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Clinical and Laboratory Characterization of Systemic Lupus Erythematosus Patients with Activity in Zagazig University Hospitals

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ABSTRACT

Background: The autoimmune disease systemic lupus erythematosus (SLE) frequently manifests as hematological abnormalities which; cytopenia of one or more blood cell lineages is one of the possible presenting symptoms of SLE.
Objective: To compare the correlation between disease activity and clinical and laboratory characterization among SLE patients.
Patients and Methods: We did a comparative cross-sectional study at Clinical Hematology and Nephrology Units, Internal Medicine Department of Zagazig University Hospitals. This study was performed on (30) SLE patients. The included patients are classified into two groups according to their activity including: Low/ moderate activity group (40%):12 patients. High to very high activity group (60%): 18 patients. Their clinical and lab parameters were assessed.
Results: There was statistically significant difference between low/moderate activity SLE and high/ very high SLE activity as regards laboratory data except for MCV. There was statistically significant difference between low/moderate activity SLE and high/ very high SLE activity as regards antiphospholipid antibodies being positive in high/ very high activity SLE more than low/moderate disease activity with p-value=0.009 and Proteinuria >500 mg/24h with p-value=0.001 being more with high/very high grade SLE group lupus nephritis with p-value =0.003 being more with high/very high SLE group. Clinical parameters (EULAR/ACR) differed significantly between low/moderate activity SLE and high/ very high SLE activity.
Conclusion: Clinical parameters (EULAR/ACR) differed significantly between low/moderate activity SLE and high/ very high SLE activity and no significant differences among labs except for MCV.
Keywords: Systemic Lupus Erythematosus, Clinical, Laboratory Characterization.

INTRODUCTION

The autoimmune disease systemic lupus erythematosus (SLE) affects people of all sexual orientations and is found in every country. Lupus typically has a varied clinical appearance with a fluctuating course of flares and remissions, and it can affect many different organs, including the skeleton, skin, mucous membranes, blood cells, brain, and kidneys [(1)].

The majority of research about 'Asian' or 'Oriental lupus' had previously been extrapolated from studies on Asian minorities living in the West, despite the fact that systemic lupus erythematosus is more widespread and severe in non-Caucasian populations [(2)].

Lupus erythematosus is diagnosed when specific autoantibodies are present in addition to the presence of classic clinical manifestations, which include signs and symptoms affecting several organ systems. Even for trained rheumatologists, SLE can be difficult to diagnose since its symptoms are often vague and may be confused with those of other, comparable systemic autoimmune illnesses[(3)].

The skin (in both its chronic and acute forms) and the joints are just two of the many organs that can be affected (ranging from persistent polyarthritis to arthralgia). Inflammation of the kidneys or the brain could be an additional complication in more severe illness conditions. Patients with glomerulonephritis are more likely to have anti dsDNA antibodies than those with other clinical characteristics [(4)].

Antiphospholipid antibodies are linked to an increased risk of venous thrombosis and stroke, but other autoantibodies such anti-Ro/SSA, anti-La/SSB, and rheumatoid factor are detected in milder disease. Nonetheless, congenital heart block is a significant issue linked to maternal anti-Ro/ SSA antibodies [(3)].

The study aims to compare the correlation between disease activity and clinical and laboratory characterization among SLE patients.

PATIENTS AND METHODS

We did this comparative cross-sectional study at Clinical Hematology and Nephrology Units, Internal Medicine Department of Zagazig University Hospitals, this study was done on (30) SLE patients.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee (IRB#5962-9-3-2020). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion Criteria: Age: ≥ 18 years, and systemic lupus erythematosus is diagnosed when patients meet the 2019 EULAR and ACR classification criteria [(5)].

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Exclusion criteria: Patients with: (1) Age: Less than 18 years old. (2) Other inflammatory autoimmune disorders. (3) Malignancy. (4) Hematological disorders.

The included patients were classified into two groups according to their activity including:

1- **Low/ moderate activity group (40%)**:12 patients. Merged two categories in 1 group: mild activity (SLEDAI=1 to 5), moderate activity (SLEDAI=6 to 10).
2- **High to very high activity group (60%):** 18 patients. Merged two categories in 1 group: high activity (SLEDAI=11 to 19), and very high activity (SLEDAI≥20).

Activity was assessed using Modified New versions of the SLEDAI index that have been developed (SLEDAI 2000 and SELENA SLEDAI) [(6)] to score persistent active disease in manifestations that were scored in the previous version only if new or recurrent (proteinuria, rash, alopecia, mucocutaneous manifestations).

On the basis of SLEDAI ratings, various types of activities have been established: no activity (SLEDAI=0), mild activity (SLEDAI=1 to 5), moderate activity (SLEDAI=6 to 10), high activity (SLEDAI=11 to 19), and very high activity (SLEDAI≥20).

All patients were submitted to a comprehensive clinical examination and history taking.

Lab investigations:

Include any investigations that verify inclusion and exclusion criteria:

(1) Complete blood count (CBC): differential leucocytic count in peripheral blood smears stained with Leishman's solution.
(2) Liver function tests. Total bilirubin, direct bilirubin, Total protein, Albumin, ALT and AST.
(3) Kidney function tests. Urea and Creatinine and (protein/creatinine ratio).
(4) Erythrocyte sedimentation Rate (ESR).
(5) CRP
(6) Special laboratory investigation: Anti-nuclear antibody (ANA), Serum complements (C3& C4), Microalbumin creatinine ratio (MACR) and Anti-double stranded deoxyribonucleic acid (anti-ds DNA).

Statistical analysis

In order to analyze the data acquired, Statistical Package of Social Sciences (SPSS) version 20 was used to execute it on a computer. In order to convey the findings, tables and graphs were employed. The quantitative data was presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (T) is used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X^2) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

Most of SLE patients were females (80%) and 20% were males with female to male ration 4:1 as presented in table **1**.

Table (1): Demographic data of the studied population (N= 30)

		Value
Age (year)		31 (18-42)
Sex	Female	24 (80.0%)
	Male	6 (20.0%)

The included systemic patients were classified into two groups according to their activity including low/ moderate activity group (40%) and high to very high activity group (60%). According to nature of SLE disease, our patients were classified into naïve group (83.3%) and relpasing group (16.7%) as presented in table **2**.

Table (2): Clinical SLE Status data of the studied population (N= 30)

SLE Status		Value
Activity	L/M	12 (40.0%)
	H/VH	18 (60.0%)
Nature	Naïve	25 (83.3%)
	Relapsing	5 (16.7%)

There was statistically significant difference between low/moderate activity SLE and high/ very high SLE activity as regards the used medications with p-value =0.019 as most of high activity group used hydroxychloroquine while most of low/ moderate activity group used NSAIDs as presented in table **3**. There was statistically significant difference between low/moderate activity SLE and high/ very high SLE activity as regards nature of the disease as all of L/M SLE activity were naïve nature while 72.2% of high/very high SLE activity group were naïve nature with p-value=0.046 as presented in table **3**.

Table (3): Comparison of medical history and demographic data based on the SLE Activity

		SLE Activity		Total N=30	Test	P
		L/M N=12	H/VH N=18			
Age		26 (18-42)	32 (18-42)	31 (18-42)	-0.57	0.566
Sex	Female	10 (83.3%)	14 (77.8%)	24 (80.0%)	0.1	0.709
	Male	2 (16.7%)	4 (22.2%)	6 (20.0%)		
Smoking	No	11 (91.7%)	16 (88.9%)	27 (90.0%)	0.1	0.804
	Yes	1 (8.3%)	2 (11.1%)	3 (10.0%)		
Co-morbidities	DM	2 (16.7%)	2 (11.1%)	4 (13.3%)	2.0	0.567
	HTN	5 (41.7%)	5 (27.8%)	10 (33.3%)		
	HTN + DM	0 (0.0%)	2 (11.1%)	2 (6.7%)		
	Non	5 (41.7%)	9 (50.0%)	14 (46.7%)		
Medications	Hydroxychloroquine	3 (25.0%)	9 (50.0%)	12 (40.0%)	11.7	0.019
	Immunosuppressives	0 (0.0%)	6 (33.3%)	6 (20.0%)		
	NSAIDs	5 (41.7%)	2 (11.1%)	7 (23.3%)		
	Steroids	4 (33.3%)	1 (5.6%)	5 (16.7%)		
Naïve or relapsing	Naïve	12 (100.0%)	13 (72.2%)	25 (83.3%)	4.0	0.046
	Relapsing	0 (0.0%)	5 (27.8%)	5 (16.7%)		

Vital signs and anthropometric data show no statistically significant difference between SLE with low/moderate activity and SLE with high/very high activity with p-value >0.05 as presented in table **4**.

Table (4): Clinical examination data based on the SLE Activity

		SLE Activity		Total N=30	Test	P
		L/M N=12	H/VH N=18			
Weight,kg		75.3 (67.5-91.5)	76.5 (62.5-88.5)	75.5 (62.5-91.5)	-0.55	0.582
Height,cm		164 (159-174)	169 (159-174)	168 (159-174)	-1.13	0.259
BMI,kg/m^2		28.9 (25.4-31.2)	26.4 (24.1-31.0)	27.4 (24.1-31.2)	-1.78	0.075
Abd. Examination	Abnormal	2 (16.7%)	7 (38.9%)	9 (30.0%)	1.7	0.193
	Normal	10 (83.3%)	11 (61.1%)	21 (70.0%)		
Systolic BP,mmHg		130 (110-170)	130 (110-170)	130 (110-170)	-0.58	0.562
Diastolic BP,mmHg		80 (70-100)	75 (70-100)	80 (70-100)	-0.87	0.384
HR,bpm		90 (72-100)	80 (70-102)	83 (70-102)	-1.63	0.102
Temperature,°c		37.0 (36.8-37.4)	37.0 (36.5-37.5)	37.0 (36.5-37.5)	-0.26	0.798

There is statistically significant difference between low/moderate activity SLE and high/ very high SLE activity as regards laboratory data except for MCV with p-value=0.019 being lower in high/very high SLE activity group, MCHC with p-value=0.006 being lower in high/very high SLE activity group, RDW% with p-value=0.04 being lower in high/very high SLE activity group, serum creatinine with p-value =0.005 being higher in high/very high SLE activity group, microalbumin creatinine ratio with p-value=0.009 being higher in high/very high SLE activity group, C3 and C4 with p-value =0.006 and 0.014 respectively being lower in high/very high SLE activity group, and ESR with p-value =0.007 being higher in high/very high SLE activity group as presented in table **5**.

Table (5): Comparison of Lab. data based on the SLE Activity

	SLE Activity		Test	P
	L/M N=12	H/VH N=18		
TLC,10^3/uL	4.6 ±1.0	4.4 ± 0.96	-0.42	0.672
ANC,10^3/uL	3.3 ±0.61	3.1 ±0.41	-0.38	0.703
AMC,10^3/uL	0.2 ±0.01	0.3 ±0.02	-0.88	0.379
ALC,10^3/uL	0.8 ±0.2	0.6 ±0.1	-0.24	0.813
HB,g/dL	9.1±1.0	8.3±1.6	-1.55	0.122
Mcv,fL	87±9	78±9	-2.35	0.019
MCHC,g/dL	33.1±1.9	30.8±2.2	-2.75	0.006
RDW %	12.7±1.1	12.0±1.0	-2.06	0.04
PLT,10^3/uL	174±4.2	192±38.5	-0.42	0.672
PDW,fL	18.3 ±4.1	12.8 ±2.8	-1.48	0.138
MPV,fL	11.1 ±2.71	12.7 ±2.81	-0.70	0.484
ALT, U/L	21 ±4.5	16 ±3.6	-1.00	0.319
AST, U/L	27 ±6.2	21 ±5.3	-1.19	0.236
Serum urea,mg/dl	30 ±6.1	53 ±7.1	-1.74	0.083
Serum creatinine,mg/dl	0.72 ±0.11	1.29 ±0.31	-2.79	0.005
Microalbumin creatinine ratio mg/g	70 ± 12.3	304 ±53.6	-2.60	0.009
C3,mg/dl	111± 24.3	36 ±7.3	-2.73	0.006
C4,mg/dl	19.0 ± 4.3	5.4 ± 1.1	-2.46	0.014
ESR,mm/hr	31 ± 7.2	85 ± 16.4	-2.71	0.007
CRP,mg/L	22 ± 4.3	23 ± 5.1	-1.06	0.289

When comparing SLE with low/moderate to high/very high activity, there is a statistically significant difference in antiphospholipid antibodies being positive in high/ very high activity SLE more than low/moderate disease activity with p-value=0.009 and Proteinuria >500 mg/24h with p-value=0.001 being more with high/very high grade SLE group lupus nephritis with p-value =0.003 being more with high/very high SLE group as presented in table **6**.

Table (6): Comparison of Special laboratory investigation based on the SLE Activity

		SLE Activity		Total N=30	Test	P
		L/M N=12	H/VH N=18			
ANA (all cases must be positive)	+ve	12 (100.0%)	18 (100.0%)	30 (100.0%)	-	-
Antiphospholipid antibodies	-ve	12 (100.0%)	9 (50.0%)	21 (70.0%)	9.4	0.009
	+ve	0 (0.0%)	9 (50.0%)	9 (30.0%)		
Proteinuria >500 mg/24h	No	12 (100.0%)	7 (38.9%)	19 (63.3%)	11.6	0.001
	Yes	0 (0.0%)	11 (61.1%)	11 (36.7%)		
Renal biopsy	--	12 (100.0%)	9 (50.0%)	21 (70.0%)	8.6	0.073
	Class II	0 (0.0%)	1 (5.6%)	1 (3.3%)		
	Class III	0 (0.0%)	2 (11.1%)	2 (6.7%)		
	Class III- IV	0 (0.0%)	4 (22.2%)	4 (13.3%)		
	Class IV	0 (0.0%)	2 (11.1%)	2 (6.7%)		
Lupus nephritis	No	12 (100.0%)	9 (50.0%)	21 (70.0%)	11.6	0.003
	Yes	0 (0.0%)	9 (50.0%)	9 (30.0%)		
Anti- ds DNA (IU/mL)		73 ± 16.3	80 ± 17.1	78 ± 15.2	-1.38	0.168

There is statistically significant difference between low/moderate activity SLE and high/ very high SLE activity as regards Clinical parameters (EULAR/ACR) including constitutional being higher with high /very high activity SLE with p-value =0.003, musclokeletal manifestations with p-value <0.001 being more with high /very high activity SLE , renal manifestations with p-value =0.009 being higher scores with high/very high grade SLE activity, immunological component with p-value =0.007 being higher with high/very high SLE activity group, and complement protein domain with p-value =0.003 being higher in high/very high SLE disease activity as presented in table **7**.

Table (7): Comparison of Clinical parameters (EULAR/ACR) as regard the SLE Activity

Clinical parameters (EULAR/ACR)		SLE Activity		Total N=30	Test	P
		L/M N=12	H/VH N=18			
Constitutional	0	10 (83.3%)	5 (27.8%)	15 (50.0%)	8.9	0.003
	2	2 (16.7%)	13 (72.2%)	15 (50.0%)		
Hematologic	0	6 (50.0%)	9 (50.0%)	15 (50.0%)	3.6	0.304
	3	0 (0.0%)	3 (16.7%)	3 (10.0%)		
	4	0 (0.0%)	1 (5.6%)	1 (3.3%)		
	7	6 (50.0%)	5 (27.8%)	11 (36.7%)		
Neuropsychiatric	0	12 (100.0%)	16 (88.9%)	28 (93.3%)	1.4	0.232
	3	0 (0.0%)	2 (11.1%)	2 (6.7%)		
Mucocutaneous	0	11 (91.7%)	11 (61.1%)	22 (73.3%)	5.0	0.287
	2	1 (8.3%)	1 (5.6%)	2 (6.7%)		
	4	0 (0.0%)	2 (11.1%)	2 (6.7%)		
	6	0 (0.0%)	1 (5.6%)	1 (3.3%)		
	8	0 (0.0%)	3 (16.7%)	3 (10.0%)		
Serosal	0	12 (100.0%)	15 (83.3%)	27 (90.0%)	2.2	0.329
	5	0 (0.0%)	2 (11.1%)	2 (6.7%)		
	6	0 (0.0%)	1 (5.6%)	1 (3.3%)		
Musculoskeletal	0	11 (91.7%)	2 (11.1%)	13 (43.3%)	19.0	<0.001
	6	1 (8.3%)	16 (88.9%)	17 (56.7%)		
Renal	0	12 (100.0%)	7 (38.9%)	19 (63.3%)	11.6	0.009
	4	0 (0.0%)	4 (22.2%)	4 (13.3%)		
	12	0 (0.0%)	1 (5.6%)	1 (3.3%)		
	14	0 (0.0%)	6 (33.3%)	6 (20.0%)		
Immunological	0	12 (100.0%)	10 (55.6%)	22 (73.3%)	7.3	0.007
	2	0 (0.0%)	8 (44.4%)	8 (26.7%)		
High specific antibodies	6	12 (100.0%)	18 (100.0%)	30 (100.0%)		
Complement protein domains	0	10 (83.3%)	5 (27.8%)	15 (50.0%)	8.9	0.003
	4	2 (16.7%)	13 (72.2%)	15 (50.0%)		
Total score (EULAR/ACR)		13 ± 3.2	31 ± 7.1	18 ± 4.1	-4.05	<0.001

DISCUSSION

Many people with SLE also deal with haematological issues, such as anaemia or a deficiency in one or more blood cell lineages (cytopenia), which may be the first sign of the condition. Immunizations against neutrophils and dysfunction of the mononuclear phagocytic system are the main causes of neutropenia[7].

The present study showed that most of SLE patients were females (80%) and 20% were males with female to male ration 4:1. The mean age was 31 years. In accordance with our findings **Wu *et al.*[8]** in their study in newly diagnosed SLE patients reported patients' ages ranged from 5 to 73, with 97 females (83.6% of the total) and 19 males making up the patient population (16.4 percent) [8]. The current results found that the patients were classified into two groups according to their activity including low/moderate activity group (40%) and high to very high activity group (60%). According to nature of SLE disease, our patients were classified into naïve group (83.3%) and relapsing group (16.7%).

Farouk *et al.* [9] according to the SLEDAI score, 16 patients (26.67%) were classified as having mild disease activity, 31 patients (51.67%) as having high disease activity, and 13 patients (21.67%) as having very high disease activity[9].

Our findings showed that There was statistically significant difference between low/moderate (L/M) activity SLE and high/ very high (H/VH) SLE activity as regards the used medications and SLE nature ($p<0.05$) as most of H/VH activity group used hydroxychloroquine while most of L/M activity group used NSAIDs. All of L/M SLE activity were naïve nature while 72.2% of H/VH SLE activity group were naïve nature.

The present study showed that there was no statistically significant difference between L/M activity SLE and H/VH SLE activity as regards anthropometric measurements and vital signs ($p>0.05$).

Regarding laboratory data the current results found that there was statistically significant difference between L/M activity SLE and H/VH SLE activity respecting MCV, MCHC, RDW%, serum creatinine,

microalbumin creatinine ratio, C3, C4, and ESR ($p<0.05$). **Wu *et al.*** [8] reported that there was statistically significant difference between low and high SLE activity concerning CRP, ESR, C3, and lymphocyte count ($p<0.05$). **Xie & Chen** [10] showed that patients with higher SLEDAI score had higher anti-dsDNA antibody, urine protein, serum IgG and ESR, whereas complement C3, C4, and albumin were decreased significantly [10].

Individualized disease activity evaluation is a cornerstone of effective treatment for patients with SLE. A laboratory measurement must meet numerous requirements, such as the ones listed here, before it can be deemed a credible marker for disease activity evaluation. Disease and health should be easily distinguishable, the procedure should be straightforward for everyday use, it should be sensitive to subtle changes in disease activity, and ideally it should have pathogenic relevance[8].

Neutrophils are the most common form of white blood cell (WBC), and it is well recognised that leukocytes play a crucial role in inflammatory processes. When the immune system is activated in response to a microbial threat, neutrophils are among the first cells to arrive on the scene. By releasing superoxide radicals and proteases, activated leukocytes contribute to oxidative stress. Meanwhile, neutrophils secrete a lot of inflammatory mediators, and their short half-life suggests that neutrophilia is linked to the quick onset of inflammation after tissue injury. WBC count and its subtypes have both been demonstrated to be effective in recent research for predicting the inflammatory process[11].

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most popular indices for measuring disease activity right now. However, there is inconclusive evidence on how hs-CRP, ESR, and disease activity relate in SLE patients[12].

Similar to our results **Barnes *et al.*** [13] we also failed to discover a correlation between SLE disease activity indices and CRP blood levels.

Serum complements have long been utilised as a diagnostic and prognostic tool for patients with SLE. Hypocomplementemia is common among lupus patients who are actively ill. Patients with SLE have been reported to have lower amounts of C3 and C4, as well as low total complements hemolytic activity[14].

The current study revealed that there was statistically significant difference between L/M activity SLE and H/VH SLE activity as regards antiphospholipid antibodies being positive in H/VH activity SLE more than L/M disease activity (p-value=0.009) and Proteinuria >500 mg/24h (p-value=0.001) being more with H/VH SLE group lupus nephritis (p-value =0.003) being more with H/VH SLE group.

The present study showed that there was statistically significant difference between low/moderate activity SLE and H/VH SLE activity as regards Clinical parameters (EULAR/ACR) including constitutional, musculoskeletal manifestations, renal manifestations, immunological component, and complement protein domain and Total score (EULAR/ACR) ($p<0.05$).

Farouk *et al.* [9] reported that eighty percent of individuals with SLE reported experiencing constitutional symptoms, while only 20% reported experiencing neuropsychiatric symptoms (5 percent).

The current study revealed that there was statistically significant difference between L/M activity SLE and H/VH SLE activity as regards SLE DAI including lupus headache, arthritis, myositis, proteinuria>5, pyuria, fever, low complement, rash, and total score ($p<0.05$). There was no significant difference between the two groups regarding leukopenia, thrombopenia, mucosal ulcer, and psychosis.

The American College of Rheumatology (ACR) Classification includes haematological abnormalities as part of the definition of SLE. Included in this category were cases with haemolytic anemia accompanied by reticulocytosis, leucopenia (4.0 x 10^9/L) or lymphopenia (1.5 x 10^9/L) on two or more occasions, or thrombocytopenia (100 x10^9/L) in the absence of offending medications[15].

A decrease in white blood cells (leucopenia) is a common symptom of SLE. This may be due to lymphopenia, neutropenia, or both. Allowing sensitized cells to remain in circulation may compensate in part for the neutropenia that is a typical hallmark of SLE and may be mediated by anti-neutrophil antibodies and reduced function of the mononuclear phagocytic system[16].

Active systemic lupus erythematosus patients typically present with a condition that includes nephritis[17].

CONCLUSION

Clinical parameters (EULAR/ACR) differed significantly between low/moderate activity SLE and high/ very high SLE activity and no significant differences among labs except for MCV.

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