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Association between optical coherence tomography biomarkers and systemic inflammatory indices in neovascular age-related macular degeneration

Özkan Kocamış[1*]

Abstract

Background Neovascular age-related macular degeneration (nAMD) is a leading cause of irreversible central vision loss in elderly individuals. Increasing evidence indicates that systemic inflammation contributes to nAMD pathogenesis. Optical coherence tomography (OCT) enables detailed evaluation of retinal microstructural changes; however, the relationship between OCT biomarkers and systemic inflammatory markers remains unclear. This study aimed to investigate the association between OCT biomarkers and systemic inflammatory indices in patients with nAMD.

Methods This retrospective case–control study included 80 treatment-naïve patients with nAMD and 80 age-matched healthy controls. All participants underwent comprehensive ophthalmologic examination and spectral-domain OCT imaging. OCT biomarkers assessed were intraretinal cysts (IRCs) and hyperreflective foci (HRFs). Systemic inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR), were obtained from routine complete blood counts. Statistical analyses and receiver operating characteristic (ROC) curve analysis were performed.

Results NLR and MLR values were significantly higher in patients with nAMD compared with controls ($p < 0.05$). ROC analysis demonstrated moderate diagnostic performance for NLR (AUC = 0.757) and MLR (AUC = 0.651). An NLR cut-off value of 2.23 showed a sensitivity of 58.8% and specificity of 81.3%. HRFs were significantly associated with the presence of SRF, whereas IRCs were associated with a lower frequency of SRF. No significant correlations were observed between OCT biomarkers and systemic inflammatory indices.

Conclusions Systemic inflammatory markers, particularly NLR and MLR, are elevated in nAMD and may serve as adjunctive biomarkers. OCT biomarkers primarily reflect localized retinal pathology and appear largely independent of systemic inflammatory status. These findings support the complementary roles of systemic and imaging-derived biomarkers in the clinical evaluation of nAMD.

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Keywords Neovascular age-related macular degeneration, Optical coherence tomography, Neutrophil-to-lymphocyte ratio, Monocyte-to-lymphocyte ratio, Inflammation

Introduction

Age-related macular degeneration (AMD) remains one of the leading causes of irreversible central vision loss among the elderly population in high-income countries [1–3]. Clinically, AMD is classified into two main subtypes: non-neovascular (dry) and neovascular (wet) AMD. While dry AMD is characterized by progressive atrophy of the retinal pigment epithelium and photoreceptors, neovascular AMD (nAMD) is defined by choroidal neovascularization, resulting in exudation, hemorrhage, and rapid visual deterioration [4].

Optical coherence tomography (OCT) has become indispensable in the diagnosis, therapeutic decision-making, and follow-up of nAMD due to its ability to provide high-resolution cross-sectional imaging of retinal microstructures [5]. Several OCT biomarkers have been identified as indicators of disease activity and prognosis. These biomarkers can be broadly categorized into fluid-related parameters, such as intraretinal cysts and subretinal fluid, and structural features, including hyperreflective foci, pigment epithelial detachment, and outer retinal tubulations [6, 7].

Accumulating evidence suggests that inflammation plays a crucial role in the pathogenesis and progression of AMD [8]. Systemic inflammatory responses involve complex interactions among immune cells, including neutrophils, lymphocytes, and macrophages. The neutrophil-to-lymphocyte ratio (NLR), derived from routine complete blood count analysis, has emerged as a simple and reliable marker of systemic inflammation and immune dysregulation [9]. Elevated NLR has been associated with various chronic inflammatory disorders and has been proposed as a prognostic indicator in multiple systemic diseases. Multiple studies have identified an association between the neutrophil-to-lymphocyte ratio and neovascular age-related macular degeneration [10].

Although both OCT biomarkers and systemic inflammatory indices have been individually associated with nAMD, data exploring their interrelationship remain limited. Clarifying whether retinal microstructural changes reflect systemic inflammatory burden may provide insight into disease mechanisms and improve risk stratification. Therefore, this study aimed to investigate the association between OCT-derived biomarkers and systemic inflammatory indices in patients with treatment-naïve nAMD.

Materials and methods

Study design and participants

This retrospective case–control study was conducted at the Department of Ophthalmology, Kırşehir Ahi Evran University, between January 2022 and July 2025. The study included 80 treatment-naïve patients diagnosed with nAMD and 80 age-matched healthy controls. Ethical approval was obtained from the Institutional Review Board of Kırşehir Ahi Evran University (approval number: 2025-15/198), and the study adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Ophthalmologic examination and diagnosis

All participants underwent a comprehensive ophthalmologic examination, including best-corrected visual acuity assessment, slit-lamp biomicroscopy, dilated fundus examination, fundus fluorescein angiography (FFA), and spectral-domain optical coherence tomography (SD-OCT) imaging (Spectralis®, Heidelberg Engineering Inc., Heidelberg, Germany).

The diagnosis of neovascular AMD was established based on clinical findings supported by FFA evidence of choroidal neovascularization and OCT-based documentation of macular thickness and morphological alterations.

Inclusion and exclusion criteria

Inclusion criteria for the nAMD group were the presence of active leakage consistent with choroidal neovascularization or macular edema on FFA, detection of subretinal fluid or intraretinal cystic changes on OCT, and absence of any prior treatment for macular degeneration. The control group consisted of patients scheduled for routine cataract surgery with normal macular anatomy on OCT.

Exclusion criteria included ocular conditions other than AMD that could impair visual acuity, such as epiretinal membrane, vitreomacular traction, glaucoma, or media opacities affecting image quality. Patients with acute ocular inflammation or infection, systemic hypertension, diabetes mellitus, chronic vascular disease, acute or chronic renal failure, chronic liver disease, known malignancy, connective tissue disorders, or recent use (within one month) of systemic steroids or non-steroidal anti-inflammatory drugs were also excluded. The majority of cases consisted of type 1 and type 2 neovascularization, whereas type 3 neovascularization was rare. Due to the limited number of cases in each subtype, subgroup analysis according to neovascularization type was not performed.

Routine laboratory data were retrospectively reviewed to identify potential systemic comorbidities. Laboratory data were retrospectively obtained from the hospital electronic medical record system. Complete blood count measurements used in the study were collected at the time of the initial ophthalmologic evaluation or within one month prior to the diagnosis of neovascular AMD. These laboratory tests were performed as part of routine clinical assessments requested by primary care physicians and were not specifically ordered for this study. To minimize potential confounding effects on inflammatory indices, patients with evidence of acute infection, inflammatory disease, or systemic conditions known to influence leukocyte counts—including known malignancies—were excluded. All included patients were treatment-naïve at the time of blood sampling and had not yet received intravitreal anti-VEGF therapy.

Evaluation of OCT biomarkers

The OCT biomarkers evaluated included intraretinal cysts (IRCs), hyperreflective foci (HRFs), subretinal fluid (SRF), and drusenoid pigment epithelial detachment (DPED).

IRCs were defined as oval-shaped hyporeflective spaces located within the neurosensory retina. HRFs were identified as small, discrete, round hyperreflective lesions within the retinal layers. To differentiate HRFs from hard exudates or microaneurysms, the following criteria were applied: (1) reflectivity comparable to the retinal nerve fiber layer, (2) diameter less than 30 µm, and (3) absence of posterior shadowing [11]. HRFs were manually counted.

SRF was defined as a hyporeflective space beneath the neurosensory retina corresponding to serous retinal detachment and was classified as either present or absent.

DPED was characterized by a well-demarcated elevation of the retinal pigment epithelium associated with confluent drusen. IRCs and HRFs were selected because they represent well-established OCT markers of retinal exudation and inflammatory activity and have been widely studied in relation to disease activity in nAMD. Although other biomarkers such as pigment epithelial detachment were evaluated descriptively, our primary analysis focused on IRCs and HRFs due to their stronger association with inflammatory and exudative processes.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation, median (minimum–maximum), frequency, and percentage, as appropriate. Normality of data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Independent samples t-tests were used for normally distributed continuous variables, while the Mann–Whitney U test was applied for non-normally distributed variables. Categorical variables were analyzed using the chi-square test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate diagnostic performance and determine optimal cut-off values. Statistical analyses were conducted using SPSS software version 27.0 (IBM Corp., Armonk, NY, USA), with p values < 0.05 considered statistically significant.

Table 1 Clinical and demographic characteristics of the nAMD and control groups

	Control Group ($n=80$) Mean ± SD / n (%)	Median	nAMD Group ($n=80$) Mean ± SD / n (%)	p value
Age (years)	70.3 ± 6.9	71.0	71.8 ± 7.7	0.136[m]
Female sex	35 (43.8%)	-	33 (41.3%)	0.749[χ^2]
Male sex	45 (56.3%)	-	47 (58.8%)	
Neutrophil count	4.26 ± 1.41	3.90	4.75 ± 1.32	0.003[m]
Lymphocyte count	2.50 ± 0.75	2.48	2.01 ± 0.68	< 0.001[m]
Monocyte count	0.59 ± 0.18	0.54	0.59 ± 0.19	0.918[m]
NLR	1.78 ± 0.52	1.80	2.59 ± 1.08	< 0.001[m]
MLR	0.26 ± 0.16	0.23	0.32 ± 0.17	0.001[m]

nAMD: neovascular Age-related Macular Degeneration, SD: Standart Deviation, NLR: Neutrophil-Lymphocyte Ratio, MLR: Monocyte-Lymphocyte Ratio

[m] Mann–Whitney U test; [χ^2] Chi-square test

Table 2 Diagnostic performance of NLR

	AUC	95% CI	p value
NLR	0.757	0.683–0.831	< 0.001

NLR: Neutrophil-Lymphocyte Ratio, AUC: Area under Curve

Results

There were no statistically significant differences between the nAMD and control groups with respect to age (71.8 ± 7.7 vs. 70.3 ± 6.9 years, $p = 0.136$) or sex distribution ($p = 0.749$) (Table 1).

Neutrophil levels were significantly higher and lymphocyte levels were significantly lower in the nAMD group compared with controls ($p < 0.05$). Monocyte counts did not differ significantly between the two groups ($p > 0.05$). In contrast, neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) values were significantly higher in patients with nAMD than in the control group ($p < 0.05$) (Table 1).

ROC curve analysis demonstrated that NLR showed significant discriminative ability between nAMD patients and controls, with an area under the curve (AUC) of 0.757 (95% CI: 0.683–0.831). An NLR cut-off value of 2.23 yielded a significant diagnostic performance (AUC = 0.700; 95% CI: 0.618–0.782) (Table 2). At this threshold, sensitivity was 58.8%, specificity 81.3%,

positive predictive value 75.8%, and negative predictive value 66.3% (Fig. 1).

Similarly, MLR demonstrated significant discriminative capacity between groups (AUC = 0.651; 95% CI: 0.566–0.736). An MLR cut-off value of 0.285 showed meaningful diagnostic performance (AUC = 0.650; 95% CI: 0.564–0.736) (Table 3). At this level, sensitivity was 53.8%, specificity 76.3%, positive predictive value 69.4%, and negative predictive value 62.2% (Fig. 2).

Patients exhibiting HRFs had a significantly higher prevalence of subretinal fluid compared with those without HRFs ($p < 0.05$). However, no significant differences were observed between HRF-positive and HRF-negative groups regarding the presence of intraretinal cysts, pigment epithelial detachment, NLR, or MLR values ($p > 0.05$ for all comparisons) (Table 4).

In contrast, patients with intraretinal cysts demonstrated a significantly lower frequency of subretinal fluid compared with those without cysts ($p < 0.05$). The presence of HRFs, pigment epithelial detachment, NLR, and MLR did not differ significantly between groups with and without intraretinal cysts ($p > 0.05$) (Table 5).

Discussion

This study demonstrates that systemic inflammatory indices, particularly NLR and MLR, are elevated in patients with nAMD, supporting the role of systemic inflammation in disease pathophysiology. However, OCT biomarkers predominantly reflect localized retinal changes and appear largely independent of systemic inflammatory status.

The moderate diagnostic performance of NLR suggests its potential utility as an adjunctive biomarker rather than a standalone diagnostic tool. The lack of correlation between OCT biomarkers and systemic inflammatory indices highlights the complex and multifactorial nature of nAMD, in which local retinal pathology and systemic inflammation may contribute through partially independent mechanisms.

Increasing evidence has highlighted the role of chronic low-grade inflammation and immune dysregulation in the development and progression of AMD. Recent molecular and clinical studies have demonstrated that activation of innate immune pathways, complement dysregulation, and recruitment of inflammatory cells play a central role in choroidal neovascularization [12, 13]. In this context, peripheral blood-derived inflammatory indices such as NLR and MLR have gained attention as accessible and cost-effective biomarkers reflecting systemic inflammatory burden. Our findings of elevated NLR and MLR in nAMD patients are consistent with recent reports suggesting that these ratios may serve as surrogate markers of disease activity and severity in retinal vascular and degenerative disorders [14, 15].

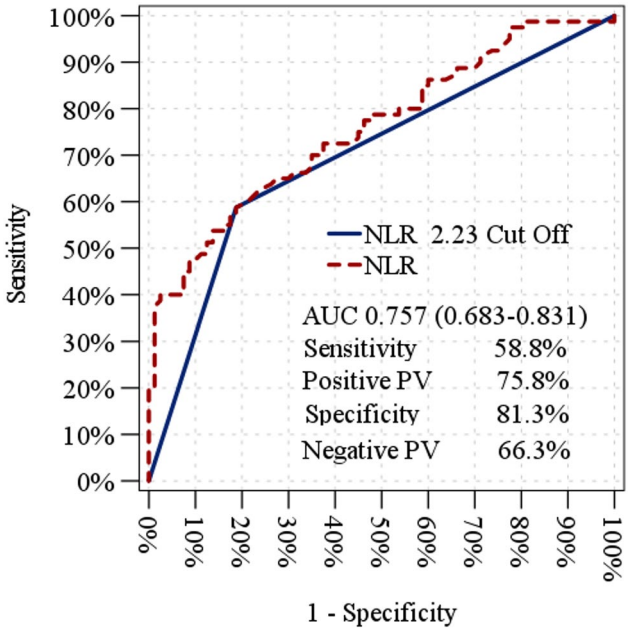

Fig. 1 Receiver operating characteristic (ROC) curve for the neutrophil-to-lymphocyte ratio (NLR) comparing patients with neovascular age-related macular degeneration and healthy controls

Table 3 Diagnostic performance of MLR

	AUC	95% CI	p value
MLR	0.651	0.566–0.736	0.001

MLR: Monocyte-Lymphocyte Ratio, AUC: Area under Curve

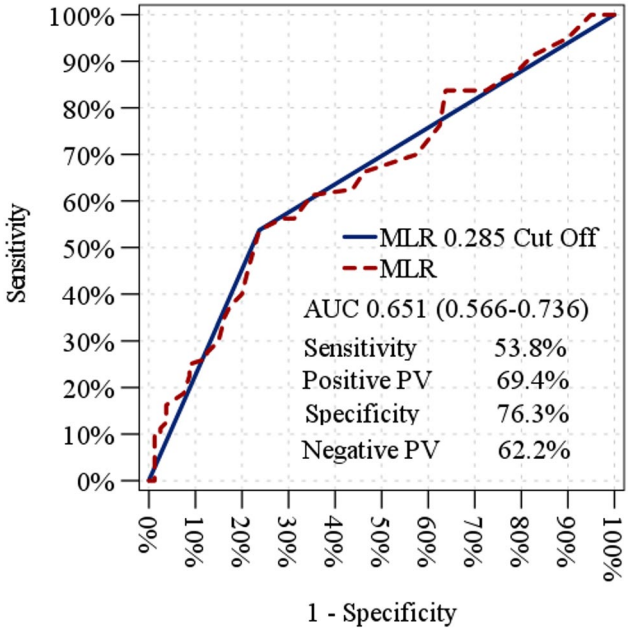

Fig. 2 Receiver operating characteristic (ROC) curve for the monocyte-lymphocyte ratio (MLR) comparing patients with neovascular age-related macular degeneration and healthy controls

Table 4 Subgroup analysis according to hyperreflective foci

	HRF (-) (*n* = 30) Mean ± SD / *n* (%)	Median	HRF (+) (*n* = 50) Mean ± SD / *n* (%)	*p* value
Subretinal fluid	21 (70.0%)	-	44 (88.0%)	0.046$^{\chi^2}$
Intraretinal cyst	14 (46.7%)	-	25 (50.0%)	0.773$^{\chi^2}$
Pigment epithelial detachment	27 (90.0%)	-	41 (82.0%)	0.332$^{\chi^2}$
Neutrophil count	4.48 ± 1.12	4.45	4.91 ± 1.40	0.116^{m}
Lymphocyte count	1.90 ± 0.70	1.80	2.08 ± 0.66	0.243^{t}
Monocyte count	0.55 ± 0.15	0.53	0.61 ± 0.21	0.249^{t}
NLR	2.69 ± 1.31	2.51	2.53 ± 0.92	0.676^{m}
MLR	0.33 ± 0.20	0.30	0.31 ± 0.20	0.665^{m}

HRF: Hyperreflective foci, SD: Standart Deviation, NLR: Neutrophil-Lymphocyte Ratio, MLR: Monocyte-Lymphocyte Ratio, ^{t} Independent samples t-test; ^{m} Mann–Whitney U test; $^{\chi^2}$ Chi-square test

Table 5 Subgroup analysis according to intraretinal cyst presence

	IRC (-) (*n* = 41) Mean ± SD / *n* (%)	Median	IRC (+) (*n* = 39) Mean ± SD / *n* (%)	*p* value
Subretinal fluid	40 (97.6%)	-	25 (64.1%)	< 0.001$^{\chi^2}$
Hyperreflective foci	25 (61.0%)	-	25 (64.1%)	0.773$^{\chi^2}$
Pigment epithelial detachment	36 (87.8%)	-	32 (82.1%)	0.471$^{\chi^2}$
Neutrophil count	4.81 ± 1.34	4.73	4.68 ± 1.30	0.658^{t}
Lymphocyte count	1.89 ± 0.67	1.72	2.14 ± 0.67	0.062^{m}
Monocyte count	0.56 ± 0.19	0.52	0.62 ± 0.19	0.093^{m}
NLR	2.81 ± 1.19	2.53	2.36 ± 0.91	0.059^{m}
MLR	0.33 ± 0.22	0.29	0.30 ± 0.10	0.881^{m}

IRC: İntra Retinal Cyst, SD: Standart Deviation, NLR: Neutrophil-Lymphocyte Ratio, MLR: Monocyte-Lymphocyte Ratio,, ^{t} Independent samples t-test; ^{m} Mann–Whitney U test; $^{\chi^2}$ Chi-square test

The diagnostic performance of NLR observed in the present study, as demonstrated by ROC curve analysis, indicates a moderate discriminative ability between nAMD patients and controls. Although the sensitivity was relatively modest, the high specificity suggests that elevated NLR may be more useful as a supportive biomarker rather than a standalone diagnostic tool. Similar observations have been reported in recent ophthalmic studies, where systemic inflammatory indices were proposed as adjunctive markers to imaging-based diagnosis rather than replacements for established diagnostic modalities [16]. The slightly lower performance of MLR compared with NLR may reflect the complex and multifactorial roles of monocytes in chronic inflammation and angiogenesis.

OCT biomarkers provide critical insight into the microstructural changes associated with nAMD and have become indispensable for both prognostic evaluation and treatment monitoring. HRFs, in particular, have been increasingly recognized as indicators of inflammatory activity, lipid-laden macrophage migration, or activated microglial cells within the retina [17, 18]. In our study, the presence of HRFs was significantly associated with subretinal fluid, supporting the hypothesis that HRFs may reflect active exudation or ongoing inflammatory processes at the level of the outer retina and retinal pigment epithelium. However, the absence of a significant relationship between HRFs and systemic inflammatory indices suggests that local retinal inflammation may not always directly mirror systemic inflammatory status.

Conversely, patients with intraretinal cysts exhibited a lower frequency of subretinal fluid, indicating potentially distinct pathogenic mechanisms underlying different fluid compartments in nAMD. Intraretinal cystic changes have been associated with Müller cell dysfunction, chronic tissue damage, and irreversible structural alterations rather than acute exudative activity [19]. The lack of association between IRCs and systemic inflammatory markers in the present study further supports the notion that intraretinal fluid may represent a more localized or degenerative process rather than a reflection of systemic inflammation.

Notably, no significant associations were observed between pigment epithelial detachment and systemic inflammatory indices. This finding aligns with recent studies suggesting that drusenoid or fibrovascular pigment epithelial detachments may be more closely related to chronic structural remodeling and extracellular matrix alterations rather than acute inflammatory responses [20].

The strengths of this study include the well-defined exclusion criteria minimizing systemic confounders, the use of standardized OCT biomarker definitions, and the evaluation of both NLR and MLR within the same cohort. Nevertheless, several limitations should be acknowledged. The retrospective design and single-center setting limit causal inference and generalizability. Inflammatory markers were assessed at a single time point, and longitudinal associations could not be evaluated.

In conclusion, the present findings support the growing body of evidence implicating systemic inflammation in the pathogenesis of nAMD. Elevated NLR and MLR values appear to be associated with the presence of nAMD, while specific OCT biomarkers reflect localized retinal inflammatory and exudative processes. Future prospective studies with longitudinal follow-up are warranted to clarify the dynamic interactions between systemic inflammatory status, retinal microstructural changes, and treatment outcomes in neovascular AMD.

Abbreviations

AMD	Age-related macular degeneration
nAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
SD-OCT	Spectral-domain optical coherence tomography

IRCs	Intraretinal cysts
HRFs	Hyperreflective foci
SRF	Subretinal fluid
DPED	Drusenoid pigment epithelial detachment
NLR	Neutrophil-to-lymphocyte ratio
MLR	Monocyte-to-lymphocyte ratio
ROC	Receiver operating characteristic
AUC	Area under the curve
FFA	Fundus fluorescein angiography
SD	Standard deviation
CI	Confidence interval

Author contributions
Ö.K. contributed to all aspects of the study.

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Data availability
The data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Institutional Review Board of Kırşehir Ahi Evran University (approval number: 2025-15/198), and the study adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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