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Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratios and Their Relation with Disease Activity in Systemic Lupus Erythematosus Patients

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ABSTRACT

Background: systemic lupus erythematosus (SLE) is a chronic disease which had diverse clinical manifestations, course and prognosis. Search for diagnostic markers is continuous process to enhance the diagnostic and treatment process.

Aim of the study: this study aimed to investigate correlation between both of neutrophil/lymphocyte and platelet/lymphocyte ratios and disease activity in SLE patients who did not receive any treatment.

Patients and Methods: a case control study involving 60 adult SLE patients and 40healthy controls was performed. NLR and PLR levels between SLE patients and healthy controls were compared, and correlations between these indices and clinical characteristics were analyzed.

Results: increased NLR and PLR were observed in SLE patients. NLR was positively correlated with erythrocyte sedimentation rate (ESR) ($r=0.621$, $p<0.001$) ,SLEDAI scores($r=0.\ 0.774$, $p<0.001$) and SLICC score($r=0.638$, $p<0.001$). PLR was positively correlated with with erythrocyte sedimentation rate (ESR) ($r=0.500$, $p<0.001$),SLEDAI scores($r=0.445$, $p<0.001$). and SLICC score($r=0.377$, $p<0.001$) SLE patients with nephritis had higher NLR and PLR levels than those without nephritis ($p<0.001$).

Conclusion: NLR and PLR could reflect inflammatory response and disease activity and disease damage in SLE patients.

Keywords: Neutrophil/lymphocyte, platelet/lymphocyte, systemic Lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with features of autoantibody production, immune complex deposition and multiple target organ damage. The disease can affect any part of the body and the course of the disease is diverse and unpredictable. In SLE, organs and cells undergo damage initially mediated by tissue-binding autoantibodies and immune complexes. In most patients, autoantibodies are present for a few years before the first clinical symptom appeared [(1)]. Many clinical and laboratory methods can be used to assess the disease activity.

The laboratory indicators of disease activity are increased as deoxyribonucleotide (DNA) binding, low complement, leukopenia and thrombocytopenia. The problem is how to evaluate disease activity with simple laboratory indicators that is available in almost every health care facility. White blood cell and its differential count can be done as part of routine investigations [(2)]. The circulating white blood cell (WBC) classification undergoes relative changes in systemic inflammation, typically represented by lymphopenia and neutrophilia. WBC and subtype counts have been identified as biomarkers of inflammation, neutrophil/ lymphocyte ratio (NLR) is a marker of subclinical inflammation and has been used in combination with other inflammatory markers to determine inflammation in both auto- and non-autoimmune diseases[(3)]. Previous studies have shown that Neutrophil/lymphocyte ratio (NLR) is a good indicator of inflammation [(4)]. Platelet/lymphocyte ratio (PLR) is also an inflammatory index in routine blood test. PLR change may be associated with inflammation and cytokines levels [(5)]. NLR and PLR can be calculated easily and less costly as compared with detection of other inflammatory cytokines that could be used as biomarkers for inflammatory response or disease activity in SLE patients[(6)].

PATIENTS AND METHODS

Patients: that is a case control study included 60 SLE patients fulfilling diagnosis according to Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE **,**none of them received any treatment either newly diagnosed SLE patients or non-compliant on treatment **.**It had been conducted on SLE patients attending the Rheumatology Outpatient Clinic or admitted to Internal Medicine and Rheumatology Department at Ain Shams University Hospitals. This study consisted of 52 female patients (86.67%) and 8 males with age ranged from 14 to

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53 years with a mean of 25.217 ±8.70440 age and sex matched apparently healthy individuals.

Inclusion criteria

Sixty SLE patients, none of them received any treatment either newly diagnosed SLE patients or non-compliant on treatment.

Exclusion criteria

1. Patients with other autoimmune disease.
2. Patients with malignant diseases.
3. Patients using medical treatment affecting the WBC count.
4. Patients with evidence of any concomitant inflammatory disease. Acute infection or chronic inflammation status.
5. Patients with hematological disease.

Data Processing: the patients were subjected to the following:

Full medical history: with special emphasis on age, sex, disease duration, SLE symptoms,Full clinical examination,Assessment of disease activity by the SLE Disease Activity Index 2000 (SLEDAI) system[7]. Damage index (SLICC/ACRDI) [8] and laboratory investigations including Complete blood picture with differential white blood cell cout With estimation of both Neutrophile to lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR) ,Erythrocyte sedimentation rate (ESR) ,C-reactie protein (CRP) ,Serum creatinine (mg/dl) ,Complete urine analysis with assessment of active urinary sediments (RBCs – WBCs – proteins or cast), Protein/creatinine ratio (P/C), ANA, Anti-dsDNA antibody and Serum Complement C3 and C4.

Statistical analysis

Analysis of data was done by personal computer using SPSS (Statistical program for social science) as follows:

- Description of quantitative variables as mean, standard deviation (SD) and range.
- Description of qualitative variables as number (no) and percentage.
- Chi-square test was used to compare qualitative variables
- Unpaired t-test was used to compare two independent groups as regard a quantitative variables.
- Mann Whitney test was used instead of t- test in non parametric data (SD more than 50%).

Spearman correlation co-efficient rank test was used to rank different variables against each other positively or inversely.

RESULTS

Among the included 60 patients there were 52 female patients (86.67%) and 8 males (13.33%) with age ranged from 14 to 53 years with the mean 25.217 ±8.704, disease duration among them ranges from 6 to 36 months with the mean 11.3 ± 6.445. Among SLE patients, constitutional symptoms were the most common (80%) and the neuropsychiatric symptoms were the least common (5%). According to SLEDAI score we found that 16 patients (26.67%) had moderate disease activity, while 31 patients(51.67%) had high disease activity and 13 patients (21.67%) had very high disease activity and SLICC SCORE ranged between 0-6 with mean ±SD (0.833±1.404), where 34 patients showed score zero(56.67%), 15 patients with score 1(25%), 9 patients with score 2(15%), 1 patient with score 3(1.67%), 1 patient with score 6(1.67%).

Table1: comparison between SLE patients and normal controls regarding WBC

		Groups		T-Test	
		SLE Patient	Control	T	P-value
WBC	Range	1.5 - 9.7	4.3 - 10	-5.419	<0.001*
	Mean ±SD	4.455 ± 1.855	6.430 ± 1.675		
Neutrophiles(N)	Range	0.5 - 8	2 - 7	-0.804	0.423
	Mean ±SD	3.384 ± 1.628	3.620 ± 1.098		
Lymphocytes(L)	Range	0.3 - 1.2	1.3 - 3.3	-19.265	<0.001*
	Mean ±SD	0.699 ± 0.227	2.216 ± 0.545		

WBCs count in SLE patients was highly significant different (P value <0.001) when compared to the healthy controls to be lower in SLE patients and neutrophiles count range showed no significant difference (P value 0.423) when compared to the healthy controls and regarding lymphocyte count was highly significant different (P value <0.001) when compared to the healthy controls being lower in patients group.

Table 2: comparison between SLE patients and normal controls regarding NLR and PLR:

NLR	Groups						T-Test	
	SLE Patient			Control			T	P-value
Range	2.5	-	7.3	1.1	-	7.1	2.765	0.007*
Mean ±SD	4.866	±	1.444	3.891	±	2.084		
PLR Range	134	-	400	59	-	284	11.565	<0.001*
Mean ±SD	281.775	±	66.788	138.238	±	50.417		

NLR in SLE patients range from 2.5 to 7.3 with mean 4.866 ± 1.444 with highly significant difference (P-value <0.007) when compared to healthy controls to be higher in patients group, while PLR in SLE patients range from 134 to 400 with mean 281.775 ± 66.788 with highly significant difference (P value <0.001) when compared to the healthy controls to be higher in patients group**.**

There was positive correlation between NLR & PLR and P/C in SLE patients and there was a statistically significant difference between SLE patients without active nephritis and LN patients as regard NLR and PLR with P value <0.001 .

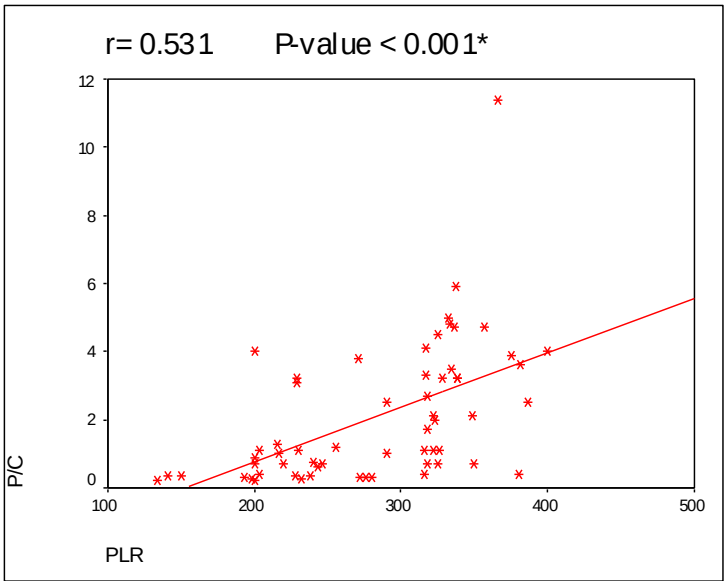

Figure1: positive correlation between NLR & PLR and P/C.

Table 3: correlation between NLR&PLR and SLEDAI and SLICC Scores in SLE patients:

	NLR		PLR	
	R	P-value	R	P-value
SLEDAI	0.774	<0.001*	0.638	<0.001*
SLICC	0.445	<0.001*	0.377	0.003*

There was a highly significant positive correlation between NLR & PLR and both of SLEDAI and SLICC scores in SLE patients.

There was a significant negative correlation between NLR&PLR and C3 in SLE patients with no correlation between NLR&PLR and C4 as shown in figures 2&3.

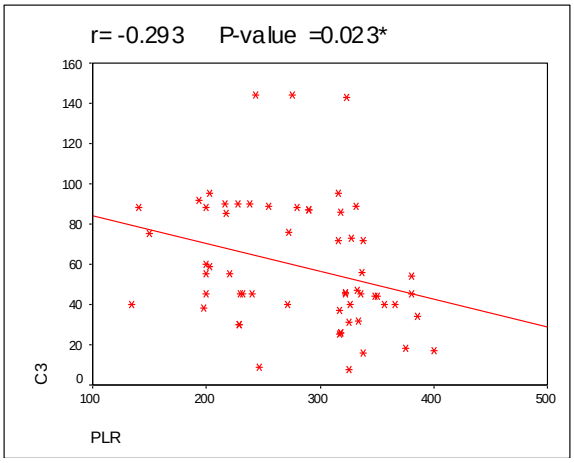

Figure2: negative correlation between PLR and C3

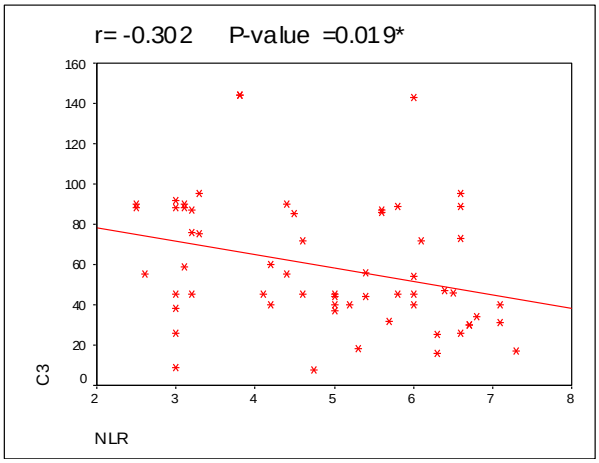

Figure3: negative Correlation between NLR and C3

Table 4: correlation between NLR&PLR and CRP& ESR in SLE patients:

Correlations				
	NLR		**PLR**	
	r	**P-value**	**r**	**P-value**
CRP	0.235	0.071	0.211	0.105
ESR	0.621	<0.001*	0.500	<0.001*

There was a significant positive correlation between NLR&PLR as and ESR in SLE patients with no correlation between NLR&PLR and CRP**.**

There was highly significant positive correlation between NLR and PLR in SLE patients as shown in figure 4.

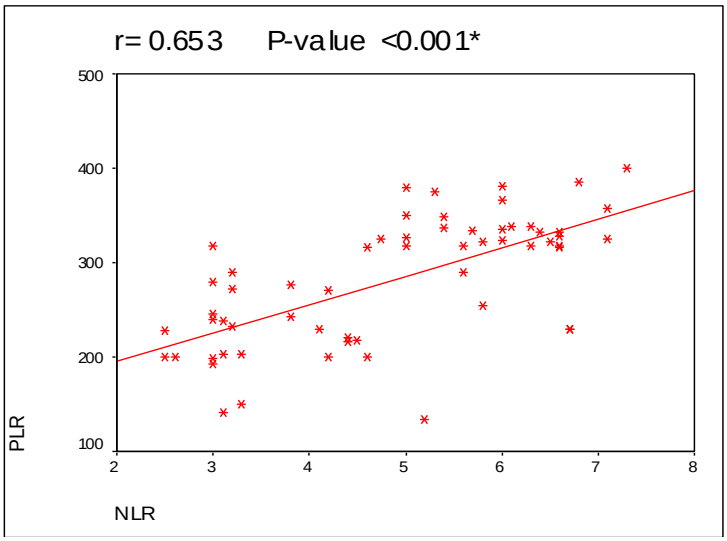

Figure 4: positive correlation between NLR and PLR.

DISCUSSION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with a wide spectrum of potentially serious symptoms that may require extensive consumption of health care resources. It is characterized by presence of autoreactive B and T cells responsible for the aberrant production of broad and heterogenous group of auto antibodies. This Autoantibody production is associated with various clinical manifestations including hematological and renal involvement [(9)]. In patients with SLE, hematological complications are frequently seen. Anemia, leucopenia and thrombocytopenia as a result of bone marrow failure or excessive peripheral cell destruction, or both of them[(10)]. Hematological disorders are included in the American College of Rheumatology (ACR)

Classification criteria for SLE. This included haemolytic anaemia with a reticulocytosis, leucopenia (<4.0 x 109/L) or lymphopenia (<1.5 x 109/L) on two or more occasions or thrombocytopenia (<100 x109/L) in the absence of offending drugs[10]. Leucopenia is a typical feature in SLE, and may occur as a result of lymphopenia, neutropenia or a combination of the two. Neutropenia is also a common feature of SLE and this may be mediated by anti-neutrophil antibodies and impaired function of the mononuclear phagocytic system, allowing sensitized cells to remain in the circulation may in part compensated for this [11]. Hematological involvement is common in SLE and close monitoring of cytopenia is warranted in most patients. Any significant changes in any previous stable cell lineage parameters are considered to be an indication of SLE flare, and will need evaluation and close monitoring[12]. NLR and PLR both increased in SLE patients and positively correlated with disease activity. NLR and PLR appear to be potentially useful inflammatory parameters of systemic inflammation in patients with SLE, and could serve as two new inflammatory markers for indicating disease activity in SLE patients [13].

In our studied group of patients (60 patients) 52 of our patients (86.67%) were females and 8 patients (13.33%) were males with a female to male ratio 6.5:1 The age of the patients ranged from 14 to 53 years with a mean of 25.217 ±8.704.This represents the most common incidence of SLE in females and accordingly matches other researches on SLE patients **(Ayna *et al.*** [14] , **Fernandez *et al.*** [15]).

Concerning common symptoms among SLE patients, constitutional symptoms were the most common (80%), while neuropsychiatric symptoms were the least common (5%) among patients. Similar results were obtained by ***Nasonov et al.*** [9] **.**

Regarding NLR and PLR , there was a significant difference between the SLE group and control group . NLR in SLE patients ranged from 2.5 to 7.3 with mean= 4.866 ± 1.444 , P=0.007 , while PLR in SLE patients ranged from 134 to 400 with mean= 281.775 ± 66.788 ,p<0.001 . This agreed with results of the study of **Wu *etal.*** [16] who conducted a study to evaluate association of NLR and PLR and disease activity in SLE patients and they reported that there was a statistically significant difference in NLR and PLR between the patient group (116 SLE patients) and the control groups (136 healthy control) both P< 0.001.

Lupus nephritis (LN) is one of the most common and severe clinical manifestation of SLE. it is defined as clinical and laboratory manifestations that was described by the American College Of Rheumatology criteria (once the SLE diagnosis was established, and clinically persistent proteinuria >0.5 g/d or greater than 3+ by dipstick, and/or cellular casts including granular, hemoglobin, red cell, tubular or mixed). The renal biopsy is considered the gold standard investigation in confirming the diagnosis of LN [17]**.**

Thus, NLR may be a predictor of LN and also may detect flares of the disease in LN patients.

In our results, NLR was significantly higher in SLE patients with nephritis and SLE patients with activity because of the neutrophilia and lymphopenia that occur in SLE activity and LN pathogensis.

Regarding NLR in both groups we found that NLR is higher in patients with active nephritis with a mean of 5.292 ±1.6 when compared to other patients without active nephritis with a mean of 3.587 ±1.136 with p=0.007 **.** This agrees with results of **Li *et al.*** [13] who conducted a study to evaluate the predictive value of the NLR in the SLE without nephritis and LN and reported that NLR values of the patients with LN were higher than those of the patients without LN P<0.001.

Regarding PLR in both groups we found that PLR is higher in patients with active nephritis with a mean of 299.233 ±57.290 when compared to other patients without active nephritis with mean 229.400 ±67.560. This finding agrees with the study of **Qin *et al.*** [18] who proved that PLR was significant higher in LN patients than in SLE patients without LN.

1. Our results showed highly significant positive correlation between each of NLR and PLR and SLEDAI score (r=0.774, p<0.01) for NLR (r=0.638, p<0.01) for PLR. This result comes in consistence with those of **Qin *et al.*** [18] who recorded that NLR and PLR was positively correlated with SLEDAI(r=0.471, p<0.0) (r=0.44, p<0.01) respectively .

By evaluation of the correlation of both of NLR and PLR with SLICC score as a damage index, our study showed significant positive correlation between NLR & PLR and SLICC score with r=0.445, p<0.001 & r=0.377, P<0.003 respectively.

In conclusion, each of NLR and PLR is independently associated with SLE activity (SLEDAI score), renal involvement and with damage index(SLICC score) in SLE patients. Because compared to other traditional indicators of activity and LN as 24h proteinuria, C3, C4 and Anti-ds DNA, both NLR and PLR are cheap, quick and easily measurable. These ratios could be promising cheap markers to follow up disease activity, reflects renal involvement and predict disease damage in SLE patients.

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