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Exploring the Impact of Inflammatory Indices on Non-Motor Symptoms in Parkinson's Disease: A Preliminary Study

Parkinson Hastalığı'nda İnflamatuar İndekslerin Motor Olmayan Semptomlar Üzerindeki Etkisinin Araştırılması: Bir Ön Çalışma

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ABSTRACT

Objectives: Emerging evidence shows that microglial activation and blood-brain barrier damage exacerbate inflammation in Parkinson's disease (PD) by linking peripheral and central immune responses. We aim to assess how peripheral inflammatory markers, including ratios like the neutrophil-to-lymphocyte (NLR) and neutrophil-to-high-density lipoprotein (NHR), affect the non-motor features of PD.

Methods: This study consists of 100 patients and 100 healthy controls. The standardized Mini-Mental State Examination (MMSE) was used to assess cognitive impairment, while the Non-Motor Symptoms Scale (NMSS) was utilized to evaluate non-motor features. According to the NMSS, patients were categorized as having mild, moderate, severe, or very severe symptoms. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-HDL ratio (NHR), and systemic immune-inflammatory index (SII) values were calculated from the patients' peripheral blood samples and compared with those of the control group.

Results: The patients' average MMSE score was 20.57±4.09, significantly lower compared to the controls ($p<0.05$). Based on the NMSS classification, 9% of the patients had mild, 30% moderate, 26% severe, and 25% had very severe non-motor symptoms. No statistically significant correlation was observed between NMSS subgroups and inflammatory indices. In comparison to the control group, the patient group exhibited notably higher levels of NLR, NHR, and SII, while HDL and triglyceride levels were notably lower ($p<0.05$). According to the ROC analysis results, the NHR value was an excellent discriminator for PD, with an area under the curve (AUC) of 0.816 and a 95% confidence interval (CI) of (0.757-0.876).

Conclusion: Although our findings do not highlight the effect of inflammatory indices on non-motor features, they suggest that dyslipidemia and inflammation are involved in the pathophysiology of the disease.

Keywords: Inflammation; NHR; NLR; Non-motor symptoms; Parkinson's disease; SII.

ÖZET

Amaç: Ortaya çıkan kanıtlar, mikroglial aktivasyon ve kan-beyin bariyeri hasarının, periferik ve santral immün sistem yanıtlarını birbirine bağlayarak Parkinson hastalığında (PH) inflamasyonu şiddetlendirdiğini göstermektedir. Nötrofil/lenfosit oranı (NLR) ve nötrofil/yüksek yoğunluklu lipoprotein oranı (NHR) gibi periferik inflamatuar belirteçlerin PH'da motor olmayan semptomları nasıl etkilediğini değerlendirmeyi amaçlıyoruz.

Yöntem: Bu çalışma, 100 hasta ve 100 sağlıklı kontrolden oluşmaktadır. Bilişsel bozukluğu değerlendirmek için standartlaştırılmış Mini Mental Durum Testi (MMSE) kullanılırken, motor olmayan semptomların tespitinde Non-Motor Semptomlar Ölçeği (NMSÖ) kullanılmıştır. NMSÖ'ye göre hastalar hafif, orta, şiddetli veya çok şiddetli semptomlara sahip olarak kategorize edildi. Nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), nötrofil-HDL oranı (NHR) ve sistemik immün inflamatuar indeks (SII) değerleri hastaların periferik kan örneklerinden hesaplandı ve kontrol grubu ile karşılaştırıldı.

Bulgular: Hastaların ortalama MMSE skoru 20.57±4.09 olup, kontrol grubuna göre anlamlı derecede düşüktü (p<0.05). NMSÖ sınıflandırmasına göre, hastaların %9'u hafif, %30'u orta, %26'sı şiddetli ve %25'i çok şiddetli motor olmayan semptomlara sahipti. NMSÖ alt grupları ile inflamatuvar indeksler arasında istatistiksel olarak anlamlı bir korelasyon gözlenmedi. Kontrol grubuna kıyasla, hasta grubunda NLR, NHR ve SII seviyeleri anlamlı derecede daha yüksek, HDL ve trigliserit seviyeleri ise anlamlı derecede daha düşüktü (p<0.05). ROC analiz sonuçlarına göre, NHR değeri, 0.816'lık bir eğri altı alan (AUC) ve %95 güven aralığı (CI) ile (0.757-0.876) PH için mükemmel bir ayırt edici oldu.

Sonuç: Bulgularımız inflamatuvar indekslerin motor olmayan semptomlar üzerindeki etkisini desteklemese de, dislipidemi ve inflamasyonun hastalığın patofizyolojisinde bir rol oynadığını düşündürmektedir.

Anahtar sözcükler: Dislipidemi; inflamasyon; NHR; NLR; non-motor semptomlar; Parkinson hastalığı; SII.

The mechanisms underlying Parkinson's disease (PD) involve a complex interplay of factors, including the accumulation of Lewy bodies, considerable decline of dopaminergic neurons in the substantia nigra pars compacta, and key contributions from oxidative stress, dyslipidemia, and inflammation. Individuals with idiopathic PD exhibit diverse patterns in the age at which symptoms first appear, the speed at which the condition advances, the intensity of both motor and non-motor manifestations, and the degree of central and peripheral inflammation.[1]

The expansion of microglial cells and the buildup of alpha-synuclein mutations in these cells constitute the pathophysiological foundation of PD. Proinflammatory mediators released by microglial cells cause neuronal damage, which in turn activates more microglia and triggers an inflammatory response. Additionally, alpha-synuclein accumulation promotes excessive activation of microglial cells, leading to a more intense inflammatory reaction.[2]

It has been demonstrated that certain neurotoxins can induce Parkinsonian syndromes. Although the blood-brain interface is believed to shield the brain from these harmful substances, research indicates that the integrity of this barrier is compromised in PD.[3]

Damage to the blood-brain interface leads to the spread of peripheral inflammation to the central neural network and the onset of central inflammation. Elevated levels of white blood cells in the bloodstream—such as neutrophils, monocytes, and lymphocytes—are associated with peripheral inflammation and contribute to developing clinical symptoms in Parkinson's patients.[4,5]

The beneficial antioxidant and anti-inflammatory effects of high-density lipoprotein cholesterol (HDL) are well-documented. A decrease in HDL is associated with systemic inflammatory response and endothelial impairment, thereby contributing to the advancement of PD.[6]

Studies have found that a decrease in plasma HDL levels is strongly associated with the high prevalence and severity of PD.[7] Subsequent studies have identified that HDL may be specifically associated with low cognitive performance in PD.[8,9]

It has been found that the neutrophil/lymphocyte ratio (NLR) and the neutrophil-to-HDL ratio (NHR) may serve as a potential marker of systemic inflammation. Furthermore, evidence indicates that NLR is closely associated with PD.[10,11] Nevertheless, the influence of these indices on non-motor findings has not been thoroughly assessed. Non-motor manifestations, including cognitive deficits, sleep issues, and mood disturbances, are both prevalent and disabling in PD. We aim to explore the effects of neuroinflammation on these non-motor symptoms, as understanding this relationship could lead to more effective treatments and improved living conditions.

Methods

The study included 100 health check-up participants and 100 individuals with PD admitted to our clinic between July and August 2024. These individuals were diagnosed with PD according to the clinical diagnostic guidelines established by the Movement Disorders Society.[12]

Our exclusion criteria were as follows: individuals diagnosed with secondary parkinsonism, those with malignancies or blood disorders affecting the immune system, those with a previous occurrence of stroke or head injury, and patients with infections, fractures, or trauma were not included. The age, gender, stature, body mass, medications, and comorbidities of all individuals were recorded on an anamnesis form. The Unified Parkinson's Disease Rating Scale (UPDRS) was utilized to assess clinical severity, and Hoehn and Yahr (H&Y) classification was applied for disease clinical staging.[13]

For cognitive assessment, the Standardized Mini-Mental State Examination (MMSE) was used.[14] The 30-item Non-Motor Symptom Scale (NMSS) for Parkinson's disease was used for evaluating non-motor symptoms. The NMSS includes nine

subdomains: gastrointestinal, urinary, sexual, cardiovascular, mood, perceptual problems, sleep and fatigue, attention and memory, and miscellaneous. All patients provided self-reported answers, and subgroup analyses were performed based on these responses. According to the NMSS, patients were categorized as having mild (1–5), moderate (6–9), severe (10–13), or very severe (≥14) symptoms.[15]

Blood samples were collected from all patients after 8 hours of fasting. Homocysteine, uric acid, HDL, LDL, total cholesterol, triglycerides, neutrophils, platelets, and lymphocytes were recorded. Additionally, inflammatory indices such as NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), and NHR (neutrophil/HDL ratio) were calculated. The Systemic Immun Inflammatory Index (SII) value was calculated using the platelet×NLR formula.

Our study was examined and endorsed by the Clinical Research Ethics Committee of Koşuyolu High Specialization Education and Research Hospital during the meeting on 02.07.2024, with decision number 2024/12/854. Informed consent was obtained from all participants, and the study was conducted under the Declaration of Helsinki.

Statistical Analyses

IBM SPSS Statistics 21.0 software was employed for statistical analyses and calculations. The distribution of continuous variables included in the study was evaluated with the Shapiro-Wilk test. For numerical data that do not follow a normal distribution, the Mann-Whitney U test was used for statistical comparisons between two sample groups. The Student's t-test was employed for statistical comparisons between groups for numerical data that follow a normal distribution. Spearman's nonparametric correlation analysis was used to evaluate the relationships between numerical variables. The ROC analysis was used to determine the threshold value of numerical parameters for predicting disease status and to assess the accuracy of this indicator. A statistical significance level of $p<0.05$ was considered.

Results

This study consists of 200 individuals, 76 of whom (38%) are women. The average age of the cases included in the study was 69.89±9.67, while in the control group, it was 70.0±10.35. The percentage of women in the patient group was 39% (n=39), and in the control group, it was 37% (n=37). The mean UPDRS score was 58.50±26.11, and the mean NMSS score was 11.89±5.34. Comprehensive demographic and clinical information of the subjects is shown in Table 1.

The patients' average MMSE score was 20.57±4.09, considerably lower compared to the controls. In contrast to the controls, the patient group had significantly higher levels of NLR, NHR, SII, homocysteine, and neutrophils, while HDL and triglyceride levels were significantly lower ($p<0.05$). A comparison of demographic data and laboratory parameters between the patient and control groups is shown in Table 2.

We could not find a statistically significant correlation between NMSS subgroups (gastrointestinal, urinary, sexual, cardiovascular, mood, perceptual problems, sleep and fatigue, attention and memory, and miscellaneous) and inflammatory indices ($p>0.05$), as shown in Table 3.

According to the ROC analysis results, the NHR value was an excellent discriminator for PD, with an area under the curve (AUC) of 0.816 and a 95% confidence interval (CI) of (0.757-0.876), as shown in Figure 1.

The ROC analysis was performed across the patient and control groups, and the PLR, SII, and NLR values are also shown in Table 4.

Table 1. Demographic and Clinical Data of the Patients

	Patients (n=100)	n (%)
Sex		
	Female	39 (39.0)
	Male	61 (61.0)
NMSS Classification		
	Mild (1-5)	9 (9.0)
	Moderate (6-9)	30 (30.0)
	Severe (10-13)	26 (26.0)
	Very severe (≥14)	35 (35.0)
Hoehn and Yahr Stage		
	Stage 1	19 (19.0)
	Stage 2	35 (35.0)
	Stage 3	30 (30.0)
	Stage 4	13 (13.0)
	Stage 5	3 (3.0)
	Mean±SD	**Median (Min-Max)**
Age	69.89±9.67	71 (44-88)
NMSS	11.89±5.34	11 (2-25)
MMSE	20.57±4.09	20 (13-28)
UPDRS	53.88±24.82	47 (10-115)

N: Number; NMSS: Non-Motor Symptoms Scale; MMSE: Mini-Mental State Examination; UPDRS:Unified Parkinson's Disease Rating Scale.

Table 2. Comparison of Demographic Data and Laboratory Parameters Between Groups

	Patients (n=100) Mean±SD/Median (min-max)	Control (n=100) Mean±SD/Median (min-max)	p
Age	69.89±9.67/71 (44 - 88)	70.0±10.35/71 (44 - 86)	0.826(m)
Sex (F/M)	39/61	37/63	0.884(p)
MMSE	20.57±4.09/20 (13 - 28)	28.32±2.15/30 (24 - 30)	***<0.001(m)**
Homocysteine	16.22±7.29/13.43 (7.08 - 35.41)	12.24±3.15/12.07 (6.68 - 17.19)	***0.018(m)**
HDL	45.13±8.08/45 (23 - 66)	60.17±13.38/60 (26 - 101)	***<0.001(m)**
LDL	129.16±35.15/125 (49 - 232)	126.85±39.63/121.5 (55 - 300)	0.492(m)
Total_Col	201.46±41.76/194 (126 - 308)	195.97±41.85/193 (111 - 303)	0.399(m)
Triglyceride	122.14±62.25/100 (44 - 314)	136.04±58.96/122 (58 - 400)	***0.024(m)**
Uric acid	5.03±1.18/4.9 (2 - 8.1)	5.46±1.44/5.2 (2.5 - 9.2)	0.065(m)
Lymphocyte	2.01±0.7/1.87 (0.71 - 5.11)	2.11±0.75/1.99 (0.86 - 5.76)	0.283(m)
Neutrophil	4.72±1.95/4.15 (1.79 - 14.1)	3.5±1.09/3.37 (1.9 - 9)	***<0.001(m)**
Platelet	242.2±60.53/234 (138 - 413)	250.33±68.99/247 (2.3 - 557)	0.177(m)
NHR	0.11±0.05/0.1 (0 - 0.34)	0.06±0.03/0.06 (0 - 0.15)	***<0.001(m)**
NLR	2.63±1.48/2.36 (0.86 - 8.81)	1.89±1.12/1.66 (0.7 - 9)	***<0.001(m)**
PLR	131.38±54.66/120.07 (0 - 395.77)	131.68±62.85/117.31 (1.05 - 403.62)	0.658(m)
SII	619.51±372.78/551.19 (0 - 1986.79)	462.92±300.14/381.81 (3.35 - 2142)	***<0.001(m)**

(m) Mann Whitney U Test; (p) Pearson Chi-Squared Test;*p<0.05; F:Female; M:Male; MMSE: Mini-mental state examination; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein; NHR: Neutrophil/ HDL Ratio; NLR: Neutrophil/ Lymphocyte ratio; PLR: Platelet/ Lymphocyte ratio; SII: Systemic immune inflammation Index.

Table 3. Correlation Between Non-Motor Symptoms and Inflammatory Parameters in Patients

	Uric_Acid		Homocysteine		NLR		SII		PlR		NHR	
	r	p*	r	p*	r	p*	r	p*	r	p*	r	p*
NMSS	-0.003	0.977	0.196	0.231	-0.084	0.409	-0.085	0.405	-0.087	0.392	-0.044	0.672
Sexual function	0.02	0.842	0.232	0.155	-0.104	0.309	-0.069	0.501	-0.173	0.088	0.15	0.146
Attention & Memory	0.059	0.561	0.19	0.247	-0.096	0.347	-0.149	0.143	-0.12	0.238	-0.016	0.879
Mood	0.074	0.463	-0.098	0.553	0.043	0.673	0.126	0.216	0.091	0.373	0.15	0.146
Gastrointestinal	-0.057	0.574	0.247	0.129	-0.09	0.38	-0.13	0.201	-0.092	0.369	-0.134	0.197
Urinary	0.15	0.136	0.136	0.408	-0.074	0.468	-0.039	0.706	0.033	0.744	-0.169	0.102
Sleep and Fatique	0.046	0.646	0.246	0.132	-0.038	0.71	-0.03	0.769	-0.061	0.553	-0.035	0.735
Cardiovascular	-0.033	0.742	0.092	0.576	-0.035	0.732	-0.026	0.802	-0.005	0.959	0.043	0.68
Perceptual problems	-0.001	0.993	-0.112	0.499	-0.165	0.105	-0.031	0.759	0.025	0.807	-0.054	0.603
Miscellaneous	-0.135	0.181	-0.206	0.208	-0.053	0.603	-0.055	0.588	-0.108	0.289	-0.021	0.836
MMSE	-0.141	0.162	-0.173	0.293	0.12	0.24	0.031	0.76	-0.076	0.458	0.066	0.527
UPDRS	-0.015	0.879	-0.106	0.521	0.069	0.501	-0.018	0.858	-0.029	0.778	0.03	0.77

Spearman's Correlation Test; NMSS: Non-Motor Symptoms Scale; MMSE:Mini-Mental State Examination; UPDRS:Unified Parkinson's Disease Rating Scale; NHR: Neutrophil/ HDL Ratio; NLR: Neutrophil/ Lymphocyte ratio; PLR: platelet// Lymphocyte ratio; SII: Systemic immune inflammation Index.

Discussion

Our study demonstrated that cognitive impairment was markedly more pronounced in subjects versus the control group. According to the NMSS classification, 9% of the patients had mild, 30% had moderate, 26% had severe, and 25% had very severe NMS. No meaningful statistical association was identified among NMSS subgroups and inflammatory indices. However, compared to the control group, inflammatory indices were notably increased, whereas HDL and triglyceride levels were considerably lower in patients. Among the inflammatory indices, the NHR value showed excellent discriminatory power for the diagnosis of PD.

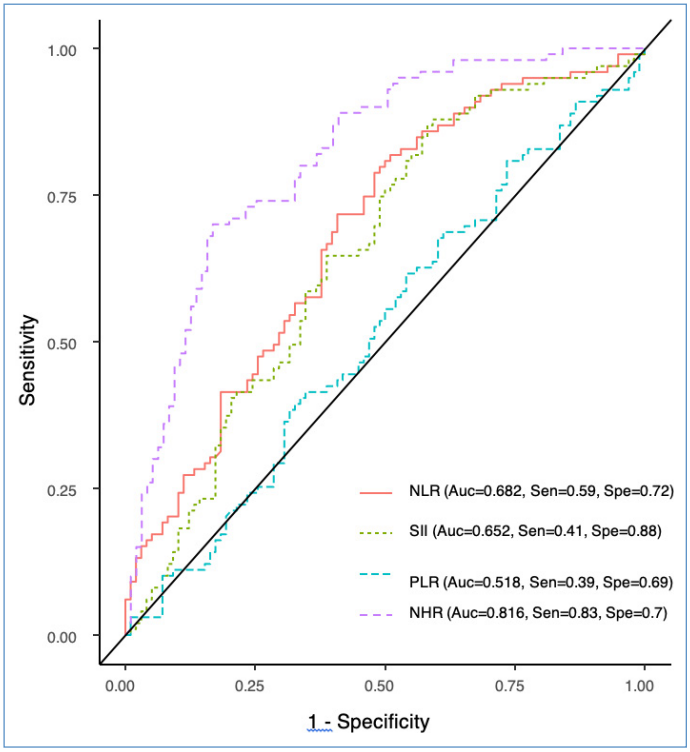

Figure 1. The ROC curve of the NLR, SII, PLR, NHR variables.

NLR: Neutrophil/Lymphocyte ratio; SII: Systemic immune inflammation Index; PLR: Platelet/Lymphocyte ratio; NHR: Neutrophil/HDL Ratio.

Various studies have observed enhanced diffusibility of the blood-brain barrier in progressed stages of PD, which is thought to affect the pathophysiology of the disease. Peripheral inflammation from blood-brain barrier damage may link increased neutrophil and monocyte counts to worsening clinical symptoms in PD patients.[4] Neutrophils are known for their ability to penetrate vascular walls and epithelial surfaces. Additionally, neutrophils mobilize, initiate, and modulate the trafficking of distinct types of leukocytes within cellular structures, and they enhance the physiological inflammatory reaction by modulating chemokine.[16,17] Our research demonstrated that neutrophil counts in PD subjects were considerably greater than in healthy individuals. It is noteworthy that past research has revealed nonsteroidal anti-inflammatory drugs (NSAIDs) are capable of reducing neutrophil counts; accordingly, it has been suggested that NSAIDs might be beneficial in the prevention and treatment of PD.[5,18]

In Parkinson's animal models, T-cell infiltration has been observed in the hippocampus, neocortex, and perivascular regions of the striatum and parenchymal regions of rodents with PD, and low lymphocyte quantities have been found to be associated with a higher likelihood of developing PD.[19]

Moreover, the study results suggest that having increased lymphocyte counts is linked to a reduced prevalence of PD.[20] Lymphocyte quantities in our patients were reduced relative to those of the controls; however, this disparity was not statistically significant.

In recent years, the neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-high-density lipoprotein ratio (NHR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been considered useful inflammatory markers for the diagnosis and monitoring of neurological diseases.[21,22]

NLR serves as a prompt and efficient marker of systemic inflammation, and various studies have indicated that NLR is higher in PD.[11,23] Nevertheless, the connection between NLR and the occurrence of PD is contentious. One study reported a strong association between NLR, Hoehn and Yahr stage, duration, and incidence of PD, whereas another reported contradictory findings.[11,24] In our cohort, NLR levels were also significantly elevated; however, we did not identify a meaningful connection between NLR and disease stage or severity. Additionally, we investigated the possibility of NLR as a diagnostic marker. Our results confirm the importance of NLR as a prognostic tool and align with previous studies.[24,25]

Table 4. ROC Analysis: Areas Under the Curve for Inflammatory Indices

Variable	AUC (%95 CI)	Sensitivity	Specificity	Threshold	Note
NHR	0.816 (0.757-0.876)	0.832	0.7	0.07	If NHR > 0.07, then Group=Patient
NLR	0.682 (0.608-0.757)	0.592	0.717	2.08	If NLR> 2.08, then Group=Patient
PLR	0.518 (0.437-0.599)	0.388	0.687	134.95	If PLR > 134.95, then Group=Patient
SII	0.652 (0.574-0.729)	0.408	0.879	613.61	If SII> 613.61, then Group=Patient

AUC: Area Under the Curve; CI: confidence interval; NHR: Neutrophil/ HDL Ratio; NLR: Neutrophil/ Lymphocyte ratio; PLR: Platelet// Lymphocyte ratio; SII: Systemic immune inflammation Index.

The stability of the blood-brain interface is tightly associated with HDL cholesterol levels.[26] Recent studies have shown that plasma HDL levels are considerably decreased or stable in patients with PD.[9,27]

It has been demonstrated that NHR levels are significantly higher in Parkinson's patients compared to healthy controls and show a negative correlation with disease duration. Another study found significant relationships between NHR levels, stage, and clinic scores of PD.[23,28] NHR levels were also significantly elevated in our patients. However, unlike other studies, we did not identify a noteworthy correlation between the NHR value and the clinical scores of the disease. We also did not observe any meaningful association between inflammatory indices (NLR, NHR, PLR, and SII) and cognition or non-motor symptoms. When examining NHR's potential as a biomarker, we observed a higher AUC compared to other inflammatory indices, which suggests that NHR could be a strong predictor of PD diagnosis.

A recent study highlighted that low serum TG levels could act as a possible predictive diagnostic tool for motor performance in PD patients. Low serum TG levels were found to be significantly associated with higher UPDRS motor scores and gait/postural instability subtypes.[29] A longitudinal study involving a Singaporean cohort investigated the relationship between blood lipid biomarkers and PD. Consistent with our findings, they observed that PD patients had significantly lower levels of lipid panels, including TG and HDL. Deng and colleagues highlighted that TG and Apo A1 could serve as biomarkers for mild cognitive impairment in PD.[30] However, unlike their study, we did not observe a link between our patients' cognitive scores or the NMSS attention and memory subgroups and their lipid profiles.

The limitations of our study include a smaller sample size compared to the literature and the evaluation of non-motor manifestations using a self-report scale. Assessing NMS, including cognition, sleep disturbances, mood changes, and autonomic findings individually, and using more detailed scales, could provide a clearer understanding of the relationship with inflammation. Our study was cross-sectional; however, supporting it with a longitudinal design, genetic subtyping, and neuroimaging methods could offer insights into the contribution of inflammation to the pathophysiology.

Conclusion

In conclusion, immune-inflammatory reactions and dyslipidemia may contribute to the progression of PD. Although inflammatory indices did not show a relationship with non-motor symptoms, NHR, in particular, has the advantage of providing a supplementary link among various pathways. It may more precisely indicate systemic inflammatory changes in PD than individual measures.

Disclosures

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Koşuyolu High Specialization Education and Research Hospital during the meeting held on 02.07.2024, with decision number 2024/12/854.

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