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ORIGINAL ARTICLE

Investigation of systemic inflammatory biomarkers in acute post-cataract surgery endophthalmitis

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Abstract

Purpose: This study aims to investigate changes in systemic inflammatory biomarkers, including neutrophil, lymphocyte, monocyte, and platelet counts, mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in acute post-cataract surgery endophthalmitis (APSE) cases.

Methods: This retrospective case–control study was conducted with 36 patients who underwent pars plana vitrectomy due to APSE and 36 age- and gender-matched healthy subjects who underwent uneventful cataract surgery. Neutrophil, lymphocyte, monocyte, and platelet counts, and MPV were obtained through peripheral blood sampling before pars plana vitrectomy in the APSE group and before cataract surgery in the control group. All these biomarkers and NLR and PLR were compared with statistical methods.

Results: The mean age and male-to-female ratio were similar between APSE and control groups (p>0.05, for both). The mean values of neutrophil, lymphocyte, monocyte, and platelet counts, MPV, and PLR were also similar between groups (p>0.05, for all). The mean values of NLR were 2.68±0.78 (1.15–4.18) in the APSE group and 2.04±0.50 (1.06–3.33) in the control group (p=0.019). NLR value of ≥2.10 was determined as a predictor of APSE with 72% sensitivity and 63% specificity.

Conclusion: NLR is a systemic inflammatory biomarker that is higher in APSE cases than in healthy subjects. Higher NLR values in presumed APSE cases can be considered as a finding in favor of APSE, which should be considered with other findings.

Keywords: Biomarker; cataract; endophthalmitis; inflammation; neutrophil-to-lymphocyte ratio.

Endophthalmitis is the most devastating intraocular inflammation caused by infection.[1] Endophthalmitis is separated as either endogenous or exogenous according to the route of transmission, and exogenous type occurs when infectious organisms spread into the eye through any defect in the ocular tissue caused by penetrating trauma or intraocular surgery.[2] In an acute presentation of exogenous endophthalmitis that occurred after cataract surgery, clinical findings include lid swelling, conjunctival and corneal edema, decreased visual acuity, hypopyon, anterior

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chamber cells, and fibrin, retinitis, and vitreous inflammation occurring within 6 weeks.[3,4] The incidence of acute post-cataract surgery endophthalmitis (APSE) has been reported to range between 0.03% and 0.2%.[5] According to the results of large series, pseudomonas-, staphylococcus-, enterococcus-, or streptococcus-related infections are responsible for most of the APSE cases.[6,7]

Neutrophil, lymphocyte, monocyte, and platelet counts, and mean platelet volume (MPV) obtained by peripheral blood sampling are simple methods to evaluate systemic inflammation. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been described as superior to total leukocyte count as an indicator of systemic low-grade inflammation.[8] These biomarkers can be used as a predictor for some systemic conditions, such as several cancers and cardiovascular diseases.[8,9] According to recent studies, some inflammation-associated ophthalmological diseases, such as diabetic retinopathy complications and neovascular glaucoma, are associated with increased NLR.[10–13]

Investigating the relationship between systemic inflammatory biomarkers and ophthalmological diseases is a relatively new concept. Neither the effects of the ophthalmological diseases on the systemic inflammatory biomarkers nor the clinical usefulness of these biomarkers to diagnose or to follow-up the ophthalmological diseases are fully elucidated. APSE is one of the most important inflammation-related acute events in ophthalmology.[14] The disease is known as ophthalmological tissue localized inflammation; however, the association with systemic inflammatory parameters has never been studied.[14] The primary goal of this study is to investigate changes in systemic inflammatory biomarkers, including neutrophil, lymphocyte, monocyte, and platelet counts, MPV, NLR, and PLR in these cases. The secondary goal is to determine a cutoff value for these biomarkers indicating APSE diagnosis according to the area under the receiver operating characteristic (ROC) curve, sensitivity, and specificity.

Materials and Methods

This retrospective observational case–control study was carried out at the ophthalmology department at a tertiary referral hospital in Ankara, Turkey, with approval granted by the local ethics committee. The procedures were applied for the ethical standards of the Declaration of Helsinki for human subjects and written informed consent was obtained from each subject after an explanation of the invasive procedures.

The medical documents of the patients who underwent pars plana vitrectomy due to presumed APSE between February 2013 and May 2017 were retrospectively investigated. The subjects had the following inclusion criteria: (1) Received cataract surgery due to senile cataract; (2) presence of endophthalmitis-related clinical findings including lid swelling, conjunctival and corneal edema, decreased visual acuity, hypopyon, anterior chamber cells and fibrin, retinitis, and vitreous inflammation within 6 weeks after the cataract surgery; and (3) having pars plana vitrectomy indications per the Endophthalmitis Vitrectomy Study criteria.[15] Exclusion criteria were as follows: (1) Clinical findings or history of ocular (e.g., uveitis, parasitic diseases, intraocular tumor, trauma, or received intraocular surgery except for cataract) or systemic (e.g., hematological malignancy, miliary diseases, or septicemia) masquerade conditions for the endophthalmitis-like clinic; (2) received intravitreal/systemic antibiotic or steroid treatment due to APSE; and (3) presence of another ocular (e.g., diabetic retinopathy, diabetic macular edema, or neovascular glaucoma) or systemic conditions which can affect the results of systemic inflammatory biomarkers (e.g., immunodeficiency, malignancy, acute or chronic systemic infection, or history of steroid use). The study group was constructed with 36 patients who met the inclusion and exclusion criteria. The control group was constructed with 36 age- and gender-matched subjects who underwent uneventful cataract surgery and met the same exclusion criteria.

All patients underwent a detailed ophthalmological evaluation. Visual acuity was examined by questioning light perception for the APSE group and by a Snellen chart for the control group. Anterior and posterior segments were evaluated by a slit-lamp biomicroscopy, and ocular ultrasonography was performed for patients with media opacity. The time of the APSE diagnosis was determined as the time patient is presented to the center. The peripheral blood sampling for neutrophil, lymphocyte, monocyte, and platelet counts and MPV values was performed on the day of APSE diagnosis in the APSE group and before cataract surgery in the control group. The samplings were evaluated with ABX Pentra DX 120 Hematology Analyzer (Horiba, Inc., Kyoto, Japan). The NLR and PLR variables were calculated by dividing the counts of neutrophil and platelet by the lymphocyte count, respectively.

Statistical analyses were done using Statistical Package for the Social Sciences 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as mean ± standard deviations and minimum-maximum values. The Kolmogorov–Smirnov test was used to test the normal distribution of

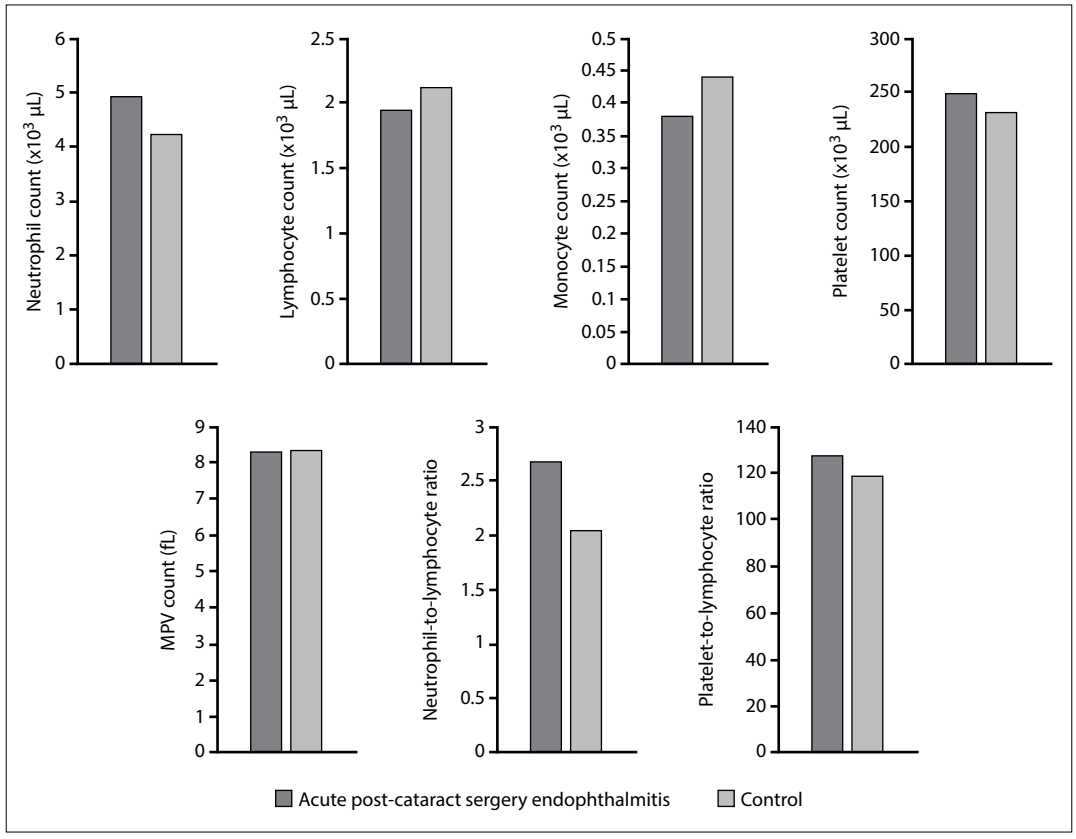

Fig. 1. The mean values of the systemic inflammatory biomarkers.

the variables. The Mann–Whitney U-test was performed in comparisons of the groups as the numerical data did not fit to a normal distribution. Statistical significance was determined as $p<0.05$. Power analysis was performed by sample size calculator (ClinCalc LLC, Indianapolis, IN, USA). ROCs curve analysis was applied using SPSS 23.0 to determine the optimal cutoff value with sensitivity and specificity values for indicating APSE diagnosis.

Results

The mean age of the subjects was 56.19±20.04 years (44–71) in the APSE group and 65.72±7.11 years (46–73) in the control group. The male-to-female ratios were 21/15 in the APSE group and 21/15 in the control group. There was no significant difference between APSE and control groups in comparisons of the mean ages and male-to-female ratios ($p>0.05$, for both).

The mean duration between cataract surgery and APSE diagnosis was 16.12±9.81 days (3–40). The mean duration between peripheral blood sampling and pars plana vitrectomy was 2.31±0.87 days (0–7). The mean values of neutrophil, lymphocyte, monocyte, and platelet counts, MPV, and PLR were similar between the APSE and control groups ($p>0.05$) (Fig. 1 and Table 1).

Table 1. The comparison of the mean values of neutrophil, lymphocyte, monocyte, and platelet counts, MPV, NLR, and PLR

	APSE group	Control group	p-value*
Neutrophil count (×10³ µL)	4.91±1.44 (2.70–8.60)	4.24±1.11 (1.90–7.00)	0.081
Lymphocyte count (×10³ µL)	1.94±0.51 (1.10–2.70)	2.12±0.55 (0.90–3.20)	0.354
Monocyte count (×10³ µL)	0.38±0.20 (0.20–0.90)	0.44±0.19 (0.20–0.70)	0.460
Platelet count (×10³ µL)	249.33±51.70 (95.45–277.27)	231.32±50.199 (147.00–336.00)	0.447
MPV (fL)	8.30±1.43 (6.40–12.20)	8.33±1.04 (7.10–10.80)	0.782
NLR	2.68±0.78 (1.15–4.18)	2.04±0.50 (1.06–3.33)	0.019
PLR	127.33±44.56 (95.45–277.27)	118.60±47.32 (49.76–247.78)	0.387

MPV: Main platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; APSE: Acute post-cataract surgery endophthalmitis. *The Mann–Whitney U-test was performed in comparisons of the groups.

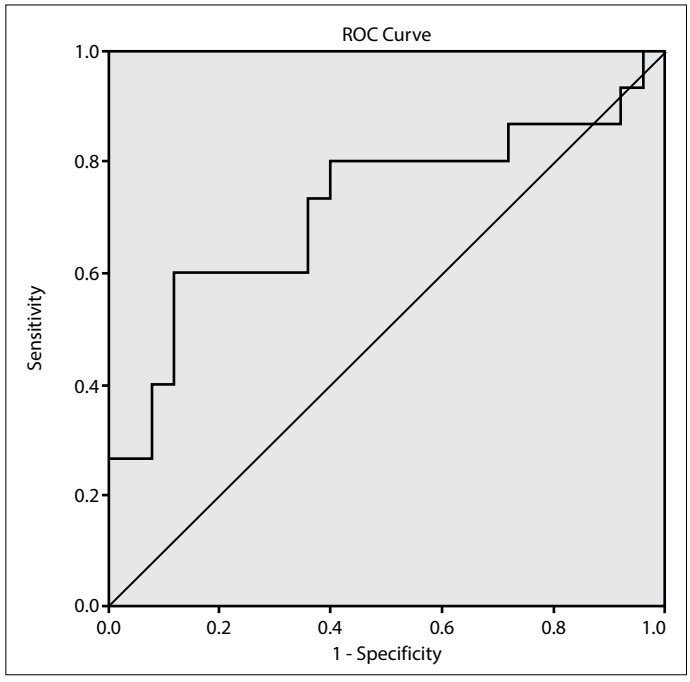

Fig. 2. The area under the receiver operating characteristics curve for neutrophil-to-lymphocyte ratio.

Table 2. The analysis of the area under the receiver operating characteristics for neutrophil-to-lymphocyte ratio

Neutrophil-to-lymphocyte ratio	2.10
Sensitivity	72%
Specificity	63%
Area under the curve	0.714
95% confidence interval	0.530–0.894
p-value	0.025

The mean value of NLR was 2.68±0.78 (1.15–4.18) in the APSE group and 2.04±0.50 (1.06–3.33) in the control group (p=0.019) (Fig. 1 and Table 1). According to the power analysis, when comparing two independent samples for the mean value of NLR, each group must contain minimally 23 subjects to have a power of 80% (enrollment ratio 1:1, α=0.05, and β=0.2), and the sample sizes of the groups in this study were following this condition. The area under the ROC curve for NLR was 0.714, and an NLR of ≥2.10 predicted APSE diagnosis with a sensitivity of 72% and specificity of 63% (Fig. 2 and Table 2).

Discussion

The most important aspect of this study is to show that APSE changes NLR, a systemic inflammatory biomarker, with high statistical power. This result can be crucial for three reasons: (1) High NLR values can be a sign for APSE to induce a systemic low-grade inflammatory response. Some vasculitis-like findings in APSE cases, including vascular leakage and sheathing,[16] can be considered as a link between isolated ocular inflammation and systemic low-grade inflammatory response. (2) Das et al.[17] have reported that the adjunctive intravitreal dexamethasone therapy provides better functional and anatomic results. In a combined analysis of two studies, Kim et al.[18] suggested that adjunctive steroid treatment may provide a better functional outcome at 3 months compared to not using adjunctive steroid treatment. In light of these studies, it can be thought that the pathophysiological mechanism of APSE to induce a systemic inflammatory response may retrogradely play a role in the effectiveness of some systemic anti-inflammatory drugs. Systemic corticosteroids or other systemic anti-inflammatory drugs may increase final visual acuity by limiting the systemic and ocular inflammation, and further studies can show their effectiveness and safety profiles. (3) Differentiation of APSE clinic from potential mimickers, including vitreous hemorrhage, retained lens material, and others, can sometimes be challenging. In cases with an atypical presentation, the diagnosis of APSE is supported by ancillary tests, such as ocular ultrasonography or culture of the obtained vitreous.[19] To indicate APSE diagnosis, this study determines an optimal cutoff value for NLR which can be easily obtained through peripheral blood sampling. ROC curve analysis is an important instrument to demonstrate the diagnostic ability of a binary classifier system and provides levels of sensitivity and specificity.[20] In this study, the cutoff value was determined as 2.10 to indicate APSE diagnosis with a sensitivity of 72% and specificity of 63%; however, the usefulness of this cutoff value is quite limited due to relatively low sensitivity and specificity values. For these reasons, higher NLR values in presumed APSE cases can be considered as a finding in favor of APSE, which should be considered with other findings.

Two important situations can be considered regarding the results of this study: (1) Higher NLR levels in APSE cases may be related to previous cataract surgery, not APSE-related inflammation. (2) Higher NLR levels may not help differentiate between APSE and toxic anterior segment syndrome (TASS) because inflammation already plays a role in the pathophysiology of both diseases.[21] Yazgan et al.[22] partially clarified these situations with their study compared NLR of the subjects who have had uneventful cataract surgery and TASS. They reported that NLR remains lower after uneventful cataract surgery and TASS is associated with higher NLR levels.[22] Nevertheless, these important questions should be answered by further studies including control, uneventful cataract surgery, TASS, and APSE groups.

There are several limitations in this study. The duration between cataract surgery and APSE diagnosis in this series was

longer than the durations reported by other studies.[6,7] The center which was conducted this study is a referral center for mainly the capital, surrounding cities, rural population, the eastern region of Turkey, and even Iraq and Syria. The time of APSE diagnosis was determined as the first presentation to the center, not the time beginning of the symptom or not the time referring of the patient. Not to investigate the reasons for this longer duration is a limitation and the design of the study is retrospective and some important information is lack. The late presentation of the patient may also be associated with the species of the causative organisms. The diagnosis was not microbiologically proven and species of the infectious pathogens were not investigated. This can also make a difference in the results because it is known that some organisms can cause a secondary inflammatory response.[23] The data were collected from a single center and this can be a reason for selection bias. The relevance of the values of the systemic inflammatory biomarkers for clinical monitoring or individual judgment on the presence of APSE may be limited by the non-specificity of these biomarkers.

As far as we know, this is the first study to report that NLR, which is a systemic inflammatory biomarker, is an indicator of APSE diagnosis. Higher NLR values in presumed APSE cases can be considered as a finding in favor of APSE, which should be considered with other findings.

Ethics Committee Approval: This study was approved by Dışkapı Yildirim Beyazit Training and Research Hospital Ethics Committee (date 02.04.2018; number 48/11).

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