Comparison of Neutrophils/Lymphocytes Ratio Between Idiopathic Epiretinal Membrane and Macular Hole

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ABSTRACT

Purpose: To evaluate the inflammatory state in patients with idiopathic macular epiretinal membrane (iERM) and Idiopathic macular hole (IMH) by utilizing neutrophils/lymphocytes ratio (NLR).

Method: We reviewed the medical records of the consecutive patients diagnosed with IMH or iERM retrospectively. Diagnosis was made by slit lamp fundus examination with a 90D lens and confirmed by spectral domain optic coherence tomography (SD-OCT). The control group composed of consecutively selected patients who underwent cataract surgery. Complete blood count values were obtained from routine preoperative laboratory examination in study groups and control group. The NLR was calculated by dividing neutrophils count by lymphocytes count.

Results: The present study enrolled 123 eyes of 123 consecutive patients, which consist of 42 eyes with iERM, 41 eyes with IMH, and 40 control eyes. Average NLR was markedly higher in the iERM group compared to other groups (both p=0.001). IMH and control group were similar with respect to mean NLR (p= 0.071). The AUROC value of the NLR to distinguish patients with iERM and control was found to be 0.847. The best cutoff value was 2.09, with a sensitivity of 77.8% and specificity of 73.5%.

Conclusion: Patients with iERM showed higher NLR compared to other groups. iERM might be accompanied by subclinical systemic inflammation, whereas IMH might not be associated with systemic process.

Key Words: Idiopathic macular epiretinal membrane, Idiopathic macular hole, Neutrophils/lymphocytes ratio.

INTRODUCTION

Idiopathic macular epiretinal membrane (iERM) is a nonvascular, fibrocellular membrane extending on the internal limiting membrane (ILM).[1] iERM frequently shows bilateral involvement and commonly occurs in patients over 50 years of age.[2,3] The cardinal etiological factors for development of iERM include vitreomacular interface (VMI) abnormalities and abnormal posterior vitreous detachment (PVD).[4] The severity of iERM varies from translucent membranes without any retinal distortions to opaque membranes with full-thickness retinal distortion. This results in some visual symptoms such as metamorphopsia, micropsia, or visual loss.[5,6] These membranes contain retinal glial cells, fibrous astrocytes, Müller cells, macrophages, and retinal pigment epithelial (RPE) cells.[5] Furthermore, studies on analysis of vitreous have revealed that some cytokines such as transforming growth factor (TGF), basic fibroblast growth factor (FGF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor, and vascular endothelial growth factor are associated with iERMs.[7-9]

Idiopathic macular hole (IMH) is one of the most common forms of macular hole (MH) that is characterized by tissue defects including the retinal internal limiting membrane (ILM) and the photoreceptor (PR) layer.[10,11] It exists in the macular region of a healthy eye, frequently in patients over 50 years of age.[10,11] Major etiological factors for development of IMH include vitreoretinal traction, perifoveal posterior vitreous detachment (PVD), and continuous adhesion.[12] IMH usually leads to visual impairment and metamorphopsia.[10-12] Similar to ERM, analysis of vitreous shows an increase in level of some

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cytokines such as transforming growth factor (TGF) and granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with IMH.[13] However, a previous study have revealed the higher intravitreal cytokine levels in ERM compared to MH.[13]

Generally inflammatory response is characterized by an increase in neutrophils with a decrease in lymphocyte. Therefore, numerous studies have presented that the increased neutrophils/lymphocytes ratio (NLR) is a rapid and low-priced marker of systemic inflammation.[14] Previous studies have found an association between NLR and some ophthalmological diseases such as age-related macular degeneration (AMD), keratoconus, primary open angle glaucoma (POAG), pseudoexfoliative glaucoma (XFG), and non-arteritic anterior ischemic optic neuropathy, idiopathic epiretinal membrane.[15-19]

Herein, we aimed to evaluate the inflammatory state in patients with iERM and IMH by utilizing neutrophils/lymphocytes ratio NLR.

METHOD

A retrospective comparative clinical study was conducted to evaluate the inflammatory state in the pathogenesis of iERM and IMH by utilizing NLR. Local ethics committee approved this study, which was conducted in accordance with the Declaration of Helsinki and Health Insurance Portability and Accountability Act.

Patient Population

We reviewed the medical records of the consecutive patients diagnosed with IMH or iERM and underwent pars plana vitrectomy from January 2011 to January 2017 retrospectively. Diagnosis of iERM and IMH was made by slit lamp fundus examination with a 90D lens and confirmed by SD-OCT (Optovue OCT V 5.1, RTVue 100-2; Optovue, Fremont, CA, USA). All diagnosis was made by a senior retinal specialist (E.U). The control group composed of consecutively selected patients who underwent cataract surgery in January 2017.

Exclusion criteria for study and control groups were as follows: 1) having any macular pathology other than IMH and iERM, 2) any sign of ocular inflammation (haze, synechias, reaction, uveitis) 3) a history of glaucoma or possibility of glaucoma (intraocular pressure higher than 21 mmHg, and/or glaucomatous optic neuropathy findings) 4) epiretinal membrane resulting from a certain ocular disease (diabetic retinopathy, venous occlusion, retinal detachment etc), 5) a history of prior intraocular surgery, local or systemic inflammatory disease, any drug use 6) insufficient medical history or recordings 7) simultaneously both MH and iERM. Patients with both IMH and iERM were also excluded.

Furthermore, patients with an erythrocyte sedimentation rate of >20 mm/h and C-reactive protein level of >5 mg/dl were also excluded.

Main Outcomes

We obtained complete blood count values from routine preoperative laboratory examination in study groups and control group. All values were measured by an automatic blood counter (Sysmex-XN 9000 Hematology Analyzer, London, UK) We recorded all parameters of the complete blood count. The NLR was calculated by dividing neutrophil count by lymphocyte count.

Statistical Analysis

We used SPSS Statistics version 22.0 software (IBM Corporation, Armonk, NY, USA) to analyze the collected data. Descriptive statistics are presented as mean ± standard deviation (min-max). One-Way ANOVA were used for comparison of the groups. Chi-square test was used to compare categorical variables. We performed Receiver operating characteristic (ROC) analysis with Youden's index to evaluate the predictive performance of NLR. Statistical significance was set at $p \leq 0.05$.

RESULTS

The present study enrolled 123 eyes of 123 consecutive patients, which consist of 42 eyes with iERM, 41 eyes with IMH, and 40 control eyes. Demographic characteristics were similar in different groups, as presented in **Table 1**.

Comparisons of neutrophil, lymphocyte and NLR between different groups were demonstrated in **Table 2**. The average neutrophil count was markedly higher in iERM group than in IMH and control group (both p= 0.001). The average lymphocyte count was markedly lower in patients with iERM compared to patients with IMH and control individuals (p=0.045 and 0.002, respectively). The average NLR was markedly higher in patients with iERM compared to patients with IMH and control subjects (both p=0.001). IMH and control group were similar with respect

Table 1. *Demographic Characteristics.*

Parameters	iERM	IMH	Control	p
Patients/eye	42/42	41/41	40/40	
Female/male	25/17	25/16	23/17	0.98*
Age	68.1 ± 8.2	67.8±7.9	67.2± 9.1	0.90**

*Chi-square test **One-Way Anowa

Table 2. *Comparison of Neutrophil, Lymphocyte and NLR between Different Groups.*

Parameters(n)	**iERM (42)**	**IMH (41)**	**Control (40)**
Neutrophil *	4.67±0.71 (6.32-3.44)	4.14±0.75 (5.97-2.94)	3.82±2.35 (5.41-2.90)
Lymphocyte**	1.93±0.45 (3.05-1.17)	2.04±0.61 (3.51-1.18)	2.19±0.59 (3.92-1.47)
NLR***	2.85±0.72 (3.93-1.71)	2.18±0.71 (3.92-1.12)	1.82±0.45 (2.68-1.02)

n: eye One Way Anova - According to bonferroni adjustment p value was significant <0.05 NLR: neutrophil lymphocyte ratio *The mean neutrophil count was significantly higher in iERM than IMH and control group (p=0.001, p=0.0001 respectively). The mean neutrophil count was similar between IMH and control group (p=0.18).
** The mean lymphocyte count was significantly lower in iERM than IMH and control group (p=0.045, p=0.002 respectively). The mean lymphocyte count was similar between IMH and control group (p=0.48).
***The mean NLR was significantly higher in iERM than IMH and control group (p=0.0001, p=0.0001 respectively). The mean NLR was similar between IMH and control group (p=0.07).

to neutrophil count, lymphocyte count and NLR (p= 0.182, 0.483 and 0.071, respectively).

The ROC analyses were shown in **Figure 1a and 1b**. According to the ROC curve, the AUROC value of the NLR to distinguish patients with iERM and control group was found to be 0.847, as shown in **Figure 1a**. The best cutoff value was 2.09, with a sensitivity of 77.8% and specificity of 73.5%. Furthermore, the AUROC value of the NLR to distinguish patients with iERM and IMH was found to be 0.680, as shown in **Figure 1b**. The best cutoff value was 2.09, with a sensitivity of 64% and specificity of 61%.

DISCUSSION

The present study evaluated the NLR in patients with iERM or IMH by comparing them with control subjects. It demonstrated that patients with iERM had a higher NLR compared to patients with IMH and normal individuals.

Recent studies showed that NLR is a valuable, easily accessible and low-priced parameter, which could reflect the inflammation level.[14] NLR was defined as a reproducible marker that could act as a diagnostic and/or prognostic marker in some eye diseases.[20] Ilhan et al.[15] presented that patients with AMD had the higher NLR values than normal individuals did. It was also shown that NLR was a predictor

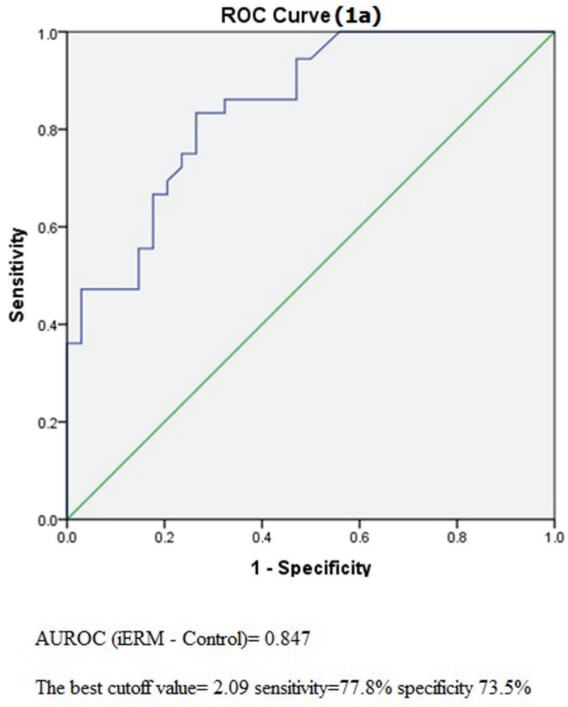

Figure 1a. *AUROC value of the NLR to distinguish patients with iERM and control.*

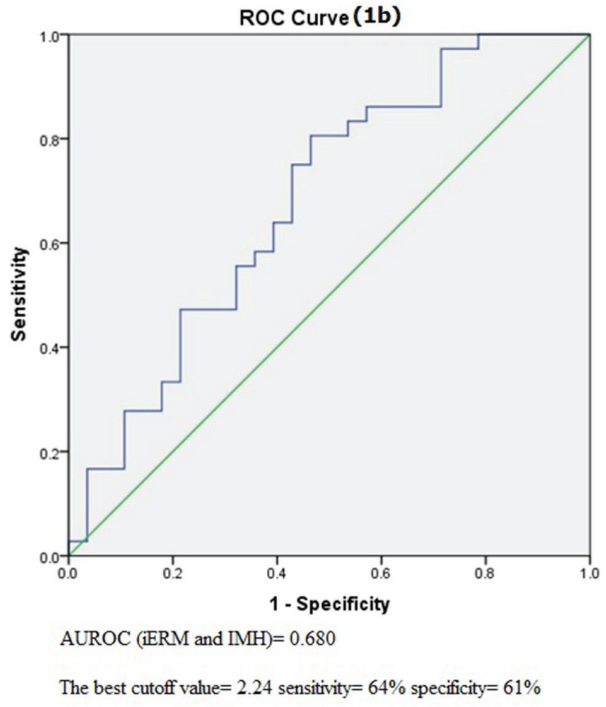

Figure 1b. *AUROC value of the NLR to distinguish patients with iERM and IMH.*

for the progression of diabetic retinopathy.[21] Additionally, Ozgonul et al.[17, 22] reported that patients with POAG and XFG had higher NLR levels than control groups.

Abnormal PVD is accepted as the major etiological factor.[4] During abnormal PVD, incomplete separation from ILM leads to cortical vitreous remnants with hyalocytes, which are responsible for the development of iERM.[23] Cellular component of iERM is composed of glial cells, fibrous astrocytes, Müller cells, macrophages, and RPE cells.[5] Additionally, a previous analysis on the vitreous underlined that active inflammatory state might be associated with iERM.[7-9] Only one study reported the higher NLR values in patients with iERM compared to cataract.[19] They presented that the NLR value for distinguishing the patients with iERM from the controls was 0.832 with a cutoff value of 1.90 (sensitivity= 72%, specificity= 70%). They underlined that subclinical systemic inflammation might associated with the development of iERM as similar to the present study. In the present study, NLR value for distinguishing the patients with iERM from the controls was 0.847 with a cutoff value of 2.09 (sensitivity=77.8%, specificity= 73.5%). We suggested that an alteration of immune mediators in the vitreous and an increase of NLR could contribute to the abnormal activity of the immune system in patients with iERM.

To our knowledge, no previous study evaluated NLR in patients with IMH in the literature. In the present study, we observed the higher NLR values in IMH group than in control group, with a statistical insignificance (p= 0.071). Furthermore, the mean NLR value was significantly higher in iERM group than in IMH group. Zandi et al.[13] reported an increase in the level of some cytokines in patients with IMH (TGF and GM-CSF). They also reported the higher intravitreal cytokine levels in ERM group compared to IMH group.[13]

The mild inflammatory reaction existing in the vitreous of patients with IMH, might not accompany subclinical systemic inflammation. Additionally, it seems that inflammatory process is more prominent in iERM compared to IMH.

Because of the limited number of subjects and retrospective design of the current study, NLR values in iERM and IMH should be evaluated with prospective studies including a large number of patients. The retrospective design of the current study made us assess only CRP and sedimentation rates of both patients and controls, and include eyes with cataract as a control group. Prospective studies that include healthy eyes as a control group should be designed. Other inflammatory factors such as interleukins and interferons should be evaluated with further studies. Additionally, the effect of pars plana vitrectomy on postoperative NLR should be assessed.

In conclusion, NLR was higher in patients with iERM than in both IMH and controls. iERM might be accompanied by subclinical systemic inflammation, whereas IMH might not be associated with systemic process.

Compliance with Ethical Standards:

Funding: No financial support was received for this submission.

Conflict of Interest: Authors declare that they have no conflict of interest**.**

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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