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Late-Onset Systemic Lupus Erythematosus: Characteristics And Outcome In Comparison To Adult-Onset Patients A Single-Center Retrospective Cohort

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Abstract:
Late-onset Systemic lupus erythematosus (LSLE) is defined as that developing after the age of 50. We analyzed a single-center retrospective cohort of 269 individuals with SLE from 2012 to 2019 (aged ≥18 years). Patients were classified into two groups based on disease onset (≥18 and <50 years old) and LSLE (≥50 years old). 51/269 (18.9%) were LSLE patients. There is a decrease in female preponderance (p=0.025). Comorbidities were present in almost 30% of elderly-onset patients, thus showing the highest prevalence (p=0.002). Fever was least common among LSLE patients (p < 0.003); We demonstrated the lowest prevalence of mucocutaneous manifestations (p=0.07), including orals ulcers (p= 0.09), and raynaud (p=0.03). Nephritis (p=0.013) and peripheral neuropathy (p = 0.08) were least prevalent in this age group. Older patients have more coronary artery disease compared to younger patients (p=0.005). Serositis (pleurisy (p=0.83), pericarditis (p=0.57)), joint manifestations (p=0.55) and myocardial involvement (p=0.32) does not seem to be common in one of the groups. Anti-ds DNA and anti-Sm was most commonly detected (p < 0.001, p=0.042 respectively). We noted an increase in the incidence of lymphopenia in the late-revealing lupus group (p=0.005). A significant difference of SELENA-SLEDAI activity score between the two groups (p=0.002). We do not object in terms of mortalities between the two groups (p=0.28).We did'nt notice a significant difference in survival between the two groups (p=0.2), but it seems that late-onset lupus is more benign, with less severe manifestations and better survival.

Keywords: *late-onset systemic lupus erythemarosus, mortality*

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I. Introduction:

Systemic lupus erythematosus (SLE) is an obscure autoimmune disease distinguished by the wide variation in its clinical and immunological characteristics, with several factors contributing to the disease's heterogeneity including the influence of female sex hormones, hence making it mostly a disease of child-bearing women [1]. Late-onset SLE, which is defined as that developing after the age of 50, occurs in 2–20% of all patients with SLE [2]. Late-onset SLE is recognized as a more benign disease entity with a favorable natural course[3], while childhood-onset SLE tends to have worse clinical outcomes [4].

Previous reports showed that mortality was significantly higher in late-onset SLE than in younger-onset SLE [2-5-6]. There are contradictory results based on the mild disease course of lateonset SLE, even after allowing for physiological age and comorbidity. Whether the higher mortality of late-onset SLE is a consequence of aging or an impact of SLE itself remains to be established [7].

Interestingly, other key players in the pathogenesis of the disease such as race and ethnicity could affect disease characteristics and outcome [8], with studies investigating LSLE in Morocco, to the best of our knowledge, lacking. Thus, we aimed to obtain more insight regarding the effect of delayed SLE disease onset on clinical phenotype and mortality.

Data on the outcome and predictors of mortality in late onset SLE patients, however, are limited and confined to small numbers of patients [9]. In an aging society, it is important to understand the disease course and mortality of late-onset SLE to provide optimal treatment decisions in elderly patients [7]. In this paper, we retrospectively observed a cohort of late-onset SLE patients and performed survival analysis to examine the independent factors influencing outcome of late-onset SLE. Thus, we aimed to obtain more insight regarding the effect of delayed SLE disease onset on clinical phenotype and mortality.

II. Materials and Methods:

Data collection

We analyzed a single-center retrospective cohort of 269 individuals with SLE from 2012 to 2019 (aged ≥18 years). The cohort included patients with SLE who satisfied four American College of Rheumatology (ACR) criteria for classification of SLE [10], or the 2012 Systemic Lupus Collaborating Clinics (SLICC) classification criteria for SLE [11]. Drug-induced lupus and pure cutaneous lupus with no systemic features were excluded. Patients were classified into two groups based on disease onset: adult-onset SLE (≥18 and <50 years old) and late-onset SLE (≥50 years old).

The following data were collected from the patients' medical records:

- Demographic and socioeconomic variables :
  Age, gender, ethnicity, educational level, age at disease onset defined by the first manifestations attributable to SLE.
- Clinical characteristics: cumulative clinical manifestations were recorded. Manifestations were defined according to the SLICC classification criteria [11], in addition to recording the prevalence of comorbidities and multimorbidity which was defined as the presence of two or more comorbidities (comorbidities ≥ 2) [12].
- Laboratory tests, such as blood and urine routine test, liver and kidney functions, complements (low complements defined as C3 and/or C4 decreased) were measured regularly at every visit. The features of autoantibodies, such as antinuclear antibody (ANA, indirect immunofluorescence using the Hep-2 cells), anti-double-stranded DNA (anti-dsDNA, immunofluorescence against Crithidia luciliae), and extractable nuclear antigens (ENA, anti-Sm, anti-U1RNP, anti-SSA, anti-SSB, and anti-Rib) were determined.
- we analyzed secondary Sjögren's syndrome and antiphospholipid syndrome, according to the accepted definitions.
- Disease activity at the last visit was assessed through the Systemic Lupus Erythematosus Disease Activity Index- 2K (SLEDAI-2K) [13]. Lupus low disease activity (LLDA) was defined as a SLEDAI-2K ≤ 4 in the absence of activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) [14]
- Clinical features included disease duration (period from disease diagnosed to last visit or death), and disease onset age (age at first symptom).
- Therapeutic variables included exposure to high-dose glucocorticoid at first diagnosed (pulse therapy or oral prednisone ≥1 mg/kg day), synthetic antimalarial, immunosuppressive agents treatment (taken methotrexate, mycophenolate mofetil, cyclophosphamide, azathioprine, or combination), biotherapy (rituximab), and medication compliance.

III. Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal–Wallis and Mann–Whitney test corrected by Bonferroni correction was used as a post hoc test. For comparing categorical data, chi-square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 . p values less than 0.05 were considered statistically significant.

IV. Results:

This retrospective cohort included 269 patients, of whom 51 (18.9%) were LSLE patients. Demographic features of the two age groups are shown in Table 1. There is a decrease in female preponderance, with an increase in the prevalence of male involvement (p=0.025).

Comorbidities were present in almost 30% of elderly-onset patients, thus showing the highest prevalence (p=0.002). The most prevalent comorbidities among LSLE patients were hypertension (7/51 (14%)), and diabete (7/51 (14%) (p=0.01 and 0.05 respectively). The

prevalence and nature of comorbidities across the two groups are shown in Table 2.

Several clinical and immunologic differences were detected across the two groups (Table 3). Among the studied constitutional manifestations, fever was least common among LSLE patients (p < 0.003); furthermore, we demonstrated the lowest prevalence of mucocutaneous manifestations (p=0.07), including orals ulcers (p= 0.09), and raynaud (p=0.03). Nephritis (p=0.013) and peripheral neuropathy (p = 0.08) were least prevalent in this age group. Older patients have more coronary artery disease compared to younger patients (p=0.005). Serositis (pleurisy (p=0.83), pericarditis (p=0.57)), joint manifestations (p=0.55) and myocardial involvement (p=0.32) does not seem to be common in one of the groups.

Among the investigated serologic investigations, anti-ds DNA and anti-Sm was most commonly detected ($p < 0.001$, $p=0.042$ respectively). In addition, we noted an increase in the incidence of lymphopenia in the late-revealing lupus group ($p=0.005$).

the mean SELENA-SLEDAI activity score was 15.06 in adolescent and adult youth patients versus 11.58 in elderly subjects with a significant difference between the two groups ($p=0.002$). In addition we do not object in terms of mortalities between the two groups ($p=0.28$) (table 4).

The overall survival of lupus patients is 86.6% with an average survival of 83.3 months +/-1.962. (figure1). The overall survival of young lupus patients is 85.6% while the survival of late-revelation lupus patients is 91.5% ($p=0.2$) (figure2).

We did not notice a significant difference in survival between the two groups, but it seems that late-onset lupus is more benign, with less severe manifestations and better survival.

V. Discussion:

Driven by the hormonal milieu, the occurrence of SLE among the elderly is rather uncommon [15], with a prevalence ranging from 3.5 to 20% across various reports [15-16]. LSLE patients constituted 17% of our cohort, which is higher than the prevalence reported in studies from Turkey (3.6%) [17], Saudi Arabia (2.9%) [18], and Egypt (8.5%) [1]; the prevalence was similar to that observed in Tunisia [19]. This variation in the prevalence of LSLE across various cohorts could be attributed to the different cutoffs in the age chosen to determine elderly onset, which ranged from 50 to 65 years. Elderly-onset SLE was determined in our study at an age of more than 50 years, in concordance with previous studies in the Middle East [1, 18, 19] and worldwide [20–21].

The reduction of female predominance in late onset SLE has been reported in many previous studies, which is attributed to the decreasing impact of female sex hormones in the pathogenesis of the disease in post-menopausal women [5, 22]. In our study, a decreased female-to-male ratio was also observed in the late-onset SLE group compared to the adult-onset SLE group ($p=0.025$).

In the late-onset SLE group lower prevalence values of cutaneous manifestations, photosensitivity, nephritis and CNS involvement were exhibited compared with the adult-onset SLE group [23, 24, 25]. Conversely, more frequent occurrences of serositis and Sjogren syndrome were observed in the late-onset SLE group [23, 26, 27].

There was a decreased tendency for the late onset SLE group to have typical manifestations of SLE in our study. Serositis was less prevalent in the late-onset SLE group in our study, without any difference between the two groups, which is not consistent with previous studies. This mild presentation of late-onset SLE is unlike the classic forms and is likely to be substantially underdiagnosed in clinical practice.

Among the serologic features investigated, positive anti-ds DNA antibodies and anti Sm were highest among our LSLE patients ($p < 0.001$ and $p=0.042$ respectively), contradictory to several reports [21, 24]. No significant differences were found in the incidence of other antibodies (anti SSA, anti SSB, anti-RNP, and anti-phospholipid antibody) [7].

The main challenge of managing LSLE patients stems from the high prevalence of comorbidities, a finding reported by various studies [28–29] and demonstrated among our elderlyonset patients ($p=0.002$). Several authors detected a higher prevalence of diabetes mellitus [28, 30], and hypertension [21, 28, 30] among their LSLE patients, thus resembling our cohort. Moreover, multimorbidity (comorbidities ≥ 2) was most commonly detected among our LSLE patients, which is similar to previous reports [31].

Late-onset SLE had lower SLEDAI scores at onset and during the first year of disease than younger SLE patients in another report [7]. Our report showed significantly lower maximum SLEDAI-2K in the late-onset SLE group compared with adult-onset SLE. This agrees with the lower disease activity of SLE in the elderly from a previous report [28]. Earlier reports have shown that the occurrence of organ damage assessed by SDI was greater in patients with late onset SLE [32, 33], thus, lupus cannot be judged to be more benign in this age group. Other reports have found no difference in SDI score between the two groups [34]. In our study, patients with late-onset lupus had low disease activity compared to younger subjects ($p=0.002$). The prevalence of mortality was comparable across the two age groups ($p = 0.28$), which is contradictory to that of previous reports [22, 35, 36] but similar to another [1, 34].

We did not notice a significant difference in survival between the two groups, but it seems that late-onset lupus is more benign, with less severe manifestations and better survival. Given the relatively favorable prognosis of late-onset SLE, cumulative damage is likely multifactorial and results from aging-related comorbidity and medication toxicity [7].

VI. Conclusion:

LSLE patients in our cohort were characterized by the lowest prevalence of major organ involvement and demonstrated the lowest disease activity and damage scores. But they showed the highest prevalence of comorbidities, hence showing several similarities and disparities to their peers across the globe which could be attributed to several factors including the retrospective nature of the studies, the rather small number of elderly-onset patients, and the different inclusion criteria, a prospective study is needed for a better evaluation of the disease.

Disclosure of interest: The authors declare that they have no competing interest.

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	Young and adult onset	Late onset	P value
Age (years)			
Age at last visit or mortality	32.1 [15-49]	56.6[50-75]	
Gender			
Male	7	11	0.025
female	204	40	
Disease duration (months)	48.8	48.2	0.92

Table 1: Demographic characteristics of the two age groups

	Young and adult onset	Late onset	P value
Comorbidities	29 (13%)	15 (30%)	0.002
Nature of comorbidities			
Diabete	4	7	0.01
Hypertension	22	7	0.05
Hypothyroidisme	0	1	~
Cerebral vascular accident	2	0	~

Table 2: The nature and prevalence of comorbidities across the two age groups

	Young and adult onset	Late onset	P value
Fever	56	3	0.003
Mucocutaneous	161	29	0.07
Malar rash	121	23	0.51
Photosensitivity	145	28	0.49
Alopecia	53	8	0.34
Oral ulcers	41	4	0.09
Disoid rash	26	5	0.81
Panniculitis	2	0	0.37
raynaud	26	3	0.03
Articular	168	39	0.55
Arthralgia	168	39	0.55
Arthritis	81	20	0.62
Jaccoud	13	6	0.12
serositis			
Pleurisy	41	8	0.83
pericarditis	56	10	0.57
myocarditis	13	1	0.32
Coronaropathy	0	3	0.005
Nephritis	94	11	0.013
Neuropsychiatric	52	11	0.90
Seizures	17	5	0.17
Cerebral vasculitis	15	3	0.23
Ischemic stroke	3	0	0.55
Psychosis	15	2	0.22
Peripheral neuropathy	7	4	0.08

Hematologic	136	22	0,014
Hemolytic anemia	13	3	0.93
Thrombocytopenia	44	7	0.11
Leukopenia	46	7	0.10
Lymphopenia	127	47	0.005
Immunologic characteristics			
ANA	205	44	0.17
Anti DNA	165	21	0.00
Anti Sm	51	18	0.042
Anti-Ro/SSA	55	15	0.25
Anti-La/SSB	34	8	0.16

Table 3: Cumulative clinical and immunologic characteristics across the two age groups

	Young and adult onset	**Late onset**	**P value**	**IC 95%**
Disease activity SELENA-SLEDAI	15.06+/-8.897	11.58+/-5.961	0.002	1.292-5.673
Mortality	31	4	0.28	0.182-1.640

Table 4: Disease activity and outcome across the two age groups

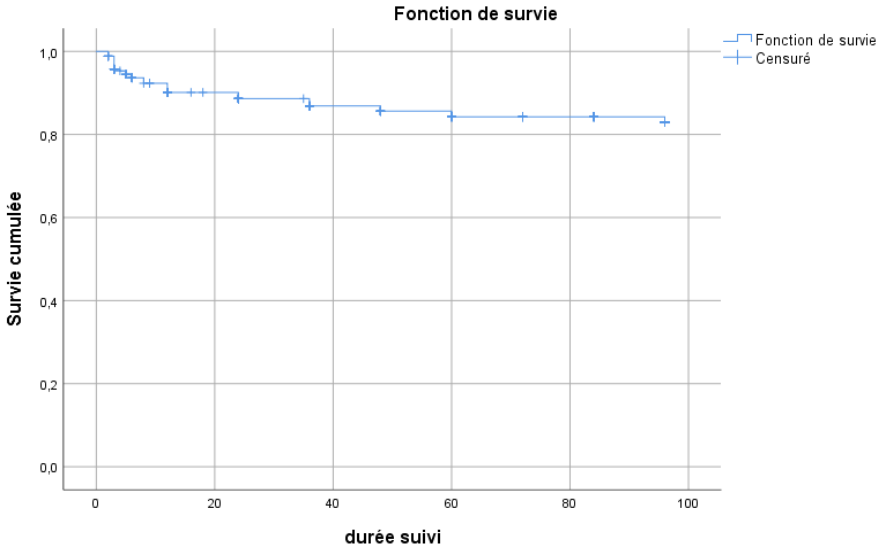

Figure 1: total survival of lupus patients

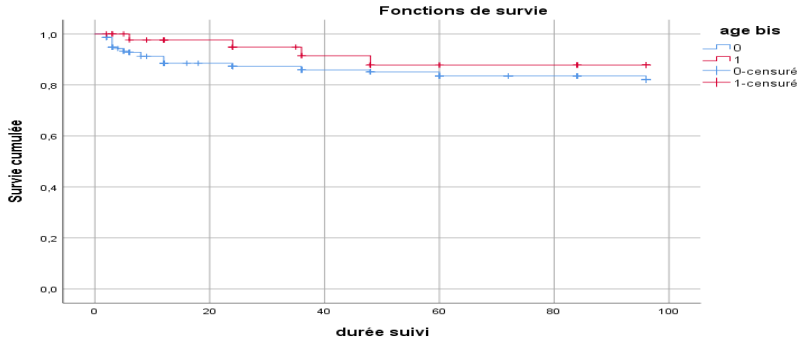

Figure 2: Kaplan-Meier survival curve of young-adult-onset and late-onset systemic lupus erythematosus.

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