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SRESEARCH

Relationship between nonmotor symptoms and neutrophil-to-lymphocyte ratio in Parkinson's disease

Parkinson hastalığında motor olmayan semptomlar ile nötrofil-lenfosit oranı arasındaki ilişki

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Abstract

Purpose: The aim of this study was to investigate the relationship between neutrophil-to-lymphocyte ratio (NLR), an inflammation marker, and nonmotor symptoms, such as fatigue, sleep disturbances, and overall quality of life, in Parkinson's disease (PD).

Materials and Methods: This study included 60 patients diagnosed with PD (17 female and 43 male). Fatigue was assessed using the Parkinson's Disease Fatigue Scale (PFS-16), sleep quality using the Parkinson's Disease Sleep Scale (PDSS), and quality of life using the Parkinson's Disease Questionnaire-8 (PDQ-8). Neutrophil and lymphocyte counts were extracted from the complete blood count results, and the NLR was calculated.

Results: A moderate, negative correlation was observed between fatigue and sleep quality; a moderate, positive correlation was observed between quality of life, motor rating, and disease staging; a moderate, negative correlation was observed between sleep quality and quality of life; a weak, negative correlation was observed between sleep quality, motor rating, and disease staging; and a weak, positive correlation was found between quality of life, motor rating, and disease staging. No significant relationship was observed between NLR and nonmotor symptoms in PD.

Conclusion: Further prospective studies with larger samples or case–control designs are warranted to explore the potential clinical utility of a simple, cost-effective biomarker, such as NLR, in assessing PD symptoms and disease progression.

Keywords: Parkinson's disease, fatigue, sleep disorders, quality of life, neutrophil-to-lymphocyte ratio.

Öz

Amaç: Bu çalışmanın amacı bir inflamasyon belirteci olan nötrofil/lenfosit oranı (NLR) ile Parkinson Hastalığında (PH) yorgunluk, uyku ve yaşam kalitesi arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Araştırma örneklemimiz PH tanısı konmuş toplam 60 hastadan (17 kadın, 43 erkek) oluşmaktadır. Yorgunluk Parkinson Hastalığı Yorgunluk Ölçeği (PFS-16), uyku kalitesi Parkinson Hastalığı Uyku Ölçeği (PDSS) ve yaşam kalitesi Parkinson Hastalığı Anketi-8 (PDQ-8) ile değerlendirilmiştir. Nötrofil ve lenfosit sayıları hemogram testi ile elde edilmiş ve oranlanarak hesaplanmıştır.

Bulgular: PH hastalarında yorgunluk ile uyku kalitesi arasında anlamlı, negatif ve orta düzeyde; yaşam kalitesi, motor derecelendirme ve hastalık evrelemesi arasında pozitif ve orta düzeyde; uyku kalitesi ile yaşam kalitesi arasında negatif ve orta düzeyde; uyku kalitesi ile motor derecelendirme ve hastalık evrelemesi arasında negatif ve zayıf düzeyde; yaşam kalitesi ile motor derecelendirme ve hastalık evrelemesi arasında pozitif ve zayıf düzeyde korelasyon bulunmuştur. Non-motor semptomlar ile NLR arasında ilişki bulunmamıştır.

Sonuç: NLR gibi basit, ucuz bir biyobelirteçin PH takibi bağlamında potansiyel klinik avantajlarını ve bu tür biyobelirteçlerin hastalık semptomları üzerindeki etkisini belirlemek için çok daha büyük bir kohort veya vaka-kontrol içeren daha ileri prospektif çalışmalar yol gösterici olabilir.

Anahtar kelimeler: Parkinson Hastalığı, yorgunluk, uyku bozuklukları, yaşam kalitesi, nötrofil/lenfosit oranı.

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the chronic loss of dopaminergic neurons in the substantia nigra pars compacta[1]. PD is also classified as an autonomic motor disease with multisystem involvement, as neurodegeneration often begins within the peripheral autonomic system[2]. PD is the second most common neurodegenerative disease after Alzheimer's disease, affecting approximately 7–10 million individuals worldwide[3].

The primary symptoms of PD affect motor function, typically manifesting as rigidity, bradykinesia, tremors, and postural instability[1,3]. Although PD is conventionally regarded as a movement disorder, it is a complex, multisystem disease characterized by both motor and nonmotor symptoms[4]. Studies have indicated that 98% of individuals diagnosed with PD experience at least one nonmotor symptom[5]. Fatigue and sleep disorders are among the most commonly reported symptoms[4,5]. Nonmotor symptoms are often under-reported by patients and caregivers, who may perceive them as inadequately recognized or addressed by healthcare providers[5], leading to reduced quality of life.

Literature review revealed a notable imbalance in clinical focus between motor and nonmotor symptoms. Motor symptoms have been extensively studied, whereas nonmotor symptoms have received less attention. Despite evidence showing that nonmotor symptoms have a greater effect on quality of life than motor symptoms, the role of inflammatory markers in predicting these symptoms remains controversial[6].

Recent studies indicate that inflammation contributes to the pathogenesis and clinical manifestations of PD[7,8]. Specifically, inflammation is a pathological finding of PD originating from activated microglial cells that proliferate in response to cellular loss in the substantia nigra. Activated microglia produce reactive oxygen and nitrogen species, leading to increased oxidative stress[9,10]. Acute inflammation is characterized by the migration of neutrophils, macrophages, cytokines, and chemokines to the affected site, whereas chronic inflammation involves macrophages, lymphocytes, and plasma cell infiltration[11]. The neutrophil-to-lymphocyte ratio (NLR) is a marker of peripheral inflammation. NLR is a biomarker derived from complete blood count. It is commonly used to indicate peripheral inflammation and reflects the balance between immunity and systemic inflammation. Emerging evidence links NLR to neurological and systemic diseases, including PD[12-14].

Thus, we hypothesized that an elevated NLR may be associated with an increased prevalence of nonmotor symptoms in patients with PD. Although several recent studies have examined the relationship between NLR and PD, the association between NLR and nonmotor symptoms in PD remains underexplored. Thus, this study aimed to assess the effect of PD-related inflammation on the development of nonmotor symptoms.

MATERIALS AND METHODS

Sample

This prospective, single-center study included 60 patients with PD who were followed up at the Department of Neurology of Niğde Ömer Halisdemir University Training and Research Hospital. Patients eligible for inclusion were aged ≥50 years, attended the Niğde Ömer Halisdemir Training and Research Hospital Neurology Outpatient Clinic, consented to participate, had a PD diagnosis based on the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria, achieved a Mini-Mental State Examination (MMSE) score >24, and were classified as MHYS grade ≤3. The exclusion criteria were coexisting neurological diseases, severe musculoskeletal conditions, active inflammatory or infectious diseases, lower extremity vascular pathology, or uncooperative behavior. Seven patients were excluded because of MMSE scores <24, six patients had MHYS scores exceeding grade 3, and five lacked current hemogram data.

Procedure

All procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Niğde Ömer Halisdemir University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee on December 22, 2022 (No. 2022-107), and informed consent was obtained from all participants.

NLR values were derived from hemogram tests performed within the past month for individuals diagnosed with PD. The study used a demographic

information form to capture descriptive data (e.g., age, height, and disease duration) as well as the Modified Hoehn–Yahr Scale (MHYS)[15] and the Unified Parkinson's Disease Rating Scale (UPDRS)[15] for disease staging. Fatigue, sleep quality, and overall quality of life were assessed using the Parkinson's Disease Fatigue Scale (PFS-16)[16], Parkinson's Disease Sleep Scale (PDSS)[17], and Parkinson's Disease Questionnaire-8 (PDQ-8)[18], respectively. A specialist neurologist conducted the demographic assessments, MHYS, and UPDRS staging, and the evaluation of nonmotor symptoms was completed by specialist physiotherapists.

Measures

Demographic and clinical data form

Patient demographic characteristics were documented using a demographic and clinical data form, which recorded protocol number, age, gender, height, weight, and body mass index (BMI). BMI was calculated using the formula weight/height^2 (kg/m^2). Additional information on participants' educational and marital statuses, which could affect evaluated parameters, was also recorded. Anamnesis included disease duration, disease history, and current medications.

Modified Hoehn–Yahr Scale

The MHYS, developed by Margaret Hoehn and Melvin Yahr in 1967, rates PD progression, with scores ranging from 0 to 5[15].

Unified Parkinson's Disease Rating Scale

The UPDRS was used to assess motor function, mental and emotional state, daily life activities, motor fluctuations, dyskinesias, and autonomic dysfunction in patients with PD. It comprises four subscales with up to 55 items if extremities are assessed individually. Subscale 1 assesses the nonmotor symptoms such as thought, behavior, and emotion; subscale 2 assesses daily life activities; subscale 3 assesses motor functions; and subscale 4 assesses treatment complications. For this study, only section 3 on motor functions was assessed[15].

Parkinson's Disease Fatigue Scale

Fatigue, a prevalent nonmotor symptom in PD, was assessed using the PFS-16. Developed by Brown et al., this is the only fatigue scale specific to PD, consisting of 16 items to evaluate the physical impact of fatigue. Of these, seven items measure the presence of fatigue, while nine assess its impact on daily life[16].

Parkinson's Disease Sleep Scale

The PDSS was used to evaluate participants' nighttime sleep quality. This 15-item scale covers various aspects, including overall sleep quality, sleep onset and maintenance difficulties, night restlessness, nocturnal psychosis, nocturia, nocturnal motor symptoms, restfulness of sleep, and daytime naps. Participants rated each item on a 10-point scale ranging from 0 (severe complaints) and 10 (no complaints)[17].

Parkinson's Disease Questionnaire-8

Participants' quality of life was assessed using the PDQ-8. Participants selected the option that best matched their condition from four options, with scores ranging from 0 to 4 per item. Higher PDQ-8 scores indicated poorer quality of life[18].

Laboratory analysis

Hemogram analysis was performed using a Sysmex XN 1000 analyzer (Sysmex Corp., Kobe, Japan) on EDTA (Greiner Tube 3-mL K2 EDTA)-treated blood samples. Fluorescence flow cytometry was used to identify leukocyte subpopulations based on size, diffuse light, and fluorescence uptake, which reflects intracellular genetic material[19]. Impedance and hydrodynamic focusing were used to count red blood cells and platelets[20], and neutrophil and lymphocyte counts were recorded.

Statistical analysis

The study power was calculated using the G* Power 3.1 statistical analysis (Erdfelder, Foul & Buchner, Düsseldorf, Germany). The sample size was determined as 61 participants with an effect size of 0.35, a significance level of 0.05, and a power $(1-\beta)$ of 0.80 at the 80% confidence level. Post hoc analysis results showed an effect size of 0.696, a significance level of 0.05, and a confidence level of 99% for the relationship analysis between sleep and quality of life in 60 individuals diagnosed with PD.

Statistical analyses were conducted using Statistical Product and Service Solutions for Windows, Version 26.0 (SPSS 26.0, IBM Corp., Armonk, New York). Normality was assessed via visual (histogram and probability plots) and analytical methods (Kolmogorov–Smirnov, skewness-kurtosis value,

and coefficient of variation). Continuous variables were presented as mean±standard deviation (X±SD), median, and interquartile range. Categorical variables were presented as numbers (n) and percentages (%). Relationships among fatigue, sleep quality, quality of life, and NLR investigated were analyzed using Pearson's correlation analysis, with correlation coefficients defined by Cohen's coefficient: 0.00–0.25=very weak, 0.26–0.49=weak, 0.50–0.69=moderate, 0.70–0.89=high, and 0.90–1.00=very high-level correlation. Data were evaluated at a 95% confidence interval, with significance set at $p<0.05$.

RESULTS

As shown in Table 1, the mean age of patients (17 [28.3%] female and 43 [71.7%] male) was 70.80 (range: 53–87) years. The mean disease duration was 3.23 (range: 1–16) years. Regarding assistive devices, 11 (18.3%) patients used hearing aids, 22 (36.7%) used glasses, and 13 (21.7%) used a cane. Regarding MHYS staging, 11 (18.3%) patients were in Stage 1, 15 (25%) in Stage 1.5, 24 (40%) in Stage 2, 1 (1.66%) in Stage 2.5, and 9 (15%) Stage 3. The dominant extremity was the right in 59 (98.33%) patients, with symptom onset in the right extremity among 42 (68.9%). Tremors were present in the upper extremity among 55 (91.66%) patients, in the lower extremity among 3 (5%), and absent among 2 (3.3%). In addition, 23 (38.33%) patients reported falls in the past year.

The patients' mean MMSE score was 25.55±1.52, and the mean PDSS score was 95.97±32.11. The mean PFS-16 scores were 9.16±5.4 (when scores of 1, 2, and 3 were considered 0 and scores of 4 and 5 were considered 1) and 3.36±1.07 (when scores were summed and divided by 16). The mean PDQ-8 score was 31.5±22.29 (range: 0–87.5), the mean UPDRS-motor score was 26.45±10.67, and the mean NLR was 2.10±0.88.

Table 1. Descriptive characteristics of participants.

Variables	Parkinson's Disease (n:60)	
	n (%)	
Gender (Female/male)	17/43 (28.3/71.7)	
Dominant limb (Right/left)	59/1 (98.3/1.7)	
Marital status (Married/single)	44/16 (73.3/26.7)	
Hearing aid (Yes/no)	11/49 (18.3/81.7)	
Glasses (Yes/no)	22/38 (36.7/63.3)	
Walking aid (Yes/no)	13/47 (21.7/78.3)	
	Mean±SD	Median (IQR)
Age (years)	70.80±8.57	71.50 (12)
Height (cm)	165.78±9.04	167 (12)
Weight (kg)	75.47±12.61	73.50 (14)
BMI (kg/m^2)	27.57±4.98	26.96 (5.93)
Disease duration (years)	3.23±3.21	2 (4)
MMSE	25.55±1.52	25 (2.5)
UPDRS-motor	26.45±10.67	25.50 (15.5)
MHYS	1.85±0.62	2 (0.5)
Neutrophil count	4.45±1.27	4.31 (1.72)
Lymphocyte count	2.46±1.34	2.08 (0.93)
NLR	2.10±0.88	1.89 (0.95)
PFS-16	3.36±1.07	3.31 (1.81)
PDSS	95.97±32.11	98.50 (49)
PDQ-8	31.35±22.29	31.25 (35.94)

BMI: Body Mass Index, MMSE: Mini-mental state examination, UPDRS-motor: Unified Parkinson's Disease Rating Scale-motor, MHYS: Modified Hoehn Yahr Scale, NLR: neutrophil-to-lymphocyte ratio, PFS-16: Parkinson's Disease Fatigue Scale-16, PDSS: Parkinson's Disease Sleep Scale, PDQ-8: The Parkinson's Disease Questionnaire-8.

There was a moderate negative correlation between PDSS scores and both PDQ-8 (r: -0.642) and PFS-16 (r: -0.677) scores. A significant positive correlation was found between PDQ-8 and PFS-16 scores (r: 0.674). Increased UPDRS-motor scores and MHYS stage were associated with higher levels of sleep

disturbance and fatigue and lower quality of life. In contrast, there was no significant relationship between NLR and any of the parameters studied, including sleep quality, fatigue, and quality of life (Table 2 and Figure 1).

Table 2. Relationship between NLR and fatigue, sleep and quality of life in patients with Parkinson's disease

Variables		NLR	PFS-16	PDSS	PDQ-8	UPDRS	MHYE	Duration
NLR	p							
	r	1.000						
PFS-16	p	0.895						
	r	-0.017	1.000					
PDSS	p	0.426	<0.001*					
	r	0.105	-0.677	1.000				
PDQ-8	p	0.945	<0.001*	<0.001*				
	r	-0.009	0.674	-0.642	1.000			
UPDRS	p	0.799	<0.001*	<0.001*	<0.001*			
	r	0.034	0.508	-0.440	0.462	1.000		
MHYS	p	0.639	<0.001*	0.003*	<0.001*	<0.001*		
	r	0.062	0.529	-0.376	0.440	0.710	1.000	
Duration	p	0.899	0.638	0.963	0.242	0.850	0.742	
	r	0.017	-0.062	-0.006	0.153	-0.025	0.043	1.000

NLR: neutrophil-to-lymphocyte ratio, PFS-16: Parkinson's Disease Fatigue Scale-16, PDSS: Parkinson's Disease Sleep Scale, PDQ-8: The Parkinson's Disease Questionnaire-8, UPDRS: Unified Parkinson's Disease Rating Scale, MHYS: Modified Hoehn Yahr Scale, p:Pearson's analysis, r: Pearson's correlation coefficient, *:p<0.05

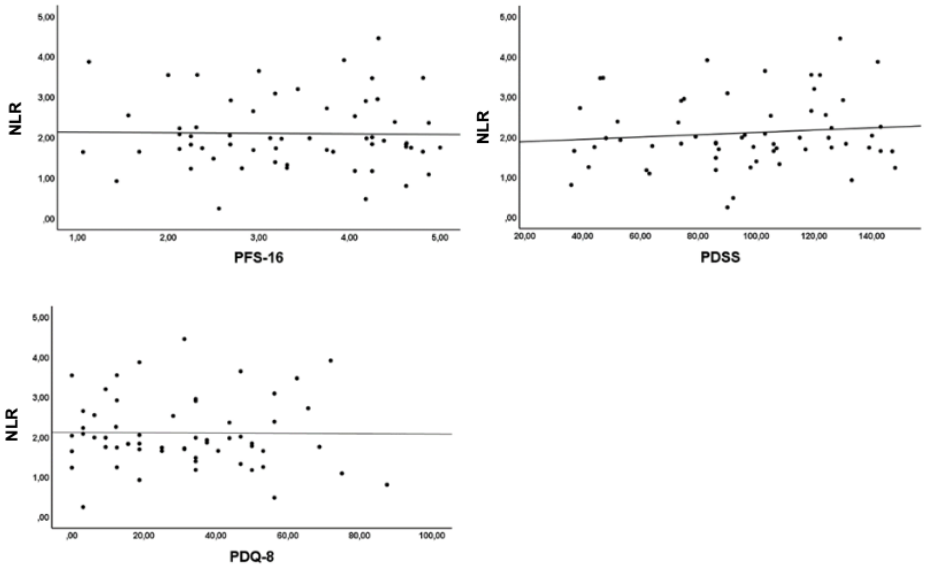

Figure 1. The relationship between NLR and fatigue, sleep and quality of life in patients with Parkinson's disease.

DISCUSSION

A total of 60 individuals with idiopathic PD were included in our study. The NLR values were obtained from routine blood samples from all patients. Nonmotor symptoms such as fatigue, sleep disturbances, and quality of life were evaluated using PFS-16, PDSS, and PDQ-8, respectively. Our findings indicated no relationship between NLR, a peripheral inflammatory marker, and fatigue, sleep,

and quality of life, which are nonmotor symptoms of PD.

Recent studies have indicated that NLR, an inflammatory marker, may be relevant in PD[6,21]. Previous studies have reported a possible link between peripheral inflammation and PD, with elevated proinflammatory serum cytokine levels associated with disease progression. However, the specific mechanisms remain unclear[22-24]. NLR is considered a reliable indicator of peripheral immune dysregulation and inflammation. A meta-analysis found that in patients with PD, lymphocytes, which support protective immune functions, tend to decrease, whereas neutrophils, which are involved in inflammation, increase, resulting in a higher NLR[25]. Nevertheless, some studies reported no significant difference in NLR between patients with PD and healthy individuals[21,26]. Solmaz et al. observed a weak relationship between NLR and both disease stage and duration, whereas another study found no relationship with disease severity or duration[25,27]. Overall, the relationship between NLR and PD remains ambiguous, with conflicting results in the literature.

A review indicated that inflammation may contribute to the development of nonmotor symptoms[28]. Recent studies have shifted the focus from motor symptoms, such as bradykinesia, tremor, rigidity, and postural instability, to nonmotor symptoms, such as fatigue, sleep disturbance, depression, cognitive impairment, and autonomic dysregulation[6]. However, only few studies have examined the relationship between nonmotor symptoms and inflammatory markers in PD. Kara et al. reported that NLR is a significant marker of peripheral inflammation in PD and is potentially useful for detecting nonmotor symptoms[29]. Another study found an association between depression, anxiety, and fatigue in patients with PD and elevated serum inflammatory cytokines[30]. Fatigue is a prevalent nonmotor symptom in patients with PD that significantly affects daily activity performance. Although the mechanisms underlying fatigue are not fully explained, low-grade but persistent neuroinflammation has been suggested as a contributor[31]. Fatigue in PD may be closely linked to proinflammatory cytokine levels and other inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and NLR[6,32].

Sleep disorders affect up to 80% of patients with PD[33], with issues including insomnia, rapid eye movement sleep behavior disorder, excessive daytime sleepiness, and sleep-disordered breathing at night. Despite its high prevalence, up to 30%–40% of patients with PD do not report sleep issues to healthcare providers[4,5,34]. Studies have indicated that sleep disturbance can independently reduce quality of life among patients with PD[35]. Previous studies have linked inflammatory markers such as IL-1, TNF-α, and IL-6 to sleep disorders[36,37]. However, other studies, including one on patients with PD, found no correlation between inflammatory cytokines and sleep[30], highlighting the inconsistencies and the need for further investigation into the relationship between inflammatory markers and sleep in PD.

Fatigue has been increasingly recognized as one of the most common and disabling symptoms of PD, affecting approximately 50% of patients. Studies indicate that fatigue is persistent in most patients, with its prevalence increasing over time[38]. Although neuroinflammation, a pathological hallmark of PD, is closely associated with fatigue, the underlying mechanisms remain inadequately understood, and the inflammatory predictors of fatigue in patients with PD are still debated[6].

In a study by Akıl et al.[22], which included 51 patients with PD and 50 healthy people, serum inflammatory markers, such as hs-CRP and NLR, were analyzed. The results showed that both serum hs-CRP and NLR levels were significantly elevated in patients with PD compared with those in healthy controls, with p-values of <0.01 and <0.001, respectively[22]. Similarly, Wang et al. enrolled 63 patients with PD, among whom 35 patients had fatigue and 28 patients did not. They analyzed the relationship between plasma cytokines and p-α-syn levels and fatigue and found that patients with PD and fatigue were older, had longer disease durations, and exhibited more severe motor symptoms. Additionally, significant differences were observed in the plasma levels of IL-1β, IL-18, TNF-α, and phosphorylated α-syn (p-α-syn) between the two groups. Higher levels of inflammatory cytokines (IL-1β, IL-18, and TNF-α) were positively correlated with fatigue scores[39]. Although several studies have shown a correlation between fatigue and inflammatory markers, our study did not find such an association. This discrepancy can be attributed to the early disease stage in our patient population.

Both motor and nonmotor symptoms are present from the earliest stages of PD, although their severity and impact can vary throughout the duration of the

disease[40,41]. In early PD, nonmotor symptoms were found to be more influential than motor symptoms in affecting quality of life[38]. Another study indicated that the quality of life of both early- and late-stage patients with PD was most frequently affected by motor and nonmotor symptoms[42]. In our study, we did not find an association between NLR, an inflammatory marker, and nonmotor symptoms, including fatigue, sleep quality, and quality of life. We believe this lack of association may be due to several factors.

First, no relationship may exist, although this appears unlikely given that the literature supports a link between inflammatory markers and the parameters we examined[6,30,32]. Second, the demographic characteristics of the patients who participated in our study might have affected the association. The relatively early disease stages of our patient cohort, with average disease duration and MHYS stage lower than those of patients in other studies, could explain the lack of correlation. While NLR is generally known to increase in PD, the average NLR value in our cohort was 2.17 ± 1.02, with almost all patients falling within the reference range of 0.78 to 3.53 for healthy adults[43]. Finally, we speculate that NLR may not fully capture the complex immune mechanisms involved in PD pathogenesis and may be insufficient to reflect peripheral inflammation.

This study has several limitations. The inclusion of only patients with early- to mid-stage PD and the use of a single inflammatory biomarker may have limited the scope of our findings. Additionally, the absence of a control group and the relatively small patient sample size are important limitations. Future studies should consider these factors and include patients at advanced disease stages. Moreover, NLR should be evaluated alongside other inflammatory markers may be beneficial.

In conclusion, this study found no relationship between NLR, a peripheral inflammatory marker, and nonmotor symptoms in PD. This may be due to the low disease stage, short duration, and relatively good general health of participants who exhibited low NLR values. Further prospective studies with larger cohorts or case–control designs may help determine the clinical utility of simple, inexpensive biomarker, such as NLR, for PD follow-up and their effect on disease symptoms.

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REFERENCES

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm. 2017;124:901-5.
2. Alexander GE. Biology of Parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder. Dialogues Clin Neurosci. 2004;6:259-80.
3. X- Tan EK, Chao YX, West A, Chan LL, Poewe W, Jankovic J. Parkinson disease and the immune system-associations, mechanisms and therapeutics. Nat Rev Neurol. 2020;16:303-318.
4. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord. 2006;21:916-23.
5. Hurt CS, Rixon L, Chaudhuri KR, Moss-Morris R, Samuel M, Brown RG. Barriers to reporting non-motor symptoms to health-care providers in people with Parkinson's. Parkinsonism Relat Disord. 2019;64:220-225.
6. Wang H, Liu Y, Zhao J, Guo X, Hu M, Chen Y. Possible inflammatory mechanisms and predictors of Parkinson's disease patients with fatigue (Brief Review). Clin Neurol Neurosurg. 2021;208:106844.
7. Borsche M, König IR, Delcambre S, Petrucci S, Balck A, Brüggemann N et al. Mitochondrial damage-associated inflammation highlights biomarkers in PRKN/PINK1 parkinsonism. Brain. 2020;143:3041-3051.
8. Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Parkinsons Dis. 2021;7:27.
9. Fischer R, Maier O. Interrelation of oxidative stress and inflammation in neurodegenerative disease: role of TNF. Oxid Med Cell Longev. 2015;610813.
10. Amor S, Puentes F, Baker D, Van der Valk P. Inflammation in neurodegenerative diseases. Immunology. 2010;129:154-69.

11. Pajares M, I Rojo A, Manda G, Boscá L, Cuadrado A. Inflammation in Parkinson's Ddsease: mechanisms and therapeutic implications. cells. 2020;9:1687.
12. Taşkıran T, Öztürk EB. Neutrophil/lymphocyte ratio as an indicator of radiological disease activity in clinically stable multiple sclerosis. Cukurova Med J. 2024;49:721-727.
13. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the ımmune system and diseases. Int J Mol Sci. 2022;23:3636.
14. Lattanzi S, Brigo F, Trinka E, Cagnetti C, Di Napoli M, Silvestrini M. Neutrophil-to-lymphocyte ratio in acute cerebral hemorrhage: a system review. Transl Stroke Res. 2019;10:137-145.
15. Nakano I, Fujimoto K. Rating scale and functional prognosis of Parkinson's disease. Nihon Rinsho. 2000;58:2132-8.
16. Brown RG, Dittner A, Findley L, Wessely SC. The Parkinson fatigue scale. Parkinsonism Relat Disord. 2005;11:49-55.
17. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2002;73:629-35.
18. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. J Neurol. 1998;245:10-14.
19. Şenlikci A, Ergüder E, Süleyman M, Koşmaz K, Durhan A, Şeneş M et al. Does monocyte distribution width (MDW) have prognostic value in acute pancreatitis? J Contemporary Med. 2021;11:335-39.
20. Velizarova M, Yacheva T, Genova M, Svinarov D. Evaluation of automated hematology analyzer DYMIND DH76 compared to SYSMEX XN 1000 system. J Med Biochem. 2021;40:367-77.
21. Uçar CA, Çokal BG, Artık HAÜ, İnan LE, Yoldaş TK. Comparison of neutrophil- lymphocyte ratio (NLR) in Parkinson's disease subtypes. Neurol Sci. 2017;38:287–93.
22. Akıl E, Bulut A, Kaplan İ, Özdemir HH, Arslan D, Aluçlu MU. The increase of carcinoembryonic antigen (CEA), high-sensitivity C-reactive protein, and neutrophil/lymphocyte ratio in Parkinson's disease. J Neurol Sci. 2015;36:423–28.
23. Mosley RL, Hutter-Saunders JA, Stone DK, Gendelman HE. Inflammation and adaptive immunity in Parkinson's disease. Cold Spring Harb Perspect Med. 2012;2:a009381.
24. Scalzo P, Kümmer A, Cardoso F, Teixeira AL. Increased serum levels of soluble tumor necrosis factor-alpha receptor-1 in patients with Parkinson's disease. J Neuroimmunol. 2009;216:122–25.
25. Muñoz-Delgado L, Macías-García D, Jesús S, Martín-Rodríguez JF, Labrador-Espinosa MÁ, Jiménez-Jaraba MV et al. Peripheral immune profile and neutrophil-to-lymphocyte ratio in Parkinson's disease. Mov Disord. 2021;36:2426–30.
26. Jin H, Gu HY, Mao CJ, Chen J, Liu CF. Association of inflammatory factors and aging in Parkinson's disease. Neurosci Let. 2020;736:1-4.
27. Solmaz V, Pekdas Genç E, Aksoy D, Çevik B, Kurt SG, Benli İ. Serum neutrophil-lymphocyte ratios, C-reactive protein and sedimentation levels in Parkinson's disease. Cukurova Med J. 2018;43:305–11.
28. Barnum CJ, Tansey MG. Neuroinflammation and non-motor symptoms: the dark passenger of Parkinson's disease? Curr Neurol Neurosci Rep. 2012;12:350-8.
29. Kara SP, Altunan B, Unal A. Investigation of the peripheral inflammation (neutrophil-lymphocyte ratio) in two neurodegenerative diseases of the central nervous system. Neurol Sci. 2022;43:1799-1807.
30. Lindqvist D, Kaufman E, Brundin L, Hall S, Surova Y, Hansson O. Non-motor symptoms in patients with Parkinson's disease - correlations with inflammatory cytokines in serum. PLoS One. 2012;7:e47387.
31. Hagell P, Brundin L. Towards an understanding of fatigue in Parkinson disease. J Neurol Neurosurg Psychiatry. 2009;80:489–92.
32. Pereira JR, Santos LVD, Santos RMS, Campos ALF, Pimenta AL, de Oliveira MS et al. IL-6 serum levels are elevated in Parkinson's disease patients with fatigue compared to patients without fatigue. J Neurol Sci. 2016;15:153-56.
33. Tibar H, El Bayad K, Bouhouche A, Ait Ben Haddou EH, Benomar A, Yahyaoui M et al. Non-motor symptoms of Parkinson's Disease and their impact on quality of life in a cohort of moroccan patients. Front Neurol. 2018;4:170.
34. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev. 2017;35:33-50.
35. Scaravilli T, Gasparoli E, Rinaldi F, Polesello G, Bracco F. Health-related quality of life and sleep disorders in Parkinson's disease. J Neurol Sci. 2003;24:209–210.
36. Kaminska M, O'Sullivan M, Mery VP, Lafontaine AL, Robinson A, Gros P et al. Inflammatory markers and BDNF in obstructive sleep apnea (OSA) in Parkinson's disease (PD). Sleep Med. 2022;90:258-61.
37. Simpson N, Dinges DF. Sleep and inflammation. Nutr Rev. 2007;65:244-52.
38. Müller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. Parkinsonism Relat Disord. 2013;19:1027-32.
39. Wang L, Yi H, Liang X, Xu F, Li T, Yang X et al. Plasma TNF-α and phosphorylated α-syn are associated with fatigue in patients with Parkinson's disease. J Neuroimmunol. 2023;15:578222.

40. Tolosa E, Gaig C, Santamaría J, Compta Y. Diagnosis and the premotor phase of Parkinson disease. Neurology. 2009;72:12-20.
41. Müller B, Larsen JP, Wentzel-Larsen T, Skeie GO, Tysnes OB; Parkwest Study Group. Autonomic and sensory symptoms and signs in incident, untreated Parkinson's disease: frequent but mild. Mov Disord. 2011;26:65-72.
42. Gökçal E, Gür VE, Selvitop R, Babacan Yildiz G, Asil T. Motor and non-motor symptoms in Parkinson's Disease: effects on quality of life. Noro Psikiyatr Ars. 2017;54:143-48.
43. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017;10:12.