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Causes of Death and Prognostic Factors in Thai Patients with Systemic Lupus Erythematosus

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SUMMARY **From a cohort study of 349 Thai patients (337 females [F] and 12 males [M]) with systemic lupus erythematosus (SLE), 52 patients (51 F, 1 M) died. Their 5- and 10-year survival rates were 84.0% and 74.9%, respectively. Seventy-nine percent of deaths occurred within the first year of diagnosis. Infection contributed to 27 deaths (51.9%). The lung and the urinary system were the 2 most common sites of infection. There were 18 SLE-related deaths (34.6%), and 7 non-SLE related deaths (13.5%). In a multivariate analysis of all causes of death, serositis, hematologic abnormality, central nervous system (CNS) and renal involvement were significantly associated with poor survival, while photosensitivity and arthritis were significantly associated with longer survival. Among SLE-related death, serositis and CNS involvement were significantly associated with poor survival, and arthritis was associated with longer survival. In conclusion, infection was the most common cause of death in Thai SLE patients. CNS and visceral involvement were associated with a poor outcome.**

Systemic lupus erythematosus (SLE) is a connective tissue disease characterized by multiple organ inflammation. The clinical course in each individual varies, with a tendency toward quiescence, remission and relapse. The disease can be mild or severe and occasionally fatal. In the past, the mortality rate was extremely high, particularly in patients with active visceral organ involvement. However, the survival rate has improved remarkably during the past decades, from a 5-year survival rate of only 50% in the 1950s[1] to a 10-year survival rate of approximately 90% in the 1990s.[2-4] This improvement has been related to a better understanding in the immunopathogenesis of SLE, the early detection of cases, the use of corticosteroids and immunosuppressive drugs, the improvement of antibiotic and antihypertensive agents, the availability of dialysis and renal replacement therapy, and the improvement in health care and life support.

It has been reported that Asian SLE patients, especially those who live in the USA and UK, have more severe internal organ involvement and a higher mortality.[5-6] However, a recent study from southern China did not support these previous findings.[7] The mortality in SLE patients has been reported to be approximately five-fold higher than in the general population.[2] Although SLE is a common disease in Thailand, study of the causes of death and the prognostic factors is limited.[8] We report herein, the causes of death and prognostic factors for survival in a cohort of 349 Thai patients seen in a university hospital.

MATERIALS AND METHODS

The study cohort included all patients diagnosed with SLE, who were seen at the Division of Rheumatology, Department of Medicine, Chiang Mai University between January 1986-December 2000. All patients fulfilled at least 4 of the 1982 and the 1997 American College of Rheumatology (ACR) revised criteria for the classification of SLE.[9,10] The following data were obtained from all patients: sex, the age at the time of diagnosis, clinical features and organ involvement. The SLE disease activity was determined using the MEX-SLEDAI score.[11] Patients were usually fol-

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lowed-up at regular intervals of 6-8 weeks. In patients with severe organ involvement or disease flare, follow-up was scheduled more frequently.

The cause of death was determined, based on detailed clinical records (including autopsy results when available), or the death certificate. The causes of death were classified into 3 groups: 1) infection related death referred to death as a result of severe infection. Majority of the patients with infections usually had active disease and received high dose corticosteroids and immunosuppressive drugs. We considered infection as a cause of death when infection was the primary event that led to death (although the patients might also had active disease), 2) SLE related death referred to death that was due to active organ involvement, either by clinical or by autopsy, such as CNS lupus, lupus nephritis with or without progressive renal failure, or lupus pneumonia (in the absence of infection), and 3) non-SLE related death referred to death that was not related to SLE activity or infection, e.g. myocardial infarction, unexplained sudden cardiac death or malignancies.

Table 1 Accumulative clinical manifestations and laboratory findings in 349 patients

Features	Accumulative (%)
Malar rash	165/349 (47.3)
Discoid rash	98/349 (28.1)
Photosensitivity	100/349 (28.7)
Oral ulcer	89/349 (25.5)
Arthritis	187/349 (53.9)
Serositis	67/349 (19.2)
Renal disorder	233/349 (66.2)
CNS involvement	69/349 (19.2)
Hematologic abnormality*	266/349 (76.2)
ANA positive**	312/341 (91.5)
Immunologic abnormality***	40/197 (20.3)

*Hematologic abnormality refers to hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia, ** ANA = antinuclear antibody, ***immunologic abnormality refers to positive anti-dsDNA, anti-Sm or antiphospholipid antibodies.[9,10] CNS = central nervous system.

Table 2 Percentage of deaths and number of patients according to time of follow-up

Duration of disease (months)	Number of patients	Death (%)
0-12	140	41 (78.8)
13-24	42	5 (9.6)
25-36	37	1 (1.9)
37-48	30	0
49-60	22	1 (1.9)
61-72	13	1 (1.9)
73-84	24	1 (1.9)
≥ 85	46	2 (3.8)

Statistical analysis

The SPSS version 10 statistical program (SPSS Inc., Chicago, Illinois, U.S.A.) was used for statistical analysis. Continuous data were described as mean and standard deviation (S.D.). Categorical variables were described as percentages. Comparisons were made using the Student's t-test for continuous variables, and the Mann Whitney's U-test for ordinal and discrete variables. Cox's proportional hazards general linear model procedure was utilized to determine which of many potentially important parameters had the greatest impact on the prognosis in SLE. A p-value < 0.05 was considered clinically significant.

RESULTS

There were 349 SLE patients (337 females and 12 males) with a mean ± S.D. age at diagnosis (well-described signs or symptoms that were compatible with the disease) of 31.6 ± 10.7 years, and a median duration of follow-up of 24 months (range 0.2-196 months). The accumulative clinical manifestations and laboratory findings of the patients studied are shown in Table 1.

During the study period, there were a total of 413 admissions. Fifty-two patients (14.9 %, 51 females and 1 male), died. Forty-nine deaths occurred in our institution. One died of pneumonia at another hospital. The remaining 2 patients died at home. One had a clinically inactive disease and died suddenly, and the other had central nervous system (CNS) involvement and died shortly after being discharged from the hospital. There was no statistically significant difference in the death rate of male and female patients (p = 0.45). Seventy-nine percent of deaths occurred within the first year of diagnosis (Table 2), with a median duration of 3 months (range 0.2-12

months) after diagnosis. The estimated 5-year and 10-year survival rate of this study cohort was 84.0% (95% CI = 1, 0.37) and 74.9% (95% CI = 1, 0.28), respectively. When compared with those still living, the death group had a higher age at the onset (34.98 ± 10.91 *vs* 30.99 ± 10.61 years, $p = 0.01$), higher MEX-SLEDAI at the time of presentation (13.11 ± 35.55 *vs* 9.67 ± 23.89, $p < 0.001$), and greater number of admissions/persons (1.52 ± 0.87 *vs* 1.13 ± 1.11, $p = 0.15$).

Details of the causes of death are shown in Table 3. Infection contributed to 27 deaths (51.9%), with 22 of those occurring within the first year of diagnosis. Bacteremia occurred in 15 of these 27 patients (55.6%). The lungs and the urinary system were the two most common sites of infection. Both gram negative and gram positive bacteria (*Salmonella* spp., *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Staphylococcus aureus*) were the major organisms responsible for death. Infections caused by opportunistic pathogens (*Aspergillus fumigatus, Penicillium marneffei*, and cytomegalovirus) were seen occasionally. These patients had an active disease prior to developing infection and death, with a MEX-SLEDAI score of ≥ 7 in 21 cases, 4-6 in 5 cases, and ≤ 3 in 1 case. These infections occurred early in the course of the disease, which had a median duration of 3.2 months. Among those with infection related death, all patients received prednisolone, and 9 patients (33.3%) received both prednisolone and cyclophosphamide. The mean ± S.D. dosage of prednisolone and oral cyclophosphamide, received within 30 days before the development of infection and death was 38.78 ± 46.23 mg/day and 1,138.89 ± 832.08 mg/month, respectively. Neutropenia occurred in 1 patient who had not been previously given cyclophosphamide.

Table 3 Causes of death in 27 patients

Cause of death	Number of patients
Infections (with bacteremia)	**27 (15)**
Bacteremia alone	5
Pneumonia	12 (4)
Urinary tract infection	5 (3)
Cellulitis	2 (2)
Septic joint	1(1)
Brain abscess	1
Liver abscess	1
SLE related deaths	**18**
CNS lupus	7
Lupus nephritis	5
Lupus pneumonitis	3
Myocarditis	2
Acute pancreatitis	1
Non-SLE related deaths	**7**
Sudden cardiac death	1
Malignancy	1
Pulmonary embolism	1
Rupture aortic aneurysm	1
Transfusion reaction	1
Iatrogenic intra-abdominal hemorrhage	1
Unknown	1

SLE-related deaths occurred in 18 patients (34.6%). There was CNS lupus, lupus nephritis, lupus pneumonitis, myocarditis and acute pancreatitis in 7 (13.5%), 5 (9.6%), 3 (5.8%), 2 (3.9%) cases and 1 (1.9%) case, respectively. All of these patients had active disease, with a MEX-SLEDAI score of ≥ 7 in 17 cases, and 4-6 in 1 case. CNS lupus, lupus nephritis, lupus pneumonitis, myocarditis and acute pancreatitis were primary or contributing causes occurring in the first year of the disease in 5, 4, 3, 2 cases and 1 case, respectively. Three of 5 patients, in whom renal disease was the primary cause of death, had uremia or chronic renal insufficiency. None of these patients received long term dialysis or kidney transplantation. Non-SLE related deaths occurred in 7 patients. There was one case each of sudden cardiac death, malignancy, pulmonary embolism, ruptured abdominal aortic aneurysm, transfusion reaction and iatrogenic intra-abdominal hemorrhage from a liver biopsy. One case died without any identifiable cause. The sudden cardiac death case was a 44-year-old patient, who had had SLE for 36 months. This patient had a clinically inactive disease. The MEX-SLEDAI score of these 7 patients was ≥ 7 in 4 cases, and 4-6 in 3 cases.

In the group of non-infection related deaths (25 cases), 17 patients received prednisolone alone, 5 patients received both prednisolone and oral cyclophosphamide, and 8 patients received neither prednisolone nor cyclophosphamide. The mean ± S.D. dose of prednisolone and oral cyclophosphamide received within 30 days before death was 28.19 ± 38.37 mg/day and 1,140.00 ± 461.52 mg/month, respectively. There was no significant difference in the mean dosage of both pred-

Table 4 Cox proportional hazard model of all-causes of mortality, in association with the clinical and laboratory parameters according to the diagnostic criteria of SLE (univariate analysis)

	Death (%) N = 52	Alive (%) N = 297	Hazard ratio	95% CI	*p*-value
Malar rash	21 (40.4)	144 (48.5)	0.66	0.38-1.15	0.15
Discoid rash	9 (17.3)	89 (30.0)	0.51	0.25-1.05	0.07
Photosensitivity	8 (15.4)	92 (31.0)	0.44	0.21-0.94	0.04*
Oral ulcer	8 (15.4)	81 (27.3)	0.53	0.25-1.13	0.10
Arthritis	14 (26.9)	173 (58.2)	0.27	0.15-0.50	< 0.01*
Serositis	18 (34.6)	49 (16.5)	2.33	1.32-4.14	< 0.01*
Renal disorder	43 (82.7)	190 (64.0)	2.38	1.16-4.89	0.02*
CNS involvement	19 (36.5)	50 (16.8)	2.69	1.53-4.73	< 0.01*
Hematologic abnormalities**	46 (88.5)	220 (74.1)	2.62	1.12-6.13	0.03*
ANA positive***	49/51 (96.1)	263/290 (90.7)	2.10	0.51-8.65	0.30
Immunologic abnormality****	8/28 (28.6)	32/169 (18.9)	1.77	0.77-4.01	0.18

* = statistical significance **Hematologic abnormality refers to hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia, ***ANA = antinuclear antibody, ****immunologic abnormality refers to positive anti-dsDNA, anti-Sm or antiphospholipid antibodies[9,10], CNS = central nervous system.

nisolone and cyclophosphamide found between the infection related and non-infection related death groups ($p = 0.60$ and $p = 0.99$, respectively).

In order to identify the prognostic factors, we analyzed the relationship between the clinical manifestation and laboratory abnormalities, according to the ACR diagnostic criteria for SLE, and death. Table 4 shows results of a univariate analysis between the ACR diagnostic criteria and all causes of death. In this model, serositis, hematologic abnormality, CNS and renal involvement were significantly associated with poor survival. In contrast, photosensitivity and arthritis were significantly associated with longer survival. The presence of ANA or immunologic abnormalities showed no association with all-cause mortality. Because the analysis had shown that age at presentation influenced survival ($p = 0.01$), we therefore examined those manifestations independently associated with mortality, with age-adjustment, using a stepwise multivariate survival analysis. In this analysis, CNS involvement and hematologic abnormality showed a tendency to be associated with poor survival, but they did not reach statistical significance. However, articular manifestations remained an independent protective factor (hazard ratio = 0.31; 95% CI = 0.17, 0.60; $p < 0.01$).

An association between clinical manifestations and laboratory abnormalities with 18 SLE-related deaths was also determined by using a univariate analysis. Serositis and CNS involvement was significantly associated with poor survival, while arthritis was still associated with longer survival (Table 5). In the multivariate analysis, with the age-adjusted model, CNS involvement and serositis remained associated with a poor survival rate (hazard ratio 3.38, 95% CI 1.28, 8.93, $p < 0.02$ for CNS involvement; and hazard ratio 3.52, 95% CI 1.36, 9.09, $p < 0.01$ for serositis). Arthritis was associated with a longer survival rate (hazard ratio 0.24, 95% CI 0.07, 0.75, $p < 0.02$).

DISCUSSION

In this report, we described the causes of death and risk factors for mortality in SLE patients who were treated in a teaching university hospital over a 15-year period. We also tried to identify the clinical and laboratory indices that may have value as a predictor of poor survival.

The 5-year and 10-year survival rates in this study were 84.0% and 74.9%, respectively. These survival rates were comparable to those reported from other countries.[2-4, 12-13] It should be noted that the mortality rate within the first year of diagnosis in our patients was extremely high (78.8%), and infection contributed to half of these deaths (22 of 41 cases).

The bimodal pattern of death in SLE was first recognized by Urowitz *et al.*,[14] who observed the pattern of mortality in their population of 81 patients. Six patients died within the first year due to active disease, while 4 of 5 late deaths (2.5-19.5 years after diagnosis) were primarily due to myocardial infarction. Since then, similar findings have been reported in large series.[15-16] Cardiovascular disease is now well recognized as a com-

Table 5 Cox proportional hazard model of SLE-related mortality, in association with the clinical and laboratory parameters according to the diagnostic criteria of SLE (univariate analysis)

	SLE related death (%) N = 18	Alive (%) N = 297	Hazard ratio	95% CI	*p*-value
Malar rash	7 (38.9)	144 (48.5)	0.63	0.25 – 1.64	0.35
Discoid rash	2 (11.1)	89 (30.0)	0.30	0.07 – 1.30	0.11
Photosensitivity	1 (5.6)	92 (31.0)	0.14	0.02 – 1.06	0.06
Oral ulcer	2 (11.1)	81 (27.3)	0.36	0.08 – 1.59	0.18
Arthritis	4 (22.2)	173 (58.2)	0.19	0.06 – 0.59	< 0.01*
Serositis	8 (44.4)	49 (16.5)	3.64	1.43 – 9.17	< 0.01*
Renal disorder	14 (77.8)	190 (64.0)	1.79	0.59 – 5.46	0.30
CNS involvement	9 (50.0)	50 (16.8)	4.57	1.81 – 11.49	< 0.01*
Hematologic abnormalities**	14 (77.8)	220 (74.1)	1.29	0.42 – 3.92	0.65
ANA positive***	15/17 (88.2)	263/290 (90.7)	0.66	0.15 – 2.90	0.58
Immunologic abnormality****	2/10 (20.0)	32/169 (18.9)	1.39	0.28 – 6.90	0.69

* = statistical significance **Hematologic abnormality refers to hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia, ***ANA = antinuclear antibody, ****immunologic abnormality refers to positive anti-dsDNA, anti-Sm or antiphospholipid antibodies[9,10], CNS = central nervous system.

Table 6 The causes of death in SLE from this study and selected series

Authors[reference]	Year	Country	MR (%)	Infection (%)	SLE related			Non-SLE related (%)
					LN (%)	CNS (%)	Other (%)	
Rosner S[17]	1982	USA	222/1103 (20.1)	74 (33.3)	41 (18.5)	15 (6.8)	17 (7.7)	75 (33.8)
Rubin LA[15]	1984	Canada	51/417 (12.2)	14 (27.5)	7 (13.7)	9 (17.7)	9 (17.7)	12 (23.5)
Helve T[18]	1985	USA	155/1427* (10.9)	24 (17.5)	39 (27.5)	10 (7.0)	25 (17.6)	44 (31.0)
Harisdangul V[19]	1987	USA	50/378 (13.2)	14 (28.0)	18 (36.0)	3 (6.0)	5 (10.0)	10 (20.0)
Nanagara R[8]	1990	Thailand	28/156 (18.0)	10 (35.7)	7 (25.0)	2 (7.1)	5 (17.7)	4 (14.3)
Ward M[20]	1995	USA	144/408 (35.3)	32 (22.2)	12 (8.33	11 (7.7)	26 (18.1)	63 (43.8)
Leong KH[21]	1997	Singapore	13/87 (15.0)	5 (38.5)		6 (46.2)		2 (15.4)
Bellomio V[22]	2000	Argentina	44/366 (12.0)	24 (54.5)		14 (31.8)		6 (13.6)
Present study	2001	Thailand	52/349 (14.9)	27 (51.9)	5 (9.6)	7 (13.5)	6 (11.5)	7 (13.5)

MR = mortality rate, LN = lupus nephritis, CNS = central nervous system, * Causes of death were described in details in 142 patient

mon cause of death in long-standing lupus. Although there was a trend of bimodal-distribution of death in this study, the second peak of death was not clearly demonstrated. This might be due to the short follow-up duration of our patients (median 24 months). Only 83 cases (23.8%) had been followed for more than 5 years. A longer duration of follow-up might be needed to demonstrate this bimodal-effect.

The causes of death in SLE from several studies have shown variable results (Table 6). Active SLE has been reported as a major cause of death in several studies,[3,8,13,18-21] while others found that infection was more common.[7,17,22-27] This difference might be related to the characteristic of the patient population, socioeconomic status, and probably the health care system of the reporting institution. Many of the reported series found that patients who died of infection usually had active disease. Our results were similar to them.

The causes of death in the early years after diagnosis of SLE are primarily due to the severity of the disease and the high dosage of immunosuppressive drugs. These conditions predispose to infection.[17] In contrast, atherosclerosis, which is the result of many factors including hypertension, chronic inflammation and chronic use of corticosteroids, increases the risk of premature death by cardiovascular event in long-standing patients.[25] We found that our patients, who died early in both the infection and

non-infection groups, had active disease. Patients with active disease tended to receive high dose corticosteroids and immunosuppressive drugs, which might be predisposed to the development of serious infection. However, our findings did not show a difference in the dosage of corticosteroids and immunosuppressive drugs given prior to death between the infection related and the non-infection related groups. This finding was in contrast to previous observations.[17]

A number of lupus and non-lupus related factors have been described in association with the prognosis of SLE. A high SLEDAI score and a large number of preliminary diagnostic criteria, which reflect disease activity, have been reported as associated with short-term mortality.[26-28] Specifically, renal involvement (proteinuria, and diffuse glomerulonephritis), CNS involvement (organic brain syndrome and seizure), thrombocytopenia, pleurisy, thrombocytopenia and leukopenia,[8,15,17,26,28-30] as well as elevation of serum creatinine and systolic hypertension at the time of diagnosis,[12,26] have been reported as poor prognostic factors. Infection has clearly been associated with a high mortality.[8,17,26] Interestingly, skin rashes and arthritis have been reported to be associated with a favorable outcome.[25,28] Our results were in line with Cook's[26] and Ward's[29] in that CNS involvement was associated with a poor prognosis, while arthritis was a protective factor.

There are several limitations in this study, in that it was retrospective. Therefore, the accuracy of the causes of death may be limited, particularly in patients who died because of SLE or infection, where exact clinical information can be observed. Fortunately, a majority of the deaths that were attributed to SLE or infection occurred in our institution, where the clinical information was available. Moreover, the median follow-up duration of our patients was short, and not all of them died during the time of this study. Therefore, the proportion of deaths due to other causes that predominated late in the course of SLE might be underestimated.

In conclusion, infection was the most common cause of death in Thai patients with SLE, followed by SLE related death due to active disease. CNS lupus and serositis were poor prognostic factors, while arthritis was a protective factor. As infection is a major cause of death in Thai patients with SLE, aggressive investigation to identify the organisms and early antimicrobial therapy is recommended, particularly in cases with suspicious of infection, to improve the chance of survival.

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