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Mortality in Systemic Lupus Erythematosus

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Objective. **To examine mortality rates in the largest systemic lupus erythematosus (SLE) cohort ever assembled.**

Methods. **Our sample was a multisite international SLE cohort (23 centers, 9,547 patients). Deaths were ascertained by vital statistics registry linkage. Standardized mortality ratio (SMR; ratio of deaths observed to deaths expected) estimates were calculated for all deaths and by cause. The effects of sex, age, SLE duration, race, and calendar-year periods were determined.**

Results. **The overall SMR was 2.4 (95% confidence interval 2.3–2.5). Particularly high mortality was seen for circulatory disease, infections, renal disease, non-Hodgkin's lymphoma, and lung cancer. The highest SMR estimates were seen in patient groups character-**

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ized by female sex, younger age, SLE duration <1 year, or black/African American race. There was a dramatic decrease in total SMR estimates across calendar-year periods, which was demonstrable for specific causes including death due to infections and death due to renal disorders. However, the SMR due to circulatory diseases tended to increase slightly from the 1970s to the year 2001.

Conclusion. **Our data from a very large multicenter international cohort emphasize what has been demonstrated previously in smaller samples. These results highlight the increased mortality rate in SLE patients compared with the general population, and they suggest particular risk associated with female sex, younger age, shorter SLE duration, and black/African American race. The risk for certain types of deaths, primarily related to lupus activity (such as renal disease), has decreased over time, while the risk for deaths due to circulatory disease does not appear to have diminished.**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can be severe and life threatening. Death in patients with SLE may be due to lupus activity (when vital organs or systems are involved), to complications of treatment (particularly infections), or to long-term sequelae (such as cardiovascular disease).

Although the literature regarding mortality in SLE has been growing, it is still important to consolidate and confirm what previous findings have suggested. Through collaborations with the Systemic Lupus International Collaborating Clinics (SLICC) (1) and the Canadian Network for Improved Outcomes in Systemic Lupus (CaNIOS) investigator groups, we have constructed a unique multicenter international cohort of unprecedented size. We compared the mortality in this SLE cohort with geographically appropriate age-, sex-, and calendar-year period–matched general population mortality rates. Because of the exceptionally large number of patients and person-years of observation in our sample, we provide novel data comparing all-cause and disease-specific relative mortality (in SLE compared with the general population) across groups characterized by sex, age, SLE duration, geographic location, race, and calendar-year period.

PATIENTS AND METHODS

Study subjects. All adult (age >16 years) patients with definite SLE according to American College of Rheumatology (ACR) (2,3) or clinical criteria were eligible for inclusion. A patient was considered to have met the clinical criteria if a rheumatologist had confirmed that he/she had a definite diagnosis of SLE whether or not 4 ACR criteria had been met. However, the vast majority of our patients did in fact meet the ACR criteria. The study base encompassed 23 collaborating lupus centers in 7 countries. These centers, listed in Appendix A, were located in North America (Canada and the US), the UK (England and Scotland), Iceland, Sweden, and South Korea. Patients have been followed up in outpatient clinics and/or in the inpatient hospital setting. Although most investigators are based at tertiary academic centers, they actively encourage the enrollment of patients from community physician practices, and thus, the patients represent a spectrum of disease. This cohort has been used to examine cancer incidence in SLE (4).

Most of the patients at the participating centers were prospectively enrolled, although some had been retrospectively enrolled after being followed up for a period of time in the clinic at the respective center (see Appendix A). At each center, patients lost to followup were not excluded; in general, patients seen more than once at any of the participating study centers were included in the study.

Data collection. Data were collected on each patient's date of birth, sex, dates of SLE diagnosis and cohort entry, and date of death, if applicable. Probabilistic linkage to vital statistics registries was performed for patients deceased or lost to followup, with the National Death Index in the US cohorts and with regional vital statistics registries for the non-US cohorts. In probabilistic linkage (the current standard for linking with administrative databases), registries are provided with key data on patients (name, date of birth, and unique numeric identifier), and previously validated algorithms are used for selecting matches on the basis of probability of a correct match. For 3 centers (2 in Canada [Winnipeg and Vancouver] and 1 in the UK [London]), linkage of lost-to-followup patients to vital status registries was not permitted by local ethics approvals; death data at these centers consisted of the information recorded in the clinical records. These 3 centers contributed only a small number of patients (513 of the sample total of 9,547 patients), very few of whom were lost to followup. To be conservative, in the primary analysis, we assumed that any lost-to-followup patients from these centers remained alive until the end of the observation interval; in sensitivity analyses, we repeated the standardized mortality ratio (SMR) calculations using the last date seen for all lost-to-followup patients.

Analysis. For death overall and for cause of death, we determined the ratio of the observed number of deaths to the expected number of deaths (the SMR). We examined the most common identified causes of death, calculating event rates and cause-specific SMRs. In secondary analyses, SMRs were estimated for subgroups according to sex, age group, duration of SLE, and geographic location (country). We also estimated SMRs across calendar-year periods (1970–1979, 1980–1989, and 1990–2001). In addition, we generated race-specific SMRs for the US patients only, since the US mortality rates were the only available general population figures that were stratified by race (for whites and blacks/African Americans).

To calculate SMRs, the expected numbers of deaths were obtained by multiplying person-years at risk in the cohort by the geographically appropriate age-, sex-, and calendar-year

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period–matched mortality rates. The person-years for each patient were determined by subtracting the later of 2 entry dates (the beginning of the vital statistics registry observation interval or the first visit to the respective lupus clinic) from the earlier of 2 exit dates (end date of vital statistics registry data or death). The SMRs were calculated by dividing the observed number of deaths by the expected number, and 95% confidence intervals (95% CIs) were calculated using methods described elsewhere (5) for Poisson parameters. Information on deaths by cause was grouped according to International Classification of Diseases, Ninth Revision (ICD-9) codes.

In additional secondary analyses, we used the entire sample to perform a multivariate hierarchical regression to determine independent effects of the factors examined (sex, age group, SLE duration, calendar-year period, country) on the SMRs among the patients in the SLE cohort. The hierarchical model allowed for differences in effects from one country to the next. Poisson regression methods were used, with the logarithm of the expected number of deaths serving as the offset variable. The model included an extra variance term to handle slight overdispersion in the data. For each variable in the model, one of the categories was chosen as a reference, and the estimate for each of the other categories is thus interpretable as the relative risk compared with the reference, adjusted for the other factors in the model. Finally, we undertook secondary analyses of the 291 deaths for which lupus was the assigned cause, evaluating stratified rates of lupus-related death for groups characterized by demographics, SLE duration, and calendar-year period.

RESULTS

The 9,547 patients were observed for a total of 76,948 person-years (average followup 8.1 years). The calendar-year period of observation was 1958–2001, although the majority of the observation interval occurred between 1970 and 2001. Most of the patients (71%) entered into the observation interval within the first 2 years of their SLE diagnosis. As expected, given that SLE is a disease primarily of women, 90% of the patients were female (n = 8,607). The number of person-years of observation was divided among the age groups <40 years (33,001 person-years), 40–59 years (30,976 person-years), and ≥60 years (12,971 person-years). Regarding SLE duration, the person-years of observation were fairly equally divided among the duration groups of 0–4 years (27,037 person-years), 5–9 years (21,931 person-years), and ≥10 years (27,980 person-years).

Within the observation interval, 1,255 deaths occurred; lupus was the assigned cause of death in 291 cases (3.8 events per 1,000 person-years). The most common types of deaths not directly attributed to SLE were deaths due to circulatory disease (ICD-9 codes 390–459); this includes all types of heart disease, arterial disease, and cerebrovascular events (strokes). Other common types of deaths resulted from neoplasms (ICD-9 codes 140–239), nephritis (ICD-9 codes 580–589), and infections (ICD-9 codes 001–139; these codes do not include pneumonia [ICD-9 codes 480–486] or the term bacteremia [ICD-9 code 790.7], although they do include the term septicemia [ICD-9 code 038]). Circulatory disease was the identified cause of 313 deaths, for a rate of 4.1 events per 1,000 person-years; cancer was the cause ascribed to 114 deaths, for a rate of 1.5 events per 1,000 person-years; and infection (not including pneumonia) was identified as the cause of 45 deaths, for a rate of 0.6 events per 1,000 person-years.

The overall (all-cause) SMR estimate was 2.4 (95% CI 2.3–2.5). For death due to circulatory disease, the SMR was 1.7 (95% CI 1.5–1.9). For the ICD category of infectious causes of death, the SMR was 5.0 (95% CI 3.7–6.7); for pneumonia (which in the ICD codes is classified under respiratory diseases), the SMR was 2.6 (95% CI 1.6–4.1). For cancer overall, the SMR was 0.8 (95% CI 0.6–1.0); in terms of cancer types, for

Table 1. Unadjusted SMR estimates for all-cause mortality and for death by cause*

Cause of death (ICD-9 code)	Observed	Expected	SMR (95% CI)
All deaths	1,255	526	2.4 (2.3–2.5)
Disease of the circulatory system†			
All disease (390–459)	313	184.3	1.7 (1.5–1.9)
Heart disease (390–429)‡	126	73.8	1.7 (1.4–2.0)
Stroke (430–459)‡	21	19.3	1.1 (0.7–1.7)
Malignancy†			
All neoplasms (140–239)	114	138	0.8 (0.6–1.0)
All hematologic cancer (200–208)‡	15	7.2	2.1 (1.2–3.4)
NHL (200, 201)‡	8	2.8	2.8 (1.2–5.6)
Lung cancer (162)‡	44	19.4	2.3 (1.6–3.0)
Infections†			
Infections (001–139)	45	9.0	5.0 (3.7–6.7)
Pneumonia (480–486)‡	19	7.2	2.6 (1.6–4.1)
Other†			
Respiratory, excluding pneumonia (460–479, 487–519)	14	10.4	1.3 (0.8–1.6)
Renal (580–589)	34	4.3	7.9 (5.5–11.0)

* Data shown are for 23 participating sites in North America, Europe, Iceland, and Asia, for a total 9,547 patients (76,948 person-years), and for the calendar-year period 1958–2001. SMR = standardized mortality ratio; ICD-9 = International Classification of Diseases, Ninth Revision; 95% CI = 95% confidence interval; NHL = non-Hodgkin's lymphoma.

† Cause-specific death data on this level of detail were available from all centers except for Iceland (n = 221), Sweden (n = 114), Saskatchewan (n = 306), and Manitoba (n = 158).

‡ Cause-specific death data on this level of detail were available from all centers except for Iceland (n = 221), Sweden (n = 114), Saskatchewan (n = 306), Manitoba (n = 158), and Scotland (n = 1,937).

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Table 2. Unadjusted SMR estimates, stratified by sex, age, and SLE duration*

	SMR (95% CI)
Sex	
Female	2.5 (2.3–2.7)
Male	1.9 (1.7–2.2)
Age, years	
<40†	10.7 (9.5–11.9)
40–59	3.7 (3.3–4)
≥60	1.4 (1.3–1.5)
SLE duration, years	
<1	5.4 (4.7–6.3)
1–4	2.5 (2.2–2.8)
5–9	2.1 (1.9–2.4)
10–19	2.0 (1.8–2.3)
≥20	2.0 (1.7–2.4)

* SMR = standardized mortality ratio; SLE = systemic lupus erythematosus; 95% CI = 95% confidence interval.
† Within the age group <40 years, the SMR for very young adults (ages 16–24 years) was particularly high, at 19.2 (95% CI 14.7–24.7). The SMR for adults ages 25–39 years was 8.0 (95% CI 7.0–9.1).

non-Hodgkin's lymphoma (NHL), the SMR was 2.8 (95% CI 1.2–5.6), and, for lung cancer, the SMR was 2.3 (95% CI 1.6–3.0) (Table 1).

Patient groups characterized by any of the following: female sex, younger age, or SLE duration <1 year, all had particularly high SMR estimates (Table 2). This phenomenon was evident not only for all-cause mortality, but also for cause-specific mortality estimates, including death due to circulatory diseases, infections, and renal disorders. Within the age group <40 years, the SMR for very young adults (ages 16–24 years) was particularly high, at 19.2 (95% CI 14.7–24.7). Figure 1 presents the unadjusted SMR estimates by calendar-year period. Across calendar-year periods, there was a dramatic decrease in total SMR estimates, which was demonstrable for specific causes, including death due to infections and death due to renal disorders. However,

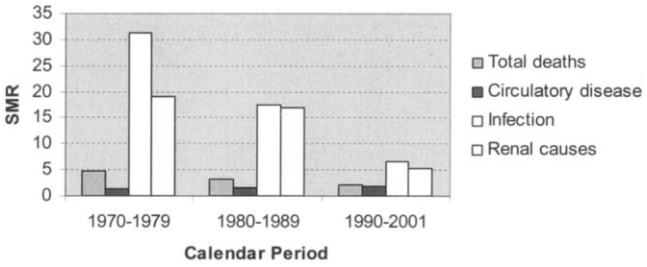

Figure 1. Unadjusted standardized mortality ratio (SMR) estimates, by calendar-year period.

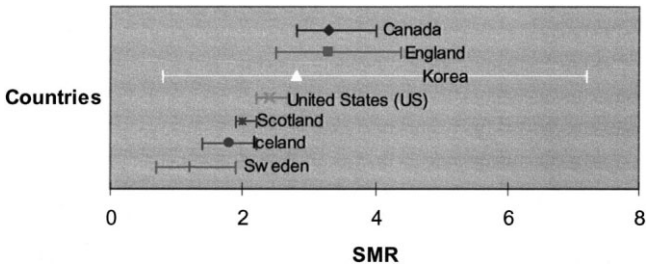

Figure 2. Unadjusted standardized mortality ratio (SMR) estimates, stratified by country. Korea represents South Korea.

the SMR due to circulatory diseases tended to increase slightly from the 1970s to the year 2001.

Unadjusted SMR estimates stratified according to geographic location are shown in Figure 2. Although slight differences may be present, overall the evidence suggests a relatively consistent increased risk of death (~2-fold) in SLE patients compared with the general population. However, although Figure 2 indicates that the unadjusted country-specific estimates are largely overlapping, it appears that the magnitude of effect may be somewhat less for certain groups, notably the Swedish. This may in part relate to various factors, including differences in demographic makeup or clinical characteristics of the cohort members; an important factor may also relate to site-specific variations in the enrollment criteria and methods (as outlined in Appendix A). Race-specific SMR estimates for the US patients were as follows: whites 1.4 (95% CI 1.2–1.7), blacks/African Americans 2.6 (95% CI 2.3–2.9). The overall race-adjusted SMR for the US sites was 2.2 (95% CI 2.0–2.4). In sensitivity analyses, when we repeated the SMR calculations using the last date seen for all lost-to-followup patients, the results were essentially unchanged.

Table 3 presents the results of the multivariate hierarchical regression to determine independent effects of the factors examined (sex, age group, SLE duration, calendar-year period of SLE diagnosis, country) on the relative SMR estimates among SLE patients. These adjusted estimates were consistent with the unadjusted results in terms of suggesting independent effects for each variable of interest (female sex, younger age, SLE duration <1 year, calendar-year period) on the risk of death among the SLE patients (relative to the general population). However, the 95% CIs were wider, and in the case of the effects of different calendar-year periods, the estimates did overlap and include the null value.

Regarding secondary stratified analyses for rates of death due to SLE, we found that lupus-related death

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Table 3. Results of adjusted multivariate regression to determine independent effect of variables on SMR estimates*

	Adjusted SMR (95% CI)†
Female sex	1.2 (1.0–1.4)
Age, years	
<40	6.4 (5.5–7.5)
40–59	2.6 (2.3–3.0)
≥60	1.0 (reference group)
SLE duration, years	
<1	7.7 (5.9–10.2)
1–4	3.2 (2.5–4.1)
5–9	2.4 (1.8–3.0)
10–19	1.8 (1.4–2.2)
≥20	1.0 (reference group)
Calendar-year period of SLE diagnosis	
1970–1979	1.3 (1.0–1.5)
1980–1989	1.2 (1.0–1.4)
1990–2001	1.0 (reference group)
Country	
Canada	1.8 (1.6–2.1)
England	1.6 (1.2–2.2)
Scotland	1.3 (1.1–1.5)
Iceland	1.2 (0.9–1.6)
US	1.0 (reference group)
Sweden	0.8 (0.5–1.4)
South Korea	0.7 (0.3–2.0)

* SMR = standardized mortality ratio; 95% CI = 95% confidence interval. SLE = systemic lupus erythematosus.
† Variables adjusted concomitantly for all others (sex, age, SLE duration, calendar-year period, and country).

rates were a little higher for men (3.6 deaths per 1,000 person-years) than for women (2.7 deaths per 1,000 person-years), although the 95% CIs for these estimates overlapped. With respect to age, very young individuals (ages <25 years) had the highest rate of deaths due to SLE (5.3 deaths per 1,000 person-years, 95% CI 3.7–7.5) compared with other age groups; the estimates across other age groups (for those ages ≥25 years) were all very similar, with an average of 2.5 deaths due to SLE per 1,000 person-years (95% CI 2.2–3.5). There were generally very few differences regarding lupus-related death rates for groups characterized by SLE duration, and no trend over calendar time was observed for deaths due to lupus.

DISCUSSION

The primary value of this work is that it formally presents the increased risk of mortality in SLE compared with that in the general population, and it examines the particular risk in groups of patients characterized by demographic and other factors. The increased risk of mortality in SLE is by no means a new phenomenon; on the contrary, it has been a point of concern for some years. However, our results do emphasize what has been demonstrated previously in smaller samples. In addition, because of the large numbers of patients and person-years of observation in the multicenter cohort, we were able to provide data comparing all-cause and disease-specific relative mortality (in SLE patients compared with the general population) across groups characterized by age, sex, SLE duration, calendar-year period, geographic location, and race.

In terms of the slightly higher total SMR estimates suggested for females, some prior work by others has suggested greater mortality in male than in female SLE patients (6,7). However, this previous work did not calculate mortality rates relative to the general population. The longevity of males is generally lower than that of females; thus, when comparing the effect of sex on mortality in SLE patients, it is preferable to use a parameter such as the SMR. Similarly, the SMR provides a clearer understanding of which age group of SLE patients has the greatest increased risk (compared with the general population counterparts), since mortality rates in the general population increase with age.

Although the highest SMR estimates for our sample were seen within the first year, there was evidence that death rates in SLE patients are much higher than those in the general population throughout the course of SLE, even up to 20 years of SLE duration. Overall, across countries, we noted a relatively consistent increased risk of death in SLE patients compared with the general population. Slight regional differences were present (Figure 2); adjusting for sex, age, SLE duration, and calendar-year period appeared to remove most of this variation (Table 3). Small residual regional differences may be due in part to differences in cohort assembly (see details in Appendix A) and may reflect variations in other factors, including disease characteristics (and severity), medication exposures, comorbidity, and racial mix. We note that the cohorts from countries with the lowest SMR point estimates (Sweden, Iceland, and Scotland) were population based. This may indicate the potential role of sample recruitment in the findings.

Among SLE patients in the US, the question of why blacks/African Americans have a higher SMR than whites is an interesting one; previous work has also shown this phenomenon (8,9). Since the results of other studies have suggested worse renal involvement and outcomes in black/African American (and also black Caribbean) patients (10–13), a reasonable hypothesis is that the higher SMR estimate in blacks is driven in part by SLE severity and comorbidity. Another related factor may be economic status, since poverty has been sug-

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gested to contribute to increased mortality in SLE (6,14). Previous work has suggested high mortality in Asian SLE patients as well (15), but estimates relative to the general population are lacking. We are unable to comment about racial groups other than white and black/African American patients in the US.

Early work by Urowitz et al (16,17) first drew attention to the importance of mortality due to circulatory disease in SLE, particularly late in the disease course. As their work and that of others has suggested, circulatory disease (related to the heart, arteries, and cerebrovascular events) is a common cause of death in SLE (9,18,19). Previous work by Manzi et al (20) has shown a very high incidence of cardiac events (specifically, myocardial infarction and angina) in SLE patients compared with the general population. Our data substantiate an increased risk of death due to circulatory causes in SLE patients compared with the general population.

We identified an increased risk of death due to specific cancers, including hematologic malignancies (particularly NHL) and lung cancer. This is of interest given recent data showing a heightened incidence of these types of cancer in SLE (4), and it is not concordant with surveillance bias as the explanation for the observed association between cancer and SLE. An increased risk of death was also estimated for infections and renal disease. It is well known that infections, often attributed to the use of immunosuppressant medications, are a frequent cause of death in SLE (9,18,21). An increase in the rate of death due to renal disease reflects the potential seriousness of nephritis in SLE (9,22).

Our work shows a dramatic 60% decrease over time in the standardized all-cause mortality rates, from 1970–1979 (SMR 4.9) to 1990–2001 (SMR 2.0). Work in several SLE cohorts over the last 3 decades has suggested an improvement in survival, at least early in the course of SLE (17,23–25). Results of our work are consistent with increased survival over time, in keeping with previous findings, although we note that the use of different methodologies may produce somewhat different estimates from one study to the next. It is important to keep in mind that, since the SMR estimate compares the observed number of deaths in SLE patients with the expected number of deaths in the general population, the decrease over the last 2 decades probably reflects improvements specific to the excess mortality in SLE rather than a general increase in population longevity. A decrease in deaths due to infections over time may be due to the evolution of strategies to limit the incidence of infections when immunomodulators are used (for example, by limiting cumulative exposure). An alternative explanation is that in more recent eras, there is more effective recognition and treatment of infectious complications.

It seems clear that certain types of deaths, primarily related to lupus activity (such as renal disease), have decreased over time. However, the trend for circulatory disease shows no such decline, a finding suggested as well by Bjornadal et al (19). This may reflect in part the complex nature of cardiovascular disease in SLE. Classic atherosclerosis risk factors, such as hypertension and hypercholesterolemia, do play a role, although recent work has suggested that additional risk is conferred by some disease-related characteristics, such as SLE duration and, perhaps, severity (26). However, other elements, such as medication exposures, may also alter atherosclerosis risk in SLE.

Limitations of our study should be considered. We cannot be certain that the causes of death in our SLE patients were identified correctly, since we relied primarily on death registry linkage results. However, important biases in our estimates would only arise if misclassification occurred differentially between SLE patients versus the general population. A fairly large number of deaths were ascribed to SLE itself; it is possible that the primary cause of death was actually another condition (e.g., cardiovascular disease or infection), but the patient's preexisting diagnosis of SLE may have led to this being listed as the cause of death. This might lead to an underestimation of some of the cause-specific SMR estimates; however, the data on causes of death recorded for SLE patients do not suggest that this effect is likely (27).

Although we believe that our cohort is probably representative of the general population of lupus patients, it is not a random sample. Therefore, claims of representativeness must be made very cautiously, since unobserved selection biases may certainly operate. Most investigators involved in our multicenter cohort are based at tertiary academic centers, although they actively encourage the enrollment of patients from community physician practices. The patients enrolled do represent a spectrum of disease severity, but sicker patients may indeed be overrepresented. We do note that our findings are consistent with the results reported by Bjornadal et al (19) in their assessment of a population-based cohort, which was assembled using administrative databases (which are not without their own sources of bias and error).

In conclusion, the data from our very large multicenter international cohort emphasize what has

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been demonstrated previously in smaller samples. The results highlight the increased mortality rate in SLE patients compared with the general population. This increased mortality is highest in patient groups characterized by female sex, younger age, or SLE duration <1 year, although an increased risk of mortality in SLE patients compared with the general population was generally seen across all demographic groups. The country-specific estimates also showed a relatively consistent increased risk of death in SLE patients compared with the general population. There was evidence of a striking increase in mortality among black/African American SLE patients in the US, although a smaller increase in mortality was also present for white SLE patients in the US. The decrease in SMR estimates over time for our lupus cohort is encouraging, but the residual increased risk of death in SLE suggests that continued efforts should focus on developing better means of preventing and treating the sequelae of SLE *as well as other comorbidity*, particularly cardiovascular disease.

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APPENDIX A: INTERNATIONAL SYSTEMIC LUPUS ERYTHEMATOSUS COHORT, PARTICIPATING CENTERS

Country (no. of patients)*	Centers
North America	
Canada (2,688)†	Calgary, Alberta‡; Halifax, Nova Scotia‡; London, Ontario§; Montreal, Quebec (Hôpital Maisonneuve-Rosemont§, Montreal General Hospital‡, Hôpital Notre-Dame¶); Saskatoon, Saskatchewan‡; Toronto, Ontario‡; Vancouver, British Columbia§; Winnipeg, Manitoba (Health Science Centre and Manitoba Clinic)§
US (3,558)†	Baltimore, Maryland¶; Birmingham, Alabama‡; Chapel Hill, North Carolina¶; Chicago, Illinois¶; New York, New York (Albert Einstein College of Medicine, Bronx§; State University of New York–Downstate Medical Center, Brooklyn‡); Pittsburgh, Pennsylvania¶
UK	
England (712)†	Birmingham‡; London‡
Scotland (1,937)#	Lanarkshire§
Other	
Sweden (114)†	Lund‡
Iceland (221)†	Reykjavik¶
South Korea (317)†	Seoul¶
Total = 9,547	

* The number of patients at each center corresponds to the number of patients present during the time that vital status registry data were available.
† At least 95% of cohort members met 4 of the American College of Rheumatology (ACR) diagnostic criteria for systemic lupus erythematosus (SLE) (2,3); patients diagnosed clinically as having SLE but meeting fewer than 4 ACR criteria are not excluded.
‡ Prospective assembly.
§ Retrospective assembly.
¶ Retrospective and prospective assembly.
# Any hospital discharge diagnosis of SLE, primary or nonprimary. Cohort entry date is first discharge date with SLE as a diagnosis.

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