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Is there a relationship between hematological inflammatory parameters and age-related macular degeneration?

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Abstract

Purpose: We aimed to analyze blood inflammation parameters in patients with age-related macular degeneration (AMD).

Methods: In this retrospective study, patients were divided into three groups: wet-type AMD ($n = 60$), dry-type AMD ($n = 60$), and healthy controls ($n = 71$). The laboratory and demographic data of the patients were analyzed. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) were calculated manually.

Results: The mean NLR was 2.26 ± 1.42 in the dry-type AMD group, 3.90 ± 1.65 in the wet-type AMD group, and 1.84 ± 0.61 in the control group ($p < 0.001$). The mean MLR was 0.30 ± 0.20 in the dry-type AMD group, 0.47 ± 0.31 in the wet-type AMD group, and 0.28 ± 0.14 in the control group ($p < 0.001$). The mean PLR was 129.31 ± 79.82 in the dry-type AMD group, 156.67 ± 83.99 in the wet-type AMD group, and 135.59 ± 58.68 in the control group ($p = 0.101$). Receiver operating characteristic (ROC) curve analyses revealed that the area under the curve (AUC) for NLR and MLR was 0.920 and 0.717, respectively, for wet-type AMD. The sensitivity and specificity of NLR for wet-type AMD were 64% and 93%, respectively, whereas MLR was 63% and 75%, respectively.

Conclusion: Simple blood tests revealed that NLR and MLR were significantly higher in patients with wet-type AMD than in patients with dry-type AMD and healthy controls, which implies low-grade inflammation.

Keywords: age-related macular degeneration, monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

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Introduction

Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide. AMD is caused by an accumulation of drusen in the macula and results in severe visual impairment.[1] There are two subgroups of AMD: dry type and wet type. In dry-type AMD, progressive deterioration of the macula and consequent loss of central vision occur. Wet-type AMD is caused by the development of abnormal blood vessels under the macula, causing fluid and blood leakage.[2] Vascular endothelial growth factor (VEGF) plays an important role in the formation of blood vessels in the eye in neovascular AMD, so anti-VEGF drugs are used in the treatment of AMD.[3] Progression of wet-type AMD is more rapid and can cause severe vision loss within a few months if left untreated.[4]

Although wet-type AMD accounts for only 10% of cases, it is the cause of 90% of cases of severe visual loss due to AMD. The risk factors for AMD include older age, female sex, a family history of AMD, genetic factors (e.g. complement factor H

polymorphisms), smoking, exposure to sunlight, obesity, hypertension, and hypercholesterolemia.[5]

Inflammation results from a complex network of interactions involving cells associated with the immune system, including neutrophils, lymphocytes, and macrophages. Clinical studies have shown that the number of lymphocytes, neutrophils, and white blood cells and the proportion of these cells may reflect chronic inflammation.[6] It has been suggested that the neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation. Therefore, NLR has been investigated in several studies as a marker of systemic immunity. It is believed that NLR may be an independent prognostic factor in several solid tumors and may be associated with chronic inflammatory diseases.[7]

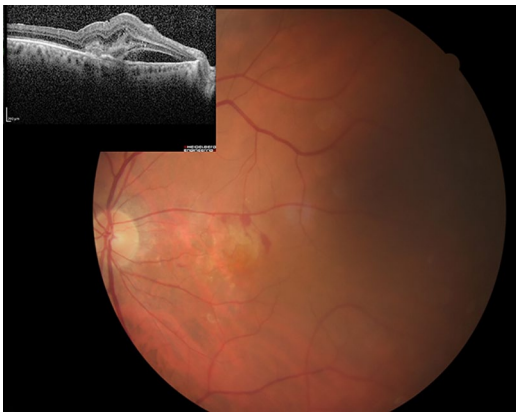

Figure 1. Fundus photograph and optical coherence tomography image of wet-type age-related macular degeneration.

Inflammation, oxidative stress, and endothelial dysfunction are thought to increase the severity and incidence of AMD. Many studies have shown the relationship between the incidence of AMD and C-reactive protein (CRP) level, tumor necrosis factor-α receptor, and oxidative stress.[8–12] Numerous recent studies have shown that NLR and PLR are indicators of systemic inflammation.[13–15]

This study aimed to analyze the importance of inflammation in the pathophysiology of the disease by comparing NLR, monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) in patients with AMD in our clinic and compare the subtypes of AMD.

Methods

Data from 120 patients in the AMD groups (60 in the dry-type AMD group and 60 in the wet-type AMD group) and 71 in the control group between January 2016 and January 2019 was examined retrospectively. The control group consisted of patients who underwent cataract surgery and had no other eye diseases.

As we provide healthcare services in a tertiary hospital, AMD patients can both directly apply to our clinic and be referred from other healthcare institutions. For anti-VEGF applications, drug approval from the tertiary health institution is required. For this reason, we have a large archive of AMD patients. The patients were divided into three groups: wet-type AMD, dry-type AMD, and a healthy control group. All ophthalmologic examination records, including anterior and posterior segment findings, best-corrected visual acuity, and intraocular pressure, were examined, and data were recorded. Existing optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany) and fundus fluorescein angiography images were analyzed. Dry-type AMD was indicated by at least one eye with drusen or geographic atrophy, and wet-type AMD was indicated as neovascular membrane, disciform scar, or pigment epithelial detachment (Figures 1–3). Patients and control group participants without detailed ophthalmologic examination and whole blood examinations, patients with hematologic disease, patients with acute and chronic infection, patients with diabetes or obesity, patients with another retinal disorder or glaucoma, patients with chronic lung disease, and patients using steroids were excluded from the study. Smoking was also recorded.

Red blood cells, white blood cells, neutrophils, monocytes, lymphocytes, and platelets were counted in whole blood. Blood tests were performed on a Mindray BC 6800 (Mindray Building, High-tech Industrial Park, Nanshan, Shenzhen, China) device with original kits. The BC 6800 hematology analyzer used sheath flow impedance, laser scatter, and SF Cube analysis technology. NLR was obtained by dividing the neutrophil count by the lymphocyte count, and PLR was obtained by dividing the platelet count by the lymphocyte count. The MLR was obtained by dividing the monocyte count by the lymphocyte count.

IBM SPSS Statistics software version 22 (IBM Corp., Chicago, IL, USA) was used to analyze the data. Continuous variables were reported as mean ± standard deviation, and categorical variables were reported as frequency and percentage. The difference between the means of the continuous variables was tested via analysis of variance (ANOVA) and post hoc Bonferroni test. We analyzed receiver operating characteristic (ROC) curves analysis to specify the sensitivity and specificity of NLR and MLR values with the optimal cutoff value for wet-type AMD prediction. A p value of <0.05 was considered statistically significant in all analyses.

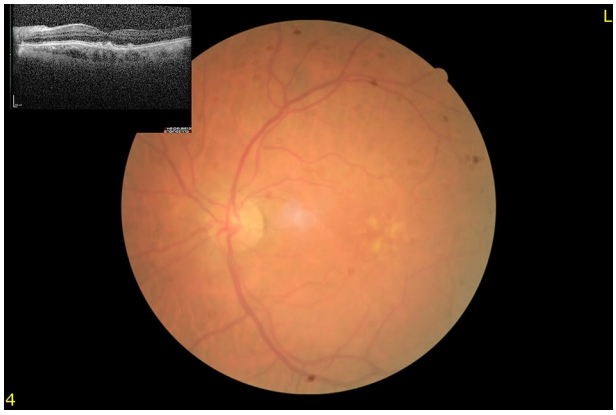

Figure 2. Fundus photograph and optical coherence tomography image of dry-type age-related macular degeneration.

Results

The mean age was 74.78 ± 7.59 years in the dry-type AMD group, 78.03 ± 8.60 years in the wet-type AMD group, and 75.25 ± 9.83 years in the control group. Of the 191 participants included in the study, 87 (45.6%) were women, and 104 (54.4%) were men (Table 1).

The mean NLR was 2.26 ± 1.42 in the dry-type AMD group, 3.90 ± 1.65 in the wet-type AMD group, and 1.84 ± 0.61 in the control group ($p < 0.001$). The mean PLR was 129.31 ± 79.82 in the dry-type AMD group, 156.67 ± 83.99 in

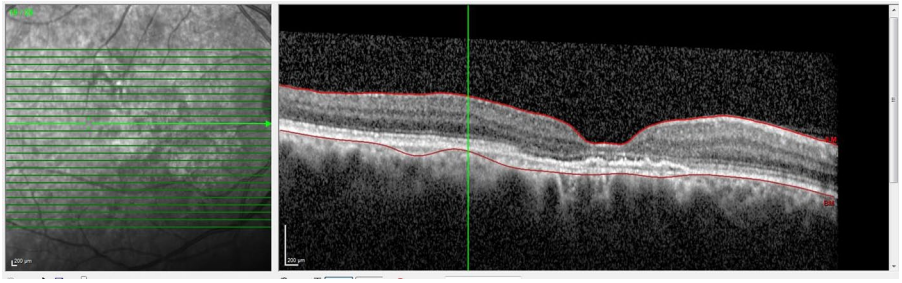

Figure 3. A representative optical coherence tomography image of atrophy due to dry-type age-related macular degeneration.

Table 1. Demographic data of patients.

Characteristic	Dry-type AMD (n = 60)	Wet-type AMD (n = 60)	Control (n = 71)	p value
Age (years)	74.78 ± 7.59	78.03 ± 8.60	75.25 ± 9.83	0.09*
Sex (n)				
Female	22	26	39	0.103†
Male	38	34	32	
Smoking (n)	8	9	11	0.937†

AMD, age-related macular degeneration.
*One-way analysis of variance was used.
†Chi-square test was used.

Table 2. Neutrophil, lymphocyte, monocyte, platelet, NLR, PLR, and MLR in patients with dry- and wet-type AMD and control group.

	Dry-type AMD	Wet-type AMD	Control	*p* value*
Neutrophil	4.80 ± 2.35	6.09 ± 1.39	4.90 ± 1.97	<0.001
Lymphocyte	2.40 ± 1.99	1.83 ± 0.47	2.10 ± 0.79	0.049
Monocyte	0.58 ± 0.23	0.58 ± 0.20	0.52 ± 0.19	0.487
Platelet	235.35 ± 69.50	246.46 ± 58.09	260.94 ± 71.42	0.095
NLR (mean ± SD)	2.26 ± 1.42	3.90 ± 1.65	1.84 ± 0.61	<0.001
PLR (mean ± SD)	129.31 ± 79.82	156.67 ± 83.99	135.59 ± 58.68	0.101
MLR (mean ± SD)	0.30 ± 0.20	0.47 ± 0.31	0.28 ± 0.14	<0.001

AMD, age-related macular degeneration; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standard deviation.
*One way analysis of variance was used, $p < 0.05$ was statistically significant.

Table 3. Multiple comparisons between groups.

	p value	95% CI (lower bound–upper bound)
Neutrophil		
Control–Wet-type AMD	**0.002**	−2.01 to −0.36
Control–Dry-type AMD	1.00	−0.72 to 0.93
Wet-type AMD–Dry-type AMD	**0.001**	0.43 to 2.15
Lymphocyte		
Control–Wet-type AMD	0.664	−0.26 to 0.79
Control–Dry-type AMD	0.515	−0.83 to 0.22
Wet-type AMD–Dry-type AMD	**0.040**	−1.12 to −0.01
NLR		
Control–Wet-type AMD	**0.001**	−2.59 to −1.51
Control–Dry-type AMD	0.174	−0.96 to 0.11
Wet-type AMD–Dry-type AMD	**0.001**	1.06 to 2.19
MLR		
Control–Wet-type AMD	**0.001**	−0.28 to −0.09
Control–Dry-type AMD	0.982	−0.12 to 0.06
Wet-type AMD–Dry-type AMD	**0.001**	0.06 to 0.26

AMD, age-related macular degeneration; CI, confidence interval; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.
Post hoc Bonferroni test, $p < 0.05$ was statistically significant.

the wet-type AMD group, and 135.59 ± 58.68 in the control group ($p = 0.101$). The mean MLR was 0.30 ± 0.20 in the dry-type AMD group, 0.47 ± 0.31 in the wet-type AMD group, and 0.28 ± 0.14 in the control group ($p < 0.001$). While there was a significant difference between the groups in terms of neutrophil and lymphocyte counts ($p < 0.001$ and $p = 0.049$, respectively), monocyte and platelet counts were similar in all three groups ($p = 0.487$ and $p = 0.095$, respectively). There were statistically significant differences between the three groups with respect to NLR and MLR (Table 2). When multiple comparisons with post hoc tests were made, the NLR values were significantly higher in wet-type AMD than in dry-type AMD and healthy control groups ($p < 0.001$). Similarly, MLR values were higher in wet-type AMD than in dry-type AMD and healthy control groups ($p < 0.001$) (Table 3).

The area under the curve (AUC) values for NLR and MLR to distinguish wet-type AMD from dry-type AMD and healthy control groups were found to be 0.920 and 0.717, respectively (Figure 4(a) and (b)).

A cutoff value of >3.07 for NLR was found to be a distinctive parameter in wet-type AMD. The sensitivity and specificity for this cutoff point were 64% and 93%, respectively.

A cutoff value of >0.31 for MLR was found to be a distinctive parameter in wet-type AMD. The

sensitivity and specificity for this cutoff point were 63% and 75%, respectively (Table 4).

Discussion

In our study, NLR and MLR were found to be higher in the wet-type AMD group than in the dry-type AMD and the control groups, and this difference was statistically significant. However, PLR was found to be higher in the wet-type AMD group than in the dry-type AMD and control groups, but this difference was not statistically significant.

AMD is a complex, chronic, progressive, neurodegenerative disease with multifactorial etiology. Chronic inflammation and hypoxia leading to oxidative stress cause aging of the normal retina. Continued oxidative stress causes inflammation and tissue damage. Complement system activation in Bruch's membrane and activation of the microglia between the retina and choroid play an important role in choroidal neovascular membrane formation. Studies are underway to investigate the effect of systemic inflammation on the possible mechanism of dry- and wet-type AMD.[16]

NLR has been shown to be associated with the activity and outcome of chronic inflammatory diseases, such as arthritis, systemic hypertension, diabetes mellitus (DM), and chronic obstructive pulmonary disease.[7,17,18]

In their meta-analysis, Niazi and colleagues[19] found a strong correlation between high NLR and wet-type AMD, but found no difference between the dry-type AMD and control groups. Ilhan and colleagues found a higher NLR in patients with AMD than in the control group. This study also found a significant difference between AMD groups and NLR associated with age and the severity of the disease and a marker of inflammation in AMD.[20] Subhi and Lykke Sørensen[21] found that systemic leukocyte activity correlated with the early stage of AMD in patients with wet-type AMD, and systemic leukocyte activity was correlated with lesion size and best-corrected visual acuity.

Kurtul and Ozer[22] found an independent relationship between wet-type AMD and increased NLR with 73% sensitivity and 60% specificity. Several studies have shown that NLR and PLR are associated with the severity of the disease and can be used as a biomarker of inflammation in AMD.[19–22]

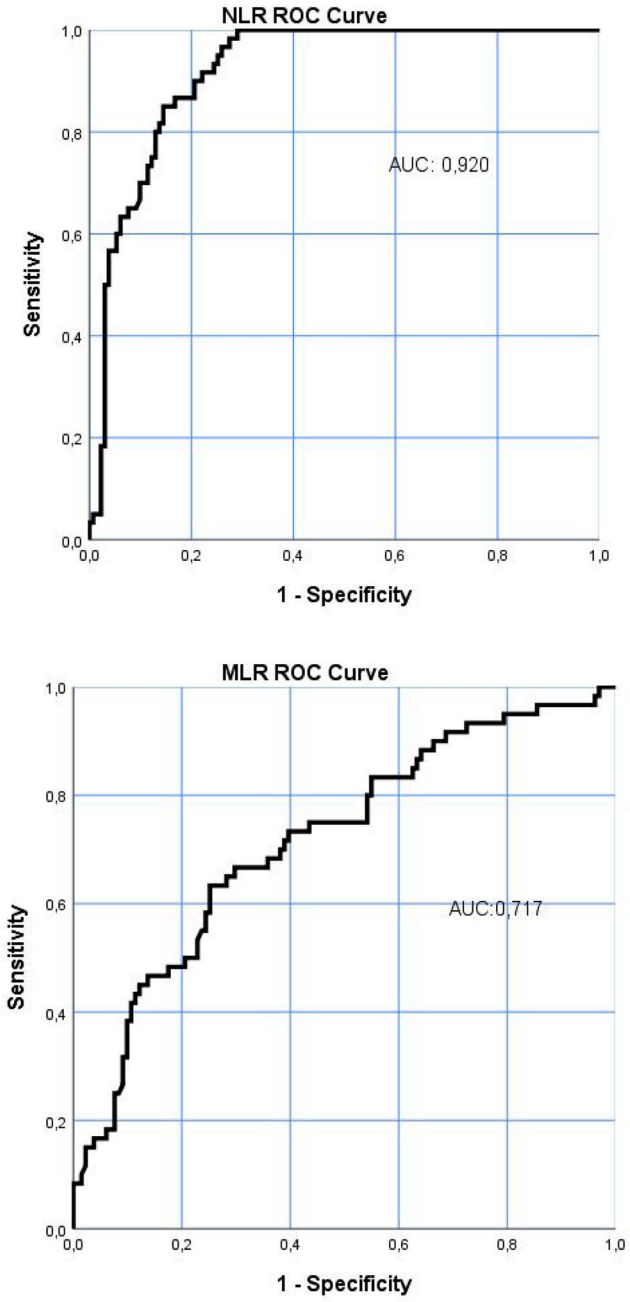

Figure 4. (a) ROC curve analysis of NLR in wet-type AMD patients (AUC for NLR: 0.920, cutoff value: 3.07, sensitivity: 64%, specificity: 93%). (b) ROC curve analysis of MLR in wet-type AMD patients (AUC for MLR: 0.717, cutoff value: 0.31, sensitivity: 63%, specificity: 75%).
AMD, age-related macular degeneration; AUC, area under the ROC curve; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.

Our study is rare in that it evaluated MLR values in wet- and dry-type AMD in addition to NLR and PLR. We found statistically significant differences between the groups in terms of NLR and MLR. NLR and MLR values were significantly

Table 4. ROC curves and prognostic accuracy of NLR and MLR.

Marker	AUC	95% CI	*p* value	Cutoff	Sensitivity (%)	Specificity (%)
NLR	0.920	0.88–0.95	<0.001	>3.07	64	93
MLR	0.717	0.63–0.79	<0.001	>0.31	63	75

AUC, area under the curve; CI, confidence interval; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.
$P < 0.05$ was statistically significant.

higher in wet-type AMD than in dry-type AMD and healthy control groups. This indicates a relationship between systemic inflammation and wet-type AMD. On the other hand, ROC analyses revealed a 64% sensitivity for NLR and 63% sensitivity for MLR in wet-type AMD.

Pinna and colleagues[23] found a significantly lower number of white blood cells in patients with AMD compared with the control group, and no statistically significant difference between the control group and male patients with AMD in terms of NLR and PLR. Wu and colleagues[24] investigated the relationship between patients with AMD and healthy controls in terms of hemostatic factors and inflammatory markers and found no association between inflammatory markers and AMD.

Our study has several limitations, including its retrospective design, the fact that the early and advanced stages of the disease are not mentioned separately but are examined under a single heading, and the fact that there were insufficient data on patients' history of medication use. In addition, as our clinic does not offer indocyanine green angiography, it cannot be stated that we have excluded polypoid choroidal vasculopathy for a limited number of patients. Finally, we did not evaluate the effect of cataracts on inflammation parameters in this study, and we consider this a limitation.

In conclusion, we found that NLR and MLR were different between wet-type AMD and dry-type AMD and healthy control groups. Therefore, these differences indicate inflammation in patients with wet-type AMD. Further studies with a larger sample size are required.

Conflict of interest statement

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

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Ethics statement

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 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the local ethics committee (Diyarbakir Training and Research Hospital, decision no. 2019/263). All patients gave written informed consent.

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