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Assessment of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume in patients with idiopathic epiretinal membrane

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Abstract

Purpose: To assess the role of inflammation in the pathogenesis of idiopathic epiretinal membrane (iERM) using the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) as indicators of inflammation and to compare these parameter levels between iERM and control subjects.

Methods: We retrospectively analyzed the medical records of 36 patients who underwent vitrectomy-ERM peeling and 39 patients who had cataract surgery. We obtained blood samples from all individuals who participated in the study to investigate these parameters.

Results: Seventy-five subjects were included in this study: 36 in the iERM group and 39 in the control group. The mean neutrophil and MPV levels were significantly higher in iERM subjects than in control subjects. The mean lymphocyte level was lower in the iERM group. The mean NLR, PLR, and MPV levels were higher in iERM subjects than in control subjects.

Conclusion: The higher NLR, PLR, and MPV levels found in patients with iERM may indicate that subclinical systemic inflammation may associate with iERM.

Keywords: idiopathic epiretinal membrane, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, subclinical systemic inflammation

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Introduction

Idiopathic epiretinal membrane (iERM) is a relatively common macular disease that threatens central vision in the elderly population.[1] It may cause micropsia, macropsia, monocular diplopia, metamorphopsia, and/or decreased visual acuity. iERM is characterized by the presence of an avascular fibrocellular contractile membrane over the macula; this membrane is composed of two major components: cells of retinal and extraretinal origin (gliocytes, fibroblasts, and hyalocytes) and extracellular matrix (ECM) proteins (mostly collagen and fibrinogen).[2,3] From the vitreous (inner) side to the retinal (outer) side, the ERM usually consists of (1) an inner cellular layer, consisting of one or multiple cell layers, and (2) an outer ECM layer containing bundles of extracellular fibrils, which usually are randomly oriented. With the increase in the level of cytokines, such as transforming growth factor (TGF), in the microenvironment, cellular components begin to transform into myofibroblast.[4] iERM is significantly associated with aging and posterior vitreous detachment (PVD).[5] As a result of aging, the accumulation of advanced glycation end products (AGEs) has been associated with vitreoschisis and PVD. The accumulation of AGEs may increase the stiffness of the tissue and may influence the mechanical properties of the iERM.[6] Both cellular changes and excessive production and accumulation of extracellular elements cause fibrosis on the retinal surface. Analysis of the

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vitreous in previous studies found that levels of different cytokines such as fibroblast growth factor (FGF), nerve growth factor (NGF), glial cell line–derived neurotrophic factor, and vascular endothelial growth factor (VEGF) were significantly higher in iERM samples compared with those in controls. It has led to the speculation that inflammatory processes are involved in iERM formation.[7–10]

The neutrophil-to-lymphocyte ratio (NLR), which assembles the harmful effects of neutrophilia (a sign of inflammation) and lymphopenia (a sign of physiological stress), has arisen as a beneficial prognostic marker of subclinical systemic inflammation.[11,12] Furthermore, in recent studies, NLR, which has a prognostic and predictive value of various systemic inflammatory diseases (malignancies and cardiovascular diseases), and another value obtained from a complete blood count, the platelet-to lymphocyte ratio (PLR), have been studied.[13,14] Moreover, NLR and PLR have properly been investigated as fast and low-cost diagnostic methods in various acute and chronic-associated inflammation disorders. Recently, NLR and PLR have also been studied in some ophthalmological diseases such as age-related macular degeneration (AMD), keratoconus, glaucoma, and non-arteritic anterior ischemic optic neuropathy.[15–19] Dikkaya and colleagues[20] demonstrated that NLR values were significantly higher in iERM subjects than in control subjects.

Mean platelet volume (MPV) indicates platelet activity. A previous study has suggested that a relationship exists between MPV values and the presence and severity of inflammation in many systemic diseases.[21] To the best of our knowledge, there is no evaluation of MPV values in patients with iERM yet.

In light of this information, we proposed to investigate the role of inflammation in the pathogenesis of iERM using NLR, PLR, and MPV, which are used as indirect indicators of inflammation, and to compare NLR, PLR, and MPV levels between iERM subjects and healthy control subjects in this study.

Methods

This is a retrospective comparative study conducted at Beyoglu Eye Training and Research Hospital, Istanbul, Turkey. We examined the medical records from 2016 to 2017 including 36 patients who underwent pars plana vitrectomy and ERM-internal limiting membrane (ILM) peeling due to iERM and 39 patients who had cataract surgery without any ocular and systemic disease. The diagnosis of iERM was clinically made by slit-lamp detailed fundoscopic examination, and also the diagnosis was confirmed by spectral-domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Germany). Fundus fluorescein angiography (FFA) was performed to rule out vascular events, inflammatory diseases such as diabetic retinopathy, retinal vascular occlusion (RVO), uveitis, or malignancies. Patients with any anterior or posterior segment pathology (synechia and/or reaction) and glaucoma in both groups were not included in the study.

The control subjects were selected from patients who underwent a complete blood examination during the preoperative preparation phase for cataract surgery. An itemized fundus examination was performed to exclude macular pathologies using SD-OCT.

Subjects who had a potential secondary ERM such as any intraocular surgery history, blunt and penetrating ocular trauma history, retinal detachment, uveitis, diabetic retinopathy, and venous occlusion history were excluded from the study. In addition, ocular diseases such as senile macular degeneration and high myopia (as greater than 6 diopters); systemic diseases such as autoimmune disorders, cardiovascular disease, and/or malignancies; and drug usage states that may affect whole blood parameters such as chemotherapeutic and iron and corticosteroid were regarded as exclusion criteria for both groups.

We obtained blood samples from all individuals who participated in the study to investigate complete blood count. Analyses were performed within 30 min following bloodletting with an automated blood cell counter (BC-2800; Mindray, China). Neutrophil, lymphocyte, platelet levels, and MPV were quantified. The NLR and PLR were computed as the ratio of neutrophils-to-lymphocytes and platelets-to-lymphocytes, respectively. We obtained blood samples from all individuals 1 day before surgery.

Statistical analysis

Descriptive statistics were used to describe study population characteristics. Continuous data were expressed as mean, standard deviation (SD),

Table 1. Demographic characteristics and statistic of laboratory values in both groups.

	Patients with iERM ($n = 36$) mean ± SD	Controls ($n = 39$) mean ± SD	*p* value
Age (years)	68 ± 5.2	65.3 ± 5.7	0.45*
Gender (M/F)	24/12	25/14	0.35†
Neutrophil (10^3/L)	4.55 ± 1.10	3.95 ± 0.80	**<0.029***
Lymphocyte (10^3/L)	2.16 ± 0.46	2.43 ± 0.36	**<0.032**‡
Platelets (10^3/L)	273 ± 52.4	226.84 ± 50.5	**<0.001***
MPV	11.56 ± 1.11	9.58 ± 0.93	**<0.012***
NLR	2.13 ± 0.43	1.63 ± 0.28	**<0.027***
PLR	132.27 ± 40.82	94.25 ± 21.33	**<0.001***

F, female; iERM, idiopathic epiretinal membrane; M, male; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standard deviation.
p values <0.05 are shown in bold.
*Independent-samples *t* test.
†Chi-square test.
‡Mann–Whitney *U* test.

median, and minimum–maximum. The distribution normality of the variables was tested using the Kolmogorov–Smirnov test. Independent-samples *t* test or Mann–Whitney *U* test was used to compare the differences between two independent groups according to the normality distribution. The Chi-square test was used to compare categorical variables. Furthermore, receiver operating characteristic (ROC) evaluation was carried out to decide the cut-off threshold and measure the precision of NLR, PLR, and platelet profiles. Sensitivity, specificity, and area under the ROC (AUROC) curve were used for an overall prediction of the accuracy of the classifier. Statistical analysis was performed using the SPSS 20.0 software (for Windows; SPSS Inc, Chicago, IL, USA), and values of $p < 0.05$ were considered statistically significant.

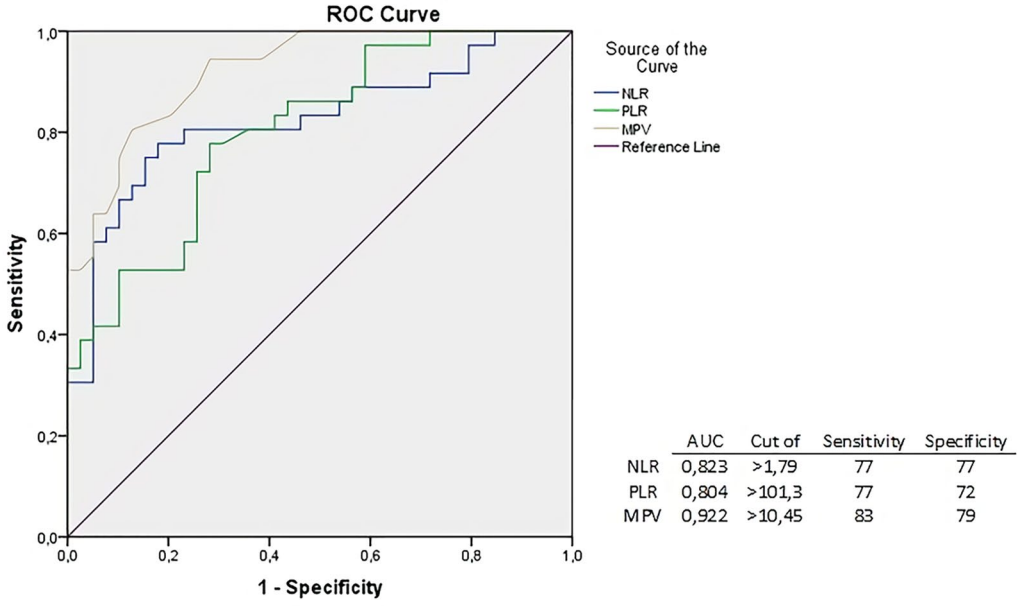
Results

A total of 75 subjects were included in this study: 36 subjects in the iERM group and 39 subjects in the control group. The mean age was 68 ± 5.2 years and 65.3 ± 5.7 years in iERM and control groups, respectively. The sex distribution was similar between the two groups. The mean neutrophil count and MPV level were significantly higher in the iERM subjects than in the control subjects ($p < 0.05$). In contrast, the lymphocyte count was lower in the iERM group ($p < 0.05$). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were within normal limits in study and control subjects. The demographic characteristics and statistics of laboratory values in both groups are summarized in Table 1.

The mean NLR, PLR, and MPV levels were significantly higher in the iERM subjects than in the control group ($p < 0.05$). The ROC analysis of the evaluated factors is demonstrated in Figure 1. According to the figure, the NLR AUROC value that was used to discriminate subjects in the iERM and control group was 0.82. When the best cut-off value was identified as 1.79, both sensitivity and specificity values were found to be 77%. The PLR AUROC value that was used to discriminate subjects in the iERM and control group was 0.804. When the best cut-off value was identified as 101.3, sensitivity and specificity values were found to be 75% and 72%, respectively. The MPV AUROC value that was used to discriminate subjects in the iERM and control group was 0.922. When the best cut-off value was identified as 10.45, sensitivity and specificity values were found to be 83% and 79%, respectively.

Discussion

In this study, we assessed NLR, PLR, and MPV levels in subjects with iERM and the control group.



	AUC	Cut of	Sensitivity	Specificity
NLR	0,823	>1,79	77	77
PLR	0,804	>101,3	77	72
MPV	0,922	>10,45	83	79

Figure 1. The ROC analyses of the studied variables (NLR, PLR, and MPV).

A literature search revealed that this study is the first to report increased PLR and MPV values, along with increased NLR, in subjects with iERM when compared with subjects in a control group. In light of these findings, we can say that systemic subclinical inflammation may be associated with idiopathic ERM.

ERM is a commonly encountered disorder of the eye affecting individuals aged 50 years and above, with a reported prevalence ranging between 7% and 11.8%.[22] ERM manifests on the vitreomacular interface via migration of different cell types onto the ILM, resulting in the overproduction of collagen. ERM has cellular and extracellular components.[23] The cellular components include Müller cells, fibrous astrocytes and microglia, hyalocytes, fibroblasts, and myofibroblasts, whereas the extracellular components include fibronectin and type I and VI collagens.[2,24]

In recent years, NLR has been identified as a simple, fast, and reliable marker for the prediction of the prognosis of such systemic inflammatory conditions as diabetes mellitus, myocardial infarction, and malignancies.[25,26] As with other systemic diseases, NLR has also been studied in various ocular diseases, such as diabetic retinopathy, AMD, RVO, optic neuritis, and glaucoma. Ilhan and colleagues[19] identified higher NLR in patients with AMD than in the control group and also found an increasing NLR correlation with disease severity. Ozgonul and colleagues[17] evaluated NLR in patients with pseudoexfoliation syndrome (PEX) and pseudoexfoliation glaucoma (PXG) and reported increased NLR in both groups when compared with the control group. Ulu and colleagues[27] used NLR as a marker of inflammation to evaluate the relationship between diabetic retinopathy and inflammation and found higher NLR in patients with diabetic retinopathy than in those without it. In another valuable study by Ozgonul and colleagues[16] evaluating NLR in patients with primary open-angle glaucoma (POAG), NLR was found to be higher in patients with POAG than in the control group, and the authors reported a correlation between pattern standard deviation and NLR.

Similar to NLR, PLR is another biomarker indicating the presence and severity of inflammation.[28] Kokcu and colleagues[29] have reported increased PLR in advanced stages of ovarian cancer. Unlike NLR, there is a limited number of studies in the literature evaluating the relationship between PLR and ocular disease. One such study that evaluated PLR in patients with POAG found significantly higher PLR in patients with POAG than in the control group.[16] In another study, Alan and colleagues[30] evaluated the relationship between PLR and the severity of Behçet's syndrome (BS) and found a positive correlation between PLR and disease severity. Ozgonul and colleagues[17] evaluated PLR in patients with PEX and PXG and reported elevated PLR compared with controls in both PEX and PXG patients.

In recent years, MPV has been introduced as a new and important marker of inflammation, with reported successes being similar to those of NLR and PLR. For example, Ekiz and colleagues[31] compared patients with BS and recurrent aphthous stomatitis with a healthy control population and recorded significantly higher MPV values in the patient group, whereas Yazici and colleagues[32] reported higher MPV values in patients with ankylosing spondylitis and rheumatoid arthritis. Similar to other studies, this study found higher MPV values in patients with iERM than in healthy subjects.

This study has some limitations. For example, the research was designed as a retrospective study, and the study featured only a small sample. The most significant limitation is the lack of any detailed analysis of inflammation other than CRP and ESR, either in the study or in the control group.

In conclusion, the study found higher NLR, PLR, and MPV values in patients with ERM than in the control group. Based on these findings, we can say that subclinical systemic inflammation may be associated with idiopathic ERM. To better understand the relationship between the systemic inflammatory process and iERM, there is a need for comprehensive studies.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by G.D., H.T., S.Ç., Z.A., and M.E.S. The first draft of the manuscript was written by G.D., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics statement

The study protocol was approved by the Clinical Studies Ethics Committee of Gaziosmanpasa Training and Research Hospital (approval no: 06-2019), and the study was conducted in accordance with the ethics principles stated in the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

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Availability of data and material

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

References

1. Pilli S, Lim P, Zawadzki RJ, *et al*. Fourier-domain optical coherence tomography of eyes with idiopathic epiretinal membrane: correlation between macular morphology and visual function. *Eye (Lond)* 2011; 25: 775–783.
2. Kritzenberger M, Junglas B, Framme C, *et al*. Different collagen types define two types of idiopathic epiretinal membranes. *Histopathology* 2011; 58: 953–965.
3. Smiddy WE, Maguire AM, Green WR, *et al*. Idiopathic epiretinal membranes. Ultrastructural characteristics and clinicopathologic correlation. *Ophthalmology* 1989; 96: 811–820.
4. Snead DR, Cullen N, James S, *et al*. Hyperconvolution of the inner limiting membrane in vitreomaculopathies. *Graefes Arch Clin Exp Ophthalmol* 2004; 242: 853–862.
5. Gupta P, Yee KM, Garcia P, *et al*. Vitreoschisis in macular diseases. *Br J Ophthalmol* 2011; 95: 376–380.
6. Bu SC, Kuijer R, Li X-R, *et al*. Idiopathic epiretinal membrane. *Retina* 2014; 34: 2317–2335.
7. Mandelcorn E, Khan Y, Javorska L, *et al*. Idiopathic epiretinal membranes: cell type, growth factor expression, and fluorescein angiographic and retinal photographic correlations. *Can J Ophthalmol* 2003; 38: 457–463.
8. Iannetti L, Accorinti M, Malagola R, *et al*. Role of the intravitreal growth factors in the pathogenesis of idiopathic epiretinal membrane. *Invest Ophthalmol Visual Sci* 2011; 52: 5786–5789.

9. Pollreisz A, Funk M, Breitwieser FP, *et al*. Quantitative proteomics of aqueous and vitreous fluid from patients with idiopathic epiretinal membranes. *Exp Eye Res* 2013; 108: 48–58.
10. Mandal N, Kofod M, Vorum H, *et al*. Proteomic analysis of human vitreous associated with idiopathic epiretinal membrane. *Acta Ophthalmol* 2013; 91: e333–e334.
11. Sertoglu E and Uyanik M. Accurate use of neutrophil/lymphocyte ratio from the perspective of laboratory experts. *Vasc Health Risk Manag* 2014; 10: 13–14.
12. Ozgonul C and Sertoglu E. Accurate use of neutrophil/lymphocyte ratio in patients with age-related macular degeneration. *Ocul Immunol Inflamm* 2016; 24: 359–360.
13. Templeton AJ, McNamara MG, Šeruga B, *et al*. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014; 106: dju124.
14. Imtiaz F, Shafique K, Mirza SS, *et al*. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med* 2012; 5: 2.
15. Polat O, Yavaş GF, Şnan S, *et al*. Neutrophil-to-lymphocyte ratio as a marker in patients with non-arteritic anterior ischemic optic neuropathy. *Balkan Med J* 2015; 32: 382.
16. Ozgonul C, Sertoglu E, Mumcuoglu T, *et al*. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as novel biomarkers of primary open-angle glaucoma. *J Glaucoma* 2016; 25: e815–e820.
17. Ozgonul C, Sertoglu E, Mumcuoglu T, *et al*. Prediction of pseudoexfoliation syndrome and pseudoexfoliation glaucoma by using neutrophil to lymphocyte ratio and platelet to lymphocyte ratio. *Ocul Immunol Inflamm* 2016; 24: 665–670.
18. Karaca EE, Özmen MC, Ekici F, *et al*. Neutrophil-to-lymphocyte ratio may predict progression in patients with keratoconus. *Cornea* 2014; 33: 1168–1173.
19. Ilhan N, Daglioglu MC, Ilhan O, *et al*. Assessment of neutrophil/lymphocyte ratio in patients with age-related macular degeneration. *Ocul Immunol Inflamm* 2015; 23: 287–290.
20. Dikkaya F, Karaman Erdur S, Ozsutcu M, *et al*. The significance of neutrophil-to-lymphocyte ratio in idiopathic epiretinal membrane. *Int Ophthalmol* 2018; 38: 1393–1397.
21. Ryu H, Lee MK, Lee KH, *et al*. AB0577 mean platelet volume is associated with Behcet's disease activity. *Ann Rheumat Dis* 2014; 73(Suppl. 2): 996–997.
22. Folk JC, Adelman RA, Flaxel CJ, *et al*. Idiopathic epiretinal membrane and vitreomacular traction preferred practice pattern((r)) guidelines. *Ophthalmology* 2016; 123: 152–181.
23. Schumann RG, Eibl KH, Zhao F, *et al*. Immunocytochemical and ultrastructural evidence of glial cells and hyalocytes in internal limiting membrane specimens of idiopathic macular holes. *Invest Ophthalmol Vis Sci* 2011; 52: 7822–7834.
24. Bu S-C, Kuijer R, van der Worp RJ, *et al*. Immunohistochemical evaluation of idiopathic epiretinal membranes and in vitro studies on the effect of TGF-β on Müller cells. *Invest Ophthalmol Vis Sci* 2015; 56: 6506–6514.
25. Seretis C, Gourgiotis S, Gemenetzis G, *et al*. The significance of neutrophil/lymphocyte ratio as a possible marker of underlying papillary microcarcinomas in thyroidal goiters: a pilot study. *Am J Surg* 2013; 205: 691–696.
26. Núñez J, Núñez E, Bodí V, *et al*. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol* 2008; 101: 747–752.
27. Ulu SM, Dogan M, Ahsen A, *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: 942–947.
28. Koseoglu HI, Altunkas F, Kanbay A, *et al*. Platelet–lymphocyte ratio is an independent predictor for cardiovascular disease in obstructive sleep apnea syndrome. *J Thromb Thrombolysis* 2015; 39: 179–185.
29. Kokcu A, Kurtoglu E, Celik H, *et al*. May the platelet to lymphocyte ratio be a prognostic factor for epithelial ovarian cancer. *Asian Pac J Cancer Prev* 2014; 15: 9781–9784.
30. Alan S, Tuna S and Türkoğlu EB. The relation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume with the presence and severity of Behcet's syndrome. *Kaohsiung J Med Sci* 2015; 31: 626–631.
31. Ekiz O, Balta I, Sen BB, *et al*. Mean platelet volume in recurrent aphthous stomatitis and Behçet disease. *Angiology* 2014; 65: 161–165.
32. Yazici S, Yazici M, Erer B, *et al*. The platelet functions in patients with ankylosing spondylitis: anti-TNF-α therapy decreases the mean platelet volume and platelet mass. *Platelets* 2010; 21: 126–131.