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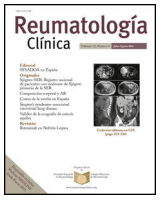

Brief Report

Association of hematological indices, disease activity, and organ damage in systemic lupus erythematosus: A multicenter analysis of 319 cases

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a variable course. There is a need for simple and accessible biomarkers to assess disease activity and prognosis.
Objectives: To analyze the relationship between hematological indices NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio) with disease activity and organ damage in patients with SLE.
Materials and methods: A multicenter retrospective study including 319 patients with SLE. Associations between NLR and PLR with disease activity (SLEDAI-2K), organ damage (SLICC/SDI), hypocomplementemia, mortality, and clinical manifestations were evaluated.
Results: Both indices showed a significant association with disease activity, even after adjusting for confounding factors. No associations were found with organ damage or specific clinical manifestations. NLR was associated with hypocomplementemia, and both indices were linked to mortality.
Conclusions: NLR and PLR may serve as useful, low-cost, and complementary tools for monitoring disease activity in SLE. Prospective studies are needed to confirm their value as independent biomarkers.

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Asociación de índices hematológicos, actividad y daño orgánico en el lupus eritematoso sistémico: análisis multicéntrico de 319 casos

Palabras clave:
Lupus eritematoso sistémico
Ratio neutrófilo-linfocito
Ratio plaqueta-linfocito

RESUMEN

Introducción: El lupus eritematoso sistémico (LES) es una enfermedad autoinmune sistémica con un curso variable. Es necesario contar con biomarcadores simples y accesibles para evaluar su actividad y pronóstico.
Objetivos: Analizar la relación entre los índices hematológicos RNL (ratio neutrófilo-linfocito) y RPL (ratio plaqueta-linfocito) con la actividad y el daño en pacientes con LES.
Material y métodos: Estudio retrospectivo multicéntrico de 319 pacientes con LES. Se evaluó la asociación de RNL y RPL con la actividad (SLEDAI-2K), el daño orgánico (SLICC/SDI), la hipocomplementemia, la mortalidad y manifestaciones clínicas.
Resultados: Ambos índices se asociaron significativamente con la actividad de la enfermedad, incluso tras ajustar por factores de confusión. No se observaron asociaciones con el daño orgánico ni con manifestaciones clínicas específicas. RNL se relacionó con hipocomplementemia, y ambos índices con la mortalidad.

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Conclusiones: RNL y RPL podrían ser herramientas útiles, económicas y complementarias para el seguimiento de la actividad en el LES. Se requieren estudios prospectivos para confirmar su valor como biomarcadores.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease that can affect multiple organs to varying degrees of severity.[1] In recent years, biomarkers such as antibodies against complement C1q, interferon alpha, and B-cell stimulatory factor, as well as its family of ligands and receptors, have been proposed as markers of disease activity and organ damage.[2,3] However, a lack of clinical validation, coupled with the high processing and analysis costs associated with determining them, represents a significant barrier to their introduction into routine practice.

Haematological indices, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), have been suggested as useful indicators of disease activity in various autoimmune and autoinflammatory conditions. Specifically, these indices have been found to be significantly higher in patients with SLE than in healthy controls.[4,5]

Several studies have demonstrated the key role played by neutrophils, lymphocytes, and platelets in the pathophysiology of SLE. However, increases in NLR and PLR indices do not necessarily indicate an absolute increase in neutrophils or platelets, since neutropenia and thrombocytopenia are prevalent among these patients. These alterations are associated with immunological mechanisms, infections, splenomegaly, or the effects of immunosuppressive therapies. Conversely, lymphopenia, affecting up to 75% of patients, can be attributed to autoantibodies targeting lymphocytes, directly influencing these indices.[6]

Although elevated NLR and PLR indices have been observed in patients with SLE,[7] more comprehensive research is needed to evaluate their diagnostic accuracy in relation to the presence and severity of the disease. This research should also assess their usefulness in identifying specific organ involvement and prognosis, particularly in Caucasian populations. Furthermore, many existing studies do not adequately control for confounding factors, such as the use of immunosuppressive therapies.

Objectives

The primary objective was to evaluate the relationship between NLR and PLR in relation to disease activity, as measured by SLEDAI-2K, and organ damage, as measured by SLICC/SDI. The secondary objectives were to estimate the relationship between these indices and different clinical manifestations and mortality in SLE.

Material and methods

A retrospective multicentre study involving 319 patients with systemic lupus erythematosus (SLE) was conducted. All patients met at least four of the 1997 American College of Rheumatology (ACR) classification criteria.[8] All patients were over 18 years of age and had been diagnosed by a rheumatologist. They were also regularly monitored in a rheumatology outpatient clinic. The study complied with the principles established in the Declaration of Helsinki. The study protocol was approved by the Ethics Committees at the Insular University Hospital of Gran Canaria, the University Hospital of the Canary Islands (Tenerife) and the Dr Negrín University Hospital of Gran Canaria.

Table 1
Demographic and clinical characteristics of the cohort.

Demography	
Sex (female)	292 (91.5)
Age at diagnosis (years)	37.4 (±13.5)
Duration of disease (years)	11 (12)
Laboratory (at time of the study)	
Neutrophils ($\times 10^3$)	2.9 (1.8)
Lymphocytes ($\times 10^3$)	1.6 (1)
Platelets ($\times 10^3$)	232.1 (±75)
Neutrophil-lymphocyte ratio	1.8 (1.42)
Platelet-lymphocyte ratio	143.6 (109.8)
Hypocomplementaemia	89 (30.7)
Positive anti-DNA	122 (43.4)
Clinical manifestations associated with SLE	
Cutaneous	200 (63.1)
Musculoskeletal	203 (64.2)
Renal	67 (21.1)
Neuropsychiatric	17 (5.4)
Gastrointestinal	11 (3.5)
Serositis	29 (10)
Haematological	102 (32.2)
Antiphospholipid syndrome	30 (15.9)
Dry syndrome	63 (19.9)
SLEDAI-2K (at time of study)	2.1 (±2.52)
Organ damage (at time of study)	173 (54.2)
Immunosuppressive therapy (at the time of the study)	
Hydroxychloroquine or chloroquine	250 (78.4)
Prednisone	87 (27.3)
Immunosuppressants (conventional and/or biological)	147 (46.1)
Cyclophosphamide[a]	27 (8.5)
Mortality	6 (2.8)

SLE: systemic lupus erythematosus.
Continuous variables: means and standard deviation are calculated for variables with normal distribution. Medians and interquartile range if they do not follow normal distribution. Categorical variables: n and percentages (%).
[a] Cyclophosphamide at any time during the course of the disease.

Demographic data, disease characteristics, activity (SLEDAI-2K), damage (SLICC/SDI), and therapy were collected. Table 1 shows the demographic and clinical characteristics of the patients. Table 2 shows the different correlations of NLR and PLR with disease damage and activity.

Descriptive statistics were calculated for quantitative and qualitative variables. Normality was assessed using the Kolmogorov-Smirnov test. Depending on the type of variable, Pearson's correlation and Wilcoxon's rank sum tests were applied. Multivariate logistic and linear regression analyses were performed to explore the association between clinical and demographic characteristics and the presence of damage (SLICC/SDI) and disease activity (SLEDAI-2K). A p-value of <.05 was considered statistically significant. The analysis was performed using STATA® MP v17.0.

Results

Of the 319 patients with lupus, 91.5% were female and had a mean age at diagnosis of 37 ± 13.5 years. Demographic, clinical, laboratory, and therapy data are summarised in Table 1.

Significant correlations were found between NLR and SLEDAI-2K-measured disease activity (p = .009), and between PLR and SLEDAI-2K (p = .032). Similarly, lymphocyte count showed a corre-

Table 2
Relationship between haematological indices and activity and damage.

		p-value
Relationship between haematological indices and disease activity and damage		
NLR with SLEDAI-2K	r = .14	.009
PLR with SLEDAI-2K	r = .13	.032
NLR with SLICC/SDI	z = –.58	.113
PLR with SLICC/SDI	z = –.96	.337
Relationship between white blood cell count and platelets with activity and damage		
Neutrophil with SLEDAI-2K	r = –.004	.947
Lymphocyte with SLEDAI-2K	r = –.19	.001
Platelet with SLEDAI-2K	r = –.05	.350
Neutrophil with SLICC/SDI	z = –.37	.712
Lymphocyte with SLICC/SDI	z = 1.37	.171
Platelet with SLICC/SDI	z = –.89	.373
Relationship between haematological indices and morbidity and mortality		
NLR with mortality	z = –2.93	.033
PLR with mortality	z = –2.15	.028
Correlation of haematological indices with serological activity		
NLR with hypocomplementaemia	z = –3.13	.002
PLR with hypocomplementaemia	z = –1.13	.260
NLR anti-DNA antibody	z = –.75	.453
PLR anti-DNA antibody	z = –1.32	.186

r: Spearman's correlation coefficient; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index;
SLICC/SDI: Systemic Lupus International Collaborating Clinics/Damage Index; z: Mann–Whitney U test.

Table 2.1
Association of NLR and PLR with activity measured by SLEDAI-2K.

	β coef. (95% CI)	p-values
Association NLR/SLEDAI-2K		
NLR	.11 (–.01–.21)	.037
Prednisone	1.26 (–.64–1.88)	<.001
IS therapy	–.44 (–.99–.1)	.108
Association PLR/SLEDAI-2K		
PLR	.003 (.001–.01)	.017
Prednisone	1.4 (.77–2.04)	<.001
IS therapy	–.38 (–.95–.18)	.185

95% CI: 95% confidence interval; IS: immunosuppressive; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

lation with SLEDAI-2K (p = .001). No significant associations were observed between NLR and PLR and the presence of organ damage (Table 2).

With regard to serological activity, NLR was associated with hypocomplementaemia (p = .002), but not with anti-DNA antibody positivity (Table 2). Similarly, no relationships were detected between haematological indices and the different clinical manifestations of SLE at diagnosis. A trend towards statistical significance was observed between PLR and the presence of antiphospholipid syndrome (p = .073), though no association was found with the different antiphospholipid antibodies.

Finally, both NLR and PLR were associated with mortality (p = .033 and p = .028, respectively) (Table 2).

In the multivariate analysis, which was adjusted for possible confounding factors, the ratios maintained their association with disease activity according to the SLEDAI-2K, but showed no relationship with organ damage (Tables 2.1).

Discussion

In this multicentre study of 319 patients with SLE, we observed that both the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) correlate significantly with clinical disease activity, as measured by the SLEDAI-2K. Furthermore, the association of absolute lymphocyte count with disease activity suggests that lymphopenia remains a relevant marker of this autoimmune disease. These results are consistent with findings from other cohorts,[9–11] as well as meta-analyses,[5,7] and could support the use of haematological indices as an accessible, inexpensive way of assessing SLE activity in clinical practice.

Han et al.[12] demonstrated that patients with SLE have higher NLR than healthy patients, and that this ratio is associated with disease activity, as measured by SLEDAI-2K. Similarly, these authors identified an elevated NLR cut-off point of 2.73; however, these results have not been validated in prospective studies. Cho et al.[13] conducted a prospective study of 290 patients with SLE and found that both NLR and PLR were associated with disease activity. In particular, NLR was related to the Systemic Lupus Erythematosus Flare Index (SFI) and to severe flare-ups, with a sensitivity of 59% and specificity of 85%.

PLR has also been associated with SLE disease activity, although less robustly. Liu et al.[14] found an association between PLR and lupus nephritis compared to a group of healthy controls. In another study, PLR was only related to anti-dsDNA antibodies, but not to serum urea, serum creatinine, or 24-h urinary protein.[11] In our study, NLR was correlated with hypocomplementaemia but not with anti-DNA antibody positivity. This suggests that NLR captures general inflammatory aspects while autoantibodies have a more complex dynamic.

Regarding the presence of organ damage, our study found no significant associations with the NLR and PLR indices. This result contradicts that of other studies. For example, Suszek et al.[10] included 136 patients with SLE who were treated with hydroxychloroquine and glucocorticoids. They found a relationship between the presence of mucocutaneous, joint, haematological, and renal damage, and NLR and PLR. The absence of a significant relationship with organ damage in our cohort can be explained by the fact that most patients either did not present damage or had low SLICC/SDI values. Similarly, it was demonstrated that NLR and PLR primarily reflect active inflammation rather than irreversible tissue damage. However, it is important to highlight the association observed between both indices and mortality in our study. Nevertheless, the results should be interpreted with caution due to the small sample size.

Although most observations support the potential clinical application of NLR and PLR, controversies remain regarding their diagnostic and prognostic value. A significant limitation is the small number of studies conducted in Europe and America, which restricts the generalisation of these findings — especially given the reported ethnic differences in NLR values in populations without autoimmune diseases.[15] Furthermore, most studies are retrospective and do not adequately adjust for common confounding factors in patients with SLE, such as cardiovascular comorbidities, infections, or immunosuppressive therapies.

Conclusion

Our findings suggest that NLR and PLR indices could be useful tools in assessing SLE activity. Multivariate analysis adjusted for confounding factors reaffirmed the relationship with disease activity, but not with organ damage. However, their applicability in clinical practice still needs to be confirmed by prospective studies analysing their value as independent serological biomarkers, considering the multiple factors that can modify their behaviour. In this regard, future studies should explore in greater depth how changes in neutrophil, platelet, and lymphocyte counts—and their respective proportions—are related to functional alterations in these cells, particularly in patients with different levels of activity, organ damage, and disease progression.

Declaration of competing interest

The authors have no conflict of interests to declare.

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