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Mortality and Causes of Death of 513 Danish Patients with Systemic Lupus Erythematosus

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A multicentre cohort of 513 clinic attenders with systemic lupus erythematosus (SLE) was retrospectively identified, representing 4185 patient-years of follow-up. Expected numbers of death were calculated by means of age- and sex-specific mortality rates of the general Danish population. The observed number of deaths was 122. The survival rates were 97%, 91%, 76%, 64% and 53% after 1, 5, 10, 15, and 20 years respectively. The overall mortality rate was 2.9% per year (95% CI 2.4 – 3.5), and the standardized mortality rate (SMR) was 4.6 (95% CI 3.8 – 5.5). The causes of death included active SLE (n = 19), end stage organ failure due to SLE (n = 16), infections (n = 25), malignancy (n = 9), cardiovascular disease (n = 32), and other causes (n = 21). SLE was directly related to one third of the excess mortality. In conclusion, SLE patients in the present cohort had a 4.6-fold increased mortality compared with the general population and half of the deaths were caused by SLE manifestations or infections, especially in young patients during the early period of the disease.

Key words: survival, mortality, standardised mortality rates, causes of death, systemic lupus erythematosus

The prognosis of systemic lupus erythematosus (SLE) is related to the type of organ involvement (1, 2). The deaths may be caused by acute exacerbations of the disease, irreversible organ damage evolved during several years, infections, and other morbidity unrelated to SLE. Previous studies have shown that the mortality in SLE has a bimodal pattern, the early deaths being mainly caused by active SLE and the late deaths mainly being unrelated to SLE (3, 4). Some studies have indicated that deaths due to atherosclerosis may occur prematurely in SLE due to treatment with prednisone, hypertension and hyperlipidaemia (5).

Demographic characteristics have also been shown to influence the outcome of SLE. American black race (6), male sex (7) and old age at diagnosis (6, 8) have been reported to have a negative effect on the survival. Such factors are highly dependent of the characteristics of the general population from which the patients stem. In this study we analyzed the mortality of a cohort of SLE patients related to a comparable background population. We also analyzed the influence of demographic factors on mortality and the causes of death.

Patients and methods

From January 1975 until December 1995 513 patients with SLE were seen at the eight participating centres and retrospectively identified by means of hospital contact lists of the in- and out-patient clinics; the study thus being a retrospective cohort study. Clinical data were registrated from the time of the first SLE related symptom. The observation period and the calculation of the risk of death started at the time when the classification criteria for SLE were fulfilled. The observation period stopped in 1995 (end of study) at the time of the most recent patient information or at death. The disease duration thus equalled the period of follow-up. No patients were lost for follow-up. The study protocol and a description of the participating centres is presented in our paper on the clinical features of the same cohort of SLE patients (9). Clinical factors of prognostic significance in this cohort have also been described previously (10).

Diagnosis

Only patients who fulfilled the American College of Rheumatology (ACR) 1982 revised criteria for the classification of SLE were included in the study (11). In this study the time of diagnosis refers to the time when the classification criteria for SLE were fulfilled. The definition of the classification criteria manifestations followed the guidelines of the ACR. However, due to differences in laboratory techniques between the participating hospitals, values for haematological and serological variables were not always comparable. For this reason local normal ranges were used instead of the limits stated in the ACR criteria.

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Outcome variables

The outcome variables of this study were survival and causes of death. Vital status at the study end was established by reviewing the clinical charts and by contacting the Danish Central Person Register. The causes of death were based on information obtained from the hospital charts and the autopsy reports (n = 102) or death certificates (n = 11). The causes of death were classified as follows, viz: active SLE, end-stage organ failure due to SLE, infections, malignancy, other causes or unknown causes. Death was considered to be due to active SLE if uncontrollable, progressing SLE related manifestations indicative of active disease were the direct cause of death. A death was considered to be caused by end-stage SLE if terminal organ failure was caused by SLE, irrespective of disease activity. Infections were diagnosed by means of clinical and paraclinical findings as documented by the clinical charts.

Statistical analyses

Data processing was performed using the software package Epi Info 6 (12). Comparison of categorical variables was performed using the chi-square test with Yates correction. Different strata of continuous variables were described and compared using non-parametric methods. Statistical significance was defined as $p \leq 0.05$. Estimation of survival and mortality rates was performed by lifetable analysis by calculating cumulated survival and hazard rates with their corresponding 95% confidence intervals (CI) quoted in square brackets. To further estimate the risk for death in the cohort and strata of it, we also calculated standardised mortality ratios (SMR) and the corresponding 95% CI. The SMR is the ratio between the observed rate of death in the cohort and the expected rate of death in a comparable age and sex matched background. The mortality rates in the general population were calculated by means of life tables, representing the period of observation, produced by The National Institute of Statistics. 95% CI for the SMR were calculated by regarding the observed number of deaths as a Poisson variable and finding its related 95% CI in statistical tables. Our procedure followed the one described by *Brennan and Jones* (13).

Results

Demographic variables

The basic demographic data of the study population are presented in Table I. The 513 patients included 454 women (88%). The sex ratio differed significantly when comparing living and deceased patients since an excess of men was found in the group of deceased patients. The deceased patients were significantly older than the living patients at the time of the first symptom and at the time of diagnosis. The disease duration did not differ significantly in living and deceased patients. The period between the first symptom and first visit at the tertiary center and the prodromal period were longer in the deceased patients than in the living patients. Two hundred and eighty-eight (56%) patients had had SLE-related symptoms for less than two years when referred to a tertiary center. These patients did not differ from the rest with regard to mortality (21% and 28%, respectively), survival rate or causes of death.

Lifetable analysis

The lifetable analysis presented in Table II shows a survival rate of 97% after one year, 95% after two

Table I. Basic demographic data of the 513 patients with systemic lupus erythematosus.

	All patients	Living patients	Deceased patients	P = *
No. of patients	513	391	122	–
Gender, no. (%)				
– male	59 (12)	37 (10)	22 (18)	
– female	454 (88)	354 (90)	100 (82)	0.02
Age at first symptom, yrs.	28.2	27.0	31.4	
– median (range)	(3.2–82.1)	(5.5–80.1)	(3.2–82.1)	0.007
Age at diagnosis, yrs.	34.3	32.8	37.7	
– median (range)	(9.0–82.1)	(9.0–81.2)	(10.8–82.1)	0.005
Symptom duration at first visit, yrs.**	1.1	0.83	2.2	
– median (range)	(–6.3–31)	(–6.3–31)	(–3.0–29)	0.03
Duration of prodrome, yrs.	2.1	1.9	3.1	
– median (range)	(0–33.1)	(0–31.1)	(0–33.1)	0.03
Duration of SLE***, yrs.	6.2	5.6	7.3	
– median (range)	(0–40.3)	(0–33.6)	(0–40.3)	0.28

* comparing living and deceased patients at the end of the observation period. ** negative values indicate that a patient was already followed by a tertiary center at the time of the first SLE related symptom. *** identical with length of follow-up.

Table II. Lifetable analysis giving the cumulated survival and mortality rate (hazard rate) with corresponding 95% confidence intervals (CI).

Strata of disease duration (years)	Patients entering stratum	Patients censored in stratum	No. of deaths in stratum	Cumulated survival		Mortality rate	
				%	95% CI	% per year	95% CI
0–1	513	30	15	97.0	95.5–98.5	3.1	1.5–4.6
1–2	468	50	8	95.2	93.0–97.0	1.8	0.5–3.1
2–5	410	95	16	90.8	88.0–93.6	1.6	0.2–2.9
5–10	299	90	42	75.8	71.0–80.6	3.6	2.5–4.7
10–15	167	72	21	63.7	57.4–70.0	3.5	2.0–5.0
15–20	74	21	11	52.6	44.6–60.6	3.8	1.5–6.1
20+	42	33	9	34.1	22.9–45.3	not calculated	

years, 91% after five years, 76% after 10 years, and 53% after 20 years. The risk of death was highest during the first year and after five years, however these mortality rates did not differ significantly.

Standardised mortality ratio

The overall mortality rate of the SLE patients was 2.9% per year. The SMR for the SLE cohort compared with the general population was 4.6 (CI of 3.8 to 5.5.). In Table III the age specific mortality rates and the SMR's are presented. The mortality rates increased with age. The SMR's, on the other hand, decreased with age.

When stratifying the cohort according to gender (table III) the men had a mortality rate twice that of the women, but the SMR for men and women did not differ (4.0 [3.8 – 5.5] and 4.7 [3.9 – 5.8], respectively). The age specific SMR showed the same distribution for men and women.

Table III also shows the effect of the age at disease onset on mortality. The patients were divided into three strata, depending on their age at the time of diagnosis viz. those under 18 years (early onset), those between 18 and 49 years (middle onset), and those who were 50 years or more (late onset). The mortality rate was highest for the patients with late onset disease, but after making corrections for age and sex, the SMR was highest for the patients with early onset disease, 57 [30 – 100] versus 2.1 [1.5 – 2.9] for those with late onset disease.

Causes of death

Thirty-five of 122 patients died of SLE, which was the most common cause of death. Infections and cardiovascular disease each were responsible for 25 deaths. Nine patients died of malignant tumours and 5 patients died of cerebro-vascular disease.

Nineteen of the 35 patients who died of SLE had active, progressive, frequently multi-systemic disease, but it was possible to single out one predominating cause of death, viz CNS involvement in 7 patients and nephropathy in 6 patients. One patient died of

Table III. Estimated risk of death, expressed by mortality rates and standardised mortality ratio, in the SLE cohort compared with the general Danish population. Patients have been stratified according to age, gender and disease duration. Patient years at risk were calculated as the time from diagnosis to end of study. Rates and ratios are presented with corresponding 95% confidence intervals (CI).

	Patient years at risk	Expected no. of deaths	Observed no. of deaths	Mortality rate		Standardised mortality ratio	
				% per year	95% CI	Ratio	95% CI
All patients	4185	26.6	122	2.9	2.4– 3.5	4.6	3.8–5.5
Age groups (years):							
5–24	607	0.20	13	2.1	1.1–3.7	67	36–114
25–64	3182	10.3	77	2.4	1.9–3.0	7.5	5.9–9.3
65–94	396	16.1	32	8.1	5.5–11.4	2.0	1.4–2.8
Gender:							
Male	406	5.6	22	5.4	3.4–8.2	4.0	3.8–5.5
Female	3779	21.1	100	2.6	2.2–3.2	4.7	3.9–5.8
Disease onset:							
Before age 18 years	483	0.21	12	2.5	1.3–4.3	57	30–100
Age 18–50 years	3074	9.1	73	2.4	1.9–3.0	8.0	6.3–10
After age 50 years	628	17.3	37	5.9	4.1–8.1	2.1	1.5–2.9

Table IV. Distribution of primary causes of death in 122 deceased patients with systemic lupus erythematosus (SLE).

		Main categories	Subgroups
A	Active SLE	19	
	CNS disease		7
	Progr. glomerulonephritis		5
	Carditis		2
	Haematologic crisis		2
	Other		3
B	End stage SLE	16	
	Renal failure		12
	Pulmonary failure		2
	Other		2
C	Infections	25	
	Pulmonary		13
	Septicaemia		7
	CNS		3
	Endocarditis		1
	Hepatitis		1
D	Malignancy	9	
	Ovarian cancer		3
	Malignant lymphoma		2
	Renal and pancreatic cancer		1
	Colonic cancer		1
	Thyroid cancer		1
	Metastatic disease of unknown origin		1
E	Other causes of death	44	
	Heart failure		13
	Acute myocardial infarction		12
	Cerebral palsy		5
	Sudden death, cause unknown		4
	Rupture of aortic aneurism		2
	Suicide		2
	Other		6
F	Unknown	9	

Table V. Sites of infection and associated microorganisms in the 25 systemic lupus erythematosus patients who died of infection.

Site or type (no.)	Microorganisms identified (no.)
Pneumonia (13)	*Staphylococcus aureus* (2)
	Pneumocystis carinii (2)
	Klebsiella pneumoniae (1)
	Unidentified (8)
Bacteraemia/septicaemia (7)	*Streptococcus pneumoniae* (3)
	Staphylococcus aureus (2)
	Unidentified (2)
Meningitis (2)	*Streptococcus pneumoniae* (1)
	Staphylococcus aureus (1)
Brain abscess (1)	Unidentified (1)
Endocarditis (1)	Unidentified (1)
Hepatitis (1)	Non-A,B, or C (1)

myocarditis and heart failure and one patient died of progressive Libman-Sacks endocarditis and heart failure.

Sixteen patients died of irreversible, end-stage damage caused by SLE, which was often inactive at the time of death. Twelve of these patients died of renal failure, two of pulmonary failure.

Fatal infections and the responsible microorganisms identified are listed in Table V. The most frequent infections were pneumonia, bacteraemia or septicaemia in 80% of the cases. *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most commonly (75%) identified microorganisms when a microbiological diagnosis was obtained.

The distribution of known causes of death was significantly influenced by gender, age at disease onset, and disease duration, Table VI. Death due to active SLE was associated with short disease duration. Male sex was associated with death due to end stage SLE and morbidity unrelated to SLE. Fatal infections were most often seen in patients with early onset disease and in patients with a disease duration of 5 to 10 years. Death due to malignancy and morbidity unrelated to SLE was associated with late onset SLE. As expected, deaths due to active SLE were most often seen during early courses of the disease, whereas deaths related to end stage SLE most often occurred after 10 years of disease duration. The sex adjusted relative risk of death due to SLE-related causes or infection was 1.9 [1.0 – 3.4] for patients with early onset disease compared with rest of the patients. Death due to atherosclerotic disease occurred 2.5 times more often in patients with more than five years of disease duration compared with rest of the patients, but after correction for sex and age effects this relative risk increased to 3.4 [1.5 – 8.3].

Discussion

In the present survival study of a cohort of 513 Danish patients with SLE, the mortality rates were compared with the expected mortality rates in a sex and age matched background population derived from mortality tables of the general Danish population, SMR. This method has only been applied on SLE mortality by the group of *Urowitz* (4, 14). The strata of age specific SMR's show that the highest surplus mortality is found in young patients with early disease onset. The deaths in these patients are mainly caused by SLE and infectious complications. After the age of 35 years the SMR decreases significantly coinciding with a decrease in the proportion of deaths caused by SLE or infections. The mortality rates have previously been described as being higher in men than in women (15). We also found this to be true in our study, but after standardisation of the mortality rates, the surplus mortality was identical in men and women. However, the distribution of the causes of death were different in the two sexes. Men had significantly higher rates of death due SLE end-stage

Table VI. Distribution of causes of death, by sex, time of disease onset, and disease duration in 513 patients with systemic lupus erythematosus.

	Active SLE N=19			End stage SLE N=16			Infections N=25			Malignancy N=9			Other/unknown causes N=53		
	No.	(%)	P=	No.	(%)	P=	No.	(%)	P=	No.	(%)		No.	(%)	P=
Gender:															
Male, n=59	1	(1.7)		4	(6.8)		5	(8.5)		1	(1.7)		11	(19)	
Female, n=454	18	(4.0)	0.44*	12	(2.6)	0.01*	20	(4.4)	0.09*	8	(1.8)	0.71*	42	(9.3)	0.001*
Onset of disease:															
Before age 18 years, n=56	2	(3.6)		3	(5.4)		6	(11)		0			1	(1.8)	
Age 18–50 years, n=354	16	(4.5)		11	(3.1)		13	(3.7)		5	(1.4)		28	(7.9)	
After age 50 years, n=103	1	(1.0)	0.35*	2	(1.9)	0.70*	6	(5.8)	0.04*	4	(3.9)	0.02*	24	(23)	0.0000*
Disease duration:															
0–5 years, n=214	13	(6.1)		2	(0.9)		9	(4.2)		1	(0.5)		14	(6.5)	
5.1–10 years, n=132	5	(3.8)		4	(3.0)		13	(9.8)		4	(3.0)		16	(12)	
over 10 years, n=167	1	(0.6)	0.02**	10	(6.0)	0.02**	3	(1.8)	0.005**	4	(2.4)	0.16**	23	(14)	0.22**

*: Log rank test using disease duration as time factor; **: 2×3 chi-square test.

disease and due to causes unrelated to SLE or infection, such as cardiovascular disease.

Twenty-nine per cent of the deaths were caused by SLE. Previous studies have shown variations of this figure ranging from 20% (16) to 52% (17). The current study is a retrospective cohort study and concern has been made with regard to the possibility of underestimating early SLE-related mortality when not studying an inception cohort. The proportion of SLE-related deaths in such an inception cohort has been reported to be 34% (3), which does not differ much from our findings. In fact, we were able to demonstrate that deaths due to active SLE was most common during the early course of the disease. Not surprisingly, deaths due to end-stage SLE most often occured among patients with long disease duration.

The proportion of deaths due to infection has been relatively stable through the last 20 years in spite of improved methods of diagnosing and treating infections. In this study 21% of the deaths were caused by infections, and corresponding figures from other large series range from 17% (17) to 33% (18). The infectious agents were often unknown in this study, but fatal infections with known etiology were mostly caused by common pathogenic bacteriae. Opportunistic infections have previously been found to play a significant role in the mortality of SLE (3, 4), which was not found in our study. However, it is possible that opportunistic infections may have occurred with a higher prevalence than reported, since antibiotic treatment was often initiated prior to the hospital admission, with a possible negative influence on microbiological culturing.

The crude mortality rate in this study was 2.9% per year. The corresponding rate in a Canadian study was 1.9% per year (4). Since the expected number of deaths in the Canadian control population was lower than in the Danish one, the SMR's turned out to be almost identical, i.e 4.6 in our study versus 4.9 in the Canadian study. The crude mortality rate in a Californian SLE population, in which half of the patients were black, was 3.4% per year (15). Our patients were practically all Caucasians. Several studies have shown that white SLE patients have a better survival compared to black SLE patients (6, 15). The effect may be mediated by a higher socioeconomic status in white than in black SLE patients (15).

The 5, 10 and 15 year survival of the present cohort was 91%, 76% and 64%. An earlier Danish study of 136 patients with definite SLE showed a 10 year survival of 79% (19). The mortality rates were stable over time, which equals a linear survival curve. However, the causes of death differed at the beginning and the end of the survival curve. In the early course of disease the deaths were mainly caused by SLE manifestations or infections, whereas the deaths in the late course of the disease are mainly due to other causes, such as cardiovascular disease and malignant tumours. These findings are in accordance with the previously described bimodal mortality pattern in SLE (20). Two out of nine fatal malignancies were malignant lymphomas, one Mb. Hodgkin and one non-Hodgkin. Non-Hodgkin lymphomas have been reported to overrepresented in SLE (21).

The number of observed deaths in the study population was 122 and the expected number was 27, showing that there was an excess mortality of 95 deaths. In 35 cases they were classified as SLE-related (37%). This leaves 60 deaths classified as having other main causes of death than SLE. However, the fact that this excess mortality does exist, indicates that it is indirectly related to SLE or treatment. This is supported by our finding of an increased risk of atherosclerotic death in patients with more than five years of disease duration even after correction for sex and age. The significance of vasculopathy and other SLE-

related factors as well as cardiovascular risk factors in the development of atherosclerotic disease has earlier been pointed out (5).

In summary, we found that SLE patients had a 4.6-fold increased mortality compared with the general population and that half of the deaths were caused by SLE manifestations or infections, especially in young patients during the early period of the disease. A third of the excess mortality was directly related to SLE. The survival and the survival pattern of Danish SLE patients are comparable with the findings in other Caucasian SLE patients.

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