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Clinical Features Clusters in Systemic Lupus Erythematosus

Mansour M, and Helaly M
Rheumatology Department, El-Galaa Military Family Hospital, Cairo, Egypt.
Corresponding author: Helaly M, e-mail: dr.marwahelaly@gmail.com

ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a multi-systemic heterogeneous autoimmune disease. Attempts have been made trying to classify lupus into more homogenous subsets with pathogenic, therapeutic, or prognostic significance. **Objective:** was to evaluate the possibility of existence of the main clinical features of Systemic Lupus Erythematosus (SLE) in clusters. **Patients and Methods:** The demographic data, cumulative clinical and laboratory features of 150 Egyptian SLE patients were studied. Some of the main clinical manifestations were then selected for cluster analysis using the K-means cluster analysis procedure. **Results:** Three distinct groups of patients were identified. Cluster 1 (n: 27) showed higher age at diagnosis and was characterized by high prevalence of mucocutaneous manifestations (malar rash, discoid rash, photosensitivity, oral ulcer) and arthritis but having low prevalence of serositis and hematologic manifestations (hemolytic anemia, leukopenia, and thrombocytopenia). Patients in cluster 2 (n: 81) showed mainly renal and hematological manifestations but had the lowest prevalence of mucocutaneous manifestations and arthritis. Cluster 3 patients (n: 42) had the most heterogeneous features; they had a high prevalence of mucocutaneous manifestations, serositis, hematologic manifestations and renal involvement. **Conclusion:** patients with systemic lupus erythematosus could be divided into clusters of distinct patterns of clinical manifestations.

Keywords: SLE, clusters, clinical features.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-systemic heterogeneous autoimmune disease with innumerable clinical and laboratory manifestations. The course of the disease is characterized by exacerbations and remissions, with the development of new organ manifestations or progression of existing manifestations. The prognosis of SLE is largely unpredictable and highly variable. Previous studies in different ethnic groups (Caucasians, Africans, Americans, and Chinese) have reported the frequency of occurrence of various clinical and laboratory features of SLE[1–4]. Attempts have been made trying to classify lupus into more homogenous subsets with pathogenic, therapeutic, or prognostic significance [2-6].

The aim of the current study was to evaluate the possibility of existence of the main clinical features of Systemic Lupus Erythematosus (SLE) in clusters.

PATIENTS AND METHODS

This was a cross-sectional study included a total of 150 Egyptian adult SLE patients attending at Rheumatology Department, El-Galaa Military Family Hospital, Cairo, Egypt. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between (March 2017 and February 2018). All patients have fulfilled at least four of the 1997 revised American College of Rheumatology (ACR) criteria for the classification of SLE[9] (all of them gave informed consents). We attempted to identify clinical patterns of organ manifestations in these patients by using the cluster analysis and compared prevalence of various clinical and laboratory features and immunosuppressive drugs among these clusters of patients.

In this study, all cumulative data used had drawn from the database. Recorded data from this database included demographic characteristics (gender and age), duration of disease, cumulative clinical features recorded since the diagnosis of SLE, autoantibody profiles and treatments (glucocorticoids, hydroxychloroquine, cyclophosphamide, azathioprine, methotrexate, cyclosporine A, mycophenolate mofetil and tracrolimus) ever or currently being received.

Clinical features [malar rash, discoid rash, photosensitivity, oral ulcers, arthralgia/arthritis, serositis (pleuritis, pericarditis, and serositis of abdominal cavity), renal disorder (persistent proteinuria >0.5 g per day; >3+ by dipstick or presence of active cellular casts; or biopsy evidence of lupus glomerulonephritis), neurological involvement (seizure and psychosis), haematological involvement [anemia, leucopenia (<4000/mm3), thrombocytopenia (<100,000/mm3)] and autoantibodies [anti-dsDNA, anti-Smith (anti-Sm), and anti-phospholipid (aPL)] were defined according to the revised ACR classification criteria for SLE[10]. Additional autoantibodies associated were also studied; including

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anti-Ro, anti-La and anti-ribonucleoprotein (anti-RNP).

Additional neurological features were defined according to the ACR nomenclature and case definitions for neuropsychiatric lupus[11]. Pulmonary manifestations included pulmonary hypertension and pulmonary fibrosis, while gastrointestinal manifestations included mesenteric vasculitis, colitis, and protein losing enteropathy.

Laboratory Studies

ANA was detected by indirect immunofluorescence by using mouse liver and Hep-2 cells as substrate. Anti-dsDNA, anti-Sm, anti-Ro, anti-La, anti-RNP and anticardiolipin (aCL) antibodies were determined by using the enzyme-linked immunosorbent assay (ELISA) kits. An autoantibody was regarded as positive if the patient was ever recorded positive for that specific autoantibody. A positive aCL was defined as a moderate to high level according to the reference ranges. Lupus anticoagulant (LAC) was screened by dilute Russell Venom Viper test and clotting time.

Statistical methods

We used the K-mean cluster analysis (non-hierarchical clustering; Quick cluster analysis) to identify groups of SLE patients with distinct patterns of clinical features. This involved quantifying the degree of similarity between the profiles of the chosen clinical features of two patients by defining a disease metric. The Euclidian distance (the square root of the sums of squared differences between the patients with respect to each clinical manifestation) was then used as a measure of similarity. The initial centers for the clusters were chosen in a first pass of data by the program, and the patients were then assigned to the closest point with respect of the fourteen chosen cumulative recorded clinical features. Then, the cluster points were recalculated based on the patients in the cluster, and the patients were then reassigned. This repetitive process continued until the clusters' means did not shift more than a given cut-off value or the iteration limit was reached.

As we did not know in advance how many clusters of clinical features would be observed, we stated two, three, and then four clusters in the K-mean cluster analysis, respectively, and ran the analysis many times. The outputs (from the analyses with two, three, and four clusters of patients) were then compared with each other with respect of the prevalence of each individual clinical feature.

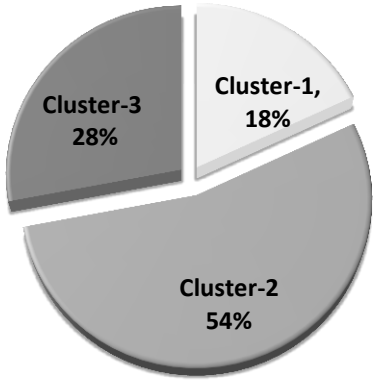
In order to be clinically meaningful in comparing different clusters of patients, we selected the model in which there were the greatest statistical differences in the prevalence of each clinical feature among the outcome clusters. Results are expressed as a mean value for continuous variables, and as numbers (percentages) for categorical variables. Comparing the continuous data was performed by one-way analysis of variance (ANOVA). Post hoc multiple comparisons were performed by using the Tukey test for unequal samples. The chi-squared test was used to compare the frequencies of categorical variables.

Data with a p-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed by SPSS for Windows XP version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 150 Egyptian adult SLE patients were studied. One hundred forty one (94%) patients of the studied group were females and 9 (6%) patients were males with a female to male ratio of (15.6:1).The age of the studied group ranged between 17 to 61 years with a mean of 31.7 ± 10.6 years. Disease duration ranged between 1 to 23 years with a mean of 8 ± 4.7 years. Age at diagnosis ranged between 16 to 48 years with a mean of 28 ± 7.3 years.

Three clusters of patients with distinct patterns of clinical features were identified by the K-mean cluster procedure. Twenty seven patients (18%) were assigned to cluster-1, 81 patients (54%) were assigned to cluster-2 and 42 patients (28%) in cluster-3 as shown in (Graph 1).



Graph (1): SLE clinical clusters of patients (n=150).

By comparing the prevalence of the various clinical manifestations of lupus among the three clusters (Table 1) we have found that; cluster 1 (27 patients; 18%) represented a group of SLE patients with predominant mucocutaneous manifestations (malar rash, discoid rash, photosensitivity, oral ulcer; 96%, 18.5%, 70.3%, and 14.8% respectively) and arthralgia/arthritis (85%) and showed the lowest prevalence of serositis (11.1%), renal manifestations (14.8%), psychosis (0), and hematological manifestations (hemolytic anemia, leucopenia, thrombocytopenia: 3.7%, 14.4%, and 11.1% respectively) among the three clusters.

Cluster 2 (81 patients; 54%) represented predominantly by serositis (22.2%), hematologic involvement (hemolytic anemia, leucopenia, and thrombocytopenia: 23.4%, 35.8%, and 27.1% respectively) and Lupus nephritis (55.5%). The prevalence was significantly higher than that of cluster 1 but was lower than that of cluster 3.

Patients in cluster 3 (42 patients; 28%) had the most heterogeneous features. Besides mucocutaneous and musculoskeletal manifestations [malar rash (100%), discoid rash (9.5%), photosensitivity (23.8%), oral ulcer (11.9%), arthralgia/arthritis (90.4%)]; serositis (30.9%), renal lupus (88%), and hematologic manifestations were also prominent in this cluster compared with cluster 1 and cluster 2.

Furthermore; it was noted that Lupus nephritis was most prevalent among patients of cluster 3; its prevalence was significantly higher than that of both cluster 1 and 2. Pulmonary manifestations (pulmonary fibrosis and pulmonary hypertension) and gastrointestinal manifestations (protein losing enteropathy, mesenteric vasculitis, and colitis) were more common in cluster 2 (7% and 6%, respectively) than the other clusters but with no statistical significance.

Table 1: Comparing the clinical features of the three clusters of SLE patients

	Cluster-1 n=27 (%)	**Cluster-2 n=81 (%)**	**Cluster-3 n=42 (%)**	**P value**
Malar rash	26 (96)*	0	42 (100)*	<0.001
Discoid rash	5 (18.5)*	1 (1.2)	4 (9.5)*	0.03
Photosensitivity	19 (70.3)*	3 (3.7)	10 (23.8)*	0.007
Oral ulcer	4 (14.8)	5 (6.1)*	5 (11.9)	0.04
Arthralgia/arthritis	23 (85)	37 (45.7)*	38 (90.4)	<0.001
Serositis	3 (11.11)*	18 (22.2)	13 (30.9)	0.04
Renal manifestations	4 (14.8)	45 (55.5)*	37 (88)*	<0.001
Seizure	2 (7.4)	5 (6.1)	4 (9.5)	1.20
Psychosis	0*	3 (3.7)	2 (4.7)	0.03
Hemolytic anemia	1 (3.7)*	19 (23.4)	12 (28.5)	0.01
Leukopenia	4 (14.8)*	29 (35.8)	19 (45.2)	0.02
Thrombocytopenia	3 (11.1)*	22 (27.1)	17 (40.4)	0.01
Pulmonary manifestations	3 (11.1)	3 (3.7)	2 (4.7)	0.23
Gastrointestinal manifestations	2 (7.4)	1 (1.2)	0	0.80

As shown in Table 2; patients of cluster **1** were significantly older at the time of SLE diagnosis compared with patients of the other two clusters. There was no significant difference regarding gender distribution among the three clusters of patients (p= 0.11). Patients of cluster 3 had the longest (12.3 years) disease duration while cluster 2 patients had the shortest disease duration (8.2 years) at last follow up with no statistical significance.

Table 2: Comparison between the 3 clusters regarding demographic data and disease duration.

	Cluster-1 n=27 (%)	**Cluster-2 n=81 (%)**	**Cluster-3 n=42**	**P value**
Females	19 (70)	72 (88.8)	34 (80.9)	0.08
Mean Age at diagnosis(years)	33.9*	22.1	23	0.03
Disease duration	9.7	8.2	12.3	0.2

Comparing prevalence of autoantibodies; Cluster 1 patients had the lowest prevalence of anti-dsDNA (22.2%) and antiphospholipid antibody (aPL) (18.5%) compared with patients in cluster 2 and cluster 3. However, there was no significant difference in the prevalence of anti-Sm, anti-Ro, anti-La, and anti-RNP antibodies among the three clusters (Table 3).

Table 3: Comparing the clusters as regarding prevalence of autoantibodies.

	Cluster-1 n=27 (%)	**Cluster-2 n=81 (%)**	**Cluster-3 n=42 (%)**	**P value**
Anti-ds DNA	6 (22.2)*	52 (64.1)	29 (67.7)	<0.001
Anti-Sm	4 (14.8)	7 (8.6)	4 (9.5)	0.21
Anti-Ro	15 (55.5)	43 (53.3)	23 (54.7)	0.98
Anti-La	4 (14.8)	8 (9.8)	4 (9.5)	0.14
aPL	5 (18.5)*	30 (37)	27 (64.2)	0.01
Anti-RNP	5 (18.5)	10 (12.3)	8 (19)	1.1

As for the immunosuppressive therapies (Table 4); patients in cluster 2 and cluster 3 significantly received more cyclophosphamide than patients in cluster 1. While Cluster 1 patients showed the highest prevalence for Methotrexate therapy in comparison with those of both cluster 2 and cluster 3.

Table 4: Comparing the clusters as regard the use of immunosuppressive drugs

	Cluster-1 n=27 (%)	**Cluster-2 n=81 (%)**	**Cluster-3 n=42(%)**	**P value**
Cyclophosphamide	2 (7.4)*	18 (22.2)	14 (33.3)	0.04
Azathioprine	8 (29.7)	40 (49.3)	23 (54.7)	0.05
Methotrexazte	19 (70.3)*	12 (14.8)	14 (33.3)	0.006
Other medications	8 (2.9)	10 (12.2)	6 (14.2)	0.14

DISCUSSION

Systemic lupus erythematosus is a systemic autoimmune disease that is characterized by its myriad clinical and laboratory manifestations, unpredictable course, and variable prognosis. Previous studies have reported the clinical features of different subsets in SLE based on gender[12–14], age at onset of the disease[15–1], individual autoantibody prevalence[5,6,19] and autoantibodies clusters[7]. For example, studies showed that male SLE patients showed a higher incidence of hemolytic anemia and lupus nephritis in comparison to female patients[12-14], childhood-onset SLE tended to have more active renal affection at presentation than adult-onset SLE[18]. Also, the presence of anti dsDNA antibody predicted more frequent and severe lupus nephritis while absence of anti extractable nuclear antibody (ENA) was associated with a more benign form of lupus nephropathy[6,20]; antibody cluster of Sm/ribonuclear protein (RNP) was associated with a lower incidence of renal affection and thrombocytopenia whereas a cluster of dsDNA/ LAC/aCL predicted cerebrovascular affection and venous thrombosis[7].

Few studies have attempted to identify subsets of SLE patients based on the similar patterns of organ manifestations. In the current study, we used the K-mean cluster procedure, a statistical method that can be used to cluster large number of variables into certain patterns. In fact, cluster analysis had been used previously to define different patient groups in SLE[6–8, 20–24]. ***Bokemeyer and Thiele***[22] divided 109 SLE patients into two subgroups using the cluster analysis. One group of patients had a higher incidence of anemia, proteinuria, renal impairment whereas the second group had infrequent renal disease and hence a benign disease course[21,22].

In the present study, data were retrieved from the databases of a main tertiary hospital in Egypt (El-Galaa military hospital), which were updated regularly for new lupus manifestations and treatments given since the diagnosis of SLE. In particular, we compared

the prevalence of the main lupus features including renal, musculoskeletal, mucocutaneous, neurological, pulmonary and gastrointestinal systems in the analysis. Eventually, we were able to demonstrate that disease clinical patterns in SLE do exist, and these may influence the long-term prognosis of the disease.

Patients in the first cluster, which included 18% of the study group of patients, presented at older age on disease onset, with predominance of mucocutaneous and joint affection. It is concomitant to previous reports that a benign clinical subset exists in SLE [8,23–25], with mainly mucocutaneous and musculoskeletal involvement. They had less severe disease and hence required lower cumulative dose of immunosuppressive therapy during their disease course. They represented the SLE subset with the most favorable prognosis. Many authors agree that age at onset of SLE influences the clinical expression of the disease, so that later onset lupus has a different profile, compared with younger patients, the less frequent renal involvement in the elderly has being reported by the majority of authors[26]. Similar clinical subsets of SLE patients were also prescribed by ***Jacobsen et al.***[8] and ***Stenszky et al.*** [23] they both identified a benign clinical subsets of SLE characterized mainly by mucocutaneous manifestations (malar rash and photosensitivity) and by infrequent severe disease, while other subsets suffered from severe renal affection with heavy proteinuria and even renal failure.

Cluster 2 patients (54% of the study group) had uncommon mucocutaneous lesions but had prevalent major organ manifestations like lupus nephritis and hematologic manifestations. Previous studies have reported the close association between lupus nephropathy and hematologic manifestations (hemolytic anemia, leucopenia or thrombocytopenia)[5,8,12,21–24] but the relationship of such disease patterns (renal and hematologic disease) with mucocutaneous lesion have not been discussed.

In cluster 3 (28% of the study group), although similar disease pattern of renal and hematological involvements association was observed; they showed also high prevalence of other systems affection including mucocutaneous, musculoskeletal or serositis. They also showed the highest association with aPL antibodies and represented the worst form of SLE. Previous studies demonstrated the association between aPL antibodies and the presence of a more severe clinical phenotype including (higher prevalence of thrombosis, pregnancy morbidity, valve disease, Pulmonary Hypertension, thrombocytopenia, hemolytic anemia, renal affection, cognitive impairment; and higher risk of organ damage), and thus a worse prognosis SLE[27]. Worth noting; Cluster 3 patients showed the most frequent use of immunosuppressive treatment (cyclophosphamide and azathioprine); unfortunately we do not have the data on the cumulative dose of immunosuppressive therapies used in the three clusters of patients to accurately confirm that association.

In the interpretation of the disease patterns of the study patients, one should take in consideration that the disease duration of the three clusters was unequal. For example cluster 3 patients who represent the worst pattern; they had the longest disease duration. This situation might have influenced the characteristics of patients in different clusters.

There may be concern regarding whether certain organ disease had not yet been manifested in patients with a relatively short duration of disease. For instance, lupus nephropathy might not all be captured. As reported previously that renal disease mostly occurred within 5 years of SLE onset[26].

CONCLUSION

the current study Support the presence of clusters of distinct clinical features in SLE. Recognition of these disease patterns or subsets might be useful in predicting the outcome of the disease and help clinical management and improve the outcome of SLE.

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