Article

chronic illness

Chronic Illness
2023, Vol. 19(4) 791–803

DOI: 10.1177/17423953221138921
journals.sagepub.com/home/chi

Sage

Comorbidities among Egyptian systemic lupus erythematosus: The COMOSLE-EGYPT study

Sherif M Gamal[1], Abir Mokbel[1,2], Marwa H. Niazy[1], Fatema T Elgengehy[1], Nora Y Elsaid[1], Nermeen A. Fouad[3], Nesreen Sobhy[1], Marwa Tantawy[4], Sally S. Mohamed[1], Rasha M Ghaleb[5], Enas A Abdelaleem[4] and Bassel El-Zorkany[1]

Abstract

Objective: To study the prevalence and impact of comorbidities among a cohort of patients with systemic lupus erythematosus (SLE).

Methods: This study is retrospective, multicenter including 902 Egyptian patients with SLE. Medical records were reviewed for demographic data, clinical characteristics, routine laboratory findings, immunological profile, and medications. Moreover, SLE Disease Activity Index (SLEDAI), and the Systemic Lupus International Collaborating Clinics/American College Rheumatology Damage Index scores were calculated.

Results: Comorbidities were found in 75.5% of the studied group with hypertension and dyslipidemia as the most frequent comorbidities (43.1% and 40.1%, respectively), followed by sicca features, avascular necrosis, diabetes, osteoporosis and renal failure (11.5%,9%, 9%,8.9%, and 7.1%, respectively). Multivariate regression model showed statistically significant relation between the presence of comorbid condition and each of age ($P = 0.006$), disease duration ($P = 0.041$), SLEDAI at onset ($P < 0.001$), cyclophosphamide intake ($P = 0.001$), and cumulative pulse intravenous methylprednisone ($P < 0.001$). Also, when adjusted to age and sex, those with multiple comorbid conditions had 18.5 increased odds of mortality compared to those without comorbidities (odds ratio (OR), 95% confidence interval (CI) = 18.5 (6.65–51.69)].

[1]Rheumatology Department, Cairo University, Cairo, Egypt
[2]Health Research Methodology Department, McMaster University, Hamilton, Canada
[3]Rheumatology Department, Fayoum University, Cairo, Egypt
[4]Rheumatology Department, Beni Suef University, Beni Suef, Egypt
[5]Rheumatology Department, Menia University, Cairo, Egypt

Corresponding author:
Sally S Mohamed, Rheumatology Department, Cairo University, Cairo 11562, Egypt.
Email: sallysamy.elmaghraby@gmail.com

Conclusion: Patients with SLE suffer from several comorbidities, with an increasing risk with age, longer disease duration, higher SLEDAI at onset, cyclophosphamide intake and cumulative pulse intravenous methylprednisone. Risk of mortality is exponentiated with multiple comorbidities.

Keywords
Systemic lupus erythematosus, comorbidities, Egyptian patients

Received 16 February 2022; accepted 15 October 2022

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory multisystem autoimmune disease that can affect many organs of the body, alter their function, causing organ damage.[1] Although the health outcomes of patients with SLE have improved over the past decades, SLE long-term prognosis remains poor. There is a higher comorbidity burden from the disease itself and/or the drug therapy notably steroids and immunosuppressants,[2] with a greater rate of mortality (about threefold) as compared to the general population.[3] People with SLE are recognized to be at increased risk of developing certain comorbidities such as cardiovascular disease (CVD),[4] insulin resistance, and metabolic syndrome,[5] which make the risk of cardiovascular morbidity and mortality 1.3 to 2.7 times higher in patients with SLE than in the general population.[6] Other comorbidities include stroke,[7] osteoporosis,[8] infection (especially pneumonias and urinary tract infections),[9] and end-stage renal failure in 16% to 45% of cases during their disease course.[10] The risk of malignancy in SLE is controversial, with the concept of chronic B and T cells activation as a driving force for the cancer comorbidity development as in Hodgkin's lymphoma.[11] Associated comorbidities can lead to a more aggressive course of management, an increased health-care costs, a negative impact on quality of life, and a worse prognosis.[12] Charlson Comorbidity Index (CCI) is a predictor of mortality risk of comorbid diseases and is negatively associated with survival. It was reported to be elevated in patients with SLE.[13] Monitoring, prevention, and management of risk factors for comorbidities are highly recommended by The European Alliance of Associations for Rheumatology.[14]

The aim of the present study is to report associated comorbidities among an Egyptian cohort of patients with SLE, its relation to different demographic and disease parameters, and to study the mortality risk in the SLE cohort in context to associated comorbidities.

Methods

Study population

This is a multicenter, retrospective cohort study which included patients attending rheumatology units in four university hospitals in Egypt (Cairo, Beni-Suef, Menia, and Fayoum) in addition to a private center in Fayoum. The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Data collection

Medical records of 1014 patients with SLE were screened. The inclusion criterion was fulfilling the 1997 American College Rheumatology (ACR) classification criteria for SLE.[15] Additionally, patients with secondary antiphospholipid syndrome (APS) fulfilling the revised Sapporo classification criteria for APS were included.[16] Out of the 1014 screened medical records, 112 patients were excluded due to: missed data, disease duration less than 6 months, and those with 3 or less follow-up visits documented in their files.

The abstracted data of 902 patients with SLE included demographics (age, age of onset, sex, and disease duration), clinical disease characteristics (constitutional, mucocutaneous, cardiopulmonary, renal, neuropsychiatric, gastrointestinal, musculoskeletal, vascular, and sicca manifestations), laboratory findings, and immunological profile. Past and current medications were recorded including cumulative pulse methylprednisolone (by calculating the doses given for each patient during the disease course from medical records).

Mortality, disease activity, and damage indices

Assessment of the disease activity was done by calculating the SLE Disease Activity Index (SLEDAI)[17] at baseline and at last visit for each patient. The Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI)[18] scores at the last visit were calculated as well. Mortality and cause of death were recorded from the patients' records.

Collected data for different comorbidities

Data for different comorbidities present at any time during the disease course were collected. Comorbidities documented for this study covered those included in the CCI in addition to five other specified comorbid conditions namely hypertension, dyslipidemia, thyroid disease, osteoporosis, avascular necrosis (AVN). This index includes 17 items: myocardial infarction, congestive heart failure, peripheral vascular disease (PVD) (recording for this item was done if the patients had digital gangrene), cerebrovascular disease (recording for this item was done if the patient had hemiplegia), dementia, chronic pulmonary disease (recording for this item was done if the patient had chronic obstructive pulmonary disease), connective tissue disease (CTD) (this item was modified for the study to include CTD other than SLE), peptic ulcer disease, mild liver disease without portal hypertension, moderate or severe liver disease, diabetes mellitus (DM), DM with end organ failure, renal diseases (recording for this item was done if the patients had renal failure), solid malignancy without metastasis, leukemia or lymphoma, metastatic solid tumor and HIV infection.[19] It is worth noting that some comorbidities (as hypertension, DM, dyslipidemia, liver cirrhosis, or renal failure) were routinely screened in all centers, while others were screened only if patients were symptomatic, or clinically suspected (as AVN, peptic ulcer disease, or tumors).

Patients' categorization and comparison

Data from all the centers were reported in a standardized sheet. Patients were classified according to the presence of comorbid condition into two groups: patients with comorbidities (group I) and patients without comorbidities (group II).

Statistical methods

Sample size. Sample size calculation was done for one sample comparison of proportions using STATA software based on a power of 80%, two-sided alpha 0.05 and considering the proportion of the least common and the most common comorbid conditions. Considering the average of 6.4% as our hypothesized value and 1% as least common alternative value then with power 80% and two-sided alpha 0.05, we should have 109 patients for a single arm study while considering 25% as most common alternative value then with power 80% and two-sided alpha 0.05 we should have 21 patients for a single arm study. Nevertheless, while ensuring fulfillment of calculated sample size, more patients were enrolled as feasible, that would increase reliability, precision, and power of results.

Statistical analysis

Data were collected, tabulated, and statistically analyzed using the SPSS software (IBM Corp.

Table 1. Demographic and clinical characteristics of the studied group.

Demographic characteristics (n = 902)	
Age (mean ± SD), year	32.47 ± 9.25
Age at onset (mean ± SD), year	23.38 ± 8.98
Disease duration (mean ± SD), year	9.11 ± 6.26
Females, n (%)	832 (92.2)
Clinical characteristics	
Constitutional manifestations, n (%)	672 (74.5)
Mucocutaneous manifestations, n (%)	804 (89.1)
Musculoskeletal manifestations, n (%)	829 (91.9)
Cardiac manifestations, n (%)	237 (26.3)
Pulmonary manifestations, n (%)	474 (52.5)
Neurological manifestations, n (%)	416 (46.1)
GIT manifestations, n (%)	181 (20.1)
Renal manifestations, n (%)	619 (68.6)
Hematological manifestations, n (%)	855 (94.8)
SLEDAI at onset range, median (IQR) (n = 823)	0–49, 12 (6–18)
SLEDAI at last visit range, median (IQR) (n = 898)	0–34, 4 (0–8)
SLICC range (median (IQR))	0–10, 1 (0–2)
Mortality, n (%)	116 (12.9)
Immunological investigations	
Positive ANA, n (%)	866/883 (98.1)
Anti-DNA, n (%)	577/796 (72.5)
Anti-Smith, n (%)	68/250 (27.2)
ACL IgG, n (%)	176/613 (28.7)
ACL IgM, n (%)	148/526 (28.1)
LAC, n (%)	180/536 (33.6)
Medications received	
Anti-malarial, n (%)	842 (93.3)
Azathioprine, n (%)	689 (76.4)
Mycophenolate mofetil, n (%)	238 (26.4)
Cyclophosphamide, n (%)	499 (55.3)
Steroid's intake (oral or IV), n (%)	878 (97.3)
Cumulative IV pulse methyl prednisolone dose range, median (IQR), g	0.5–25, 3(3–6)

ACL: anticardiolipin; ANA: antinuclear antibody; GIT: gastrointestinal tract; Ig: immunoglobulin; IQR: interquartile range; IV: intravenous; LAC: lupus anticoagulant; n: number; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus Erythematosus International Collaboration Clinic; DNA: deoxyribonucleic acid.

Released 2011. IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY, USA: IBM Corp.). Quantitative data were expressed as mean ± standard deviation when normally distributed or median, range when otherwise not normally distributed. Qualitative data were expressed as numbers (percentages). The student's *t*-test was used to analyze the difference between two independent groups when data were parametric, while the Mann–Whitney U-test was used when the data were nonparametric. Percentages of categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate. Regression analysis was used to find factors associated with comorbidities and mortality and the odds ratio was calculated. A two-tailed probability value (*P* value) <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the patients

The mean age of 902 included patients was 32.47 ± 9.25 years, while the mean disease duration was 9.11 ± 6.26 years. As many as 92.2% of the patients were females. Regarding treatments used, 93.3% of the studied group had received antimalarials, azathioprine (76.4%), cyclophosphamide (46.8%), and mycophenolate mofetil (26.4%), at some point during their disease. Almost three-quarters of the SLE cohort (74.9%) had pulse intravenous methylprednisone during their disease course. The cumulative pulse intravenous methylprednisolone dose ranged from 0.5 to 25g with a median of 3 g. Among the studied cohort, 116 (12.9%) patients died after the diagnosis of SLE (Table 1).

Distribution of different comorbidities in patients with SLE

Comorbidities were found in 75.5% of the studied group. Results showed that hypertension and dyslipidemia were the most frequently

Table 2. Prevalence of comorbidities and CCI in the studied group.

Comorbid condition (n = 902)	n (%)
I. Comorbidities not included in the CCI	
Hypertension	389 (43.1)
Dyslipidemia	362 (40.1)
Thyroid disease	52 (5.8)
Avascular necrosis	81 (9.0)
Osteoporosis	80 (8.9)
II. Comorbidities included in the CCI	
Myocardial infarction	5 (0.6)
Heart failure	20 (2.2)
PVD	37 (4.1)
CVD	35 (3.9)
Dementia	0 (0)
Chronic obstructive pulmonary disease	0 (0)
CT disease (Sicca features)	104 (11.5)
Peptic ulcer disease	60 (6.7)
Mild liver disease without portal hypertension or cirrhosis (HCV infection)	46 (5.1)
Moderate or severe liver disease (cirrhosis)	9 (1.0)
Diabetes mellitus	81 (9.0)
Diabetes mellitus with end organ damage	0 (0)
Moderate or severe renal disease	64 (7.1)
Any tumor	4 (0.4)
Solid tumor without metastasis	1 (0.1)
Leukemia and lymphoma	1 (0.1)
Metastatic disease	2 (0.2)
HIV	0 (0)
All comorbidities, n (%)	681 (75.5)
One comorbid condition, n (%)	246 (27.3)
More than one comorbid condition, n (%)	435 (48.2)

CCI: Charlson Comorbidity Index; CT disease: connective tissue disease; CVD: cerebrovascular disease; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PVD: peripheral vascular disease.

detected comorbidities (43.1% and 40.1%, respectively). This may explain the prevalence of PVD, CVA, myocardial infarction, and heart failure in our cohort (4.1%, 3.9%, 0.6%, and 2.2%, respectively). Less frequently reported comorbidities were sicca features, AVN, and diabetes (11.5%, 9%, and 9%, respectively). In addition, we found that 8.9% of our study group had osteoporosis (OP), thyroid dysfunction was present in 5.8% of our patients and renal failure in 7.1%. Finally, in our cohort, 0.4% of patients developed malignancy (Table 2).

Comparison between patients with comorbidities and those without regarding disease parameter

Patients were classified according to the presence of comorbid condition into two groups: patients with comorbidities (group I) which included 681 patients (75.5%) and patients without comorbidities (group II) which included 221 patients (24.5%). Patients with SLE with recorded comorbidities (group I) were older and had longer disease duration than those without comorbidities. Patients with comorbidities showed significantly more clinical manifestations than the group without comorbidities except for musculoskeletal manifestations. Group I had higher median SLEDAI at onset. They also had more damage as their median SLICC was significantly higher than the median for group II at study time. Mortality rate was significantly higher in group I (16.4%) than in group II (1.8%) ($P < 0.001$) (Table 3).

Anti-double stranded DNA antibodies positivity was found to have a statistically significant higher frequency in those patients with comorbidities (76%) compared to those without comorbidities (62%) ($P < 0.001$). Similarly, the frequency of anticardiolipin immunoglobulin G (ACL IgG) antibodies and lupus anticoagulant (LAC) antibodies positivity were significantly higher in patients with SLE with comorbidities (33.2%, 36.8%) than those without comorbidities (14.4%, 23.9%), ($P < 0.001$, 0.006), respectively. Azathioprine and cyclophosphamide were more frequently received in patients with SLE with comorbidities ($P < 0.001$). The cumulative intravenous pulse methylprednisolone dose was

significantly higher in patients with SLE with comorbidities than those without comorbidities ($P = <0.001$) (Table 3).

Regression analysis for factors associated with the presence of comorbidity

Univariate regression showed significant relation between the presence of comorbidity and each of the age, disease duration, SLEDAI at onset, SLEDAI last visit, cyclophosphamide intake, and cumulative pulse intravenous methylprednisone dose. A multivariable regression model showed statistically significant relation between the presence of comorbid condition and each of age, disease duration, SLEDAI at onset, cyclophosphamide intake, and cumulative pulse intravenous methylprednisone. Cyclophosphamide intake was found to have a strong association with the presence of comorbid conditions when adjusted for age, disease duration, SLEDAI at onset, and cumulative pulse intravenous (IV) methylprednisone dose odds ratio (OR), 95% confidence interval (CI) (2.299 (1.572–3.363)) (Table 4).

Comorbidity as a predictor of mortality

Mortality in the studied cohort were analyzed according to the presence and number of the comorbid conditions. When adjusted to age and sex, patients with one comorbid condition had 4.3 increased odds of mortality compared to those with no comorbidities (OR, 95% CI = 4.31 (1.42–13.12)). Those with multiple comorbid conditions had 18.5 increased odds of mortality compared to those without comorbidities (OR, 95% CI = 18.5 (6.65–51.69)) (Table 5).

Discussion

SLE is commonly accompanied by several comorbidities that can affect patients' quality of life and their survival. It may occur because of the disease itself or the medical intervention.[2,20]

Several comorbidities might be encountered in the context of SLE, with hypertension among the commonest, yet with variable prevalence. Prevalence of hypertension varies greatly among different reports; however, it remains among the highly prevalent comorbidities in SLE and is significantly higher than non-SLE within the same age and sex category. In the cohort by Sabio et al.,[21] the prevalence of hypertension among patients with SLE was 56%. Similar to our study, an international cohort of 918 patients with SLE found that 33% of the patients had hypertension and 36% had hypercholesterolemia. In addition, the prevalence rate of hypertension, diabetes, and dyslipidemia were found significantly higher in lupus patients than those in healthy population.[22]

Patients with SLE have a 2 to 50 fold increased risk of cerebral, cardiac, or peripheral arterial atherosclerosis diseases than in the general population.[4,6] This may explain the prevalence of PVD, CVD, myocardial infarction, and heart failure in (4.1%, 3.9%, 0.6%, and 2.2%, respectively) of our cohort. In fact, traditional cardiovascular risk factors (such as hypertension, dyslipidemia, age, sex, and obesity) alone do not completely elucidate the extent of this risk; inflammatory process, increased levels of C-reactive protein, complement activation, and prothrombotic mechanisms lie beneath this premature atherosclerosis and atheroma plaque formation in SLE.[23]

Osteoporosis is a serious cause of morbidity in SLE. In total, 8.9% of our study group had OP. Similar results were reported in the literature as in a recent meta-analysis where the prevalence of OP was 16%.[24] Some reports tend to give a higher prevalence. A study from Egypt found a prevalence of OP to be 20% and osteopenia to be 35.7%.[25] Many factors contribute to the increased incidence of OP in patients with SLE. Not only the prolonged steroid use but disrupted inflammatory status-driven mainly through interleukin 1 (IL-1), IL-6, IL-17, and tumor necrosis alpha (TNF-α) with subsequent impact on receptor activator of nuclear factor kβ (RANK) receptor activator of

Table 3. Comparison between patients with comorbidities and patients without comorbidities regarding disease parameters.

Variable (n = 902)	Group I (n = 681)	Group II (n = 221)	*P* value
Demographic characteristics			
Age, mean ± SD	33.06 ± 9.33	30.65 ± 8.77	**0.001**
Age at onset, mean ± SD	23.45 ± 9.24	23.18 ± 8.17	0.985
Disease duration, mean ± SD	9.626 ± 6.33	7.51 ± 5.79	**<0.001**
Gender (females), n (%)	630 (92.5)	202 (91.4)	0.593
Clinical characteristics			
Constitutional, n (%)	522 (76.7)	150 (67.9)	**0.009**
Mucocutaneous, n (%)	615 (90.3)	189 (85.5)	**0.047**
Musculoskeletal, n (%)	632 (92.8)	197 (89.1)	0.083
Cardiac, n (%)	206 (30.2)	31 (14.0)	**<0.001**
Pulmonary, n (%)	385 (56.5)	89 (40.3)	**<0.001**
Pulmonary hypertension, n (%)	109 (16.0)	5 (2.3)	**<0.001**
Neurological, n (%)	340 (49.9)	76 (34.4)	**<0.001**
GIT, n (%)	168 (24.7)	13 (5.9)	**<0.001**
Renal, n (%)	509 (74.7)	110 (49.8)	**<0.001**
Renal failure, n (%)	64 (9.4)	0(0)	**<0.001**
Hematological, n (%)	656 (96.3)	199 (90.0)	**<0.001**
SLEDAI at onset range, median (IQR)	0–49, 13 (8–19)	0–48, 8 (4–12)	**<0.001**
SLEDAI at last range, median (IQR)	0–34, 4 (0–8)	0–30, 4 (0–8)	**0.008**
SLICC-DI range, median (IQR)	0–10, 1 (0–3)	0–5, 0 (0–1)	**<0.001**
Mortality, n (%)	112 (16.4)	4 (1.8)	**<0.001**
Immunological investigations of the studied group (n = 902)			
Positive ANA, n (%)	655/666 (98.2)	211/217 (97.2)	0.30
Positive anti-ds DNA, n (%)	453/596 (76.0)	124/200 (62.0)	**<0.001**
Positive ACL IgG, n (%)	155/467 (33.2)	21/146 (14.4)	**<0.001**
Positive ACL IgM, n (%)	121/407 (29.7)	27/119 (22.7)	**0.133**
Positive LAC, n (%)	148/402 (36.8)	32/134 (23.9)	**0.006**
Medications received			
Azathioprine, n (%)	555/681 (81.5)	134/221 (60.6)	**<0.001**
Hydroxychloroquine, n (%)			
Mycophenolate mofetil, n (%)	203/681 (29.8)	35/221 (15.8)	**<0.001**
Cyclophosphamide, n (%)	426 (62.6)	73 (33.0)	**<0.001**
Steroids (oral or IV), n (%)	666/681 (97.8)	211 (95.5)	0.068
Cumulative IV methylprednisolone dose (g) range, median (IQR)	0.5–25, 3(3–6)	1–12, 3(2–3.9)	**<0.001**

ACL: anticardiolipin; ANA: antinuclear antibody; GIT: gastrointestinal tract; Ig: immunoglobulin; IQR: interquartile range; IV: intravenous; LAC: lupus anticoagulant; n: number; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI: Systemic Lupus Erythematosus International Collaboration Clinic Damage Index; ds DNA: double stranded deoxyribonucleic acid.

nuclear factor kβ ligand (RANKL)–osteoprotegrin (OPG) axis, leading to stimulation of osteoclast differentiation and activity and inhibition of osteoblast activity.[26] Another cause is the premature menopause in patients with SLE, which may result from the effects of treatment or from an autoimmune-mediated ovarian injury.[27]

Table 4. Factors associated with comorbidity.

Independent variable	B coefficient	SE	Wald	df	OR	(95% CI) for OR	*P* value
I. Univariate analysis							
Age	0.030	0.009	11.20	1	1.030	1.012–1.048	0.001
Gender	−0.15	0.281	0.286	1	0.861	.496–1.492	0.593
Disease duration	0.060	0.014	18.59	1	1.061	1.033–1.091	**<0.001**
SLEDAI at onset	0.081	0.013	41.634	1	1.085	1.058–1.112	**<0.001**
SLEDAI at last visit	0.037	0.015	6.492	1	1.038	1.009–1.068	0.011
Pulse IV methylprednisone	0.934	0.170	30.052	1	2.544	1.822–3.552	**<0.001**
Cumulative IV pulse methyl prednisolone	0.212	0.035	36.633	1	1.236	1.154–1.324	**<0.001**
II. Multivariable analysis							
Age	0.029	0.010	7.455	1	1.029	1.008–1.050	0.006
Duration in years	0.034	0.016	4.169	1	1.034	1.001–1.068	0.041
SLEDAI at onset	0.069	0.014	25.915	1	1.072	1.044–1.101	**<0.001**
Cyclophosphamide	0.833	0.194	18.422	1	2.299	1.572–3.363	**<0.001**
Cumulative pulse methyl prednisolone (g)	0.151	0.040	14.424	1	1.163	1.076–1.258	**<0.001**

CI: confidence interval; df: degree of freedom; OR: odds ratio; SE: standard error; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; B coeff: B coefficient.

Table 5. Comorbidity as a predictor of mortality.

Independent variable	B coefficient	SE	Wald	df	OR	(95% CI) for OR	*P* value
Age	−0.042	0.012	12.170	1	0.959	0.937–0.982	<0.001
Sex	1.129	0.319	12.543	1	3.092	1.655–5.775	<0.001
COMO_0			51.890	2			0.010
COMO_1	1.463	0.567	6.659	1	4.319	1.422–13.121	<0.001
COMO_2	2.920	0.523	31.127	1	18.533	6.645–51.685	<0.001

CI: confidence interval; COMO_0: no comorbid condition; COMO_1: patients have one comorbid condition; COMO_2: patients have more than one comorbid condition; OR: odds ratio; SE: standard error; df: degree of freedom; B coeff: B coefficient.

AVN is another disabling comorbidity that is also prevalent in our cohort. Similar results were obtained in literature, with a quite identical result in a study conducted by Gontero et al.[28] amongst 158 patients with SLE, 9.5% of patients had AVN. In a meta-analysis, the prevalence of symptomatic AVN was 9% while the asymptomatic was high up to 30%. AVN was clearly related to glucocorticoid doses, disease activity and antiphospholipid antigenicity.[29] AVN is a major cause of poor quality of life which may improve markedly after surgery.[30] To improve overall health and satisfaction in life in our patients with SLE, AVN must be addressed early and thoroughly by screening, monitoring, and adequate management.

The incidence of type 2 DM in patients with SLE is debatable. While some reports state the increased incidence of metabolic syndrome including DM and insulin resistance, some find that patients with SLE have the same chance of developing DM as in the general population.[5,31] While Egypt is one of the top 10 countries in type 2 DM list,[32] it is not

surprising that our population with SLE had a high incidence of developing DM, which in fact was higher than that found in other reports from other countries.[31] Glucocorticoids' intake can have a direct link to the development of DM in patients with SLE.[33]

In line with our study, Appenzeller et al.[34] reported thyroid disorders in 6.1% patients with SLE. A meta-analysis in 2018 demonstrated that SLE is significantly associated with increased risk of hypothyroidism and subclinical hypothyroidism with little influence on hyperthyroidism and subclinical hyperthyroidism.[35]

The percentage of renal failure in our group of patients was 7.1%, which is consistent with previous studies. It is to be noted that one of the most important predictors of end-stage renal disease (ESRD) is early detection of proteinuria within the first year of diagnosis of SLE. Other important predictors of renal failure are younger age at SLE diagnosis, low C3 and African American ethnicity.[36] In a cohort of 928 Egyptian patients, ESRD was found to be 4.2%, and the authors stated that the main risk factors for poor renal outcome were elevated baseline serum creatinine, hypertension, failure to achieve remission, and nephritic flare.[37]

In our cohort, 0.4% developed malignancy. The overall rates of malignancy in patients with SLE compared to the general population controls were assessed by several authors. In a large multinational study involving 16,409 patients, a mildly increased overall risk of malignancy in patients with SLE, as compared with controls (standardized incidence ratio 1.14, 95% CI, 1.05, 1.23).[38] Similar results were reported in the Taiwanese cohort,[39] and in the Danish cohort.[40] Patients with SLE may show an increased risk of non-Hodgkin's lymphoma, liver, lung, and thyroid malignancies, on the other hand, the risk of hormone-sensitive cancers such as breast and prostate may be decreased due to presence of lupus autoantibodies and downregulation of certain proteins in SLE.[41] The overall increased rates of malignancy in SLE may be related to the inflammatory nature of the disease and interrupted immune surveillance, besides the use of immunosuppressive drugs for treatment.[40]

Our study showed that patients with comorbidities were older in age, with longer disease duration, with higher frequency of most SLE clinical manifestations, had higher mean SLEDAI at onset and they also had more damage, had significantly positive anti-ds DNA, LAC, ACL IgG antibodies, and more frequent treatment with azathioprine, pulse cyclophosphamide, and methylprednisone.

The association between lupus-related morbidity and medications, is well documented.[20] Also, Thamer et al., had found that the risk of damage accrual increased with the high cumulative dose of prednisone, even after adjusting for multiple variables, including baseline SLE activity,[42] while higher damage SLICC index in comorbidity group may be a result of active disease and the medications used.

Anti-ds DNA antibody is one of the diagnostic and prognostic markers in lupus patients, its titer may rise with disease flare[43] and this may explain its significant association with comorbidity group. APS is a known predictor of damage in lupus patients.[44] Antiphospholipid antibodies may be present prior to diagnosis of APS[43] and are possibly implicated in the development of neuropsychiatric and cardiovascular damage in SLE,[44] thus the association of LAC, ACL IgG antibodies with comorbidity could be expected.

In a Korean study, the association of organ damage with higher CCI and SLEDAI scores was established. They emphasized the role of cumulative therapeutic medications, disease activity, and comorbid conditions as contributing factors for the development of organ damage in patients with SLE.[45] In another study from Egypt, they found that CCI scores were significantly higher in patients with steroid intake >10 mg/day, male patients and significantly correlated with the disease duration, SLEDAI, and SDI.[13] Similarly, the main predictors of comorbidity in our cohort were age, disease duration, SLEDAI at onset, cyclophosphamide use, and cumulative methylprednisone.

In the current study, when adjusted to age and sex, patients with one comorbid condition had 4.3 increased odds of mortality compared to those with no comorbidities (OR, 95% CI = 4.31(1.42–13.12)). Those with multiple comorbid conditions had 18.5 increased odds of mortality compared to those without comorbidities (OR, 95% CI = 18.5 (6.65–51.69)). This trend has been demonstrated in multiple other cohorts,[46] and this may help to explain, why despite better care, patients with SLE have a 2 to 5 fold increase in mortality rate more than the general population, further, it is well recognized that death is attributed to side effects of treatments and organ damage during the late course of SLE,[47] in addition to the combined influence of the effects of SLE and comorbidity, suggesting that treatment of comorbidities should be included as a fundamental part of clinical care for patients with SLE. Therefore, successful treatment of comorbidity would lessen the mortality caused by comorbidity itself, and possibly also the mortality caused by the synergistic effect between comorbidity and SLE.[48]

Although this study had some strengths such as the large number of patients and being multicenter, it also had some limitations. The comorbidities evaluated were nominated by the study working group and were not all-inclusive. Some other comorbidities, for example infection, were not included in the study. The absence of a comparator group without SLE did not permit comparison between the perceived prevalence of comorbidities among patients with SLE with that found in the general population or between patients with other disease states. However, comparing patients with and without comorbidities in the context of the study can be viewed as a positive add-on. Nevertheless, one of the major limitations in this study is the estimation of the incidence of some comorbidities as osteoporosis and peptic ulcers, while their proper diagnostic investigation tool, for example, endoscopy and dual-energy X-ray absorptiometry were not done for all patients included in the study, but only for complaining or suspicious patients. So, it would be perceived that the reported percentage is not a true representation of the prevalence of such comorbidity, as asymptomatic patients were not investigated and subsequently reported. Another limitation is that screening for malignancy was not always done, which is a commonly observed problem in patients with rheumatic diseases.[49]

In conclusion, 75% of patients with SLE had comorbidities, hypertension and dyslipidemia as the most prevalent. Comorbidity risk is increased with age, longer disease duration, higher SLEDAI at onset, cyclophosphamide intake, and with higher cumulative pulse intravenous methylprednisone intake. Risk of mortality is increased in patients with SLE with comorbidities; and is exponentiated when patients have several comorbid conditions.

Acknowledgments

We would like to thank the study participants.

Contributors

All authors have participated sufficiently in this work; in drafting the article or revising it critically for important intellectual content, and all authors approved the final version of the manuscript.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Compliance with ethics guidance

The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Availability of data and materials

All data and materials are available upon request.

Consent for publication

All authors gave their consent for publication.

ORCID iD

Sally S. Mohamed https://orcid.org/0000-0002-4537-6373

References

1. Bertsias G, Cervera R, and Boumpas DT. Systemic lupus erythematosus: pathogenesis and clinical features. In: *EULAR textbook of rheumatology*. Geneva: European League Against Rheumatism 2012: 476–505.
2. Chan PC, Yu CH, Yeh KW, et al. Comorbidities of pediatric systemic lupus erythematosus: a 6-year nationwide population-based study. *J Microbiol Immunol Infect* 2016; 49: 257–263.
3. Reese T, Dickson AL, Shuey MM, et al. Increased blood pressure visit-to-visit variability in patients with systemic lupus erythematosus: association with inflammation and comorbidity burden. *Lupus* 2019; 28: 954–960.
4. Rees F, Doherty M, Grainge M, et al. Burden of comorbidity in systemic lupus erythematosus in the UK, 1999–2012. *Arthritis Care Res (Hoboken)* 2016; 68: 819–827.
5. Gheita TA, Raafat HA, Sayed S, et al. Metabolic syndrome and insulin resistance comorbidity in systemic lupus erythematosus. *Z Rheumatol* 2013; 72: 172–177.
6. Hesselvig JH, Ahlehoff O, Dreyer L, et al. Cutaneous lupus erythematosus and systemic lupus erythematosus are associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. *Lupus* 2017; 26: 48–53.
7. Mok CC, Ho LY, and To CH. Annual incidence and standardized incidence ratio of cerebrovascular accidents in patients with systemic lupus erythematosus. *Scand J Rheumatol* 2009; 38: 362–368.
8. Fischer LM, Schlienger RG, Matter C, et al. Effect of rheumatoid arthritis or systemic lupus erythematosus on the risk of first-time acute myocardial infarction. *Am J Cardiol* 2004; 93: 198–200.
9. Navarro-Zarza JE, Alvarez-Hernández E, Casasola-Vargas JC, et al. Prevalence of community-acquired and nosocomial infections in hospitalized patients with systemic lupus erythematosus. *Lupus* 2010; 19: 43–48.
10. Hermansen ML, Lindhardsen J, Torp-Pedersen C, et al. Incidence of systemic lupus erythematosus and lupus nephritis in Denmark: a nationwide cohort study. *J Rheumatol* 2016; 43: 1335–1339.
11. Turesson C and Matteson E. Malignancy as a comorbidity in rheumatic diseases. *Rheumatology (Oxford)* 2013; 52: 5–14.
12. Radner H, Yoshida K, Smolen JS, et al. Multimorbidity and rheumatic conditions-enhancing the concept of comorbidity. *Nat Rev Rheumatol* 2014; 10: 252–256.
13. Alian SM, Khalil SS, and Zaghlol RS. Charlson comorbidity Index in patients with systemic lupus erythematosus in Egypt and its relation with disease characteristics. *Indian J Rheumatol* 2019; 14: 277–282.
14. Mosca M, Tani C, Aringer M, et al. European League against rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis* 2010; 69: 1269–1274.
15. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725–1725.
16. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295–306.
17. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. *Arthritis Rheum* 1992; 35: 630–640.
18. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39: 363–369.
19. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
20. Greenstein L, Makan K, and Tikly M. Burden of comorbidities in South Africans with systemic lupus erythematosus. *Clin Rheumatol* 2019; 38: 2077–2082.
21. Sabio JM, Vargas-Hitos JA, Navarrete-Navarrete N, et al. Prevalence of and factors associated with hypertension in young and old women with

systemic lupus erythematosus. *J Rheumatol* 2011; 38: 1026–1032.
22. Bruce IN, Urowitz MB, Gladman DD, et al. Risk factors for coronary heart disease (CHD) in women with systemic lupus erythematosus (SLE): the Toronto risk factor study. *Arthritis Rheum* 2003; 48: 3159–3167.
23. Lertratanakul A, Wu P, Dyer AR, et al. Risk factors in the progression of subclinical atherosclerosis in women with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2014; 66: 1177–1185.
24. Gu C, Zhao R, Zhang X, et al. A meta-analysis of secondary osteoporosis in systemic lupus erythematosus: prevalence and risk factors. *Arch Osteoporos* 2019; 15: 1.
25. Hafez EA, ElBakry SA, Ibrahim SI, et al. Assessment of fracture risk in a cohort of Egyptian female systemic lupus erythematosus patients. *Egypt Rheumatol* 2018; 40: 85–91.
26. Adami G, Fassio A, Rossini M, et al. Osteoporosis in rheumatic diseases. *Int J Mol Sci* 2019; 20: 5867.
27. Sammaritano LR. Menopause in patients with autoimmune diseases. *Autoimmun Rev* 2012; 11: A430–A436.
28. Gontero RP, Bedoya ME, Benavente E, et al. Osteonecrosis in systemic lupus erythematosus. *Reumatol Clin* 2015; 11: 151–155.
29. Nevskaya T, Gamble MP, and Pope JE. A meta-analysis of avascular necrosis in systemic lupus erythematosus: prevalence and risk factors. *Clin Exp Rheumatol* 2017; 35: 700–710.
30. Abbas-Zadeh MR, Azizi A, Abbas-Zadeh L, et al. Effect of surgical treatment on the quality of life in patients with non-traumatic avascular necrosis of the femoral head. *Rev Bras Ortop* 2018; 53: 773–777.
31. Muñoz C and Isenberg DA. Review of major endocrine abnormalities in patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2019; 37: 791–796.
32. Hegazi R, El-Gamal M, Abdel-Hady N, et al. Epidemiology of and risk factors for type 2 diabetes in Egypt. *Ann Glob Health* 2018; 81: 814–820.
33. Gagliardi L and Le Jeunne C. Corticothérapie et diabète. *Presse Med* 2012; 41: 393–399.
34. Appenzeller S, Pallone AT, Natalin RA, et al. Prevalence of thyroid dysfunction in systemic lupus erythematosus. *J Clin Rheumatol* 2009; 15: 117–119.
35. Luo W, Mao P, Zhang L, et al. Association between systemic lupus erythematosus and thyroid dysfunction: a meta-analysis. *Lupus* 2018; 27: 2120–2128.
36. Petri M, Barr E, and Magder LS. Risk of renal failure within 10 or 20 years of systemic lupus erythematosus diagnosis. *J Rheumatol* 2021; 48: 222–227.
37. Momtaz M, Fayed A, Wadie M, et al. Retrospective analysis of nephritis response and renal outcome in a cohort of 928 Egyptian lupus nephritis patients: a university hospital experience. *Lupus* 2017; 26: 1564–1570.
38. Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. *J Autoimmun* 2013; 42: 130–135.
39. Chen YJ, Chang YT, Wang CB, et al. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. *Am J Med* 2010; 123: 1150.e1–1150.e6.
40. Dreyer L, Faurschou M, Mogensen M, et al. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term followup study in a Danish cohort. *Arthritis Rheum* 2011; 63: 3032–3037.
41. Goobie GC, Bernatsky S, Ramsey-Goldman R, et al. Malignancies in systemic lupus erythematosus: a 2015 update. *Curr Opin Rheumatol* 2015; 27: 454–460.
42. Thamer M, Hernán MA, Zhang Y, et al. Prednisone, lupus activity, and permanent organ damage. *J Rheumatol* 2009; 36: 560–564.
43. Gamal SM, Fawzy S, and Siam I. Does anti-DNA positivity increase the incidence of secondary antiphospholipid syndrome in lupus patients? *Egypt Rheumatol* 2013; 35: 141–144.
44. Amigo MC and Alba P. Damage index in lupus: the role of antiphospholipid antibodies. *Lupus* 2020; 29: 3–5.
45. Kim SK, Choe JY, and Lee SS. Charlson Comorbidity Index is related to organ damage in systemic lupus erythematosus: data from Korean lupus network (KORNET) registry. *J Rheumatol* 2017; 44: 452–458.
46. Yang Y, Thumboo J, Earnest A, et al. The effect of comorbidity on hospital mortality in patients with SLE from an Asian tertiary hospital. *Lupus* 2014; 23: 714–720.

47. Fors Nieves CE and Izmirly PM. Mortality in systemic lupus erythematosus: an updated review. *Curr Rheumatol Rep* 2016; 18: 21.
48. González LA and Alarcón GS. The evolving concept of SLE comorbidities. *Expert Rev Clin Immunol* 2017; 13: 753–768.
49. Dougados M, Soubrier M, Antunez A, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis* 2014; 73: 62–68.