BRIEF REPORT

Peripheral Immune Profile and Neutrophil-to-Lymphocyte Ratio in Parkinson's Disease

Laura Muñoz-Delgado, MD,[1,2] Daniel Macías-García, MD,[1,2] Silvia Jesús, MD, PhD,[1,2] Juan Francisco Martín-Rodríguez, PhD,[1,2,3] Miguel Ángel Labrador-Espinosa, MSc,[1,2,4] María Valle Jiménez-Jaraba, BSc,[1] Astrid Adarmes-Gómez, MD,[1,2] Fátima Carrillo, MD, PhD,[1,2] and Pablo Mir, MD, PhD[1,2,4*]

[1]*Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain* [2]*Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain* [3]*Departamento de Psicología Experimental, Facultad de Psicología, Universidad de Sevilla, Seville, Spain* [4]*Departamento de Medicina, Facultad de Medicina, Universidad de Sevilla, Seville, Spain*

ABSTRACT: Background: The neutrophil-to-lymphocyte ratio (NLR) in peripheral blood is a well-established inflammatory marker, but its role in Parkinson's disease (PD) remains unclear.
Objectives: To determine whether a different peripheral immune profile and NLR were present in PD patients.
Methods: We conducted a case–control study that included 377 PD patients and 355 healthy controls (HCs). Leukocytes, subpopulations, and the NLR were measured. Multivariate linear regression analyses were applied to determine the differences between groups and the association between NLR and clinical characteristics in PD. A meta-analysis was performed to clarify the association between NLR and PD.
Results: In our case–control study, the NLR was significantly higher in PD patients compared with HCs (2.47 ± 1.1 vs. 1.98 ± 0.91, $P < 0.001$). No association between NLR and age at onset, disease severity, or disease duration was found. The meta-analysis showed that the NLR was likely to be higher in PD patients.
Conclusions: PD patients had an altered peripheral immune profile and a higher NLR compared with HCs.

Key Words: Parkinson's disease; neutrophil-to-lymphocyte ratio; neuroinflammation; inflammatory markers; meta-analysis

*Correspondence to: Dr. Pablo Mir, Unidad de Trastornos del Movimiento, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Avda. Manuel Siurot s/n, 41013, Seville, Spain; E-mail: pmir@us.es

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Parkinson's disease (PD) is one of the most common neurodegenerative disorders.[1] The etiopathogenesis of PD remains unclear, but current evidence points to neuroinflammation as a major contributor to the etiology and progression of neurodegeneration in PD.[1-4] Neuroinflammation is not a simple response to neurodegeneration and PD is associated with both central and peripheral immune responses.[2-5] Evidence suggests that there is a brain–periphery interaction in PD, either by the glial–lymphatic pathway or by a disturbed blood–brain barrier.[4,6] Proinflammatory cytokines (which communicate and modulate the peripheral and central immune compartments) have been described to be elevated in the blood, cerebrospinal fluid (CSF), and brains of PD patients compared with healthy controls (HCs).[3,7-9] Quantitative and qualitative changes in leukocytes and their subpopulations have been reported in the peripheral blood of PD patients.[2,10-13] The neutrophil-to-lymphocyte ratio (NLR) is a well-established indicator of the overall inflammatory status of the organism. This ratio integrates information from two leukocyte subpopulations and complementary immune pathways: neutrophils are associated with chronic inflammation[14] and lymphocytes might represent the regulatory pathway. It has been used as a prognostic factor in cancer, cardiovascular, and inflammatory diseases, and as a marker of cognitive impairment in Alzheimer's disease.[15-20] The NLR has been suggested to be elevated in PD as a

biomarker of peripheral inflammation, with controversial results.[21-29]

The present study aimed to examine whether there was a proinflammatory peripheral immune status in PD patients compared with HCs. We first investigated the differences in the peripheral immune profile between PD patients and HCs through a case–control study. Then, we aimed to investigate if the NLR was related to the clinical characteristics of PD. Subsequently, we performed a meta-analysis to clarify the role of NLR in PD.

Patients and Methods

Observational Case–Control Study

Participants and Clinical Assessment

We included 456 PD patients from the Movement Disorders Clinic at the Hospital Universitario Virgen del Rocio in Seville (Spain), diagnosed following the Movement Disorder Society Clinical Diagnostic Criteria.[30] We also included 501 HCs who were non-blood relatives of PD patients from the same geographic area.

Medical records were retrospectively evaluated. All participants were examined for exclusion criteria that could influence the immune profile at the time of the blood extraction or any other relevant neurological disease.

Total leukocyte count and subpopulations (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) were measured in peripheral blood. The NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count. The local ethics committee approved the study, and written informed consent was obtained from all study participants.

Statistical Analysis

Continuous and categorical variables were compared using Welch's two-sample *t* tests and Fisher's or the chi-squared test, as appropriate. Leukocytes, subpopulations, and the NLR between the PD and HC groups as well as the association between NLR and clinical characteristics in PD were assessed using multivariate linear regression. An a priori power analysis (for sample size estimation to achieve a statistical power = 0.80) and a post hoc power analysis (to evaluate the power of our study) were performed. All statistical analyses were performed using the R studio software package. A P value <0.05 was considered statistically significant.

Meta-Analysis

We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Detailed information about meta-analysis methods can be found in Supplementary Material 1 (Tables S1 and S2).

Results

Observational Case–Control Study

After applying inclusion and exclusion criteria, a total of 377 PD patients and 355 HCs were included. Differences in age, sex, tobacco consumption, and hyperlipidemia were found between the groups. Demographic and clinical data, as well as the immune profile in peripheral blood of both cohorts, are shown in Table 1.

PD patients showed a significantly lower lymphocyte count and a trend towards a higher neutrophil count compared with HCs. No significant differences were found in the absolute leukocyte count. The NLR was higher in the PD patients compared with the HCs (2.47 ± 1.1 vs. 1.98 ± 0.91, $P < 0.001$), which remained statistically significant after adjusting for baseline factors such as age, sex, and vascular risk factors.

In the PD group, no significant differences in the NLR according to age at onset, disease severity (based on Hoehn & Yahr stage [HY]), presence of motor complications, or total disease duration were found. The NLR had a weak positive association with levodopa equivalent daily dose (LEDD). Results were reported after performing a multicollinearity analysis and adjusting for age, sex, and LEDD, as appropriate. (Supplementary Material 2, Tables S3–S8).

The power analysis indicated that the sample size needed to detect a difference in NLR between PD patients and HCs of d = 0.249 was 510 individuals (255 per group). Our study achieved a statistical power of 99%.

Meta-Analysis

After applying inclusion and exclusion criteria, seven articles were selected for this meta-analysis.[21-26,29] The Jiang et al study was divided into two, as it presented two well-differentiated cohorts according to the age at PD onset: Jiang et al-EOPD (early-onset PD) and Jiang et al-LOPD (late-onset PD).[25] Along with our study, nine NLR mean differences with a case–control design were included, comprising 1219 PD patients and 862 HCs.

Overall heterogeneity was high; hence the random-effects model was applied. The standardized mean difference (SMD) for each individual study and the overall effect size (ES) were shown in Figure 1. PD patients had a higher NLR compared with HCs (SMD = 0.27; 95% CI −0.05 to 0.60).

No significant risk of publication bias was detected. The sensitivity analyses showed that the Akil et al study had a major influence on the global heterogeneity with little impact on the global ES, whereas our study was the most influential on the global ES. In the "leave-one-out" analysis, neither the overall ES varied, nor did the heterogeneity decrease substantially when excluding each of the individual studies.

TABLE 1 *Demographic, clinical data, and immune profile in peripheral blood in healthy controls and Parkinson's disease cohorts*

Parameter	HC (N = 355)	PD (N = 377)	*P* value
Age (y), mean ± SD	59.23 ± 15.06	63.7 ± 11.91	<0.001[a]
Sex (% men)	47.89%	58.09%	<0.05[b]
Alcohol consumption (n) (yes/no)	20/185	34/277	0.77[c]
Tobacco consumption (n) (yes/no/former)	46/142/57	40/251/51	<0.001[c]
Hypertension (%)	38.97	35.56	0.36[c]
Diabetes mellitus (%)	14.04	13.37	0.83[c]
Hyperlipidemia (%)	32.18	19.52	<0.001[c]
Age at onset (y), mean ± SD	-	55.21 ± 12.42	
Disease duration (y), mean ± SD	-	8.44 ± 6.21	
Hoehn & Yahr, mean ± SD	-	2.29 ± 0.78	
LEDD, mean ± SD	-	712.84 ± 458.23	
Leukocyte count ($\times 10^3$ cells/μL), mean ± SD	6.85 ± 1.69	6.67 ± 1.6	0.42[d]
Lymphocytes ($\times 10^3$ cells/μL), mean ± SD	2.14 ± 0.66	1.83 ± 0.59	<0.001[d]
Neutrophils ($\times 10^3$ cells/μL), mean ± SD	3.9 ± 1.25	4.13 ± 1.32	0.11[d]
Monocytes ($\times 10^3$ cells/μL), mean ± SD	0.5 ± 0.34	0.45 ± 0.15	<0.05[d]
Eosinophils ($\times 10^3$ cells/μL), mean ± SD	0.23 ± 0.34	0.16 ± 0.32	<0.05[d]
Basophils ($\times 10^3$ cells/μL), mean ± SD	0.07 ± 0.5	0.02 ± 0.08	0.18[d]
NLR, mean ± SD	1.98 ± 0.91	2.47 ± 1.1	<0.001[d]

Abbreviations: HC, healthy control; PD, Parkinson's disease; N, total number of subjects; y, years; SD, standard deviation; LEDD, levodopa equivalent daily dose; NLR, neutrophil-to-lymphocyte ratio.
[a]Based on Welch two-sample *t* tests.
[b]Based on chi-squared test.
[c]Based on Fisher's test.
[d]Multivariate linear regression adjusting for age, sex, alcohol consumption, smoking status, hypertension, diabetes, and hyperlipidemia.

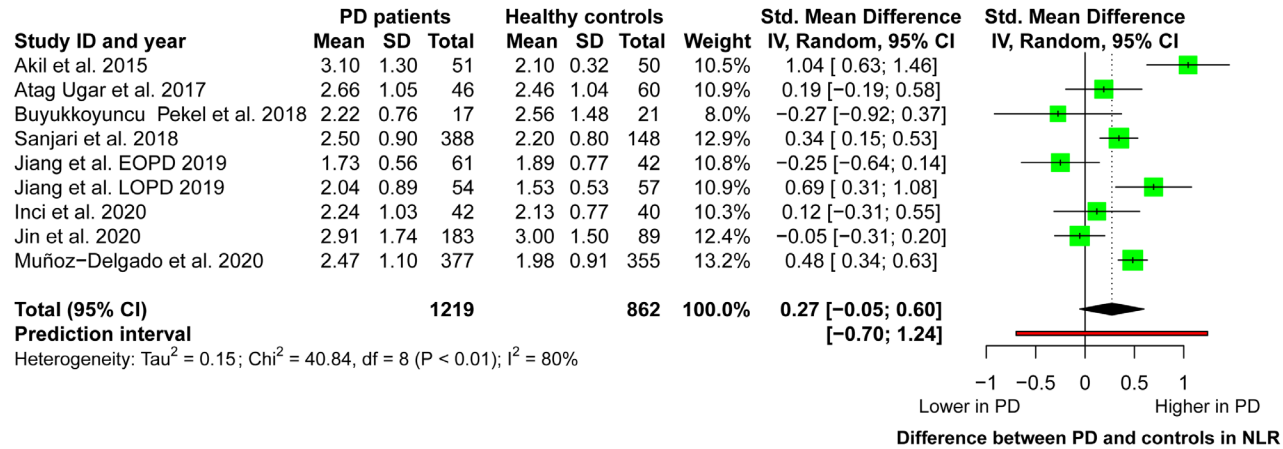

FIG. 1. Forest plot displays random-effects meta-analysis results of the association between neutrophil-to-lymphocyte ratio (NLR) and Parkinson's disease (PD). The overall standard mean difference between groups and its 95% confidence interval are represented by the black diamond. [Color figure can be viewed at wileyonlinelibrary.com]

A subgroup analysis based on the study design (retrospective or prospective review of clinical records) did not identify heterogeneity ($I^2 = 80\%$, $P = 0.94$). Meta-regression analyses did not identify heterogeneity among studies according to the year of publication, age, or sex of PD patients.

Detailed meta-analyses can be found in Figures S1–S4, Tables S1 and S2.

Discussion

PD patients had a lower absolute number of lymphocytes and showed a trend towards a higher neutrophil count compared with HCs. More importantly, PD patients had a significantly higher NLR in peripheral blood compared with HCs, regardless of disease severity or disease duration. A higher NLR in PD patients was supported by the meta-analysis performed.

The decreased absolute lymphocyte count in PD patients found in our study is consistent with the data reported in the literature.[2,3] Based on previous studies, this finding could indicate a loss of the protective immune function of lymphocytes in PD.[2,31] Conversely, neutrophils are protagonists in chronic inflammation. We found a trend towards an increased absolute neutrophil count in PD, which is in line with other studies.[21,22,27,32,33]

In our cohort, the NLR was significantly higher in PD patients compared with HCs, which supported the premise that peripheral immune dysregulation was present in PD patients. Within the PD group, we did not find differences in the NLR according to the disease severity based on the HY stage. Other studies have also found no association between the NLR and the Unified Parkinson's Disease Rating Scale (UPDRS) score[23,24] or the PD motor subtype.[22,24] In our study, the NLR was not related to the disease duration either, which is in line with previous reports.[22-24] In contrast to the negative results exposed above, only Solmaz et al[27] found a weak positive correlation between the NLR, HY stage, and disease duration. Unlike other groups,[25,26] we found no differences in the NLR according to the age at onset of PD patients. It has been previously suggested that the immune factor could be more predominant in LOPD compared with EOPD, but further investigations are needed.

Finally, the meta-analysis performed confirmed that the NLR was higher in the PD patients. The small size of most of the studies included (<120 individuals) could have limited the statistical power to achieve significant differences, underestimating the overall ES. It is noteworthy that our case–control study included the largest sample size published to date (n = 732), followed by Sanjari et al (n = 536), and both studies indicated that the NLR was significantly higher in PD patients. The "leave-one-out" sensitivity analysis supported the strength and robustness of this meta-analysis.

The substantial heterogeneity observed among all the included studies could not be clarified. Dopaminergic treatment of PD patients should be considered since dopaminergic receptors are expressed in immune cells.[34,35] In our study, we observed an association between LEDD and both lymphocytes and the NLR. Given that most of the PD patients included in this meta-analysis were on dopaminergic treatment, it could have affected the NLR value. It is worth mentioning that the NLR has been evaluated in two studies involving drug-naive PD patients, and both reported a higher NLR in PD patients suggesting that this alteration was independent of LEDD.[24,27]

The findings of our study indicate that the NLR is higher in PD patients, regardless of the disease severity, the age at onset, or duration of the disease. In contrast to the NLR, other inflammatory biomarkers (such as cytokines) have been linked to motor disease severity.[8,28,36] However, studies that correlate the NLR with other inflammatory biomarkers are lacking to date. According to our results, the NLR is probably a good indicator of the overall peripheral immune dysregulation and inflammatory status in PD, but it might not be sensible enough to disentangle the complex underlying immune mechanisms involved in PD pathogenesis. So, whether the alteration in the NLR is a cause or a consequence in the progression of PD is still unclear.

Even so, the NLR might represent a potential noninvasive diagnosis biomarker in PD. Although further investigations are also needed to study the role of the NLR in the physiopathology and in the differential diagnosis among atypical parkinsonisms, the NLR could be integrated with other clinical, biological, and imaging sources of information into a diagnostic decision support system in PD.[21,27,29,37]

The main limitation of our study was its retrospective nature. However, we applied rigorous exclusion criteria and we performed statistical analyses with multivariate adjustment to avoid confounding factors. Other inflammatory markers were not available to support systemic inflammation and we could not perform a longitudinal analysis.

In conclusion, our work indicated a more proinflammatory peripheral immune profile in PD patients compared with HCs. A higher NLR was found in PD patients, regardless of disease severity or disease duration. Moreover, PD patients had a lower lymphocyte count, without differences in the absolute leukocytes count. These findings could support the role of chronic inflammation and immune dysregulation in the pathogenesis of PD, and the integration of the NLR as a potential biomarker in PD. Further studies in specific subgroups of PD as well as prospective studies are needed to clarify the role of peripheral inflammation in the pathogenesis of the disease.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.