Incidence and Mortality of Systemic Lupus Erythematosus in a Southern Chinese Population, 2000-2006

CHI CHIU MOK, CHI HUNG TO, LING YIN HO, and KA LUNG YU

ABSTRACT. ***Objective.*** To study the annual incidence and standardized mortality ratio (SMR) of a longitudinal cohort of Chinese patients with systemic lupus erythematosus (SLE).

Methods. Annual numbers of new cases and deaths in a longitudinal cohort of patients with SLE between 2000 and 2006 retrieved from a database were compared with regional population and death rates expected from the annual death statistics maintained by our hospital and population census data.

Results. Our cohort of SLE had grown from 272 to 442 patients from 2000 to 2006. The annual incidence of SLE showed mild fluctuation (mean incidence 3.1/100,000 population; 5.4/100,000 in women). The annual death rate and SMR in year 2000 were 25.7/1000 and 7.88 (range 3.7–16.7; $p < 0.001$), respectively, compared to the general population. A trend of reduction in annual death rates and SMR was observed, the annual death rate and SMR in year 2006 being 6.8/1000 and 2.17 (range 0.7–6.7; $p = 0.34$). The SMR was higher in men than women and had a less obvious trend of improvement. A negative correlation of SMR with age was observed. The SMR of SLE patients aged above 60 years was not significantly higher than expected from population statistics. There was also a trend of fewer deaths due to infection over time.

Conclusion. In this single-center study, the incidence of SLE remained static. The SMR of SLE was significantly increased in younger patients, indicating a greater effect of the disease on younger individuals. There was a trend of improvement in SMR for SLE in recent years, probably as a result of fewer infectious complications. (First Release Aug 1 2008; J Rheumatol 2008;35:1978–82)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS | CHINESE | SURVIVAL
INCIDENCE | MORBIDITY | DAMAGE

The survival of systemic lupus erythematosus (SLE) has improved in the past few decades. The 5-year survival of patients with SLE was below 50% in the 1960s, but it is now more than 90% in most series reported in the 1990s[1]. This is attributed to the increased awareness of the condition and hence early diagnosis and treatment, the availability of newer immunosuppressive agents with less toxicity, and the improvement in supportive care for disease and treatment related complications such as uremia, infection, and thromboembolism. However, survival rates of SLE patients are poorer in less developed areas[2,3], and the improvement in survival seems to have plateaued in the last decade[1], indicating that efforts must be made to improve the outcome of the disease further.

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Hong Kong is a small city in the southern part of China. It had been under British rule until 1997 when it was handed back to China; the economic, legal, and social system of the region remains unchanged. SLE is fairly common in Hong Kong Chinese, with an estimated prevalence of 0.06% (0.1% in women)[4]. A prospective study conducted in an academic hospital in Hong Kong reported a 5-year cumulative survival of SLE to be 93%[5]. As referral bias is prone to occur in academic units, another cohort study performed in a nonacademic hospital showed a similar survival rate[6]. In that study, the cumulative 5, 10, and 15-year survival rates were 92%, 83%, and 80%, respectively. Infection remained the main cause of death, followed by cardiovascular and cerebrovascular complications. However, in these 2 studies, comparison of the mortality rates of SLE with those of the general population was not performed.

We investigated the incidence and trend for mortality of our cohort of SLE patients from year 2000 and 2006 by calculating the standardized mortality ratio (SMR) from the cohort and death registries, as well as general population statistics. The relationship between age and SMR in SLE patients was also evaluated.

MATERIALS AND METHODS

Tuen Mun Hospital is a large regional public hospital in the western New Territories of Hong Kong that serves a population of 1 million. Every citizen in Hong Kong receives the heavily government subsidized public healthcare service without purchasing mandatory medical insurance. As there are no private SLE specialists in this region of the New Territories, SLE patients followed in our hospital are either referred from primary care physicians or diagnosed by doctors in the Department of Medicine and Department of Pediatrics. Before 1999, a rheumatology service was not available, and SLE patients were followed by the nephrologists, hematologists, and pediatricians.

In 1999, rheumatology and lupus clinics were set up in the Department of Medicine, and SLE patients were directed from the other clinics; a few SLE patients remained under the care of other medical specialists. A database for SLE patients was also established in early 1999, with the aim of studying disease manifestations and treatment related complications. The database is maintained by rheumatologists in the Department of Medicine and includes data from pediatricians and all other physicians who look after patients with SLE. Patients with SLE must fulfill at least 4 of the American College of Rheumatology (ACR) classification criteria for SLE[7].

We retrieved data on the annual number of newly diagnosed or referred SLE patients and SLE deaths between 2000 and 2006 from our cohort database. The annual incidence of SLE was estimated by dividing the number of new cases of SLE every year by the population residing in the catchment area of our hospital; this information was obtained from the government population census from years 1996, 2001, and 2006, with the assumption of linear growth of population.

The annual mortality rate of SLE patients was calculated by dividing the number of SLE deaths by the size of our SLE cohort each year. The standardized mortality ratio (SMR) of SLE was the ratio of the observed SLE mortality rate to the expected mortality rate of the population of the catchment area, calculated from information from the death registry of our hospital and the population census data. As there are no other public or private hospitals in our region, the death registry of our hospital accurately represents the mortality rate of the regional population.

In addition to the trend of annual incidence and SMR of SLE, we also looked at the age-specific SMR and causes of death in our patients.

RESULTS

Demographic and clinical characteristics of SLE patients. In year 2000, there were 272 patients in our SLE cohort. The number of patients had increased to 442 in year 2006. Table 1 shows demographic and cumulative clinical features of these 442 patients up to December 2006. The mean age at SLE onset was 32.3 ± 14 years and the female to male ratio was 9.8:1. The mean duration of SLE was 8.5 ± 6.1 years. Two hundred fifty-four (57%) patients had disease duration > 5 years.

Incidence of SLE. Figure 1 shows the annual incidence of SLE in our hospital. The overall incidence was 3.1/100,000 population (4.9/100,000 in women) in year 2000 and 2.8/100,000 population (5.1/100,000 in women) in year 2006. The annual incidence figures showed only mild fluctuation, and the mean incidence of SLE within the study period was 3.1/100,000 (5.4/100,000 in women).

Annual mortality rate and SMR. The annual mortality rates and SMR of SLE patients are shown in Table 2. There was a trend of reduction in annual mortality rate and SMR from year 2000 to 2006. The annual mortality rate dropped from 25.7 to 6.79 per 1000 persons from 2000 to 2006. The SMR of our SLE patients was 7.88 in year 2000, significantly higher than that of the general population. The SMR dropped to 2.17 in year 2006, and this figure was not significantly different from that of the general population. The SMR of male SLE patients were higher than those of female patients, but the trend of improvement was less obvious, probably because of the small number of male patients in the cohort. Figure 2 shows the trend in SMR from 2000 to 2006 (error bars show 95% confidence intervals).

Table 1. Demographic and clinical characteristics of SLE patients (n = 442).

Characteristic	Number (%), mean ± SD
Age at SLE onset, yrs	32.3 ± 14.0
Women	401 (91)
Duration of SLE, yrs	8.5 ± 6.1
Cumulative clinical features	
Arthritis	341 (77)
Malar rash	241 (55)
Photosensitivity	133 (30)
Discoid rash	41 (9)
Oral ulcers	76 (17)
Hemolytic anemia	107 (24)
Leukopenia (< 4.0×10^9/l)	199 (45)
Thrombocytopenia (< 100×10^9/l)	124 (28)
Lymphopenia (< 1.5×10^9/l)	352 (80)
Lymphadenopathy	76 (17)
Seizure	37 (8)
Psychosis	22 (5)
Renal disease	250 (57)
Serositis	86 (19)
Cutaneous vasculitis	95 (21)
Gastrointestinal disease	28 (6)
Autoantibodies	
dsDNA	312 (71)
Sm	68 (15)
Ro	239 (54)
La	60 (14)
U1RNP	111 (25)
Phospholipid	126 (29)

Table 3 shows the trend of annual mortality rate and SMR with regard to duration of SLE. A reduction in annual mortality rate and SMR was observed in the groups of patients with SLE duration greater and less than 5 years. However, the trend of improvement was greater in those with disease duration of more than 5 years.

Causes of death. Table 4 shows the causes of death of our SLE patients. There were 30 deaths from year 2000 to 2006. The mean SLE duration of these deceased patients was 5.1 ± 5.9 years (19 patients had disease duration ≤ 5 years and 11 patients had duration > 5 years). The mean age of the patients at the time of death was 43.8 ± 17.4 years. The common causes of death were infection (60%), followed by cerebrovascular accident (10%), and uncontrolled renal disease (7%). Death was sudden in 3 patients, and the exact causes were unknown, even with an autopsy examination in

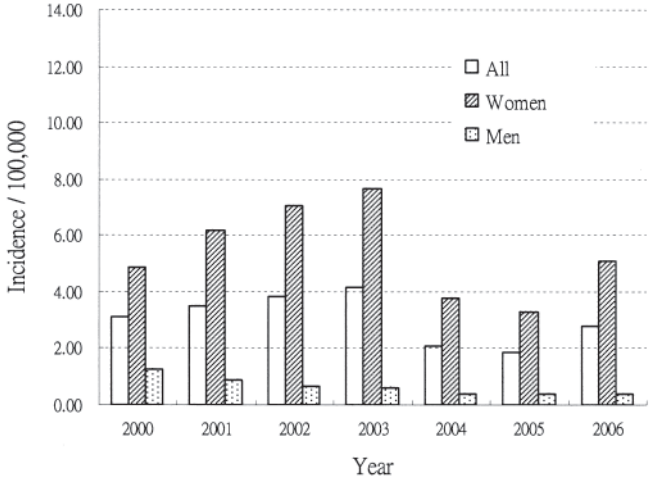

Figure 1. Trend of incidence of SLE from 2000 to 2006.

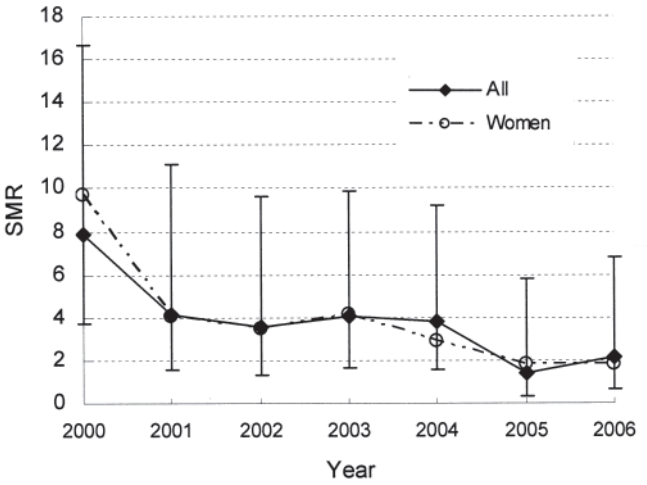

Figure 2. Trend of standardized mortality ratio (SMR) between year 2000 and 2006.

one patient. Two patients who died of cerebrovascular accident fulfilled the criteria for secondary antiphospholipid antibody syndrome. Rates of death due to infection and vascular events from year 2000 to 2006 are shown in Figure 3. There appears to be a trend of reduction in deaths caused by infections within the study period. Because of the small number of vascular deaths, a definite trend is not apparent. Figure 4 shows the trend of annual mortality rates due to infections with regard to SLE duration. A reduction in mortality rate due to infections is predominantly observed in those patients with disease duration ≥ 5 years.

Age-specific SMR and mortality rates. Table 5 shows the SMR and mortality rates of SLE patients according to age ranges. The SMR was highest in patients under 30 years of age [54.2 (range 23.7–124)] and the figures decreased with increasing age. In patients older than 60 years of age, the SMR were no longer significantly higher than those of the age-matched general population. This observation was similar in both female and male patients. The actual death rates of SLE patients increased with age, with the highest figure in patients above age 70 years (80/1000).

DISCUSSION

This was a single-center study of recent trends in the incidence and mortality of patients with SLE in a southern Chinese population. As our hospital is situated in the rural area of Hong Kong and no other hospitals in the area provide specialist service, our figures accurately reflect the situation in the 1 million population served by our hospital (one-seventh of the total population in Hong Kong). Mild underestimation of the incidence figures is bound to occur as a minority of patients might still travel to other parts of the city for medical consultations. However, this effect is likely to be minimal because of the very strict rule of regionalization of service laid down by the Hospital Authority of Hong Kong.

We have shown that the annual incidence of SLE is between 1.9 to 4.2 per 100,000 population within the study period. As expected, the incidence is higher in women, with figures ranging from 3.3 to 7.7 per 100,000 women. The incidence figures are similar to those reported for Swedish and North American Indian SLE patients[8,9], but direct comparison is confounded by factors such as referral pattern, method of data collection, function of the study center, year of study, and whether the point incidence of a particular year or over a certain period of time was reported.

The cumulative mortality risk of our patients has been

Table 2. Trend in standardized mortality ratio (SMR) of our cohort of SLE patients.

Year	Cohort Size	Expected Death Rate per 1000	Actual Death Rate per 1000	SMR (95% CI)	p*	SMR in Female Patients	SMR in Male Patients
2000	272	3.27	25.7	7.88 (3.72–16.7)	< 0.001	9.68	—
2001	305	3.18	13.1	4.12 (1.54–11.1)	0.01	4.04	9.70
2002	342	3.26	11.7	3.59 (1.34–9.62)	0.003	3.44	8.66
2003	381	3.21	13.1	4.08 (1.69–9.87)	0.003	4.12	8.09
2004	399	3.29	12.5	3.81 (1.57–9.20)	0.006	2.92	14.7
2005	416	3.32	4.81	1.45 (0.36–5.81)	0.92	1.87	—
2006	442	3.12	6.79	2.17 (0.70–6.77)	0.34	1.84	6.89

* Between SLE cohort and general population.

Table 3. Trend in standardized mortality ratio (SMR) and annual mortality rate for SLE duration.

	2000	2001	2002	2003	2004	2005	2006
SMR							
SLE duration ≤ 5 yrs	7.25	3.40	4.62	7.27	4.49	1.61	3.41
SLE duration > 5 yrs	8.92	5.24	2.14	—	3.10	1.31	1.26
Annual mortality rate (per 1000)							
SLE duration ≤ 5 yrs	23.67	10.81	15.08	23.36	14.78	5.35	10.64
SLE duration > 5 yrs	29.13	16.67	6.99	0.0	10.20	4.37	3.94

Table 4. Cause of death of our SLE patients between 2000 and 2006.

Cause of Death	Number (%)
Infection	18 (60)
Hemorrhagic stroke	2 (7)
Ischemic stroke	1 (3)
Myocardial infarction	1 (3)
Pulmonary hypertension	1 (3)
Malignancy	1 (3)
Suicide	1 (3)
Renal failure	2 (7)
Sudden death, unknown cause	3 (10)
Total	30 (100)

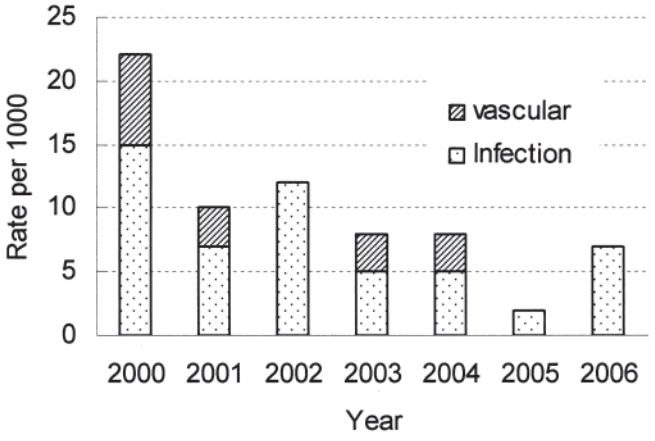

Figure 3. Infective and vascular causes of mortality between year 2000 and 2006.

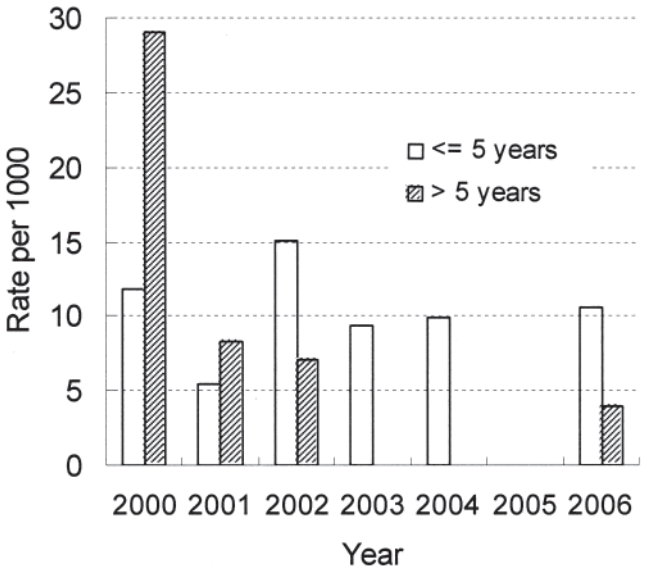

Figure 4. Annual mortality rate due to infections with regard to SLE duration.

reported in a separate study[6]; the 5, 10, and 15-year survival rates were 92%, 83%, and 80%, respectively. However, data on the mortality rate compared to the general population and its yearly trend were unavailable. In the current study, we report a significantly increased SMR of our SLE patients compared to the general population. The overall mean SMR over the 7-year period between 2000 and 2006 was 3.87. This is in agreement with figures reported in an international collaboration cohort of SLE patients that consisted of predominantly Caucasians[10] and an earlier study by Urowitz, *et al*[11].

In addition, we observed a trend of improvement in the SMR of our patients from year 2000 to 2006. This can be attributed to many factors that include the availability of rheumatology service and lupus clinics led by rheumatologists since 1999 in our hospital, standardization of treatment protocols, better communication among physicians, more judicious use of immunosuppressive regimens, and the availability of more potent antibiotics and supportive facilities. The trend of reduction in SMR was more marked in patients with disease duration > 5 years, and appeared to be related to a reduction in the rate of infectious complications. This could be the result of more judicious use of corticosteroids in recent years, the shift from cyclophosphamide to newer immunosuppressive agents such as mycophenolate mofetil and the calcineurin inhibitors for treatment of major lupus manifestations, and the increased awareness of infection as a cause of any new symptoms in our patients.

With improvement in survival due to a reduction in the frequency of severe infectious complications, particularly in patients with longer disease duration, we expect cardiovascular and cerebrovascular diseases will become the major causes of patient mortality on longer followup. Although prophylactic measures against atherosclerosis, such as more aggressive control of blood pressure, use of statins to lower

Table 5. Mean age-specific standardized mortality ratios (SMR) and death rates.

Age, yrs	SMR (95% CI)						Death rate per 1000
	Women	p*	Men	p*	All patients	p*	
≤ 30	59.4 (23.9–147)	< 0.001	78.1 (10.1–603)	< 0.001	54.2 (23.7–124)	< 0.001	7.23
31–40	42.8 (18.4–99.3)	< 0.001	54.2 (6.51–452)	< 0.001	34.8 (16.0–75.6)	< 0.001	11.6
41–50	10.5 (4.24–26.0)	< 0.001	27.0 (5.73–127)	< 0.001	10.1 (4.66–21.7)	< 0.001	10.7
51–60	5.70 (1.76–18.4)	0.009	6.22 (0.75–51.7)	0.11	4.18 (1.50–11.6)	0.01	12.1
61–70	3.57 (0.80–16.0)	0.26	—	0.75	2.10 (0.47–9.32)	0.63	22.7
≥ 71	2.03 (0.51–8.13)	0.55	3.83 (0.24–61.2)	0.88	2.26 (0.66–7.70)	0.34	80.0
All	3.84 (2.54–5.82)	< 0.001	7.10 (2.98–17.0)	< 0.001	3.67 (2.52–5.31)	< 0.001	11.7

lipid levels, education on exercise, smoking cessation and weight reduction, and the use of prophylactic aspirin in high-risk patients, have been carried out in our unit in recent years, their effect on late mortality due to vascular event is not obvious yet. A longer period of observation is needed to see if these measures are effective in reducing vascular events and hence late mortality in our patients.

An additional observation from our study is that there was an inverse relationship between SMR and age in our cohort of patients. The SMR was particularly high in patients younger than age 30 years, and it showed a gradual reduction with increasing age. Although the mean annual mortality rates of older patients were higher than those of younger patients, the SMR of patients older than 60 were no longer significantly higher than those of the general population. This reflects that the higher mortality rate of older SLE patients is probably related to their age per se rather than the disease itself. This is consistent with recent data from a large international cohort in which younger age was found to be a risk factor for higher SMR[10], and emphasizes the greater influence of the disease on younger individuals.

This is the first study in southern China on the incidence and standardized mortality ratio in patients with SLE. Our study shows that the incidence of SLE remained static in the past few years. SMR of SLE was significantly increased in younger patients, and there was a trend of improvement in SMR in recent years, probably as a result of fewer infectious complications related to the more judicious use and choice of immunosuppressive agents in our unit and better supportive care for these complications.

REFERENCES

1. Petri M. Epidemiology of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2002;16:847-58.
2. Malaviya AN, Chandrasekaran AN, Kumar A, Shamar PN. Systemic lupus erythematosus in India. Lupus 1997;6:690-700.
3. Wadee S, Tikly M, Hopley M. Causes and predictors of death in South Africans with systemic lupus erythematosus. Rheumatology Oxford 2007;46:1487-91.
4. Mok CC, Lau CS. Lupus in Hong Kong Chinese. Lupus 2003;12:717-22.
5. Mok CC, Lee KW, Ho CTK, Lau CS, Wong RWS. A prospective study of survival and prognostic indicators of systemic lupus erythematosus in a southern Chinese population. Rheumatology Oxford 2000;39:399-406.
6. Mok CC, Mak A, Chu WP, To CH, Wong SN. Long term survival of southern Chinese patients with systemic lupus erythematosus: a prospective study of all age groups. Medicine Baltimore 2005;84:218-24.
7. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
8. Stahl-Hallengren C, Jonsen A, Nived O, Sturfelt G. Incidence studies of systemic lupus erythematosus in southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis. J Rheumatol 2000;27:685-91.
9. Peschken CA, Esdaile JM. Systemic lupus erythematosus in North American Indians: a population based study. J Rheumatol 2000;27:1884-91.
10. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54:2550-7.
11. Urowitz MB, Gladman DD, Abu-Shakra M, Farewell VT. Mortality studies in systemic lupus erythematosus. Results from a single center. III. Improved survival over 24 years. J Rheumatol 1997;24:1061-5.