RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2026.2025-139
Cyprus J Med Sci 2026;11(4):310-314

Systemic Inflammatory Response Index and Systemic Immune-Inflammation Index in Parkinson's Disease

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Abstract

BACKGROUND/AIMS: Peripheral immune activity may contribute to Parkinson's disease (PD), but the clinical usefulness of blood cell-derived composite indices is not established. We compared the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) between patients with PD and healthy controls (HCs) and explored their relationships with disease stage, duration, and motor severity.

MATERIALS AND METHODS: Data from 76 patients with PD and 44 HCs were evaluated in a cross-sectional case-control study. Disease severity was characterized using the Hoehn-Yahr (HY) stage and the motor section of the Unified PD rating scale (UPDRS). SII and SIRI were calculated from complete blood count parameters, and analyses were performed using non-parametric statistical methods.

RESULTS: Patients with PD had higher SIRI and monocyte values and lower lymphocyte counts than HCs (p=0.008, p=0.047, and p=0.029, respectively). The groups were comparable with respect to neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII. No inflammatory index showed a significant relationship with HY stage, disease duration, or UPDRS motor score.

CONCLUSION: An increased SIRI value may represent a peripheral inflammatory feature of PD. Nevertheless, the absence of group differences in NLR, PLR, and SII and the lack of associations with clinical severity indicate that this finding should not be interpreted as a marker of disease progression. Multicenter longitudinal research with adjustment for potential confounders is warranted.

Keywords: Parkinson's disease, systemic inflammation, SIRI, SII, motor severity

INTRODUCTION

Parkinson's disease (PD) is clinically characterized by a broad spectrum of motor and non-motor manifestations. Degeneration of dopaminergic neurons in the substantia nigra is a central feature of PD, but does not fully explain the biological processes underlying the disorder. Immune dysregulation and inflammation have therefore received increasing attention as possible contributors to its development and progression.[1-5]

Peripheral immune signals can influence the central nervous system and may aggravate neuronal injury in neurodegenerative conditions. In PD, activated microglia can sustain an inflammatory environment within the substantia nigra.[6] These cells release mediators such as interleukin-1beta and tumour necrosis factor alpha together with reactive oxygen species. Such products may damage dopaminergic neurons, weaken blood-brain barrier integrity, and facilitate the entry of circulating immune cells into neural tissue.[7] Immunohistochemical findings also support a pro-inflammatory phenotype of glial cells, particularly microglia, during neurodegeneration.[8]

Routine complete blood counts provide several low-cost measures that may capture different aspects of systemic immune activity. Among them, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) combine circulating cell populations into summary indicators. These measures have been investigated across inflammatory and neurological disorders, although their diagnostic and prognostic relevance in PD remains uncertain.[9] Evidence from

To cite this article: Yetiş A, Duran S. Systemic inflammatory response index and systemic immune-inflammation index in Parkinson's disease. Cyprus J Med Sci. 2026;11(4):310-314

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Received: 19.11.2025
Accepted: 06.08.2026
Publication Date: 27.08.2026

both experimental models and clinical samples has not yet clarified how closely peripheral immune changes reflect the neurodegenerative process.[10]

Accordingly, this study compared peripheral inflammatory indices between patients with PD and healthy controls (HCs) and examined whether these indices varied with Hoehn-Yahr (HY) stage, disease duration, or motor symptom severity.

MATERIALS AND METHODS

Study Design

A cross-sectional case-control design was used. Patients with idiopathic PD who had been monitored for at least six months in the neurology outpatient clinic of Kırşehir Ahi Evran University Training and Research Hospital were enrolled between 2024 and 2025. Ethical approval was obtained from the Kırşehir Ahi Evran University Local Research Ethics Committee (approval no: 2024-09/64, date: 30.04.2024), and written informed consent was obtained from all participants. A neurologist established a diagnosis of idiopathic PD according to the United Kingdom PD Society Brain Bank clinical diagnostic criteria. The HCs group comprised volunteers assessed during the same period who had neither PD nor any other neurodegenerative condition and met the exclusion criteria applied to the patient group.

Demographic and clinical data, including age, sex, education, comorbidities, and medication use, were collected from medical records and participant assessments. Both groups excluded individuals with rheumatologic, hematologic, oncologic, endocrine, infectious, or other inflammatory disorders; users of anti-inflammatory drugs, antidepressants, or corticosteroids; and those with another degenerative neurological disease, including Alzheimer's disease. The HY scale was used to stage PD, whereas motor impairment was quantified with the motor section of the Unified PD Rating Scale (UPDRS). Each UPDRS motor examination was completed in the OFF-medication state. Following a 12-hour fast, routine blood samples were used to obtain neutrophil, lymphocyte, monocyte, and platelet counts, together with 25-hydroxyvitamin D, folate, and vitamin B12 levels. SII was calculated as the product of neutrophils and platelets divided by lymphocytes. SIRI was obtained by multiplying neutrophils by monocytes and dividing by lymphocytes. Comorbidities and medication exposure were considered during the eligibility assessment, but no multivariable adjustment was undertaken.

Statistical Analysis

Analyses were conducted in SPSS 25.0 (IBM Corp., Armonk, NY, USA). Categorical data are presented as numbers and percentages. Continuous variables are described using mean ± standard deviation and median, as appropriate. Distributional assumptions were examined with the Kolmogorov-Smirnov test. As the relevant variables were non-normally distributed, two-group comparisons used the Mann-Whitney U test, while comparisons across more than two groups used the Kruskal-Wallis test. Associations between continuous measures were assessed with Spearman's rho. A two-sided p-value below 0.05 was considered statistically significant. Because adjusted models were not constructed, possible confounding was considered when interpreting the results.

RESULTS

The analysis included 76 patients with PD and 44 HCs. Women accounted for 42 of the patients (55.3%). Disease duration was most commonly 1-5 years (n=33, 43.4%). Based on body mass index (BMI), 46 patients (60.5%) were overweight, 25 (32.9%) were obese, and 5(6.6%) had a normal BMI. HY stage 2 was the most frequent category (n=33, 43.4%), followed by HY stage 1.5 (n=28, 36.8%). Five patients (6.6%) were at stage 1; five (6.6%) were at stage 2.5; three (3.9%) were at stage 3; one (1.3%) was at stage 4; and one (1.3%) was at stage 0. The UPDRS motor score averaged 20.6±11.7, with a median of 18. The corresponding mini-mental test values were 25.2±2.2 and 25. Table 1 provides the clinical and sociodemographic profile of the PD group.

Comparison of hematological measures showed that the PD group had higher monocyte counts and SIRI values than the HCs (p=0.047 and p=0.008, respectively). Conversely, lymphocyte counts were lower among patients with PD (p=0.029). None of the remaining variables listed in Table 2 differed significantly between the groups (all p>0.05).

As shown in Table 3, HY stage was not significantly correlated with NLR, PLR, SII, or SIRI (all p>0.05). The coefficients were small and centered near zero, providing no evidence that these circulating inflammatory indices changed in parallel with stage-defined disease severity.

Table 1. Clinical and socio-demographic profile of the patients

	Number (n)	Percent (%)
BMI		
Normal	5	6.60
Overweight	46	60.50
Obese	25	32.90
Education		
Illiterate	8	10.50
Elementary school	44	57.90
Middle school	6	7.90
High school	16	21.10
University	2	2.60
Duration of illness		
Less than 1 year	13	17.10
1-5 years	33	43.40
5-10 years	17	22.40
Over 10 years	13	17.10
DM	18	23.70
HT	40	52.60
HPL	28	36.80
CAD	20	26.30
Thyroid disease	9	12
HY		
0	1	1.3
1	5	6.60
1.5	28	36.80
2	33	43.40
2.5	5	6.60
3	3	3.90
4	1	1.30

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, HPL: Hyperlipidemia, CAD: Coronary artery disease, HY: Hoehn-Yahr.

When patients were categorized by disease duration (<1 year, 1-5 years, 5-10 years, and >10 years), NLR, PLR, SII, and SIRI did not differ significantly across categories (all p>0.05; Table 4). Although group means varied numerically, no consistent duration-related pattern was evident.

UPDRS motor scores were unrelated to NLR, PLR, SII, and SIRI (all p>0.05; Table 5). BMI, however, showed weak positive correlations with PLR (r=0.253, p<0.05) and SII (r=0.284, p<0.05), as reported in Table 6.

Table 2. Comparison of blood parameters between HCs and PD groups

	PD (n=76)	HC (n=44)	Total (n=120)	p†
	n (%)	n (%)	n (%)	
Gender				
Female	42 (55.30)	24 (54.50)	66 (55)	0.939
Male	34 (44.70)	20 (45.50)	54 (45)	
	PD (n=76)	HC (n=44)	Total (n=120)	p‡
	Mean ± SD (Med)	Mean ± SD (Med)	Mean ± SD (Med)	
UPDRS	20.60±11.70 (18)			
MMT	25.20±2.20 (25)			
Vitamin B12	314.30±110.20 (293.50)	347.80±118.80 (336)	326.60±114.10 (303)	0.108
Folate	7.63±3.30 (7)	7.73±2.90 (7)	7.67±3.10 (7)	0.625
25-hydroxy vitamin D	17.4±8.0 (16)	17±6.6 (16)	17.30±7.50 (16)	0.943
Neutrophil	4.58±1.20 (4.50)	4.52±1.30 (4.70)	4.56±1.20 (4.60)	0.987
Lymphocyte	2.04±0.70 (1.82)	2.30±0.70 (2.20)	2.14±0.70 (1.96)	**0.029***
Platelet	261.70±83.50 (245)	272.80±51.60 (272.50)	265.80±73.40 (258.50)	0.139
Monocyte	0.72±0.90 (0.56)	0.52±0.10 (0.51)	0.65±0.79 (0.54)	**0.047***
NLR	2.49±1.20 (2.22)	2.06±0.60 (2.06)	2.33±1 (2.13)	0.063
PLR	137.30±47.60 (132)	122.80±38.10 (120.50)	131.90±44.70 (127.50)	0.156
SII	637.80±315.40 (571.50)	555.90±166.20 (566.50)	607.80±272.50 (567.50)	0.428
SIRI	1.64±1.60 (1.20)	1.05±0.30 (1.01)	1.42±1.30 (1.12)	**0.008***

†Chi-square test; ‡Mann-Whitney U test. *p<0.05.
PD: Parkinson's disease, HC: Healthy control, UPDRS: Unified Parkinson's disease rating scale, MMT: Mini-mental test, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index, SD: Standard deviation.

Table 3. Correlations between Hoehn-Yahr stage and inflammatory parameters

	HY	
	r	p
NLR	0.075	0.521
PLR	0.158	0.172
SII	0.070	0.547
SIRI	-0.005	0.966

p<0.05; Spearman's rho.
HY: Hoehn-Yahr; NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index.

Table 4. Differences between disease duration and inflammation parameters

	Less than 1 year (n=13)	1-5 years (n=33)	5-10 years (n=17)	Over 10 years (n=13)	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
NLR	2.01±0.90 (1.71)	2.72±1.50 (2.44)	2.48±0.60 (2.59)	1.85±2.90 (0.96)	0.095
PLR	113.90±44.60 (106)	146.30±54.80 (132)	143.50±34.20 (157)	129.75±40.89 (130)	0.087
SII	510.60±194.30 (464)	700.90±360.50 (651)	618.70±225.10 (588)	629.80±375.30 (548)	0.329
SIRI	1.85±2.97 (0.96)	1.79±1.40 (1.27)	1.38±0.60 (1.30)	1.38±0.80 (1.20)	0.261

Kruskal-Wallis test.
NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index, SD: Standard deviation.

Table 5. Correlations between UPDRS scores and inflammatory parameters

	UPDRS	
	r	p
NLR	0.027	0.818
PLR	0.149	0.198
SII	0.098	0.402
SIRI	0.056	0.630

Spearman's rho.
UPDRS: Unified Parkinson's disease rating scale, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index.

Table 6. Correlations between BMI and inflammatory parameters

	BMI	
	r	p
NLR	0.172	0.138
PLR	0.253*	0.028
SII	0.284*	0.013
SIRI	0.125	0.282

*p<0.05; Spearman's rho.
BMI: Body mass index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index.

DISCUSSION

This study compared several blood-cell-derived inflammatory measures in PD and HCs. The principal observation was a higher SIRI value in the PD group, accompanied by increased monocytes and reduced lymphocytes. By contrast, NLR, PLR, and SII did not distinguish the groups. Moreover, none of the indices was related to HY stage, disease duration, or UPDRS motor performance. Thus, SIRI may capture a peripheral immune alteration associated with PD, but the present data do not support its use as an indicator of clinical advancement.

Inflammatory activity in PD may involve bidirectional interaction between peripheral immunity and the central nervous system. Infectious agents, including influenza A, HSV-1, EBV, varicella-zoster virus, Japanese encephalitis virus, human immunodeficiency virus, and *Helicobacter pylori*, have been discussed in relation to parkinsonian mechanisms.[11] Molecular mimicry between viral proteins and alpha-synuclein (α-Syn) may promote immune responses within nigrostriatal pathways and facilitate α-Syn aggregation. α-Syn itself can also affect the recruitment of neutrophils and monocytes after infection, linking systemic immune activation with neuroinflammation. Although persistent inflammation is unlikely to initiate every case of PD, it may accelerate neuronal injury once neurodegeneration is underway.[12,13] Positron emission tomography findings in early PD further suggest that greater microglial activation accompanies lower dopaminergic terminal density and worse motor function.[14]

SII integrates neutrophil, platelet, and lymphocyte counts and summarizes the balance between inflammatory activation and immune competence. Studies in PD have produced conflicting results. Zhao et al.[15] associated higher SII with greater odds of PD, whereas Li et al.[10] linked elevated SII to poorer motor performance. Conversely, a study from Türkiye detected neither a group difference in SII nor a convincing association with clinical severity.[16] Our findings align with the latter report: SII was similar in PD and HCs and showed no relationship with HY stage or UPDRS motor score. Variation in disease distribution, participant comorbidities, medication exposure, and lifestyle characteristics may account for these discrepancies.

SIRI, which combines neutrophil, monocyte, and lymphocyte counts, was originally proposed by Qi et al.[17] as an indicator of systemic inflammatory burden. Its relevance to PD has been examined less often than that of SII. Wang et al.[18] observed no association of either SII or SIRI with PD risk, and Alagoz et al.[16] reported similar SIRI values in PD and HCs. In the current cohort, however, SIRI was elevated in PD. This result likely reflects the simultaneous increase in monocytes and a decrease in lymphocytes, both of which directly influence the index. SIRI may, therefore, respond to a cellular pattern not captured to the same extent by SII.

The elevated SIRI value was not associated with HY stage, disease duration, or UPDRS motor score. NLR, PLR, and SII showed a similar lack of clinical association. One interpretation is that these indices represent a general peripheral inflammatory state rather than the extent of neurological impairment. Their values may also fluctuate and need not mirror ongoing changes within the central nervous system. In addition, the concentration of this sample during early and moderate HY stages narrowed the range of disease severity and may have weakened the detectable correlations.

BMI was weakly correlated with PLR and SII. Because adipose tissue can sustain chronic, low-grade inflammatory signaling, body composition may influence cell-count-derived indices independently of PD. Age, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, metabolic status, and medication use may exert similar effects. Future analyses should therefore account for these variables when estimating the independent relationship between PD and systemic inflammatory measures.

Study Limitations

Several issues limit the interpretation. Recruitment from a single center and the modest sample size reduce external validity. The cross-sectional case-control design also prevents the evaluation of temporal sequence and does not permit causal conclusions regarding inflammation and PD progression. Although eligibility criteria excluded recognized inflammatory conditions and selected medications, residual confounding by age, BMI, cardiometabolic disease, medication exposure, lifestyle, or clinically silent inflammation remains possible because adjusted analyses were not performed. Patients with advanced PD were uncommon, which further limited evaluation across the full severity spectrum. Even so, simultaneous assessment of SII and SIRI provides comparative information on two composite indices. Larger multicenter cohorts, repeated measurements, central and peripheral inflammatory markers, and multivariable modeling are needed to determine their clinical value.

CONCLUSION

Patients with PD displayed a distinct pattern of higher SIRI and monocyte values together with lower lymphocyte counts relative to HCs. NLR, PLR, and SII did not differ between groups, and none of the examined indices were related to HY stage, disease duration, or UPDRS motor score. These

results suggest altered peripheral immune activity but do not establish peripheral immune activity as a marker of PD severity or progression. Longitudinal studies that include broader disease stages and control for relevant confounders are required.

MAIN POINTS

- Compared with healthy controls (HCs), patients with Parkinson's disease (PD) had higher systemic inflammatory response index (SIRI) and monocyte values but lower lymphocyte counts.
- Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index were similar in the PD and HCs.
- Hoehn-Yahr stage, disease duration, and unified Parkinson's disease rating scale motor scores were not related to the inflammatory indices.
- SIRI may reflect peripheral immune alterations in PD, although its clinical and prognostic value requires confirmation in longitudinal studies.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Kırşehir Ahi Evran University Local Research Ethics Committee (approval no: 2024-09/64, date: 30.04.2024).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Y., Concept: A.Y., S.D., Design: A.Y., S.D., Data Collection and/or Processing: A.Y., Analysis and/or Interpretation: A.Y., S.D., Literature Search: A.Y., S.D., Writing: A.Y.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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

Declaration of Generative AI and AI-assisted Technologies in the Writing Process: During the preparation of this work, the author(s) used ChatGPT to improve "readability" and "language". After using this tool/service, the author(s) reviewed and edited the content as needed and took full responsibility for the content of the publication.

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