.65±0.42	>0.05	>0.05	>0.05
MONO%	8.08±3.47	6.85±2.26	7.40±2.34	>0.05	>0.05	>0.05
NEU	4.79±1.7	4.85±2.37	5.08±2.20	>0.05	>0.05	>0.05
NEU%	57.09±10.12	55.76±11.64	59.17±9.19	>0.05	>0.05	>0.05
NLR	1.81±0.72	1.99±1.69	2.3±1.19	>0.05	>0.05	>0.05
PLR	104.09±35.14	96.47±31.04	113.24±48.44	>0.05	>0.05	>0.05

WBC: White blood cell count, RBC: Red blood cell count, Hgb: Hemoglobin, RDW: Red cell distribution width, PLT: Platelet count, LYM: lymphocyte, MONO: Monocyte, NEU: Neutrophil, NLR: Neutrophil-to-lymphocyte ratio, and PLR: Platelet-to-lymphocyte ratio

Table 3: Comparison of hemogram results in bilateral and unilateral KC patients

	Bilateral KC (*n*=25) Mean±SD	Unilateral KC (*n*=15) Mean±SD	*P*
Age (years)	27.72±10.29	23.4±5.67	0.552
WBC	8.34±2.93	8.53±2.54	0.908
RBC	5.04±0.56	5.07±0.76	0.227
Hgb	14.06±1.86	14.2±1.99	0.193
Hct	42.74±4.96	42.71±5.15	0.096
MCV	84.84±5.36	85.01±9.65	0.534
MCH	27.95±2.65	28.3±4.01	0.143
RDW	12.45±1.35	13.09±2.64	0.650
PLT	261.49±69.68	239.83±75.06	0.441
MPV	8.48±1.39	8.69±2.04	0.651
LYM%	31.13±10.5	33.55±8.03	0.625
LYM	2.48±0.86	2.79±0.88	0.299
MONO%	7.06±2.48	7.24±2.03	0.391
NEU	5.04±2.54	4.84±1.81	0.920
NEU%	58.44±11.82	55.84±7.93	0.734
MONO	0.61±0.38	0.63±0.25	0.345
NLR	2.3±1.63	1.89±1.1	0.584
PLR	114.34±46.76	89.06±22.76	0.208

KC: Keratoconus, WBC: White blood cell count, RBC: Red blood cell count, Hgb: Hemoglobin, Hct: Hematocrit, RDW: Red cell distribution width, PLT: Platelet count, LYM: Lymphocyte, MONO: Monocyte, NEU: Neutrophil, NLR: Neutrophil-to-lymphocyte ratio, and PLR: Platelet-to-lymphocyte ratio.

Table 4: Correlations between corneal topographical parameters and the NLR and PLR values

Corneal topography parameters	Correlation coefficient	NLR	PLR
CCT	R	0.095	0.018
	P	0.453	0.887
SimK1	R	0.118	0.049
	P	0.351	0.701
SimK2	R	0.162	0.041
	P	0.196	0.743
Thk	R	0.021	-0.012
	P	0.865	0.925
Slf	R	0.278*	0.157
	P	0.025	0.210
KVf	R	0.247*	0.149
	P	0.048	0.237
BCVf	R	0.273*	0.124
	P	0.028	0.324
Slb	R	0.166	0.085
	P	0.187	0.501
KVb	R	0.219	0.209
	P	0.079	0.096
BCVb	R	0.227	0.189
	P	0.069	0.131

r: Spearman rank correlation coefficient, *Significant at 0.05 level

the last month. We ensured that the CBC measurements were taken for routine screening purposes (preoperative preparation, check-up examination, etc.) and the patients did not have any pathology that would affect the results from the moment the blood was given. CBC measurements were performed with an automated analyzer (Beckman Coulter Inc., Miami, FL). NLR and PLR values were calculated based on CBC measurements.

Comparisons were performed based on the presence/absence of KC (healthy controls vs. patients) and eye involvement in patients with KC (unilateral vs. bilateral). In the KC group, we also evaluated the relationships between corneal topography parameters and the values of NLR and PLR.

Whether continuous variables were normally distributed was analyzed using the Shapiro–Wilk test. Student's *t*-test was used for normally distributed data and Mann–Whitney U-test for nonnormally distributed data to compare quantitative variables between two independent groups. One way ANOVA test was used for normally distributed data to compare quantitative variables between three independent groups. The Chi-square test was used to analyze the distribution of categorical variables among groups. Spearman's rank correlation coefficient was used for correlation analysis between numerical variables. Statistical Package for the Social Sciences (SPSS, version 24.0) was used for all statistical analyzes. Any *P* value of <0.05 was accepted as significant statistically.

Results

Forty patients with KC (25 bilateral, 15 unilateral) and 40 healthy volunteers were included in the study. Forty-six (57.5%) of the participants were female and 34 (42.5%) were male. The mean age was determined as 26.10 ± 9.01 years in the KC group and 25.75 ± 9.13 years in the control group. There was no statistical difference between the two groups in terms of age and gender ($P = 0.780$ and $P = 1.000$, respectively). When the hemogram results were compared, there was no statistically significant difference in parameters such as white blood cell count, red blood cell count, hemoglobin, platelet count, and also white blood cell subgroups (neutrophil, lymphocyte, monocyte counts). A significant difference was found in mean RDW values ($P = 0.001$) between the two groups. No statistically significant difference was found between the two groups in the mean values of NLR and PLR ($P = 0.658$ and $P = 0.893$, respectively). The hemogram results of the two study groups are given in Table 1: The mean NLR value was 2.3 ± 1.19 in the progressive KC group; nonprogressive keratoconus values were 1.99 ± 1.69 and 1.81 ± 0.72 in the control group. The mean PLR value was 113.24 ± 48.44 in the progressive keratoconus group; nonprogressive keratoconus values were 96.47 ± 31.04 and 104.09 ± 35.14 in the control group. At the same time, when hemogram results were compared between the progressive KC (grup 2), nonprogressive KC (grup1), and the control group (grup 0), white blood cell count, red blood cell count, hemoglobin, platelet count, and also white blood cell subgroups (neutrophil, lymphocyte, monocyte count), NLR, and PLR, there was no statistically significant difference ($P > 0.05$) [Table 2]. When hemogram results were compared in bilateral and unilateral KC patients, no statistically significant difference was found in any of the parameters [Table 3]. With regard to the relationships between corneal topography parameters and white blood cell indices in the KC group, we found that Slf, Kvf, and BcVF were positively correlated with NLR values (r: 0.278, P: 0.025; r: 0.247, P: 0.048, and r: 0.273, P: 0.028, respectively) [Table 3]. There

was no significant relationship between corneal topography parameters and PLR values [Table 4].

Discussion

The present study investigated NLR and PLR indices in cases with advanced KC disease. We conclude that there is no difference in these indices between normal and advanced KC. Also, there is no difference in progressive KC and nonprogressive KC than the control group. At the same time, correlations between NLR values and some of the KC markers measured by the Sirius corneal topography device were observed. The etiopathogenesis in the emergence and progression of KC is still not fully understood. It has been shown that environmental factors, proteolytic enzymes, inflammatory cytokines, oxidative stress, free radicals, along with genetic predisposition, may play a role in etiopathogenesis.[21,22]

Many studies have been conducted on the relationship between KC and local inflammatory mediators.[23,24] Lema and Durán reported that the expression of IL-6, TNF-alpha, and MMP-9 increased in the tear fluid of patients with KC.[14] Abalain *et al*.[25] indicated the presence of increased collagen breakdown products in the tear fluid of cases with KC. Arnal *et al*.[26], and Wojcik *et al*.[27] reported that free oxygen radicals and reactive species were higher in the cornea of patients with KC compared to the control group and argued that these could cause stromal thinning of the cornea. In another study using tear samples, Balasubramanian Balasubramanian *et al*.[28] suggested that collagenases, gelatinases, metalloproteinases such as MMP-1, MMP-3, MMP-7, and MMP-13, and cytokines such as TNF-α, TNF-β, IL-1, and IL-6 could contribute to the progression of KC by causing collagen denaturation. All these and similar findings suggest the role of inflammation in the etiopathogenesis of KC contrary to traditional opinion.

It still remains unexplained whether the changes observed in the cornea with KC disease are due to the effect of systemic oxidative stress. Toprak *et al*.[23] showed that serum levels of oxidative stress markers were higher in cases with KC than controls and reported that oxidative stress factors may play a role in KC etiopathogenesis. On the other hand, Jun and colleagues[24] found no differences in serum cytokines and chemokines such as IL-1, IL-4, IL-6, IL-10, IL-12, IL13, IL-17, IFN-γ, CC motif ligand 5, and TNF-α, between KC patients and controls. Furthermore, in their large population-based study, Xu *et al*.[29] could not find a significant correlation between KC disease and serum C-reactive protein levels, a commonly used inflammatory marker.

The inflammatory process consists of a complex network of interactions includes neutrophils, macrophages, and lymphocytes involved in immunity. CBC is a simple and cheap test that provides the numbers and percentages of WBC, lymphocytes, platelets, and neutrophils. These parameters could be considered as inflammatory markers. PLR and NLR have prognostic value for many systemic diseases and are among the most commonly used inflammatory markers.[30-33] Recently, studies conducted with patients with DM, coronary artery disease, Behçet's disease, and cancer reported that high PLR and/or NLR values could be considered as systemic inflammatory markers and could indicate poor prognosis.[30-33] Studies in ocular diseases such as dry eye disease, open-angle glaucoma, degenerative myopia, acute anterior uveitis, diabetic retinopathy, retinal vein occlusion, and macular degeneration have reported that PLR and NLR could be prognostic factors for these diseases.[34-38]

We observed higher but statistically insignificant PLR and NLR values in cases with advanced stage KC than controls. Karaca *et al*.[39] reported significantly higher NLR values in cases with progressive KC than cases with stable KC and controls. In the study conducted by Katipoğlu *et al*.[40] in patients with KC disease, it was reported that NLR values were significantly higher compared to the control group. In parallel with our study, Bozkurt *et al*.[41] found higher but statistically insignificant PLR and NLR values in cases with KC than controls.

A significant difference was observed only in RDW values among CBC parameters between the KC and control groups. RDW indicates the distribution of erythrocyte volume and diameter. Erythropoietin (EPO) is the main physiological determinant of RDW. The proinflammatory cytokines seen in chronic inflammation can cause an increase in RDW value by inhibiting EPO synthesis and activity, disrupting iron metabolism, and shortening erythrocyte lifespan.[42] Bozkurt and colleagues[41] found no significant difference in RDW values between cases with KC and controls, contrary to our study. It was thought that this variation in the literature might be caused by the differences in the study population and some possible inflammatory diseases that could not be detected by CBC measurements.

The Sirius corneal topography device utilizes KVf, KVb, SIf, SIb, BCVf, and BCVb values as reference in the diagnosis and classification of KC. In the KC group, it was observed that there was a positive correlation between several KC index values (SIf, Kvf, BcVF) and NLR values. With this finding, it was thought that NLR could be a useful biomarker that could show the inflammation status and predict the prognosis of KC patients.

Study limitations

The present study is single-center and retrospective conducted with a small study population. Some other systemic inflammatory markers like complements, interleukins, and TNF-α could not be evaluated. It was thought that possible systemic inflammatory diseases that could not be detected by these laboratory tests might have had an effect on the results.

Conclusion

Although no significant difference was found between the cases with KC (progressive and nonprogressive) and controls in inflammatory parameters such as NLR and PLR, a positive correlation was observed between the NLR value and some corneal topography findings used in the diagnosis of KC. The relationship between inflammation and KC can be better elucidated by further prospective clinical studies and laboratory analyses with higher study populations that include biochemical analysis of tear fluid in conjunction with blood tests.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998;42:297-319.
2. Najmi H, Mobarki Y, Mania K, Altowairqi B, Basehi M, Mahfouz MS, *et al*. The correlation between keratoconus and eye rubbing: A review. Int J Ophthalmol 2019;12:1775.
3. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol 1984;28:293-322.
4. Hashemi K, Guber I, Bergin C, Majo F. Reduced precision of the Pentacam HR in eyes with mild to moderate keratoconus. Ophthalmology 2015;122:211-2.
5. Li Y, Meisler DM, Tang M, Lu AT, Thakrar V, Reiser BJ, *et al*. Keratoconus diagnosis with optical coherence tomography pachymetry mapping. Ophthalmology 2008;115:2159-66.
6. Gobbe M, Guillon M. Corneal wavefront aberration measurement to detect keratoconus patients. Cont Lens Anterior Eye 2005;28:57-66.
7. Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: A review. Cont Lens Anterior Eye 2010;33:157-66.
8. Gordon MO, Steger-May K, Szczotka-Flynn L, Riley C, Joslin CE, Weissman BA. Baseline factors predictive of incident penetrating keratoplasty in keratoconus. Am J Ophthalmol 2006;142:923-30.
9. Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ. Prognostic factors for the progression of keratoconus. Ophthalmology 1994;101:439-47.
10. Lema I, Sobrino T, Durán JA, Brea D, Diez-Feijoo E. Subclinical keratoconus and inflammatory molecules from tears. Br J Ophthalmol 2009;93:820-4.
11. Fukuchi T, Yue BY, Sugar J, Lam S. Lysosomal enzyme activities in con- junctival tissues of patients with keratoconus. Arch Ophthalmol 1994;112:1368-74.
12. Sawaguchi S, Yue BY, Sugar J, Gilboy JE. Lysosomal abnormalities in kerato- conus. Arch Ophthalmol 1989;107:1507-10.
13. Sawaguchi S, Twining SS, Yue BY, Chang SH, Zhou X, Loushin G, *et al*. Alpha 2 macroglobulin levels in normal human and keratoconus corneas. Invest Ophthalmol Vis Sci 1994;35:4008-14.
14. Lema I, Durán JA. Inflammatory molecules in the tears of patients with keratoconus. Ophthalmology 2005;112:654-9.
15. Balasubramanian SA, Pye DC, Willcox MD. Levels of lactoferrin, secretory IgA and serum albumin in the tear film of people with keratoconus. Exp Eye Res 2012;96:132-7.
16. Fankhauser CD, Sander S, Roth L, Gross O, Eberli D, Sulser T, *et al*. Systemic inflammatory markers have independent prognostic value in patients with metastatic testicular germ cell tumours undergoing first-line chemotherapy. Br J Cancer 2018;118:825-30.
17. Yao C, Zhang Z, Yao Y, Xu X, Jiang Q, Shi D. Predictive value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio for acute deep vein thrombosis after total joint arthroplasty: A retrospective study. J Orthop Surg Res 2018;13:40.
18. Pichler M, Hutterer GC, Stoeckigt C, Chromecki TF, Stojakovic T, Golbeck S, *et al*. Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostik factor in a large European cohort of renal cell carcinoma patients. Br J Cancer 2013;108:901-7.
19. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008;102:653-7.
20. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, *et al*. Prognostic role of platelet to lymphocyte ratio in solid tumors: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:1204-12.
21. Sugar J, Macsai MS. What causes keratoconus? Cornea 2012;31:716-9.
22. Wisse RPL, Kuiper JJW, Gans R, Imhof S, Radstake TRDJ. Van der Lelij A. Cytokine expression in keratoconus and its corneal microenvironment: A systematic review. Ocul Surf 2015;13:272-83.
23. Toprak I, Kucukatay V, Yıldırım C, Kilic-Toprak E, Kilic-Erkek O. Increased systemic oxidative stress in patients with keratoconus. Eye 2014;28:285-9.
24. Jun AS, Cope L, Speck C, Feng X, Lee S, Meng H, *et al*. Subnormal cytokine profile in the tear fluid of keratoconus patients. PloS One 2011;6:16437.
25. Abalain JH, Dossou H, Colin J, Floch HH. Levels of collagen degradation products (telopeptides) in the tear film of patients with keratoconus. Cornea 2000;19:474-6.
26. Arnal E, Peris-Martínez C, Menezo JL, Johnsen-Soriano S, Romero FJ. Oxidative stress in keratoconus? Invest Ophthalmol Vis Sci 2011;52:8592-7.
27. Wojcik KA, Kaminska A, Blasiak J, Szaflik J, Szaflik JP. Oxidative stress in the pathogenesis of keratoconus and Fuchs endothelial corneal dystrophy. Int J Mol Sci 2013;14:19294-308.
28. Balasubramanian SA, Pye DC, Willcox MDP. Effects of eye rubbing on the levels of protease, protease activity and cytokines in tears: Relevance in keratoconus. Clin Exp Optom 2013;96:214-8.
29. Xu L, Wang YX, Guo Y, You QS, Jonas JB. Prevalence and associations of steep cornea/keratoconus in Greater Beijing. The Beijing Eye Study. PLoS One 2012;7:e39313.
30. Prajapati JH, Sahoo S, Nikam T, Shah KH, Maheriya B, Parmar M. Association of high density lipoprotein with platelet to lymphocyte and neutrophil to lymphocyte ratios in coronary artery disease patients. J Lipids 2014;2014:1-8.
31. Feng JF, Huang Y, Chen QX. The combination of platelet count and neutrophil lymphocyte ratio is a predictive factor in patients with esophageal squamous cell carcinoma. Transl Oncol 2014;7:632-7.
32. Azab B, Daoud J, Ben NF, Nasr R, Ross J, Ghimire P, *et al*. Neutrophil-to-lymphocyte ratio as a predictor of worsening renal function in diabetic patients (3-year follow-up study). Ren Fail 2012;34:571-6.
33. Jiang Y, Zang M, Li S. Serum PLR and LMR in Behçet's disease. Medicine (United States) 2017;96:1-6.
34. Ulu SM, Dogan M, Ahsen A, Altug A, Demir K, Acartürk G, *et al*. Neutrophil-to-lymphocyte ratio as a quick and reliable predictive marker to diagnose the severity of diabetic retinopathy. Diabetes Technol Ther 2013;15:942-7.
35. Ilhan N, Daglioglu MC, Ilhan O, Coskun M, Tuzcu EA, Kahraman H, *et al*. The significance of the neutrophil/lymphocyte ratio as a simple indicator of inflammation in age-related macular degeneration. Ocul Immunol Inflamm 2016;24:362-3.
36. Çelik T. Assessment of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with dry eye disease. Ocular Immunol Inflamm 2018;26:1219-22.
37. Ozgonul C, Sertoglu E, Mumcuoglu T, Kucukevcilioglu M. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as novel biomarkers of primary open-angle glaucoma. J Glaucoma 2016;25:815-20.
38. Icel E, Ucak T, Karakurt Y, Yilmaz H, Tasli NG, Turk A. The relation of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with high axial myopia. Ocular Immunol Inflamm 2020;28:396-401.
39. Karaca EE, Özmen MC, Ekici F, Yüksel E, Türkoğlu Z. Neutrophil-to-lymphocyte ratio may predict progression in patients with keratoconus. Cornea 2014;33:1168-73.
40. Katipoğlu Z, Mirza E, Oltulu R, Katipoglu B. May monocyte/HDL cholesterol ratio (mhr) and neutrophil/lymphocyte ratio (nlr) be an indicator of inflammation and oxidative stress in patients with keratoconus? Ocular Immunol Inflamm 2020;28:632-6.
41. Bozkurt E, Ucak T. Serum Inflammation biomarkers in patients with keratoconus. Ocular Immunol Inflamm 2020:1-4. doi: 10.1080/09273948.2020.1741648.
42. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. J Interferon Cytokine Res 1998;18:555-9.