Predictive Role of Increased Systemic Immuno-Inflammation Index Level in the Diagnosis of Pseudoexfoliation Syndrome

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ABSTRACT

Purpose: The aims of this study were to analyze the level of systemic immune-inflammation index (SII) and other hematological parameters in patients with pseudo exfoliation syndrome (PES) and to determine the predictive capacity of SII in the diagnosis of PES.

Materials and Methods: A retrospective, cross-sectional comparative study. Thirty-two patients with PES undergone cataract surgery and 32 age- and sex-matched healthy controls were included. Complete blood count parameters of all participants were analyzed. Neutrophil-to-lymphocyte ratio (NLR) and SII levels were compared. Receiver operating characteristic (ROC) analysis was also performed to calculate the sensitivity and specificity, and the optimal cut-off values of SII and NLR.

Results: The mean age was 71.38 ± 6.64 years (54-80) in the patient group and 70.41 ± 7.11 (59-87) years in the control group. NLR ($p = 0.043$) and SII ($p = 0.006$) levels were significantly higher in the PES group. There was no difference in other hematological parameters between groups ($p > 0.05$). SII was slightly more predictive than NLR in the diagnosis of PES. While the optimal cut-off value of NLR was >2.12 with 59.6% sensitivity and 59.4% specificity ($p=0.043$), the optimal cut-off value of SII was >566 with 62.5% sensitivity and 59.4% specificity ($p=0.019$).

Conclusions: In patients with PES, NLR and SII, known as markers of systemic inflammation, were significantly higher, but the predictive capacity of SII was found to be slightly better than NLR. As a cheap, easy and reliable test, SII can be used in the diagnosis and follow-up of PES.

Keywords: Pseudoexfoliation syndrome, neutrophile-to- lymphocyte ratio, systemic inflammation, systemic immune-inflammation index, local inflammation

INTRODUCTION

Pseudoexfoliation syndrome (PES) is characterised by grey-white fibrillar deposits in the anterior segment, including the subconjunctival area, pupillary margin, ciliary epithelium, lens epithelium, lens capsule, iris pigment epithelium, trabecular meshwork, cornea, zonules.[1] These deposits can also be found in other organs and structures in the body, such as the skin, heart, lungs, liver and kidneys.[2] Patients with PES may have an increase in intraocular pressure over time and may develop pseudoexfoliation glaucoma (PEG).[3]

Although the exact pathophysiological mechanism of PES is not fully understood, genetic (LOXL1 gene) and non-genetic factors (age, race, ultraviolet radiation, autoimmune diseases, viral infections, inflammation and oxidative stress) have been implicated.[2,4-5] In a previous study, YKL-40, a pro-inflammatory protein that has been implicated in the pathogenesis of endothelial dysfunction and atherosclerosis, was found to be elevated in patients with PES.[6] Another study found elevated levels of

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Received: 11.10.2023
Accepted: 24.08.2024
TJ-CEO 2025; 20: 16-21
DOI: 10.37844/TJ-CEO.2025.20.3

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C-reactive protein and tumour necrosis factor alpha in patients with PES, and reported that this is an indicator of inflammation and peripheral endothelial dysfunction and may be a risk factor for the development of systemic and ocular symptoms of PES.[7]

Haematological indices such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (TLR), mean platelet volume, lymphocyte/monocyte ratio (LMR) and systemic immune-inflammation index (SII) are used in many disciplines such as cardiology, oncology and rheumatology to study the pathophysiology of disease, evaluate treatment efficacy and predict prognosis.[8-10] In ophthalmology, NLR is used as an inflammatory marker to determine the presence and effect of systemic inflammation in many diseases such as glaucoma, age-related macular degeneration, central serous chorioretinopathy, retinal vascular diseases and uveitis.[11-16] SII is a novel biomarker of systemic inflammation and has been widely used in recent years in the diagnosis, follow-up and prognosis of many diseases, ranging from gastroenterological diseases such as cancer, cardiovascular diseases, pancreatitis, hepatitis to ophthalmological diseases such as retinal artery occlusion, dry eye, diabetic macular oedema. [17-22] Endothelial dysfunction and subsequent disruption of the blood-retinal barrier may lead to elevated serum inflammatory markers in patients with PES. There is a very limited number of studies in the literature evaluating systemic immuno-inflammatory index levels and the development of pseudoexfoliation syndrome.

In our study, we aimed to evaluate systemic immune-inflammation index levels in the presence of pseudoexfoliation syndrome and to analyse its relationship with the presence of PES and its predictive ability in the diagnosis of PES.

MATERIALS AND METHODS

Retrospectively, 32 patients with pseudoexfoliation and cataract who presented to our outpatient ophthalmology clinic between March 2020 and April 2022 and underwent cataract surgery, and 32 age- and sex-matched healthy controls who underwent only cataract surgery without pseudoexfoliation were included in the study. The study was conducted in accordance with the tenets of the Declaration of Helsinki with the approval of the Education and Planning Committee of Ankara Training and Research Hospital (Ankara, Turkey, ethics number: E-22-1117).

Patients with pseudoexfoliation material at the pupillary margin and anterior lens capsule, peripupillary iris translumination defect and cataract were included in the PES group. The following criteria were used to exclude participants from the study: current pregnancy or breastfeeding status; any systemic disease, including diabetes mellitus; systemic inflammation findings, such as high fever, high white blood cell count, or infectious disease history within the last year; ocular surgery other than cataract surgery; and a history of ocular trauma. Furthermore, patients diagnosed with glaucoma or with a history of topical anti-glaucomatous drug use due to suspected glaucoma, patients with PES and intraocular pressure above 25 mmHg or normal intraocular pressure but glaucomatous optic nerve damage, and patients under 18 years of age with topical or systemic steroid or anti-inflammatory drug use in the last two months were excluded from the study.

Haematological analysis

Following a 12-hour overnight fast, blood samples were collected from the antecubital vein and transferred into tubes. White blood cell (WBC), lymphocyte (LYM), neutrophil (NEU), platelet (PLT), and monocyte (MONO) counts in the patient and control groups were obtained from complete blood count results determined with a Sysmex XN 3000 analyser (Kobe, Japan). LMR and NLR were calculated manually as the lymphocyte-monocyte ratio and neutrophil-lymphocyte ratio, respectively, while SII was calculated by the formula neutrophil x platelet/lymphocyte. PES patients and healthy controls were compared in terms of these haematological indices.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM SPSS Inc.). Normality was evaluated using the Kolmogorov-Smirnov test. T tests and Mann-Whitney U tests were used to evaluate statistical differences between the PES and control groups. The descriptive statistics are presented as follows: for the continuous variables, the median (minimum-maximum) or mean ± standard deviation; for the categorical variables, the frequency (percentage). Furthermore, the receiver operating characteristic (ROC)

curve was utilised to ascertain the sensitivity and specificity of SII and NLR in diagnosing PES, and to determine the optimal cut-off point value of these indices. The statistical significance level was set at $P \leq 0.05$.

RESULTS

The study included 32 patients with PES who had undergone cataract surgery and 32 age- and sex-matched healthy controls. In the PES group, 19 patients were male (59%) and 13 were female (41%). In the control group, 16 males and 16 females were present. The mean age of the patients and the control group were 71.38 ± 6.64 years (range 54-80) and 70.41 ± 7.11 years (range 59-87), respectively. There was no significant difference between the groups with regard to age and gender. However, the neutrophil-to-lymphocyte ratio (NLR) (p=0.043) and systemic immune-inflammation index (SII) (p=0.006) were significantly higher in the PES group. No significant difference was found in other haematological indices between the groups. Table 1 shows the demographic characteristics and haematological comparisons of patients and controls.

In the ROC curve analysis, the predictive values of NLR and SII in the diagnosis of PES were calculated according to the area under the curve (AUC). The AUC area was 0.647 for NLR and 0.67 for SII. SII was found to be a more effective predictor of systemic inflammation in patients with PES than NLR. In the diagnosis of PES, the optimal cut-off point of NLR was determined to be >2.12, exhibiting 59.6% sensitivity and 59.4% specificity (0.513 - 0.782, 95% confidence interval, p=0.043), while the optimal cut-off point of SII was determined to be >566 with 62.5% sensitivity and 59.4% specificity (0.538-0.802, 95% confidence interval, p=0.019). The results of the ROC analysis are presented in Table 2 and Figure 1.

Table 1. *Demographic Characteristics and Haematological Comparisons of PES and Control Group*

Parameters	Group 1 (PES)	Group 2 (Control)	P
Age	71.38 ± 6.64 (54-80)	70.41 ± 7.11 (59-87)	0.575*
Gender(M/F)	19/13	16/16	0.451§
WBC	8.0 ± 2.12 (5.53-14.6)	7.5 ± 1.81 (2.99-10.14)	0.615**
PLT	261.41 ± 52.93 (160-399)	249.62 ± 72.85 (11.83-410.0)	0.634**
NEU	5.03 ± 1.44 (3.11-9.44)	4.5 ± 1.25 (2.73-8.23)	0.133**
LYM	2.16 ± 0.58 (1.16-3.6)	2.3 ± 0.65 (1.17-3.71)	0.345*
Mono	0.64 ± 0.14 (0.39-0.98)	0.62 ± 0.16 (0.25-0.9)	0.569*
LMR	3.47 ± 0.88 (1.49-4.88)	3.89 ± 1.19 (2.47-6.96)	0.386**
NLR	2.41 ± 0.66 (1.45-4.22)	2.04 ± 0.59 (1.09-3.26)	**0.043****
PLR	128.56 ± 39.72 (71.38-239.1)	114.33 ± 36.8 (4.55-197.73)	0.33**
SII	624.26 ± 189.25 (256.49-1046.27)	494.02 ± 173.34 (37.45-756.98)	**0.006***

PES: Pseudoexfoliation syndrome, WBC=White blood counts, NEU= Neutrophil counts, LYM= Lymphocyte counts, MONO= Monocyte counts, PLT= Platelet counts, NLR= Neutrophil-to-lymphocyte ratio, LMR= lymphocyte -to- monocyte ratio, SII= Systemic immune-inflammation index, PLR= Platelet-to- lymphocyte ratio

* T- test was used to generate the P-value

§ Pearson Chi-Square test was used to generate the P-value

** Mann-Whitney U test was used to generate the P-value

$P \leq 0.05$ was considered statistically significant.

Table 2. *ROC Analysis Results Showing the Predictive Value of NLR and SII in the Diagnosis of PES*

Parameters	Area Under the Curve (%95 CI)	Cut-Off	P	Sensitivity	Specificity
NLR	0.647 (0.513 - 0.782)	2.126	**0.043**	0.594	0.594
SII	0.670 (0.538 - 0.802)	566.470	**0.019**	0.625	0.594

NLR= Neutrophil-to-lymphocyte ratio, SII= Systemic immune-inflammation index, PES: Pseudoexfoliation syndrome

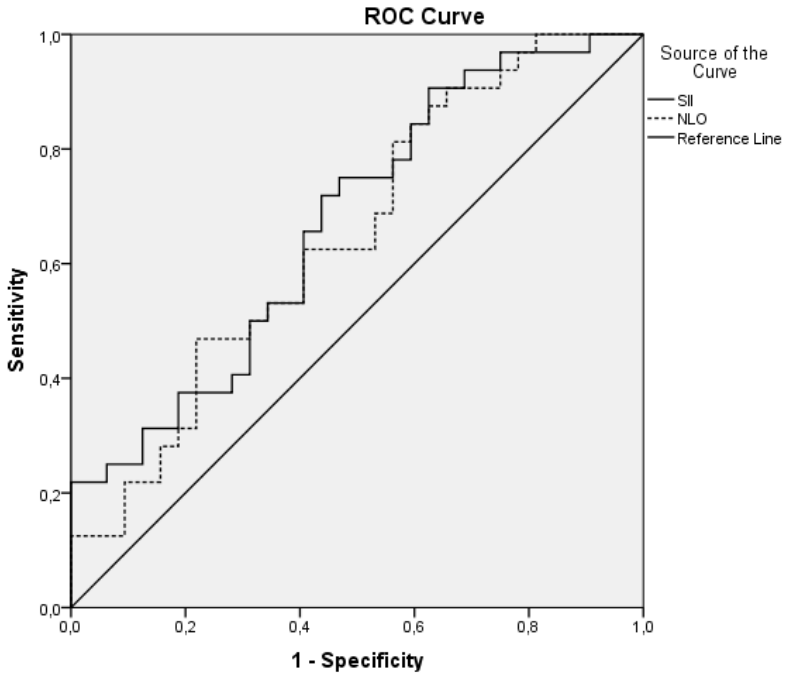

Figure 1. *Systemic immune inflammation index (SII) and neutrophil/lymphocyte ratio (NLR) ROC curve graph to diagnose PES*

PES: Pseudoexfoliation syndrome

DISCUSSION

Despite the identification of a genetic pathology associated with the LOXL1 gene in the pathophysiology of pseudoexfoliation syndrome, the precise mechanism remains to be fully elucidated. Additionally, reports have indicated the potential involvement of oxidative stress, inflammation, ischaemia and hypoxia in the pathophysiology of PES.[23] The present study found increased systemic inflammation to be associated with the presence of PES. Furthermore, the systemic immune-inflammation index was found to be more sensitive than the neutrophil-to-lymphocyte ratio in quantitative measurements.

Previous studies have reported the presence of inflammation and the development of endothelial damage in patients diagnosed with PES.[6,7] In a further study, elevated levels of complement 3 (C3), kininogen-1 (KNG-1), antithrombin III and vitamin D binding protein (GC), alongside diminished levels of retinol binding protein 3 (RBP 3), glutathione peroxidase, calcineurin-1 and carboxypeptidase E, were identified in the aqueous humour of the eyes of patients with PES who had undergone cataract surgery.[24] RBP3 is a transport protein that is synthesised in the ciliary epithelium and secreted into the aqueous humour.[25] In the context of autoimmune uveitis, a decline in RBP3 concentration within the aqueous humour has been observed, with subsequent restoration to normal levels following treatment.[26] The presence of decreased RBP3 and increased C3 concentrations in the aqueous humour of eyes with PES may be indicative of an inflammatory process affecting the blood-aqueous barrier. A review of the literature reveals a number of studies that have investigated the relationship between PES and systemic inflammation. Furthermore, an increasing number of studies have analysed the relationship between increased NLR and the presence of PES. Kurtul et al. reported that neutrophil to lymphocyte ratio is a reliable biomarker of systemic inflammation in patients with PES and found that NLR ≥ 1.72 predicted the diagnosis of PES with 77% sensitivity and 71% specificity.[27] Gökçe et al. demonstrated that NLR could verify the diagnosis of PES and pseudoexfoliation glaucoma (PEG) by employing a higher cut-off value (2.68 ± 0.73 in the group with complications and 2.01 ± 0.81 in the group without complications) than those utilised in Kurtul et al.'s study. Furthermore, they established that an NLR cut-off value of 2.33 could serve as a predictor of complications during cataract surgery in PES patients, exhibiting 87.5% sensitivity and 78.1% specificity.[28] In a further study, RDW (red cell distribution width) levels

were found to be significantly higher in patients with PES and PEG compared to the control group. It was emphasised that RDW is a reliable marker for predicting PES patients and for predicting progression to PEG.[29] In the present study, NLR demonstrated 59.6% sensitivity and 59.4% specificity in predicting the diagnosis of PES. The optimal cut-off point value was determined to be >2.12, a finding that correlates with the results reported by Gökçe et al.

SII has been identified as a novel marker of inflammation and is increasingly utilised in the diagnosis and prognosis prediction of diseases, especially in the fields of oncology and immunology.[30-31] In the field of ophthalmology, it has been documented that SII can be utilised as a alternative to NLR in the monitoring of systemic inflammation, exhibiting a higher predictive value than NLR in various contexts. These include the prediction of cystoid macular oedema following cataract surgery, the prediction of the development of macular oedema in diabetic patients, and the detection of disease severity in uveitis patients.[22,32,33] To the best of our knowledge, only one study has examined the relationship between SII and PES, and this study was conducted recently.[34] The results of this study indicate that SII and NLR levels were elevated in patients with PES and PEG compared to the control group. Furthermore, SII was identified as a valuable supplementary parameter in conjunction with NLR for the diagnosis of PES. However, NLR emerged as a more substantial predictor of PEG risk. In the present study, SII was found to demonstrate a comparatively superior capacity to NLR in the identification of PES patients (AUC: 0.647 in NLR; 0.67 in SII). The results of the current study demonstrated that NLR exhibited 59.6% sensitivity and 59.4% specificity in the diagnosis of PES, while SII demonstrated 62.5% sensitivity and 59.4% specificity. In the study conducted by Dikmen et al., the optimal cut-off point values for diagnosing PES were determined to be greater than 449.4 for SII and greater than 1.78 for NLR. In contrast to the findings of this study, our study identified higher cut-off point values for SII, greater than 566, and for NLR, greater than 2.12, for the diagnosis of PES. These values are higher than those reported in the study by Dikmen et al. The present study demonstrated that, in contrast to the findings of Dikmen et al. (cut-off point >1.78), higher NLR cut-off point values (cut-off point >2.12) were consistent with the studies referenced in the literature. The only study reporting the cut-off point value of SII for the diagnosis of PES is Dikmen's study, in which the cut-off point value was found to be lower than in this study (>449.4 versus >566 in this study). One study in the literature reported that there was a positive correlation between age and NLR values and that NLR increased with increasing age.[35] In our study, the mean age of our patients (71.38 ± 6.64 years) was higher than in the study by Dikmen et al (68.12 ± 7.4 years), which may explain the high cut-off value in our study.

The present study is subject to several limitations. Firstly, it is a retrospective case series, and secondly, the number of cases is relatively limited. Furthermore, the predictive value of SII and NLR in predicting the diagnosis of PES was analysed, but not their predictive capacity in the risk of PEG.

In conclusion, the present study found that SII and NLR levels were elevated in patients with PES compared to the control group, thus indicating the role of systemic inflammation in the pathophysiology of PES. The results of the present study demonstrate that, since SII is relatively more sensitive than NLR in the diagnosis of PES, it can be used alone or as an auxiliary parameter to NLR as a cost-effective and reliable marker of inflammation in patients with PES. Further prospective, randomised controlled trials with a larger number of patients may provide stronger evidence for the success of the systemic immune inflammation index in predicting the diagnosis and prognosis of PES and the risk of PEG development, and may provide the most accurate cut-off point value of SII.

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