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ORIGINAL ARTICLE

Causes of death in hospitalized patients with systemic lupus erythematosus: a 10-year multicenter nationwide Chinese cohort

Xin-yao Wu[1] · Min Yang[2] · Yue-sheng Xie[3] · Wei-guo Xiao[4] · Jin Lin[5] · Bin Zhou[6] · Xin Guan[7] · Cai-nan Luo[8] · Nan Che[9] · Xing-zhen Liu[10] · Chao Wang[11] · Jia-lin Teng[1] · Xiao-bing Cheng[1] · Jun-na Ye[1] · Yu-tong Su[1] · Hui Shi[1] · Yu-feng Yin[1] · Meng-ru Liu[1] · Yue Sun[1] · Qiong-Yi Hu[1] · Zhuo-chao Zhou[1] · Hui-hui Chi[1] · Yi Liu[2] · Xiao Zhang[3] · Jin-wei Chen[7] · Miao-jia Zhang[9] · Dong-bao Zhao[10] · Cheng-de Yang[1] · Li-jun Wu[8] · Hong-lei Liu[1]

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Abstract

To estimate the mortality and describe the causes of death in a large multicenter cohort of hospitalized patients with SLE in China. This was a retrospective study of a nationwide SLE cohort (10 centers, 29,510 hospitalized patients) from 2005 to 2014 in China. Standardized mortality ratios (SMRs) were calculated for all death and were stratified by sex and age. Chi-square test was used to determine whether the major causes of death vary in age, sex, duration of SLE, disease activity, or medications. Comparison between dead patients and survival controls was used to identify the risk factors for mortality. Logistic regression analysis was used to evaluate the risk factors for mortality. A total of 360 patients died during the study period, accounting for 1.22%. The overall SMR was 2.13 (95% CI 1.96, 2.30), with a particularly high SMR seen in subgroups characterized by younger age. Infection (65.8%) was the most common cause of death, followed by lupus nephritis (48.6%), hematological abnormality (18.1%), neuropsychiatric lupus/NPSLE (15.8%), and interstitial pneumonia (13.1%). Cardiovascular disease and malignancy contributed little to the causes of death. Infection, in particular severe pulmonary infection, emerged as the foremost risk factor for mortality, followed by lupus encephalopathy. However, lupus nephritis and hematological abnormalities occurred more frequently in survival patients. SLE patients at a younger age of diagnosis have a poorer prognosis. Infection dominated the causes of death in recent China. Ethnicity and medications might account for the differences in causes of death compared with western populations.

Keywords Cardiovascular disease · Cause of death · Infection · Standardized mortality ratio · Systemic lupus erythematosus

Xin-yao Wu, Min Yang, Yue-sheng Xie, Wei-guo Xiao, Jin Lin, Bin Zhou, Xin Guan, Cai-nan Luo, Nan Che and Xing-zhen Liu contributed equally to this work.

✉ Cheng-de Yang
yangchengde@sina.com

✉ Li-jun Wu
wwlj330@126.com

✉ Hong-lei Liu
hong-lei-liu@163.com

[1] Department of Rheumatology and Immunology, Shanghai Jiao Tong University School of Medicine Affiliated Ruijin Hospital, No. 197 Ruijin Second Road, Huangpu District, Shanghai 200025, China

[2] Department of Rheumatology and Immunology, Sichuan University West China Hospital, Chengdu, China

[3] Department of Rheumatology and Immunology, Guangdong General Hospital, Guangzhou, China

[4] Department of Rheumatology and Immunology, The First Hospital Affiliated to China Medical University, Shenyang, China

[5] Department of Rheumatology and Immunology, Zhejiang University School of Medicine First Affiliated Hospital, Hangzhou, China

[6] Department of Rheumatology and Immunology, Sichuan People's Hospital, Chengdu, China

[7] Department of Rheumatology and Immunology, Second Xiangya Hospital, Changsha, China

[8] Department of Rheumatology and Immunology, Xinjiang Uygur People's Hospital, No. 91 Tianchi Road, Tianshan District, Urumqi 830001, Xinjiang Uygur Autonomous Region, China

[9] Department of Rheumatology and Immunology, Jiangsu People's Hospital, Nanjing, China

[10] Department of Rheumatology and Immunology, Changhai Hospital, Shanghai, China

[11] Beijing Institute of Traumatology and Orthopaedics, Beijing Jishuitan Hospital, Fourth Clinical Medical College, Peking University, Beijing, China

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with heterogeneous, multisystem involvements which can sometimes be severe and life threatening. Early in the first half of the twentieth century, SLE was regarded an almost invariably fatal disease with rapid progress [1]. Then with the advent and application of cyclophosphamide therapy in combination with corticosteroids as treatment for lupus nephritis, there has been a remarkably persistent improvement in the survival rate of SLE patients [2]. The overall expected 5-year survival in the USA rose from approximately 70% in the 1960s and 90% in the 1980s to over 95% in recent years, and similar increases were seen in European countries as well as in 10-year survival [3–7]. Nonetheless, the impressive rise has stopped since 1990s and the 5-year survival of SLE currently fluctuates over 90% [8]. The overall standardized mortality ratio (SMR) was 2.4 (95% confidence interval (CI) 2.3–2.5) and the meta-SMR was 2.98 (95% CI 2.32–3.83) reported by long-term, large, multisite international cohort studies, which highlighted a 2~3-fold increased risk of all-cause mortality in patients with SLE compared to the general population [9, 10]. As a consequence, the mortality in SLE remained a problem worthy of attention and there was still substantial room for improvement.

Unlike a consistent tendency in mortality, the distribution of causes of death in SLE patients apparently varied among studies. The most common causes of death were reported to be active SLE, infection, cardiovascular disease (CVD), or to change according to age at diagnosis and disease duration [11–14]. Despite the variations in the proportion of different causes of death, lupus nephritis, NPSLE, infection, and CVD remained the major causes of deaths all the time [15–17]. Malignancy, in particular hematological tumors, appeared a considerable cause of death not to be neglected [16, 18]. Accompanied by the extensive administration of high-dose glucocorticoids and immunosuppressive agents, infections have played an increasingly important role in the causes of death in SLE patients [19–21]. The 5-year survival and overall mortality reported in previous studies of SLE in China and Asia were similar to those in western countries. The 5-year survival ranged from 73 to 89% in the 1970s and from 91.2 to 97% in the past two decades [4, 19–23]. However, these studies from several regions of China represented only a limited part of the Chinese population.

Here, we organized a multicenter nationwide cohort of unprecedented size to estimate the mortality and to describe the causes of death in hospitalized SLE patients in China. Our study intended to provide a better understanding of recent mortality and causes of death in Chinese SLE patients.

Methods

Patients

All hospitalized patients (from 1 to 94 years old) who were admitted to the 10 collaborating tertiary referral centers between January 2005 and December 2014 and diagnosed with SLE according to the diagnostic criteria of the American College of Rheumatology (ACR) in 1982 or 1997 were recruited [24, 25]. The 10 general hospitals are located in the eastern, northeast, southwest, northwest, southern, and central regions of China respectively, which covered a majority of Chinese population. Those patients lost to follow up were excluded from our analysis.

Data collection

We presented the baseline characteristics of enrolled patients since the first recorded admissions. Information of sex and age was collected for all hospitalized SLE patients. Data on sex, age at diagnosis, disease duration, age at death, SLEDAI score [26], and medications were collected for the deceased patients. The variable medications used to treat SLE included systemic glucocorticoids, hydroxychloroquine, cyclophosphamide, mycophenolate mofetil, tacrolimus or ciclosporin, and other immunosuppressive agents like azathioprine, methotrexate, total glucosides of paeony (an herb from the traditional Chinese medicine), thalidomide, leflunomide, vincristine, and rituximab. The SLEDAI score was calculated according to the disease status at the final hospitalization before death and at the first admission for the survival controls. The causes of death were ascertained by review of the patient's clinical process and determined by the physicians in charge. Given the complex multiple organ damages happening simultaneously in SLE patients, it is often difficult to distinguish a major cause of death from a minor one, so the coexistence of multiple critical causes of death in one patient was permitted in our study. All causes of death were classified into three categories: (1) events caused by SLE disease activity, such as lupus nephritis, NPSLE, hematological abnormality, and interstitial lung disease; (2) events caused by non-SLE disease activity, which referred to complications of the disease and/or its treatment, like infection, CVD, malignancy, etc.; and (3) events unrelated to SLE disease, for example, suicide. The abovementioned "hematological abnormality" was defined as the decline of blood cell counts, including leukopenia, anemia, and thrombocytopenia, excluding the effect of confounding factors such as hematuria and drug-induced bone marrow suppression. Although the normal ranges of blood cell counts in ten centers differed slightly from each other, the effect could be ignored. "Interstitial lung disease" referred to pneumonia caused by SLE rather than pneumonia infiltrating interstitial caused by pathogens like bacteria, viruses, and fungi.

Suggestive radiology patterns by HRCT include non-specific interstitial pneumonia, organizing pneumonia, and lymphoid interstitial pneumonia. In addition, we conducted a comparison of the five most common causes of death as five important damage events between 360 deceased patients and 296 age- and sex-matched survival patients to detect the potential risk factors for mortality. Patients discharged against medical advice were excluded from both groups.

Statistical methods

SMR was the ratio of observed deaths in the study group to expected deaths in the general population [2]. SMR and its 95% CI were calculated as follows:

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

$$95\%\mathrm{CI} = \left(\mathrm{SMR} - 1.96 \times \frac{\sqrt{O}}{E}, \mathrm{SMR} + 1.96 \times \frac{\sqrt{O}}{E}\right)$$

where O represented the observed number of deaths and E represented the expected number of deaths [27]. Demographic data on sex- and age-specific population mortality were provided by *the China Population & development Statistics Yearbook*.

The categorical values were expressed as numbers (in percent) and the continuous variables as mean and standard deviation (SD). Comparison of major causes of death by groups was made by the chi-square test and a value of $p < 0.05$ was considered statistically significant. Univariate analysis using the logistic regression was used to evaluate the risk factors for all-cause mortality in SLE patients. Multivariate logistic regression analysis was conducted for the variables with statistical significance in the univariate analysis and the results were expressed as odds ratio (OR) and its 95% CI. Statistical analyses were performed using the SAS (Statistical Analysis Software) 9.2.

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Results

Demographic characteristics

Of the 29,510 hospitalized SLE patients, 26,293 (89.1%) were female and 3217 (10.9%) were male. Mean age at recruitment was 36.18 years. Three hundred sixty patients died during the study period, accounting for 1.22%. Of the 360 deceased patients, 314 (87.2%) were female and 46 (12.8%) were male. Mean age at diagnosis was 37.0 ± 16.8 years (range 9–86 years) and mean age at death was 43.0 ± 17.6 years (range 9–89 years). The demographics of the death cohort were shown in Table 1. The number of patients whose SLEDAI score ranging from low active (0–4), mild active (5–9), high active (10–14) to extremely high active (> 15) and the number of patients exposed to medications used for SLE treatment during follow-up lasting at least half a year were also summarized in Table 1. As a multicenter cohort, there were little differences among centers in male-female ratio, mean age at death, and disease duration. However, differences did exist in number of patients and medications. The largest center contained 68 cases while the smallest contained only six. Except for the common use of systemic glucocorticoids (95.0%) and cyclophosphamide (CTX, 35.6%), the treatment strategies were variable. In addition, there were a small number of patients (1.4%) whose age at diagnosis and disease duration was not known at death.

SMR

The overall SMR was 2.13 (95% CI 1.96, 2.5). Patient groups characterized by female sex and younger age had higher SMR estimates (Table 2). Within the age group of < 40 years, the

Table 1 Demographics and clinical characteristics of the death cases in our SLE cohort ($n = 360$)

Patient characteristic	Value
Sex, no (%)	
Male	46 (12.8)
Female	314 (87.2)
Age at diagnosis, mean ± S.D., years	37.0 ± 16.8
Unknown, no. (%)	5 (1.4)
Disease duration, mean ± S.D., years	5.9 ± 7.2
Unknown, no (%)	5 (1.4)
Age at death, mean ± S.D., years	43.0 ± 17.6
SLEDAI score, no (%)	
0–4	51 (14.2)
5–9	83 (23.1)
10–14	107 (29.7)
≥ 15	119 (33.1)
Medications, no (%)	
Systemic glucocorticoids	342 (95.0)
HCQ	42 (11.7)
CTX	128 (35.6)
MMF	37 (10.3)
Tacrolimus or ciclosporin	23 (6.4)
Other immunosuppressive agents	52 (14.4)
No medications	7 (1.9)
Unknown	11 (3.1)

HCQ, hydroxychloroquine; *CTX*, cyclophosphamide; *MMF*, mycophenolate mofetil

Table 2 Unadjusted SMRs stratified by sex and age

Group	SMR (95% CI)
Sex	
Female	2.43 (2.26, 2.63)
Male	2.20 (2.01, 2.39)
Age, years	
0–19	11.37 (9.69, 13.05)
20–39	9.22 (7.98, 10.46)
40–59	3.45 (2.68, 4.22)
≥ 60	1.36 (1.05, 1.67)
Overall	2.13 (1.96, 2.30)

SMR, standardized mortality ratio; *CI*, confidence interval

SMR were extremely high, at 11.37 (95% CI 9.69, 13.05) for the youngster age 0–19 years and 9.22 (95% CI 7.98, 10.46) for the young adults age 20–39 years. The SMR showed a diminishing trend by age.

Table 3 Causes of death divided into three groups in the deceased SLE patients ($n = 360$)

Causes of death	Number (%)
I. Events caused by SLE disease activity	
Neuropsychiatric lupus	*57 (15.8)*
Pulmonary artery hypertension	30 (8.3)
Interstitial lung disease	*47 (13.1)*
Acute pulmonary embolism	14 (3.9)
Diffuse alveolar hemorrhage	14 (3.9)
Lupus cardiomyopathy	20 (5.6)
Hematological abnormality	*65 (18.1)*
Intestinal vasculitis	19 (5.3)
Lupus nephritis	*175 (48.6)*
Catastrophic antiphospholipid syndrome	5 (1.4)
Acute pancreatitis	3 (0.8)
II. Events caused by non-SLE disease activity (complications of the disease and/or its treatment)	
Infection	*237 (65.8)*
Gastrointestinal bleeding	18 (5.0)
Intracranial hemorrhage	5 (1.4)
Acute cardiovascular events	4 (1.1)
Malignancy	6 (1.7)
Hepatic complication	25 (6.9)
Bone marrow suppression	2 (0.6)
III. Events unrelated to SLE disease	
Suicide	3 (0.8)
Others	7 (1.9)
Total	756*

*The total number of all causes of death was 756, with more than one cause of death permitted in one patient. The five most common causes of death are emphasized in italic text

Causes of death

All causes of death in the 360 SLE deceased patients were summarized in Table 3, divided into three groups: events caused by active SLE, events caused by complications of SLE or its treatment, and events unrelated to SLE. The total number of death events altogether was 756, with more than one cause of death permitted in one patient, indicating that an average of at least two causes of death existed simultaneously in a death case. Actually, patients with two ($n = 134$, 37.2%) and three ($n = 71$, 19.7%) causes of death accounted for the majority of the death cohort, while only 118 patients (32.8%) died of a single cause.

The most common cause of death was infection ($n = 237$, 65.8%), followed by lupus nephritis ($n = 175$, 48.6%), hematological abnormality ($n = 65$, 18.1%), NPSLE ($n = 57$, 15.8%), and interstitial lung disease ($n = 47$, 13.1%). On the contrary, CVD ($n = 4$, 1.1%) and malignancy ($n = 6$, 1.7%) occupied a surprisingly small proportion of all causes of death in our study.

For the specific sites of infection, 171 patients (72.2%) who suffered pulmonary infection alone dominated the whole 237 cases dying of infection. Infection with two or more sites ($n = 41$, 17.3%) had a strikingly high incidence. Intracranial infection, septicemia, urinary tract, intestinal tract, biliary tract, and even lower limbs could be the possible site of infection in SLE patients.

For the pathogens of infection, data of 72 dead patients from two centers were collected. Among 48 patients who died of infection, 28 patients had positive microbiological cultures: 14 bacterial infections, 8 fungal infections, and 6 mixed infections. The common pathogens of infection were *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Candida species*, and *Stenotrophomonas maltophilia*.

Risk factors for mortality

To identify the association between specific causes of death and patient characteristics, we examined the distribution of the five most common causes of death in subgroups stratified by sex, age at diagnosis, age at death, disease duration, SLEDAI score, and medications. Using the chi-square test, our findings (Table 4) indicated that the causes of death differed significantly neither between male and female patients ($p = 0.188$), nor between early-onset (< 50 years old) and late-onset (≥ 50 years old) patients ($p = 0.311$). Likewise, the distribution of five causes of death remained similar in subgroups by disease duration ($p = 0.834$) and by medications ($p = 0.607$). Possible association could be seen between cause of death and age at death ($p = 0.05$). Among elderly patients > 60 years old, infection happened more frequently while lupus nephritis

Table 4 Distribution of the five major causes of death stratified by sex, age at diagnosis, age at death, disease duration, SLEDAI, and medications

Groups	Total	Infection	Lupus nephritis	Hematological abnormality	Lupus encephalopathy	Interstitial lung disease	*p* value
Sex							0.188
Male	71	32 (45)	25 (35)	8 (11)	5 (7)	1 (1)	
Female	510	205 (40)	150 (29)	57 (11)	52 (10)	46 (9)	
Age at diagnosis							0.311
0–49	446	171 (38)	143 (32)	49 (11)	46 (10)	37 (8)	
≥ 50	130	63 (48)	32 (25)	14 (11)	11 (8)	10 (8)	
Age at death							0.050
0–19	67	26 (39)	20 (30)	5 (7)	12 (18)	4 (6)	
20–39	230	89 (39)	78 (34)	19 (8)	24 (10)	20 (9)	
40–59	183	70 (38)	55 (30)	29 (16)	12 (7)	17 (9)	
≥ 60	101	52 (51)	22 (22)	12 (12)	9 (9)	6 (6)	
Disease duration							0.834
≤ 1 year	227	95 (42)	61 (27)	25 (11)	28 (12)	18 (8)	
1–5 years	122	49 (40)	40 (33)	13 (11)	11 (9)	9 (7)	
≥ 5 years	227	90 (40)	74 (33)	25 (11)	18 (8)	20 (9)	
SLEDAI							<0.001
0–4	54	35 (65)	8 (15)	4 (7)	1 (2)	6 (11)	
5–9	123	54 (44)	41 (33)	15 (12)	0 (0)	13 (11)	
10–14	187	70 (37)	62 (33)	23 (12)	19 (10)	13 (7)	
≥ 15	217	78 (36)	64 (29)	23 (11)	37 (17)	15 (7)	
Medications							0.607
Only GC	205	83 (40)	57 (28)	29 (14)	17 (8)	19 (9)	
GC + ISA	349	143 (41)	111 (32)	32 (9)	36 (10)	27 (8)	
None/unknown	27	11 (41)	7 (26)	4 (15)	4 (15)	1 (4)	

Values within parentheses are in percent

**SLEDAI*, systemic lupus erythematosus disease activity index; *GC*, glucocorticoids; *ISA*, immunosuppressive agents

occurred less often. The young ≤ 20 years old were susceptible to NPSLE. Moreover, the SLEDAI, accepted assessment method of disease activity in SLE, elevated prominently in patients dying of NPSLE, lupus nephritis, and hematological abnormality. Deceased patients with lower SLEDAI scores inclined to suffer from infection and interstitial lung disease.

Univariate and multivariate logistic regression analysis was performed to detect prognostic factors for mortality, and the results were shown in Table 5. Age at diagnosis, NPSLE, hematological abnormality, lupus nephritis, and infection were both univariately and multivariately associated with mortality. Our findings showed that infection was the most prominent independent risk factor for mortality. There was a 3.88-fold increase in incidence rate of infection for univariate analysis and a 4.16-fold increase for multivariate in the death group ($p < 0.001$). NPSLE appeared to be the second important risk factor for mortality ($p < 0.01$). However, lupus nephritis and hematology abnormality occurred more frequently in the sex- and age-matched survival group compared with the death group ($p < 0.001$).

Discussion

This was the first nationwide multicenter SLE cohort of unprecedented size to describe the mortality and causes of death in recent China over a 10-year period. The highlights of our study were large cohort scale up to nearly 30,000 hospitalized patients and 10 collaborating hospital centers located in six major geographical zones of China, which possessed a typical and representative sample of the whole Chinese population.

Although there have been several previous studies on survival and mortality analysis of Chinese population, not many studies were organized as multicenter cohort and focused on standardized mortality ratios [20, 22, 28]. The overall SMR was 2.13 in our study, which demonstrated a higher than 2-fold increase of mortality in hospitalized patients with SLE compared to the general Chinese population. As shown in previous studies [9, 10, 27], the unadjusted SMR for all-death mortality ranged from 2 to 3 despite the strikingly improved survival rate of SLE, indicating that SLE remained a life-threatening disease with poor prognosis. A SMR up to 11.37 in subgroup of age 0–19 and 9.22 in age 20–39 revealed

Table 5 Risk factors for mortality by univariate and multivariate logistic regression analysis

Risk factors	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age at diagnosis	1.02 (1.009, 1.03)	0.0002	1.02 (1.003, 1.028)	0.0119
Sex	0.75 (0.456, 1.227)	0.2504		
SLEDAI	1.01 (0.983, 1.031)	0.5676		
Neuropsychiatric lupus	2.27 (1.362, 3.786)	0.0017	2.72 (1.452, 5.086)	0.0018
Interstitial lung disease	1.52 (0.921, 2.508)	0.1011		
Hematological abnormality	0.28 (0.198, 0.404)	< 0.0001	0.23 (0.152, 0.347)	< 0.0001
Lupus nephritis	0.44 (0.318, 0.605)	< 0.0001	0.37 (0.252, 0.551)	< 0.0001
Infection	4.88 (3.492, 6.821)	< 0.0001	5.16 (3.529, 7.538)	< 0.0001

OR, odds ratio; *CI*, confidence interval; *SLEDAI*, systemic lupus erythematosus disease activity index

extremely high risk of death in young people, especially in childbearing women. The premature mortality exerted harmful effects on patients' quality of life. This result is in keeping with the results of other studies. Admittedly, there is still substantial room for improvement.

For 360 deceased patients, the total number of death events was 756, indicating that one patient owned more than two causes of death on average. We compared the composition of causes of death in several recent studies from western and Asian populations (Table 5). Great differences could be observed that Asian studies showed a higher proportion of infection and NPSLE, as well as a lower percentage of CVD and malignancy than western studies.

Infection remained the leading cause of death in recent Chinese and Asian studies, consistently accounting for over 30% [20, 22, 27–29]. Our findings also emphasized infection as the most common cause of death which occurred in nearly two-thirds of the deceased patients. Beyond the impaired immune functions and disease activity in SLE patients, high doses of glucocorticoids and immunosuppressive agents like cyclophosphamide are well-recognized risk factors for infection [30]. Much more patients received systemic glucocorticoids (95.0%) and cyclophosphamide (35.6%) in our study than those in a large-scale British cohort [31]. The aggressive therapeutic strategies played a key role in the dramatically high incidence of infection. Pulmonary involvement of SLE like interstitial lung disease and pleural effusion might potentially increase susceptibility to pulmonary infections.

As reported in most recent studies from western countries, CVD is a significant even leading cause of death in patients with SLE [7, 9, 13]. In a SLE cohort at Karolinska University Hospital, CVD accounted for nearly half of the death causes [32]. However, our study presented only 4 deaths (1.1%) caused by acute cardiovascular events, 20 deaths (5.6%) caused by lupus cardiomyopathy, and 5 deaths caused by intracranial hemorrhage. The total number of deaths caused by CVD was 86 when NPSLE was included, accounting for 28.9% of 360 deceased patients and 11.4% of 756 death events. Reports on the epidemiology of CVD in Europe and the Americas have shown that coronary heart disease or ischemic heart disease is the leading component, whose percentage is almost twice as much as the following percentage of cerebrovascular disease like stroke [33, 34]. On the contrary, the report on CVD in China demonstrates that the mortality of cerebrovascular disease is higher than that of coronary heart disease [35]. For the overall mortality of CVD, no ethnic differences have been found among the general population in different countries. Therefore, the remarkable composition difference of CVD between Chinese and western populations might play a critical role in the great disparity of CVD as death cause in SLE patients. Moreover, the patients enrolled in our cohort were mainly from department of rheumatology and immunology, so patients directly admitted to department of cardiology or emergency ward were missed. This resulted in the underestimation of CVD mortality in SLE patients. Malignancy was responsible for six deaths (1.7%) in our SLE cohort, which was similarly lower than the results reported in European studies [7, 13]. Considering that the deaths due to malignancy observed in the control group without SLE were more than those in SLE group according to the above two studies, omission of patients in other related departments could be an important bias in our study (Table 6).

In our study, lupus nephritis and hematology abnormality, despite the second and third common causes of death, occurred more frequently in the survivals than in the deaths. The logistic regression analysis confirmed the strong correlation between them. Owing to more than one cause of death permitted in one patient in our study, the result implied that lupus nephritis and hematology abnormality themselves were not risk factors for mortality. The complications of powerful treatment like infection were the actual causes of death.

The major limitations of our study were the heterogeneity between centers in a multicenter cohort and the underestimation of mortality during hospitalization due to discharge against medical advice. As a mutual disadvantage, the heterogeneity in multiple centers was unavoidable in the

Table 6 Characteristics of nine recent studies related to mortality and causes of death in SLE patients compared with our study

Variables	Our study	S.B, 2006 [9]	J.A, 2015 [29]	F.R, 2016 [13]	K.L, 2014 [7]	K.K, 2011 [30]	C.M, 2011 [27]	X. Feng, 2016 [28]	Y·F, 2014 [22]	G·W, 2014 [20]
Region	China	International	USA	UK	Norway	South Korea	Hong Kong	China	China	China
Cases	29,510	9547	42,221	2740	325	1010	5243	1372	3831	665
Period	2005–2014	1958–2001	2000–2006	1999–2012	1999–2009	1997–2007	1999–2008	1999–2015	1986–2012	2006–2009
Deaths	360	1255	2058	227	50	59	514	236	268	81
SMR	2.13	2.4	19.07[#]	15.84[#]	3.0	97.8%[*]	2.63	NA	NA	91.2%[*]
Causes of death										
-1st	Infection	Circulatory disease	NA	Circulatory disease	CVD	Infection	Infection	Infection	Infection	Infection
-2nd	Lupus nephritis	Active lupus	NA	Malignancy	Infection	Active SLE	Disease activity	Neuropsychiatric	Neuropsychiatric	CVD
-3rd	Hematological abnormality	Malignancy	NA	Disease of MSK system and CT	Malignancy	Cerebrovascular disease	Malignancy	Renal failure	Renal involvement	Renal failure
-4th	Neuropsychiatric lupus	Infection	NA	Respiratory disease	Renal disease	NA	CVD	Cardiopulmonary	Pulmonary hypertension	Disease activity
-5th	Interstitial lung disease	NA	NA	Digestive disease	NA	NA	Cerebrovascular disease	Gastrointestinal	Alveolar hemorrhage	Cerebrovascular disease

NA, not available; *MSK*, musculoskeletal; *CT*, connective tissue; *CVD*, cardiovascular disease

[*] 5-year survival rate

[#] /1000 person-years

identification of death causes and the collection of data like various medication use in clinical practice. Given the traditional customs in China, a number of patients are willing to go back home when facing death, so the failure to follow up the end-stage patients who left hospital without effective treatment did underestimate the actual mortality in our cohort. The percentage of this kind of patients varied from centers.

In summary, SLE remained a life-threatening disease and patients at younger age of diagnosis had poorer prognosis. Infection was the leading cause of death in recent China, followed by active SLE organ damages. CVD and malignancy were insignificant in the composition of death causes. Ethnicity and medications might offer an explanation for the difference in causes of death between Asian and western countries. However, further research was required to understand the mechanisms behind it.

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Compliance with ethical standards

Ethics approval and consent to participate This study was approved by the Clinical Ethics Committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, West China Hospital of Sichuan University, People's Hospital of Guangdong Province, The First Hospital Affiliated to China Medical University, The First Hospital Affiliated to Zhejiang University, People's Hospital of Sichuan Province, The Second Xiangya Hospital of Central South University, People's Hospital of Xinjiang Uygur Autonomous Region, People's Hospital of Jiangsu Province, and Changhai Hospital.

Consent for publication Written consents to publication from the participants to report individual patient data were obtained. All necessary consents from any patients or parents of the patients (children) involved in the study, including consent to participate in the study where appropriate were obtained.

Disclosures None.

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