• Clinical Research •

Correlation of neutrophil/lymphocyte and platelet/lymphocyte ratio with visual acuity and macular thickness in age-related macular degeneration

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Abstract

• AIM: To investigate the place of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in the diagnosis of and prognosis for neovascular age-related macular degeneration (AMD).

• METHODS: One hundred AMD patients and 100 healthy controls were included in the study. Blood samples were obtained from the venous blood, which is used for routine analysis, and these samples were subjected to complete blood count. NLR was defined as the neutrophil count divided by the number of lymphocytes, and PLR was defined as the platelet count divided by the number of lymphocytes.

• RESULTS: No statistically significant difference was observed between the two groups under consideration in terms of demographic features (P>0.05). The average NLR in the patient group was found to be significantly higher than that in the healthy control group (P<0.05). The average PLR was significantly higher in the patient group as compared to the control group (P<0.05). As best corrected visual acuity (BCVA) increased, both NLR and PLR decreased (significant negative correlations at 49.8% and 63.0%, respectively), whereas as central macular thickness (CMT) increased, both NLR and PLR increased (significant positive correlations at 59.3% and 70.0%, respectively).

• CONCLUSION: NLR and PLR levels are higher among neovascular AMD patients as compared to healthy control group. NLR and PLR levels were found to be inversely proportional to BCVA and directly proportional to CMT.

• KEYWORDS: age-related macular degeneration; inflammation; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio

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INTRODUCTION

Age-related macular degeneration (AMD) is the most common cause of central visual loss among those aged 65 and above. Its frequency was found to be 10% among those aged between 65 and 75 and 25% among those aged above 75[1-2]. The pathogenesis of neovascular AMD, which is responsible for 90% of AMD-induced blindness cases, has not been fully understood. In the context of the pathogeneses of these two types of AMD, in addition to genetic and environmental factors, inflammation has been deemed responsible[3-5].

Inflammation, oxidative stress and endothelial dysfunction are thought to increase the incidence and severity of AMD. There are several studies showing the association between the incidence of AMD and high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor α receptor 2 and oxidative stress[6-10]. In the structure of drusen, a large number of plasma proteins secondary to inflammation have been detected, and complementary elements were isolated from the blood of AMD patients[11-14]. Degenerative changes in the retinal pigment epithelium (RPE) cells and age-related changes in the immune system begin an inflammatory cascade in the retina and choroid[15-17].

In recent years, many studies have confirmed that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are indicators of systemic inflammation[18-21]. Because prolonged inflammation leads to increased neutrophil and monocyte counts and elevated lymphocyte

apoptosis, a tendency toward lymphopenia will also emerge. Moreover, relative thrombocytosis will result from a triggered megakaryocytic series[22-25]. NLR and PLR levels are associated with increased coronary artery disease severity and worsened prognoses for many cancer types[26-29]. PLR is a more sensitive marker in the diagnosis of and prognosis of arteriosclerosis, as well as many malignancies. To the best of our knowledge, there is no study indicating a link between NLR and PLR and AMD-related findings. Thus, this study was designed to investigate the place of NLR and PLR in the diagnosis and staging of AMD, where inflammation plays an important role in AMD's etiopathogenesis.

SUBJECTS AND METHODS

After obtaining informed consent from the patients, a retrospective analysis was conducted on the medical documentation of 100 patients with neovascular AMD and 100 healthy controls. Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the study was approved by the local Ethics Committee.

The inclusion criteria were set as follows: the existence of leakage demonstrative of choroidal neovascularization (CNV) or macular edema according to fundus fluorescein angiography; the presence of subretinal fluid, cystic maculopathy or central macular thickness (CMT) of at least 250 μm, as detected by optic coherence tomography (OCT) (Optovue, Fremont, USA), and having never been treated for macular degeneration. On the other hand, the exclusion criteria were any of the following: the existence of any disease other than AMD that might reduce visual acuity; aphakia or the posterior capsule not being solid, the presence of glaucoma; the existence of acute inflammation and infection, systemic hypertension, diabetes mellitus, hyperlipidemia, chronic arterial disease, chronic and acute renal failure, chronic liver failure or connective tissue disease and the patient having used steroids or non-steroid anti-inflammatory drugs within 1mo prior to the onset of the study.

After the patients were diagnosed with AMD, routine blood test results were retrospectively analyzed in order to determine whether they had any other systemic disease. On the other hand, a control group was formed that contained 100 healthy people who had compatible ages and sexes and were found to be in good health as a result of a check-up. During the initial visit, AMD patients' best corrected visual acuity (BCVA) was measured *via* an Early Treatment Diabetic Retinopathy Study acuity chart. Each visit incorporated a biomicroscopic examination of the anterior segment, measurement of intraocular pressure, fundus examination, fundus fluorescein angiography and CMT measurement *via* OCT. Using the complete blood samples of each patient and healthy control included in the study, which were placed with into individual tubes with ethylene diamine tetraacetic acid (EDTA), platelet, neutrophil, and lymphocyte counts were measured, and mean platelet volume figures were assessed *via* the flow cytometry method. Measurements were conducted on the device called a Roche Sysmex XT-2000i. The electro-chemiluminescence immunoassay (ECLIA) method was used for the determination of high sensitive hsCRP rates in the serum samples of the patient and control groups included in the study, with the help of a Roche modular system Cobas E 601.

Table 1 Demographic features of patients and controls

n=100 each, mean±SD

Demographic features	Patients with neovascular AMD	Control	*P*
Sex			
F	53	53	-
M	47	47	
Smoking			
Yes	21	25	0.307
No	79	75	
Age	72.190±6.101	71.170±5.549	0.218
BMI	23.532±1.013	23.446±0.980	0.542

Statistical Analysis SPSS 22.0 software is used for statistical analysis. Frequency, percent, mean and standard deviation are used for the evaluation of descriptive data. Pearson Chi-square test is used for an alyzing categoric data and *t*-test forinter-group comparison of parameters. Pearson correlation analysis is used for an alyzing the relationship between BCVA, NLR, PLR and CMT in patientgroup. Logistic regression analysis is used for multiple variable analysis of risk factors which were found to be significant in univariate analyzes. Roc Curve analysis is used for determining the cut-off point between patient and control group. It is also used for cut-off points in diagnostic tests. Sensitivity, specifity, positive and negative predictive values are calculated according to the cut-off value. Results are evaluated within 95% confidence interval and according to $P<0.05$ significance level.

RESULTS

There was no significant difference between the patient and control groups in terms of sex, age, body mass index (BMI) and smoking habits ($P>0.05$) (Table 1). The average CRP level in the patient group was significantly higher than that in the control group. The average lymphocyte count was significantly lower in the patient group as compared to the control group. The average neutrophil count was significantly higher in the patient group than that in the control group. The average platelet count was significantly higher in the patient group than that in the control group. The average NLR in the patient group was significantly higher than that in the control group. The average PLR in the patient group was significantly

Table 2 Comparison of baseline characteristics and laboratory measurements among the groups

n=100 each, mean±SD

Laboratory measurements	Patients	Control	*t*	*P*
hsCRP	2.755±0.553	1.477±0.444	18.022	0.000
NLR	2.520±0.434	1.921±0.441	9.675	0.000
PLR	131.482±18.609	110.090±15.628	8.803	0.000
BCVA	53.010±8.837	-	-	-
CMT	333.700±61.807	-	-	-
Lympocyte count	2.095±0.303	2.449±0.330	-7.904	0.000
Neutrophil count	5.171±0.514	4.596±0.445	8.461	0.000
Platetet count	270.520±19.174	265.300±18.206	1.974	0.050

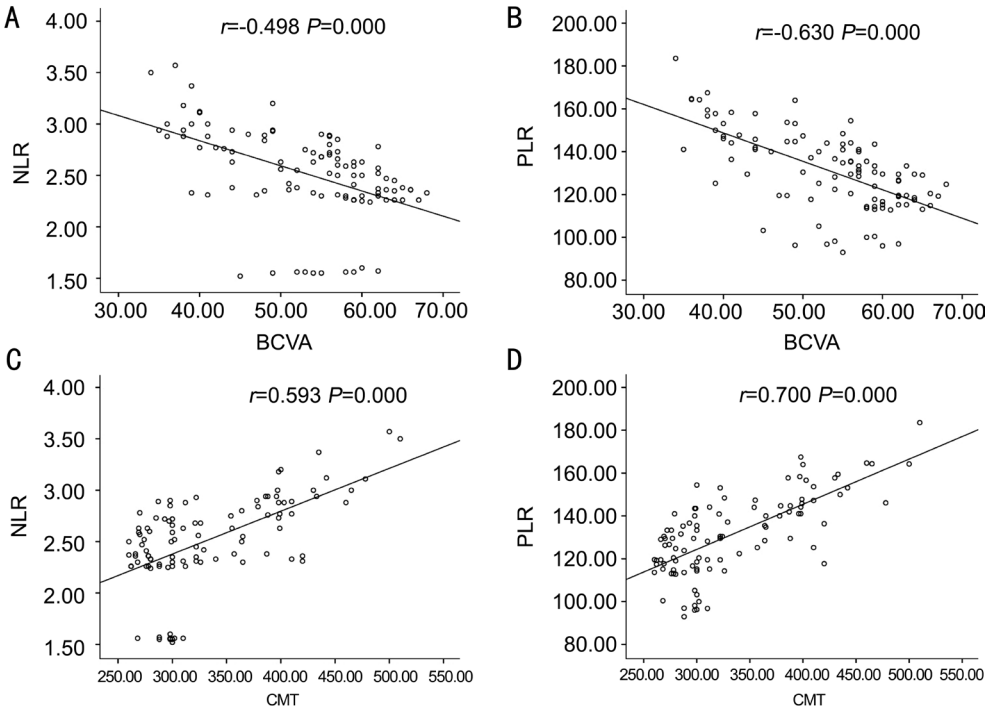

Figure 1 Correlation of groups with BCVA and CMT A: Correlation of NLR with BCVA; B: Correlation of PLR with BCVA; C: Correlation of NLR with CMT; D: Correlation of PLR with CMT.

higher than that in the control group (Table 2). A significant negative correlation, at a rate of 49.8%, was found between NLR and BCVA. As BCVA increased, NLR decreased (Figure 1A). Similarly, a significant negative correlation, at the rate of 63.0%, was found between PLR and BCVA. As BCVA increased, PLR decreased (Figure 1B). One the other hand, a significant positive correlation was detected between NLR and CMT, at 59.3%. As CMT increased, NLR increased (Figure 1C). Correspondingly, a significant positive correlation was detected between PLR and CMT, at 70.0%. As CMT increased, PLR increased (Figure 1D). The area under the receiver operating characteristics curve for NLR was 0.816, and an NLR of 2 or higher predicted neovascular AMD with a sensitivity of 90% and a specificity of 90% (Figure 2). The area under the receiver operating characteristics curve for NLR was 0.828, and a PLR of 112.72 or higher predicted neovascular AMD with a sensitivity of 90% and a specificity of 87% (Figure 3).

DISCUSSION

With a multifactorial etiology, AMD is a complex, chronic, neurodegenerative and progressive disease. Chronic low-grade inflammation and hypoxia are believed to be responsible for the formation and accumulation of ROSs, giving rise to normal aging of the retina. Continued oxidative stress leads to the formation of chronic para-inflammation and extended tissue damage. This para-inflammation, which comes into existence as a result of the alternative complement system within Bruch's membrane, and microglial activation within the retina-choroid interface, plays an important role in the formation of the CNV membrane[30-31].

Many studies reported that independent of age, sex, smoking and the use of statin drugs, a high incidence of AMD was

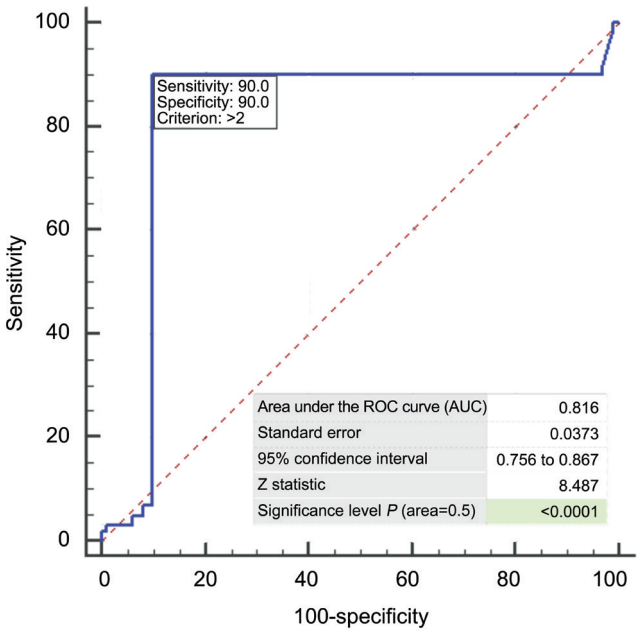

Figure 2 The receiver operating characteristics analysis for NLR in predicting neovascular AMD AUC: Area under the curve.

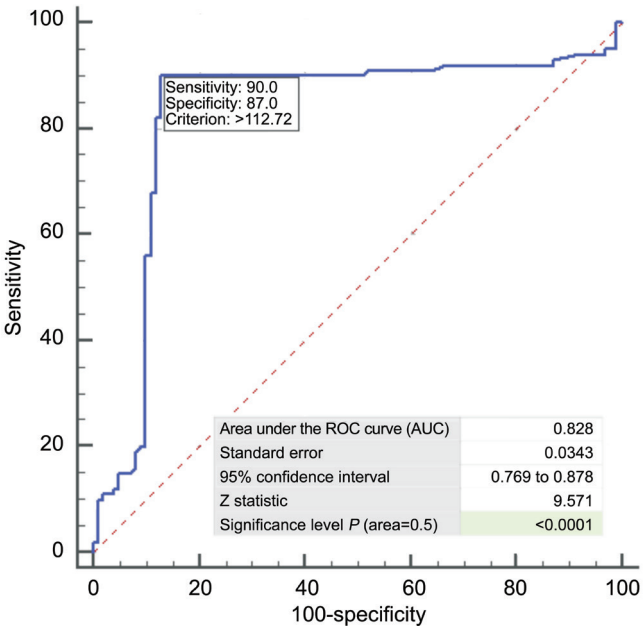

Figure 3 The receiver operating characteristics analysis for PLR ratio in predicting neovascular AMD AUC: Area under the curve.

associated with high serum levels of hsCRP, TNF- αR2, IL-6 and VCAM-1. Many other studies have focused on the relationship between hsCRP and AMD. Notably, in the individuals with mutant complement factor H gene, para-inflammation caused by normal ageing is believed to trigger inflammation at the retinal pigment epithelium-Bruch's membrane complex, leading to the development of AMD, and as an acute-phase reactant, hsCRP level is believed to be increased in those individuals[32-34].

In recent years, studies have estabslished that NLR is a simple and reliable marker of systemic inflammation. NLR was also reported to be a good indicator of the prognosis for coronary artery disease, Behcet's disease, rheumatoid arthritis and many cancer types[18-21,35-37]. A study by Ilhan *et al*[38] detected higher NLR levels in the patients with AMD as compared to controls and found that those high levels of NLR were correlated with patients' age and disease stage. That study found NLR levels to be 2.39, 2.79 and 1.7 among dry AMD patients, wet AMD patients and controls, respectively. Another study designed to investigate the link between AMD and NLR found NLR levels in dry type (group 1) and wet type (group 2) AMD patients to be significantly higher than that in a control group, at 1.65, 1.98 and 1.46, respectively[39]. In our study, neovascular AMD patients were found to have statistically significantly higher NLR and PLR levels as compared to controls. NLR was calculated as 2.52 and 1.92, and PLR was found to be 131.82 and 110.09 respectively.

In the case of inflammation, the thrombocytic series is also activated. In response to inflammation, platelet count increases, leading to lymphopenia. Increased PLR, which occurs as a result of an increase in platelet count and a decrease in lymphocyte count, was found to be a negative prognostic factor for inflammatory diseases[27-28]. Azab *et al*[40] report that independent of platelet count and lymphopenia, an increase in PLR affects the prognosis for patients with non-ST segment elevation myocardial infarction.

As BCVA increased, both NLR and PLR decreased (a significant negative correlation, at 49.8% and 63%, respectively), whereas as CMT increased, both NLR and PLR increased (a significant positive correlation, at 59.3% and 70% respectively). BCVA had a negative correlation with NLR and PLR, at 49.8% and 63%, respectively. On the other hand, CMT was determined to have a positive correlation with NLR and PLR, at 59.3% and 70%, respectively. The greater BCVA and the lower CMT were at the time of admission to the hospital, the higher NLR and PLR levels patients had. This implies that there may be a strong correlation with inflammation at later stages of the disease. Moreover, the fact that as BCVA decreases and CMT increases, both NLR and PLR increase shows that these parameters are reliable for use in monitoring the stages of this disease. Further studies will focus on the use of these parameters in the prognosis for and monitoring of the disease, including the patient's response to treatment.

The limitations of this study are its retrospective mode and the low number of patients. In addition, we are of the opinion that the most significant challenge to the use of blood parameters in diagnosis and treatment follow-up is that these values are affected by various factors (such as BMI, inflammatory disease and systemic disease).

Because complete blood count is a cheap and easily accessible test, questions such as which parameters best indicate inflammation, which have the highest repeatability and which are most relevant in determining the disease grade are all generating interest. Parameters allowing for complete

blood count have been used in the context of many diseases that involve inflammation in their etiopathogeneses. In this study, we determined the parameters that are most affected in the early diagnosis of inflammation in the context of AMD etiopathogenesis, as well as the correlation of these parameters with the visual acuity and CMT of the patients at the time of admission to the hospital. The present authors also believe that these efforts will pave the way for studies focusing on determining prognosis and response to treatment *via* the complete blood count method, which is cheap and easily accessible.

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