• Review Article •

Neutrophil-to-lymphocyte ratio in ocular diseases: a systematic review

Bengi Ece Kurtul[1], Pinar Altiaylik Ozer[2]

[1]Department of Ophthalmology, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Hatay 31040, Turkey
[2]Department of Ophthalmology, Ufuk University Faculty of Medicine, Ankara 06830, Turkey
Correspondence to: Bengi Ece Kurtul. Department of Ophthalmology, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Hatay 31040, Turkey. becekurtul@yahoo.com
Received: 2018-05-24 Accepted: 2019-05-18

Abstract

• AIM: To summarize the results of studies investigating neutrophil-to-lymphocyte ratio (NLR) and to identify the role of NLR in ocular diseases.

• METHODS: With the aim of identifying the studies related to NLR, a search was conducted on http://www.ncbi.nlm.nih.gov/pubmed by utilizing the key words "neutrophil lymphocyte ratio, ocular diseases, and eye diseases" up to February 2018. All of the original articles were assessed according to date of publications, countries, clinics and topics. Studies about ocular inflammatory diseases were evaluated according to their qualifications, review methods and results.

• RESULTS: A total of 4473 publications, including original research articles and reviews were screened. The number of publications was shown a regular logarithmic increase over the years. The majority of studies were performed by clinics in Turkey and many of these publications were performed by oncology and cardiology clinics. A total of 75 publications were identified to be about ocular diseases.

• CONCLUSION: Elevated NLR as a cheap, reproducible, and readily available marker could be used as a diagnostic and/or prognostic marker in ocular diseases.

• KEYWORDS: neutrophil-to-lymphocyte ratio; ocular diseases; inflammation; publication

DOI:10.18240/ijo.2019.12.18

Citation: Kurtul BE, Ozer PA. Neutrophil-to-lymphocyte ratio in ocular diseases: a systematic review. *Int J Ophthalmol* 2019; 12(12):1951-1958

INTRODUCTION

Ocular inflammatory and vascular diseases are one of the most common diseases resulting in irreversible blindness worldwide. In the past decades, numerous studies have highlighted that different inflammatory reactions play crucial roles in various eye disorders, including neovascular age-related macular degeneration (AMD), retinopathy of prematurity (ROP), and proliferative vitreoretinopathy[1-3]. Neutrophil-to-lymphocyte ratio (NLR) is a novel and widely accepted inflammatory marker which has been identified to be associated with the severity and prognosis of many oncologic and cardiovascular diseases[4-9]. The predictive value of the NLR has also been discussed with regard to ocular vascular and inflammatory diseases such as diabetic retinopathy (DR), AMD, retinal vein occlusion (RVO), glaucoma, and dry eye disease (DED)[10-14]. However, reviews regarding the role of NLR in these diseases are inadequate. In this review, therefore, we aimed to present the recent scientific literature on NLR, its usage areas and limitations in patients affected by ocular diseases.

MATERIALS AND METHODS

A systematic search of PubMed, Embase.com, and Web of Science was made to elucidate all comparative studies that compared the NLR value in several ocular diseases.

Search Strategy We examined PubMed, ScienceDirect, ClinicalTrials.gov and Cochrane Library databases for articles up to February 2018, with no language restrictions. Key words used to describe studies were "ocular" OR "eye" OR "disease" OR "inflammation" AND "lymphocyte" OR "neutrophil" OR "neutrophil to lymphocyte ratio". We adapted search phrases based on diverse bibliographic databases and index terms. The references from selected papers were also reached in this review process. Studies investigating NLR and its potential role in the ocular diseases such as AMD, glaucoma, retinal vascular diseases have been described in this review.

NEUTROPHIL-TO-LYMPHOCYTE RATIO & OCULAR DISEASES

Studies of the predictive value of the NLR in patients with ocular diseases are summarized in Table 1. Scheme summarizing the role of NLR in ocular diseases is presented in Figure 1. As shown in the Figure 1, the number of lymphocytes decreases when the inflammation takes place in the eye. On the one hand inflammation induces neutrophilia. On the other hand,

Table 1 Studies of the predictive value of the NLR in patients with ocular disorders

Study	Year	Participants	Cutoff	Outcomes
Chittawar *et al*[10]	2017	Consecutive T2DM patients	>2	NLR of 2.00 had sensitivity and specificity of 64.2% and 63% in predicting retinopathy.
Dursun *et al*[12]	2015	RVO *vs* healthy controls	>1.89	The NLR values were elevated in RVO patients than the control subjects.
Ozgonul *et al*[13]	2016	POAG/OHT patients *vs* healthy controls	>2.1	Patients with POAG have increased NLR and PLR levels compared with controls. In addition, there was a linear relation between PSD, a predictor of glaucomatous visual field defects, and NLR.
Sengul *et al*[25]	2017	AMD patients *vs* healthy controls	>2	The NLR and PLR in neovascular AMD group was found to be significantly higher than controls. NLR and PLR were conversely proportional to BCVA and directly proportional to CMT.
Erol *et al*[26]	2017	Patients with CSCR *vs* healthy controls	>1.93	NLR and CRP were higher in acute CSCR. NLR, CRP, and MPV were independent variables for chronic CSCR.
Hu *et al*[39]	2017	Infants who were screened for ROP	-	LMR levels were higher but NLR levels were lower in ROP group. Higher LMR is independently associated with the development of ROP.
Li *et al*[50]	2017	PACG patients *vs* healthy contros	>1.854	Neutrophil count, NLR, and WBC counts were higher in PACG. In multiple linear regression, WBC, neutrophil, NLR, and LMR were found to be related with PACG.
Kurtul *et al*[54]	2016	Patients with PEXS/with PXG *vs* healthy controls	>1.72 for PEX	The NLR was significantly higher in PEXS and PXG group than healthy controls.
Ozgonul *et al*[55]	2017	Male patients with idiopathic AAU *vs* male healthy controls	>1.51	This study demonstrated that patients with idiopathic AAU had increased NLR and PLR levels compared with control subjects. There was also a correlation between CRP and NLR (P=0.002, r=0.461).
Gunes *et al*[66]	2017	Patients with NAION *vs* healthy controls	>1.64	NLR measurements were remarkably higher in patients with NAION than those with healthy participants and were related with erythrocyte sedimentation rate. Furthermore, the NLR was related with vision outcomes.
Bisgaard *et al*[67]	2017	Patients with MS and ON *vs* healthy controls	-	The NLR was higher in MS and ON than healthy controls.
Hu *et al*[70]	2014	Patients with pSS *vs* healthy controls	-	RDW and NLR are significantly correlated with disease activity in patients with pSS.
Karaca *et al*[74]	2014	Patients with keratoconus *vs* healthy controls	>2.24	NLR value was higher in the progressive keratoconus group. There was also a linear correlation between NLR and progression.

NLR: Neutrophil-to-lymphocyte ratio; RVO: Retinal vein occlusion; POAG: Primary open angle glaucoma; OHT: Ocular hypertension; PLR: Platelet to lymphocyte ratio; BCVA: Best corrected visual acuity; CMT: Central macular thickness; CSCR: Central serous chorioretinopathy; CRP: C-reactive protein; MPV: Mean platelet volume; LMR: Lymphocyte-to-monocyte ratio; WBC: White blood cell count; PEXS: Pseudoexfoliation syndrome; PXG: Pseudoexfoliation glaucoma; AAU: Acute anterior uveitis; NAION: Non-arteritic anterior ischemic optic neuropathy; MS: Multiple sclerosis; ON: Optic neuritis; pSS: Primary Sjögren's syndrome.

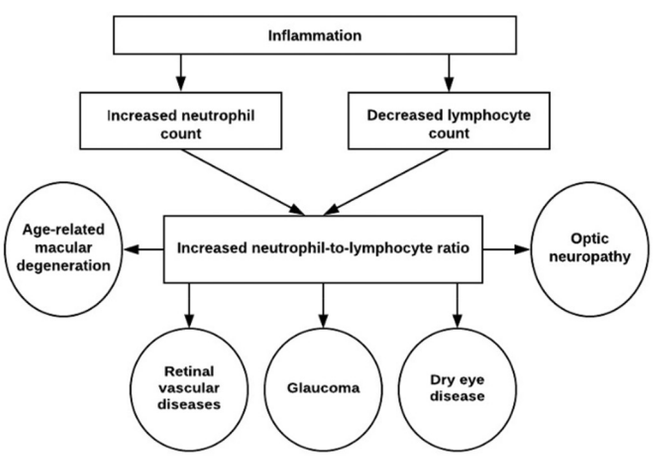

Figure 1 Scheme summarizing the role of neutrophil-to-lymphocyte ratio in ocular diseases.

physiologic stress induces lymphopenia. In other words, the release of endogenous glucocorticoids in reply to local/systemic disorders, including ocular disorders may play a significant role in the production of the lymphopenia[13].

Age-related Macular Degeneration AMD is a multifactorial, progressive disease and is the most common cause of central vision loss in the individuals >50y, with the rate of 0.05% before the age of 50 rising to 30% after 74 years of age[15-17]. The pathogenesis of AMD has not been fully understood, although many possible factors such as oxidative stress, atherosclerotic-like changes, and inflammatory processes have been proposed[18]. There is growing proof to suggest a role for retinal pigment epithelial (RPE) cell destruction and death, caused by diverse mechanisms including elevated inflammatory response and oxidative stress in AMD producing photoreceptor death and vision loss. The RPE cells exposed to oxidative stress can elicit inflammation. The accumulation of lipids, mainly in the form of drusen, is related with a chronic inflammation[19].

Studies in recent years appointed to a pronounced role of inflammation in AMD pathogenesis. There is a large body of evidence demonstrating the association of C-reactive protein (CRP) with endothelial dysfunction, oxidative stress and reactive oxygen species (ROS) production in AMD patients[20].

There are some studies presenting the association of the incidence of AMD with CRP, tumor necrosis factor-α and oxidative stress[21-22].

Ilhan *et al*[23] concluded elevated NLR levels in AMD patients than controls and demonstrated that those higher NLR levels were linked with patients' age and disease stage. NLR values were 2.39, 2.79 and 1.7 among dry AMD, wet AMD, and controls, respectively. In another study we investigated the link between AMD and NLR and found that NLR levels in dry type and wet type AMD patients were higher than controls, at 1.65, 1.98 and 1.46, respectively[24]. Additionally, neovascular AMD patients had higher NLR and platelet to lymphocyte ratio (PLR) levels than controls. Mean NLR values were 2.52 and 1.92, and PLR values were 131.82 and 110.09 respectively[25]. In the lights of these studies, it seems that the relation between elevated NLR and AMD may have stronger consequence to the wet subtype of AMD and possibly related to angiogenesis-related inflammatory mechanisms. It is clear that further studies are needed to explore this relationship in terms of prognosis of the disease.

Central Serous Chorioretinopathy Central serous chorioretinopathy (CSCR) is defined as serous detachment of neurosensory retina and causes vision threat. It commonly affects middle-aged male subjects. The accurate pathophysiologic mechanism remains unknown[26]. However, studies on this subject suggest that CSCR is an inflammatory disorder. Choroidal perfusion or vascular endothelial growth factor (VEGF) abnormalities are present[27]. Numerous cytokines such as VEGF, IL-6, and IL-8 besides other proinflammatory cytokines might also be elevated in CSCR patients[28]. In the study performed by Erol *et al*[26], they demonstrated elevated NLR in patients with acute CSCR than those with chronic CSCR and controls. They supported the idea that neutrophils play a main role in acute CSCR, while platelets are involved in advancement to chronic CSCR. Although many previous studies have found a significant connection between CSM and local proinflammatory markers such as VEGF, IL-6, IL-8, studies investigating the relationship between CSCR and systemic inflammatory markers such as NLR are sparse. So there is limited information about NLR role on the pathogenesis of CSCR in the literature. We therefore suggest that large-scale, prospective investigations are needed on this issue.

Retinal Vascular Diseases

Diabetic retinopathy It has been highlighted that chronic inflammation is crucial in both development and acceleration of microangiopathy and macroangiopathy in patients with diabetes mellitus[29]. DR is a diabetes-induced microangiopathy affecting the retinal vascular structures. The pathogenesis of the disease includes inflammation, ischemia, and progressive RPE cell degeneration. The most common cause of visual deterioration in diabetic patients[30-31]. DR is a progressive disorder that develops in phases, from mild nonproliferative DR to moderate-severe nonproliferative DR and lastly to the final stage of proliferative DR. In terms of pathogenesis of DR studies have shown that inflammation plays a role[32-33]. In a previous study, the systemic neutrophil count was found elevated and associated with the presence and severity of DR, and investigators concluded that neutrophil-mediated inflammation may play an important role in the pathogenesis of DR[34]. Afterwards, Ulu *et al*[11] explored the relationship between DR and inflammation by using NLR, which is an established inflammatory marker being measured routinely in complete blood count tests. In that study, when compared with controls, diabetes patients had significantly elevated NLR values (P<0.001). Additionally, DR patients had higher NLR levels compared to patients without DR (P<0.001). Furthermore, NLR values were associated with the occurrence of DR (r=0.466, P<0.001) and DR grades (r=0.630, P<0.001). In a similar study, NLR was associated with retinopathy, as well as nephropathy and coronary artery disease, in Indians with type-2 diabetes[10]. Taken together, it seems that the NLR is associated with both the presence of DR and the degree of DR. We can speculate on the basis of the studies data mentioned above that there is a strong relationship between DR and systemic chronic inflammation.

Retinal vein occlusion The ethiopathogenetic mechanism of RVO is not fully elucidated, but, RVO is known as a disease that goes with thrombotic and inflammatory processes. In a previous study carried out by Dursun *et al*[12], the association between NLR and the development of RVO was assessed. The NLR values of the patients (n=40) and the control group (n=40) were compared. The NLR values were found to be elevated in RVO patients than the controls (3.0±2.7 *vs* 1.5±0.3, P<0.001). In the receiver operating characteristics (ROC) analysis, to predict RVO, the cutoff value for NLR was found as 1.89, with 72.5% sensitivity and 100% specificity. According to study results, they concluded that higher NLR was associated with the development of RVO. Although it cannot be said accurately according to only the results of this study, it is understood that inflammatory processes as well as thrombotic pathways may take part in the etiopathogenesis of RVO.

Retinopathy of prematurity ROP is leading cause of blindness in premature babies worldwide. The disease affects the immature retinal vascular system and thus occurs in premature infants with an partly vascularized retina. Angiogenic factors, cytokines, and oxidative and growth factors play role in ROP processes[35]. Inflammation has also been implicated in ROP pathogenesis beyond immaturity[2,36-37].

Given the role of inflammatory processes in ROP development, in the previous study, we evaluated the relationship between serum NLR and development of ROP. We found higher NLR values in the ROP group relative to non-ROP group (P=0.02). The lymphocyte count was significantly lower in the ROP group compared to the non-ROP group (P=0.001). But, in multivariate analysis, only lymphocyte count detected independent predictor of ROP [odds ratio (OR) 0.599; 95% confidence interval (CI), 0.430-0.836; P=0.003][38].

In addition to our study, in a recently published study, Hu *et al*[39] aimed to evaluate the associations between development of ROP and serum lymphocyte-to-monocyte ratio (LMR), NLR, and PLR. The LMR levels were significantly higher and NLR levels were significantly lower in ROP group than controls. Logistic regression analysis suggested that not NLR but LMR was an independent risk factor for ROP. In the light of the results of these two studies, we can say that the diagnostic and prognostic role of NLR in patients with ROP remain controversial. A possible reason for this discrepancy is that the size of the sample in these studies is relatively small. Additionally, subject heterogeneity and accompanying comorbidities may also account for this discrepancy. Despite all of these limitations, we can conclude that there is no significant relationship between NLR and ROP yet. Perhaps the mechanisms those are more dominant than inflammation may be involved in ROP development.

Glaucoma Glaucoma is a neurodegenerative disease that leads to progressive optic disc atrophy and visual field defects, and it is frequently linked to an elevated intraocular pressure (IOP). Elevated IOP is a risk factor for disease progression that can give rise to progressive irreversible blindness[40]. Progressive degeneration of retinal ganglion cells and axons is the main cause of glaucomatous visual loss[41-42]. This is particularly so with a rapidly aging worldwide and the relatively high incidence of glaucoma being observed among the elderly[43-44]. Primary angle closure glaucoma (PACG) is an important subgroup of glaucoma. Increasing evidences are thought that inflammatory mechanisms may have a role in the pathophysiology of glaucoma[45-48]. In patients with PACG, circulating leucocyte and platelet counts will increase. As mentioned earlier, the NLR, PLR and LMR investigated as predictors of adverse events in various cancer types and cardiovascular diseases. However, to date there are only four papers which showed that NLR and PLR may be helpful as biomarkers in patients with normal-tension glaucoma[49], primary open angle glaucoma (POAG)[13,50], and pseudoexfoliation glaucoma (PXG)[51]. These studies provide significant information that there is a probable role for inflammation as an initiating or progressing factor in PACG patients.

When it comes to the POAG, Ozgonul *et al*[13] assessed the NLR and PLR values in patients with POAG and compared the NLR and PLR results of patients with POAG and ocular hypertension, and healthy controls. They found elevated NLR (P=0.003) and PLR (P=0.049) levels in POAG patients. Thus we suggest that these parameters may be useful in patients with POAG.

Pseudoexfoliation syndrome Pseudoexfoliation syndrome (PEXS) is an age-related, systemic, and multifactorial disease. The pathogenesis of PEXS consists of genetic and nongenetic causes, such as age, race, ultraviolet beams, autoimmune disorders, trauma, infections, inflammation, and oxidative stress[13,52-53]. Inflammatory biomarkers may have a key role in clinical practice for these patients. In this context, we previously investigated the relationship between serum NLR and PEXS[54]. We divided participants into three groups: group 1: 55 patients with PEXS, group 2: 19 patients with PXG, and group 3: 48 control subjects. The NLR was considerably elevated in group 1 and 2 than the group 3 (P<0.001). In ROC analysis, the area under the curve for NLR for predicting PEXS was 0.776, and NLR of >1.72 with a sensitivity of 77% and specificity of 71%. In a consequence, we concluded that elevated NLR is significantly associated with PEXS and this parker can provide useful information for risk evaluation in these population.

In another study, Ozgonul *et al*[51] found a substantial difference in favor of NLR and PLR levels between PEXS and control groups (P=0.012) and PXG and control groups (P=0.003 and P=0.024, respectively). These 2 studies show that there is a significant positive correlation between inflammation and PXG development. However, it is necessary to investigate whether there is a relationship between NLR and the course and prognosis of the disease or not.

Uveitis The term “uveitis” determines all inflammatory disorders of intraocular structures. The link among uveitis and inflammatory processes are being investigated for ages. Uveitis is a vision-threatening disease with intraocular inflammation that originating from different causes. And it is one of the leading causes of functional loss of vision and blindness at Western countries[55]. The categorization of uveitis, may be derived from anatomical involvement or aetiology of the intraocular inflammation. Anatomically the disease is categorized as anterior, intermediate, posterior, and panuveitis. With regard to intraocular inflammation, uveitis can also be classified as an aetiological, such as, infections, autoimmune/immunity-mediated systemic disorders, traumatic, drug-induced and lens-induced uveitis. The most frequent uveitis type is acute anterior uveitis (AAU), which is related to intraocular inflammation influencing the anterior part of the eye. CRP is a dependable indicator of inflammatory

disorders and prior published studies demonstrated that elevated serum CRP values were detected in patients with uveitis[56-57]. Although documents from the ophthalmology centers associated with NLR and PLR have a tendency to increase and they have rose to importance as a reliable tool of several ophthalmic disorders, studies searching the clinical significance of these tools, as indicator of idiopathic AAU patients are inadequate.

In a previous published study, investigators assessed the levels of the NLR and the PLR in patients with idiopathic AAU and compared with healthy controls[55]. They showed a substantial difference in NLR between idiopathic AAU and control groups. Moreover, correlation analysis showed a linear association between CRP and NLR (P=0.002, r=0.461). According to ROC analysis, the area under the curve for NLR (cut-off value: 1.51) to discriminate patients and controls was found to be 0.689, with a sensitivity of 77.8% and a specificity of 55.6%. Therefore, the predictive power of NLR was better than PLR. Finally, in a study was compared the value of hematological parameters, NLR, PLR, and mean platelet volume (MPV), as reflectors of anterior uveal segment involvement in Behcet's disease (BD)[58]. That study showed that all MPV, PLR, and NLR levels of patients with anterior uveitis were considerably higher than other patients and healthy subjects. The area under the curves for NLR was 0.725, P<0.001 for PLR was 0.600, P=0.012, and for MPV was 0.358, P<0.001. In consideration of these findings, the authors recommended that MPV, PLR, and NLR are all useful for evaluation of anterior uveal segment involvement in BD. But, the NLR is more sensibly compared with the PLR and MPV in predicting the disease.

Ischemic Optic Neuropathy Non-arteritic anterior ischemic optic neuropathy (NAION) can cause loss of vision in middle age and elderly population. The pathogenesis of this situation is not elucidated, but it is believed to be a multifactorial disorder where different combinations of some local and systemic risk factors play a role in the development of NAION[59]. Acute ischemia of the optic nerve head is commonly accepted in the pathogenesis of NAION[60-61]. Also, early inflammation components were determined in clinical NAION[62-63]. NAION initially causes early cytokine mediated changes[64], and then progressive activation of inflammatory cells are taken place[62]. Bernstein *et al*[63] tested optic nerve changes in primate NAION models where capillary thrombosis was triggered by laser light and demonstrated that early post-infarct happenings showed inflammatory response and recommended that modulation of inflammation might be helpful in the management of NAION. In a case-control study, Polat *et al*[65] evaluated the utility of NLR in NAION patients. They found elevated NLR levels in patients with NAION than control subjects. Moreover it was inversely association regarding best corrected visual acuity at the initial and third month exam between groups. In ROC curve analysis, cut-off value of NLR for predicting NAION was 1.94, with the 60% sensitivity and 63% specificity. As the sensitivity and specificity of the cut-off value of NLR was determined somewhat lower in this study, we recommended that the cutoff value may not be beneficial for NAION patients in daily practice. Similarly, Gunes *et al*[66] found considerably elevated NLR levels in NAION patients than in healthy subjects, but in their study the cut-off value for NLR was 1.64, with 85% sensitivity and 41% specificity. Also, the NLR value was correlated with visual results. In patients with higher NLR, the initial and final visual acuities were significantly poor than in patients with lower NLR. Lastly, in a retrospective study, it was shown that NLR was higher in multiple sclerosis and optic neuritis patients compared to healthy controls[67]. In consideration of these studies above mentioned, we can say that NLR may be helpful in clinical performances to predict a NAION patient's visual outcomes. But we should keep in mind that certain diseases may affect the neutrophil and/or lymphocyte count (and therefore NLR). So, there is also a need to compare the NLR with other markers of inflammation, such as CRP and IL-6.

Dry Eye Disease DED is a chronic ophthalmic situation that affects roughly 10%-30% of the people older than 50 years old[68]. Chronic ocular surface inflammation is a key component of DED and the disease leads to ocular pain, discomfort, and visual symptoms. Although the substantial role of inflammation in its pathogenesis is widely accepted, the precise mechanism of the inflammatory response is not elucidated yet. In the tear fluid increased levels of several proinflammatory mediators have been demonstrated by various studies. Because anti-inflammatory medications alleviate signs and symptoms of DED, the idea of inflammatory pathways in the pathophysiology of the disease has been supported[69].

In addition to these studies, Hu *et al*[70] investigated the clinical significance of red blood cell distribution width (RDW) and NLR in primary Sjögren's syndrome (pSS) patients. They suggested that RDW and NLR may be useful tools to guess pSS disease activity. Sekeryapan *et al*[71] assessed the role of NLR in patients with DED as an indicator of inflammation. The NLR values were higher in non-Sjögren dry eye patients compared with control subjects. Consequently, they suggested that non-Sjögren DED may be related with inflammation and the NLR levels increases in inflammatory ophthalmic disorders. Recently, Celik[14] calculated the NLR and PLR values in patients with DED and controls, he found a statistically significant difference in the NLR and PLR values between groups (P=0.032 and P=0.026, respectively). Consequently, both PLR and NLR may be helpful to foresee the inflammatory response in DED. These results suggest that non-Sjögren DED

may be associated with systemic inflammation besides local inflammation. In the light of these studies, we have thought that further studies with large-scale are needed to confirm these outcomes and reveal the significance of NLR values in grading DED and monitoring therapy.

Keratoconus Keratoconus is an ectatic corneal disorder and leads to astigmatism, myopia, and vision disorder[72]. Even though keratoconus is known as a noninflammatory disorder, current reports have demonstrated that proinflammatory factors may also play a role in the pathogenesis of the disease[73-74]. The relation between NLR and keratoconus has been investigated, and the NLR values were higher in progressive keratoconus patients compared to nonprogressive group and controls[74]. There was also a positive correlation between NLR and disease progression (P<0.05). In the ROC curve analysis, an NLR≥2.24 cutoff value predicted the disease progression. However, in a large population size study, the investigators found no significant relationship between CRP and keratoconus[75]. Like non-Sjögren DED, keratoconus is a local inflammatory disease of the eye, so local inflammatory ocular conditions may be thought to increase the serum NLR values.

CONCLUSION

In this review, we have presented a useful summary of the evidence available in literature about the association of NLR with ocular diseases. In conclusion, we think that several eye diseases may also be associated with systemic inflammation in addition to local inflammation. Thus, it seems that the NLR is easily performed, reproducible, cheap, and reliable laboratory biomarkers to test the inflammatory response in ocular inflammatory diseases. These NLR studies may also give us important information to find some new potential clues or mechanisms for several eye diseases. Nevertheless, these observations explain the need to improve further prospective studies.

ACKNOWLEDGEMENTS

Conflicts of Interest: Kurtul BE, None; **Ozer PA,** None.

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