J Chin Med Assoc

ORIGINAL ARTICLE

Risk factors for mortality in systemic lupus erythematosus patients: Analysis of adult and pediatric cohorts in Taiwan

Chien-Chih Lai[a,b,c], Yi-Syuan Sun[a,b,c], Wei-Sheng Chen[a,b,c], Hsien-Tzung Liao[a,c], Ming-Han Chen[a,c], Chang-Youh Tsai[a,c,d], De-Feng Huang[a], Chung-Tei Chou[a], Deh-Ming Chang[a,b,e,f,*]

[a]Division of Allergy, Immunology, and Rheumatology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Institute of Clinical Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC [c]Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [d]Division of Immunology and Rheumatology, Fu Jen Catholic University Hospital, New Taipei City, Taiwan, ROC; [e]Graduate Institutes of Life Sciences, National Defense Medical Center, Taipei, Taiwan, ROC; [f]Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, ROC

Abstract

Background: Overall survival of systemic lupus erythematosus (SLE) patients significantly increased in recent decades, however, the relative risk of mortality is still high. Long-term survival outcome of pediatric SLE remains unclear. This study aims to explore the long-term survival rate and its predictors in patients with systemic lupus erythematosus (SLE).

Methods: A retrospective, hospital-based cohort study was performed between 2004 and 2018 in a tertiary referral medical center in Taiwan. Data on comorbidities, medications, and causes of admission were collected for risk factor analysis using time-dependent multivariate Cox proportional hazards models.

Results: A total of 2392 adults and 115 pediatric SLE patients were enrolled (female, n = 2157 and 95, respectively). The 10-year survival rates were 93.2%, 90.2%, 98.9%, and 100% in adult women, adult men, girls, and boys with SLE, respectively. The overall mortality rate was 2.09 case/100 patient-years (PY) for male SLE and 1.39 case/100 PY for female SLE patients. Male SLE patients did not have a statistically significantly higher mortality rate than female SLE patients in each age stratification. Infectious disease (n = 119), heart failure (n = 21), and cerebrovascular accident (n = 14) were the leading causes of death in adult SLE patients. Advanced age (hazard ratio [HR]: 1.04, 95% confidence interval [CI]: 1.03-1.05), treatment with mean dosage of systemic glucocorticoid equivalent to >10 mg/d of prednisolone (HR: 1.71, 95% CI: 1.14-2.57), comorbidities with malignancy (HR: 1.94, 95% CI: 1.22-3.09), chronic kidney disease (HR: 1.86, 95% CI: 1.25-2.77), hypertension (HR: 1.42, 95% CI: 1.01-1.98), and admission due to bacterial pneumonia (HR: 1.92, 95% CI: 1.12-3.31) and sepsis (HR: 2.78, 95% CI: 1.51-5.13) were independent risk factors for mortality in SLE patients.

Conclusion: SLE patients with advanced age, malignancy, chronic kidney disease, hypertension, treated with a higher average dosage of glucocorticoids, and admission due to bacterial pneumonia and sepsis have an increased risk of mortality.

Keywords: Chronic kidney disease; Glucocorticoid; Hypertension; Malignancy; Mortality; Risk factor; Sepsis; Systemic lupus erythematosus

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease characterized by immune disorders that involves multiple organs and systems through autoimmunity and systemic inflammations. SLE is also associated with irreversible damage to multiple organs if the disease activity is not adequately controlled by immunosuppressive agents. Thus, SLE patients also have an increased mortality rate than the general population.[1–3] Although the treatment of SLE has progressed in recent decades, its relative risk of mortality is high.[3–6] The attempt to improve survival in SLE patients cannot neglect the management of risk factors of mortality.

SLE patients who are men[7] with a larger cumulative steroid exposure,[8,9] advanced age with comorbidities,[10,11] and presence of serious infections[2] have an increased risk of mortality. Infectious diseases, cardiovascular diseases, and malignancy are the common causes of death in SLE patients.[12–14] However, the impact of sex difference on long-term survival remains controversial in SLE.[15,16] In addition, several risk factors only predict a 120-day survival,[9] risk factors of long-term mortality, especially predictors of 10-year mortality, were not fully investigated so far. The rate of long-term end organ damage is reported to be high in children with SLE.[17] Further, few studies described long-term survival outcome in pediatric SLE patients.

*Address correspondence. Dr. Deh-Ming Chang, Division of Allergy, Immunology, and Rheumatology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: ming0503@ms3.hinet.net (D.-M. Chang).

Conflicts of interest: Dr. Chang-Youh Tsai and Dr. Deh-Ming Chang, editorial board members at Journal of the Chinese Medical Association, have no roles in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 1044-1050.

Received June 5, 2022; accepted June 20, 2022.

doi: 10.1097/JCMA.0000000000000783.

To improve the survival in SLE patients, we explored detailed comorbidities that affect the survival in SLE patients as well as the long-term outcome in adult and pediatric SLE patients. Longitudinal cohorts of adult and pediatric SLE patients of a tertiary referral medical center in Taiwan were utilized. SLE-related characteristics and long-term survival rates were analyzed.

2. METHODS

2.1. Patient enrollment

The outpatient and discharge notes from Taipei Veterans General Hospital between November 20, 2004, and June 23, 2018, were retrospectively reviewed, and 3186 patients who ever received hospital admissions with diagnostic codes of SLE were identified. The diagnostic codes of SLE are included in Supplementary Table 1 (http://links.lww.com/JCMA/A160). The index date of enrollment was defined as the date that the patient started to receive outpatient care or underwent hospitalization in our hospital. The pediatric SLE patients were identified based on the age of disease onset <18 years and the adult patients were those with a disease onset of ≥18 years.[18] We excluded the patients who were followed up for <2 weeks (n = 679). Finally, a total of 2507 patients were enrolled in this study. The study protocol was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (2017-03-010C and 2020-07-026CC). The waiver of the requirement of the informed consent form was approved by the IRB since this study was based on retrospective chart reviews.

2.2. Study endpoints

The endpoint of this study was the survival status of each patient. The follow-up period was continued until the occurrence of mortality or termination of the database. For the dead SLE patients, the cause of death was verified according to the death certificates prescribed by the primary care physicians and two independent rheumatologists (C.-C. Lai and Y.-S. Sun).

2.3. Risk factor analysis of mortality

The background characteristics and comorbidities that may influence the mortality rate were identified using the medical records or relevant diagnostic codes in outpatient and discharge notes. These comorbidities included hypertension, diabetes, chronic kidney disease (CKD), cerebrovascular accident, deep vein thrombosis (DVT), viral hepatitis, gouty arthritis, antiphospholipid syndrome, and previous abortions. To study the impact of malignant neoplasms on mortality in SLE patients, the most common causes of cancer mortality were identified by the diagnostic codes in discharge notes (Supplementary Table 1, http://links.lww.com/JCMA/A160). Medications and therapeutics include the use of antiplatelet agents, anticoagulants, novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban), and plasma exchange were collected. Other risk factors included the immunosuppressants and average daily dosage of systemic glucocorticoids in prednisolone or its equivalence that were used during the study period, admission times, history of intensive care unit (ICU) admission, sepsis that requires vasopressors despite fluid resuscitations, and causes of admission.

2.4. Statistical analysis

Categorical data were analyzed by χ^2 test and numerical data by Student's t test. To identify the influence of sex differences in survival status, the adult and pediatric SLE patients were grouped according to sex and further analyzed in different age subgroups. The age- and sex-specific mortality rate (per 100 PY) and mortality rate ratio (95% confidence interval [CI]) for male compared to female SLE patients were calculated according to Poisson distribution. To explore the risk factors of mortality in the SLE patients, including the time-varying comorbidities and causes of hospital admission, a Cox proportional hazards model with time-dependent covariates was utilized. Parameters with a p value <0.05 were all included in the multivariate analysis. The survival status was estimated by Kaplan-Meier method and Mantel-Haenszel test. A p value <0.05 was considered statistically significant. SQL Server 2012 (Microsoft, Redmond, WA, USA) was used for data linkage, processing, and sampling. All statistical analyses were performed with IBM SPSS (version 19; Chicago, IL, USA), R foundation (R) version 4.1.2 (2021-11-01), or StataSE (version 11; College Station, TX, USA) software.

3. RESULTS

3.1. Characteristics of the enrolled SLE patients

A total of 2392 adult and 115 pediatric SLE patients were enrolled in this study. The background characteristics of the adult and pediatric patients are revealed in Tables 1 and 2, respectively.

These patients were followed up for a median (interquartile range) of 4.1 (1.5-8.1) years for adult SLE patients and 6.8 (2.7-10.3) years for pediatric SLE patients. Female sex accounted for the majority of the enrolled populations (whole SLE: 89.8%, adult SLE: 90.2%, and pediatric SLE: 82.6%). A minority of these patients had biopsy-proven lupus nephritis (LN). The classification of LN did not differ between women and men (Supplementary Table 2, http://links.lww.com/JCMA/A160).

In the adult SLE cohort, the mean (standard deviation [SD]) enrollment age in women and men was 41.3 (14.4) years and 48.0 (20.1) years, respectively. The mean enrollment age was statistically lesser in women with SLE than that in men (p < 0.001). There were several other characteristics with sex differences that exist in the adult SLE patients. As compared to women with SLE, male SLE patients had significantly higher rates of hypertension, coronary artery disease, CKD, cerebrovascular accident, and gouty arthritis and were treated more frequently with clopidogrel (Table 1).

Breast cancers, followed by lung cancers, colonorectoanal cancer, and non-Hodgkin's lymphoma were the most common cancer types in adult female SLE patients. Although no difference was found between female and male SLE patients in terms of overall malignancy rate, men with SLE experienced a significantly higher rate of non-Hodgkin's lymphoma (2.1% vs. 0.6%), hepatobiliary cancer (2.6% vs. 0.6%), and esophageal cancer (0.9% vs. 0.05%) than women. Male SLE patients had a significantly higher rate of ICU admission than female patients (22.1% vs. 14.5%, p = 0.002). In terms of the cause of admission, male SLE patients had a significantly higher rate of bacterial pneumonia (11.1% vs. 6.1%, p = 0.003) than female SLE patients. The 5-year survival rates were numerically lower in male than in female SLE patients (91.9% vs. 94.9%).

The pediatric SLE patients were enrolled at a mean (SD) age of 14.4 (3.4) years in girls and 13.9 (5) years in boys (Table 2). These patients were followed up for 6.4 (5.6-7.1) years. As compared to boys with SLE, the girls with SLE had a significantly higher rate of hypertension (23.2% vs. 0, p = 0.017) and treatment with systemic glucocorticoids during the follow-up period (88.4% vs. 70%, p = 0.035). No statistical difference was found in terms of admission times, ICU admission rate, the specific cause of admission, and survival status between the girls and boys with SLE. The 5-year and 10-year survival rates were 99.1% and 99.1% for all children, 98.9% and 98.9% for girls, and 100% and 100% for boys with SLE, respectively.

Table 1

Background characteristics of the adult systemic lupus erythematosus patients

Parameter	Women (n = 2157)	Men (n = 235)	*p*
Enrollment age, y	41.3 (14.4)	48.0 (20.1)	<0.001
Follow-up period, y	5.0 (3.8)	4.2 (3.7)	0.004
Lupus nephritis[a]	202 (9.4)	26 (11.1)	0.4
Comorbidity			
Hypertension	607 (28.10)	102 (43.4)	<0.001
Chronic kidney disease	274 (12.7)	47 (20.0)	0.002
Antiphospholipid syndrome	274 (12.7)	27 (11.5)	0.594
Coronary artery disease	116 (5.4)	33 (14.0)	<0.001
Cerebrovascular accident	114 (5.3)	20 (8.5)	0.041
Malignancy	147 (6.8)	22 (9.4)	0.148
Breast cancer	34 (1.6)	0	0.104
Lung cancer	24 (1.1)	3 (1.3)	0.821
Colonorectoanal cancer	14 (0.6)	3 (1.3)	0.277
Non-Hodgkin's lymphoma	13 (0.6)	5 (2.1)	0.010
Ovarian cancer	13 (0.6)	0	0.233
Hepatobiliary cancer	12 (0.6)	6 (2.6)	0.001
Cervical cancer	10 (0.5)	0	0.296
Leukemia	9 (0.4)	1 (0.4)	0.985
Uterine cancer	7 (0.3)	0	0.382
Renal cellular carcinoma	7 (0.3)	0	0.382
Bladder cancer	4 (0.2)	2 (0.9)	0.053
Gastric cancer	4 (0.2)	1 (0.4)	0.444
Oral cancer	4 (0.2)	2 (0.9)	0.053
Pancreatic cancer	4 (0.2)	0	0.509
Nasopharyngeal cancer	2 (0.1)	0	0.641
Esophageal cancer	1 (0.05)	2 (0.9)	0.001
Gouty arthritis	91 (4.2)	25 (10.6)	<0.001
Viral hepatitis	62 (2.9)	12 (5.1)	0.061
Deep vein thrombosis	39 (1.8)	6 (2.6)	0.425
Diabetes mellitus	35 (1.6)	8 (3.4)	0.051
Previous abortion	13 (0.6)	0	0.233
Medication and therapeutics			
Systemic glucocorticoid	1736 (80.5)	174 (74.0)	0.019
Prednisolone >10 mg/d[b]	371 (17.2)	42 (17.9)	0.883
Hydroxychloroquine	1187 (55.0)	104 (44.3)	0.002
Azathioprine	895 (41.5)	83 (35.3)	0.068
Mycophenolate	405 (18.8)	51 (21.7)	0.278
Calcineurin inhibitor	212 (9.8)	24 (10.2)	0.851
Methotrexate	101 (4.7)	10 (4.3)	0.768
Leflunomide	36 (1.7)	4 (1.7)	0.970
Rituximab	180 (8.3)	21 (8.9)	0.756
Belimumab	5 (0.2)	0	0.460
Aspirin	409 (19)	52 (22.1)	0.243
Clopidogrel	71 (3.3)	22 (9.4)	<0.001
Warfarin	200 (9.3)	27 (11.5)	0.271
Enoxaparin	20 (0.9)	2 (0.9)	0.908
Heparin	7 (0.3)	2 (0.9)	0.211
NOAC	13 (0.6)	3 (1.3)	0.229
Plasma exchange	57 (2.6)	6 (2.6)	0.935
Admission time(s)	4.9 (5.6)	4.6 (4.8)	0.448
Admission ≥8 times	405 (18.8)	38 (16.2)	0.329
ICU admission, ever	313 (14.5)	52 (22.1)	0.002
Cause of admission			
Bacterial pneumonia	131 (6.1)	26 (11.1)	0.003
Sepsis	106 (4.9)	16 (6.8)	0.210
Acute kidney injury	69 (3.2)	13 (5.5)	0.062
VZV or HSV infection	66 (3.1)	12 (5.1)	0.093
Respiratory failure or ARDS	51 (2.4)	7 (3.0)	0.561
Pulmonary edema	14 (0.6)	4 (1.7)	0.076
Meningitis	13 (0.6)	0	0.233
CMV infection	13 (0.6)	0	0.233
Pulmonary embolism	5 (0.2)	1 (0.4)	0.573
5-y survival status	2048 (94.9)	216 (91.9)	0.050
10-y survival status	2010 (93.2)	212 (90.2)	0.092
Overall survival status	2000 (92.7)	212 (90.2)	0.166

Data were presented as number (%) or mean (standard deviation).

[a]Only available in 228 patients.

[b]Dose of systemic glucocorticoid is converted into prednisolone or its equivalence.

ARDS = adult respiratory distress syndrome; CMV = cytomegalovirus; HSV = herpes simplex virus; ICU = intensive care unit; NOAC = novel oral anticoagulants; VZV = varicella zoster virus.

3.2. Sex difference in survival status of SLE patients

To investigate the impact of sex differences on overall survival status, we analyzed the difference in mortality rates based on sex in each age subgroup (Table 3).

The overall mortality rates were 2.09/100 PY for male SLE and 1.39/100 PY for female SLE patients. No statistically significant higher mortality rate was found for male SLE patients as compared to female SLE patients (Table 3).

3.3. Cause of death among the SLE patients

A total of 157 women and 23 men with SLE died during the follow-up period. The causes of death are summarized in Table 4.

The most common causes of death in female SLE patients were infectious diseases (65% of all mortality cases), followed by heart failure (12.1%), cerebrovascular accidents (8.9%), pulmonary hemorrhage (8.3%), and malignancy (8.3%). Infectious diseases were also a common cause of death in male SLE patients (73.9%). The other causes of death in male SLE patients were malignancy (13%) and heart failure (8.7%). Pneumonia was the most common infectious disease that led to death in both sexes.

Two female children with SLE died during the study period; the cause of death was pneumonia (n = 1) and blood-stream infection (n = 1).

3.4. Risk factors of mortality in SLE patients

To explore the risk factor of mortality, background characteristics, medications, comorbidities, and causes of admission were analyzed and summarized in Table 5.

The multivariable model revealed that the enrollment age (hazard ratio [HR]: 1.04, 95% CI: 1.03-1.05), use of prednisolone equivalent dose of >10 mg/d (HR: 1.71, 95% CI: 1.14-2.57), comorbidities with malignancy (HR: 1.94, 95% CI: 1.22-3.09), CKD (HR: 1.86, 95% CI: 1.25-2.77), hypertension (HR: 1.42, 95% CI: 1.01-1.98), and admission due to bacterial pneumonia (HR: 1.92; 95% CI: 1.12-3.31) and sepsis (HR: 2.78, 95% CI: 1.51-5.13) independently increased the risk of mortality in SLE patients (Table 5). Other comorbidities, including diabetes, DVT, cerebrovascular accident, gout, or coronary artery disease, and other causes of admission did not independently associate with increased mortality in SLE patients.

To confirm the impact of the above independent risk factors, the survival rates estimated by Kaplan-Meier analysis are illustrated in Fig. 1. Among the age subgroups, the survival rates decreased with the advanced age during the follow-up period (log-rank p for trend <0.001, Fig. 1A). SLE patients treated with systemic glucocorticoid equivalent to prednisolone >10 mg/d (log-rank p = 0.003, Fig. 1B), having malignancy (log-rank p < 0.001, Fig. 1C), CKD (log-rank p = 0.001, Fig. 1D), hypertension (log-rank p = 0.027, Fig. 1E), hospital admission due to bacterial pneumonia (log-rank p < 0.001, Fig. 1F), and sepsis (log-rank p < 0.001, Fig. 1G) had significantly lower survival rates than patients without the above factors.

Table 2

Background characteristics of the pediatric systemic lupus erythematosus patients

Parameter	Girls (n = 95)	Boys (n = 20)	*p*
Enrollment age, y	14.4 (3.4)	13.9 (5.0)	0.547
Follow-up period, y	6.6 (4.1)	5.2 (4.0)	0.149
Lupus nephritis[a]	15 (15.8)	5 (25)	0.323
Comorbidity			
Hypertension	22 (23.2)	0	0.017
Antiphospholipid syndrome	15 (15.8)	2 (10)	0.507
Chronic kidney disease	10 (10.5)	4 (20.0)	0.239
Medication and therapeutics			
Systemic glucocorticoid	84 (88.4)	14 (70)	0.035
Prednisolone >10 mg/d[b]	8 (8.4)	3 (15)	0.363
Hydroxychloroquine	64 (67.4)	10 (50)	0.140
Azathioprine	46 (48.4)	8 (40)	0.493
Mycophenolate	32 (33.7)	9 (45)	0.337
Calcineurin inhibitor	20 (21.1)	5 (25)	0.697
Methotrexate	2 (2.1)	0	0.513
Rituximab	8 (8.4)	4 (20)	0.124
Belimumab	0	1 (5)	0.029
Aspirin	10 (10.5)	0	0.129
Clopidogrel	8 (8.4)	0	0.178
Warfarin	8 (8.4)	0	0.178
Heparin	1 (1.1)	1 (5)	0.220
Plasma exchange	7 (7.4)	1 (5)	0.705
Admission time(s)	8.5 (9.9)	9.6 (7.2)	0.662
Admission ≥8 times	36 (37.9)	11 (55.0)	0.157
ICU admission, ever	22 (23.2)	5 (25.0)	0.860
Cause of admission			
VZV or HSV infection	6 (6.3)	3 (15)	0.189
Acute kidney injury	6 (6.3)	2 (10)	0.556
Bacterial pneumonia	5 (5.3)	1 (5)	0.962
Sepsis	6 (6.3)	0	0.248
Respiratory failure or ARDS	2 (2.1)	0	0.513
Influenza	2 (2.1)	0	0.513
5-y survival status	94 (98.9)	20 (100)	0.645
10-y survival status	94 (98.9)	20 (100)	0.645
Overall survival status	93 (97.9)	20 (100)	0.513

Data were presented as number (%) or mean (standard deviation).

[a]Only available in 20 patients.

[b]Dose of systemic glucocorticoid is convered into prednisolone or its equivalence.

ARDS = adult respiratory distress syndrome; HSV = herpes simplex virus; ICU = intensive care unit; VZV = varicella zoster virus.

Table 3

The mortality rate and mortality rate ratio among different subgroups of SLE patients

	Mortality rate, per 100 patient-years (95% CI)		Mortality rate ratio	*p*
Age subgroup	Male SLE	Female SLE	(95% CI)	
0-17 y	0	0.32 (0.08-1.27)	0 (0-32.36)	0.737
18-30 y	1.23 (0.4-3.78)	0.85 (0.59-1.23)	1.44 (0.28-4.64)	0.528
31-40 y	0.42 (0.06-2.97)	1.1 (0.78-1.56)	0.38 (0.01-2.28)	0.348
41-50 y	2.81 (1.28-6.18)	1.1 (0.75-1.63)	2.55 (0.85-6.36)	0.06
51-60 y	1.31 (0.33-5.17)	2.5 (1.8-3.47)	0.52 (0.06-2.03)	0.389
61-70 y	4.08 (1.05-15.84)	3.79 (2.56-5.61)	1.08 (0.12-4.33)	0.854
>70 y	9.08 (4.87-16.93)	6.66 (3.85-11.5)	1.36 (0.51-3.53)	0.484
Total	2.09 (1.39-3.13)	1.39 (1.19-1.63)	1.5 (0.92-2.33)	0.081

CI = confidence interval; SLE = systemic lupus erythematosus.

Table 4

Causes of death among the adult and pediatric SLE patients

Parameter	Women	Men
Adult SLE patient	n = 157	n = 23
Infectious disease	102 (65)	17 (73.9)
Pneumonia	46 (29.3)	11 (47.8)
Intra-abdominal infection	15 (9.6)	3 (13)
Soft tissue infection	12 (7.6)	0
Blood-stream infection, including IE	6 (3.8)	2 (8.7)
Invasive fungal infection	4 (2.5)	2 (8.7)
Pancreatitis	3 (1.9)	0
Meningitis	2 (1.3)	1 (4.3)
Urosepsis	2 (1.3)	0
Heart failure	19 (12.1)	2 (8.7)
Pulmonary arterial hypertension	6 (3.8)	0
Myocardial infarction	5 (3.2)	1 (4.3)
Arrhythmia	2 (1.3)	0
Cerebrovascular accident	14 (8.9)	0
Intracranial hemorrhage	9 (5.7)	0
Subarachnoid hemorrhage	3 (1.9)	0
Cerebral infarction	3 (1.9)	0
Malignancy	13 (8.3)	3 (13)
Pulmonary hemorrhage	13 (8.3)	0
SLE	2 (1.3)	0
Catastrophic antiphospholipid syndrome	0	1 (4.3)
Posterior reversible encephalopathy syndrome	1 (0.6)	0
Pediatric SLE patient	n = 2	n = 0
Infectious disease	2 (100)	0
Pneumonia	1 (50)	0
Blood-stream infection	1 (50)	0

Data were presented as number (%).

IE = infected endocarditis; SLE = systemic lupus erythematosus.

4. DISCUSSION

Adult and pediatric SLE patients who ever received hospital admission were investigated and the 10-year survival rates were all >90% in both sexes. Additionally, our data revealed that children with SLE have more favorable survival outcomes than adult SLE patients. Breast cancer, lung cancer, colonorectoanal cancer, and non-Hodgkin's lymphoma were the leading malignancies in female SLE patients in our cohort. We also found that the advanced age had a higher impact on survival than sex difference. The mortality rate increased when the adult SLE patients were treated with an average dose of systemic glucocorticoids equivalent to prednisolone >10 mg/d and hospitalized for bacterial pneumonia and sepsis. Moreover, our data discovered that comorbidities with malignancy, CKD, and hypertension reduce the survival rate of SLE patients.

Compared to general populations, SLE patients have relatively higher mortality rates.[1,3,6] The 10-year survival rate in the present study falls within the range of recent investigations (68.8%-94.9%).[4,5,19–22] Due to the development of novel pharmaceutical agents, the trend in mortality rates decreased in recent years as compared to that few decades ago.[1,3,23,24] Ethnic, geographic, and secular changes and social-economic differences contribute to the heterogeneity of survival rates in SLE patients. Our study specifically enrolled SLE patients with history of hospitalizations, which would be more severe in disease activities than patients who just require outpatient care.

Male SLE patients were recognized to have a higher age of SLE disease onset, more severe disease in both renal and extrarenal manifestations, and higher lupus-related organ damage, end-stage renal disease, and higher mortality rates.[7,15,23] The enrollment age of male SLE patients was also found to be higher than female patients in our adult cohort. Several comorbidities including hypertension, CKD, and cerebrovascular accidents were more prevalent in men than in women, which are

Table 5

Multivariable analysis for the risk factors of mortality among the adult and pediatric systemic lupus erythematosus patients

Parameter	HR (95% CI)	*p*
Enrollment age, y	1.04 (1.03-1.05)	<0.001
Prednisolone >10 mg/d	1.71 (1.14-2.57)	0.010
Comorbidity		
Malignancy	1.94 (1.22-3.09)	0.005
Chronic kidney disease	1.86 (1.25-2.77)	0.002
Hypertension	1.42 (1.01-1.98)	0.042
Diabetes mellitus	1.96 (0.94-4.08)	0.073
Deep vein thrombosis	1.43 (0.58-3.52)	0.352
Cerebrovascular accident	1.14 (0.64-2.05)	0.658
Gout	1.64 (0.99-2.70)	0.051
Coronary artery disease	1.30 (0.77-2.20)	0.326
Cause of admission		
Bacterial pneumonia	1.92 (1.12-3.31)	0.018
Sepsis	2.78 (1.51-5.13)	0.001
Acute kidney injury	1.42 (0.67-3.00)	0.367
Respiratory failure or ARDS	1.35 (0.48-3.81)	0.576
Cytomegalovirus infection	2.20 (0.49-9.78)	0.302

ARDS = adult respiratory distress syndrome; CI = confidence interval; HR = hazard ratio.

consistent with the findings of previous studies.[7,15,16] However, we did not find a statistically significant higher mortality rate ratio for male SLE as compared to female SLE patients. Several studies also revealed that the mortality rate in male SLE patients was not statistically different from that in female patients.[8,15,16]

Exposure to systemic glucocorticoids is considered to increase the mortality rate of SLE. Cumulative exposure of systemic glucocorticoids or recent high-dose glucocorticoid treatment has the risk of invasive fungal infections and is associated with an increased risk of mortality in SLE.[8,25,26] Furthermore, the present study revealed that the average daily dose of systemic glucocorticoids equivalent to >10 mg of prednisolone increases the mortality in adult SLE patients who ever received hospital admission. A higher average daily dose of steroid treatment is aimed to control disease activities in severe SLE patients, and the risk of sepsis usually increased according to our risk factor analysis.

SLE patients have increased rate of multiple malignancies, including lymphoma, hematologic malignancy, cancer of the lung, cervix, thyroid, and bladder.[27,28] Malignancy remains the major cause of death reported in many SLE studies.[1,4,14] All of the abovementioned cancers were found in our adult SLE cohort. Breast cancer, lung cancer, colonorectoanal cancer, and non-Hodgkin's lymphoma were the most common cancer types in female SLE; hepatobiliary cancer, non-Hodgkin's lymphoma, lung cancer, and colonorectoanal cancers were the leading cancer types in male SLE patients. The mortality rate would markedly increase with the advanced staging of malignancy and could decrease with the remission of the tumor under treatment. Additionally, malignancy independently increased the mortality rate in our time-dependent multivariable Cox proportional hazard model. Although one meta-analysis indicated that the standardized mortality ratio (SMR) did not increase in SLE patients with cancer,[29] several issues still need to be addressed. First, the equivalent cancer-specific SMR in SLE still cannot exempt its survival impact on SLE patients. Malignancy remains the major cause of death reported in many studies.[1,4,14] Second, the composition of cancer types, staging, and treatment responses may differ in each ethnic and geographic region.

Hypertension, mean daily dose of prednisolone >5 mg/d, antiphospholipid syndrome, and cumulative organ damage were associated with the development of thrombotic events in SLE.[30] Hypertension was associated with more severe renal interstitial fibrosis and tubular atrophy in patients with LN and was also an independent predictor of mortality.[31] We further found that hypertension and CKD increased the mortality rate of SLE patients. According to the present data, aggressive monitoring and management of hypertension is a crucial treatment target in all SLE patients.

Infectious diseases, cardiovascular diseases, and malignancy were major causes of death in our adult SLE patients, and the findings are consistent with many previous studies.[1,2,4,12,14,19,20,32] Judicious use of systemic glucocorticoids and early diagnosis and precise treatment of infections could improve the survival status in SLE patients. However, no universal protocols for infection surveillance were developed and validated till date. Thus, we suggest to be aware of the signs and symptoms of infectious diseases, especially for SLE patients with a history of hospital admission.

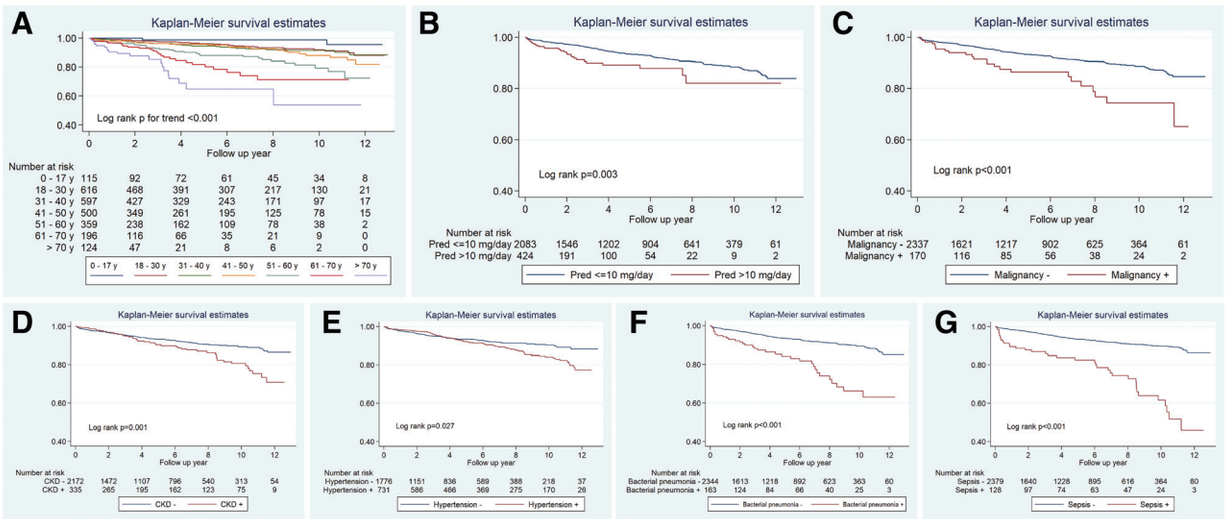

Fig. 1 The Kaplan-Meier survival estimates for the systemic lupus erythematosus patients according to the age subgroups (A), use of systemic glucocorticoids equivalent to prednisolone >10 mg/d (B), comorbidities with malignancy (C), CKD (D), hypertension (E), and medical history of bacterial pneumonia (F), and sepsis (G). Pred = prednisolone; CKD = chronic kidney disease.

Our study has several limitations. First, the study was a single-center study, and the findings cannot be generalized. Second, there were few cases that were lost to follow-up due to a change of medical care feasibility. Major outcomes, including infection, malignancy, and mortality, could not be identified throughout. This condition could be minimized since our hospital is recognized as a tertiary referral center in Taiwan, especially for critically ill SLE patients. Besides, our hospital earned the credential of 2018 Center of Excellence of Asia Pacific League of Associations for Rheumatology. Third, the case number of pediatric and male SLE cohorts was not sufficiently large to observe the mortality outcome and further analyze its risk factors. A larger longitudinal multicentre study is warranted to investigate the survival of pediatric and adult SLE patients. A survival prediction model tailored for SLE patients is also required to monitor the mortality risk in clinical practice.

In conclusion, the 10-year survival rates were >90% in both sexes in adult SLE patients and >98% in pediatric SLE patients with history of hospital admissions. Advanced age, instead of sex difference, contributed to mortality in SLE patients. Use of prednisolone or its equivalence of >10 mg/d, admission due to bacterial pneumonia, sepsis, and presence of malignancy, CKD, and hypertension were associated with higher mortality in SLE patients.

ACKNOWLEDGMENTS

The authors thank the staff of the Division of Allergy, Immunology, and Rheumatology of Taipei Veterans General Hospital as well as Hsin Yea, Yi Chung, Yi-Ting Wang, and Ching-Ti Keng for their support. This work was supported in part by the Ministry of Science and Technology, Taiwan (MOST 109-2628-B-075-014, MOST 110-2628-B-075-019, MOST 111-2314-B-075-005) and grants from Taipei Veterans General Hospital, Taipei, Taiwan (V110B-014, V110B-036, V111C-153). The funders have no role in study design, data collection, analysis, interpretation, or writing of the manuscript.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A160.

REFERENCES

1. Rees F, Doherty M, Grainge MJ, Lanyon P, Davenport G, Zhang W. Mortality in systemic lupus erythematosus in the United Kingdom 1999-2012. *Rheumatology (Oxford)* 2016;**55**:854–60.
2. Kedves M, Kósa F, Kunovszki P, Takács P, Szabó MZ, Karyekar C, et al. Large-scale mortality gap between SLE and control population is associated with increased infection-related mortality in lupus. *Rheumatology (Oxford)* 2020;**59**:3443–51.
3. Yen EY, Shaheen M, Woo JMP, Mercer N, Li N, McCurdy DK, et al. 46-Year Trends in systemic lupus erythematosus mortality in the United States, 1968 to 2013: a nationwide population-based study. *Ann Intern Med* 2017;**167**:777–85.
4. Elfving P, Kariniemi S, Kautiainen H, Virta LJ, Kaipiainen-Seppänen O, Puolakka K. Mortality in SLE patients compared with population controls in Finland in years 2000-2015. *Rheumatology (Oxford)* 2021;**60**:4238–44.
5. Mohammed RHA, Lotfy Fayed H, Ibrahim Emara N. Mortality and disease related comorbidities in systemic lupus erythematosus: data from an Egyptian cohort. *Lupus* 2022;**31**:628–36.
6. Bournia VK, Fragoulis GE, Mitrou P, Mathioudakis K, Tsolakidis A, Konstantonis G, et al. All-cause mortality in systemic rheumatic diseases under treatment compared with the general population, 2015-2019. *RMD Open* 2021;**7**:e001694.
7. Tan TC, Fang H, Magder LS, Petri MA. Differences between male and female systemic lupus erythematosus in a multiethnic population. *J Rheumatol* 2012;**39**:759–69.
8. Bultink IEM, de Vries F, van Vollenhoven RF, Lalmohamed A. Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls. *Rheumatology (Oxford)* 2021;**60**:207–16.
9. Yang Y, Jiang H, Wang C, Jiang N, Wu C, Zhang S, et al. Clinical characteristics and prognoses of patients with systemic lupus erythematosus hospitalized for pulmonary infections. *Front Med (Lausanne)* 2021;**8**:732681.
10. Riveros Frutos A, Casas I, Rúa-Figueroa I, López-Longo FJ, Calvo-Alén J, Galindo M, et al; RELESSER Group, part of the Spanish Society of Rheumatology Systemic Autoimmune Diseases Study Group (EASSER). Systemic lupus erythematosus in Spanish males: a study of the Spanish Rheumatology Society Lupus Registry (RELESSER) cohort. *Lupus* 2017;**26**:698–706.
11. Kuo CF, Chou IJ, Rees F, Grainge MJ, Lanyon P, Davenport G, et al. Temporal relationships between systemic lupus erythematosus and comorbidities. *Rheumatology (Oxford)* 2019;**58**:840–8.
12. Wu XY, Yang M, Xie YS, Xiao WG, Lin J, Zhou B, et al. Causes of death in hospitalized patients with systemic lupus erythematosus: a 10-year multicenter nationwide Chinese cohort. *Clin Rheumatol* 2019;**38**:107–15.
13. Dhital R, Pandey RK, Poudel DR, Oladunjoye O, Paudel P, Karmacharya P. All-cause hospitalizations and mortality in systemic lupus erythematosus in the US: results from a national inpatient database. *Rheumatol Int* 2020;**40**:393–7.
14. Lorenzo-Vizcaya A, Isenberg D. Analysis of trends and causes of death in SLE patients over a 40-years period in a cohort of patients in the United Kingdom. *Lupus* 2021;**30**:702–6.
15. Ramírez Sepúlveda JI, Bolin K, Mofors J, Leonard D, Svenungsson E, Jönsen A, et al; DISSECT Consortium. Sex differences in clinical presentation of systemic lupus erythematosus. *Biol Sex Differ* 2019;**10**:60.
16. Alonso MD, Martínez-Vázquez F, Riancho-Zarrabeitia L, Díaz de Terán T, Miranda-Filloy JA, Blanco R, et al. Sex differences in patients with systemic lupus erythematosus from Northwest Spain. *Rheumatol Int* 2014;**34**:11–24.
17. Cann MP, Sage AM, McKinnon E, Lee SJ, Tunbridge D, Larkins NG, et al. Childhood systemic lupus erythematosus: presentation, management and long-term outcomes in an Australian cohort. *Lupus* 2022;**31**:246–55.
18. Smith EMD, Egbivwie N, Jorgensen AL, Ciurtin C, Al-Abadi E, Armon K, et al. Real world treatment of juvenile-onset systemic lupus erythematosus: data from the UK JSLE cohort study. *Clin Immunol* 2022;**239**:109028.
19. Mok CC. Epidemiology and survival of systemic lupus erythematosus in Hong Kong Chinese. *Lupus* 2011;**20**:767–71.
20. Kang KY, Kwok SK, Ju JH, Park KS, Cho CS, Kim HY, et al. The causes of death in Korean patients with systemic lupus erythematosus over 11 years. *Lupus* 2011;**20**:989–97.
21. Pamuk ON, Akbay FG, Dönmez S, Yilmaz N, Calayir GB, Yavuz S. The clinical manifestations and survival of systemic lupus erythematosus patients in Turkey: report from two centers. *Lupus* 2013;**22**:1416–24.
22. Yang Y, Thumboo J, Earnest A, Yong SL, Fong KY. The effect of comorbidity on hospital mortality in patients with SLE from an Asian tertiary hospital. *Lupus* 2014;**23**:714–20.
23. Chang DM, Chang CC, Kuo SY, Chu SJ, Chang ML. The clinical features and prognosis of male lupus in Taiwan. *Lupus* 1998;**7**:462–8.
24. Mak A, Cheung MW, Chiew HJ, Liu Y, Ho RC. Global trend of survival and damage of systemic lupus erythematosus: meta-analysis and meta-regression of observational studies from the 1950s to 2000s. *Semin Arthritis Rheum* 2012;**41**:830–9.
25. Hung ML, Liao HT, Chen WS, Chen MH, Lai CC, Tsai CY, et al. Invasive aspergillosis in patients with systemic lupus erythematosus: a retrospective study on clinical characteristics and risk factors for mortality. *Lupus* 2018;**27**:1944–52.
26. Su CF, Lai CC, Li TH, Chang YF, Lin YT, Chen WS, et al. Epidemiology and risk of invasive fungal infections in systemic lupus erythematosus: a nationwide population-based cohort study. *Ther Adv Musculoskelet Dis* 2021;**13**:1759720X211058502.
27. Ladouceur A, Clarke AE, Ramsey-Goldman R, Bernatsky S. Malignancies in systemic lupus erythematosus: an update. *Curr Opin Rheumatol* 2019;**31**:678–81.
28. Clarke AE, Pooley N, Marjenberg Z, Langham J, Nicholson L, Langham S, et al. Risk of malignancy in patients with systemic lupus erythematosus: systematic review and meta-analysis. *Semin Arthritis Rheum* 2021;**51**:1230–41.

29. Lee YH, Choi SJ, Ji JD, Song GG. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. *Lupus* 2016;**25**:727–34.
30. Park DJ, Yoon CS, Choi SE, Xu H, Kang JH, Lee SS. Risk factors for thrombotic events in Korean patients with systemic lupus erythematosus. *Sci Rep* 2021;**11**:23529.
31. Rong R, Wen Q, Wang Y, Zhou Q, Qiu Y, Lu M, et al. Prognostic significance of hypertension at the onset of lupus nephritis in Chinese patients: prevalence and clinical outcomes. *J Hum Hypertens* 2022;**36**:153–62.
32. Mu L, Hao Y, Fan Y, Huang H, Yang X, Xie A, et al. Mortality and prognostic factors in Chinese patients with systemic lupus erythematosus. *Lupus* 2018;**27**:1742–52.