Changing Patterns in Mortality and Disease Outcomes for Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Survival of patients with systemic lupus erythematosus (SLE) has improved significantly, but new morbidities have emerged, leading to altered patterns of outcome in this disease. We examined changes in mortality and other outcomes over time in a large SLE cohort.

Methods. A group of 1241 patients from the University of Toronto Lupus Clinic followed prospectively were divided into 4 entry cohorts — 1: 1970–1978, 2: 1979–1987, 3: 1988–1996, 4: 1997–2005. These cohorts were followed through four 9-year calendar periods defined over the same intervals. Both cohort and calendar effects were assessed for the following outcomes: mortality (standardized mortality ratio; SMR), disease activity over time (adjusted mean SLEDAI; AMS), cumulative damage (Systemic Lupus International Collaborating Clinics Damage Index; SDI), coronary artery disease (CAD), and osteonecrosis (ON). Cox regression models were used to further investigate mortality and the influence on it of the disease-related factors.

Results. Over the 36-year period of the study, 211 deaths occurred. The overall SMR in the first and last decades were 12.60 (95% CI: 9.13, 17.39) and 3.46 (95% CI: 2.71, 4.40) respectively. When SMR were stratified by the entry cohort and calendar period, there is evidence of a calendar-period effect but no cohort effect. The AMS decreased over the decades, while SDI, CAD, and ON increased. There were significant detrimental effects for male sex, CAD, AMS, SDI, and use of immunosuppressive drugs and significant protective effects for use of antimalarials and the effect of calendar period on mortality.

Conclusion. Our study demonstrates improved survival in patients with SLE over a 36-year period. Disease-related variables included in the model are important factors for mortality in this SLE cohort, but could not completely explain the trend of improved survival over calendar period observed. (First Release Sept 15 2008; J Rheumatol 2008;35:2152–8; doi:10.3899/jrheum.080214)

Key Indexing Terms:
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Survival of patients with systemic lupus erythematosus (SLE), both adults and children, over the past 3 decades has improved significantly[1-4]. Whereas a study in 1955 showed a survival of less than 50% at 5 years, recent studies report survival of 85% at 10 years and 75% at 20 years[1,5]. In addition, as patients with SLE live longer they develop new morbidities such as accrual of organ damage and development of osteonecrosis and coronary artery disease[6-10].

The University of Toronto Lupus Clinic provides a unique opportunity to address the issue of changing patterns in SLE outcomes over time: it represents a single cohort of patients that is followed, using a standardized protocol, every 2–6 months regardless of disease activity or severity and supervised by the same researchers over the entire period. Patients are seen and investigated as necessary in a universal government funded healthcare system. In this cohort, the major approaches to therapy have been oral corticosteroids, antimalarials, and the antimetabolites azathioprine and methotrexate, with mycophenylate not being introduced until after 2005. A minority of patients have been treated with cyclophosphamide[11]. Biologic agents have not been available to the cohort to date. The loss to followup has been low in our cohort, and has been shown not to influence overall outcomes[12]. The clinic therefore allows us to address disease and therapy related factors that could contribute to any changes observed. The reasons for the observed improved survival are unclear. In a previous investigation we found no evidence to support the influence of changing demographics, severity of lupus at presentation, major change in disease pattern, or new modalities of treatment[13]. That study, however, did not include time-dependent explanatory variables.

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In the current study we extended our investigation of mortality over a longer period of followup. Moreover, we analyzed other SLE patient outcomes over time in this large SLE cohort followed prospectively. We also examined whether these patient outcomes are associated with mortality.

MATERIALS AND METHODS

Research setting. The University of Toronto Lupus Clinic provided the data for a population of patients with SLE that is followed longitudinally.

Patients. Patients have been followed prospectively at 2–6 month intervals since 1970. At each visit, a complete history, physical examination, and laboratory evaluation according to a standard protocol are recorded. All information is tracked on an ORACLE database. This patient population represents a mixture of primary, secondary, and tertiary referrals, and is similar to other North American lupus patient populations[14]. All patients fulfilled 4 or more of the American College of Rheumatology criteria for SLE, or 3 criteria plus a typical histological lesion of SLE on renal or skin biopsy. Patients were identified on the basis of year of entry to the clinic (regardless of disease duration) and grouped into 4 entry cohorts representing the four 9-year intervals — 1: 1970–1978, 2: 1979–1987, 3: 1988–1996, 4: 1997–2005. These cohorts were followed through four 9-year calendar periods defined over the same intervals as the entry cohorts, and denoted A, B, C, and D, respectively. Both cohort and calendar effects were assessed for all outcomes. Patient data were administratively truncated at December 31, 2005, for the purpose of this study.

Mortality. All-cause mortality is documented in the database. Deaths are retrieved from death certificates or physician or family contact. To investigate whether this clinic of patients with SLE had an excess number of deaths compared to the Ontario provincial population, standardized mortality ratios (SMR) were computed.

Disease activity. SLEDAI. Overall disease activity of SLE was systematically evaluated using the SLE Disease Activity Index (SLEDAI-2K)[15]. This is a validated modification of the SLEDAI, an instrument validated to assess disease activity in SLE, which has been shown to be reliable, sensitive to change, and easily performed by both experts and nonexperts[16-19]. All disease variables necessary to calculate the SLEDAI-2K are collected prospectively in the lupus protocol.

Adjusted mean SLEDAI (AMS). The adjusted mean SLEDAI, a validated measure that assesses disease activity over time, was constructed within each defined calendar period for each patient from a patient's SLEDAI-2K measurements within the calendar period[20].

Cumulative damage. Organ damage was documented according to the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology Damage Index (SDI)[21]. This measure includes descriptors of nonreversible change that occur after the onset of SLE, whether they are related to the disease process or its treatment or not. This instrument has been shown to be valid and reproducible and is completed in the lupus clinic at yearly intervals[22,23]. The population-averaged level of damage within each calendar period was computed for each entry cohort.

Steroid use. The prevalence of steroid use at clinic visits within each calendar period for each entry cohort was computed.

Coronary artery disease (CAD). CAD was defined as ever having symptomatic myocardial infarction (MI) or angina. MI was defined as one of definite (1) electrocardiographic (ECG) abnormalities; (2) typical symptoms with probable ECG abnormalities and abnormal enzymes (≥ 2 times upper limit of normal); or (3) typical symptoms and abnormal enzymes.

Angina was defined as severe pain or discomfort over the upper or lower sternum or anterior left chest and left arm, of short duration, relieved by rest or vasodilators[24].

The prevalences of CAD in different calendar periods by entry cohort were calculated.

Osteonecrosis (ON). Osteonecrosis was defined on the basis of pain in the affected joint(s) and confirmed with imaging[10]. The prevalences of ON in different calendar periods by entry cohort were calculated.

Statistical methods. Demographic and disease related characteristics of patients with SLE at entry into clinic were described for each of the 4 entry cohorts. Means and standard deviations were presented for continuous variables. Frequencies and percentages were provided for categorical variables. Analysis of variance and chi-squared tests were performed to assess statistical significance at the 5% level.

In the primary analyses, patients were censored at their last visit. In addition, sensitivity analyses were performed under the assumption that patients lost to followup were still alive at December 31, 2005. These analyses represent 2 extreme scenarios for patient followup in terms of the shortest and longest followup possible.

Mortality data for the Ontario population, stratified by 5-year age bands, sex, and calendar year from 1970 to 2005, were used to calculate the reference rates. SMR were calculated overall, and by men and women separately, through Poisson regression models for the observed deaths, with the logarithm of the expected number of deaths as an offset in the models[25]. These SMR effectively compare mortality in SLE clinic patients with the Ontario population adjusting for age, sex, and calendar period, which also implicitly adjusts for birth cohort to the extent possible. Time-trend analyses were performed through use of 10-year "rolling average" SMR. In addition, SMR were tabulated by entry cohort and calendar period. Entry cohorts were defined by the period of entry into the clinic (1: 1970–1978, 2:1979–1987, 3: 1988–1996, and 4: 1997–2005). The calendar effect was defined by the followup-specific period as A: 1970–1978, B: 1979–1987, C: 1988–1996, and D: 1997–2005. Life-years lost were calculated overall and separately by men and women based on the SMR[26].

To examine if SMR patterns can be explained by differential patient characteristics in the clinic over time, and to investigate the effects on mortality of SLE disease related factors in the presence of cohort and calendar effects, we fitted Cox regression models with time-dependent covariates to our data. The time scale used was age.

Age adjustment, in a very general manner, is achieved through use of age as the time scale, and since the analysis is based on individual records, the non-identifiability features of age-period-cohort models may be avoided. All Cox models took into account delayed entry (or left truncation of the risk set), and were adjusted for sex, race, age at SLE diagnosis (which equivalently adjusts for disease duration), and the main effects of entry cohort (1 to 4) and calendar period (A to D). The interaction effect between cohort and calendar was not statistically significant when assessed in the Cox regression and was excluded in further models. The modeling strategy was to test all disease related variables on time to death separately, and then build the multivariate Cox model based on those considered important.

The variables considered for inclusion in the multivariate analysis were SDI, CAD, ON, either AMS or SLEDAI-2K, corticosteroid use, and use of antimalarial and immunosuppressive drugs.

RESULTS

During the period from January 1, 1970, to December 31, 2005, 1241 patients (1083 women, 158 men) were enrolled into the University of Toronto Lupus Clinic. Two hundred twenty-eight patients first presented at the clinic between 1970 and 1978 (Cohort 1), 364 in the period 1979-1987 (Cohort 2), 260 in the period 1988-1996 (Cohort 3), and 389 in the period 1997-2005 (Cohort 4). The demographic and disease related characteristics of the 4 entry cohorts are shown in Table 1.

Cohort characteristics. There was a decreasing trend in the percentage of Caucasians across entry cohorts. This was coupled with an increasing trend in the percentage of Blacks

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Table 1. Demographic and disease-related characteristics of the SLE clinic population at presentation to clinic.

Variable	Entry Cohort, Period of Entry 1 1970–1978, n = 228	2 1979–1987, n = 364	3 1988–1996, n = 260	4 1997–2005, n = 389	p*
Sex, n (%)					0.0073
Female	203 (89)	303 (83)	240 (92)	337 (87)	
Male	25 (11)	61 (17)	20 (8)	52 (13)	
Race, n (%)					< 0.0001
Caucasian	209 (92)	308 (85)	192 (74)	225 (61)	
Black	11 (5)	26 (7)	23 (9)	47 (13)	
Chinese	2 (1)	22 (6)	25 (10)	52 (14)	
Other	6 (3)	8 (2)	20 (8)	46 (12)	
Mean age at presentation, yrs (SD)	36.3 (13.2)	36.2 (14.7)	36.8 (12.7)	33.9 (13.0)	0.03
Mean disease duration at presentation, yrs (SD)	3.7 (5.2)	3.1 (4.7)	3.3 (5.1)	4.8 (6.6)	0.0002
Mean SLEDAI-2K at presentation (SD)	11.7 (9.2)	10.7 (8.6)	8.6 (7.3)	9.6 (7.4)	0.0001
Steroid used at presentation, n (%)	160 (70)	197 (54)	156 (60)	247 (63)	0.0009
Immunosuppression used at presentation, n (%)	33 (14)	36 (10)	40 (15)	119 (31)	< 0.0001
Antimalarials used at presentation, n (%)	34 (15)	89 (24)	99 (38)	178 (46)	< 0.0001
Mean SDI at presentation (SD)	0.4218 (0.9136)	0.2840 (0.7627)	0.3011 (0.8918)	0.2400 (0.8204)	0.2184

* Analysis of variance (continuous variables) and chi-squared tests (frequencies) were performed to assess statistical significance at the 5% level.

and Chinese entering the clinic over time. Younger mean age and longer mean SLE duration at presentation for Cohort 4 were observed. This was likely because patients released from the Hospital for Sick Children Lupus Clinic were referred to the adult University of Toronto Lupus Clinic only in the past 9 years. There was some evidence that the baseline levels of disease activity (mean SLEDAI-2K at presentation) in the first 2 entry cohorts were significantly higher than in the later 2 entry cohorts. Steroid use at presentation appeared to decrease slightly from Cohort 1. Immunosuppressive drug usage at presentation increased dramatically in Cohort 4 compared to the 3 earlier cohorts. Further, antimalarial usage at presentation increased continually across the 4 cohorts from the earliest to the latest. There was no evidence of any differences in level of damage at presentation among the 4 cohorts ($p = 0.218$).

Excess mortality. Over the 36-year period of the study, 211 deaths occurred, 171 in women and 40 in men. The total number of person-years of followup was 11,391. The overall SMR over the period 1970–2005, under the assumption that patients lost to followup were censored at last visit, was estimated to be 4.53 (95% CI 3.96, 5.19). The sex-specific SMR were 3.96 for men (95% CI 2.90, 5.40) and 4.69 for women (95% CI 4.04, 5.45). The estimated life-years lost by this cohort overall were 14.2 years (95% CI 12.69, 15.76), 13.24 years for men (95% CI 10.4, 15.98) and 14.38 years for women (95% CI 13.01, 15.73). Under the alternative assumption that patients lost to followup were alive at the end of 2005, the SMR were 2.30 (95% CI 2.01, 2.63) overall: for men 2.27 (95% CI 1.67, 3.10) and for women 2.30 (95% CI 1.98, 2.67).

Figure 1 presents the 10-year rolling average SMR; a clear decline with calendar time is present overall and for women. The overall SMR in the first and last "decades" were 12.60 (95% CI 9.13, 17.39) and 3.46 (95% CI 2.71, 4.40), respectively.

Table 2 presents SMR stratified by the entry cohort (1 to 4) and calendar period (A to D). While the confidence intervals are wide, there is evidence of a calendar period effect (periods A to D; $p < 0.0001$), with no evidence to suggest an overall cohort effect (cohorts 1 to 4; $p = 0.586$). In particular, there is a strong indication ($p = 0.0001$) when comparing the SMR along the principal diagonal (corresponding to the first 9 years within the clinic for different cohorts) that the rates have declined, from 13.84 to 3.81, from the early years of the clinic to the present.

Other outcomes. Tables 3 and 4 summarize the cohort by calendar results for the other major SLE related outcomes (CAD, AMS, SDI, steroid use, and osteonecrosis). There are clear differences among cohort-calendar period cells in each of the tables. Overall statistical tests for any variation across cells are highly statistically significant ($p < 0.0001$). Patterns in these outcomes are as follows.

Adjusted mean SLEDAI. Disease activity, as measured by AMS, decreased with followup time and for comparable followup time (Table 3).

SLICC Damage Index. The damage measured by SDI

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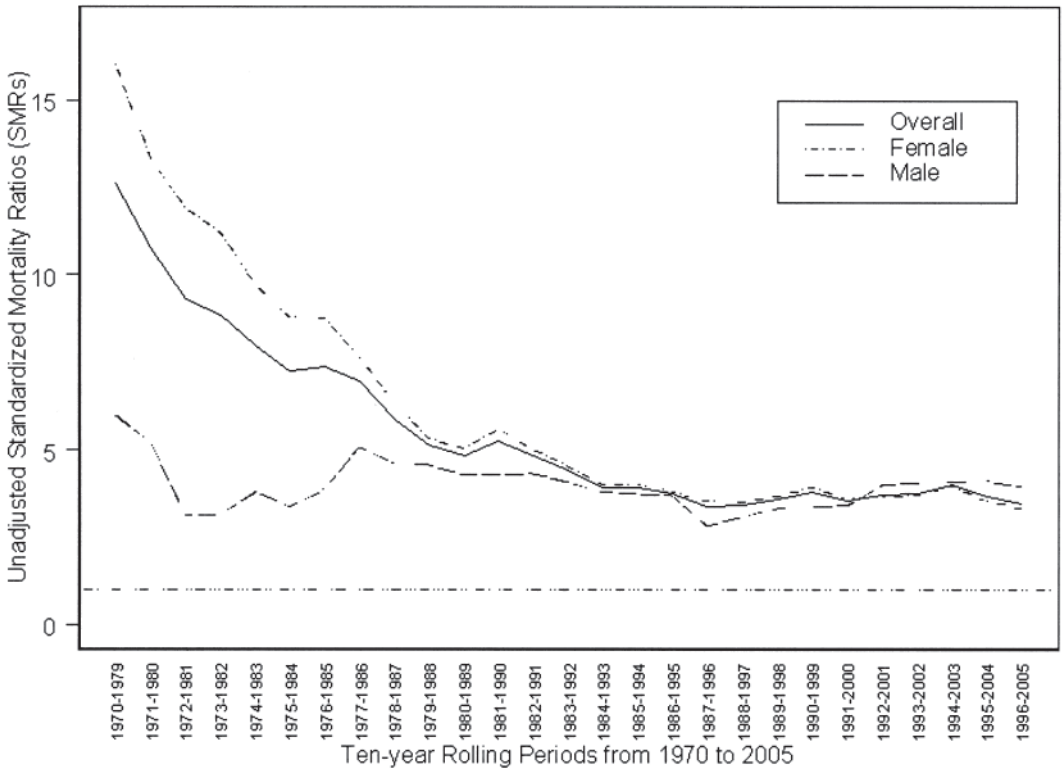

Figure 1. Unadjusted rolling 10-year standardized mortality ratios for the period 1970 to 2005.

Table 2. SMR (bold type) by entry cohort and calendar period, with 95% confidence intervals and number of patients (number of deaths) in each cell.

	Followup (Calendar) Period			
	A	B	C	D
Cohort	1970–1978	1979–1987	1988–1996	1997–2005
1 (1970–1978)	**13.84**	**4.86**	**3.07**	**3.23**
	9.78–19.56	3.31–7.13	1.93–4.87	1.98–5.28
	220 (32)	168 (26)	119 (18)	82 (16)
2 (1979–1987)		**6.45**	**3.54**	**3.92**
		4.51–9.22	2.50–5.01	2.53–6.08
		351 (30)	277 (32)	155 (20)
3 (1988–1996)			**4.24**	**3.93**
			2.28–7.88	2.47–6.23
			255 (10)	192 (18)
4 (1997–2005)				**3.81**
				1.98–7.32
				383 (9)

increased with followup time, as expected. It decreased with later entry cohort within each calendar period and remained relatively unchanged across cohorts for the equivalent length of followup in the clinic (Table 3).

Steroid use. No obvious patterns were observed in the prevalence of use of corticosteroids (Table 3).

Coronary artery disease and osteonecrosis (Table 4). There was an increasing trend in the prevalences with time in clinic and a decline in the prevalences with later entry cohort within calendar period (Table 3).

Factors affecting mortality. The above results for mortality and the other SLE related outcomes clearly demonstrate evidence of variations with cohort and calendar period. In particular, they illustrate the need to adjust for the effects of SLE related outcomes when investigating mortality.

To investigate mortality further and to attempt to assign effects seen in Table 2 to particular time scales, we fit a Cox regression model including sex, race, age at diagnosis, cohort, period, and the interaction between cohort and period. We found that the interaction effect was not statistically significant ($p = 0.397$). Dropping the interaction effect, we found a statistically significant period effect ($p < 0.0001$), with evidence of a statistically significant downward linear trend ($p = 0.0001$). The cohort effect did not attain statistical significance ($p = 0.657$).

The results from an initial screening of the SLE disease related outcomes showed that all except for osteonecrosis were associated with mortality (results not shown). Thus all of the outcomes except osteonecrosis were considered for the multivariate Cox regression model.

Table 5 presents results for the multivariate Cox regression model of the mortality risk associated with other disease related outcomes adjusting for sex, race, age at diagnosis, cohort, and period. There were statistically significant positive (detrimental) effects of disease related variables such as CAD, AMS, SDI, and use of immunosuppressive drugs, and significant negative (protective) effect for anti-

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Table 3. SLE related factors (95% CI) by entry cohort and calendar period.

Cohort	Followup (Calendar) Period A 1970–1978	B 1979–1987	C 1988–1996	D 1997–2005
Average AMS*				
1 (1970–1978)	8.45 (7.74, 9.17)	6.06 (5.42, 6.71)	4.07 (3.59, 4.56)	3.78 (3.07, 4.49)
2 (1979–1987)		7.1 (6.54, 7.66)	4.5 (4.14, 4.87)	4.19 (3.59, 4.79)
3 (1988–1996)			5.21 (4.79, 5.64)	4.5 (4.07, 5.01)
4 (1997–2005)				5.99 (5.57, 6.40)
Average level of damage**				
1 (1970–1978)	0.80 (0.55, 1.06)	1.19 (0.86, 1.53)	1.82 (1.47, 2.17)	3.09 (2.53, 3.64)
2 (1979–1987)		0.47 (0.33, 0.60)	1.19 (0.98, 1.39)	2.22 (1.83, 2.61)
3 (1988–1996)			0.83 (0.63, 1.03)	1.72 (1.41, 2.03)
4 (1997–2005)				0.86 (0.71–1.01)
Steroid prevalence (within followup period), %				
1 (1970–1978)	72.6 (66.6, 78.5)	67.2 (60.5, 74.0)	47.5 (39.8, 55.2)	68.5 (61.0, 76.0)
2 (1979–1987)		63.0 (58.0, 68.0)	58.2 (52.8, 63.6)	60.1 (54.5, 65.6)
3 (1988–1996)			67.2 (61.4, 72.9)	71.6 (65.9, 77.3)
4 (1997–2005)				77.9 (73.8, 82.0)

* AMS: adjusted mean SLEDAI; ** SLEDAI Damage Index.

Table 4. Coronary artery disease and osteonecrosis by entry cohort and calendar period (95% CI). Data are percentages.

Coronary artery disease prevalence (ever)				
1 (1970–1978)	7.7 (4.1, 11.4)	10.1 (5.4, 14.7)	21.1 (13.4, 28.8)	27.6 (17.6, 37.7)
2 (1979–1987)		6.1 (3.6, 8.6)	8.3 (5.0, 11.6)	19.2 (12.9, 25.5)
3 (1988–1996)			3.6 (1.3, 5.9)	11.4 (6.8, 15.9)
4 (1997–2005)				5.0 (2.8, 7.1)
Osteonecrosis prevalence (ever)				
1 (1970–1978)	12.1 (7.6, 16.5)	17.6 (11.7, 23.5)	27.5 (19.1, 35.9)	25.0 (15.3, 34.7)
2 (1979–1987)		4.9 (2.6, 7.2)	13.9 (9.8, 18.1)	20.5 (14.1, 27.0)
3 (1988–1996)			10.4 (6.6, 14.1)	15.7 (10.4, 20.9)
4 (1997–2005)				9.4 (6.5, 12.3)

malarials on mortality. The effect of calendar period on mortality remained (p = 0.009, with p = 0.001 for test for linear trend). The results were qualitatively the same (in interpretation and conclusions) when SLEDAI-2K replaced AMS in the Cox model.

DISCUSSION

Our findings indicate that the mortality risk in patients with lupus has decreased progressively over 36 years. There was a significant calendar-period effect in the SMR results and in the Cox model, even after adjusting for disease related

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Table 5. Multivariate Cox regression model, using AMS instead of SLEDAI-2K.

Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI	p
Sex				
Male vs female	1.76	1.15	2.69	0.009
Race				0.059
Black vs Caucasian	1.52	0.87	2.69	
Chinese vs Caucasian	1.96	0.97	3.94	
Other vs Caucasian	1.95	0.92	4.15	
Age at diagnosis	1.01	0.98	1.03	0.508
Entry cohort				0.544
1979–1987 vs 1970–1978	1.30	0.83	2.03	
1988–1996 vs 1970–1978	0.99	0.50	1.96	
1997–2005 vs 1970–1978	0.97	0.34	2.76	
Calendar period				0.009
1979–1987 vs 1970–1978	0.77	0.44	1.34	
1988–1996 vs 1970–1978	0.43	0.22	0.82	
1997–2005 vs 1970–1978	0.27	0.12	0.61	
CAD event ever				
Yes vs no	1.52	1.02	2.26	0.041
AMS	1.15	1.11	1.20	< 0.0001
SDI	1.24	1.14	1.35	< 0.0001
Immunosuppressives ever used				
Yes vs no	1.71	1.17	2.51	0.006
Steroids at assessment				
Yes vs no	1.12	0.72	1.75	0.624
Antimalarials at assessment				
Yes vs no	0.58	0.39	0.87	0.009

CAD: coronary artery disease; AMS: adjusted mean SLEDAI; SDI: SLEDAI Damage Index.

outcomes, medication usage, and patient characteristics. The SMR was 12.60 in the 1970s and decreased to 3.46 in the last decade. Improving survival has been reported in SLE over the past several decades and has been summarized until 2005[1,4]. Subsequent reports confirm this improved survival in adult and childhood onset SLE[2,27,28]. While there is an impressive reduction in mortality, there is still a significant estimated mortality risk of over 3 times that of the general population. A similar SMR (3.02) was recently reported for Korean patients with SLE[29]. In our study this resulted in an estimated 14.2 years of life-years lost.

These SMR are based on censoring at last visit. Our sensitivity analysis showed that even if we consider all patients not seen to be alive at the end of 2005, there is still an overall excess mortality risk of 2.3.

Our data show that disease activity decreased over the calendar period and as well decreased over cohort entry time for comparable followup periods. This suggests that either the disease has become less aggressive or that it is being treated more successfully. Although the same medications have been used for the past 36 years, there has been an increase in the use of both immunosuppressive agents and antimalarials, as shown, and perhaps a more judicious use of corticosteroids. Although there has been an increase in non-Caucasian patients in our cohort in the past decade or so, the majority of our patients are Caucasian. Moreover, although there has been an increase in non-Caucasian patients, the last cohort still showed improved survival. This may be because in Canada all patients have access to medical care. This finding will have to be tested in cohorts that have a significantly different ethnic composition, such as the Hopkins Cohort and the LUMINA cohort, which have fewer Caucasian and more African American and Hispanic patients[30,31].

As patients with SLE live longer, cumulative damage has become an important outcome. The LUMINA and Danish studies showed that deceased patients experienced more damage accrual from the outset of their disease compared to survivors[32,33]. Damage accumulation has been described in 70% of 210 Mexican patients after 10 years of disease[8]. A recent multicenter cohort of SLE patients revealed evidence of damage within a mean of 3.8 years after onset[34]. Patients followed for at least 15 years accumulated damage over time, and corticosteroids were identified as important contributors to damage[35]. Older patients are at higher risk of accumulating damage than younger patients with SLE[36]. In our study damage accumulation was comparable in each of the cohorts for the equivalent length of followup. However, when patients were followed throughout their course, cumulative damage increased progressively as expected, reaching its highest level of 3.09 in the first cohort followed for the longest period.

CAD is a major morbidity among patients with SLE[9]. Clinical CAD occurs in 6%–10% of SLE patients[37-39]. In our study, the prevalence of CAD decreased with later cohorts for corresponding calendar period, and increased with followup period. Therefore, despite more judicious use of medications and better management of risk factors for CAD, when patients are followed throughout their course, the prevalence of CAD increases dramatically, reaching 27.6% in the first cohort after 3 decades[40].

In a Cox regression model to assess the effects on mortality of these outcomes and therapy factors while controlling for sex, race, age at diagnosis, cohort, and period, we found significant detrimental effects for male sex, CAD, AMS, SDI, and use of immunosuppressive drugs. There were significant protective effects for antimalarials and the effect of calendar period. The protective effect of antimalarials has recently been reported by others[41,42]. Therefore it is possible that more prevalent use of antimalarials in later calendar periods may have had a beneficial effect, perhaps offsetting some of the deleterious effects of the disease activity and immunosuppressive medications.

Thus, our study demonstrates improved survival in patients with SLE over a 36-year period. Disease related variables included in the model are important factors for mortality in this SLE cohort, but could not completely explain the trend of improved survival over calendar period observed.

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