EXTENDED REPORT

Outcome of a cohort of 300 patients with systemic lupus erythematosus attending a dedicated clinic for over two decades

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Objective: To examine the mortality rate and causes of death in a cohort of 300 patients with systemic lupus erythematosus (SLE).

Methods: A retrospective analysis was performed on all patients attending the SLE clinic between 1978 and 2000. Information was obtained on those patients lost to follow up. Cause of death was analysed and categorised as early (<5 years after diagnosis of SLE) and late (>5 years after diagnosis of SLE). Standardised mortality rates were obtained.

Results: The patients were followed up for a median of 8.3 years. Seventy three (24%) patients were no longer followed up at the end of the study period, of whom 41 (14%) had died. Of the 32 patients lost to follow up, 14 were being actively followed up within the UK, 16 were followed up outside the UK, and two patients were untraceable. The most common cause of death was malignancy, which accounted for eight (20%) deaths, followed by infection and vascular disease, which accounted for seven (17%) deaths each.

Conclusions: Malignancy was the most common cause of death. Cause of death varied depending on disease duration. Forty per cent of early deaths were due to SLE related renal disease, whereas 23% of late deaths were due to vascular causes. Death due to infection occurred throughout the follow up period. There was a fourfold increased risk of death in our cohort of patients with SLE compared with the general population.

During the past four decades the incidence of systemic lupus erythematosus (SLE) has increased,¹ and the prognosis has improved from <50% five year survival in 1955² to >90% five year survival in recent studies.^{3,4} There are now a number of dedicated SLE clinics established to provide close follow up of these patients enabling doctors to detect disease flares quickly and act promptly in the hope of limiting long term damage. Death in patients with SLE may be due to active SLE, organ failure, or a complication of treatment. Improved survival is attributed to earlier diagnosis, the more judicious use of corticosteroids, the advent of immunosuppressive regimens such as cyclophosphamide, and advances in medical treatment in general.

Cause of death has been shown to vary with disease duration. This is reflected in a study by Urowitz *et al*, which found a bimodal pattern of death in patients with SLE,⁵ with early deaths (<2 years after diagnosis of SLE) due to active SLE or infection and late deaths (>2 years) due to atherosclerosis or infection.

The centre for rheumatology at University College, London has followed up a cohort of 300 patients with SLE since it was established 22 years ago. We present the clinical and laboratory features of this cohort together with an analysis of the outcome with respect to mortality and other causes of loss to follow up. We describe the cause of death and examine associations between major causes of death and duration of SLE.

METHODS

A retrospective analysis of 300 patients registered at the Bloomsbury Rheumatology Unit SLE clinic between 1 January 1978 and 1 July 2000 was performed. This analysis included primary, secondary, and tertiary referrals. All patients fulfilled the 1982 revised criteria for the classification of SLE of the

American College of Rheumatology (ACR).⁶ Patients with drug induced or discoid lupus were excluded. Disease duration was defined as the time interval from SLE diagnosis (fulfilling at least four ACR criteria) until 1 July 2000 or time of death. Survival time was defined as the time interval between diagnosis of SLE and death. Survival time was therefore equal to disease duration for those patients who died during the follow up period. Patient-years of follow up were defined as the time from registration at the clinic to the 1 July 2000 or death. Information was obtained from patient case notes and our separately stored database. Case notes were obtained of patients who had not been reviewed since 1 January 1999. From the notes, reasons for becoming lost to follow up were ascertained where possible. If no information was available, the patient's general practitioner was contacted to ask whether the patient was still registered with them and receiving care from a rheumatologist. If a patient had moved, local health authorities were approached to obtain details of the patient's current/last known general practitioner.

The cause of death was ascertained by a review of hospital files and death certificates, by discussion with the doctor who cared for the patient during the terminal illness and, wherever possible, from postmortem findings. The primary cause of death was categorised as renal; infection; malignancy; vascular; other miscellaneous causes. The primary cause of death was defined as the main clinical or pathological process directly responsible for death. Deaths were considered as early in patients who died <5 years from the time of diagnosis of SLE and late in patients who died >5 years after diagnosis.

Abbreviations: APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus; SMR, standardised mortality ratio

Table 1 Demographics of living patients and those that have died

Demographic information	Living patients	Deceased patients	All patients
	No (%)	No (%)	No (%)
Number	259	41	300
Sex			
Female	239 (92)	38 (93)	277 (92)
Male	20 (8)	3 (7)	23 (8)
Race			
White	174 (67)	27 (66)	201 (67)
Afro-Caribbean	37 (14)	11 (27) NS	48 (16)
Asian	26 (10)	1 (2)	27 (9)
Oriental	10 (4)	0	10 (3)
Other	12 (5)	2 (5)	14 (5)
Age at diagnosis (years)			
Mean (range)	29.5 (10–62)	36.8 (15–77)*	30.7 (10–77)
Duration of disease (years)			
Mean (range)	12.8 (1–37)	15.8 (1–47) NS	13 (1–37)
Age at death	–	52.6 (16–87)	–

*p<0.001.
NS, not significant.

Statistical analysis

A χ^2 analysis was used for comparison of dichotomous variables. Student's *t* test was used to analyse continuous variables. To estimate the risk of death for the SLE cohort we used the standardised mortality ratio (SMR), which compares the ratio of observed deaths to expected deaths.⁷ The expected number of deaths (E) was determined by using comparable age matched mortality rates from the southeast England 1995 data obtained from the Office of National Statistics, and is given by

$$E = \sum n_i \times R_i$$

where R_i = the age-specific mortality rate in age group *i* of the southeast England population and n_i = person-years in age group *i* of the SLE cohort.

The expected number of deaths was calculated separately for men and women, and amalgamated to obtain the total expected number of deaths. The 95% confidence interval for the SMR was obtained by regarding the observed number of deaths as a Poisson variable and finding its related interval from tables based on the Poisson distribution.⁸

RESULTS

Three hundred patients were registered over the study period. Table 1 presents the demographic details. The patients who died developed SLE at a significantly older age (36.8 years) than the patients who survived (29.5 years). Mean disease duration was 13 years and median follow up was 8.3 years. Thus the mean time between diagnosis of SLE and first attendance at the Bloomsbury Rheumatology Unit was 4.7 years. However, 69% of patients entered this clinic less than five years after diagnosis of SLE.

A total of 227 (76%) patients continued to be followed up on 1 July 2000. Of the 73 patients no longer followed up, 41 are known to have died. Ten patients had moved within the UK and were receiving local follow up. Four patients preferred local hospital follow up but had not moved and 16 patients were being followed up outside the UK. Two (0.7%) patients were untraceable and were considered "true loss to follow up".

It was postulated that the patients followed up elsewhere may have milder disease than those being actively followed up at our centre. Therefore we compared the disease severity of this group of 30 patients with the disease severity of those who continued to be followed up here. To ascertain this we compared the number of major organs affected by SLE in each patient who had left the cohort with those of two patients

Table 2 Clinical features of SLE cohort

Organ involvement	No	% Of total
Alopecia	51	17
Oral ulcers	84	28
Joints	290	97
Jaccoud's	7	
Erosive	15	
Serositis	153	51
Kidney	100	33
CNS	70	23
Lung	7	2
Haemolytic anaemia	16	5
Thrombocytopenia	52	17
Sjögren's syndrome	36	12
Antiphospholipid antibody syndrome	25	8

CNS, central nervous system.

matched for ethnic origin, sex, and time since diagnosis of SLE and currently receiving active follow up. However, there was no statistically significant difference between the two groups in the extent of major organ involvement (skin, central nervous system, musculoskeletal, serositis, renal).

Of the 16 patients who had moved outside the UK, three (19%) moved to Africa, three (19%) moved to the West Indies, six (37%) moved to the Far East, and four (25%) moved elsewhere. This shows a modest degree of population movement, which we thought might reflect the increased prevalence of SLE in non-white ethnic groups. We therefore looked at the number of patients who had moved to the country of their ethnic origin. Of the 16 patients now living outside Europe, nine (56%) had moved to the country of their ethnic origin. We also compared the ethnicity of those who moved overseas with those who continued to be followed up: five (31%) of those who moved overseas were white subjects, six (38%) were Afro-Caribbean, and five (31%) were Oriental. Thus there was a significantly increased proportion of patients of Oriental ethnicity in the group who had moved overseas compared with those receiving active follow up. Tables 2 and 3 present the clinical and serological features of the SLE cohort.

Mortality

Forty one deaths occurred during the follow up period, 38 women and three men. Determination of cause of death was based on postmortem findings in 10 (24%), death certificate in 11 (27%), clinical records in 20 (49%), and history from the patient's doctor in 10 (24%) cases.

Table 4 shows the primary cause of death related to SLE disease duration. The most common cause of death was

Table 3 Serological findings

Serology	Number	% Of total SLE cohort
ANA	297	99
RF	68	23
dsDNA	175	58
Sm	26	9
RNP	56	19
Ro	95	32
La	35	12
Low C3	120	40
Lupus anticoagulant	43	14
Anticardiolipin IgG	74	25
Anticardiolipin IgM	35	12
Two antiphospholipid antibodies present	21	7
Three antiphospholipid antibodies present	12	4

ANA, antinuclear antibody; RF, rheumatoid factor.

malignancy, which accounted for eight (20%) deaths. There were two cases of breast cancer and two cases of Hodgkin's lymphoma (although one case of lymphoma and one case of breast cancer predated the diagnosis of SLE). The other patient with Hodgkin's lymphoma developed septicaemia 10 weeks after chemotherapy. None of the patients who died of malignancy had received treatment with cyclophosphamide or methotrexate. Sjögren's syndrome was present in three of the patients who died of malignancy, two of whom had lymphoma. The other malignancies leading to death were cholangiocarcinoma, lung cancer, colonic adenocarcinoma, and prostate cancer.

Pneumonia was the most common cause of death in the patients who died of infection, accounting for four (57%) of seven deaths in this group. Two of the patients who died of pneumonia had pre-existing pulmonary fibrosis. Five patients were receiving immunosuppressive drugs, three were taking low dose prednisolone (<7.5 mg) and azathioprine, one was taking high dose prednisolone (>7.5 mg), and the other patient was receiving low dose prednisolone alone. Only two had active SLE at the time of death.

Seven (17%) patients died of vascular disease. Three patients died of a myocardial infarction and three died of cerebrovascular accidents. The other patient died after developing cardiac failure and adult respiratory distress syndrome in the intensive therapy unit. Risk factors for atherosclerosis were renal dialysis in two patients, high dose prednisolone in four patients, and secondary antiphospholipid syndrome (APS) in one patient. Asymptomatic atheroma was found in three of 10 (30%) post mortems performed. All the patients who developed atheroma had been treated with prednisolone in the past.

Six (15%) patients died owing to SLE related renal disease, five of whom were Afro-Caribbean. In one patient in this category active renal disease can be attributed to the patient's

Table 5 Standardised mortality ratio for all patients compared with southeast England population 1995

Age group (years)	Observed deaths	Expected deaths	SMR	95% CI
0-24	4	0.1	40	0.8 to 79.2
25-34	5	0.4	12.5	1.5 to 23.5
35-44	8	1.1	7.3	2.2 to 9.5
45-54	6	1.8	3.3	0.7 to 6.0
55-64	6	2.3	2.6	-8 to 13.6
65-74	7	2.6	2.7	0.7 to 4.7
75-84	4	1.8	2.2	0 to 4.4
85+	1	0.2	5.0	-5.4 to 14.2
Total	41	10.3	4.0	2.8 to 5.2

own decision to stop her treatment. Another patient developed recurrent renal failure after an initially successful renal transplant.

Overall 11 (27%) deaths were attributed to SLE, of which six were due to renal SLE. Other causes of death directly attributed to SLE were autoimmune hepatitis, widespread vasculitis, thrombotic thrombocytopenic purpura, acute pancreatitis, and lung fibrosis with pulmonary hypertension complicated by a massive pulmonary embolism in a patient with lupus anticoagulant and IgG anticardiolipin antibody but no history of thromboembolism.

Three patients died of old age and one patient, who had a known alcohol problem, died of acute alcohol intoxication.

The patients who died had a high incidence of major organ involvement. In particular, renal SLE was present in 17 (41%) of those who died (compared with 30.9% of survivors); Coombs positive autoimmune haemolytic anaemia was found in seven (17%) of those patients who died (compared with 3.5% of survivors). However, secondary APS was found in 25 (8%) of the cohort and was no more common in the patients who died than in those who survived. Anticardiolipin antibodies and/or lupus anticoagulant were found in 86 (20%) of the total cohort and there was no significant difference in the frequency of these antibodies between those who died and those who survived.

Risk of death compared with the general population

Table 5 shows the overall age-specific SMR for the total SLE cohort compared with the general population. A fourfold increased risk of death was seen (95% CI 2.8 to 5.2). The increase in mortality was most pronounced in patients who died aged <44 years.

Number of deaths related to length of follow up

The mean SLE disease duration at time of entry to our clinic was 4.7 years. We therefore analysed the number of deaths depending on duration of follow up to look for any trends in

Table 4 Cause of death related to SLE disease duration

Cause of death	No (%)	Early death <5 years after diagnosis of SLE No (%)	Late death >5 years after diagnosis of SLE No (%)	Mean survival Years (range)
Renal	6 (15)	4 (40)*	2 (6)	6 (2-11)
Infection	7 (17)	2 (20)	5 (16)	16.9 (1-32)
Malignancy	8 (20)	3 (30)	5 (16)	15.9 (1-31)
Vascular	7 (17)	0	7 (23)	17.3 (6-29)
Other	9 (22)	1 (10)	8 (26)	17.7 (1-47)
Not known	4 (10)	0	4 (13)	27 (19-35)
Total	41	10	31	15.8 (1-47)

*p<0.001.

Figure 1 Number of deaths according to length of follow up.

deaths related to length of follow up. Figure 1 displays the length of follow up of the SLE cohort divided into five year bands with the number of deaths in each category. This shows an increased number of deaths in those patients followed up for 0–5 years and 16–20 years compared with the other groups, although this did not reach statistical significance.

DISCUSSION

There is no doubt that true survival of patients with SLE has improved over the past four decades from <50% five year survival before 1955² to >90% five year survival in recent studies.^{3–4} Our survival rates reflect this improvement. This study follows on from a previous study at this centre which showed a five year survival of 88% and a 10 year survival of 86% of 100 patients with SLE followed up for a mean of five years.⁹ The SMR of 4.0 in our study compares favourably with previous studies, which found SMRs of 4.6–4.9.^{10–12} The lower SMR in our study is likely to be due to differences in characteristics of the groups studied. However, it may reflect the continuing improvement in survival with time as illustrated in a study by Urowitz *et al*, which showed that the SMR declined from 10.1 in patients who entered the study between 1970 and 1977, to 3.3 in patients entering between 1986 and 1994.¹³

A most striking finding in our study was that no early deaths were due to cardiovascular or cerebrovascular disease, whereas these causes accounted for 23% of late deaths. Deaths due to renal disease were more common in patients who died <5 years after diagnosis of SLE. In the 1970s Urowitz recognised that the cause of death in patients with SLE was related to the duration of SLE and he termed this “the bimodal pattern of mortality”.⁵ He found that SLE related deaths and infection accounted for most early deaths, whereas atherosclerotic complications and malignancy were more common causes of late death. Ward *et al* showed that the risk of death due to SLE was greatest in the first three years after diagnosis but occurred throughout the follow up period.¹⁴

Our study found that malignancy was the most common cause of death, followed by infection and vascular causes. However, malignancy may be overrepresented because two patients developed malignancy before the diagnosis of SLE. Several other studies have shown infection to be the leading cause of death.^{15–16}

In our study there was a significantly higher incidence of renal disease in the patients who died compared with those who survived. Renal disease has been associated with poor prognosis in several studies^{3–17} and was found to be an independent predictor of survival in a study by Wallace *et al*.¹⁸ Abu-Shakra showed that renal damage, thrombocytopenia, lung disease, age >50 years at diagnosis, and SLEDAI score

>20 at presentation were independent risk factors for mortality in the multivariate analysis.¹⁹

Thrombocytopenia has also been found to be associated with poor prognosis in several studies.^{3–16} Reveille *et al* found that a moderate to severe thrombocytopenia (platelet count <100×10⁹/l) during the first two years of SLE was an independent risk factor for poor outcome.¹⁶ However, in our study, there was no significant difference between the incidence of thrombocytopenia in those who died and those who survived.

In our study the patients who died developed SLE at a significantly older age than those who survived. Some previous studies have suggested that patients who develop SLE at an older age have a worse prognosis,^{16–19} but other studies have suggested that older patients tend to have more indolent disease.²⁰

Ethnicity did not influence mortality. Although more patients of Afro-Caribbean origin died, this did not reach statistical significance. Fifty per cent of the patients who died of SLE related renal disease were Afro-Caribbean, reflecting the previously documented high prevalence of renal disease in this ethnic group.²¹ Previous studies have shown a worse prognosis for black patients with SLE than for white patients.^{16–18–21} Ginzler *et al* found that black patients had more severe disease at study entry than white patients.²² However, others found no effect of ethnic origin on survival,^{3–18} but only small numbers of non-white subjects were studied. It is likely that the apparent racial differences in prevalence and severity of SLE may be due to socioeconomic factors rather than to race itself.^{16–21–23} In our study no data on socioeconomic status were available.

Previous studies have shown opportunistic infection to be an important cause of fatal infection.^{11–14} Ward *et al* found that fungal infection accounted for >20% of fatal infections.¹⁴ However, in our study no opportunistic organisms were isolated. Patients with pre-existing lung disease, such as pulmonary fibrosis and pulmonary hypertension, are more susceptible to pneumonia and this is reflected in our cohort where 50% of patients who died of pneumonia had pre-existing lung disease attributable to SLE.

None of the patients who died of malignancy had been treated with cyclophosphamide or methotrexate. Some studies have suggested an association between SLE and malignancy, which may be partially attributable to long term exposure to these drugs.²⁴ There were two cases of Hodgkin's lymphoma, however, but in one case the diagnosis of lymphoma predated the diagnosis of SLE. Non-Hodgkin's lymphomas have been reported to be overrepresented in patients with SLE previously,²⁵ and an occasional association has been found between SLE and Hodgkin's lymphoma.²⁶

Atherosclerosis was an incidental finding in 30% of the postmortem examinations performed. Four of seven patients who died of atherosclerotic complications had been treated with high dose prednisolone. These patients had all had persistently active disease and it has been postulated that inflammation itself may cause changes to the blood vessel wall together with immune-complex deposition, leading to vasculitis²⁷ and resulting in atherosclerosis. The increased incidence of atherosclerotic complications in SLE has been previously documented²⁸ and is thought to be partially attributable to the advent of steroid treatment as they have only been seen since steroids were introduced. Atherosclerosis is also associated with longer SLE disease duration.¹⁰ However, other predisposing factors such as hypertension and hyperlipidaemia are also more common in patients with SLE. Fifty per cent of patients who died of a cardiovascular cause had undergone renal dialysis for end stage renal failure, which is also a recognised risk factor for atherosclerosis.

Antiphospholipid antibodies were present in 29% of the total cohort. The APS predisposes to atherosclerosis, although,

surprisingly, only one of seven patients dying of atherosclerotic complications had antiphospholipid antibodies. A previous study by Drenkard *et al* showed that secondary APS, but not the presence of antiphospholipid antibodies alone, contributes to decreased survival in patients with SLE independently of other risk factors.²⁹

Many studies have examined mortality in patients with SLE, but there are difficulties in comparing studies from different referral centres. Studies from tertiary referral centres such as ours may underestimate early deaths because a proportion of patients die before referral, or deaths may be overestimated because milder cases are followed up at district general hospitals rather than at tertiary referral centres. Ward *et al* attributed 34% of deaths to SLE in their inception cohort, which should avoid bias due to early deaths before study entry.¹⁴ We found that 11/41 (27%) deaths were SLE related. In our centre 69% of the patients were referred within three years of diagnosis of SLE. The relatively long lag period, between diagnosis of SLE and first clinic visit, of 4.7 years, was skewed by a small number of patients who were referred to our centre after an extended period of follow up elsewhere. Another difficulty is that some earlier studies, such as that by Merrell and Shulman,² take the starting point of SLE as being the date of diagnosis. However, it has been shown in many studies that the delay between the first symptom and diagnosis is still long. A study by Jonsson *et al* found that the median time between the first symptom and diagnosis of SLE was three years.³⁰

In this study, 32 (11%) patients were lost to follow up because they had moved away or no longer attended the clinic for other reasons. Every effort was made to ascertain any deaths in this group. However, Sackett *et al* have suggested that loss to follow up rates of <20% are acceptable for determining the survival of a cohort, whereas rates that exceed 20% make interpretation of survival data more difficult.³¹

Common causes of late death (atherosclerosis and malignancy) increase in frequency with increasing length of follow up, accounting for only 6% of deaths in patients followed up for a mean of 3.6 years,¹⁵ 21% of patients followed up for a mean of 6 years,³² and 37% of deaths in patients followed up for a mean of 10 years.⁹ In our study 39% of deaths were due to atherosclerosis or malignancy; however, malignancy may be overrepresented as two patients developed malignancy before the diagnosis of SLE.

We have reported the outcome of this cohort in terms of the loss to follow up and mortality. However, with improved survival other outcome measures of morbidity and quality of life are needed to assess their impact on SLE survival.

In conclusion, our study shows that patients with SLE have a death rate four times that of the general population. The most common cause of death in our cohort was malignancy, followed by infection and vascular disease. Early deaths were more often due to renal disease, whereas late deaths tended to be caused by atherosclerosis. Determination of factors predicting poor prognosis in SLE should help to identify those at high risk, allowing appropriate management of these patients.

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