Effect of Renal Disease on the Standardized Mortality Ratio and Life Expectancy of Patients With Systemic Lupus Erythematosus

C. C. Mok,1 Raymond C. L. Kwok,2 and Paul S. F. Yip2

Objective. To study the effect of renal disease on the standardized mortality ratio (SMR) and life expectancy of patients with systemic lupus erythematosus (SLE).

Methods. Patients whose diagnosis met ≥4 American College of Rheumatology criteria for SLE were longitudinally followed up from 1995 to 2011. The cumulative survival rate, SMR, and life expectancy were calculated, and the effect of renal involvement, histologic class of lupus nephritis, renal damage, and end-stage renal disease (ESRD) on these parameters was evaluated.

Results. Of the 694 SLE patients studied, 368 (53%) had renal disease, and the distribution of histologic classes (among 285 patients) was class I (1%), class II (6%), class III (19%), class IV (47%), class III/IV + class V (10%), and class V (16%). Renal damage was present in 79 patients (11%), and 24 (3%) developed ESRD. The age- and sex-adjusted hazard ratios (HRs) of mortality in SLE patients with renal disease, those with renal damage, and those with ESRD, as compared to those without, were 2.23 (95% confidence interval [95% CI] 1.29–3.85), 3.59 (95% CI 2.20–5.87), and 9.20 (95% CI 4.92–17.2), respectively. Proliferative lupus nephritis (adjusted HR 2.28, 95% CI 1.22–4.24), but not the pure membranous type (adjusted HR 1.09, 95% CI 0.38–3.14), was associated with a significant increase in mortality. The age- and sex-adjusted SMRs of SLE patients without renal involvement, those with lupus nephritis, those with proliferative nephritis, those with pure membranous nephritis, those with renal damage, and those with ESRD were 4.8 (95% CI 2.8–7.5), 9.0 (95% CI 6.7–11.9), 9.8 (95% CI 6.5–14.1), 6.1 (95% CI 2.0–14.1), 14.0 (95% CI 9.1–20.5), and 63.1 (95% CI 33.6–108.0), respectively. The life expectancy of SLE patients with renal disease and those with renal damage was reduced by 15.1 years and 23.7 years, respectively, compared to the general population.

Conclusion. The presence of renal disease, in particular proliferative nephritis causing renal insufficiency, significantly reduces the survival and life expectancy of SLE patients.

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease of unknown etiology. Renal disease is one of the most common and most serious manifestations of SLE and adversely affects its prognosis, in terms of patient and renal survival rates as well as quality of life and work disability (1). Lupus renal disease appears to be more prevalent in certain ethnic groups, such as Asians, African Americans, and Hispanics (2–6). Up to 60% of SLE patients in these ethnic groups develop renal disease of differing severity during the course of their illness.

The rates of renal survival (i.e., survival without dialysis) in patients with lupus nephritis in the 1990s ranged from 83% to 92% over 5 years of followup and from 74% to 84% over 10 years of followup (7–10). The risk of end-stage renal disease (ESRD) has been particularly high in patients with diffuse proliferative glomerulonephritis, with risk estimates ranging from 11% to 33% over 5 years of followup (2,7,8,10–13). The prognosis of lupus nephritis depends on a large number of demographic, racial, genetic, histopathologic, immunologic, and time-dependent factors (14). Renal disease that fails to remit with immunosuppressive therapies is a
major risk factor for subsequent deterioration of renal function and poor outcome (7,13,15). Recent studies have reiterated that lupus nephritis patients of African, Hispanic, or Asian ethnicity have generally experienced poorer outcomes (16–19). Other unfavorable prognostic factors for lupus nephritis include younger age, male sex, histologic cellular crescents, fibrinoid necrosis, subendothelial deposits, glomerular scarring, tubular atrophy and interstitial fibrosis, impaired renal function at presentation, persistent hypertension, hypocomplementemia, and low hematocrit level, as well as delay in treatment due to problems of access to health care and poor compliance (14).

In most previous studies on the mortality associated with SLE and lupus nephritis, either the absolute annual mortality rate or the cumulative risk of death over time has been reported (2,7–13,15,20,21). More recent studies have focused on the relative mortality of patients with lupus renal disease as compared to different reference groups (22–29). However, the effect of different histologic classes of lupus glomerulonephritis on the relative mortality of SLE, as compared to mortality rates in the general population, has been largely unreported. Moreover, data on the life expectancy of patients with lupus nephritis are not available in the literature. Therefore, the present study was carried out to evaluate the effect of renal disease, histologic class of lupus nephritis, renal damage, and renal failure on the standardized mortality ratio (SMR) and life expectancy in a longitudinal cohort of SLE patients from China.

PATIENTS AND METHODS

Study population and data collection. Between 1995 and 2011, patients who were newly diagnosed as having SLE in the outpatient clinics of Tuen Mun Hospital (Hong Kong, China) or newly diagnosed during hospitalization, as well as patients who were referred to us within 12 months of SLE diagnosis, were recruited into our longitudinal cohort database. Patients under the care of all specialists (rheumatologists, nephrologists, hematologists, pediatricians, and geriatricians) were included. All patients were ethnic Chinese and fulfilled ≥4 of the American College of Rheumatology (ACR) revised criteria for SLE (30). These patients were longitudinally followed up by the same group of physicians, with a usual interval of 12 weeks. More frequent clinic visits were arranged for those with active/unstable disease or complications.

The demographic and clinical characteristics of these patients were obtained and updated periodically. Lupus renal disease, with occurrence at any time during the course of SLE, was defined according to the criteria for renal involvement delineated in the ACR SLE classification criteria set (30), namely, presence of persistent proteinuria (urine protein concentration >0.5 gm/day on ≥2 occasions), urinary cellular casts (red cell, hemoglobin, granular, tubular, or mixed), or histologic evidence of lupus glomerulonephritis. Quantification of urine protein was performed in all patients at diagnosis, and was repeated when the urine dipstick test revealed positive findings of protein at any followup visit. The prevalence of renal disease in our cohort of patients, the distribution of histologic classes of lupus nephritis (according to the International Society of Nephrology/Renal Pathology Society criteria [31]), and the proportion of patients with renal damage and ESRD were evaluated in this study. The effect of renal disease, renal damage, and ESRD on the survival and life expectancy of the SLE patients was also examined.

Assessment of SLE renal damage. Damage related to SLE was measured using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (32), a validated instrument that measures irreversible organ damage unrelated to active inflammation in 12 organ systems. Patients in the cohort were assessed annually for the occurrence of new damage. Damage in the renal system was defined as one of the following features: 1) a glomerular filtration rate (GFR) of <50 ml/minute (assigned an SDI score of 1); 2) persistent nephrotic-range proteinuria (assigned an SDI score of 1); and 3) ESRD (assigned an SDI score of 3). Damage had to have been present for at least 6 consecutive months in order to be scored. The GFR was estimated using the Modification of Diet in Renal Disease formula for each patient, assessed at least once per year; more frequent estimation in patients with renal damage would be performed at the discretion of the attending physicians. ESRD was defined when the estimated GFR was <15 ml/minute (i.e., stage 5 chronic kidney disease) or when renal replacement therapy was required.

Calculation of the cumulative risk of mortality and SMR. The cumulative risk of mortality in SLE was calculated using Kaplan-Meier survival curve plots, in which time zero was the time when SLE was diagnosed. The effect of renal involvement, different histologic classes of lupus nephritis, renal damage, and ESRD (at any time during the disease course) on survival in SLE was evaluated using Cox proportional hazards models, with adjustment for age, sex, and use of various immunosuppressive drugs.

The indirect SMRs (adjusted for age and sex) (with exact 95% confidence intervals [95% CIs]) in the SLE patient groups, as compared to the general population, were determined by calculating the ratio of the observed mortality rate to the expected mortality rate within the same period of time, using the method described by Ulm (33) as follows:

$$\text{SMR} = \frac{O}{E}$$

95% CI = \left(\frac{\chi^2_{0.05,20}}{2E} \cdot \frac{\chi^2_{0.025,20+1}}{2E}\right)

where $O$ is the number of observed deaths in the study population, $E$ is the expected number of deaths, and $\chi^2_{a,k}$ is the value of chi-square distribution with level of significance $\alpha$ and degree of freedom $k$. Observed deaths referred to the actual number of deaths of SLE patients from 1995 to 2011. Expected deaths referred to the number of deaths expected from the population statistics within the same period of time, stratified by sex and the same ranges of age. The age- and sex-specific
mortality rates in the general population were obtained from the Census and Statistics Department of the Hong Kong Government, which utilizes the population census data in the years 1991, 1996, 2001, 2006, and 2011, with annual adjustment according to birth, death, and immigration/emigration status.

Life expectancy analysis. Estimation of the patients’ life expectancy was performed using standard single-decrement life-table analysis, as described by Preston et al (34), with inclusion of the observed mortality data from all SLE patients. Male and female patients were pooled in this calculation, due to the relatively small number of male patients. The age-specific death rates were estimated by calculating the total number of deaths divided by the number of person-years of exposure of the corresponding age groups over the period from 1991 to 2011, as follows:

$$m_x = \frac{d_x}{n_x^1 + n_x^{1991} + \cdots + n_x^{2011}}$$

where $d_x$ is the total number of observed deaths for age group $x$ and $n_x^k$ is the number of patients for age group $x$ in the year $k$. The life expectancy of subjects in the general population in the same time period was obtained from the Census and Statistics Department, and the average value was calculated and presented for comparison.

RESULTS

Clinical characteristics of the SLE cohort. In total, 694 SLE patients were studied (92% women). The mean ± SD age at onset of SLE was 32.9 ± 13.4 years (range 6–78 years). Renal disease, according to the ACR definition of renal involvement, was evident in 368 patients (53%) during the course of SLE. Among the patients with lupus renal disease, 285 (77%) had undergone renal biopsy at least once. The distribution of the initial histologic classes of lupus nephritis was as follows: class I (1%), class II (6%), class III (19%), class IV (47%), class III/IV (10%), class V (16%), and other classes (1%).

All patients with proliferative or membranous lupus nephritis were treated with high-dose glucocorticoids, and the proportion of patients who had

**Table 1.** Age- and sex-adjusted hazard ratios for mortality in systemic lupus erythematosus patients with renal disease compared to those without renal disease*

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>(95% confidence interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>2.23 (1.29–3.85)</td>
<td>0.004</td>
</tr>
<tr>
<td>Renal damage</td>
<td>3.59 (2.20–5.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>9.20 (4.92–17.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proliferative types of lupus nephritis</td>
<td>2.28 (1.22–4.24)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pure membranous lupus nephritis</td>
<td>1.09 (0.38–3.14)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

* Renal disease was defined as the presence of persistent proteinuria (urine protein concentration >0.5 gm/day on ≥2 occasions), urinary cellular casts, or biopsy-proven lupus nephritis. Renal damage was defined as a glomerular filtration rate (GFR) of <50 ml/minute for ≥6 months. End-stage renal disease was defined as a GFR of <15 ml/minute or requirement for renal replacement therapy.

**Figure 1.** Age- and sex-adjusted standardized mortality ratios (SMRs) of systemic lupus erythematosus (SLE) patients with or without renal involvement. Results are shown as the SMR with 95% confidence intervals. CKD = chronic kidney disease; ESRD = end-stage renal disease (stage 5 CKD); LN = lupus nephritis.
ever received other immunosuppressive agents in combination was as follows: azathioprine (89%), cyclophosphamide (51%), mycophenolate mofetil (MMF) (50%), cyclosporin A (25%), and tacrolimus (31%). In addition, 56% of patients with lupus nephritis had taken hydroxychloroquine, primarily for treatment of concomitant non-renal manifestations. At the time of analysis, the mean ± SD followup of our patients since SLE diagnosis was 9.6 ± 7.3 years. Thirty-four patients (4.9%) were lost to followup.

Cumulative survival rate of patients with lupus renal disease. Among the patients with lupus renal disease, 79 patients (11%) had renal damage, as assessed by the the SDI, and 24 patients (3%) developed ESRD. The cumulative 5-, 10-, and 15-year survival rates of patients with renal involvement were 92.3%, 88.8%, and 84.3%, respectively. These rates were significantly lower than those of patients without renal involvement (97.0%, 93.7%, and 91.6%, respectively; P = 0.004). Cox regression demonstrated that the age- and sex-adjusted hazard ratio (HR) of mortality in patients with renal disease and patients with renal damage, as compared with those without renal involvement, was 2.23 (95% CI 1.29–3.85) (P = 0.004) and 3.59 (95% CI 2.20–5.87) (P < 0.001), respectively (Table 1). The corresponding HR for mortality in patients who developed ESRD was 9.20 (95% CI 4.92–17.2) (P < 0.001).

Patients with proliferative types of lupus nephritis (class III, class IV, and class III/IV plus class V) had significantly increased mortality as compared with patients without renal disease (adjusted HR 2.28 [95% CI 1.22–4.24]; P = 0.01). In contrast, pure membranous lupus nephropathy was not associated with increased mortality (adjusted HR 1.09 [95% CI 0.38–3.14]; P = 0.88) as compared to that in patients without lupus renal disease. Adjustment for the use of immunosuppressive agents (prednisolone, azathioprine, cyclophosphamide, MMF, cyclosporin A, tacrolimus, and hydroxychloroquine) in the Cox regression models did not materially affect the overall HRs for mortality in patients with these histologic types of lupus nephritis (results not shown).

SMR of patients with lupus renal disease. The age- and sex-adjusted SMRs of all SLE patients, those
without renal disease, those with renal disease, those with proliferative nephritis, those with pure membranous nephropathy, those with renal damage, and those with end-stage renal failure, as compared to the general population, were 7.3 (95% CI 5.7–9.3), 4.8 (95% CI 2.8–7.5), 9.0 (95% CI 6.7–11.9), 9.8 (95% CI 6.5–14.1), 6.1 (95% CI 2.0–14.1), 14.0 (95% CI 9.1–20.5), and 63.1 (95% CI 33.6–108), respectively (Figure 1). The corresponding SMRs of SLE patients with renal disease but no renal biopsy, SLE patients with stage 3 or stage 4 chronic kidney disease (GFR 15–60 ml/minute), SLE patients with proliferative nephritis and renal damage, and SLE patients with proliferative or membranous nephritis and renal damage were 9.2 (95% CI 5.2–15.2), 7.9 (95% CI 4.2–13.4), 13.1 (95% CI 7.5–21.2), and 11.4 (95% CI 6.5–18.5), respectively.

**Life expectancy of patients with lupus renal disease.** Figure 2 shows the life expectancy curves of patients with SLE, those with SLE renal disease, those with SLE renal damage, and the general population. A life expectancy curve could not be plotted for SLE patients with ESRD, because the number of patients was too small. As the age at onset of SLE in our patients was 32.9 years (within the 30–34-year range), we compared the life expectancy of SLE patients at this age range with that in the general population. The life expectancies of patients with SLE, those with SLE renal disease, those with SLE renal damage, and the general population were 39.0 years, 36.3 years, 27.7 years, and 51.4 years, respectively. In other words, life expectancy was reduced by 12.4 years, 15.1 years, and 23.7 years, respectively, in SLE patients, SLE patients with renal disease, and SLE patients with renal damage as compared to the general population.

**DISCUSSION**

Patients with SLE have increased mortality. This is due to multiple factors that include an increased susceptibility to infection, accelerated atherosclerosis,
and malignancies, as well as organ damage due to treatment failure or complications (35). The survival of patients with SLE has improved tremendously in the past 3–4 decades, which is attributed to earlier diagnosis and treatment, more judicious use of corticosteroids, the emergence of novel treatments, and better supportive care for organ failure and infection-related complications (35). However, the improvement in the SLE survival rate appears to have reached a plateau since the 1990s (36). Patients with SLE still have a mortality rate higher than that of the general population (23,26,27,29), although a dropping trend has been observed (37).

Renal disease is a major organ manifestation of SLE, and its presence further increases the risk of death, because the disease still progresses to ESRD in a constant proportion of patients over time (22–29). Other factors that adversely affect the survival of SLE patients are ethnicity, poor socioeconomic status, poverty, and organ damage (24,38,39).

A number of previous studies have focused on the relative mortality in lupus renal disease, but the reference groups were heterogeneous (22–29). Only a few studies reported specifically the SMR of patients with lupus nephritis (23,26,27,29,37), but data on life expectancy were unavailable.

Our current study involves a relatively large cohort of Chinese patients with SLE who were followed up longitudinally for 10 years, and SMRs were calculated using data from our regular population census in the past 20 years. We demonstrated that having renal disease in SLE, in particular the proliferative types of glomerulonephritis, was associated with a significantly higher HR for mortality as compared to patients without renal involvement. The HRs for mortality were even higher for those with renal damage and ESRD. The mortality of SLE patients in our cohort was significantly higher than that of the general population regardless of renal involvement and histologic class, but the presence of renal disease further raised the SMR. The SMRs observed in our cohort of Chinese SLE patients with renal disease and renal damage are comparable to those reported in other European and American studies (Table 2).

Among the different histologic types of lupus nephritis, it is well known that diffuse and focal proliferative nephritis carries a worse prognosis than the pure membranous type of nephritis, in terms of progression to ESRD. Our data confirmed this observation, in that the HR for mortality in patients with proliferative lupus nephritis was significantly increased compared to that in SLE patients without renal disease. However, the corresponding HR for mortality in patients with pure membranous lupus nephritis was not significantly higher than that in patients without renal involvement. In fact, the SMR of patients with pure membranous lupus nephritis (SMR 6.1) was very similar to that of SLE patients as a whole (SMR 7.3) and was not significantly higher than that of patients without renal disease (SMR 4.8). This illustrates that pure membranous lupus nephritis has a better long-term prognosis than its proliferative histologic counterpart, although the incidence of vascular thrombosis was reported to be higher in patients with the pure membranous type (40).

Our study is the first to demonstrate a loss of life expectancy in SLE patients with renal disease. We were able to show that there was a reduction of 12.4 years of life expectancy in SLE patients as a whole as compared to the general population at the age of 32.9 years (the mean age at onset of SLE in our cohort). Having renal disease and having renal damage in SLE further reduced the life expectancy by 2.7 years (absolute loss of life expectancy = 15.1 years) and 11.3 years (absolute loss of life expectancy = 23.7 years), respectively. Thus, the occurrence of renal damage is an important adverse factor for survival in patients with SLE.

In summary, in this study on the cumulative survival, SMR, and life expectancy of a large longitudinal cohort of southern Chinese patients with SLE, we showed that the presence of glomerulonephritis, in particular the proliferative types causing renal insufficiency, significantly reduces the survival and life expectancy of patients with SLE. Better management of lupus renal disease may help to improve the ultimate prognosis of the disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mok had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Mok, Kwok, Yip.

Acquisition of data. Mok, Kwok, Yip.

Analysis and interpretation of data. Mok, Kwok.

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