# Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period

## *A Comparison of Early and Late Manifestations in a Cohort of 1,000 Patients*

*Ricard Cervera, Munther A. Khamashta, Josep Font, Gian Domenico Sebastiani, Antonio Gil, Paz Lavilla, Juan Carlos Mejía, A. Olcay Aydintug, Hanna Chwalinska-Sadowska, Enrique de Ramón, Antonio Fernández-Nebro, Mauro Galeazzi, Merete Valen, Alessandro Mathieu, Frédéric Houssiau, Natividad Caro, Paula Alba, Manuel Ramos-Casals, Miguel Ingelmo, Graham R.V. Hughes, and the European Working Party on Systemic Lupus Erythematosus**

**Abstract:** In the present study, we assessed the frequency and characteristics of the main causes of morbidity and mortality in systemic lupus erythematosus (SLE) during a 10-year period and compared the frequency of early manifestations with those that appeared later in the evolution of the disease. In 1990, we started a multicenter study of 1,000 patients from 7 European countries. All had medical histories documented and underwent medical interview and routine general physical examination when entered in the study, and all were followed prospectively by the same physicians during the ensuing 10 years (1990–2000).

A total of 481 (48.1%) patients presented 1 or more episodes of arthritis at any time during the 10 years, 311 (31.1%) patients had malar rash, 279 (27.9%) active nephropathy, 194 (19.4%) neurologic involvement, 166 (16.6%) fever, 163 (16.3%) Raynaud phenomenon, 160 (16.0%) serositis (pleuritis and/or pericarditis), 134 (13.4%) thrombocytopenia, and 92 (9.2%) thrombosis. When the prevalences of the clinical manifestations during the initial 5 years of follow-up (1990–1995) were compared with those during the ensuing 5 years (1995–2000), most manifestations were found to be more frequent during the initial 5 years. Of the 1,000 patients, 360 (36%) presented infections, 169 (16.9%) hypertension, 121 (12.1%) osteoporosis, and 81 (8.1%) cytopenia due to immunosuppressive agents. Twenty-three (2.3%) patients developed malignancies; the most frequent primary localizations were the uterus and the breast. Sixty-eight (6.8%) patients died, and the most frequent causes of death were similarly divided between active SLE (26.5%), thromboses (26.5%), and infections (25%). A survival probability of 92% at 10 years was found. A lower survival probability was detected in those patients who presented at the beginning of the study with nephropathy (88% versus 94% in patients without nephropathy, $p = 0.045$). When the causes of death during the initial 5 years of follow-up (1990–1995) were compared with those during the ensuing 5 years (1995–2000), active SLE and infections (28.9% each) appeared to be the most common causes during the initial 5 years, while thromboses (26.1%) became the most common cause of death during the last 5 years.

In conclusion, most of the SLE inflammatory manifestations appear to be less common after a long-term evolution of the disease, probably reflecting the effect of therapy as well as the progressive remission of the disease in many patients. Meanwhile, a more prominent role of thrombotic events is becoming evident, affecting both morbidity and mortality in SLE.

(*Medicine* 2003;82:299–308)

From Department of Autoimmune Diseases, Institut Clínic d'Infeccions i Immunologia, IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer), Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain (RC, JF, JCM, MR-C, MI); Lupus Unit, Rayne Institute, St. Thomas' Hospital, London, UK (MAK, NC, PA, GRVH); Divisione di Reumatologia, Ospedale San Camillo de Lellis, Rome, Italy (GDS); Servicio de Medicina Interna, Hospital ''La Paz,'' Madrid, Spain (AG, PL); Department of Clinical Immunology and Rheumatology, Medical School of Ankara University, Ankara, Turkey (AOA); Department of Connective Tissue Diseases, Institute of Rheumatology, Warsaw, Poland (HC-S); Unidad de Enfermedades Autoinmunes Sistémicas, Servicio de Medicina Interna & Servicio de Nefrología, Hospital Regional ''Carlos Haya,'' Málaga, Spain (ER); Servicio de Medicina Interna & Sección de Reumatología, Hospital Clínico Universitario, Málaga, Spain (AF-N); Istituto di Reumatologia, Università di Siena, Siena, Italy (MG); Department of Rheumatology, Haukeland Sykehus, Bergen, Norway (MV); II Cattedra di Reumatologia, Università di Cagliari, Cagliari, Italy (AM); Service de Rhumatologie, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium (FH).

Supported in part by grants from the European Commission (BIOMED BMH1-CT94-1260), Lupus UK, and the Fondo de Investigaciones Sanitarias de la Seguridad Social of Spain (92/0385, 93/0271, 94/0323, 96/0580, 97/0669, 99/148, and 00/1048).

Address reprint requests to: Ricard Cervera, MD, Servei de Malalties Autoimmunes, Hospital Clínic, Villarroel 170, 08036-Barcelona, Catalonia, Spain. E-mail: cervera@medicina.ub.es.

*See complete list of members of the European Working Party on Systemic Lupus Erythematosus in the Appendix.



ISSN: 0025-7974/03/8205-0299
DOI: 10.1097/01.md.0000091181.93122.55

## INTRODUCTION

Systemic lupus erythematosus (SLE) may affect any organ of the body and displays a broad spectrum of clinical and immunologic manifestations. Its natural history is characterized by episodes of relapses or flares interchanging with remissions, and the outcome is highly variable, ranging from permanent remission to death. In recent years, both morbidity and mortality have been modified due to a number of possible reasons, including a better knowledge of the pathogenetic mechanisms and prognostic factors of SLE[9,12,16] and the use of immunosuppressive regimes.

It has been suggested that the spectrum of clinical manifestations and the causes of death differ depending on the time of evolution of the disease[38]. Furthermore, some have postulated that SLE tends to enter into remission in many patients after a long time of evolution[14]. However, other studies have shown that SLE patients with a long disease duration (more than 10 years) still have active disease[34].

In an attempt to clarify the long-term evolution of patients with SLE, in 1990 we started a multicenter observational study of 1,000 European patients. The clinical and immunologic characteristics of these patients when entered in the study and after a 5-year follow-up have been reported previously[11,12]. In the present study we assess the frequency and characteristics of the main causes of morbidity and mortality after a 10-year follow-up and compare the frequency of the early manifestations in this cohort with the frequency of manifestations that appeared later in the evolution of the disease.

## METHODS

### Patient Selection

The study (''Euro-Lupus'' Project) started in 1990 with a multicenter, consecutive, and prospective design. In order to gather a sizeable series of patients, 12 tertiary referral university centers, with substantial experience in the management of SLE patients, from 7 European countries agreed to take part in the study. The final cohort (survival cohort) included 1,000 unselected patients who came consecutively to Hospital Clínic, Barcelona, Catalonia, Spain; St Thomas' Hospital, London, United Kingdom; Hospital ''La Paz,'' Madrid, Spain; Hospital Regional ''Carlos Haya,'' Málaga, Spain; Medical School of Ankara University, Ankara, Turkey; Institute of Rheumatology, Warsaw, Poland; Hospital Clínico Universitario, Málaga, Spain; Ospedale San Camillo de Lellis, Rome, Italy; Haukeland Sykehus, Bergen, Norway; Università di Cagliari, Cagliari, Italy; and Université Catholique de Louvain, Brussels, Belgium. A total of 350 patients were from Spain, 250 from Italy, 248 from the United Kingdom, 50 from Poland, 50 from Turkey, 37 from Norway, and 15 from Belgium. All met the 1982 revised criteria of the American College of Rheumatology (ACR) for the classification of SLE[37].

The patients had medical histories documented and underwent medical interview and routine general physical examination by a qualified internist and/or rheumatologist when entered in the study in 1990. All the patients have been followed prospectively by the same physicians during the ensuing 10 years (1990–2000) with regular visits to the outpatient clinics at least every 3–6 months, depending on the severity of the disease, and hospitalized if necessary. Only 195 (19.5%) patients were lost to follow-up (34 in the first year, 32 in the second, 31 in the third, 10 in the fourth, 8 in the fifth, 27 in the sixth, 21 in the seventh, 14 in the eighth, 11 in the ninth, and 7 in the tenth). The observation period stopped in the year 2000, at the time of the last patient information if patient was lost to follow-up, or at death.

Clinical and serologic characteristics of all patients were collected in a protocol form. Salient features included in this protocol are the following: 1) age at onset of the disease, defined as the initial manifestation clearly attributable to SLE; 2) age at diagnosis, defined as the age when the patient fulfilled 4 or more of the 1982 revised ACR criteria for the classification of SLE; 3) age at protocol, defined as the age when the patient entered in the prospective study; 4) clinical manifestations at the onset of the disease; 5) previous cumulative clinical manifestations (from the onset of the disease until the beginning of the prospective study); 6) laboratory features at protocol; 7) prospective cumulative clinical manifestations (from 1990 until 2000); 8) treatment; and 9) causes of death. Information collected on the protocol forms was transferred to a computerized database program.

### Definition of Outcome Variables

To minimize possible interobserver bias, the outcome variables of the protocol form were carefully discussed by all participating physicians on several occasions. These variables included causes of morbidity (SLE manifestations and other associated medical problems), causes of death, and survival.

The main SLE clinical manifestations evaluated in this prospective study were defined according to the American Rheumatism Association glossary committee[5] and are described in detail elsewhere[11]. Diagnoses of the other associated medical problems that appeared during the study were performed on clinical grounds and confirmed by appropriate complementary techniques. The causes of death were based on information obtained from the clinicians in charge, autopsy reports, and death certificates. They were classified as due to active SLE, infections, thromboses, malignancies, or other causes. Death was considered to be due to active SLE if uncontrollable, progressing SLE-related

manifestations indicative of active disease[8] were the direct cause of death. Infections, thromboses, and malignancies were diagnosed on clinical grounds and confirmed by complementary techniques.

## Statistical Analysis

The statistical analysis was performed by means of the SPSS 9.0 program using the information stored in the database program. Results of the analysis of continuous variables are indicated as mean ± standard deviation. Conventional chi-square and Fisher exact tests were used for analyzing qualitative differences, in the univariate analysis. A p value <0.05 was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was performed for multivariate analysis to rule out possible confounding variables. In this case, only those variables showing statistical significance in the multivariate analysis were considered as significant in the results of the study. The relative risk (RR) was calculated for assessing the risk of appearance of each variable. A lower limit of the 95% confidence interval (CI) that exceeded 1.0 was taken to indicate statistical significance in the case of positive association, and an upper limit lower than 1.0 in the case of negative association. Survival time was defined as the interval from the time the patient entered in the study until death or last contact. Survival probabilities were calculated according to the Kaplan-Meier lifetime analysis method.

# RESULTS

## General Characteristics at the Beginning of the Prospective Study

The entire cohort consisted of 908 (90.8%) female and 92 (9.2%) male patients (female:male ratio, 10:1). There were 971 (97.1%) white patients, 19 (1.9%) black patients, and 10 (1%) patients of other races. Mean age when the patients entered in the prospective study was 37 ± 14 years (range, 12–82 yr). The main clinical manifestations at the onset of the disease, the cumulative clinical manifestations from the onset until the beginning of the prospective study, the immunologic findings when the patients entered in the prospective study, and the clinical manifestations and causes of death during the initial 5 years of the observational period have been reported in detail elsewhere[9,10].

## SLE Manifestations and Treatment During the Study

In Table 1 we show the frequencies of the main SLE clinical manifestations during the 10-year prospective study and compare the manifestations that appeared during the initial 5 years of the observational period (1990–1995) with those that appeared in the ensuing 5 years (1995–2000). A total of 481 (48.1%) patients presented 1 or more episodes of arthritis at any time during the 10-year period, 311 (31.1%) had malar rash, 279 (27.9%) active nephropathy, 229 (22.9%) photosensitivity, 194 (19.4%) neurologic

**TABLE 1.** Clinical Manifestations Related to SLE in the Total Cohort of 1,000 Patients During the 10-year Prospective Study (1999–2000)

| SLE Manifestation | 1990–2000 (n = 1,000) No. (%) | 1990–1995 (n = 1,000) No. (%) | 1995–2000 (n = 840)* No. (%) | p Value† |
|---|---|---|---|---|
| Malar rash | 311 (31.1) | 264 (26.4) | 144 (17.1) | <0.001 |
| Discoid lesions | 78 (7.8) | 54 (5.4) | 50 (5.9) | |
| Subacute cutaneous lesions | 67 (6.7) | 46 (4.6) | 21 (2.5) | 0.023 |
| Photosensitivity | 229 (22.9) | 187 (18.7) | 112 (13.3) | 0.002 |
| Oral ulcers | 125 (12.5) | 89 (8.9) | 61 (7.3) | |
| Arthritis | 481 (48.1) | 413 (41.3) | 240 (28.6) | <0.001 |
| Serositis | 160 (16) | 129 (12.9) | 52 (6.2) | <0.001 |
| Nephropathy | 279 (27.9) | 222 (22.2) | 57 (6.8) | <0.001 |
| Neurologic involvment | 194 (19.4) | 136 (13.6) | 97 (11.5) | |
| Thrombocytopenia | 134 (13.4) | 95 (9.5) | 76 (9.0) | |
| Hemolytic anemia | 48 (4.8) | 33 (3.3) | 24 (2.9) | |
| Fever | 166 (16.6) | 139 (13.9) | 62 (7.4) | <0.001 |
| Raynaud phenomenon | 163 (16.3) | 132 (13.2) | 74 (8.9) | 0.003 |
| Livedo reticularis | 70 (7.0) | 55 (5.5) | 30 (3.6) | |
| Thrombosis | 92 (9.2) | 72 (7.2) | 41 (4.9) | 0.049 |
| Myositis | 43 (4.3) | 40 (4) | 11 (1.3) | <0.001 |

*Number of patients that continued in the study in 1995.
†All p values are a comparison between the frequencies in the 1990–1995 and in the 1995–2000 periods.

**TABLE 2.** SLE Therapies Prescribed to the Total Cohort During the 10-year Prospective Study (1990–2000)

| Treatment | 1990–2000 (n = 1,000) No. (%) | 1990–1995 (n = 1,000) No. (%) | 1995–2000 (n = 840)* No. (%) | p Value† |
|---|---|---|---|---|
| NSAID | 368 (36.8) | 284 (28.4) | 207 (24.6) | |
| Antimalarials | 478 (47.8) | 402 (40.2) | 292 (34.8) | 0.018 |
| Oral steroids | 725 (72.5) | 652 (65.2) | 425 (50.6) | <0.001 |
| Pulse steroids | 95 (9.5) | 63 (6.3) | 45 (5.4) | |
| Oral cyclophosphamide | 90 (9.0) | 74 (7.4) | 29 (3.5) | 0.004 |
| Pulse cyclophosphamide | 114 (11.4) | 85 (8.5) | 46 (5.4) | 0.015 |
| Azathioprine | 163 (16.3) | 131 (13.1) | 77 (9.2) | 0.001 |
| Methotrexate | 60 (6) | 44 (4.4) | 31 (3.7) | |
| Antiaggregants | 201 (20.1) | 136 (13.6) | 131 (15.6) | |
| Anticoagulants | 94 (9.4) | 69 (6.9) | 64 (7.6) | |
| Hemodialisis | 26 (2.6) | 21 (2.1) | 13 (1.5) | |
| Kidney transplantation | 11 (1.1) | 8 (0.8) | 6 (0.7) | |
| Plasmapheresis | 9 (0.9) | 9 (0.9) | 3 (0.4) | |

*Number of patients that continued in the study in 1995.
†All p values are a comparison between the frequencies in the 1990–1995 and in the 1995–2000 periods.
Abbreviation: NSAID = non-steroidal antiinflammatory drugs.

**TABLE 3.** Associated Medical Problems That Appeared in the Total Cohort During the 10-year Prospective Study (1990–2000)

| Associated Medical Problem | 1990–2000 (n = 1,000) No. (%) | 1990–1995 (n = 1,000) No. (%) | 1995–2000 (n = 840)* No. (%) | p Value† |
|---|---|---|---|---|
| Infection | 360 (36) | 270 (27) | 161 (19.2) | <0.001 |
| Urinary | 169 (16.9) | 113 (11.3) | 84 (10) | |
| Cutaneous | 102 (10.2) | 76 (7.6) | 39 (4.6) | 0.01 |
| Respiratory | 117 (11.7) | 74 (7.4) | 60 (7.1) | |
| Abdominal | 43 (4.3) | 34 (3.4) | 17 (2) | |
| Central nervous system | 7 (0.7) | 5 (0.5) | 3 (0.4) | |
| Sepsis | 26 (2.6) | 25 (2.5) | 5 (0.6) | 0.002 |
| Other | | 62 (6.2) | 31 (3.7) | 0.019 |
| Hypertension | 169 (16.9) | 113 (11.3) | 108 (12.9) | |
| Osteoporosis | 121 (12.1) | 75 (7.5) | 83 (9.9) | |
| Drug-induced cytopenia | 81 (8.1) | 59 (5.9) | 40 (4.8) | |
| Gastrointestinal bleeding | 49 (4.9) | 31 (3.1) | 28 (3.3) | |
| Cataracts | 47 (4.7) | 29 (2.9) | 26 (3.1) | |
| Diabetes | 30 (3) | 27 (2.7) | 10 (1.2) | |
| Avascular necrosis of bone | 29 (2.9) | 23 (2.3) | 14 (1.7) | |
| Retinopathy | 22 (2.2) | 17 (1.7) | 10 (1.2) | |
| Malignancy | 23 (2.3) | 16 (1.6) | 7 (0.8) | |
| Uterus | 8 (0.8) | 7 (0.7) | 1 (0.1) | |
| Breast | 4 (0.4) | 3 (0.3) | 1 (0.1) | |
| Non-Hodgkin lymphoma | 2 (0.2) | 2 (0.2) | 0 (0) | |
| Colon | 1 (0.1) | 1 (0.1) | 0 (0) | |
| Lung | 3 (0.3) | 1 (0.1) | 2 (0.2) | |
| Other | 5 (0.5) | 2 (0.2) | 3 (0.4) | |

*Number of patients that continued in the study in 1995.
†All p values area a comparison between the frequencies in the 1990–1995 and in the 1995–2000 periods.

involvement, 166 (16.6%) fever, 163 (16.3%) Raynaud phenomenon, 160 (16%) serositis (pleuritis and/or pericarditis), 134 (13.4%) thrombocytopenia, 125 (12.5%) oral ulcers, and 92 (9.2%) thrombosis. When the frequencies of the clinical manifestations during the initial 5 years of follow-up were compared with those during the ensuing 5 years, the majority of manifestations were found to be more frequent during the initial 5 years: arthritis (41.3% in the initial 5 yr versus 28.6% in the ensuing 5 yr, $p < 0.001$; RR = 1.28; 95% CI = 1.18–1.39), malar rash (26.4% versus 17.1%, $p < 0.001$; RR = 1.26; 95% CI = 1.15–1.37), photosensitivity (18.7% versus 13.3%, $p = 0.002$; RR = 1.18; 95% CI = 1.07–1.30), subacute cutaneous lesions (4.6% versus 2.5%, $p = 0.023$; RR = 1.28; 95% CI = 1.08–1,51), active nephropathy (22.2% versus 6.8%, $p < 0.001$; RR = 1.60; 95% CI = 1.48–1.73), serositis (12.9% versus 6.2%, $p < 0.001$; RR = 1.36; 95% CI = 1.22–1.51), fever (13.9% versus 7.4%, $p < 0.001$; RR = 1.32; 95% CI = 1.19–1.46), Raynaud phenomenon (13.2% versus 8.9%, $p = 0.003$; RR = 1.21; 95% CI = 1.08–1.35), thrombosis (7.2% versus 4.9%, $p = 0.049$; RR = 1.19; 95% CI = 1.02–1.37), and myositis (4% versus 1.3%, $p < 0.001$; RR = 1.46; 95% CI = 1.26–1.70).

In Table 2 we summarize the main SLE therapies prescribed during the study period and compare the drugs prescribed during the initial 5 years of the observational period with those prescribed in the ensuing 5 years. Oral steroids were used in 725 (72.5%) patients, antimalarials (chloroquine or hydroxychloroquine) in 478 (47.8%), nonsteroidal antiinflammatory drugs in 368 (36.8%), antiaggregants (mainly aspirin) in 201 (20.1%), azathioprine in 163 (16.3%), pulse cyclophosphamide in 114 (11.4%), anticoagulants (heparin, warfarin, or coumadin) in 94 (9.4%), and oral cyclophosphamide in 90 (9.0%). Hemodialysis for endstage renal failure was required in 26 (2.6%) patients, and kidney transplantation was performed in 11 (1.1%). When the frequencies of the different therapies prescribed during the initial 5 years of follow-up were compared with those prescribed during the ensuing 5 years, most drugs were found to be more prescribed during the initial 5 years: oral steroids (65.2% in the initial 5 yr versus 50.6% in the ensuing 5 yr, $p < 0.001$; RR = 1.33; 95% CI = 1.21–1.45), antimalarials (40.2% versus 34.8%, $p = 0.018$; RR = 1.11; 95% CI = 1.02–1.21), azathioprine (13.1% versus 9.2%, $p = 0.01$; RR = 1.1; 95% CI = 1.06–1.33), pulse cyclophosphamide (8.5% versus 5.5%, $p = 0.015$; RR = 1.21; 95% CI = 1.06–1.38), and oral cyclophosphamide (7.4% versus 3.5%, $p = 0.004$; RR = 1.35; 95% CI = 1.18–1.53).

## Other Associated Medical Problems During the Study

In Table 3 we list the frequencies of other medical problems that appeared during the 10-year prospective study and compare the problems that appeared during the initial 5 years with those that appeared in the ensuing 5 years: 360 (36%) patients presented infections (excluding minor viral upper respiratory tract infections), 169 (16.9%) hypertension, 121 (12.1%) osteoporosis (confirmed by bone densitometry), and 81 (8.1%) cytopenia due to immunosuppressive agents. When the frequencies of the associated medical problems during the initial 5 years of follow-up were compared with those of problems that appeared during the ensuing 5 years, infections were found to be more frequent during the initial 5 years (27% in the initial 5 yr versus 19.2% in the ensuing 5 yr, $p < 0.001$; RR = 1.21; 95% CI = 1.11–1.32), especially cutaneous infections (7.6% versus 4.6%, $p = 0.01$; RR = 1.23; 95% CI = 1.07–1.42) and sepsis (2.5% versus 0.6%, $p = 0.02$; RR = 1.55; 95% CI = 1.31–1.83).

Twenty-three (2.3%) patients developed malignancies. The most frequent primary localizations were the uterus (8 patients) and the breast (4 patients). All cancers were diagnosed antemortem. Only 8 of these patients received immunosuppressives (5 cyclophosphamide and 3 azathioprine) before the diagnosis of cancer.

## Mortality and Causes of Death During the Study

During the 10-year period, 68 (6.8%) patients died (10 in the first year, 11 in the second, 8 in the third, 7 in the fourth, 9 in the fifth, 7 in the sixth, 4 in the seventh, 4 in the eighth, 7 in the ninth, and 3 in the tenth). They included 60 (88.2%) female patients and 8 (11.8%) males. All except 1 were white. Autopsy was performed in 18 patients. Mean age at death was 44 ± 15 years (range, 18–81 yr). Evolution of the disease before death ranged from 3 and 488 months (mean, 144 ± 110 mo). Figure 1 shows the survival curve of the total cohort. A survival probability of 92% was found at 10 years from the time of entry into the study. A lower survival probability was detected in those patients who

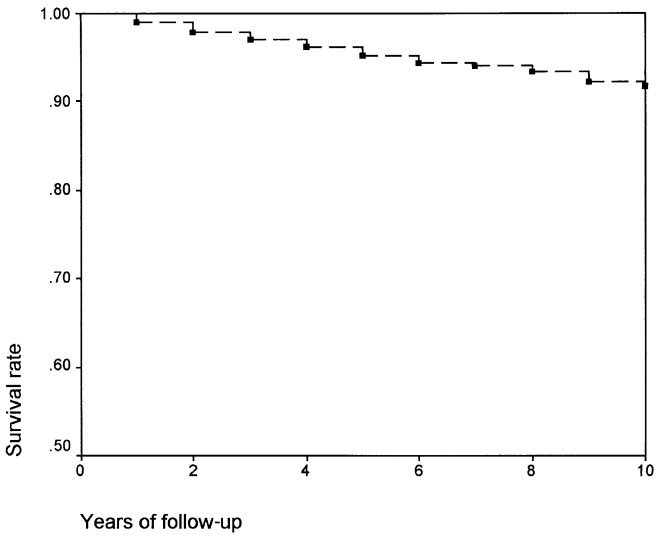


**FIGURE 1.** Survival curve of the total cohort.

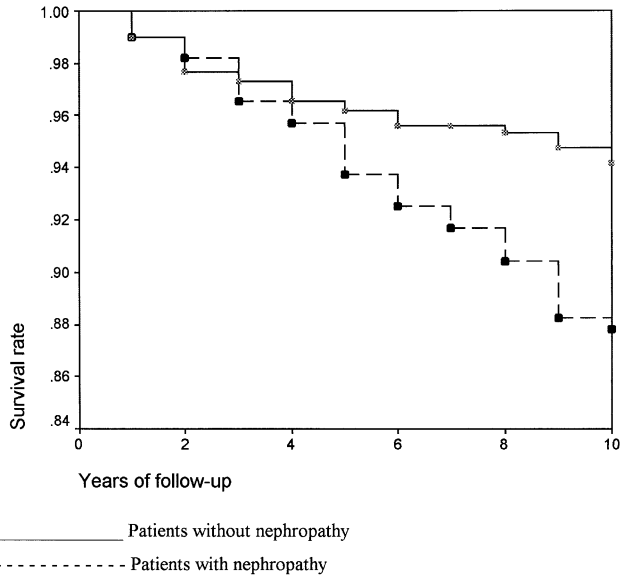


**FIGURE 2.** Survival curves of patients with and without nephropathy at the beginning of the prospective study.

presented at the beginning of the study with nephropathy (88% versus 94% in patients without nephropathy, p = 0.045) (Figure 2).

The most frequent causes of death were active SLE (26.5%), thromboses (26.5%), and infections (25%) (Table 4). Most patients who died of active SLE had progressive, frequently multisystem disease. The most frequent infections were bacterial sepsis of pulmonary (8.8%), abdominal (7.4%), and urinary (5.9%) origin. Active SLE plus infection was considered to be combined causes of death in 6 patients.

Thromboses were a predominant cause of death in 18 patients and were always associated with the presence of aPL (antiphospholipid syndrome). The most common thrombotic events were cerebrovascular accidents (11.8%), coronary occlusions (7.4%), and pulmonary embolisms (5.9%).

When the causes of death during the initial 5 years of follow-up were compared with those during the ensuing 5 years, active SLE and infections (28.9% each) appeared to be the most common causes during the initial 5 years, while thromboses (26.1%) became the most common cause of death during the last 5 years.

## DISCUSSION

In the present study, we describe the frequency and characteristics of the main SLE clinical manifestations and of other associated medical problems as well as the mortality rate and causes of death in a large cohort of European patients followed during a 10-year-period (1990–2000). Furthermore, we compare the early manifestations[12] with the manifestations that appeared later in the evolution of the disease.

This cohort consisted of 1,000 patients gathered by a European consortium, the Euro-Lupus Project Group. This consortium was created in 1990 as part of the network promoted by the European Working Party on SLE, a study group devoted to the development of multicenter projects with large populations of SLE patients[10]. The patients of the present study were collected consecutively at 12 university centers that follow all the cases diagnosed in their referral area, including all varieties of SLE manifestations, and were assessed by a wide range of specialists and subspecialists (that is, internists, rheumatologists, dermatologists, hematologists, neurologists, etc.). Only patients with well-defined

**TABLE 4.** Causes of Death in the Total SLE Cohort During the 10-year Prospective Study (1990–2000)

| Cause of Death | 1990–2000 (total = 68) No. (%) | 1990–1995 (total = 45) No. (%) | 1995–2000 (total = 23) No. (%) |
|---|---|---|---|
| Active SLE | 18 (26.5) | 13 (28.9) | 5 (21.7) |
| Multisystem | 5 (7.4) | 4 (8.9) | 1 (4.3) |
| Renal | 6 (8.8) | 4 (8.9) | 2 (8.7) |
| Cardiopulmonary | 3 (4.4) | 3 (6.7) | 0 (0) |
| Hematologic | 1 (1.5) | 1 (2.2) | 0 (0) |
| Neurologic | 3 (4.4) | 1 (2.2) | 2 (8.7) |
| Infection | 17 (25) | 13 (28.9)* | 4 (17.4)† |
| Bacterial sepsis | 15 (22.1) | 11 (24.4) | 4 (17.4) |
| Pulmonary | 6 (8.8) | 4 (8.9) | 2 (8.7) |
| Abdominal | 5 (7.4) | 4 (8.9) | 1 (4.3) |
| Urinary | 4 (5.9) | 3 (6.7) | 1 (4.3) |
| Fungal | 1 (1.5) | 1 (2.2) | 0 |
| Viral | 1 (1.5) | 1 (2.2) | 0 |
| Thrombosis | 18 (26.5) | 12 (26.7) | 6 (26.1) |
| Cerebral | 8 (11.8) | 5 (11.1) | 3 (13) |
| Pulmonary | 4 (5.9) | 3 (6.7) | 1 (4.3) |
| Coronary | 5 (7.4) | 3 (6.7) | 2 (8.7) |
| Other | 1 (1.5) | 1 (2.2) | 0 (0) |
| Malignancy | 4 (5.9) | 3 (6.7) | 1 (4.3) |
| Breast | 1 (1.5) | 1 (2.2) | 0 (0) |
| Lung | 2 (2.9) | 1 (2.2) | 0 (0) |
| Lymphoma | 1 (1.5) | 1 (2.2) | 0 (0) |
| Gastric bleeding | 2 (2.9) | 2 (4.4)‡ | 0 (0) |
| Obstetric | 1 (1.5) | 1 (2.2) | 0 (0) |
| Suicide | 1 (1.5) | 1 (2.2) | 0 (0) |
| Surgical | 1 (1.5) | 1 (2.2) | 0 (0) |
| Accident | 1 (1.5) | 0 (0) | 1 (4.3) |
| Unknown | 14 (20.6) | 7 (15.6) | 7 (30.4) |

*In 6 patients, the cause of death was attributed to infection plus other factors (active SLE in 5 and thrombosis in 1).

†In 1 patient, the cause of death was attributed to infection plus active SLE.

‡In 2 patients, the cause of death was attributed to gastric bleeding plus other factors (active SLE in 1 and infection in 1).

SLE, meeting the 1982 revised criteria of the ACR,[37] were included in the cohort, thus avoiding equivocal cases. Additionally, this study covers a representative European SLE population, including patients from northern, southern, central, western, and eastern Europe. The problem of potentially different medical care in the participating hospitals has been overcome by the careful selection of tertiary referral university centers having clinicians with substantial experience in the management of SLE patients and with a common background, and by a careful discussion of the definition of all outcome variables. Furthermore, in order to avoid a left censorship bias,[18] we conducted a prospective cohort study, thus ensuring that outcome data were available for all patients. Although 195 (19.5%) patients were lost to follow-up, this accounted for only 1%–3% per year (34 in the first year, 32 in the second, 31 in the third, 10 in the fourth, 8 in the fifth, 27 in the sixth, 21 in the seventh, 14 in the eighth, 11 in the ninth, and 7 in the tenth), and the appearance or absence of the different outcome variables during the period of time that these patients participated in the study was also registered. Therefore, this cohort can be considered representative of what are currently accepted to be SLE patients in Europe.

The frequencies of the main clinical manifestations related to SLE that appeared during the 10 years of the prospective study in the present European cohort are slightly lower than those reported in several large series from America[4,26] and Asia[39] published in the last decade (Table 5). In this European cohort, active nephropathy was diagnosed in 27.9% of the patients during the prospective study, while the frequencies in other studies ranges between 40.2% in an American series[4] and 74% in an Asian series[39]. These lower frequencies of SLE clinical manifestations could be due to genetic or environmental differences between Europeans and Americans or Asians, but could also reflect the effect of medical care during the study because of the prospective nature of the Euro-Lupus Project. Furthermore, we found a lower frequency of most SLE manifestations during the last 5 years of this prospective study (1995–2000), compared with the cumulative clinical manifestations during the initial 5 years of the study (1990–1995)[12]. For instance, the frequency of active lupus nephropathy during the last 5 years was 6.8%, while previously we had found a cumulative prevalence of 22.2% during the initial 5 years of the study[12]. These lower frequencies in the last 5 years probably reflect the effect of therapy and of medical care during the study, but also may be due to less severe activity of the disease after a long time of evolution.

As for the frequency and characteristics of other medical problems that caused morbidity in SLE patients, infections, hypertension, osteoporosis, and drug-induced cytopenias were the most frequent associated conditions both in the initial 5 years[12] of the present study and in the ensuing years. It is noteworthy that their frequency was higher than that of most SLE manifestations, especially in the last 5 years of the observational period. As some of these associated medical problems are probably due to or influenced by the therapy employed in SLE, this reinforces the importance of maintaining a careful balance between benefits and side effects when selecting medication to control SLE.

Malignant tumors occurred in only 23 (2.3%) of our patients. The most frequent primary localizations were the uterus (8 patients) and the breast (4 patients), which are also the most common malignancies in women. The relationship between SLE and malignancy is uncertain, and whether malignant neoplasms occur more commonly in patients with

**TABLE 5.** Main Clinical Manifestations Related to SLE in Several Large Series Reported During the Last Decade

| | First Author (reference) | | | |
|---|---|---|---|---|
| | **Petri[26]** | **Wang[39]** | **Alarcon[4]** | **Present Report** |
| No. of patients | 574 | 539 | 555 | 1,000 |
| Geographic area | America | Asia | America | Europe |
| Clinical manifestation | | | | |
| Malar rash | 331 (57.7) | 410 (76.1) | 322 (58) | 311 (31.1) |
| Discoid lesions | 162 (28.2) | 30 (5.6) | 107 (19.3) | 78 (7.8) |
| Photosensitivity | 335 (58.4) | 222 (41.2) | 334 (60.2) | 229 (22.9) |
| Oral ulcers | 219 (38.2) | 185 (34.3) | 293 (52.8) | 125 (12.5) |
| Arthritis | NR | 272 (50.5) | 489 (88.1) | 481 (48.1) |
| Nephropathy | 319 (55.6) | 399 (74) | 223 (40.2) | 279 (27.9) |
| Neurologic involvement | NR | 123 (22.8) | 67 (12.1) | 194 (19.4) |
| Thrombocytopenia | NR | 161 (29.9) | NR | 134 (13.4) |
| Hemolytic anemia | NR | 102 (18.9) | NR | 48 (4.8) |

Abbreviation: NR = not reported.

**TABLE 6.** Main Causes of Death in a North American Series and the Present European Cohort

| | Abu-Shakra[3] | | | Present Report | | |
|---|---|---|---|---|---|---|
| Geographic area | North America | | | Europe | | |
| Period of death | 0–5 yr | >5 yr | Total | 0–5 yr | >5 yr | Total |
| No. of deaths | 46 | 78 | 124 | 45 | 23 | 68 |
| Cause of death | | | | | | |
| Active SLE | 12 (26.1) | 8 (1.03) | 20 (16.1) | 13 (28.9) | 5 (21.7) | 18 (26.5) |
| Infection | 17 (37) | 23 (29.5) | 40 (32.3) | 13 (28.9) | 4 (17.4) | 17 (25) |
| Thrombosis | 7 (15.2) | 14 (17.9) | 21 (16.9) | 12 (26.7) | 6 (26.1) | 18 (26.5) |
| Malignancy | 3 (6.5) | 5 (6.4) | 8 (6.5) | 3 (6.7) | 1 (4.3) | 4 (5.9) |

SLE compared with the general population is unclear. There have been at least 8 clinical cohort studies, 3 hospital discharge linking studies, a meta-analysis, and several editorials and reviews produced in an attempt to clarify this question[1,2,6,7,13,19,22,24,25,27,29,30,35,36]. The recent meta-analysis of the 8 clinical cohort studies[6] showed an estimated risk for all malignancies of 1.5 (95% CI = 1.3–1.8); for hematologic, 4.2 (95% CI = 2.9–5.9); and for non-Hodgkin lymphomas, 9.3 (95% CI = 5.9–14.0). For several other malignancies, the confidence intervals included the possibility of either an increased or a reduced risk among SLE patients. It is not possible to confirm from the present analysis if the occurrence of malignancy is increased in patients with SLE in this European cohort, but several retrospective and prospective large studies are currently under way to resolve this question[19].

Over the past 50 years, the survival of patients with SLE has improved significantly. Whereas an earlier study[23] in 1955 reported a survival rate of less than 50% at 5 years, more recent studies[17,21,28,32–34] indicated that over 93% of patients with SLE survive for 5 years, and 85% survive for 10 years. In our European cohort, we found a 92% survival rate after 10 years from time of entry into the study. These improved survival rates may be related to the advanced medical therapy in general (antihypertensive agents, availability of renal dialysis, transplantation, and antibiotics), along with a better understanding of the pathogenesis of the disease, earlier diagnosis, and inclusion of milder cases in recent studies, but they also may be caused by the more intensive forms of treatment, such as the use of cytotoxic drugs, immunosuppressive drugs, and high-dose prednisolone.[34] The slightly higher survival in this European cohort compared with that in the American series also may be due to the predominance of white patients in the present cohort (97.1%); it is known that race influences outcome in SLE, and blacks and Hispanic Americans of mestizo or Native American origin have a poorer outcome[4].

The improved survival of patients with SLE has been associated with an alteration in the patterns of mortality[15,20,31,38]. Although determining a cause of death for SLE patients can be difficult because many patients present multisystem SLE involvement in their last days of life (that is, renal, cardiac, pulmonary, and hematologic involvement) and other combined complications (such as infections and thromboses), we found a similar percentage of active SLE (26.5%), thromboses (26.5%), and infections (25%) as the main causes of death in the total 10-year observational period. However, it is important to stress that when the causes of death during the initial 5 years of follow-up were compared with those during the ensuing 5 years, active SLE and infections (28.9% each) appeared to be the most common causes during the initial 5 years, while thromboses (26.1%) became the most common cause during the last 5 years. These findings are similar to those reported in a large Canadian series[3] published in the last decade (Table 6).

In conclusion, the present study provides updated information on morbidity and mortality characteristics of SLE in the last decade of the 20th century. It is noteworthy that most of the SLE inflammatory manifestations were less common after a long-term evolution of the disease, probably reflecting the effect of therapy as well as the progressive remission of the disease in many patients. Conversely, a more prominent role of thrombotic events is becoming evident, affecting both morbidity and mortality in SLE.

## ACKNOWLEDGMENTS

The authors thank Ana Paula Vilas, Núria Calcerrada, Judith García, and Fabián Ramírez for their assistance in database processing.

## APPENDIX: EUROPEAN WORKING PARTY ON SYSTEMIC LUPUS ERYTHEMATOSUS

Coordinators: Ricard Cervera, Gian Domenico Sebastiani, Josep Font, Munther A. Khamashta, and Graham R. V. Hughes. Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain: Ricard Cervera, Josep Font, Juan Carlos Mejía, Manuel Ramos-Casals, Mario García-Carrasco, Gerard Espinosa, Sònia Giménez, Gloria

de la Red, Víctor Gil, and Miguel Ingelmo. Lupus Research Unit, The Rayne Institute, St. Thomas' Hospital, London, UK: Munther A. Khamashta, Natividad Caro, Paula Alba, and Graham R. V. Hughes. Servicio de Medicina Interna, Hospital ''La Paz,'' Madrid, Spain: Antonio Gil, Paz Lavilla, Ignacio Bernardino, Leyre Diez-Porres, A. Robles, and Marta Mora. Divisione di Reumatologia, Ospedale San Camillo de Lellis, Rome, Italy: Gian Domenico Sebastiani. Department of Clinical Immunology and Rheumatology, Medical School of Ankara University, Ankara, Turkey: Guner Tokgöz and A. Olcay Aydintug. Department of Connective Tissue Diseases, Institute of Rheumatology, Warsaw, Poland: Hanna Chwalinska-Sadowska, Bogna Dratwianka, and Anna Jedryka-Góral. Unidad de Enfermedades Autoinmunes Sistémicas, Servicio de Medicina Interna & Servicio de Nefrología, Hospital Regional Carlos Haya, Málaga, Spain: Enrique de Ramón, María Teresa Camps, Miguel Angel Frutos, Mariela Grana, Javier Sánchez-Lora, Nuria Muñoz Roca, Julio Martínez González, and Carolina Díaz Cobos. Servicio de Medicina Interna & Sección de Reumatología, Hospital Clínico Universitario, Málaga, Spain: Antonio Fernández Nebro, Pedro González Santos, and Manuel Abarca. Istituto di Reumatologia, Università di Siena, Siena, Italy: Mauro Galeazzi. Department of Rheumatology, Haukeland Sykehus, Bergen, Norway: Merete Valen and Hans-Jacob Haga. II Cattedra di Reumatologia, Università di Cagliari, Cagliari, Italy: Alessandro Mathieu, Giuseppe Passiu, Giovanni Sanna, and Alberto Cauli. Service de Rhumatologie, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium: Frédéric Houssiau.

## REFERENCES

1. Abu-Shakra M, Ehrenfeld M, Shoenfeld Y. Systemic lupus erythematosus and cancer: Associated or not? *Lupus*. 2002;11:137–144.
2. Abu-Shakra M, Gladman DD, Urowitz MB. Malignancy in systemic lupus erythematosus. *Arthritis Rheum*. 1996;39:1050–1054.
3. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus. Results from a single center. I. Causes of death. *J Rheumatol*. 1995;22:1259–1264.
4. Alarcon GS, McGwin G Jr, Petri M, Reveille JD, Ramsey-Goldman R, Kimberly RP. Baseline characteristics of a multiethnic lupus cohort: PROFILE. *Lupus*. 2002;11:95–101.
5. American Rheumatism Association Glossary Committee. Dictionary of the Rheumatic Diseases. Signs and Symptoms Vol. 1. 1st ed. Bayport, NY: Contact Associates International Ltd., pp 1–80, 1982.
6. Bernatsky X, Boivin JF, Clarke A, Rajan R. Cancer risk in systemic lupus erythematosus: A meta-analysis [abstract]. *Arthritis Rheum*. 2001; 44(Suppl 9):1147.
7. Black KA, Zilko PJ, Dawkins RL, Armstrong BK, Mastaglia GL. Cancer in connective tissue disease. *Arthritis Rheum*. 1982;25:1130–1133.
8. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI: A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum*. 1992;35:630–640.
9. Boumpas DT, Fessler BJ, Austin HA III, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: Emerging concepts. Part. 2: Dermatologic and joint disease, the antiphospholipid syndrome, pregnancy and hormonal therapy, morbidity and mortality, and pathogenesis. *Ann Intern Med*. 1995;123:42–53.
10. Cervera R, Khamashta MA, Font J, Hughes GRV on behalf of the European Working Party on Systemic Lupus Erythematosus. European Working Party on Systemic Lupus Erythematosus: A 10 year report. *Lupus*. 2001;10:892–894.
11. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, Domenech I, Aydintug AO, Jedryka-Goral A, de Ramon E, Galeazzi M, Haga HJ, Mathieu A, Houssiau F, Ingelmo M, Hughes GRV, and the European Working Party on Systemic Lupus Erythematosus. Systemic lupus erythematosus: Clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. *Medicine (Baltimore)*. 1993; 72:113–124.
12. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, Aydintug AO, Jedryka-Goral A, de Ramon E, Fernandez-Nebro A, Galeazzi M, Haga HJ, Mathieu A, Houssiau F, Ruiz-Irastorza G, Ingelmo M, Hughes GRV, and the European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus. A multicenter prospective study of 1,000 patients. *Medicine (Baltimore)*. 1999;78:167–175.
13. Cibere J, Sibley J, Haga M. SLE and the risk of malignancy. *Lupus*. 2001;10:394–400.
14. Drenkard C, Villa AR, Garcia-Padilla C, Perez-Vazquez ME, Alarcon-Segovia D. Remission of systemic lupus erythematosus. *Medicine (Baltimore)*. 1996;75:88–98.
15. Estes D, Christian C. The natural history of systemic lupus erythematosus by prospective analysis. *Medicine (Baltimore)*. 1971; 50:85–95.
16. Gladman DD. Prognosis and treatment of systemic lupus erythematosus. *Curr Opin Rheumatol*. 1996;8:430–437.
17. Gripenberg M, Helve T. Outcome of systemic lupus erythematosus. A study of 66 patients over 7 years with special reference to the predictive value of anti-DNA antibody determination. *Scand J Rheumatol*. 1991; 20:104–109.
18. Hay EM, Croft P. Predicting outcome in current clinic attenders: A biased view. *Ann Rheum Dis*. 1994;53:357–358.
19. Isenberg D, Ramsey-Goldman R, Clarke A, Bernatsky S on behalf of the SLICC Group. Lupus and malignancy. *Lupus*. 2002;11:199.
20. Kellum RE, Hasericke JR. Systemic lupus erythematosus, a statistical evaluation of mortality based on a consecutive series of 229 patients. *Arch Intern Med*. 1964;113:200–207.
21. Manger K, Manger B, Repp R, Geisselbrecht M, Geiger A, Pfahlberg A, Harrer T, Kalden JR. Definition of risk factors for death, end stage renal disease, and thromboembolic events in a monocentric cohort of 338 patients with systemic lupus erythematosus. *Ann Rheum Dis*. 2002;61: 1065–1070.
22. Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:761–768.
23. Merrell M, Shulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. *J Chron Dis*. 1955;1:12–32.
24. Nashi E, Clarke A, Joseph L, Fortin P. The incidence of cancer in patients with SLE [abstract]. *Arthritis Rheum*. 2000;43:S165.
25. Nived O, Bengtsson A, Jonsen A, Sturfelt G, Olsson H. Malignancies during follow-up in an epidemiologically defined systemic lupus erythematosus inception cohort in southern Sweden. *Lupus*. 2001;10: 500–504.
26. Petri M. The effect of race on the presentation and course of SLE in the United States [abstract]. *Arthritis Rheum*. 1997;40:S162.
27. Petterson T, Pukkala E, Teppo L, Friman C. Increased risk of cancer in patients with systemic lupus erythematosus. *Ann Rheum Dis*. 1992;51: 437–439.
28. Pistiner M, Wallace DJ, Nessim S, Metzger AL, Klineberg JR. Lupus erythematosus in the 1980s: A survey of 570 patients. *Semin Arthritis Rheum*. 1991;21:55–64.
29. Ramsey-Goldman R, Clarke AE. Double-trouble: Are lupus and malignancies associated? *Lupus*. 2001;10:388–391.
30. Ramsey-Goldman R, Mattai SA, Schilling E, Chiu YL, Alo CJ, Howe HL, Manzi S. Increased risk of malignancy in patients with SLE. *J Invest Med*. 1998;46:217–222.

 

31. Rubin LA, Urowitz MB, Gladman DD. Mortality in systemic lupus erythematosus: The bimodal pattern revisited. *Q J Med*. 1985;55:87–98.
32. Seleznick MJ, Fries JF. Variables associated with decreased survival in systemic lupus erythematosus. *Semin Arthritis Rheum*. 1991;21:73–80.
33. Swaak AJG, Nossent JC, Bronsveld W, Van Rooyen AV, Nieuwenhuys EJ, Theuns L, Smeenk RJT. Systemic lupus erythematosus: I. Outcome and survival: Dutch experience with 110 patients studied prospectively. *Ann Rheum Dis*. 1989;48:447–454.
34. Swaak AJG, van den Brink HG, Smeenk RJT, Manger K, Kalden JR, Tosi S, Domljan Z, Rozman B, Logar D, Pokorny G, Kovacs L, Vlachoyiannopoulos PG, Moutsopoulos HM, Chwalinska-Sadowska H, Kiss E, Cikes N, Anic B, Schneider M, Fischer R, Bombardieri S, Mosca M, Graninger W, Smolen JS. Systemic lupus erythematosus. Disease outcome in patients with a disease duration of at least 10 years: Second evaluation. *Lupus*. 2001;10:51–58.
35. Sultan SM, Ioannou Y, Isenberg DA. Is there an association of malignancy with SLE? An analysis of 276 patients under long-term review. *Rheumatology*. 2000;39:1147–1152.
36. Sweeney DM, Manzi S, Janosky J, Selvaggi KJ, Ferri W, Medsger TA, Ramsey-Goldman R. Risk of malignancy in women with SLE. *J Rheumatol*. 1995;22:1478–1482.
37. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982; 25:1271–1277.
38. Urowitz MB, Bookman AAM, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med*. 1976;60:221–225.
39. Wang F, Wang CL, Tan CT, Manivasagar M. Systemic lupus erythematosus in Malaysia: A study of 539 patients and comparison of prevalence and disease expression in different racial and gender groups. *Lupus*. 1997;6:248–253.