Official Journal of Erciyes University Faculty of Medicine

DOI: 10.14744/cpr.2024.36036
J Clin Pract Res 2024;46(1):19–23

Can the Pan-Immune Inflammation Value, Systemic Inflammatory Response Index, and Other Hematological Inflammatory Indices Be Clinically Used to Predict Pseudoexfoliation?

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ABSTRACT

Objective: Pseudoexfoliation (PEX) syndrome is a systemic condition associated with age, and its exact cause remains elusive. Inflammatory processes heighten the risk of PEX development. This study marks the first attempt to jointly investigate the Systemic Inflammatory Response Index (SIRI) and Pan-Immune Inflammation Value (PIV) biomarkers in PEX patients.

Materials and Methods: A total of 84 patients and 71 healthy controls underwent examination. Ratios of neutrophils to lymphocytes (NLR) and platelets to lymphocytes (PLR), along with the Systemic Inflammation Index (SII), SIRI, and PIV values, were computed as indicators linked to the inflammatory cascade.

Results: The study encompassed 155 subjects, including 71 healthy controls averaging 73.8±7.7 years and 84 PEX patients averaging 71.3±8.9 years. Statistically significant differences in neutrophil and lymphocyte levels were evident between the groups ($p<0.05$). A notable statistical distinction was observed in the NLR, PLR, derived Neutrophil to Lymphocyte Ratio (dNLR), SII, SIRI, and PIV indices when comparing the groups ($p<0.05$). However, hemoglobin, platelet, mean platelet volume (MPV), white blood cell (WBC), and C-reactive protein (CRP) values did not show significant differences between the groups ($p>0.05$).

Conclusion: This study highlights that SIRI and PIV could provide insights into the relationship between PEX and inflammation, offering a glimpse into the potential systemic implications of PEX-related inflammation.

Keywords: Pseudoexfoliation, inflammation, SIRI, PIV.

Cite this article as:
Erdal H, Kılıc AO, Akbulut Yagcı B, Yasar E. Can the Pan-Immune Inflammation Value, Systemic Inflammatory Response Index, and Other Hematological Inflammatory Indices Be Clinically Used to Predict Pseudoexfoliation? J Clin Pract Res 2024; 46(1): 19–23.

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Submitted: 26.09.2023
Revised: 06.11.2023
Accepted: 27.12.2023
Available Online: 18.01.2024

Erciyes University Faculty of Medicine Publications - Available online at www.jcpres.com

INTRODUCTION

Pseudoexfoliation (PEX) syndrome is a systemic ailment influenced by age, predominantly impacting the anterior structures of the eye.[1] Its specific cause remains unknown; however, it likely involves a complex interplay of both genetic and environmental factors. PEX syndrome is more

prevalent in older individuals, particularly those aged 60 and above, and its frequency varies across specific populations. This syndrome is often identified during comprehensive eye examinations, highlighting the importance of routine eye check-ups, especially for those at higher risk, to manage potential complications like glaucoma. Treatment primarily focuses on managing associated conditions such as glaucoma and cataracts to preserve vision. The hallmark of PEX syndrome is the accumulation of pseudoexfoliation material, characterized by protein fibers with a granular, amyloid-like structure, in various anterior eye segment structures.[2] This material, indicative of a significant systemic disorder of the extracellular matrix, accumulates in various organs as well as the anterior eye segment.[3] Prevalence of PEX syndrome varies, typically ranging from 6–10%, and is more common in women than men, increasing with age.[4] Inflammation is a fundamental biological response that occurs when the body's immune system reacts to harmful stimuli, such as pathogens (like bacteria or viruses), damaged cells, irritants, or other potentially harmful agents. Inflammatory indices like the the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Lymphocyte-to-Monocyte Ratio (LMR) are reported as indicators of both systemic and ocular inflammation.[5–7] In PEX, a systemic syndrome with inflammatory properties, increased levels of pro-inflammatory cytokines have been reported in the serum of individuals with PEX.[8] High sensitivity C-reactive protein (CRP) and Tumor Necrosis Factor-alpha (TNF-α), considered markers of inflammation and peripheral endothelial dysfunction, were also found to be elevated in patients with PEX.[9] Serum levels of Vascular Endothelial Growth Factor (VEGF), a pro-inflammatory cytokine known to increase vascular permeability, are also higher in this patient group compared to controls.[10] Systemic Inflammation Response Index (SIRI) and Prognostic Inflammation Value (PIV), recently developed indices, are regarded as comprehensive benchmarks for assessing immune response and systemic inflammation, exhibiting minimal resemblance to each other. These indices play a vital role in determining the prognosis or treatment response in patients with cancers, acute coronary syndrome, and various sepsis cases.[11–13] This study presents the first report evaluating NLR, PLR, derived NLR (dNLR), Systemic Immune-Inflammation Index (SII), SIRI, and PIV parameters in PEX.

MATERIALS AND METHODS

This case-control trial was conducted at the Ophthalmology Clinics of Aksaray Education and Research Hospital from January 2022 to January 2023. The study comprised a total of 84 patients diagnosed with PEX. Medical records for the study and healthy subjects were collected from the hospital's automated healthcare facility system. The control group consisted of 71 healthy individuals who were demographically comparable to the study group. The study protocol received approval from the local ethics committee at Aksaray University, and was assigned the protocol number 26SBKAYK. This study adhered to the ethical guidelines of the Helsinki Declaration. Exclusion criteria included systemic infectious diseases, autoimmune disorders, malignancies, chronic kidney and liver failure, asthma, rheumatologic diseases, hematologic diseases, and any history of surgery within the past three months. Individuals with chronic or recurrent inflammatory eye conditions, ocular injuries, ocular infections, severe retinal disorders, corneal irregularities, or a history of ocular surgery were also excluded.

Diagnosis was made when characteristic findings, such as white, flaky, dandruff-like PEX material, were observed along the pupillary margin and anterior lens capsule during biomicroscopic examination. Patients were selected from a group without systemic cardiovascular disease, PEX-associated glaucoma, or cataracts graded 2 or above. All patients in our study had bilateral PEX. The patients had normal intraocular pressure and were phakic. The healthy group was selected from individuals with similar demographics and ophthalmological findings, excluding PEX. The diagnostic criteria for PEX syndrome need to be described in detail, including any accompanying eye diseases in patients (such as cataracts or glaucoma, if present). Additionally, both patient and healthy groups were classified according to the presence or absence of diabetes mellitus (DM). The examination included evaluating hemogram parameters and CRP levels. The calculation of dNLR involved dividing the absolute neutrophil count by the absolute white blood cell (WBC) count minus the absolute neutrophil count. SII was computed by multiplying the neutrophil count by the platelet count, then dividing by the lymphocyte count. SIRI was calculated by multiplying the neutrophil count by the monocyte count, and then dividing by the lymphocyte count. Conversely, PIV was determined by multiplying the neutrophil count, the monocyte count, and the platelet count, then dividing by the lymphocyte count. Using these formulas, SIRI, PIV, and other indicators were computed in Excel, and the data were organized for analysis.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22 was utilized for the statistical analysis of the study groups. The normality of the data was evaluated using the Kolmogorov-Smirnov test. Continuous variables were compared using a t-test, with the results presented as means and their respective standard deviations. For variables that did not follow a normal distribution, the Mann-Whitney U test was used for comparison. Statistical significance was established at a threshold of $p<0.05$.

Table 1. Demographic information of the study groups

Parameters	PEX (n=84) Mean±SD	Control (n=71) Mean±SD	p
Gender			0.61*
Male	47 (56%)	40 (51.9%)	
Female	37 (44%)	37 (48.1%)	
Age (years)	73.8±7.7	71.3±8.9	0.06¥
Diabetes mellitus (DM)	28 (33.3%)	35 (45.5%)	0.131¥

*: Chi-Square test; ¥: Student's t-test; SD: Standard deviation; PEX: Pseudoexfoliation.

Table 2. Comparison of blood parameters of the study and control groups

Parameters	PEX (n=84) Median (Min–Max)	Control (n=71) Median (Min–Max)	p*
White blood cell (10^3 µL)	7.4 (2.3–19.3)	6.7 (3.6–13.6)	0.304
Neutrophil (10^3 µL)	4.3 (0.9–17.8)	3.8 (2.1–7.5)	**0.018**
Lymphocyte (10^3 µL)	1.9 (0.3–5.4)	2.3 (0.64–5.4)	**0.001**
Monocyte (10^3 µL)	0.48 (0.07–1.06)	0.5 (0.15–1.07)	0.438
Hemoglobin (g/dL)	14 (8.4–17.5)	13.5 (8.1–17.7)	0.441
Platelet (10^3 µL)	208 (50–445)	227 (57–350)	0.717
MPV (fL)	10 (7.1–12.6)	9.6 (7.9–15.0)	0.551
CRP (mg/L)	5.7 (1.2–65.1)	4.1 (1.1–22.8)	0.468
SII	443.9 (140.8–4560)	379.5 (98.2–835.5)	**0.002**
SIRI	1.04 (0.20–11.03)	0.83 (0.15–2.1)	**0.004**
PIV	224.2 (16.4–2873)	167.2 (19.6–501.3)	**0.001**
NLR	2.1 (0.8–19.4)	2.03 (0.79–16.1)	**0.001**
PLR	108.1 (44.5–638.2)	93.4 (40.8–181.2)	**0.013**
dNLR	1.58 (0.67–13.1)	1.3 (0.6–2.5)	<**0.001**

*Mann-Whitney U test; CRP: C-reactive protein; dNLR: Derived NLR ratio (neutrophil count divided by the result of the WBC count minus the neutrophil count); MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PIV: Pan-immune Inflammation value (neutrophil × platelet × monocyte/lymphocyte count): PLR: Platelet-to-lymphocyte ratio, SII: Systemic Inflammatory Index (neutrophil × platelet/lymphocyte count); SIRI: Systemic Inflammatory Response Index (neutrophil × monocyte/lymphocyte count); Min: Minimum; Max: Maximum.

RESULTS

This study involved a total of 155 participants, comprising 71 healthy controls with an average age of 73.8±7.7 years and 84 patients with pseudoexfoliation syndrome (PEX) with an average age of 71.3±8.9 years. No statistically significant differences were observed in terms of age and gender between the case and control groups (Table 1). Diabetes mellitus was present in 33.3% of the PEX patients and 45.5% of the control subjects, with no significant difference in the prevalence of diabetes mellitus (DM) between the two groups (p=0.131). Table 2 presents the median (min–max) outcomes of hemogram parameters and indices between the groups. Notably, neutrophil and lymphocyte levels were altered in PEX compared to healthy subjects (p<0.05). Additionally, inflammatory indices were computed for both the study and control groups, revealing differences between individuals with the condition and healthy subjects (p<0.05, Table 2). However, no notable variances were detected in Hemoglobin, Platelet, Mean Platelet Volume (MPV), white blood cells, and CRP values between the groups (p>0.05).

DISCUSSION

To the best of our current knowledge, this study marks the first exploration into hemogram parameters and emerging inflammatory indices such as NLR, PLR, LMR, SII, SIRI, and PIV in individuals with PEX syndrome. The aim of our research was to evaluate and compare hemogram parameters and inflammatory indices within both patient and control groups. Our findings indicate that, in terms of hemogram parameters,

neutrophil levels were notably higher, whereas lymphocyte counts were lower in the PEX group compared to the control subjects. Simultaneously, inflammatory indices were significantly elevated in PEX patients. Interestingly, C-reactive protein (CRP), an inflammatory marker, exhibited similar levels between the two groups. The existing literature has highlighted the association of PEX syndrome with local or systemic inflammation, with elevated levels of various cytokines and chemokines reported in the aqueous humor and serum.[14–16] Moreover, PEX syndrome has been linked to high serum YKL-40 levels, a pro-inflammatory protein.[17] Studies by Sorkhabi et al.[18] and Yuksel et al.[19] reported higher levels of high-sensitivity CRP (hsCRP) and TNF-α in the serum of PEX patients compared to controls. Our investigation aligns with these studies, revealing no statistically notable distinction in CRP levels between patient and control subjects. This study is crucial as it highlights that general inflammation markers like CRP may not be sufficient in PEX patients, emphasizing the potential of inflammatory indices associated with hematological parameters, including NLR, PLR, dNLR, SII, SIRI, and PIV, as novel biomarkers.

NLR, PLR, and SII, calculated using hemogram parameters, have been reported as biomarkers in various inflammatory ocular diseases.[20–22] Studies associated with PEX indicate elevated levels of Red Cell Distribution Width (RDW), NLR, and PLR in PEX patients compared to healthy individuals.[23,24] Moreover, increased NLR levels in PEX patients with systemic involvement have been linked to an increased likelihood of cardiovascular disease.[25] Mirza et al.[26] compared Monocyte-to-HDL Ratio (MHR) and LMR indices in PEX and control groups, finding higher MHR and lower LMR in the PEX group. Within our investigation, NLR, PLR, and SII were statistically significant in PEX patients compared to healthy groups, suggesting their potential as predictive markers of inflammation in PEX patients. SIRI and PIV, recently developed indices, are recognized for their ease of calculation and comprehensive role as indicators of immune response and systemic inflammation. While these indices have been reported in various inflammatory systemic diseases[27–30] their evaluation in inflammatory eye diseases is novel. In our study, PEX syndrome showed a significant association with SIRI and PIV, with elevated levels of all inflammatory indices observed in PEX patients.

CONCLUSION

In conclusion, SII, SIRI, and PIV emerge as innovative inflammatory indices suitable for evaluating individuals with PEX. These indices hold the potential to serve as cost-effective and reliable markers of inflammatory status in PEX patients. However, further extensive, prospective, randomized controlled studies involving larger patient populations are imperative to obtain more robust evidence.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: The Aksaray University Clinical Research Ethics Committee granted approval for this study (date: 02.03.2023, number: 26SBKAYK).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Concept – HE; Design – HE, BAY; Supervision – HE, AOK, BAY, EY; Resource – HE, BAY, EY; Materials – BAY, AOK, EY; Data Collection and/or Processing – HE, BAY, AOK, EY; Analysis and/or Interpretation – HE, BAY, EY; Literature Search – HE, BAY, AOK, EY; Writing – HE, BAY; Critical Reviews – HE, AOK, BAY, EY.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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