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Study of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio as Inflammatory Markers in Systemic Lupus Erythematosus Egyptian Patients

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Research Article

Abstract

Background: Systemic lupus erythematosus 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.

Objective: It was to investigate Neutrophil/ Lymphocyte Ratio (NLR) and platelet/lymphocyte ratio (PLR) as activity markers in Systemic Lupus Erythematous (SLE) patients.

Patients and methods: This study was carried out on 60 patients with SLE selected from outpatient's clinic and Internal Medicine Department of AL-Azhar University hospital and 20 healthy volunteers as a control group. The patients and controls included in this study were divided as follow: 1) Group A: forty (40) SLE patients with mild or moderate activity; 2) Group B: twenty (20) SLE patients without activity; and 3) Group C: twenty (20) normal healthy volunteers as a control. All patients and controls were subjected to: complete history and clinical assessment, abdominal ultrasonography and laboratory and assessment of NLR by dividing the absolute neutrophil count on the absolute lymphocyte count and assessment of PLR by the platelet count dividing on the absolute lymphocyte count.

Results: Group A showed significant increase of NLR, ESR, CRP, serum creatinine, ANA, AdsDNA and significant decrease of C3 and C4 when compared to group B. In addition, there was significant increase of NLR and PLR in group A when compared to control group. Also, there was significant increase of NLR and ESR in group B when compared to control group. In group A there was moderate, proportional, significant correlation between PLR and C3, while in group B, there was no significant correlation was found. In diagnosis of SLE, NLR had area under the curve of 0.843 denoting a good diagnostic power; with sensitivity of 100% and specificity of 70%, at a cut-off value of 2.17; while PLR had a low diagnostic power (AUC=0.554); with sensitivity of 70.0% and specificity of 55.0% at a cut-off value of 87.05. In addition, NLR had a good diagnostic value of disease activity (AUC=0.776); with sensitivity of 57.5% and specificity of 95.0% at NLR cutoff value of 3.15; while PLR had a low diagnostic power of disease activity (AUC=0.559).

Conclusion: Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) can be used as diagnostic markers of SLE on the other hand Neutrophil Lymphocyte Ratio (NLR) can be used as activity marker in active lupus patients.

Keywords: Systemic lupus; Neutrophil lymphocyte ratio; Platelet lymphocyte ratio.

1. Introduction

Systemic lupus erythematous (SLE) is a chronic autoimmune inflammatory disease with unknown etiology which has diverse clinical manifestation, course of the illness and prognosis [1]. Lupus is characterized by the presence of antibodies against a person's own proteins; these are most commonly anti-nuclear antibodies, which are found in nearly all cases [2]. There are many kinds of lupus; the most common type is systemic lupus erythematosus (SLE), which affects many internal organs in the body. SLE most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system [3]. SLE can be categorized as mild or severe and life threatening disease, in severe activity, leukopenia and lymphopenia can be found. Many clinical and laboratory parameters can be used to evaluate disease activity including low complement, increased Deoxyribonucleotide (DNA) binding, thrombocytopenia and leucopenia [4].

Evaluation of the disease activity with simple laboratory parameters which is available in almost every health care facility remains a problem. White blood cell and differential count can be done as a part of routine automated hematology analyzer. Recently, neutrophil lymphocyte ratio (NLR) has been evaluated

and used as inflammatory marker in malignancies, infection and coronary artery diseases [3]. Celikbilek et al. [5] observed that Neutrophil/Lymphocyte Ratio (NLR) and Platelet/Lymphocyte Ratio (PLR) in peripheral blood are simple Systemic Inflammatory Response (SIR) markers which are evaluated by blood parameters and showed that NLR possesses a diagnostic value in certain pathologies characterized by systemic or local inflammatory response such as diabetes mellitus, coronary artery disease, ulcerative colitis and inflammatory arthritis. Turkmen et al. [6] showed that platelets can interact with various cell types, including endo-thelial cells, T-lymphocytes, neutrophils and mononuclear phagocytes, leading to chronic inflammation, may contribute to the development of atherosclerosis. They confirmed that PLR was higher in RA patients compared with healthy controls. In contrast to that finding also showed that there is no association between NLR, CRP and RA.

In patients with SLE hematological complications are frequently seen including Anemia, leucopenia and thrombocytopenia as a result of bone marrow failure or excessive peripheral cell destruction [1]. Amaylia et al. [3] found that NLR was significantly higher in SLE than normal subjects.

The aim of this work was to investigate neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) as activity markers in systemic lupus erythematous (SLE) patients.

2. Patients and Methods

This study was carried out on 60 patients with SLE selected from outpatient's clinic and internal medicine department of AL-Azhar University hospital and 20 normal healthy volunteers as a control in a period from 1/9/2015 to 10/3/2016.The patients with SLE were diagnosed according to Bertsias et al. [7] criteria; and lupus activity was scored on the basis of SLEDAI scoring [3]. The patients and controls included in this study were divided as follow: 1) Group A: forty (40) SLE patients with mild or moderate activity; 2) Group B: twenty (20) SLE patients without activity; and 3) Group C: twenty (20) normal healthy volunteers as a control.

Exclusion Criteria: patient with one or more of the following criteria were excluded from the study: 1) infection (especially bacterial and also Hepatitis C Virus or Hepatitis B Virus infection), 2) Severe disease activity, 3) ttreatment with cyclophosphamide in the last 28 days, azathioprine or methotrexate, 4) diabetes mellitus, coronary artery disease, uulcerative colitis and inflammatory arthritis.

All patients and controls were subjected to the following: complete history and through clinical assessment, aassessment of the degree of SLE activity according to SLEDAI score, aabdominal ultrasonography and laboratory investigations (ANA, Anti ds DNA abs, C3 and C4, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), serum creatinine, serum uric acid, liver function tests, serum albumin and urine analysis for proteinuria and microscopic hematuria, hhepatitis C Virus antibody and Hepatitis B Virus surface antigen, rrandom blood glucose), specific laboratory assessment especially complete blood count including absolute neutophillic count, absolute lymphocytic count and platelet count were examined with fully automated cell counter, assessment of NLR by dividing the absolute neutrophil count on the absolute lymphocyte count and assessment of PLR by the platelet count dividing on the absolute lymphocyte count [8].

2.1 Statistical methodology

Data entry and analysis were done using SPSS version 16. Data were presented as mean, SD, number and percentage. Chi-square test was used to compare qualitative data between the two groups of patients. Independent samples T-test was used to compare means of both groups. Paired samples T-test was used to compare means before and after the procedure (CA or PCI) in the same group. P-value considered significant when it is ≤ 0.05. Regression analysis was done and or was calculated for independent risk factors.

3. Results

This study was carried out on 60 patients with SLE and 20 normal healthy volunteers as a control. In group A, 40 SLE patients with activity were included. They were 3 males and 37 females, their ages ranged between 16-43 years with mean ± SD (25.45 ± 6.42 years). 36 out of them have moderate activity (2 males and 34 females) and 4 of them have mild activity (one male and 3 females). Group B included 20 SLE patients without activity (3 males and 17 females), their ages ranged between (19-39 years) with mean ± SD (26.85 ± 6.18 years). Group C included 20 normal healthy volunteers as a control (5 males and 15 females), their ages ranged between (18-39 years) with mean ± SD (28.15 ± 6.53 years).group A (lupus with activity) showed statistically significant increase of NLR, ESR, CRP, serum creatinine, ANA, AdsDNA and significant decrease of C3 and C4 when compared to group B (Table 1). In addition, there was statistically significant increase of NLR and PLR in group A when compared to control group (Table 2). Also, there was significant increase of NLR and ESR in group B when compared to control group, but PLR showed non-statistical difference (Table 3). In group A there was moderate, proportional, significant correlation between PLR and C3, while in group B, there was no significant correlation was found (Table 4).

In diagnosis of SLE, NLR had area under the curve of 0.843 denoting a good diagnostic power (AUC>0.75); with sensitivity of 100% and specificity of 70%, at a cutoff value of 2.17; while PLR had a low diagnostic power (AUC=0.554); with sensitivity of 70.0% and specificity of 55.0% at a cutoff value of 87.05. In addition, NLR had a good diagnostic value of disease

Table 1. Statistical comparison between group A (lupus with activity) and group B (lupus without activity) as regards studied parameters.

Parameters		Group A	Group B	Test	P value
Sex (n,%)	Male	3 (7.5%)	3 (15.0%)	0.90	0.37(ns)
	Female	37 (92.5%)	17 (85.0%)		
Age		25.45 ± 6.42	26.85 ± 6.18	0.806	0.423
NLR		3.27 ± 0.66	2.75 ± 0.38	3.260	0.002*
PLR		157.20 ±106.18	129.70 ± 96.75	0.973	0.335
ESR		123.78 ± 33.27	106.50 ± 26.26	2.025	0.047*
CRP		14.35 ± 14.02	4.45 ± 2.52	4.327	<0.001*
S. Createnine		1.62 ± 1.18	1.17 ± 0.29	2.309	0.025*
ANA		220.30 ±140.85	122.65 ± 66.90	2.930	0.005*
AdsDNA		390.40 ±105.88	123.15 ± 47.90	13.447	<0.001*
C3		77.60 ± 28.35	143.40 ± 36.07	7.131	<0.001*
C4		17.23 ± 11.30	26.50 ± 10.31	3.082	0.003*
Cast in urine	Granular	15 (37.5%)	3 (15.0%)	3.21	0.07
	Nil	25 (62.5%)	17 (85.0%)		

Table 2. Statistical comparison between group A (lupus with activity) and control group as regards studied parameters.

Parameters		Group A	Control Group	Test	P Value
Sex (n,%)	Male	3 (7.5%)	5 (25.0%)	1.62	0.12
	Female	37 (92.5%)	15 (75.0%)		
Age		25.45 ± 6.42	28.15 ± 6.53	1.527	0.132
NLR		3.27 ± 0.66	2.21 ± 0.44	6.46	<0.001*
PLR		157.20 ±106.18	99.80 ± 38.53	3.04	0.004 *

Table 3. Statistical comparison between group B and control group as regards studied parameters.

Parameters		Group B	Control Group	Test	P Value
Sex (n%)	Male	3 (15.0%)	5 (25.0%)	0.77	0.44
	Female	17 (85.0%)	15 (75.0%)		
Age		26.85 ± 6.18	28.15 ± 6.53	0.646	0.522
NLR		2.75 ± 0.38	2.21 ± 0.44	4.146	<0.001*
PLR		129.70 ± 96.75	99.80 ± 38.53	1.284	0.207
ESR		106.50 ± 26.26	6.10 ± 2.63	17.012	<0.001*

Table 4. Correlation between different parameters in groups A and B.

	Group A				Group B			
	NLR		PLR		NLR		PLR	
	r	P	r	P	r	P	r	P
PLR	0.099	0.544	-	-	0.382	0.097	-	-
ESR	0.086	0.598	-0.045	0.782	-0.042	0.861	0.178	0.452
CRP	-0.024	0.884	-0.091	0.576	0.196	0.408	0.206	0.384
C3	-0.202	0.211	0.394	0.012*	0.003	0.991	-0.357	0.122
C4	0.058	0.722	-0.088	0.588	-0.228	0.333	0.228	0.334
ANA	-0.008	0.959	0.046	0.779	0.163	0.493	0.136	0.566
AdsDNA	-0.32	0.05	0.126	0.439	-0.167	0.483	-0.258	0.272
Albumin	0.126	0.438	0.059	0.716	-0.038	0.874	0.120	0.614
UA protein	-	-	-	-	0.188	0.426	-0.062	0.795

activity (AUC=0.776); with sensitivity of 57.5% and specificity of 95.0% at NLR cutoff value of 3.15; while PLR had a low diagnostic power of disease activity (AUC=0.559) (Table 5).

4. Discussion

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue binding autoantibodies and immune complexes [2]. Many clinical and laboratory parameters can be used to evaluate disease activity including low complement, increased deoxyribonucleotide (DNA) binding, thrombocytopenia and leucopenia [4]. The possibility to evaluate disease activity with simple laboratory parameters which is available in almost every health care facility may be a great value [3]. The current study

Table 5. ROC curve of NLR, PLR in group A with group B.

	In Diagnosis of Activity		In Diagnosis of Disease	
	NLR	**PLR**	**NLR**	**PLR**
Cut off point	3.15	126.0	2.17	87.05
Area under the curve	0.776	0.599	0.843	0.554
Sensitivity	57.5%	55%	100%	70%
Specificity	95%	75%	70%	55%
P value	0.001*	0.213	<0.001*	0.561

was performed to evaluate Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) as activity markers in SLE patients admitted at AL-Azhar University Hospital (New Damietta) including 60 patients with SLE and 20 normal healthy volunteers as controls. The patients and controls included in this study were divided into: Group (A): Includes 40 SLE patients with activity (3 males and 37 females), their ages ranged between (16-43 years) with mean ± SD (25.45 ± 6.42). 36 out of them have moderate activity (2males and 34 females) and 4 of them have mild activity (one male and 3 females). Group (B): Includes 20 SLE patients without activity (3 males and 17 females), their ages ranged between (19-39 years) with mean ± SD (26.85 ± 6.18). Group (C): Includes 20 normal healthy volunteers as a control (5 males and 15 females), their ages ranged between (18-39 years) with mean ± SD (28.15 ± 6.53).There are a higher percentage of SLE patients females over males in both group A (lupus with activity) and group B (lupus without activity). These Findings was in agreement with Ginzler et al. [9] who reported that More than 90% of cases of SLE occur in women frequently starting at childbearing age.

In the present work, there was a highly statistical significant increase in NLR in patients of group A (lupus with activity) in comparison to group B (lupus without activity) and group C (controls). Also there was statistical significant increase in NLR in patients of group B (lupus without activity) in comparison to group C (controls). In addition, there was a positive correlation of NLR in patients of group A (lupus with activity) in relation to (PLR, ESR, C4 and S. Albumin). Also there was a positive correlation in NLR in patients of in group B (lupus without activity) in relation to (PLR, CRP, C3 and ANA) but without statistical significance. On the other hand ROC curve (receiver operating characteristic curve) of NLR of group A (lupus with activity) showed cut off point 3.15 with sensitivity 57.5% and specificity 95% in comparison to group B (lupus without activity). While ROC curve (receiver operating characteristic curve) of NLR of group B (lupus without activity) showed cut off point 2.17 with sensitivity 100% and specificity 70% in comparison to group C (controls). In agreement with these findings, Amaylia et al. [3] found that NLR was significantly higher in SLE than normal subjects. Also Lixiu et al. [10] found that NLR is independently associated with SLE, and showed a significant increase in NLR in Lupus nephritis patients. In addition, Chua et al. [11] observed that Neutrophil lymphocyte ratio (NLR) has been evaluated and used as inflammatory marker in malignancies, infection and coronary artery diseases. Furthermore, Baodong et al. [12] observed that NLR was increased in SLE and positivity correlated with CRP, ESR and SLEDAI. They also observed that NLR was increased in lupus nephritis in comparison to SLE without nephritis. They stated that NLR could reflect inflammatory response and disease activity in SLE patients. On the other hand, Yunxiu et al. [13] reported that NLR was increased in SLE patients in comparison to control. They also reported that NLR was increased in active group in comparison to non-active group. On contrast with our findings Delgado et al. [14] showed that NLR is not superior to lymphocyte alone in differentiating disease activity in SLE. Platelet Lymphocyte ratio (PLR) is novel inflammatory biomarkers used as prognostic factors in various diseases such as diabetes mellitus, coronary artery disease, ulcerative colitis and inflammatory arthritis. Akkaya et al. [15] reported that the PLR is associated with outcomes of patients with ankylosing spondylitis, non-small cell lung cancer and acute coronary syndrome.

In the present study, there was increase in PLR in patients of group A (lupus with activity) in comparison to group B (lupus without activity) and group C (controls) but without statistical significant increased. While there was a statistical significant increase in PLR in group A (lupus with activity) in comparison to group C (controls). In addition, there was a positive correlation of PLR in patients of group A (lupus with activity) in relation to (NLR, ANA, AdsDNA, C3 and S. Albumin). Also there was a positive correlation in PLR in patients of in group B (lupus without activity) in relation to (NLR, ESR, CRP, ANA, C4 and S. Albumin) but without statistical significance except there was a statistically significant positive correlation was found between PLR and C3 (P value <0.05) in group A (lupus with activity). On the other hand ROC curve (receiver operating characteristic curve) of PLR of group A (lupus with activity) showed cut off point 126 with sensitivity 55% and specificity 75% in comparison to group B (lupus without activity). While ROC curve (receiver operating characteristic curve) of PLR of group B (lupus without activity) show cut-off point 87.05 with sensitivity 70% and specificity 55% in comparison to group C (controls). In agreement with our finding Baodong et al. [12] who observed that PLR was increased in SLE, lupus nephritis in comparison to SLE without nephritis .They observed that PLR could reflect inflammatory response and disease activity in SLE patients, PLR was positivity correlated with SLEDAI. Also, Yunxiu et al. [13] reported that

PLR was increased in SLE patients in comparison to control. They also significantly reported that PLR was increased in active group in comparison to non-active group. The present study showed highly statistical significant increase in Anti-dsDNA in patients of group A (lupus with activity) in comparison to group B (lupus without activity) ($p<0.001$).

In agreement with our finding Gorenwold et al. [16] which reported that Anti-dsDNA is a protein directed against double-stranded DNA. The test is very specific for lupus. Therefore, a positive test can be useful in confirming a diagnosis. For many people, the titer, or level, of the antibodies rises as the disease becomes more active. So, it can also use to help measure disease activity. Also, the presence of anti-dsDNA indicates a greater risk of lupus nephritis, a kidney inflammation that occurs with lupus. So a positive test can alert doctors to the need to monitor the kidneys.

In the present series, there was a highly statistical significant deceased in C3 was found in group A (lupus with activity) in comparison to group B (lupus without activity) and there was a statistical significant deceased in C4 was found in patients of group A (lupus with activity) in comparison to group B (lupus without activity). In agreement with our finding Nived et al. [17] which Observed that low complement concentrations and also of activation of the complement system are characteristic findings in active SLE and have led to the practice of using measurement of complement for the diagnosis.

In the present work, there was a statistical significant increase in ESR in group A (lupus with activity) in comparison to group B (lupus without activity) ($p=0.047$), while there was a highly statistical significant statistical increased in ESR in patients of group A (lupus with activity) in comparison to group C (controls) ($p<0.001$). Stoll et al. [18] said that ESR is used as a marker of inflammation. Inflammation could indicate lupus activity. This test could be used to monitor inflammation, which could indicate changes in disease activity or response to treatment. But Haq et al. [19] said that there are many causes for a positive result, including infection; the test is not diagnostic for lupus. Nor can it distinguish a lupus flare from an infection. Also, the level doesn't directly correlate with lupus disease activity. So it is not necessarily useful for monitoring disease activity. Also Jennings et al. [20] reported that the erythrocyte sedimentation rate is a sensitive but non-specific indicator of activity in SLE and is slow to reflect changes in disease activity.

In the present study, there was a highly statistical significant increase in CRP was found in group A (lupus with activity) in comparison to group B (lupus without activity) ($p<0.001$). Mok et al. [21] said that CRP is elevated with activity of lupus and correlate significantly with lupus disease activity. Also Zein et al. [22] reported that CRP might be raised in severe lupus serositis.

In our study, there was a statistical significant increase in ANA was found in group A (lupus with activity) in comparison to group B (lupus without activity) ($p=0.005$).Jennings et al. [20] said that ANA test is highly sensitive in that it is positive in more than 95% of people with SLE.

5. Conclusion

From this study we can concluded that Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) can be used as diagnostic markers of SLE on the other hand Neutrophil lymphocyte ratio (NLR) can be used as activity marker in active lupus patients.

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