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Original Article

Clinical features, serological findings, and survival rate comparison between early versus late-onset systemic lupus erythematosus from 2000 to 2010, two centers experience

Mousa N. Alrashdi[1], Alrasheedi, Sami Meateq[1], Ahmad Alkhdairi[1], H. A. Alsulmi[2], Al Anzi Faisal[3], A. Almutlaq[4], Naila A. Shaheen[5,6], Abdulrahman Balkhoyor[5], Abdulrahman S. Alamri[5], Abdulrahman Alrashid[5,7], Hesham Almaimony[5,7], Saleh Al Motywea[5,7], Ghassan Aljehani[5,7]

[1]Department of Medicine, College of Medicine, Unaizah College of Medicine and Medical Sciences, Qassim University, Kingdom of Saudi Arabia, [2]Department of Medicine, Collage of Medicine, Qassim University, Kingdom of Saudi Arabia, [3]Department of Medicine, College of Medicine, Majmaah University, Al-Majmaah, Saudi Arabia, [4]Department of Rheumatology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [5]King Abdullah International Medical Research Center Riyadh, Saudi Arabia, [6]Department of Biostatistics and Bioinformatics, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [7]Department of Rheumatology, Ministry of National Guard - Health Affairs, Riyadh, Saudi Arabia

Address for correspondence:
Mousa N. Alrashdi, Department of Medicine, College of Medicine, Unaizah College of Medicine and Medical Sciences, Qassim University, P.O. Box 911, Onaizah 51911, Kingdom of Saudi Arabia.
Tel.: +966 163610902/+966501802880.
E-mail: mosa4444@hotmail.com

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ABSTRACT

Objective: The study aimed to compare the differences in patients diagnosed with early versus late-onset systemic lupus erythematosus (SLE) in terms of clinical features, disease activity, laboratory findings, and the 5-year survival rate.

Methods: All newly diagnosed SLE patients from 2000 to 2010 in two tertiary centers in Saudi Arabia were enrolled. Retrospectively, early-onset SLE (18–49 years at the age of diagnosis) was compared to late-onset SLE (≥50 years at the age of diagnosis) using chart review of their clinical features, serology, and organ damage and disease activity.

Results: A 196 SLE patients were included, 156 were in the early-onset SLE group while 40 in the late-onset SLE group. Arthritis was a frequent symptom in both groups. Proteinuria and anemia were prevalent in the early-onset SLE group (46.4%, 82.1%). The majority of the early-onset SLE (78.2%) group were anti-dsDNA positive compared to 42.5% in the late-onset SLE group. Similarly, 78.4% of the early-onset SLE group had hypocomplementemia compared to 44.7% in the late-onset SLE group. Renal insufficiency and thromboembolic events were more prevalent in the early-onset SLE group (24.2%, 13.6%), while pulmonary hypertension and hepatitis more prevalent in the late-onset SLE group (15% and 20%, respectively). Estimated 5-year survival analysis was lower in the late-onset SLE group compared to the early-onset SLE group.

Conclusion: Early-onset SLE had a higher frequency of American College of Rheumatology criteria than the late-onset SLE group. However, the late-onset SLE group exhibited a higher frequency of medical comorbidities with a lower 5-year survival rate.

Keywords: Early-onset systemic lupus erythematosus, late-onset systemic lupus erythematosus, prognosis, Saudi Arabia, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease resulting from chronic and recurrent activation of the immune system contributing to inflammation and tissue destruction involving different organs. It frequently occurs in reproductive-age women and the onset of SLE after 50 years occurs in only 3–18% of patients.[1] Late-onset SLE (age ≥50 years at diagnosis) has a strong modifying effect on the clinical presentation, disease course, response to treatment,

and prognosis of SLE.[2,3] In comparison with Early-onset SLE (age <50 years at diagnosis), late-onset SLE has a more insidious onset of the disease and a lower prevalence of severe manifestations.[4,5] The diagnosis of late-onset SLE is often delayed and only established after more extensive investigations. Late-onset SLE has a higher mortality rate compared to early-onset SLE; probably due to the negative impact of age and associated comorbidities, and the specific effect of lupus in these patients.[5-9] There are also variations in clinical features, organ involvement, and differences in laboratory findings of SLE in the different age groups. Just more than one third (35%) of mortality in SLE is caused by the active disease in young patients compared to the elderly.[3,10-12] Comparative studies reported variable conclusions, while one study reporting similar clinical features and prognosis in all age groups; the others indicated that cutaneous, renal, and hematological manifestations are more prevalent in early-onset SLE, in addition, late-onset SLE patients had a poor prognosis due to higher comorbidities and risks of cardiovascular diseases.[8,13-15] The aim of this study is to compare clinical features, laboratory findings, and survival rates between early and late-onset SLE groups in the Saudi Arabian population.

Materials and Methods

This was a retrospective cohort study of patients diagnosed with SLE at King Abdulaziz Medical City (KAMC) and King Faisal Hospital and Research Center (KFH and RC) in Riyadh, Saudi Arabia, from January 2000 to December 2010. Ethical approval was obtained from the Institutional Review Board of King Abdullah International Medical Research Center and KFH and RC, Riyadh, Saudi Arabia. The diagnosis was based on the presence of at least four of the revised American College of Rheumatology (ACR) criteria. Clinical presentation, laboratory findings, organ involvement, and the European Consensus Lupus Activity Measurement (ECLAM) score based on the available data at the time of diagnosis were collected. The patient data were collected from the time of diagnosis to the latest documented visit to the hospital and entered in an excel sheet for analysis.

Patient's characteristics

All newly diagnosed SLE patients after January 2000, older than 18 years, were included in the study. Early-onset SLE was categorized as age <50 years and late-onset SLE as an age ≥50 years at the time of diagnosis. Patients who did not meet at least four of the revised ACR criteria, drug-induced SLE, as well as mixed and undifferentiated connective tissue diseases were excluded from the study.

Variable selection

Demographic variables included age at diagnosis, duration of disease at the time of data collection, and gender. Clinical manifestations and laboratory findings included the revised ACR criteria and other such as fever, fatigue, weight loss, and red eyes.[9] Comorbidities at the time of SLE diagnosis, including diabetes mellitus, hypertension, congestive heart failure, dyslipidemia, hypothyroidism, chronic liver disease, and chronic obstructive pulmonary disease. In addition, data were collected for other rheumatologic diseases such as rheumatoid arthritis, Sjogren's syndrome, and antiphospholipid syndrome diagnosed by a rheumatologist. Disease activity was retrospectively measured with the validated ECLAM score.[16] Organ involvement variables included ophthalmological (optic neuropathy or retinal vasculopathy), renal involvement (proteinuria "24-h urine proteinuria ≥0.5 mg" or biopsy-based lupus nephritis), central nervous system involvement (unprovoked seizure disorder, psychosis, or cerebrovascular accident), pulmonary involvement (pulmonary hypertension, interstitial lung disease, or alveolar hemorrhage), gastrointestinal involvement (esophagitis, peptic ulcer disease, pancreatitis, hepatitis, or mesenteric ischemia), and cardiac involvement (pericarditis, myocarditis, or pericardial effusion) were collected if present at any stage of the disease period. Finally, the date of death and the last consultation date were collected.

Statistical analysis

Categorical variables included gender, diabetes, hypertension, dyslipidemia, hypothyroidism, chronic obstructive pulmonary disease, alveolar hemorrhage, pulmonary hypertension, interstitial lung disease, pleuritis, rheumatoid arthritis, Sjögren's syndrome, antiphospholipid syndrome, thromboembolic event, malar rash, discoid rash, photosensitivity, oral ulcer, arthritis, fatigue, fever, weight loss, pericarditis, pericardial effusion, myocarditis, hematuria, proteinuria, lupus nephritis stages, decreased creatinine clearance, seizure, psychosis, stroke, esophagitis, peptic ulcer disease, pancreatitis, hepatitis, mesenteric ischemia, episcleritis, red-eye, optic neuropathy, retinal vasculopathy, anemia, leukopenia, thrombocytopenia, positive anti-dsDNA, positive anti-Sm, positive antinuclear antibodies (ANA), low complement 3, and low complement 4 are summarized as frequency and percentage. Continuous variables included that age at diagnosis and ECLAM score is reported as mean and standard deviation (M ± SD). All the variables of the two groups were compared using a Chi-square test of independence and a *t*-test. Statistical tests were declared significant at (α-level <0.05). Kaplan-Meier survival was used to estimate the 5-year survival rate. The survival rates between early and late-onset SLE were compared using a log-rank test. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographic and baseline characteristics

From Table 1, a total of 196 SLE patients were included, 131 from KAMC and 65 from KFSH and RC. The majority

Table 1: Demographic and baseline characteristics of adult-onset and late-onset SLE

Variable	Early-onset SLE (18–49) *n*=156	Late-onset SLE (≥50) *n*=40	*P*-value
Age at diagnosis (mean±SD)	27.09±8.16	56.61±6.12	
Gender			
Female *n* (%)	142 (91.1)	29 (72.5)	0.002*
Male	14 (8.9)	11 (27.5)	
Comorbidities			
Diabetes mellitus	5 (3.3)	10 (25)	<0.0001**
Hypertension	19 (12.3)	20 (50)	<0.0001*
Dyslipidemia	5 (3.3)	5 (12.5)	0.033**
Hypothyroidism	11 (7.1)	32.5 (13)	<0.0001**
COPD[a]	0 (0)	2 (5)	0.041**
Rheumatologic disease			
Rheumatoid arthritis	4 (2.61)	2 (5)	0.605**
Sjögren syndrome	2.61 (4)	4 (10)	0.059**
Antiphospholipid syndrome	24 (15.7)	1 (2.5)	0.027*

[a]Chronic obstructive pulmonary disease. **P* is based on Chi-square test.***P* is based on Fisher's exact test. SLE: Systemic lupus erythematosus

(79.6%, $n = 156$) had early-onset SLE with a small proportion (20.4%, $n = 40$) late-onset SLE. All were Saudis. The mean age for the early-onset SLE group was 27.09 ± 8.16 and for the late-onset SLE group 56.61 ± 6.12. The majority in both groups were female (91.1% and 72.5% in Early-onset SLE and Late-onset SLE, respectively). Overall, there was a higher prevalence of medical comorbidities in the late-onset SLE group [Table 1]. Diabetes mellitus and hypertension at the time of SLE diagnosis were more prevalent in the late-onset SLE group compared to the early-onset SLE (25% and 50% vs. 3.3% and 12.3%, $P < 0.0001$). Antiphospholipid syndrome was associated more with the early-onset SLE group compared with the late-onset SLE (15.7% vs. 2.5%, $P = 0.027$), while Sjögren's syndrome was more prevalent in the late-onset SLE (10% vs. 4%, $P < 0.059$).

ACR criteria and clinical presentation [Table 2]

Arthritis was the most frequent clinical presentation for both groups (early-onset-SLE 81.4% and late-onset SLE 85%). In early-onset SLE malar rash, proteinuria and anemia were more frequent (32.9% $P = 0.057$, 46.4% $P = 0.0006$, and 82.1% $P < 0.0001$, respectively). In addition, in the early-onset SLE group, fever (38.5%, $P = 0.059$) was more prevalent, but fatigue and weight loss showed no difference. No patients in the late-onset SLE group developed pericarditis or seizure, but it was the presenting symptoms in eight patients (5.1%) and 12 patients (7.7%) in the early-onset SLE group, but not statistically significant.

All patients were positive for immunofluorescence ANA and 78.2% were anti-dsDNA positive in early-onset SLE with 42.5% in late-onset SLE ($P < 0.0001$). In addition, a significantly lower complement level was recorded in the early-onset SLE group compared to the late-onset SLE group (78.4%, 44.7%, $P < 0.05$). Although a higher proportion of the early-onset SLE had anti-SM, the difference was not statistically significant.

Disease activity and organ involvement

Table 3 displays the involvement of various organs. Decreased creatinine clearance and thromboembolic events were significantly higher in the early-onset SLE (24.1%, $P = 0.050$ and 13.5%, $P = 0.008$) with pulmonary hypertension, interstitial lung disease, and hepatitis higher in late-onset SLE group (15%, $P = 0.010$, 15%, $P = 0.002$, and 20%, $P = 0.009$). A renal biopsy was done in 57 patients with early-onset SLE and five patients with late-onset disease. Class IV lupus nephritis was the most frequent histopathological abnormality. Eye involvement was observed in three patients with early-onset SLE, optic neuropathy in one, and retinal vasculopathy in the other two. The seizure occurred in 12 patients with early-onset SLE with none in the late-onset SLE group. The involvement of the other organs is displayed in Table 3.

The difference in disease activity, as measured with the mean ECLAM Score, in both groups, was not statistically significant (5.2 vs. 4.6, $P = 0.107$).

Five-year survival rate

Using the Cox proportional model and reporting the results as a hazard ratio and 95% confidence interval, the overall 5-year survival analysis was probably lower in the late-onset SLE group compared to the early-onset SLE group [Figure 1]. However, in both groups, three patients died. The cause of death in the early-onset SLE group was severe sepsis due to lower respiratory tract infection, hemorrhagic stroke, and cardiogenic shock. In the late-onset SLE group, one died due to a massive pulmonary embolism and two patients died due to septic shock with no clear focus.

Table 2: Comparison of ACR[a] criteria and clinical presentations between early-onset and late-onset SLE

Variables	Early-onset SLE (18–49) *n*=156	Late-onset SLE (≥50) *n*=40	*P*-value
Malar rash *n* (%)	51 (32.9)	7 (17.5)	0.057*
Discoid rash	10 (6.5)	2 (5)	1.000**
Photosensitivity	28 (18)	5 (12.5)	0.411*
Oral ulcer	34 (21.9)	7 (17.5)	0.539*
Arthritis	127 (81.4)	34 (85)	0.596*
Serositis			
Pleuritis	26 (16.67)	10 (25)	0.224*
Pericarditis	8 (5.2)	0 (0)	0.209*
Renal disorder			
Proteinuria	71 (46.4)	6 (15.8)	0.0006*
Lupus nephritis	57 (37)	5 (12.5)	0.003*
Neurological disorder			
Seizure	12 (7.7)	0 (0)	0.131**
Psychosis	7 (4.5)	3 (7.5)	0.431**
Hematological disorder			
Anemia	124 (82.1)	15 (37.5)	<0.0001*
Leukopenia	59 (38.8)	9 (22.5)	0.054*
Thrombocytopenia	34 (22.3)	5 (12.5)	0.167*
Immunological marker positivity			
Anti-dsDNA[b]	115 (78.2)	17 (42.5)	<0.0001*
Anti-Sm	21 (25.6)	5 (16.6)	<0.320*
ANA[c]	156 (100)	40 (100)	
Clinical presentations			
Fatigue	73 (46.8)	20 (50)	0.717*
Fever	60 (38.5)	9 (22.5)	0.059*
Weight loss	35 (22.4)	11 (27.5)	0.500*
Episcleritis	1 (0.7)	1 (2.5)	0.372**
Red eye	6 (3.9)	0 (0)	0.349**
Hematuria	12 (7.7)	3 (7.5)	1.000**
Low complement 3	113 (78.5)	17 (44.7)	<0.0001*
Low complement 4	67 (46.5)	10 (26.3)	0.0249*

[a]American College of Rheumatology, [b]Anti-double Strand DNA antibodies, [c]Immunofluorescence Antinuclear Antibodies, **P* is based on Chi-square test. ***P* is based on Fisher's exact test. SLE: Systemic lupus erythematosus

Discussion

The age at disease onset plays a fundamental role in the expression and course of SLE. Early-onset SLE patients differ from late-onset SLE patients in the severity of the disease, clinical presentation, prognosis, and pattern of organ involvement. There could also be inter-ethnic differences in some of these clinical features.[5-7,17] Therefore, the study aimed to compare the differences in patients diagnosed with early versus late-onset SLE in terms of clinical features, disease activity, laboratory findings, and the 5-year survival rate.

In the current study, the prevalence of late-onset SLE was lower than the early-onset SLE. Similar results have been reported in literature.[18-20] In terms of gender, the majority was female (91.1% in early-onset SLE and 72.5% in Late-onset SLE). The study of Boddaert *et al*. supported the finding reporting that 93% of the early-onset SLE group and 72.3% of the late-onset SLE group was female.[4] Mohamed *et al*. reported a female:male ratio of adult SLE as 10:1.[21] The Das Chagas Medeiros *et al*. study also reported 93.5% female, but this high ratio could be because 81% of their sample was adult-onset SLE.[15] The finding was expected as SLE affects women predominantly young women (childbearing age) 9 times more frequently than men, with the frequent exacerbations during pregnancy, indicating a role of estrogens as a precipitating factor.[17] In addition, the cultural requirement for women to cover-up caused a high prevalence of Vitamin D deficiency, which could play an additional role in autoimmune diseases.[21] Based on the current results, the female-to-male ratio declines in Late-onset SLE, as supported in literature.[4,18,22] Menopause and the reduced production of estrogen may explain the

Table 3: ECLAM score and organ involvement in early versus late-onset SLE

Organ involved	Early-onset SLE (18–49) *n*=156	Late-onset SLE (≥50) *n*=40	*P*-value
ECLAM[a] score (mean)	5.23±2.14	4.60±2.13	0.107
Ocular			
Optic neuropathy	1 (1.3)	0 (0)	1.000*
Retinal vasculopathy	2 (1.3)	0 (0)	1.000*
Renal			
Decreased CrC[b]	37 (24.2)	4 (10)	0.050*
Lupus nephritis	57	5	
Lupus nephritis Class I	2	1	
Lupus nephritis Class II	4	0	
Lupus nephritis Class III	8	0	
Lupus nephritis Class IV	26	2	
Lupus nephritis Class V	17	2	
CNS			
Seizure	12 (7.7)	0 (0)	0.069*
Psychosis	7 (4.5)	3 (7.5)	0.431**
Stroke	7 (4.6)	1 (2.5)	1.000**
Pulmonary			
Alveolar hemorrhage	3 (1.9)	2 (5)	0.272**
Pulmonary hypertension	5 (3.3)	6 (15)	0.010**
Interstitial lung disease	3 (2)	6 (15)	0.002**
Gastrointestinal			
Esophagitis	3 (2)	2 (5)	0.274**
Peptic ulcer disease	10 (6.5)	2 (5)	1.000**
Pancreatitis	1 (0.7)	0 (0)	1.000**
Hepatitis	9 (5.8)	8 (20)	0.009**
Mesenteric ischemia	4 (2.6)	0 (0)	0.583**
Cardiac			
Pericardial effusion	15 (9.7)	2 (5)	0.532**
Pericarditis	8 (5.2)	0 (0)	0.209**
Myocarditis	5 (3.2)	2 (5)	0.633**
Thromboembolic events	21 (13.6)	0 (0)	0.008**

[a]European consensus lupus activity measurement. [b]Creatinine clearance. **P* is based on Chi-square test. ***P* is based on Fisher's exact test. SLE: Systemic lupus erythematosus

decrease of both the SLE incidence and the gender ratio with aging.[4] In contrast, Aljohani *et al*. reported that the female-to-male ratio was the same in early and late-onset SLE.[6]

Regarding the comorbidities associated with SLE, the current study found that diabetes mellitus and hypertension were more prevalent in late-onset SLE compared to early-onset SLE. Das Chagas Medeiros *et al*. reported similar results in their study in Brazil and Sonia *et al*. in Tunis.[15,18] The higher frequency of SLE comorbidities in older individuals could be due to aging, longer exposure to classical risk factors, and use of corticosteroids.[18] In the present study, there was a significant increase in the number of patients with Sjögren syndrome in the late-onset SLE group; this finding is also supported in literature, but contrasted by Sonia *et al*. who found no significant difference in the frequency of Sjögren's syndrome between the two groups.[18,23,24] The symptoms of Sjögren syndrome may be associated with other frequent causes of mucosal dryness in an elderly population, such as polypharmacy, chronic debilitating diseases, and senile salivary gland atrophy.[18]

Regarding clinical presentation, arthritis was the most frequent clinical presentation for both groups, a similar finding is also reported by Budhoo *et al*.[25] In the current study, the late-onset group had a slightly higher prevalence (85% vs. 81.4%). In contrast, several studies reported arthritis to be less frequent in late-onset SLE patients.[4,26,27] In the present study, the frequency of malar rash was higher in the early-onset SLE group which is in contrast to Tomic-Lucic *et al*. and Appenzeller *et al*. who reported an increase in the frequency of malar rash in the late-onset SLE group.[13,26] Similarly, anemia was more frequent in the early-onset SLE group (82.1%) in contrast with Tomic-Lucic *et al*. reporting hematological

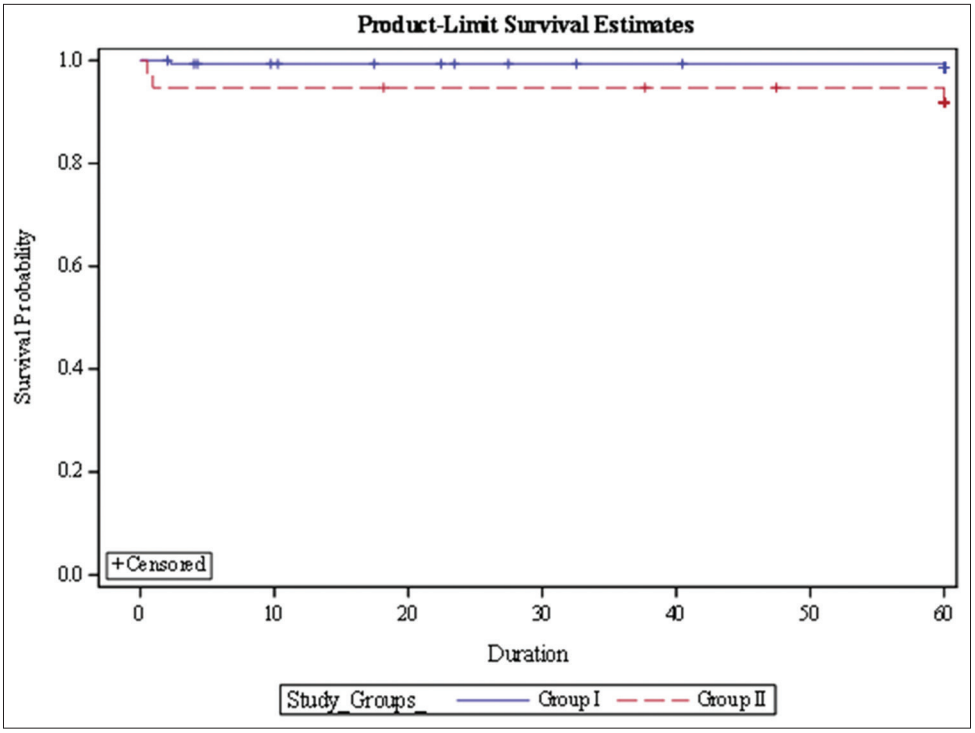

Figure 1: Five year (60 months) overall survival. Group I = Early-onset SLE, Group II = Late-onset SLE

abnormalities equal in the two groups and Appenzeller *et al*. who reported that hemolytic anemia and thrombocytopenia were more frequently in the Late-onset SLE group.[13,26]

Serological findings in the current study reported all patients positive for ANA with anti-dsDNA positivity and anti-SM higher in the early-onset SLE group. These results were confirmed by Tomic-Lucic *et al*., who reported a lower prevalence of anti-dsDNA and anti-SM antibodies in the late-onset SLE group but in contrast to Sonia *et al*. who found the same results higher in the early-onset SLE group.[13,18] The effect of SLE on the organs of patients differed in the two groups. In the current study, proteinuria was higher in the early-onset SLE group (46.4%). Proteinuria identifies patients with renal damage, those at risk for deteriorating renal disease and increased cardiovascular morbidity. The finding is consistent with Tomic-Lucic *et al*. and Aljohani *et al*., reporting a lower prevalence of nephritis in the late-onset SLE group.[6,13] Pulmonary hypertension, interstitial lung disease, and hepatitis had a higher frequency in the late-onset SLE group (current study), because the degree of cumulative organ damage correlates directly with the age of onset, increasing with age.[13]

This study used the ECLAM score to assess disease activity and the difference in disease activity in both groups was not statistically significant. Using the cox proportional model and reporting the results as a hazard ratio, the overall 5-year survival analysis was probably lower in the late-onset SLE group compared to the early-onset SLE group. Literature consistently reports a higher mortality rate in the late-onset SLE group, possibly due to aging, the lack of efficiency of the body organs as a result of aging and SLE, as well as complications due to comorbidities, and an increased risk of toxicities from immunosuppressive drugs.[6,8,18,26]

Conclusion

This study conducted on Saudi patients suffering from SLE highlighted differences in between the early-onset and late-onset SLE. Compared with the early-onset SLE group, the late-onset SLE group exhibited a higher frequency of medical comorbidities such as diabetes mellitus and hypertension. The early-onset SLE had a higher frequency of ACR criteria and other clinical presentations such as malar rash. Hematological abnormalities, specifically anemia, renal impairment due to lupus nephritis, and thromboembolic events, had a significantly higher frequency in the early-onset SLE group. More patients with late-onset SLE presented with respiratory and gastrointestinal involvement. An analysis of the estimated 5-year survival rate was lower in the late-onset SLE group; however, it was not significant. It is important for the health-care practitioner treating a patient with late-onset SLE to manage the medical comorbidities and use preventive medicine to achieve a better patient outcome.

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Institutional Review Board of King Abdullah International Medical Research Center and KFH and RC, Riyadh, Saudi Arabia. It is unnecessary to yield informed consent for its retrospective character.

Availability of Data and Material

The data used in this study are available and will be provided by the corresponding author on a reasonable request.

Competing Interests

All authors declare that they have no conflicts of interest.

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Authors' Contributions

All authors were involved in data collection, data interpretation, and manuscript drafting, but the study was designed by the corresponding author.

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