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ORIGINAL

Hematological ratios as markers of lupus activity in Paraguayan patients with systemic lupus erythematosus.

Ratios hematológicos como marcadores de la actividad del lupus en pacientes paraguayos con lupus eritematoso sistémico.

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Conflicts of interests
The authors declare that there is no conflict of interest.

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ABSTRACT

Introduction: The neutrophil/lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR) are markers of inflammation and prognosis in systemic diseases. This study determined the association between hematological indices, and disease activity in patients with systemic lupus erythematosus (SLE). **Methods:** This prospective, observational and analytical cross-sectional study included 87 Paraguayan patients diagnosed with SLE, according to the ACR/EULAR 2019 criteria. We investigate four hematological indices: neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), eosinophil/lymphocyte ratio (ELR), and monocytes/lymphocyte ratio (MLR). **Results:** Eighty-seven percent were female, with a median age of 34.9 ±12.3 years. SLEDAI mean of 3.68 ± 4.76 was found. SLEDAI mean was 3.68 ± 4.76. Positivity of anti-DNAds was found in 52% of the patients. CRP mean was 3.5 ± 4.6. Regarding values of hematological indices, we found: NLR mean of 2.4 ± 1.6 was obtained, ELR 0.07 ± 0.09, MRL 0.07 ± 0.07 and PLR 155.89 ± 80.69. A significant positive correlation was found with SLEDAI and NLR (r=0.34, p=0.001). Based on the ROC curve, the best cut-off value for our patient cohort capable of predicting patients with high activity is for NLR values ≥ 2.283 (AUC: 0.66). **Conclusion:** NLR could be a valuable and accessible biomarker to identify elevated activity in patients with SLE.

Keywords: Systemic lupus erythematosus; Neutrophil/lymphocyte ratio; Platelet/lymphocyte ratio; Eosinophil/lymphocyte ratio; Monocyte/Lymphocyte ratio.

RESUMEN

Introducción: La relación neutrófilos/linfocitos (NLR) y la relación plaquetas/linfocitos (PLR) son marcadores de inflamación y pronóstico en enfermedades sistémicas. Este estudio determinó la asociación entre los índices hematológicos y la actividad de la enfermedad en pacientes con lupus eritematoso sistémico (LES). **Métodos:** Este estudio transversal prospectivo, observacional y analítico incluyó a 87 pacientes paraguayos diagnosticados con LES, según los criterios ACR/EULAR 2019. Investigamos cuatro índices hematológicos: la relación neutrófilos/linfocitos (NLR), la relación plaquetas/linfocitos (PLR), la relación eosinófilos/linfocitos (ELR) y la relación monocitos/linfocitos (MLR). **Resultados:** El 87% eran mujeres, con una edad media de 34,9 ± 12,3 años. Se encontró una media del SLEDAI de 3,68 ± 4,76. El 52% de los pacientes presentaron positividad para anti-DNA de doble cadena. La media de la PCR fue de 3,5 ± 4,6. En cuanto a los valores de los índices hematológicos, se encontraron los siguientes promedios: NLR de 2,4 ± 1,6, ELR 0,07 ± 0,09, MRL 0,07 ± 0,07 y PLR 155,89 ± 80,69. Se encontró una correlación positiva significativa entre el SLEDAI y el NLR (r=0,34, p=0,001). Según la curva ROC, el mejor valor de corte para predecir pacientes con alta actividad fue para NLR ≥ 2,283 (AUC: 0,66). **Conclusión:** El NLR podría ser un biomarcador valioso y accesible para identificar la actividad elevada en pacientes con LES.

Palabras clave: Lupus eritematoso sistémico (LES); Relación neutrófilos/linfocitos (NLR); Relación plaquetas/linfocitos (PLR); Relación eosinófilos/linfocitos (ELR); Relación monocitos/linfocitos (MLR).

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INTRODUCTION

Since the discovery of the granulopoiesis signature in lupus, some hematological indices have been studied as markers of inflammation and prognosis. Hematological manifestations are common in systemic lupus erythematosus (SLE). Leukopenia occurs in 50-60% of SLE cases (1), and lymphopenia and neutropenia are common in SLE (2-3). Lymphopenia of less than 1500 cells/ml is the most prevalent initial laboratory abnormality in SLE, occurring more frequently than any of the preliminary criteria for its classification (4).

Hematological indices have gained importance in the study of various diseases including systemic autoimmune diseases. The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have been used as markers of inflammation and prognosis in several systemic diseases such as cardiovascular diseases, diabetes mellitus, cancer, and autoimmune diseases (5-8).

Some studies have suggested that these ratios may constitute possible inflammatory biomarkers in SLE (9-15). A meta-analysis by Wang et al. (11), NLR is significantly higher in patients with SLE than in healthy controls with a mean of 1.43 (95% CI, 0.98–1.88). A meta-analysis by Ma et al. (13), PLR was significantly higher in patients with SLE than in healthy controls, with a mean of 0.709 (95% CI, 0.58–0.838). The eosinophil/lymphocyte ratio (ELR) is also positively correlated with SLEDAI (10). In this study, we determined the association between hematological indices and other markers of inflammation and disease activity in patients with SLE.

METHODS

Prospective, observational, analytical, and cross-sectional studies included patients diagnosed with SLE according to the ACR/EULAR 2019 criteria from the Department of Rheumatology of the Hospital de Clínicas, National University of Asunción. The control group consisted of healthy individuals with no history of autoimmune pathology or current infections. This study was approved by the local ethics committee.

This study was conducted between March 2018 and December 2019. A clinical and sociodemographic questionnaire, laboratory studies including blood count, C-reactive protein (CRP), high-sensitivity C-reactive protein (hs-CRP), anti-DNAds, erythrocyte sedimentation rate (ESR), and SLEDAI measurements were performed. In our study, we grouped the patients according to their SLEDAI values into Group 1 (low activity): ≤5 points and Group 2 (moderate and high activity): ≥6 points (16). The neutrophil/lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The platelet/lymphocyte ratio (PLR) was calculated as the absolute platelet count divided by the absolute lymphocyte count. The eosinophil/lymphocyte ratio (ELR) was calculated as the absolute eosinophil count divided by the absolute number of lymphocytes. The monocyte/lymphocyte ratio (MLR) was calculated by dividing the absolute monocyte count by the absolute number of lymphocytes (5-10).

For quantitative variables, the mean and standard deviation were calculated. A non-parametric test (Mann–Whitney U test) was performed to compare the values of the variables of the control group with those of the SLE group. The resulting P-value is provided. For qualitative variables, Fisher's exact test was performed to compare the distributions of the control group with those of the SLE group (both global and individual). The resulting P-value is provided. Correlation analysis was performed between quantitative variables, and the correlations between the set of hematological variables and activity were analyzed. Spearman's correlation coefficient (non-parametric) was analyzed for each group. ROC curve analysis was performed to determine the sensitivity and specificity of NLR in predicting high SLEDAI scores. Statistical significance was defined as $p<0.05$. The R (4.1.2) software was used for statistical analysis.

RESULTS

Eighty-seven patients diagnosed with SLE were included, of whom 85 % were female, with a median age of 34.9 ±12.3 years. Regarding the SLEDAI, a median of 3.7 ± 4.7 was found. Group 1 (low SLEDAI activity) included 68 patients (78%), and Group 2 (moderate and high activity) included 19 patients (21.8%) (Figure 1).

The control group consisted of 54 people, mostly women (87%), with a median age of 45.2 ±15.

Fifty-two percent of the patients had positive anti-DNA antibodies, and the median hs-CRP level was 3.5 ± 4.6. Regarding NLR, a median value of 2.4 ± 1.6 was obtained, ELR with a median value of 0.07 ± 0.09, MLR 0.07± 0.07 and PLR 155.89 ± 80.69 (Table 1).

FIGURE 1. SLEDAI IN PATIENTS WITH SLE INCLUDED IN THE STUDY (N=87).

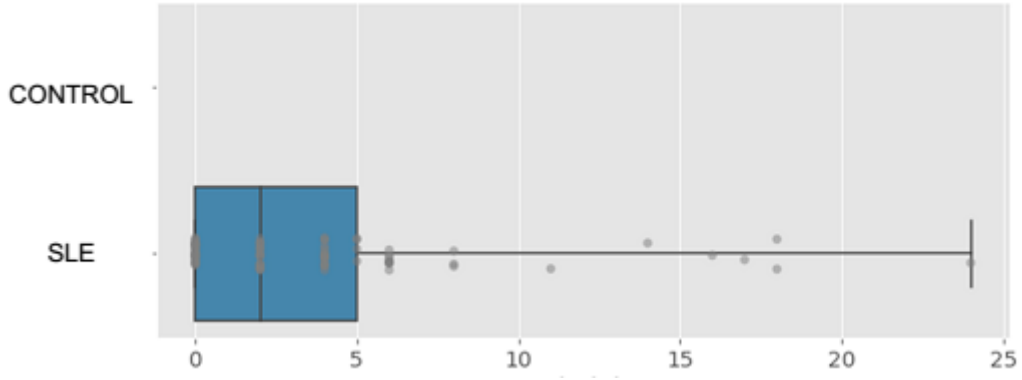

TABLE 1. CHARACTERISTICS OF PATIENTS WITH SLE AND CONTROL (N=87).

VARIABLES	N	SLE PATIENTS	N	CONTROL	P
Age	87	34.9 (±12.3)	54	45.2 (±15.8)	<0.001
Gender	87	M: 13 (14.94 %) F: 74 (85%)	54	M: 7 (13%) F: 47 (87%)	0.80
Leukocytes	87	5990.8 ± 1916.3	54	7109.3 ± 4861.3	0.04
Neutrophils	87	3909.6 ± 1676.0	54	4080.1 ± 2540.0	<0.001
Lymphocytes	87	1845.4 ± 698.5	54	2581.2 ± 1991.9	<0.001
Monocytes	87	119.4 ± 106.9	54	269.5 ± 295.1	0.04
Eosinophils	87	116.4 ± 123.25	54	178.5 ± 236.5	0.99
Platelets	87	245597.7 ± 65690.2	54	238092.6 ± 41042.2	0.003
NLR	87	2.5 ± 1.6	54	1.7 ± 0.6	0.0038
MLR	87	0.05 (0.02-0.11)	54	0.08 (0.05-0.14)	0.0033
ELR	87	0.05 (0.00-0.08)	54	0.06 (0.03-0.10)	0.22
PLR	87	155.9 ± 80.7	54	109.7 ± 39.3	<0.001
ANA	87	100%			
anti-DNAds	85	Positive: 45 (52%) Negative: 40 (46%)			
SLEDAI	87	3.7 ± 4.7			
Hs-CRP	87	3.5 ± 4.6	54	2.5 ± 3	0.65
Quantitative CRP	54	9.9 ± 9.5	54	7.4 ± 6,9	0,26
ESR	54	33.7 ± 23.2	54	25.1 ± 19.4	0.01

An association was found between SLE patients and a higher NLR compared to the control group, with a median of 2.49 ± 1.63 (p=0.003); also with the PLR, with a median of 155.89 ±80.69 (p=0.0002), MLR with a median of 0.07 ± 0.07 (p=0.003), and the ESR rate in the 1st hour, with a median of 33.7 ± 23.25 (p=0.012) (Table 2).

When correlating the hematological ratios with the values of SLEDAI, CRP, hs-CRP, and ESR, a significant positive correlation was observed between the NLR values (r= 0.344, p=0.001) and SLEDAI, NLR (r=0.337, P=0.002), and PLR (r=0.422, p=0.001) regarding ESR in the 1st hour (Figure 2).

Based on the ROC curve (Figure 3 and Table 3), the best cut-off value for our patient cohort, Lupus-Paraguay (PY), capable of predicting patients with high activity is NLR values ≥ 2.283, with a sensitivity of 57.9% and specificity of 67.6% (AUC:0.66).

TABLE 2. HEMATOLOGICAL INDICES AND ACUTE PHASE REACTANTS IN PATIENTS WITH SLE and CONTROLS.

		POPULATION	MEAN (STD)	MEDIAN (IQR)	MIN/MAX	NORMALITY P	P-VALUE
N/L	**Control**	54 (100%)	1.7 (0.6)	1.6 (1.3-2.2)	0.6/3.2	0.180013	
	SLE	87 (100%)	2.5 (1.6)	2.0 (1.5-2.9)	0.5/9.0	0.0	0.004
M/L	**Control**	54 (100%)	0.1 (0.1)	0.1 (0.1-0.1)	0.0/0.4	<0.001	
	SLE	87 (100%)	0.1 (0.1)	0.1 (0.1-0.1)	0.0/0.3	0.0	0.003
E/L	**Control**	54 (100%)	0.1 (0.1)	0.1 (0.1-0.1)	0.0/0.2	0.004132	
	SLE	87 (100%)	0.1 (0.1)	0.1 (0.1-0.1)	0.0/0.4	0.0	0.224
P/L	**Control**	54 (100%)	109.7 (39.3)	104.4 (85.8-123.5)	12.6/281.5	0.0	
	SLE	87 (100%)	155.9 (80.7)	136.1 (97.0-177.9)	63.7/520.0	0.0	<0.001

FIGURE 2. HEAT MAP OF THE CORRELATION BETWEEN THE HEMATOLOGICALMETRIC INDICES, SLEDAI, AND ACUTE PHASE REACTANTS IN PATIENTS WITH SLE (A) AND IN CONTROLS (B) (N=87)

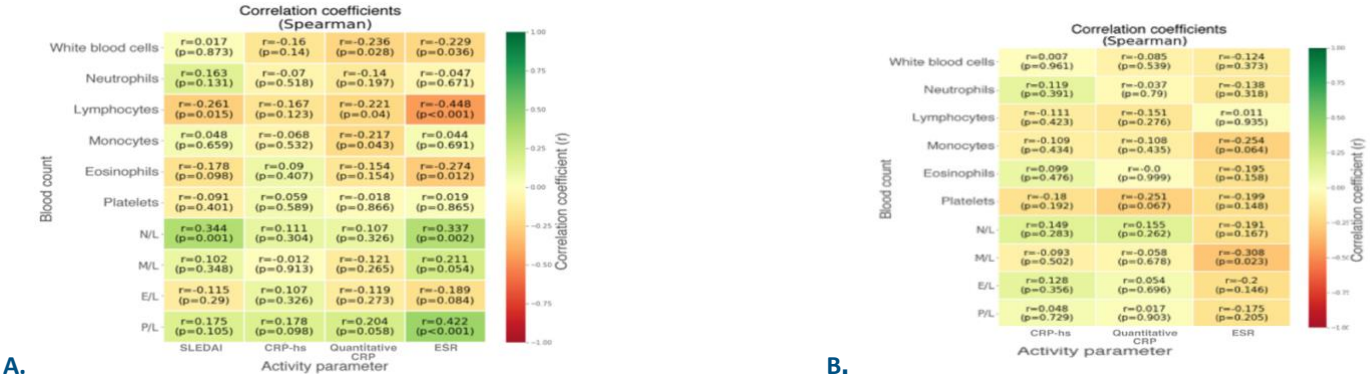

FIGURE 3. ROC CURVE FOR NLR, PLR AND SLEDAI (≥6). (N=87)

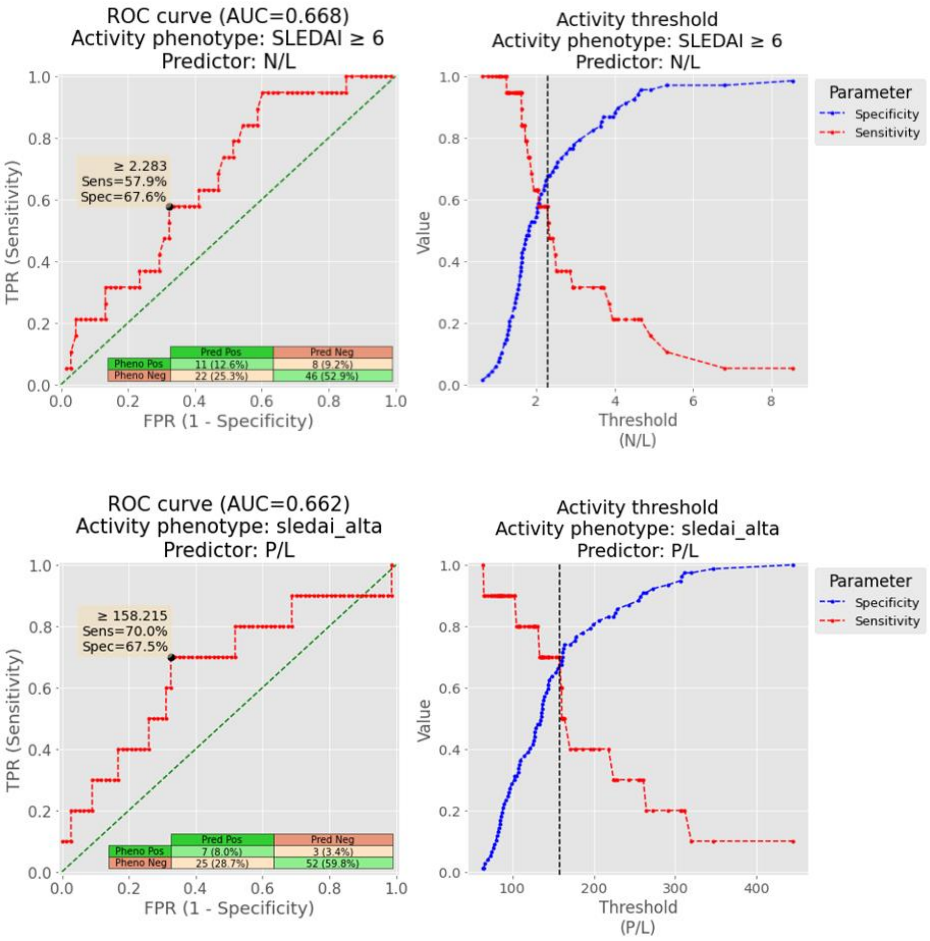

TABLE 3. SPECIFICITY AND SENSITIVITY OF DIFFERENT PARAMETERS IN RELATION TO SLEDAI ≥6 (MODERATE AND HIGH ACTIVITY) (N=87).

PARAMETER	DIRECTION	AUC	POSITIVE CONDITION	SENSITIVITY	SPECIFICITY
NLR	Positive	0.66	≥ 2.283	57.9	67.6
MLR	Positive	0.632	≥ 0.055	68.4	57.4
ELR	Negative	0.611	≤ 0.01	52.6	75.0
PLR	Positive	0.540	≥ 158.2	47.4	66.2

DISCUSSION

In this study, we found that NLR was elevated in patients with SLE. NLR was significantly positively correlated with SLEDAI score, and both NLR and PLR were positively correlated with ESR. Neutrophils, lymphocytes, monocytes, eosinophils, and platelets play essential roles in the pathophysiology of inflammation (17). NLR, ELR, and PLR have been used along with other biomarkers to estimate the inflammatory activity of numerous rheumatic diseases (13-15). Several studies have demonstrated a connection between NLR and SLE activity in different groups of patients (9-13), in relation to SLEDAI, ESR, CRP, hs-CRP, and complement. In this study, we found a relationship between the SLEDAI and hs-CRP levels.

Firizal et al. (18), in a study of 112 patients with SLE, ROC analysis showed that the optimal cutoff point for NLR was 2.94 with a sensitivity and specificity of 60.71% and 76.79%, respectively. Both in the value of the cut-off point and, in the sensitivity, the results match with our work, but not in the specificity where the value found by them was significantly higher than ours. In the same way, the NLR, showed a correlation with SLE activity in different studies (9,13,14,19).

Qin et al. (9) reported that the PLR level was found to be relatively higher in SLE patients with nephritis compared to those without nephritis. This finding supports the notion that PLR can reflect disease activity in patients with SLE. Similarly, in this study, we found an association between PLR, SLEDAI, and hs-CRP. Interestingly, this relationship between NLR and PLR and inflammation in systemic autoimmune diseases is apparently not affected by differences in patient age, since this same relationship was found in juvenile SLE (20).

Regarding ELR, a positive correlation was found, but this was not statistically significant, unlike in other studies (10,21). The present study has several limitations. First, the sample size is small. Second, the relationship between the NLR and organ-specific inflammation was not analyzed. Third, the influence of disease treatment on these index values has not been studied. In conclusion, NLR is a useful and accessible biomarker for identifying elevated activity in SLE patients in the Lupus-PY cohort. This finding indicates that, like well-known and easily measurable laboratory parameters, the NLR may reflect the inflammatory response in patients with SLE. Further studies are needed to determine the associations between these hematologic indices in other populations with SLE.

AUTHORS CONTRIBUTIONS

ZM: analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript and approval of its final version. RA, AP: conception and design of the work, collection and obtaining results. PdeA, OAC, MTMF: conception and design of the work, collection and acquisition of results, analysis and interpretation of data. SCV, GAP, MEA: conception and design of the work, collection of results, critical revision of the manuscript and approval of its final version. YFSilva: drafting of the manuscript, critical revision of the manuscript and approval of its final version. IAC: conception and design of the work, collection and obtaining results, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript and approval of its final version.

DATA AVAILABILITY

Data are available upon request to the corresponding author.

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