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ORIGINAL ARTICLE

Mortality in a cohort of Egyptian systemic lupus erythematosus patients: A comparison with African, Arabic, and Mediterranean studies

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ABSTRACT

Objectives: The study aimed to examine the frequency, causes, and predictors of mortality in a cohort of Egyptian systemic lupus erythematosus (SLE) patients and compare mortality causes and the survival rate in our cohort to African, Arabic, and Mediterranean studies.

Patients and methods: In this retrospective study, a review of medical records of 563 SLE patients (516 females, 47 males; median of age: 32 [IQR: 26-38 years]; range, 14 to 63 years) fulfilling the 1997 American College of Rheumatology (ACR) criteria between January 2015 and December 2019 was done. The data extracted included demographic, clinical, and laboratory features, treatments used, disease activity as measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and damage index as measured by Systemic Lupus International Collaborating Clinics (SLICC) damage index. Causes of mortality were also reported.

Results: Out of 563 reviewed medical records, 50 (8.9%) patients died. Infection (28%) and organ damage (18%) were the most commonly reported causes of death. Multivariate Cox regression analysis showed that patients with cardiac manifestations, renal failure, those receiving higher doses of either oral (in their last visit) or intravenous (higher cumulative pulse steroids) steroids were at increased risk of mortality (p=0.011, p<0.001, p=0.01, and p<0.001, respectively; 95% confidence intervals 7.2, 63.9, 1.2, and 1.09, respectively). The overall survival at 5, 10, 15, and 20 years was 96.6%, 93.3%, 91.0%, and 83.2%, respectively, and 56.2% at 25 years until the end of the follow-up.

Conclusion: Cardiac manifestations, renal failure, and higher steroid doses were independent predictors of mortality in our cohort. As in most African countries, infection was the main cause of death in our study; however, the mortality rate and the five-year survival among our cohort were better than in African (sub-Saharan) countries and similar to Arabic and Mediterranean countries.

Keywords: Egyptian patients, mortality, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease[1] characterized by organ damage and a flare-remission pattern.[2] SLE affects women in their reproductive age and is associated with significant morbidity and mortality.[3] SLE is the second most common autoimmune disorder after thyroid disease in childbearing age women[4] and is ranked as the 10th cause of mortality in women aged 15 to 24 years.[5]

The revolution in early diagnosis, use of immunosuppressive agents, better care of patients with organ failure and a better understanding of immunopathogenesis of SLE have contributed to the reduction in SLE-associated mortality[6,7] and the improvement of five-year survival from an appalling 40-50% during the 1950s[6,8] to 64-87% in the 1980s.[9] This rate exceeded 90% in the 1990s in some industrialized countries[3] and in a

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few studies in developing countries.[10,11] However, the situation is less optimistic in most of the developing countries, and studies from Thailand, Tunisia, Senegal, and India have found that even in the 1990s and early 21st century, five-year survival rates were below 90%.[7,11-13] Furthermore, even with the improved survival rates in SLE, the mortality rates are two-to three-fold higher compared to age-and sex-matched populations,[3,14] which may be attributed to the disease itself and its treatments.[8]

As mortality rates seem to vary across race, ethnicity, sex, and country and as most of the available literature on mortality in SLE patients are from geographic areas other than Africa and Arab countries, the data cannot be extrapolated to the Egyptian population. Therefore, this study aimed to investigate the frequency and predictors of mortality in a cohort of Egyptian SLE patients attending a large tertiary care hospital and compare them to other African, Arab, and Mediterranean countries.

PATIENTS AND METHODS

In this retrospective study, medical records of 563 SLE patients (516 females, 47 males; median of age: 32 [IQR: 26-38 years]; range, 14 to 63 years) fulfilling the 1997 American College of Rheumatology (ACR) classification criteria[15] and who were followed at a tertiary care rheumatology unit in the Cairo University Hospital between January 2015 and December 2019 were reviewed. Data was extracted from medical records in 2020 and 2021. The follow-up period of the patients was considered starting from disease onset until the date of the last visit or death.

Demographic data, clinical and laboratory features, immunological profile, medical treatment, and outcome were abstracted from medical records. Clinical manifestations of the patients were considered present if found at any time during the disease course from disease onset until the last visit. Similarly, the treatment used was reported if applied at any time during the disease course (from disease onset until the last visit).

Disease activity was calculated for all patients using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),[16] and the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index was utilized.[17]

The records of patients who died during the follow-up were inspected for the causes of death, which were categorized into known and unknown causes. Known causes were further subdivided into infections, disease activity, organ failure, vascular, combined causes, and others. Unknown causes of death were mostly for patients who died at home and when the exact cause of death could not be identified. The overall 5-, 10-, 15-, and 20-year survival rates were also calculated. Survival was calculated from the onset of disease manifestations until the date of the last follow-up visit or death. Causes of death and survival and mortality rates in our study were compared to previous studies in the literature from African, Arabic, and Mediterranean countries.

Statistical analysis

Data were analyzed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Data were explored for normal distribution using the Kolmogorov-Smirnov test. Quantitative data were expressed as median and interquartile range, whereas qualitative data were presented as frequency. The chi-square test and Fisher exact test were used to detect differences between qualitative variables. The Mann-Whitney U test was used to detect differences between quantitative variables. Patient survival patterns of the study population were analyzed. The risk factors associated with mortality were also assessed using multivariate Cox regression analysis. A p value ≤ 0.05 were considered statistically significant. All tests were two tailed.

RESULTS

The disease duration ranged from 0.2 to 34 years with a median of 9 (5-14) years. Of the patient, 513 (91.1%) lived, and 50 (8.9%) patients were deceased. Detailed demographic data of both groups are illustrated in Table 1.

Regarding the clinical presentation of the disease, we found that constitutional manifestations, cardiac manifestations, serositis, nephritis, and renal failure were statistically

Table 1. Demographic data of living and deceased patients

	Living					Dead					
	n	%	Median	IQR	Range	n	%	Median	IQR	Range	*p*
Sex											0.05
Female	474	92.4				42	84				
Male	39	7.6*				8	16*				
Age (year)			32	26-38	15-63			32	25-36	14-58	0.18
Disease duration (year)			9	5-14	0.2-30			7	4-17	0.5-34	0.9

IQR: Interquartile range; Percentage of male in each group.

significantly higher in deceased patients compared to living patients, as shown in Table 2. Concerning the laboratory manifestations, we found that deceased patients tended to have thrombocytopenia, increased serum creatinine for more than six months, and increased complement consumption that reached statistical significance compared to the living patients, as shown in Table 2.

Systemic Lupus Erythematosus Disease Activity Index at onset was recorded in 470 living patients. It ranged from 1 to 48 with a median of 11 (6-18), while SLEDAI at the last visit was recorded in 510 living patients, and it ranged from 1 to 26 with a median of 2 (0-4). SLEDAI was recorded in all dead patients, both at onset and at the last follow-up visit. At onset, it ranged from 2 to 49 with a median of 12 (7-18.25), while

Table 2. Clinical and laboratory manifestations of the studied patients

	Total (n=563)		Living (n=513)		Dead (n=50)		
Clinical/laboratory manifestation	n	%	n	%	n	%	*p*
Constitutional	412	73.2	366	71.3	46	92	0.002*
Thrombosis	97	17.2	84	16.4	13	26	0.08
Secondary vasculitis	180	32	159	31	21	42	0.11
Pulmonary hypertension	68	12	59	11.5	9	18	0.18
Pulmonary manifestations	316	56.1	282	55	34	68	0.07
Cardiac manifestations	161	28.6	134	26.1	27	54	<0.001*
Neurological manifestations	225	40	202	39.3	23	46	0.36
Musculoskeletal manifestations	518	92	472	92	46	92	1
Serositis	337	59.9	298	58	39	78	0.006*
Nephritis	398	70.7	356	69.4	44	88	0.006*
Renal failure	36	6.4	18	3.5	18	36	<0.001*
Anemia throughout the disease course	526/562	93.6	477/512	93.1	49	98	0.23
Autoimmune hemolytic anemia	71/562	12.6	63/512	12.3	8	16	0.50
Leucopenia	301/562	53.6	271/512	52.9	30	60	0.37
Thrombocytopenia	195	34.6	168	32.7	27	54	0.005*
Increased creatinine more than 6 months	78/562	13.9	54/512	10.5	24	48	<0.001*
ANA	554/561	98.8	504/511	98.6	50	100	1
Anti-DNA	353/473	74.6	322/433	74.4	31/40	77.5	0.84
Consumed complement last visit	160/457	(35	134/410	32.7	26/47	55.3	0.003*
APL antibodies	189/389	48.6	165/344	48	24/45	53.3	0.52

ANA: Anti-nuclear antibody; DNA: Deoxyribonucleic acid; APL: Antiphospholipid; * Significant differences (p<0.05).

at the last visit, it ranged from 0 to 34 with a median of 7 (7-12). No statistical significance was found regarding SLEDAI at onset between the groups (p=0.55). On the other hand, SLEDAI at the last visit was statistically significantly higher in the deceased group (p<0.001).

Systemic Lupus International Collaborating Clinics damage index was calculated in 503 living patients, and it ranged from 0 to 8 with a median of 1 (0-2). In the deceased group it ranged from 0 to 10 with a median of 2 (1-5). The difference between the groups reached statistical significance (p<0.001).

Dead patients were statistically significantly more prone to having hypertension, dyslipidemia, and hepatitis C virus (HCV) antibody positivity, as shown in Table 3. Among the known causes of death, we found that infection was the most common reason (28%), followed by organ damage (18%). The detailed mortality causes are shown in Table 5.

Regarding treatment given to the patients, we found that the median steroid dosage prescribed at the last visit was statistically significantly higher among the deceased than the living (20 mg/day *vs.* 10 mg/day, p=0.00). Furthermore, the median cumulative dose of intravenous steroids was higher in dead patients compared to the living (6.75 g *vs.* 3 g), reaching statistical significance (p=0.00). Mycophenolate mofetil consumption was also found to be more frequent in the deceased compared to the living (p<0.001). Detailed treatment given to the studied patients is illustrated in Table 4.

Regression analysis was done to identify risk factors for mortality, and it was found that patients with cardiac manifestations, patients with renal failure, those receiving higher doses of oral steroids in their last visit, and those receiving higher cumulative intravenous pulse steroids were at higher risk of mortality (p=0.011, p<0.001, p=0.01, and p<0.001, respectively; Table 6). The median follow up time in our study was 9 (0.2-34) years. Overall survival at 5, 10, 15, and 20 years was 96.6%, 93.3%, 91.0%, and 83.2%, respectively, and 56.2% at 25 years until the end of the follow-up.

Table 3. Comorbid conditions associated with SLE among the studied patients

	Total (n=563)		Living (n=513)		Dead (n=50)		
Comorbid condition	n	%	n	%	n	%	*p*
Hypertension	240/562	42.7	207/512	40.4	33	66	0.001*
Dyslipidemia	217/562	38.6	188/512	36.7	29	58	0.004*
Diabetes	50	8.9	42	8.2	8	16	0.07
Thyroid	39/561	7	35/511	6.8	4	8	0.76
Malignancy	4/562	0.7	3/512	0.58	1	2	0.31
Hepatitis C virus antibody positivity	30	5.3	23	4.5	7	14	0.012*

SLE: Systemic lupus erythematosus; * Significant differences (p<0.05); Due to missing data, the total number of patients is not always equal to 563.

Table 4. Detailed treatment given to the studied patients

	Total (n=563)		Living (n=513)		Dead (n=50)		
Treatment	n	%	n	%	n	%	*p*
Cyclophosphamide	312/560	55.7	278/510	54.5	34	68	0.07
Azathioprine	453/558	81.2	411/508	81	42	84	0.70
Mycophenolate mofetil	160/558	28.8	133/508	26.2	27	54	<0.001*
Pulse steroids	465/555	84.8	420/505	83.2	45	90	0.31
Anti-malarials	521/555	93.9	475/505	94	46	92	0.53

* Significant differences (p<0.05); Due to missing data, the total number of patients is not always equal to 563.

Table 5. Causes of death among deceased SLE patients

Cause of death	n	%
Infection*	14	28
Organ damage	9	18
Renal failure	6	12
Liver failure	1	2
Cardiac failure	1	2
Respiratory failure	1	2
Vascular disorder	4	8
Malignant hypertension	1	2
Stroke	1	2
Disseminated intravascular coagulopathy	2	4
Infection and organ damage by lupus	4	8
Activity and infection	1	2
Activity and vascular disorder	1	2
Activity**	1	2
Others	6	12
Increase intracranial tension	1	2
During surgery	2	4
Pulmonary edema	2	4
Malignancy	1	2

SLE: Systemic lupus erythematosus; * In patients who died due to infection, the most common causes were septicemia and chest infection, ** Activity means SLE disease activity.

DISCUSSION

Although SLE treatment and care is under continuous progression with subsequent improvement in survival rate, mortality in SLE patients is still high compared to the general population, with varying mortality rates depending on ethnicity and country development.[18] Data available from African countries regarding SLE mortality are limited.[19] Available reports from African countries show high mortality rates,[20] which could be attributed to many factors as limited resources, diagnostic delay and more aggressive lupus nephritis in black African patients.[21,22] Egypt is an Arabic, Middle Eastern, Mediterranean, and African country. Being a Mediterranean country in North Africa, its population may show different features compared to other African countries, particularly sub-Saharan countries. Additionally, resources and rheumatological care availability may differ from many other African countries. Thus, Egyptian SLE patients may be expected

Table 6. Risk factors of mortality by multivariate Cox regression analysis

	95.0% CI for Exp(B)		
	Lower	Upper	*p*
SLEDAI last visit	0.983	1.152	0.126
Constitutional	0.582	6.267	0.286
Cardiac manifestations	1.286	7.297	0.011
Serositis	0.432	3.363	0.721
Renal failure	3.469	63.900	<0.001
Hypertension	0.179	1.118	0.085
Dyslipidemia	0.600	3.453	0.415
Hepatitis C virus	0.334	3.503	0.895
ESR value last visit	0.999	1.013	0.100
Thrombocytopenia throughout disease	0.503	2.156	0.912
Increased creatinine more than 6 months	0.122	2.140	0.359
Consumed complement last visit	0.536	2.964	0.596
SLICC calculated	0.758	1.191	0.655
Number of doses cyclophosphamide	0.764	1.318	0.978
Cumulative cyclophosphamide	0.674	1.259	0.608
Mofetil	0.556	3.312	0.502
Age at onset	0.983	1.075	0.225
Cumulative Methylprednisolone in grams	1.020	1.206	0.015
Steroids dose last visit	1.014	1.092	0.007
Renal	0.307	3.309	0.990

CI: Confidence interval; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ESR: Erythrocyte sedimentation rate; SLICC: Systemic Lupus International Collaborating Clinics.

to show disease patterns different than other African countries.

In our study, the mortality rate was 8.9%, and the overall survival at 5, 10, 15, and 20 years was 96.6%, 93.3%, 91.0%, and 83.2%, respectively. In a study from South Africa, the mortality was about 24%, the five-year survival ranged from 57 to 72% and infection was the most commonly reported cause of death.[6] A study from Ghana reported the death of 43% of admitted SLE patients, with infection and renal failure reported as the main cause of mortality.[23] Another study from Tunisia, which is also a Mediterranean African country, reported a five-year survival rate of 86% in 100 SLE patients.[11]

In comparison to other Arab countries, five-year survival was slightly higher than a study from Saudia Arabia (92%), whereas a mortality of 9% was found to be quite similar to our result.[24] Al-Adhoubi et al.,[25] reported a mortality rate of 5% in Oman, with sepsis being the most common cause of death; the five-year survival was 100%. Adwan[26] analyzed 22 articles on lupus, including 3,273 patients from Arab countries, and reported that the mortality rate was recorded in nine studies, ranging from 3.1 to 15% and giving a mortality rate of 7.6%. In the mentioned studies, it was also found that the main cause of death was infection, followed by disease activity and cardiac causes.[24-26]

A study from Greece reported mortality as 6.7%, and the five-year survival rate was 96.8%, whereas the 10-year survival rate was 90.3%.[27] In an Italian cohort of 511 patients, 7.1% died. Cancer (33.3%), organ failure (22.2%), and cardiovascular disease (16.7%) were the most commonly reported causes of deaths.[28] A Croatian study in 2018 reported that the main cause of death was cardiovascular disease, followed by infection.[29] Such results from European Mediterranean countries showed comparable five-and 10-year survival rates and slightly lower mortality (6.7% and 7.1%) than our study's 8.9%. However, unlike our results, the primary cause of death was not infection.

Infection was the most common cause of death in our patient cohort (28%), followed by organ damage (18%). Infection was also postulated as the main cause of death in multiple Asian studies[3,330,31] and in African[6,32] and Latin American studies.[18,33] On the other hand, some studies from western countries reveal cardiovascular disease to be the leading cause of death among lupus patients.[34,35] This may be explained by the bimodal pattern of mortality in SLE; infection and active disease are accused as the leading causes of early deaths, as in developing countries, where lower socioeconomic status, some illiterate healthcare patterns, and the limited availability of diagnostic tools prevail.[19,29] Cardiovascular diseases and malignancy were considered the major causes of late deaths, as in most of the developed countries.[6] Additionally, poor outcomes were reported with certain ethnicities, as for nephritis in African Americans compared to Caucasians.[19]

In addition to comparing mortality rates and causes to countries of similar geographic distribution, our study aimed to identify factors associated with mortality in Egyptian SLE patients. We found that constitutional manifestations, cardiac manifestations, serositis, nephritis, and renal failure were statistically significantly higher in the deceased group. In addition, thrombocytopenia, elevated serum creatinine for more than six months and complement consumption were also significantly higher among them. A recent study in India has found fever, myositis, neurological, cardiovascular, and gastrointestinal involvement, vasculitis, and higher serum creatinine to be associated with higher risk of mortality, in addition to thrombocytopenia and low C3.[3] In our study, SLEDAI at the last visit was statistically significantly higher in the deceased compared to the living. High disease activity was reported as an important cause of mortality by several studies.[14,36] SLICC damage index was also significantly higher among the deceased. Organ damage, specifically renal, is known to be a negative prognostic factor for mortality in SLE.[18,34,37] The frequency of hypertension, dyslipidemia, and HCV antibody positivity were significantly higher among the deceased group. This is in line with Szabó et al.'s[38] findings; they stated that cardiovascular diseases, including hypertension and dyslipidemia, are major causes of mortality in lupus patients. In our study, the risk of hypertension and dyslipidemia is increased with impaired renal function and higher steroid dose in the deceased group, which substantiates our claim that tight control of renal activity with judicious

steroid use is crucial to improve the survival of lupus patients. Similarly, HCV infection, which is higher in the deceased group, is reported to be associated with increased risk of atherosclerosis and cardiovascular disease.[39]

Regarding treatment given to the studied patients, we found that the median steroid dosage given at the last visit, the median cumulative dose of intravenous steroids, and the frequency of mycophenolate mofetil administration were significantly higher in deceased patients. This could be a reflection of more active disease, renal affection, and higher predisposition to infections and damage in this group.

To identify independent risk factors for mortality, regression analysis was done, and it revealed that patients with cardiac manifestations, renal failure, and those receiving higher doses of either oral or intravenous steroids were at higher risk of mortality ($p=0.011$, $p<0.001$, $p=0.01$, and $p<0.001$, respectively). This is in accordance with the study of Lee et al.,[14] who found that the risk of mortality was significantly increased due to renal disease and cardiovascular disease. A previous study on Egyptian SLE patients also found renal affection and a high steroid dose to be independent risk factors.[32]

Finally, we can say that mortality and five-year survival among this cohort of Egyptian SLE patients are different from African, particularly sub-Saharan, countries and similar to Arabic and European Mediterranean countries. In addition, the main cause of mortality in our cohort was infection, which is reported as the main cause of SLE-related mortality in most African and Arabic studies but not in European Mediterranean studies, where cardiovascular causes were the most commonly reported. The main predictors of mortality in our cohort were cardiac manifestations, renal failure, and higher doses of steroids.

There are several limitations to this study. Our results cannot be generalized as the study is hospital based. Additionally, due to the retrospective design, we were not able to identify exact causes of deaths in patients who died outside the hospital, and we have some missing data regarding clinical manifestations and laboratory findings. Thus, we recommend future multicenter prospective studies in African countries to avoid such limitations. Furthermore, it is to be noted that our study was conducted at a center with many resources and qualified doctors available. Such facilities may not be available in all rheumatology centers all over the country, further signifying the importance of future multicenter studies in representing the mortality and survival rates of lupus patients in Egypt.

In conclusion, cardiac manifestations, renal failure, and higher steroid use were independent predictors of mortality in our cohort. Infection was the main cause of death in our study as in most African countries, while the mortality rate and five-year survival among our cohort were better than in African (sub-Saharan) countries and similar to Arabic and Mediterranean countries.

Ethics Committee Approval: The study protocol was approved by the National Research Center Ethics Committee (date: 05.08.2021, no: NRC- 2448092021). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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