

## Assessment of 10-year mortality causes among inpatients with systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a potentially life-threatening systemic autoimmune disease that increases the patient's risk of mortality if left untreated. This study examined the causes of mortality over 10 years in rheumatologic hospitals as referral centers for patients from southern Iran.

Medical records and death certificates of patients diagnosed with SLE as the underlying cause of death were retrospectively assessed. Patients were of similar ages (more than 16 years) and had been admitted to Hafez, Shahid Faghihi, or Namazi teaching hospital (affiliated with Shiraz University of Medical Sciences) during the 10-year period from April 2001 to March 2011.

A total of 101 (3.3%) SLE inpatients (from 3026 admissions) died in the named hospitals during the study period. Approximately nine deaths had occurred per year. Among them were 85 females and 16 males (female-to-male ratio of 5.3:1). The mean patient age was 36.9±12.8 years (ranging from 16-85) on admission before death. Moreover, the mean disease duration was 5.4±5.8 years. Dyspnea, a decrease in the level of consciousness, chills, and fever were the chief complaints of the majority of patients upon admission. Infections (34.7%) and cardiovascular diseases (28.7%) were the most common causes of death.

Infections followed by cardiovascular diseases are still the most frequent causes of in-hospital deaths in SLE patients. No in-hospital deaths occurred due to malignancy during this study.

**Keywords:** Systemic lupus erythematosus, mortality, Cause of Death.

### Introduction

Systemic lupus erythematosus (SLE) is a systemic connective tissue disease with a broad spectrum of clinical manifestations [1]. In Iran, an Asian/Middle Eastern country, SLE is relatively common and has a prevalence of 40 cases per 100,000 people [2]. Recent studies have reported a 10-year survival rate of 85%, whereas a study in 1955 showed a 5-year survival of less than 50%. Despite the improvement in survival rate, lupus patients still have a mortality risk equal to three times that of the general population [3, 4].

A bimodal distribution of the causes of death has been reported in studies done in the US and Europe; late mortality is more often due to cardiovascular disease, and early mortality is more frequently due to active disease or infection. In Asia, infections and active SLE are reported as the main causes of mortality during both the early and late courses of the disease [5, 6].

In the current study, the causes of mortality over a 10-year period in our rheumatologic hospitals as a referral center

were investigated, and the relationship between mortality and duration of the disease and clinical manifestations of patients was evaluated.

### Materials and Methods

The medical records and death certificates of patients with SLE as the underlying cause of death were assessed; patients were similar in age and more than 16 years old and had been admitted to the Hafez, Faghihi, or Namazee teaching hospital (affiliated with Shiraz University of Medical Sciences) during a 10-year period from April 2001 to March 2011. Patients were classified as having SLE when they met at least 4 of the American College of Rheumatology Revised Classification Criteria for Systemic Lupus Erythematosus or were identified in their charts by their rheumatologist as a known case of SLE with the above criteria [7]. In all cases, a full blood cell count and biochemistry profile including antinuclear antibody (ANA), Erythrocyte Sedimentation Rate (ESR), and C-reactive protein (CRP) tests were recorded on the data gathering forms. The exclusion criteria included having overlap syn-

drome or incomplete documentation.

The demographic characteristics of the patients, chief complaints at admission, disease duration, treatment regimens, lab data, comorbidities (hypertension, hypercholesterolemia, diabetes, and lupus nephritis), lupus manifestations, SLE Disease Activity Index (SLEDAI) on arrival, and causes of death were extracted from patients' charts. A SLEDAI score of 0–11 points was considered to indicate inactive disease, and a score  $\geq 12$  points indicated active disease [8,9].

All statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). Data was presented as mean  $\pm$  standard deviation (SD). The 95% confidence intervals for the means of data were calculated. For categorical variables, the values were presented as raw frequencies with corresponding percentages. The chi-square test was used to assess the homogeneity of sub-group proportions, and

the T-test was used for comparisons between the groups.

**Results**

The total number of patients with SLE admitted during the studied period was 3026. A total of 101 SLE patients (3.3% during 10 years) died in the named hospitals during the study period. Approximately, 9 deaths occurred per year. There were 85 females and 16 males (a female-to-male ratio of 5.3:1). The mean age of the patients was  $36.9 \pm 12.8$  (with a range of 16-85) years, and it was higher in male patients than in female patients, although the difference was not significant ( $41.2 \pm 18.1$ ,  $36.1 \pm 11.5$ ,  $P$  value=0.47). The mean disease duration was  $5.4 \pm 5.8$  years. Patients' organ involvement based on ACR criteria is shown in Table 1. Demographic data stratified by year is shown in Table 2.

Dyspnea, a decrease in consciousness level, chills, and fever were the chief complaints on admission (Table 3).

**Table1.** Accumulative clinical manifestations and laboratory findings based on the ACR Revised Classification Criteria for Systemic Lupus Erythematosus

Features	Number (Total:101)	Percent %
Malar Rash	26	25.74
Discoid Rash	9	8.91
Photosensitivity	19	18.81
Oral Ulcers	33	32.67
Arthritis	48	47.52
Serositis	65	64.35
Renal Disorder	47	46.53
Neurologic Disorder	48	47.52
Hematologic Disorder	55	54.45

**Table2.** Demographics characteristics of the patients stratified by year

SLE-related death	2001 April	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011 March
Total number (percent)	7 (6.9%)	13 (12.9%)	13 (12.9%)	6 (5.9%)	10 (9.9%)	7 (6.9%)	7 (6.9%)	10 (9.9%)	16 (15.8%)	8 (7.9%)	4 (4%)
Age, mean	37.7 $\pm$ 9.1	30.5 $\pm$ 8.8	38.8 $\pm$ 7.5	41.1 $\pm$ 14.6	33.9 $\pm$ 10.7	29 $\pm$ 5.1	38.1 $\pm$ 18.1	39.4 $\pm$ 9.5	35.1 $\pm$ 13.5	38.1 $\pm$ 14.6	62 $\pm$ 18.9
Female	5	9	12	6	9	7	4	9	14	7	3
Male	2	4	1	0	1	0	3	1	2	1	1
Ratio female/male	2.5	2.25	12	-	9	-	1.33	9	7	7	3
Disease duration (mean $\pm$ SD)	7.2 $\pm$ 5.4	11.3 $\pm$ 11.2	17.5 $\pm$ 18.1	7.6 $\pm$ 6.6	15.5 $\pm$ 12.8	10.5 $\pm$ 18.6	12.2 $\pm$ 15.4	15.1 $\pm$ 15.3	13.8 $\pm$ 9.3	18.6 $\pm$ 18.6	12.2 $\pm$ 3.6

**Table3.** Chief complaints of the studied patients on admission

Chief complaints	Number of the patients (%)
Dyspnea	24 (23.8%)
Decrease level of consciousness	19 (18.8%)
Fever, Chills	17 (16.8%)
Generalized edema	13 (12.9%)
Abdominal pain	9 (8.9%)
Bloody vomiting, melena	6 (6%)
Convulsion	5 (5%)
Oliguria	5 (5%)
Others	3 (3%)

The length of hospital stay (LOC) of the patients until death had a mean of 13.4±12.8 days. The most common comorbidities were hypertension (n=22; 21.8%) followed by diabetes (n=15; 14.9%). Lupus nephritis was present in 28 (27.7%) of patients, and the mean duration of the disease in them was 2.9±3.4 years. In addition, the mean SLEDAI score of patients at the time of arrival at a hospital was 12.1±4.8. According to the classification, 57 patients who died had active disease and 44 deaths occurred in patients with inactive disease. There was no significant difference between the number of patients with active or inactive lupus (based on SLEDAI score) and their mortality in their last admission (*P* value=0.28).

On Admission, 54.7% of patients had a leukocyte count lower than 4000/mm<sup>3</sup>, and 40% had a platelet count less than 100,000/mm<sup>3</sup> (thrombocytopenia). Hemolytic anemia

was noted in 16.8% of patients. Abnormal kidney function (creatinine >2.5) was detected in 34.6% of the patients on admission.

The results showed that mortality was significantly greater in patients aged ≥40 than in those aged less than 40 years [62 (62.4%), 39 (38.6%), respectively; *P* value=0.02].

Based on disease duration, early mortality (≤3 years) occurred in 55 (54.5%) patients and late death (>3 years) occurred in 46 (45.5%) patients. There was no significant difference in disease duration between these two groups considering the mortality rate (*P* value=0.37).

The causes of death noted in this cohort are summarized in Table 4. Infections and cardiovascular diseases were the most common causes of death in all patients, in both the early and late death groups. There were no in-hospital deaths due to malignancy.

**Table4.** Causes of death in SLE patients

Causes	All patients (n=101)	Early group (<3 years) (n=55)	Late group (>3 years) (n=46)
Infections	35 (34.7%)	19 (34.5%)	16 (34.8%)
Cardiovascular diseases	29 (28.7%)	14 (25.5%)	15 (32.6%)
Cerebrovascular diseases	16 (15%)	8 (14.5%)	8 (17.4%)
Pulmonary involvement	10 (9.9%)	8 (14.5%)	2 (4.3%)
Multiple organ failure	5 (5%)	4 (7.3%)	1 (2.1%)
Renal involvement	4 (4%)	2 (3.6%)	2 (4.3%)
Gastrointestinal Bleeding	2 (2%)	0	2 (4.3%)

## Discussion

In this report, the causes of death for SLE patients admitted to our hospitals over a 10-year period were identified, and their clinical and laboratory findings were described. Despite improvements in treatment and care of patients with SLE, the mortality rate among these patients is high compared with the general population [10]. In a study which evaluated mortality in the United Kingdom during 1999-2012, the results showed a 67% higher mortality in patients with SLE compared with the controls, particularly at younger ages [11].

The mean age at death in the patients in the current study was  $36.9 \pm 12.8$  years. Age was seen to be higher in males than in female patients, although the difference was not significant. This is similar to what was reported by a Brazilian study [12], which showed that the mean age at death was  $35.7 \pm 15.1$  years. Inconsistently, the mean age at death was  $63.5 \pm 18.4$  years in a large French study [13]. In conclusion, the current results are consistent with more recent data on mortality among SLE patients in Brazil and Malaysia. Although life expectancy is usually lower among men than women in the general population, there was no difference in age at death between men and women with SLE in the current study; indeed, age was slightly higher in men. In other studies, the mortality was higher in men with lupus [11, 12, 14].

In the current study, the inpatient mortality rate for those with SLE was about 3.3% during the 10 years of this study, and no decreasing trend in the annual number of deaths was observed. In an 8-year study on 841 inpatients with SLE in Singapore, a hospital mortality rate of 9.2% was reported [15]. A study carried out in Washington showed a trend toward decrease in in-hospital mortality and in about 50% of their patients with SLE during an 8-year follow up. The authors attributed this change in clinical outcome to improvements in treatment using newer agents with reduced toxicity [16]. Although the current study was performed until 2010 and because the 2011 study was not completely included, newer studies using new medications and improved hospital care will probably show different results. A Brazilian study showed that the mean age at death increased from 35 years in 1985 to 1989 to 38 years in 2003 to 2007 [12]. During the current study, the mean age of death was not different between years, although it increased from  $30.5 \pm 8.8$  in 2002 to  $38.1 \pm 14.6$  in 2010.

The duration of disease in patients at the time of death in the current study was  $5.4 \pm 5.8$  years. This result is similar to the results of a study done in Malaysia in 2012 ( $4.4 \pm 5$  years) in which the mean LOS was  $15.62 \pm 13.31$  days, while in the current study it was  $13.4 \pm 12.8$  days. Moreover, the most common comorbidity in lupus patients in the 2012 study was hypertension (43.8%) [17]. In the pres-

ent study, the common comorbidities were hypertension ( $n=22$ ; 21.8%) followed by diabetes ( $n=15$ ; 14.9%). Although this rate was lower in the current study than in the 2012 study, these comorbid diseases should always be kept in mind when treating lupus patients.

A Malaysian study also reported that a SLEDAI score of more than 8 was not predictive of mortality. In the current study, there was no correlation between SLEDAI and mortality [17]. Although the SLEDAI scores of living and dead lupus patients were not compared, the results of Lopez et al. showed that a one-point increase in the adjusted mean total BILAG score was associated with a 15% increase in mortality risk [18].

Although most studies have found infections, cardiovascular disease, thrombophilia, and malignancy to be the most common causes of death [12], there is a lack of agreement between the frequency of various causes of death and the type of predictors associated with mortality. Infections and cardiovascular diseases were the most common causes of death in the present study, but malignancy was not the cause of death in any patient. A review of observational studies in China revealed that infection, renal involvement, lupus encephalopathy, and cardiovascular disease were the top 4 causes of death [12]. On the other hand, the most common causes of death were cardiovascular disease followed by infectious and renal diseases in a French epidemiological study [13]. Circulatory system disease and malignancy were the most frequent causes of death in both cases and the control population of a UK study as well [11]. This diversity in the frequency of mortality causes can be related to differences in study design, patient populations, referral types, or types of analyses of predictor variables for mortality [4].

Typically, it has been shown that in the first few years of disease, the major causes of death are infections due to immunosuppressive medications and major organ involvement, and in the late stages of the disease long-term damage, especially chronic renal failure and cardiovascular diseases, are the main causes of death [19]. However, in the current study, infections and cardiovascular diseases were the most common causes of death in all patients in the early (<3 years) and late (>3 years) groups.

A significant number of mortality reports have been based on retrospective analyses of the records of hospitalized patients or those seen at outpatient clinics. Less common reports are based on prospective longitudinal studies on patients followed at lupus clinics and their data are recorded using a standard protocol. Such data is probably more accurate [20]. In most trials, causes of death are determined by the review of hospital charts, autopsy reports, and contact with the physician who cared for the patient during the terminal illness; few studies have reviewed the death certificates. The present study was based on death certifi-

icates, which increases the strength of the work, although the rate of out-of-hospital mortalities was not available, and that is the shortcoming of this study. Similarly, Souza et al. reported on a descriptive epidemiological study of the causes of death recorded on the death certificates of a large group of SLE patients in the state of Sao Paulo, Brazil [12]. The main characteristics of the study were its population-based design, the large number of deaths, multiple causes-of-death (MCD) analyses, and the analysis of trends over time. Their results showed that compared to the normal population, renal failure and infectious diseases, and in younger patients, circulatory system diseases were the main causes of mortality. The researchers expressed their concern about the increasing rate of infections during recent years due to the greater use of immunosuppressants for controlling disease, especially renal diseases. These findings are in line with the results of the present study, except for those regarding renal failure. They also showed a trend toward decrease during recent years. However, in the present study, the presence of renal insufficiency (creatinine >2.5) and hematologic abnormalities was one of the main complications of lupus patients on their last admission to the hospital.

Therefore, it seems that the trend toward using more intense immunosuppressants to better control the disease, especially its renal manifestations, still makes infections a

main concern for lupus patients. More judicious protocols for vaccinations and care of infections is needed; furthermore, vigorous screening protocols are recommended for preventing, detecting, and treating cardiovascular comorbidities in order to successfully manage and improve the survival rate of SLE patients.

### Conclusion

Infections and then cardiovascular diseases are still the most frequent causes of in-hospital death in early (<3 years from the onset of disease) and late (>3 years after the onset of disease) SLE patients. No deaths occurred due to malignancy in this study.

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### Conflict of interest

There is no conflict of interest in writing this article.

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