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Survival analysis and causes of mortality in patients with lupus nephritis

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Abstract

Background. This study aimed to define the causes and associated risks of death compared with the local general population in Chinese patients with lupus nephritis in the recent era.

Methods. The records of all lupus nephritis patients followed in a single centre during 1968–2008 were reviewed. The causes of death were identified, the survival curves constructed and the standardized mortality ratios (SMRs) of potential risk factors were calculated with reference to the local general population.

Results. Two hundred and thirty systemic lupus erythematosus patients with history of renal involvement (predominantly Class III/IV lupus nephritis with or without membranous features) were included. The follow-up was 4076.6 person-years (mean 17.7 ± 8.9 years). Twenty-four patients (10.4%) died, and 85% of the deaths occurred after 10 years of follow-up. The 5-, 10-, and 20-year survival rates were 98.6, 98.2 and 90.5%, respectively. The leading causes of death were infection (50.0%), cardiovascular disease (20.8%) and malignancy (12.5%). The renal survival rates at 5, 10 and 20 years were 99.5, 98.0 and 89.7%, respectively. The SMR in patients with renal involvement, end-stage renal disease (ESRD), malignancy or cardiovascular disease was 5.9, 26.1, 12.9 and 13.6, respectively.

Conclusions. Lupus nephritis is associated with a 6-fold increase in mortality compared with the general population. Lupus patients who develop ESRD have a 26-fold excess in the risk of death, which is more than twice the risk associated with malignancy or cardiovascular disease in these patients.

Keywords: end-stage renal disease; lupus nephritis; mortality; risk factor; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an important cause of renal parenchymal disease in young adults and a leading cause of secondary renal disease resulting in chronic renal failure in Asians. Previous studies reported that 30–50% of SLE patients had renal involvement, while 10% of lupus patients would eventually develop end-stage renal failure [1, 2].

Over the past few decades, the survival of lupus nephritis patients has improved significantly because of advances in immunosuppressive and supportive treatments, better socio-economic conditions and earlier diagnosis. The causes of death have also changed. Early mortality due to uncontrolled disease or acute renal failure is now rare. While infection remains an important cause of mortality, with longer patient survival cardiovascular complications have emerged as important causes for late mortality [3, 4].

There is relatively little long-term information on the mortality rate and the causes of death in Chinese patients with lupus nephritis. This retrospective single-centre study compares the survival of patients with lupus nephritis against age- and gender-matched controls in the general population, in the era of effective immunosuppressive treatment regimens, and defines the causes of excessive mortality. The data are prerequisite to designing interventions to improve long-term patient survival.

Materials and methods

The inpatient and outpatient records of all patients who had attended the SLE clinic of Queen Mary Hospital within the period 1968–2008 were reviewed. Over 80% of the SLE patients managed at this clinic had a history of lupus nephritis and only patients with renal involvement were included in this analysis. All patients included in our study were ethnic

Chinese (defined as both parents being ethnic Chinese). Clinical information and the causes of death were ascertained from the hospital records and the computer database of the Hong Kong Hospital Authority. Data retrieval was approved by the University of Hong Kong/Queen Mary Hospital ethics committee.

The diagnosis of SLE was according to the American College of Rheumatology (ACR) classification [5]. Over 90% of the patients with renal involvement had undergone renal biopsy when they presented with the first episode of severe renal involvement. The indications for renal biopsy included unknown diagnosis, proteinuria of 1 g daily or more or deteriorating renal function. Re-biopsies were performed in most, but not all, subsequent renal flares. Histological classification of biopsy findings was based on the 1982 WHO classification for lupus nephritis until 2004, when the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification was adopted [6, 7]. Renal biopsies were reviewed by the same renal pathologist and classified according to the ISN/RPS 2003 classifications.

In the late 1960s and 1970s, patients with active nephritis were treated with high-dose corticosteroid with or without azathioprine. Standard immunosuppressive treatment protocols were adopted in the late 1980s. Patients with Class III (focal proliferative) or Class IV (diffuse proliferative) lupus nephritis were given induction immunosuppressive treatment that comprised corticosteroid and either cyclophosphamide or mycophenolate mofetil (available since 1997) for 6 months, followed by low-dose prednisolone and either azathioprine or mycophenolate mofetil as long-term maintenance immunosuppression. Mixed Class III+Class V or Class IV+Class V nephritis were treated as for Class III or Class IV, respectively. Cyclophosphamide was given orally at 2–3 mg/kg daily, for 6 months. Intravenous cyclophosphamide was not used. The target dose of mycophenolate mofetil during the induction phase (i.e. the first 6 months) was 2 g/day. Patients with pure Class V (membranous) lupus nephritis and proteinuria of <2 g daily were treated with angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker. Those with Class V nephritis and higher levels of proteinuria were given induction immunosuppression as for Class IV for 6 months and patients with persistent proteinuria of ≥ 2 g/day were treated with tacrolimus and low-dose prednisolone. Class II (mesangial) lupus nephritis was treated with prednisolone 30 mg/day, which was then tapered progressively, with or without azathioprine for steroid sparing.

Patients with dyslipidaemia were managed with dietary control before statins were available in our centre in 1988. Since 1988, target lipid levels were according to the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) guidelines (NCEP-ATP I: 1988–92; NCEP-ATP II: 1993–2001). After 2002, the NCEP-ATP III guidelines (target low-density lipoprotein level < 3.4 mmol/L) were followed. Optimal control of blood pressure has always been ascribed great importance, even before the advent of treatment guidelines. Our target of 120–125/75–80 mmHg could be more stringent than what had been recommended in the earlier versions of the Joint National Committee (JCN) for Prevention, Detection, Evaluation and Treatment of high blood pressure guidelines (JCN-1: 1976–79; JCN-2: 1980–83; JCN-3: 1984–87; JCN-4: 1988–91; JCN-5: 1992–97) and is similar to the recommendation in the JCN-6 guidelines.

Patients were seen at 2- to 14-week intervals depending on their clinical status. Clinical parameters, such as urinalysis, blood pressure, complete blood picture, renal and liver biochemistry, anti-double-stranded DNA and C3 levels, were monitored at every visit. Quantitation for proteinuria was performed as indicated, and lipid profile was measured every 6 months.

The standardized mortality ratio (SMR) of patients was calculated with reference to age- and gender-matched data in the local general population obtained from the local Department of Health. SMR was obtained by dividing the observed death by the expected death, the latter generated by multiplying the mortality rate in the reference general population by the number of study patients. SMR of lupus nephritis patients according to the decade of presentation was calculated using the mortality rate of the general population observed in the same decade. The impact of various parameters, such as end-stage renal disease, cardiovascular complications, malignancy and central nervous system involvement, on the SMR was ascertained. We also investigated the relationship between the era (based on the year of presentation) and clinical outcome.

Cardiovascular complications were defined as clinically evident ischaemic heart disease, acute myocardial infarction, atrial fibrillation attributed to coronary ischaemia, cerebral infarction or haemorrhage,

transient ischaemic attack, symptomatic or radiologically significant carotid stenosis ($\geq 70\%$ stenosis using Doppler ultrasound or magnetic resonance angiography) and significant peripheral vascular disease (with relevant symptoms and/or ankle brachial index of <0.9). End-stage renal disease (ESRD) was defined as need for renal replacement therapy, being that of dialysis or renal transplantation. All patients with ESRD were offered renal replacement therapy. Renal survival rate was defined as percentage of patients who had preservation of renal function independent of dialysis or transplantation. Death-censored renal survival rate referred to the renal survival rate when cases who died during the follow-up period were excluded for analysis.

Statistical analysis

Results are presented as frequencies and percentages for categorical variables and as means and SDs for continuous variables. Patient and renal survival patterns of study population were analysed and survival curves were constructed with the Kaplan–Meier method. The risk factors associated with mortality were also assessed using multivariate Cox regression analysis adjusted for sex and age at diagnosis. Statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc., Cary, NC). P-values <0.05 were considered as statistically significant.

Results

Two hundred and thirty lupus nephritis patients who were followed up in our clinic were included for analysis. The duration of follow-up was 4076.6 person-years, with a mean of 17.7 ± 8.9 years per patient. The mean age at diagnosis was 28.4 ± 10.5 years and 204 patients (88.7%) were females (Table 1). Twenty-one patients (9.1%) were lost to follow-up. All 230 patients were of Chinese ethnicity. Among the 208 renal biopsies, 85 showed Class IV (Subclass A 63.5%, A/C 36.5%), 16 showed Class III (Subclass A 62.5%, A/C 37.5%), 39 showed Class V, 38 showed mixed Class V and III/IV and 28 showed Class I/II lupus nephritis (Figure 1).

Twenty-four patients (10.4%) died during follow-up. The patient survival rates at 5, 10 and 20 years were 98.6, 98.2 and 90.5%, respectively (Figure 2). The leading causes of death were infection (50.0%), cardiovascular disease (20.8%) and malignancy (12.5%). One patient (4.3%) died during active disease and one patient died from ESRD after declining renal replacement therapy. For the 12 patients who died of infection, 5 (41.7%) were due to bacterial pneumonia. Other infections that led to mortality included peritoneal dialysis (PD)-related peritonitis ($n = 3$), *Pneumocystis jiroveci* pneumonia ($n = 1$), miliary tuberculosis ($n = 1$) and infected retroperitoneal haematoma ($n = 1$). Nine of the 12 patients who died from infection were on maintenance immunosuppression when the

Table 1. Baseline characteristics of 230 Chinese patients with lupus nephritis

Sex (female/male)	204/26
Age at last follow-up (years)	45.9 \pm 11.3
Duration of follow-up (years)	17.7 \pm 8.9
Age at diagnosis (years)	28.4 \pm 10.5
Number of patients ever exposed to	
Prednisolone (%)	228 (99.1)
Cyclophosphamide (%)	120 (52.2)
Azathioprine (%)	149 (64.8)
Mycophenolate mofetil (%)	68 (29.6)
Hydroxychloroquine (%)	51 (22.2)

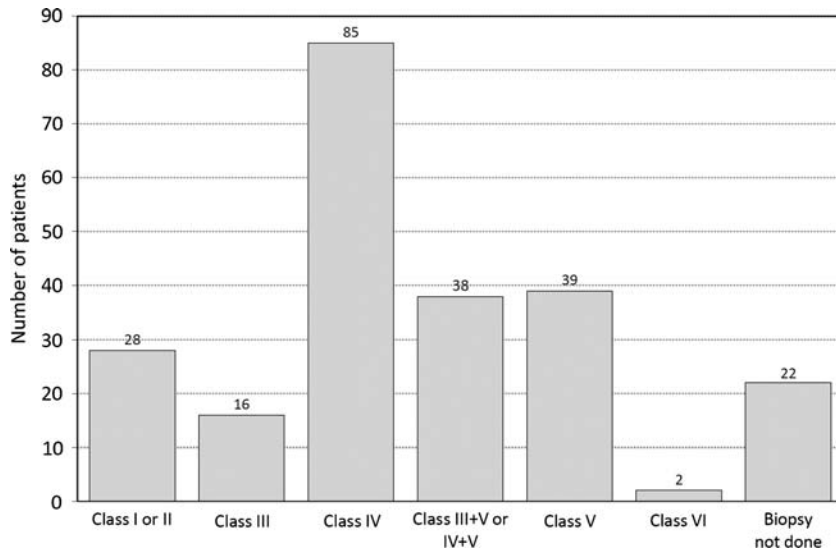


Fig. 1. Pattern of renal involvement in 230 Chinese patients with lupus nephritis.

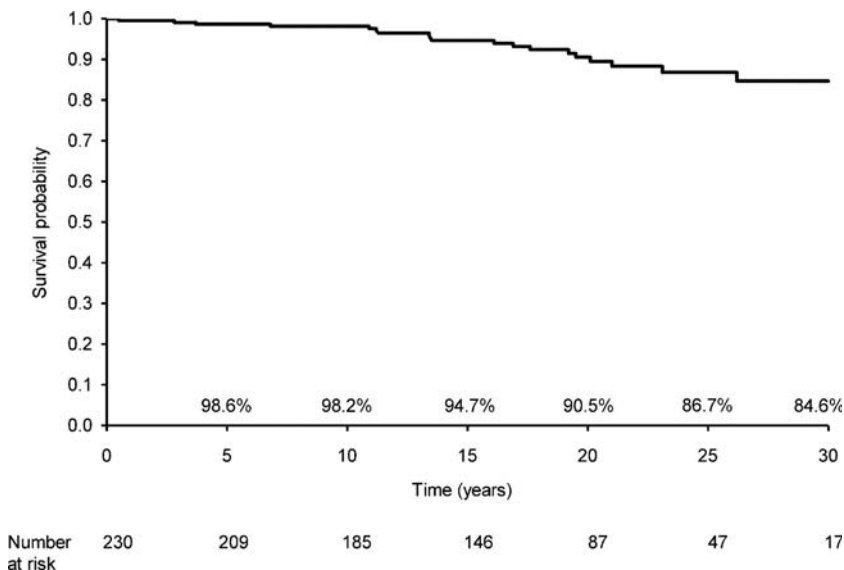


Fig. 2. Kaplan–Meier plot of patient survival in 230 Chinese patients with lupus nephritis.

infection occurred. Twenty-one patients (9.1%) developed ESRD during follow-up. Thirteen patients were treated with PD (1 subsequently underwent kidney transplantation), 6 patients were treated with long-term haemodialysis (one subsequently had kidney transplantation) and none switched their mode of dialysis. One patient underwent pre-emptive kidney transplantation and one declined dialysis. Seven (33.3%) of the 21 ESRD patients died during follow-up, and the deaths occurred at a median of 24 months after reaching ESRD. Five of them died of infection (two related to peritonitis complicating PD), one died of cardiovascular disease and one due to malignancy. Eighteen patients developed cardiovascular complications—10 had myocardial infarction (2 had recurrence), 2 developed atrial fibrillation, 3 had transient ischaemic attack, 2 had a stroke and 1 had carotid stenosis. The

renal survival rates were 99.5, 98.0 and 89.7% at 5, 10 and 20 years, respectively (Figure 3A). Patients with membranous lupus nephritis had significantly better renal survival than those with severe proliferative changes (Class III/IV ± V) at 5, 10 and 20 years ($P=0.045$) (Figure 3B).

The overall SMR for patients with lupus nephritis was 5.9. Patients with lupus nephritis who developed ESRD had an SMR of 26.1, while those with clinically evident cardiovascular disease or malignancy had SMRs of 13.6 and 12.9, respectively. ESRD, cardiovascular disease and malignancy remained strong predictors of mortality after multivariate Cox regression analysis. The relative risks of mortality for ESRD, cardiovascular disease and malignancy were 6.22 [95% confidence interval (CI) 2.07–18.64, $P < 0.001$], 4.61 (95% CI 1.41–15.08, $P=0.012$)

Survival of patients with lupus nephritis

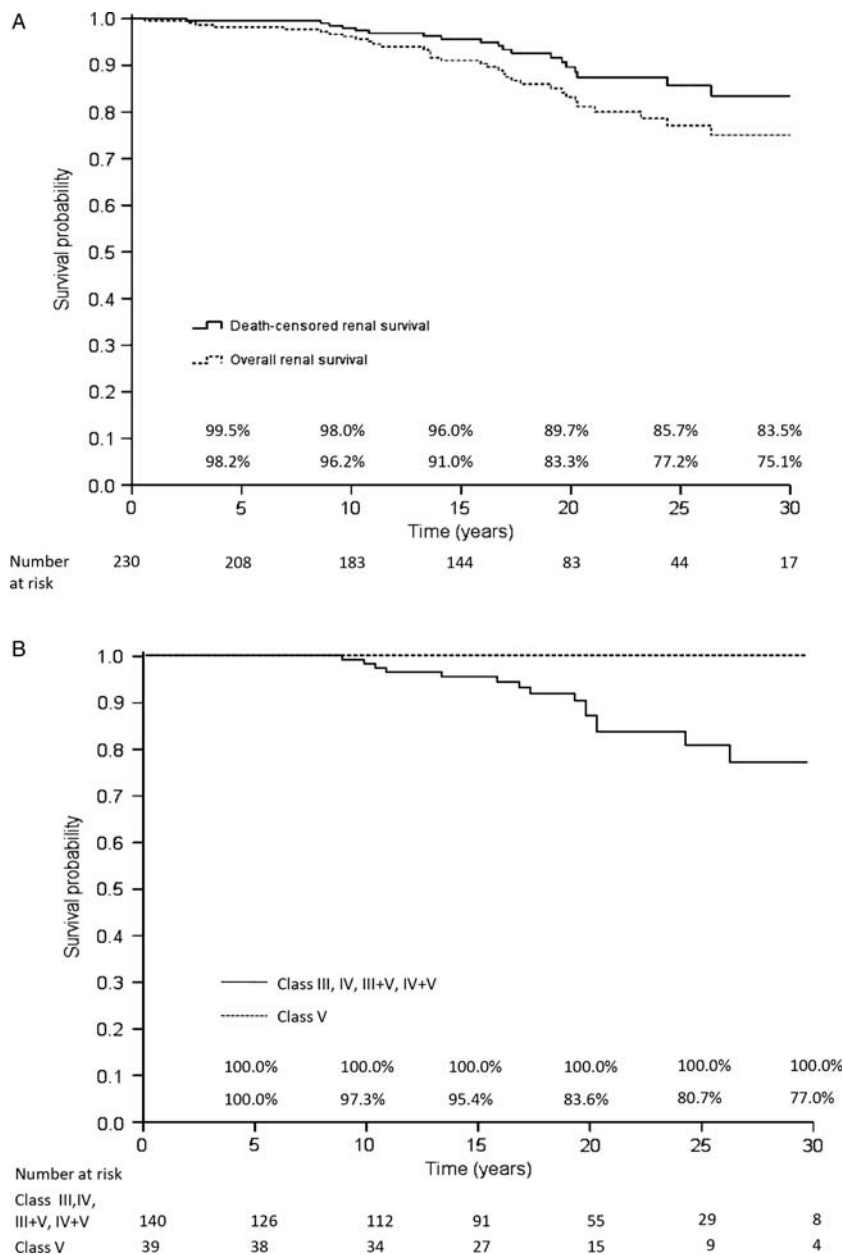


Fig. 3. (A) Kaplan–Meier plot of renal survival in 230 patients with lupus nephritis. (B) Kaplan–Meier plot of renal survival in patients with Class III/IV lupus nephritis ± membranous features versus Class V lupus nephritis.

and 4.23 (95% CI 1.01–18.84, $P=0.049$), respectively. Patients who had renal relapse had inferior renal survival than those without renal relapse (84.0 versus 97.0% at 20 years, $P=0.04$).

We also stratified patients according to the decade of presentation and we observed no significant variation in SMR across the different time periods (1968–78 versus 1979–88, $P=0.16$; 1968–78 versus 1989–98, $P=0.36$; 1968–78 versus 1999–2008, $P=0.65$). The causes of death according to decade were—for 1968–78, cardiovascular ($n=2$), malignancy ($n=1$), infection ($n=1$); for 1979–1988, infection ($n=6$), malignancy ($n=2$), ESRD ($n=1$), cardiovascular ($n=1$); for 1989–1998, infection ($n=4$), cardiovascular ($n=2$), gastrointestinal bleeding

($n=2$), refractory disease ($n=1$) and for 1999–2008, infection ($n=1$).

Discussion

The survival of patients with SLE is influenced by medical factors such as the efficacy and adverse effects of immunosuppressants and the prompt diagnosis and treatment of complications and non-medical factors such as ethnicity and socio-economic status [8–10]. Survival analysis published over the past few decades has shown an overall trend of improvement in patient survival, most notably in the reduction of early mortality, while

excessive mortality compared with the general population was still observed [11, 12]. Recent reports have shown that the 5-, 10- and 20-year patient survival rates were 95, 91 and 78%, respectively [13, 14]. These data were derived from patients in Europe and USA, with 20–30% of patients having a history of renal involvement.

The present series included a high proportion of patients with severe lupus nephritis. Despite this, we observed relatively high long-term patient survival rates of 98.6, 98.2 and 90.5% at 5, 10 and 20 years, respectively. Ten per cent of patients died during a mean follow-up of ~18 years. For comparison, a recent report on Japanese lupus patients, 46% of whom had lupus nephritis, showed 5-, 10- and 20-year survival rates of 94, 92 and 77%, respectively [15]. Most of the deaths in our cohort occurred late. With effective induction immunosuppressive treatment and improvements in the prevention and treatment of complications, the high early mortality rate that had been associated with renal lupus previously can be avoided in the present era [16]. Similar to other reports, infection, malignancy and cardiovascular disease are the leading causes of death [17–19]. In our series, infection and cardiovascular complications accounted for 70% of all deaths, while malignancy accounted 12.5% of all mortalities. For comparison, infection and cardiovascular disease are the leading causes of death in patients with ESRD irrespective of underlying aetiology. The present data highlight the detrimental impact of renal failure on vascular status and the importance of preventing malignancies in the management of lupus nephritis patients in general. Although one need to consider ethnicity and socio-economic status in assessing the mortality of SLE patients, we reckon that these factors could not be adequately examined in our cohort since all the patients were Chinese and the socio-economic data were not fully available in the retrospective analysis of long-term mortality data. While there is insufficient data to allow definitive conclusions on this issue, it is unlikely that these factors have influenced the clinical outcomes significantly. In the public health care system in Hong Kong, which takes care of 93% of all patients, patients can present themselves to a specialist clinical service, which charges a nominal fee of US\$ 13/day of hospitalization or US\$ 8 per outpatient clinic visit. As a result, the socio-economically underprivileged patients do not suffer from impaired access to medical care. In fact, due to a deficient primary care system, some patients present quite early to specialists. The relatively early presentation might imply a higher degree of reversibility of the renal inflammatory lesions and thus potentially better prognosis compared to patients who present late, when significant fibrosis has set in.

The renal survival rates at 10 and 20 years after severe lupus nephritis have been reported as 83–90 and 73–81%, respectively [19–21]. Although not a direct comparison, the relatively high 10- and 20-year renal survival rates in the present series, at 98.0 and 89.7%, respectively, may be related to the high response rates to induction immunosuppression which have been reported previously [22–26]. Ethnic or racial variations could also contribute to the better outcome in Chinese

patients compared with African-Americans or Hispanic patients [27]. For comparison, data from a large multi-ethnic study showed that African-Americans and Hispanics have an earlier onset of nephritis [28]. In our experience, progressive renal failure in Chinese subjects is more often heralded by cumulative nephron loss with repeated relapses than lack of response to immunosuppression. It is thus imperative to minimize damage to normal renal parenchyma with prompt diagnosis and treatment and institute renal protective measures in patients with compromised renal reserve [29].

Bernatsky *et al.* [11] have reported that the overall SMR of SLE patients has been reduced almost by half over the past few decades. In contrast, Faurischou *et al.* [19] have reported similar SMR between patients diagnosed in 1980–89 and those diagnosed in 1990–95. The apparent discrepancy could be related to the narrower time frame in the latter series compared to the report by Bernatsky *et al.* In addition, a high proportion of patients in the report by Faurischou *et al.* had renal involvement, the treatment for which had not undergone any major change over the study period. In this regard, other investigators have also reported no significant change in renal survival over time from the 1970s to the late 1990s [21]. In the present study, we found no significant variation in SMR across the different decades of presentation and this phenomenon could be related to the similarly high response rates to induction immunosuppressive treatments incorporating initially cyclophosphamide and later mycophenolate mofetil. Intuitively, we had expected an improvement in patient survival in patients who presented more recently, but this was not shown by the data. The authors recognize that there may be potential confounding factors, such as sample size, the impact of age and comorbidities, on the mortality of patients with different durations of follow-up and the possibility of selection bias with survival advantage in patients with long follow-up durations.

Renal involvement is a severe disease manifestation in lupus and has been associated with excessive mortality [14, 30, 31]. The inferior survival in African-American and Hispanic patients compared with Caucasian lupus patients has been attributed to a higher incidence of lupus nephritis [16]. Apart from higher incidence, Burgos *et al.* [28] have also reported that African-Americans or Hispanic patients had earlier onset of renal involvement when compared to the Caucasians. Furthermore, data from the same cohort showed that renal damage is the most important predictor of mortality in SLE patients, irrespectively of ethnicity [32]. These data not only demonstrated the ethnic difference in disease presentation but also exemplified the impact of renal damage in lupus and have echoed our findings that renal involvement be a strong predictor for excess mortality. Our data showed an SMR of ~6-fold in Chinese patients with lupus nephritis. It is of interest to note that the SMR in our patients is similar to the SMR of 6.8 observed in a recent series of predominantly Caucasian patients with lupus nephritis [19]. We could not compare local Chinese lupus patients with or without renal involvement since our centre predominantly takes care of patients with nephritis. In this context, an SMR

of 2.4 for lupus patients in general has been reported recently by Bernatsky *et al.* [11].

The important impact of chronic renal failure on the long-term outcome of patients with lupus nephritis cannot be overemphasized. Our data show that lupus nephritis with ESRD has an extremely high SMR of 26.1, despite the access to dialysis. The SMR values of 6.8–7.9 for renal involvement in recent reports did not address the issue of severity of renal failure [11, 19]. Furthermore, since infection and cardiovascular complications are the major causes of death in patients on dialysis, the impact of underlying ESRD might have been under-appreciated [33]. An SMR value of 11.9 has been reported in dialysis patients with a low prevalence of SLE [33]. Using the data from our dialysis centre, we have found an SMR of 9.2 in Chinese non-lupus ESRD patients, which was numerically considerably lower than the 26.1 in patients with lupus nephritis and ESRD. It is likely that the lifetime exposure to heavy immunosuppressive treatment and toxic medications contributes to the excessive mortality. These findings highlight the pivotal importance of preserving renal function in securing long-term patient survival in patients with lupus nephritis [12, 21].

Consequent to the advent of effective immunosuppressive treatment and the prolongation of patient survival, cardiovascular disease has emerged as an important long-term complication [34–38]. Since vascular complications are also accelerated in patients with renal failure, the risk of cardiovascular complications is compounded in patients with ESRD and SLE [39, 40]. Our data showed that patients with lupus nephritis and clinically evident cardiovascular disease had an SMR of 13.6, and 20.8% of deaths were due to cardiovascular causes. For comparison, SMR in Chinese non-lupus patients with cardiovascular disease was reported as 1.4 in the early 1990s [41]. Our results showed that lupus nephritis patients with malignancy had a 13-fold increase in the risk of death. For comparison, data from the 1990s showed an SMR of 1.2 in Chinese non-lupus patients with malignancy [42]. Patients with lupus are more prone to develop malignancies, especially those involving the haematological and respiratory systems, although the relative contribution of immunosuppressive treatment and the lupus disease remains controversial [43–45]. Among the commonly used immunosuppressive medications, the carcinogenic potential of cyclophosphamide is well established [46, 47]. An incidence rate of 4.6% at 5 years has been reported for malignancies in lupus patients who had been treated with cytotoxics [48]. It remains to be determined whether this risk may vary with alternative immunosuppressive or immunomodulatory agents such as mycophenolate mofetil or antibodies against CD20.

In summary, our data demonstrate that ESRD, malignancy and cardiovascular disease are the leading risk factors of excessive mortality in patients with lupus nephritis and that ESRD complicating lupus nephritis, with an associated SMR of 26.1, is a leading mortality risk factor doubling that of cardiovascular disease or malignancy.

Conflict of interest statement. None declared.

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