Original Article

Monocyte to high-density lipoprotein and neutrophil-to-lymphocyte ratios in patients with acute central serous chorioretinopathy

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Purpose: To investigate monocyte to high-density lipoprotein (HDL) ratio (MHR) and neutrophil-to-lymphocyte ratio (NLR) as indicators of systemic inflammation in acute central serous chorioretinopathy (CSC). **Methods:** The HDL levels, hematological profiles, erythrocyte sedimentation rates (ESR), and C-reactive protein (CRP) levels of 38 patients with acute CSC (Group I) and 38 controls without CSC (Group II) were measured. **Results:** MHRs were significantly higher in Group I (13.30 ± 2.95) than in Group II (11.52 ± 2.42, *P* = 0.005), whereas NLRs, CR*P* values, and ESR values did not significantly differ between the groups (*P* = 0.726, *P* = 0.219, and *P* = 0.441, respectively). Multivariate analysis revealed that the MHR was an independent predictor of acute CSC (OR = 1.266, 95% CI = 1.054-1.521, *P* = 0.012). **Conclusion:** Indicating an association between increased MHRs and acute CSC, the MHR might represent simple, inexpensive, reliable biomarkers of inflammation in acute CSC.

Key words: Acute central serous chorioretinopathy, monocyte to high-density lipoprotein ratio, neutrophil-to-lymphocyte ratio, systemic inflammation

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1327_19

Quick Response Code:

Central serous chorioretinopathy (CSC) is a retinal disorder characterized by an exudation of serous fluid under the neurosensory retina from the choroidal capillaries and the detachment of the neurosensory retina.[1,2] Among individuals aged 20–50 years, men are more prone to CSC than women.[3] Although several risk factors have been attributed to the etiology of CSC; including the use of corticosteroid medications, high blood cortisol levels, smoking, stress, hypertension, type A personality, pregnancy, sleep apnea syndrome, and genetic traits, the exact pathophysiological mechanisms of the disorder remains unclear.[4,5]

Among factors of the etiopathogenesis of CSC, chronic inflammation and oxidative stress have received attention from researchers and practitioners. The main theory for the development of CSC is the hyperpermeability of the choroidal vessels, resulting in excess fluid deposition in the retinal pigment epithelium (RPE).[1,6] Previous studies have demonstrated that the cause of this hyperpermeability of the choroidal circulation may be inflammation and free radicals.[7,8] Turkcu *et al.* observed that antioxidative parameters in the plasma such as total antioxidant capacity, overall oxidant status, and levels of dehydroepiandrosterone sulfate were less in cases of acute CSC than in healthy individuals.[9] Furthermore, researchers who have shown that glucocorticoids aggravate CSC have cited evidence of systemic inflammation in its pathogenesis.[10] Among them, Yang *et al.* have reported that systemic mineralocorticoid antagonists may be used to treat CSC.[11] Taken together, such findings suggest that oxidative stress and inflammation play an important role in the development of CSC.

Some biochemical and radiological aspects, including C-reactive protein (CRP) levels, endothelium-dependent flow-mediated vasodilation, disulfide-to-thiol ratios, and neutrophil-to-lymphocyte ratios (NLR), have recently been studied as predictors of inflammation in patients with CSC.[12-14] At the same time, monocytes are important cells for inflammatory reactions and high-density lipoprotein (HDL) is known for its anti-inflammatory and antioxidant effects.[15,16] Thus, elevated monocyte counts and reduced high-density lipoprotein levels have been assessed as possible biomarkers of the systemic inflammatory process of the disorder. Researchers have also demonstrated that monocyte-to-HDL ratios (MHR) are relatively high in several systemic and ocular disorders associated with inflammation including ischemic stroke, coronary artery stenosis, pseudoexfoliation syndrome or glaucoma, and branch retinal vein occlusion.[17-20]

Although MHR has been studied in several diseases related to systemic and local inflammation, such as branch retinal vein occlusion, diabetic retinopathy, and exfoliation syndrome, its association with CSC has not been reported yet.[19-21] Since the pathogenesis of CSC seems to be related to systemic inflammation, we aimed to investigate whether elevated MHRs and NLRs are important predictors of CSC. To our knowledge,

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Received: 20-Jul-2019 Revision: 16-Sep-2019
Accepted: 01-Nov-2019 Published: 20-Apr-2020

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Cite this article as: Sirakaya E, Duru Z, Kuçuk B, Duru N. Monocyte to high-density lipoprotein and neutrophil-to-lymphocyte ratios in patients with acute central serous chorioretinopathy. Indian J Ophthalmol 2020;68:854-8.

our study marks the first to have involved the evaluation of MHRs in patients with CSC.

Methods

We conducted our cross-sectional, prospective, comparative study after obtaining approval from the institutional review board and ethics committee. In compliance with the guidelines of the Declaration of Helsinki, all participants provided both their oral and written informed consent to participate prior to the outset of the study.

Our sample consisted of 38 patients with acute CSC (Group I) who were compared with 38 age- and gender-matched individuals without CSC (Group II). For Group I, only patients newly diagnosed with acute CSC and without any prior systemic or ocular treatment were eligible, whereas participants in Group II were selected from healthy individuals who applied to the clinic of ophthalmology.

In our study, acute CSC was defined as the loss of visual acuity and visual symptoms (e.g., micropsia, metamorphopsia, chromatopsia, and central scotomata) within 3 months, along with the localized detachment of the neurosensory retina and one or more focal angiographic leaks with ink-blot and smokestack patterns in the RPE without other possible etiologies for the accumulation of serous fluids (e.g., infiltration, inflammation, or choroidal neovascularization). To confirm the diagnosis of CSC, a retina specialist performed fundus fluorescein angiography (Visucam NM/FA, Carl Zeiss Meditec AG, Dublin, CA, USA) and optical coherence tomography (Spectralis, Heidelberg Engineering, Heidelberg, Germany) on all participants. Choroidal thickness was also examined with enhanced depth imaging optical coherence tomography from each participant to diagnose CSC.

Exclusion criteria for participants included any history of significant ocular disease (e.g., uveitis, scleritis, ocular trauma, or retinal disease except for CSC), ocular surgery, hematological disease, acute or chronic infection, systemic inflammatory disorder, chronic obstructive pulmonary disorder, hyperlipidemia, malignancy, smoking or alcohol consumption, steroid use 6 months prior to the study, or use of ocular medication or systemic steroid therapy. Patients who were suspected to have polypoidal choroidal vasculopathy on clinical and imaging were excluded from the study. For that purpose, clinical features for the polypoidal choroidal vasculopathy included bilaterally serous, serosanguineous, and hemorrhagic detachments of the retina, and RPE in the posterior pole or periphery in a relatively elderly patient; exudation, reddish-orange "inner choroidal" vascular abnormalities and nodules; general rarity of drusen; wide and shallow RPE elevation and the sharply peaked polyps with different sizes on optical coherence tomography; an occult choroidal neovascularization picture on fluorescein angiography.

Each participant received a complete ophthalmologic evaluation involving best-corrected visual acuity, slit-lamp biomicroscopy, a dilated fundus examination, and the measurement of intraocular pressure with Goldmann applanation tonometry. All of their blood lipid profiles, hematological profiles, erythrocyte sedimentation rates (ESR), and CRP levels were analyzed in venous blood samples. Complete blood count and blood lipid profiles analyses were performed using an automated complete blood cell counter SysmexXN-9000 analyzer (Sysmex Corporation, Kobe, Japan) and Cobas® 8000 System (Roche Diagnostics, Mannheim, Germany) in 2 h. The MHR was defined as the ratio of the monocyte count to the level of HDL and the NLR as the ratio of the neutrophil count to the lymphocyte count. Each blood sample was collected from the participant's antecubital vein between 8:30 and 10:30 a.m. after 10 h of fasting.

All data were analyzed in the Statistical Package for the Social Sciences version 25 (IBM, Armonk, NY, USA). In the power analysis for our research, an alpha error was found 5% and the observed power was 80%. Thus, the sample size was found to be adequate for this study. Normality distribution was checked with the Shapiro-Wilk test, and an independent sample *t*-test was used to compare variables between the groups. In addition to multivariate logistic regression analyses, a receiver operating characteristic analysis was performed to determine the sensitivity and specificity of admission and the discriminative value of the between-group difference for some variables. In all tests, results with *P* values of less than 0.05 were considered to be statistically significant.

Results

The mean age of participants was 36.03 ± 5.15 years in Group I, which had 26 men and 12 women, and 36.18 ± 5.75 years in Group II, which had 27 men and 11 women. The mean age and gender distribution between the groups did not differ significantly ($P = 0.803$ and $P = 0.900$, respectively). Table 1 lists the baseline characteristics and laboratory measurements of participants in both groups. MHRs were significantly higher in Group I (13.30 ± 2.95) than in Group II (11.52 ± 2.42, $P = 0.005$), although NLRs, CRP values, and ESR values did not significantly differ between the groups ($P = 0.726$, $P = 0.219$, and $P = 0.441$, respectively). As shown in Table 2, results of the multivariate logistic regression analysis performed to identify any distinguishing independent risk factors for CSC, including MHR, NLR, CRP level, and ESR value, between the groups revealed that only the MHR was significant (OR = 1.266, 95% CI = 1.054-1.521, $P = 0.012$). On the receiver

Table 1: Patient characteristics and baseline laboratory measurements between the groups

	Group I (*n*=38)	Group II (*n*=38)	*P*
Gender, Male/Female	26/12	27/11	0.803[a]
Age, years	36.03±5.15	36.18±5.75	0.900[b]
Neutrophil count, 10^3/lL	4.41±0.78	4.21±0.62	0.217[b]
Lymphocyte count, 10^3/lL	2.34±0.35	2.24±0.46	0.311[b]
Monocyte count, 10^9/lL	585.30±118.79	538.20±102.24	0.068[b]
HDL, (mg/dL)	44.68±6.30	47.18±5.11	0.062[b]
C-reactive protein, (mg/dL)	2.88±1.96	2.39±1.46	0.219[b]
ESR, (mm/h)	8.81±4.39	8.07±3.88	0.441[b]
Neutrophil-to-lymphocyte ratio	1.92±0.43	1.96±0.52	0.726[b]
Monocyte-to-HDL ratio	13.30±2.95	11.52±2.42	0.005[b]

HDL: High-density lipoprotein, ESR: Erythrocyte sedimentation rate. Values are expressed as *n* or mean±standard deviation, [a]Chi-square test, [b]Independent sample *t*-test

Table 2: Predictors of acute central serous chorioretinopathy in multivariate regression analysis

Variable	Odds ratio (95% confidence interval)	P
MHR	1.266 (1.054-1.521)	0.012
NLR	0.760 (0.279-2.071)	0.592
CRP	1.135 (0.821-1.569)	0.444
ESR	0.993 (0.866-1.138)	0.915

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MHR: Monocyte-to-high-density lipoprotein ratio, NLR: Neutrophil-to-lymphocyte ratio

operating characteristics curve, the area under the curve was 0.678 for the MHR, and the optimal cutoff value of MHRs in CSC was 13.58, with 52% sensitivity and 79% specificity [Fig. 1].

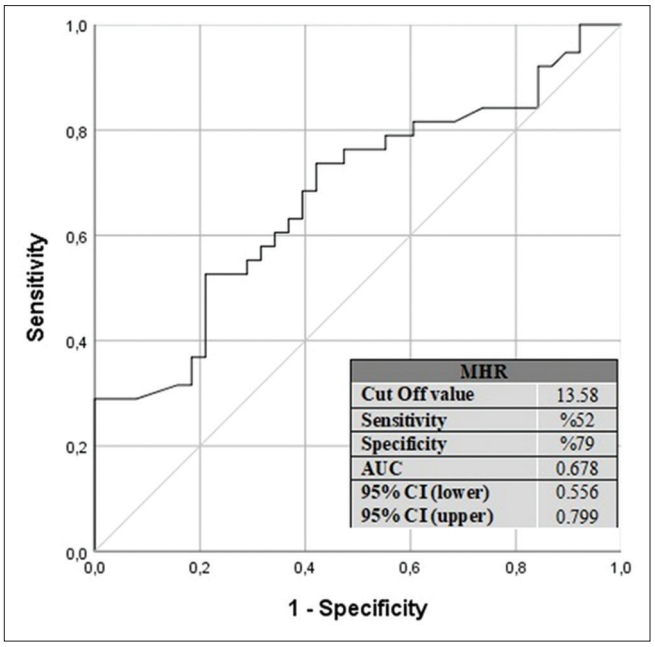

Figure 1: The receiver operating characteristics analysis for monocyte-to-high-density lipoprotein ratio (MHR) in predicting acute central serous chorioretinopathy. AUC; area under the curve, CI; confidence interval

Discussion

The results of our study indicate that the MHR was not only significantly higher in patients with than without acute CSC but also an independent predictor of acute CSC. Such increased MHRs reveal that the balance of proinflammatory and anti-inflammatory responses shifted towards the former. Accordingly, the results suggest that increased systemic inflammatory processes contribute to the pathophysiology of acute CSC. To our knowledge, our study is the first to evaluate the relationship between MHRs and CSC.

Although the pathological mechanisms of CSC remain poorly understood, the currently accepted theory of the disorder's pathogenesis maintains that the mechanism entails choroidal vascular hyperpermeability and abnormal leakage due to nitric oxide, prostaglandins, and reactive oxidative species resulting from oxidative stress and proinflammation.[7,9,22] These pathophysiological changes can lead to secondary RPE changes and result in the accumulation of subretinal fluid. In their assessment of oxidative damage in CSC with retinal flavoprotein fluorescence (FPF), which can be used to detect increased oxidative stress caused by impaired mitochondrial metabolism, Field *et al.* observed significantly greater retinal FPF in patients with CSC than in controls.[8] Systemic inflammatory mediators such as nitric oxide, tumor necrosis factor-α, and interleukins can cause several retinal diseases by increasing local oxidative stress.[23,24] Therefore, CSC has been associated with systemic conditions including the use of psychotropic medication, the use of corticosteroids, stress, smoking, hypertension, pregnancy, and obstructive sleep apnea.[4,7] For this reason, increased systemic inflammation may contribute to the development of CSC. In other research, Ratanasukon *et al.* treated patients with acute CSC with high-dose oral antioxidants, for results revealing that the patients showed less fluorescein leakage at the end of the third month of treatment than individuals without the disorder.[25] All of those results suggest that systemic inflammation plays a pivotal role in the pathogenesis of CSC.

Numerous biomarkers that can be analyzed from peripheral blood, serum, or plasma are used in diagnosing and monitoring some inflammation-related diseases. Since the pathogenesis of CSC is associated with systemic inflammation, some researchers have used a range of candidate biomarkers from peripheral blood to investigate the systemic inflammatory and oxidative status in patients with CSC.[12,14,26,27] In two studies, in particular, the thiol-to-disulfide ratio from peripheral blood samples was investigated as a biomarker of oxidative stress in patients with either acute or chronic CSC.[14,26] The results of both studies indicated that the thiol-to-disulfide ratio was significantly lower in patients with chronic or acute CSC when compared with healthy subjects. From another perspective, Erol *et al.* investigated NLRs and CRP levels in patients with acute or chronic CSC and found that both factors were significantly higher in patients with acute CSC than all others.[12] However, in multivariate analysis, NLRs and CRP values did not emerge as independent predictors of acute CSC. Their results are comparable with our findings. In our study, NLRs and CRP levels did not significantly differ between patients with acute CSC and the controls. Moreover, NLR and CRP were not an independent predictor of acute CSC, as the results of our regression analysis highlighted. The difference between the cited study and ours can likely be explained by the smaller number of patients in our sample. Furthermore, if our sample contained more patients, then we probably could have obtained significant NLRs and CRP levels.

The MHR is a new inflammatory biomarker easily calculated via routine peripheral blood analysis. Crucial to the inflammatory process, monocytes secrete proinflammatory and pro-oxidant cytokines. By contrast, HDL, which is an antioxidant and anti-inflammatory molecule, lessens the transmigration of monocytes and the aggregation of mononuclear cells, as well as supports endothelial cells by elevating the expression of nitric oxide synthase. Therefore, the MHR provides information about the balance of pro- and anti-inflammatory conditions. MHR was found to be clearly associated with inflammation as a close correlation exists with CRP in its prediction of measurements of monocytes and HDL cholesterol individually.[28] With the significant association of MHR values with CRP levels, it may be proposed that MHR has a role in systemic inflammation as well as being a possible predictor of development and progression

of disorders related to systemic inflammation. In several cardiovascular diseases, such as coronary atherosclerosis, hypertension, angina pectoris, and aortic aneurysm, increased MHR values were found to relevant with inflammation and oxidative stress and it has been reported that the MHR is a new prognostic marker for these inflammatory diseases.[29-32] Besides these, MHR has been associated with many local or systemic disorders affected various organs.[33-35] Among the several researchers who have examined the relationship between ocular inflammatory diseases and the MHR, Mirza *et al.* demonstrated that the MHR was significantly higher in patients with than without pseudoexfoliation syndrome or glaucoma.[18-20,36] In addition, Satirtav *et al*. found that increased MHRs significantly related to branch retinal vein occlusion.[20] In both articles, the authors reported that MHR was elevated due to increased systemic inflammation. Nevertheless, no investigation of MHRs in patients with CSC had been conducted prior to our study. According to our results, patients with acute CSC have significantly higher MHRs than their counterparts without the disorder. Moreover, the MHR was a significant independent parameter for predicting acute CSC. Considering the relationship between systemic inflammation and CSC, the MHR might be a reliable biomarker for predicting systemic inflammation in patients with CSC.

Although we minimized potential sources of error in our study, a few limitations merit attention. For one, our sample size could have been greater. Furthermore, the results of our cross-sectional study do not reflect the long-term inflammatory status of patients. Therefore, our findings should be supported by prospective controlled trials with larger sample sizes.

Conclusion

In summary, our findings demonstrate that systemic inflammation has a significant association with CSC and may play an important role in its pathogenesis. Therefore, the MHR might be used as a simple, inexpensive, reliable biomarker of inflammation in acute CSC. The measurement of MHR may be used to monitor the systemic inflammatory state during the management of CSC. In addition, the increased MHR in acute CSC may be helpful for elucidating the pathogenesis, evaluating the progression of CSC, or understanding the association with other concomitant disorders and may inspire researchers to study and clarify the possible effects of the other biomarkers in CSC. However, additional studies with larger sample sizes remain necessary to clarify the association of the MHR and CSC. Furthermore, long-term prospective follow-up studies should also be performed to understand how MHR has an impact on the prognosis of CSC.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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