Differences in Clinical Features and Mortality between Childhood-onset and Adult-onset Systemic Lupus Erythematosus: A Prospective Single-center Study

Young Bin Joo, So-Yeon Park, Soyoung Won, and Sang-Cheol Bae

ABSTRACT. ***Objective.*** To compare clinical features and mortality between childhood-onset systemic lupus erythematosus (cSLE) and adult-onset SLE (aSLE) in a prospective single-center cohort.

Methods. A total of 1112 patients with SLE (133 cSLE and 979 aSLE) were enrolled and followed from 1998 to 2012. The 2 groups were compared regarding American College of Rheumatology (ACR) classification criteria for SLE, autoantibodies, disease activity measured by the Adjusted Mean SLE Disease Activity Index (AMS), damage measured by the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI), and medication. The standardized mortality ratio (SMR) was calculated. Predictors of mortality in SLE were evaluated using Cox proportional hazard models.

Results. After a mean followup of 7.6 years, patients with cSLE had a higher number of cumulative ACR criteria and a higher AMS ($p < 0.001$ each), but there was no difference in SDI ($p = 0.797$). Immunosuppressants were used more frequently by patients with cSLE ($p < 0.001$). The SMR of cSLE was 18.8 (95% CI 8.6–35.6), significantly higher than that of aSLE (2.9, 95% CI 2.1–3.9). We found cSLE to be an independent predictor of mortality (HR 3.6, $p = 0.008$). Moreover, presence of hemolytic anemia (7.2, $p = 0.034$) and antiphospholipid antibody (aPL; 3.8, $p = 0.041$) increased the magnitude of risk of early mortality more in the patients with cSLE than in those with aSLE.

Conclusion. The clinical course of cSLE as measured by number of clinical manifestations and disease activity is worse than that of aSLE. Also, cSLE patients with hemolytic anemia and aPL are at greater risk of death than patients with aSLE who have those features. (First Release June 1 2016; J Rheumatol 2016;43:1490–7; doi:10.3899/jrheum.151129)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
CLINICAL FEATURE
CHILDHOOD ONSET
MORTALITY

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that predominantly affects women of childbearing age. Patients diagnosed in childhood or adolescence (10%-20%)[1] tend to have worse clinical outcomes[2,3,4,5,6,7,8,9].

Efforts have been made to compare patients with childhood-onset SLE (cSLE) and adult-onset SLE (aSLE). For example, a nested case-control study was conducted in the LUMINA cohort. However, the information obtained on cSLE was limited because cSLE in that cohort included only adolescent-onset SLE (≥ 11 yrs old)[9]. Another study was performed in a Canadian cohort, in which patients with cSLE and aSLE received care in the same academic hospital and came from similar social and environmental backgrounds[6]. However, these patients were in separate pediatric and adult cohorts.

A comparison between patients with cSLE and aSLE in a single cohort with similar backgrounds including environmental, genetic, and ethnic factors and receiving similar treatments is needed, because these factors could substantially affect SLE phenotypes and outcomes. The Hanyang BAE Lupus cohort is a prospective single-center cohort of homogeneous Korean ethnicity in a tertiary academic hospital that has been enrolling patients with cSLE and with aSLE since 1998. The background of this cohort seems to be more homogeneous than other cohorts regarding genetic, ethnic, and treatment factors. Thus, this study should provide more reliable comparisons between cSLE and aSLE without the compounding effects of these factors.

We have for the first time, to our knowledge, compared patients with cSLE versus aSLE from a single ethnic group in a single prospective cohort. Differences in clinical features

From the Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul; Department of Rheumatology, Myoungji Hospital, Goyang-si; Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, Republic of Korea.

Y.B. Joo, MD, Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases; S.Y. Park*, MD, PhD, Department of Rheumatology, Myoungji Hospital; S. Won, PhD, CRCRA; S.C. Bae, MD, PhD, MPH, Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, and CRCRA.*

**Dr. Joo and Dr. Park contributed equally to this study.*

Address correspondence to Dr. S.C. Bae, Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea. E-mail: scbae@hanyang.ac.kr

Accepted for publication April 18, 2016.

and outcomes including standardized mortality ratios (SMR) between the 2 groups were investigated and predictors of death were also evaluated.

MATERIALS AND METHODS

Study population. Between February 1998 and December 2012, 1112 patients with SLE were enrolled in the Hanyang BAE Lupus cohort, regardless of age[10]. This is a prevalent cohort; hence patients with SLE could be enrolled at any point after diagnosis. Patients diagnosed while under the age of 16 were defined as cSLE. All patients were Korean, and informed consent was obtained from all participants. This study protocol was approved by the Institutional Ethics Review Board of Hanyang University Hospital.

Data collection. All data are investigated annually except disease activity, which is evaluated at every clinical visit as well as annually. For data collection, standardized case report forms were used at enrollment and annual followup.

At baseline, the patients' sex and age at SLE diagnosis were recorded, and they were assessed for clinical manifestations represented by the 1997 American College of Rheumatology (ACR)[11] classification criteria, autoantibodies, disease activity measured by the SLE Disease Activity Index-2000 (SLEDAI-2K)[12], and organ damage measured by the Systemic Lupus International Collaborating Clinics/ACR SLE Damage Index (SDI)[13].

Cumulative results for the ACR criteria, autoantibodies, SLEDAI-2K, SDI, and prescribed medication were also collected. If a new manifestation expressed as an ACR criterion appeared between annual visits, it was recorded in cumulative ACR classification criteria based on medical records, even if it stopped after treatment. The antiphospholipid antibody (aPL) defined the presence of either lupus anticoagulant (LAC) or anticardiolipin antibody (aCL). Thirty patients whose LAC was not examined and for whom the result for aCL was negative were excluded from the estimation of the prevalence of aPL. To measure disease activity, we calculated the Adjusted Mean SLEDAI-2K (AMS), which corresponds to the area under the curve of the SLEDAI-2K scores over time[14], because the intervals between patients' visits could vary. Medications investigated included oral corticosteroid and high-dose intravenous (IV) corticosteroid defined as 500 mg/day or higher of methylprednisolone or hydroxychloroquine, and other immunosuppressants such as cyclophosphamide, mycophenolate mofetil, methotrexate, azathioprine, and cyclosporine.

Estimation of SMR and causes of death. Mortality data were derived by linking with data from the Korean National Statistics Office (KNSO)[15], and standardized mortality ratios (SMR) were calculated by comparison with the age- and sex-matched general population from 1998 to 2012, as recorded by the KNSO. Observed deaths were ascertained by linkage of the study patients' information to data available in the KNSO national death registry, and date and cause of death were identified. The person-years (PY) at risk for each patient were calculated by subtracting the date of enrollment in the cohort from the earlier of 2 exit dates (date of death or the end of the observation period, December 31, 2012). Expected mortality was calculated by multiplying each PY at risk in the cohort by the age- and sex-matched mortality. The SMR was calculated by dividing the observed number of deaths by the expected number, and 95% CI were based on the Poisson distribution.

Statistical analysis. Patient characteristics are expressed by means (SD) or numbers with proportions, as appropriate. Differences between the 2 groups were compared using 2-sample independent t tests, the chi-square test, or Fisher's exact test.

Cox proportional hazard models were used to assess predictors of mortality.

Two multivariable models were run. Model 1 used cSLE, number of ACR criteria, AMS, SDI score, and anti-Ro antibody as well as baseline age, sex, and disease duration as covariates. To determine whether important SLE manifestations including damage and activity were associated with mortality, we further analyzed those factors using model 2. In model 2, the individual ACR criteria and SDI domains with $p < 0.05$ in the univariate analysis were entered instead of the mean number of ACR criteria and mean SDI score, and the other covariates were the same as in model 1. To assess the influence of observations in our data on the models, and to check whether any outlier had a disproportionate effect on the models, we carried out model diagnostics using DFBETA analysis, which measures standardized differences between regression coefficients when a given observation is included or excluded. Further, we checked the model assumptions for the Cox proportional hazards model using proportional hazard assumption tests.

All statistical analyses were performed using SAS statistical software (Release 9.1, SAS). A p value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics. Table 1 lists patient demographic and clinical characteristics. A total of 1112 patients were analyzed, 133 (12.0%) with cSLE and 979 (88.0%) with aSLE. The mean age at the time of diagnosis was 12.5 years (SD 2.4, range 5–15) in the cSLE group and 29.4 years (SD 9.5, range 16–68) in the aSLE group. The female:male ratio in the cSLE group was lower than in the aSLE group (4:1 vs 17:1, cSLE vs aSLE, respectively, $p < 0.001$).

Clinical features represented by the ACR classification criteria and autoantibodies. The cumulative number of ACR criteria was significantly higher in the cSLE group than the aSLE group (6.0, SD 1.5 vs 5.5, SD 1.4, respectively, $p < 0.001$; Table 1). Among the cumulative disease-specific features, significant differences were found for malar rash ($p < 0.001$), photosensitivity ($p = 0.031$), renal involvement ($p = 0.001$), neurologic involvement ($p < 0.001$), and hemolytic anemia ($p = 0.003$), which were all seen more often in the cSLE group. Arthritis ($p < 0.001$) and leukopenia ($p = 0.029$) were more common in the aSLE group (Supplementary Table 1, available from the authors on request).

In the cSLE group, anti-dsDNA ($p = 0.024$) and aPL ($p < 0.001$) were more common than in the aSLE group, and anti-Ro antibody ($p = 0.004$) was less common (Table 1). In multiple testing using the Bonferroni correction, however, only anti-Ro antibody and LAC were significant.

Medication. The majority of patients were treated with oral corticosteroids. The frequency of immunosuppressant use was higher in the cSLE group ($p < 0.001$). Among the immunosuppressants, mycophenolate mofetil (39.1% vs 17.3%; $p < 0.001$) and azathioprine (41.4% vs 29.7%; $p = 0.009$) were the ones most frequently used during the followup period (Table 1).

Disease activity and organ damage. During the followup period, the cSLE group had a higher maximum SLEDAI score than the aSLE group ($p = 0.003$), and a higher AMS score ($p = 0.001$), whereas their cumulative damage was similar, although consisting of different components (Table 2). Of the SDI domains, the frequencies of musculoskeletal damage ($p = 0.018$) differed between the 2 groups. Of the SDI items, frequencies of cerebrovascular ($p = 0.034$), seizure ($p = 0.004$), and proteinuria ($p = 0.033$) were higher in the cSLE group, whereas erosive arthritis ($p = 0.019$) was lower.

Table 1. Characteristics of childhood-onset and adult-onset SLE.

Characteristics	Childhood-onset, n = 133	Adult-onset, n = 979	p
Age at diagnosis, yrs, mean ± SD (range)	12.5 ± 2.4 (5–15)	29.4 ± 9.5 (16–68)	< 0.001
Median (IQR)	13.0 (11, 14)	28.0 (22, 36)	< 0.001
Sex: female, n (%)	107 (80.5)	924 (94.4)	< 0.001
Followup period, yrs, mean ± SD (range)	7.2 ± 4.3 (0–15)	7.6 ± 4.4 (0–15)	0.344
ACR criteria, no.			
Cumulative, mean ± SD (range)	6.0 ± 1.5 (3–10)	5.5 ± 1.4 (2–10)	< 0.001
Cumulative autoantibody positivity, n (%)			
Anti-dsDNA, n = 1112	121/133 (91.0)	811/979 (82.8)	0.024
Anti-Smith, n = 1101	25/132 (18.9)	136/969 (14.0)	0.172
Anti-nRNP, n = 1093	35 /131 (26.7)	308 /962 (32.0)	0.260
Anti-Ro, n = 1093	35/131 (26.7)	387/962 (40.2)	0.004
Anti-La, n = 1093	9/131 (6.9)	71/962 (7.4)	0.975
aPL, n = 1082	71/131 (54.2)	353/951 (37.1)	< 0.001
aCL, n = 1112	46/133 (34.6)	253/979 (25.8)	0.042
Lupus anticoagulant, n = 1064	37/131 (28.2)	146/933 (15.7)	< 0.001
ANA, n = 1112	133 (100.0)	979 (100.0)	—
Treatment (ever), n (%)			
Oral corticosteroid, n (%)	126 (94.7)	942 (96.2)	0.558
Hydroxychloroquine	123 (92.5)	909 (92.9)	1.000
High-dose intravenous corticosteroid	6 (4.5)	32 (3.3)	0.444
Immunosuppressant	110 (82.7)	657 (67.1)	< 0.001
Cyclophosphamide	30 (22.6)	168 (17.2)	0.160
Mycophenolate mofetil	52 (39.1)	169 (17.3)	< 0.001
Methotrexate	33 (24.8)	236 (24.1)	0.944
Azathioprine	55 (41.4)	291 (29.7)	0.009
Cyclosporine	31 (23.3)	172 (17.6)	0.137

SLE: systemic lupus erythematosus; IQR: interquartile range; ACR: American College of Rheumatology; aPL: antiphospholipid antibody; aCL: anticardiolipin antibody; ANA: antinuclear antibody.

Table 2. Disease activity and organ damage in childhood-onset and adult-onset SLE.

	Childhood-onset, n = 133	Adult-onset, n = 979	p
Disease activity			
SLEDAI score, at enrollment, mean ± SD (range)	5.5 ± 4.5 (0–28)	5.4 ± 4.2 (0–24)	0.656
SLEDAI score, maximum, mean ± SD (range)	11.5 ± 7.1 (0–45)	9.6 ± 5.3 (0–38)	0.003
AMS, mean ± SD (range)	5.1 ± 3.1 (0–16)	4.2 ± 2.6 (0–18)	0.001
Cumulative organ damage			
Mean SDI score, mean ± SD (range)	0.9 ± 0.6 (0–8)	0.9 ± 1.5 (0–9)	0.797
SDI domain, n (%)			
Musculoskeletal damage	11 (8.3)	163 (16.7)	0.018
SDI items, n (%)			
Seizure	9 (6.8)	19 (1.9)	0.004
Proteinuria	18 (13.5)	75 (7.7)	0.033
Deforming or erosive arthritis	0	47 (4.8)	0.019

SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; AMS: adjusted mean SLEDAI score; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

All-cause SMR and causes of death. Survival rates at 5 and 10 years were 96.5% and 94.0% in the patients with SLE. During 8396.3 person-years of followup, 53 deaths were observed; 9 occurred in the 133 patients with cSLE, and 44 in the 979 with aSLE. The mean age at death in the cSLE group was 21.6 years (range 12–34) and the mean age at cSLE diagnosis was 12.5 years (range 5–15).

Table 3 shows the SMR of patients with cSLE and aSLE, compared to an age- and sex-matched sample of the general population. The overall SMR was significantly higher in the cSLE group (18.75, 95% CI 8.57–35.59) than in the aSLE group (2.89, 95% CI 2.10–3.88). In the aSLE group, subgroup analysis according to age showed that the highest SMR of 11.68 (95% CI 7.40–17.52) was observed in patients

Table 3. Standardized mortality ratios (SMR) stratified by age group and sex.

Condition	Person-yrs	Observed Deaths	Expected Deaths	SMR (95% CI)
Total	8396.3	53	15.71	3.37 (2.53–4.41)
Childhood-onset	958.7	9	0.48	18.75 (8.57–35.59)
Age, yrs				
10–19	106.8	3	0.03	100.00 (20.62–292.24)
20–39	843.4	6	0.44	13.64 (5.00–29.68)
Sex				
Female	749.3	8	0.32	25.00 (10.79–49.26)
Male	209.3	1	0.16	6.25 (0.16–34.82)
Adult-onset	7437.6	44	15.22	2.89 (2.10–3.88)
Age, yrs				
20–39	2985.9	23	1.97	11.68 (7.40–17.52)
40–59	3842.1	14	7.01	2.00 (1.09–3.35)
60–79	592.7	7	5.66	1.24 (0.50–2.55)
Sex				
Female	7094.1	41	13.33	3.08 (2.21–4.17)
Male	343.5	3	1.89	1.59 (0.33–4.64)

The SMR was calculated by comparison with the general population from 1998 to 2012 as recorded by the Korean National Statistics Office. The range of age at death was 12–34 years in childhood-onset SLE, and 21–71 years in adult-onset SLE.

of 20–39 years, and this then decreased in patients 40–59 years (2.00, 95% CI 1.09–3.35) and 60-79 years (1.24, 95% CI 0.50–2.55). No effect of age was evident in the cSLE group. Sex did not have any effect on SMR in either group.

The causes of death in the present cohort were SLE-related diseases (n = 26), infectious disease (n = 11), cerebrovascular disease (n = 4), and malignancy (n = 4; Table 4). Of the 9 deaths in the cSLE group, SLE-related deaths occurred in 6 patients: 1 each for alveolar hemorrhage, autoimmune hepatitis, renal failure, central nervous system (CNS) lupus, bronchiolitis obliterans, and high disease activity without specific organ involvement. The other 3 deaths were due to pneumonia, concomitant Wilson disease, and an accident.

Predictors of mortality in patients with SLE. To investigate whether cSLE itself increases the risk of death, we performed a Cox regression analysis adjusting for baseline age, sex, disease duration, and other potential predictors. In univariate analysis, during followup these factors were associated with death of patients with SLE (data not shown): cumulative number of ACR criteria ($p = 0.045$), photosensitivity ($p = 0.021$), serositis ($p < 0.001$), neurologic disorder ($p < 0.001$), thrombocytopenia ($p < 0.001$), anti-Ro antibody ($p = 0.027$), AMS ($p < 0.001$), cumulative SDI score ($p < 0.001$), presence of cardiovascular damage ($p = 0.020$), neuropsychiatric damage ($p = 0.001$), pulmonary damage ($p < 0.001$), and gastrointestinal (GI) damage ($p = 0.002$). Because neurologic disorder and neuropsychiatric damage considerably overlap, only neuropsychiatric damage was entered in the multivariable model.

In multivariable model 1, independent predictors of death were cSLE (HR 3.6, $p = 0.008$), baseline age (1.1, $p < 0.001$),

Table 4. Causes of death in childhood-onset and adult-onset SLE.

Cause of death	Total SLE	Childhood-onset	Adult-onset
SLE-related disease	26	6	20
Interstitial lung disease	2	0	2
Alveolar hemorrhage	3	1	2
Pulmonary hypertension	3	0	3
Autoimmune hepatitis	3	1	2
Lupus enteritis	1	0	1
Renal failure	2	1	1
CNS lupus	2	1	1
Bronchiolitis obliterans	1	1	0
Unknown*	9	1	8
Infectious disease	11	1	10
Pneumonia	8	1	7
Panperitonitis	1	0	1
Sepsis, unknown origin	1	0	1
CNS infection	1	0	1
Cerebrovascular disease	4	0	4
Cerebral hemorrhage	2	0	2
Ischemic heart diseases	2	0	2
Malignancy	4	0	4
Pancreas	1	0	1
Lymphoma	1	0	1
Lung	1	0	1
Stomach	1	0	1
Others	8	2	6
Interstitial tubular nephritis	1	0	1
Obstetric complication	1	0	1
Accident/suicide	4	1	3
Wilson disease	1	1	0
Unknown	1	0	1
Total	53	9	44

*Patients who died who had no specific organ involvement but high disease activity were classified into "unknown" among the SLE-related disease. SLE: systemic lupus erythematosus; CNS: central nervous system.

AMS (1.2, p < 0.001), and SDI score (1.2, p = 0.007). In model 2, independent predictors were cSLE (3.6, p = 0.012), baseline age (1.1, p = 0.001), AMS (1.2, p < 0.001), thrombocytopenia (1.8, p = 0.047), neuropsychiatric damage (2.2, p = 0.041), pulmonary damage (2.9, p = 0.003), and GI damage (3.9, p = 0.039; Table 5). In model assumption tests and outlying and/or influential observations analysis, all variables used in the Cox proportional hazards models satisfied the model assumptions, and there were no potential or effect outliers.

Next, we investigated whether the association between cSLE and death was related to specific features of cSLE compared to aSLE with the same features. The specific features were malar rash, photosensitivity, renal disorder, neurologic disorder, hemolytic anemia, anti-dsDNA, aPL, and cerebrovascular damage, which were more prevalent in cSLE than aSLE. In a Cox regression analysis adjusting for baseline age, sex, disease duration, and AMS, the magnitude of risk was increased in cSLE patients with hemolytic anemia (7.2, p = 0.034) and with aPL (3.8, p = 0.041) relative to an HR of 3.3 for all cSLE (Figure 1). Among the aPL, aCL increased the magnitude of risk to 9.6 (p = 0.009). However, there were no deaths among the patients with cSLE who had LAC. Other features reduced the hazard risk (anti-dsDNA antibody, HR 3.1) or did not differ significantly between cSLE and aSLE.

DISCUSSION

Age at diagnosis can affect the clinical features and outcomes of SLE[16]. There has been ongoing interest in differences between cSLE and aSLE. A different sex ratio, genetic factors, hormonal effects, and environmental factors have been suggested as responsible for the differences between the 2 groups. We have compared patients with cSLE and aSLE in a relatively homogeneous cohort and found that the clinical course and outcomes of cSLE are worse than those of aSLE.

Serious clinical manifestations such as renal disorder, neurologic disorder, and hemolytic anemia were significantly more frequent in cSLE compared to aSLE. Malar rash and photosensitivity were also frequent in the cSLE group. These results are consistent with a metaanalysis by Livingston, *et al*[16] except for thrombocytopenia. In our cohort, the frequency of thrombocytopenia was not different in the 2 groups. Consistent with other reports[4,5,17,18,19,20], anti-dsDNA antibody was more frequent in cSLE than aSLE. In previous studies considered in a metaanalysis of differences in autoantibody profiles[20], the prevalence of anti-dsDNA antibody varied between 49% and 100% and 25% and 84% in cSLE and aSLE, respectively. In our study, the prevalence of anti-dsDNA antibody was 91% in cSLE and 83% in aSLE. The prevalence of aPL was also a little higher than in the previous studies, which ranged from 35% to 44% and 29% to 31% in cSLE and aSLE, respectively[8,9]. The reasons for this higher prevalence are unclear, but it is likely that our cohort included a greater proportion of severely affected patients with SLE, because our hospital is one of the largest tertiary referral hospitals in Korea.

As outcomes, we compared disease activity and organ damage in the 2 groups. The maximum and cumulative SLEDAI scores were all higher in the cSLE group than the

Table 5. Multivariable Cox regression analyses for risk factors of mortality in SLE.

Risk Factors	Model 1		Model 2	
	HR (95% CI)	p	HR (95% CI)	p
Childhood-onset SLE	3.6 (1.4–9.4)	0.008	3.6 (1.3–9.8)	0.012
Age at enrollment	1.1 (1.0–1.1)	< 0.001	1.1 (1.0–1.1)	0.001
Sex, male	1.4 (0.5–4.2)	0.509	1.2 (0.4–3.6)	0.743
Disease duration, yrs	1.0 (0.9–1.1)	0.874	1.0 (0.9–1.1)	0.922
No. ACR criteria	1.0 (0.9–1.3)	0.693		
AMS	1.2 (1.1–1.4)	< 0.001	1.2 (1.1–1.4)	< 0.001
SDI score	1.2 (1.0–1.4)	0.007		
Anti-Ro antibody	0.5 (0.3–1.0)	0.067	0.5 (0.3–1.0)	0.056
Photosensitivity			0.5 (0.2–1.0)	0.051
Serositis			1.4 (0.7–2.6)	0.354
Thrombocytopenia			1.8 (1.0–3.4)	0.047
Cardiovascular damage			1.3 (0.4–3.9)	0.623
Neuropsychiatric damage			2.2 (1.0–4.5)	0.041
Pulmonary damage			2.9 (1.4–6.0)	0.003
Gastrointestinal damage			3.9 (1.1–13.9)	0.039

Model 1 adjusted for baseline age, sex, disease duration, childhood-onset SLE, no. ACR criteria, AMS, SDI score, and anti-Ro antibody. Model 2 adjusted for baseline age, sex, disease duration, childhood-onset SLE, AMS, anti-Ro antibody, photosensitivity, serositis, thrombocytopenia, and cardiovascular, neuropsychiatric, pulmonary, and gastrointestinal damage. SLE: systemic lupus erythematosus; ACR: American College of Rheumatology; AMS: adjusted mean SLE Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index.

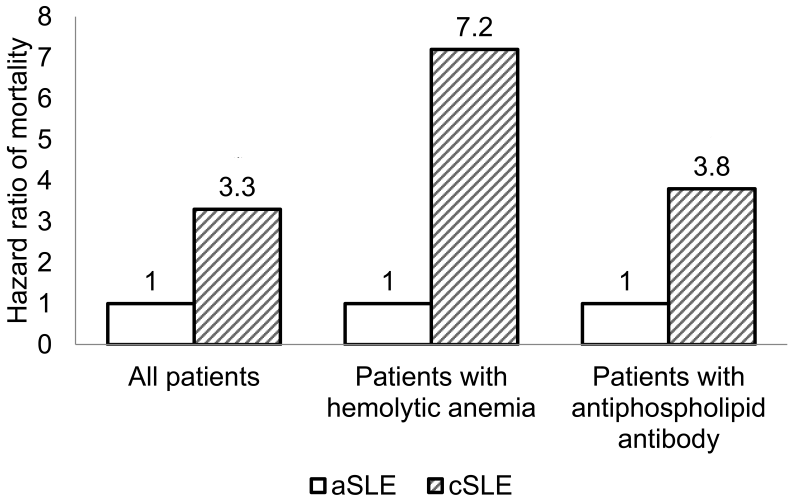

Figure 1. Comparison of mortality between childhood-onset and adult-onset SLE according to the presence of hemolytic anemia and antiphospholipid antibody. Compared to aSLE, the HR of mortality of cSLE was 3.3 greater (95% CI 1.3–8.3, p = 0.013). The magnitude of risk increased in cSLE with hemolytic anemia (HR 7.2, 95% CI 1.2–44.6, p = 0.034) or antiphospholipid antibody (HR 3.8, 95% CI 1.1–13.6, p = 0.041), adjusted for baseline age, sex, disease duration, and AMS. aSLE: adult-onset systemic lupus erythematosus; cSLE: childhood-onset SLE; AMS: adjusted mean Systemic Lupus Erythematosus Disease Activity Index.

aSLE group. However, the higher disease activity in the cSLE group did not lead to significantly higher cumulative organ damage than in the aSLE group. Some authors have reported that patients with cSLE develop significantly more organ damage than patients with aSLE[6,9]. However, the SDI score in our cohort was not significantly different between the 2 groups. Our results support the results of the metaanalysis by Livingston and colleagues, which found no significant difference in disease damage between the 2 groups[20]. Because medication such as corticosteroid can cause organ damage, the similar frequency of high-dose IV corticosteroid given to the 2 groups in our cohort (contrasting with the result of Hersh, *et al,* showing that patients with cSLE received more IV corticosteroid[21]) may have led to the similarity in the development of organ damage between our 2 groups. Also, followup for a limited time and loss of patients to followup (8%) may have affected this result, because we compared organ damage according to the domain or item, not the total SDI score. Cerebrovascular damage, seizure, and proteinuria occurred more frequently in the cSLE group. We observed similar patterns to those described in the previous metaanalysis, in which the OR of seizure and proteinuria in cSLE were 2.32 and 1.49, respectively, compared to aSLE[16].

The overall SMR of our cohort was 3.37, which is consistent with the results of a metaanalysis[22] and a population-based cohort study[23]. The SMR of the cSLE group was 18.75, significantly higher than that of the aSLE group. The SMR (95% CI) of the cSLE subgroup of those 10-19 years old was 100.00 (20.62–292.24). Two patients with cSLE died at ages 12 and 13, which was rare in the general population. The SMR (95% CI) of the cSLE subgroup of those 20–39 years old was 13.64 (5.00–29.68), similar to results in previous studies. The SMR (95% CI) was reported as 19.2 (14.7–24.7) for those 16–24 years old and 20.4 (9.3–38.7) for those 19–34 years old in the previous studies[24,25]. These analyses showed that the largest SMR occurred in the cSLE and the lowest in the aSLE. However, this difference should be interpreted with caution in view of the different risks of dying according to age group in the general population, which are lower in the young.

In previous mortality studies of SLE, cardiovascular disease, infection, renal disease, and malignancy were reported to be leading causes of death[22,24,26]. In our study, SLE-related disease and infection were the major causes of death, followed by cerebrovascular disease and malignancy.

Reports of the causes of death in patients with cSLE are rare. In our present study, SLE-specific diseases, including alveolar hemorrhage, autoimmune hepatitis, renal failure, and CNS lupus, were the main causes of death in the cSLE group. One patient died of uncontrolled pneumonia. The significantly higher disease activity in the cSLE group could have resulted in the higher proportion of deaths associated with SLE-specific diseases. Associated comorbidities and the higher age of the aSLE group could have been the reasons for more infectious disease–associated deaths than in the cSLE group. In a study published in 1987, younger patients more often died of active renal disease and infectious complication than did older patients[27]. However, that was about 30 years ago. As much as outcomes of patients with SLE have changed and improved, contemporary studies on the cause of death in cSLE are needed.

In our patients with SLE, cSLE was an independent

predictor of mortality, as shown in several studies[25,28]. Neuropsychiatric, pulmonary, and GI damage as well as age at enrollment were also independent predictors of mortality. Moreover, hemolytic anemia and aPL increased the risk of death more in patients with cSLE than in patients with aSLE. In the Hopkins Lupus Cohort study[29], hemolytic anemia increased the risk of death. In the LUMINA cohort study[30], hemolytic anemia had an effect on increased organ damage, but not on mortality. Because not all studies have enough power to determine predictors of death and organ damage, our study may lack generalizability to other cohorts. Studies also reported aPL to be a risk factor for organ damage, and it was associated with mortality[31,32]. We do not have a ready explanation for why cSLE with these characteristics carried a higher risk of early mortality than aSLE. However, it could be due to the greater severity of cSLE with these characteristics, and the more extensive use of immunosuppressive agents. Thus, because patients with cSLE had these features as well as neuropsychiatric, pulmonary, and GI damage (predictors of mortality in all patients with SLE), close observation and prompt treatment is needed in these patients to improve survival.

One strength of our study is that differences between cSLE and aSLE were analyzed in a large prospective cohort in a single center enrolling both types of patient. The similar treatments and followup patterns permitted a more accurate comparison of the outcomes. A second strength is the accurate evaluation of SMR, because we obtained information about deaths by linkage with the KNSO and were able to collect all deaths.

A limitation of our study is that our cohort was not an inception cohort. The mean disease duration of our cohort was 3.2 years. This period is not long compared to an inception cohort. The AMS might miss some disease flares or disease status at certain times if patients did not visit our hospital when their disease was active. Also, the conclusions should be interpreted in the context of a potential survival bias, because mortality data were available only over the followup period after enrollment, not from the date of diagnosis.

In this prospective cSLE and aSLE cohort, cumulative clinical features and disease activity were significantly higher in the cSLE than in the aSLE group. Moreover, serious manifestations such as renal disorder, neurologic disorder, and hemolytic anemia were more frequent. Although cumulative organ damage was not significantly different, mortality was higher in the cSLE than in the aSLE group. We found that cSLE was an independent predictor of mortality and the risk of death from SLE was more than 3-fold greater in the cSLE group than in the aSLE group. Also, the risk of death for cSLE was higher in the patients with hemolytic anemia, aPL, and aCL, indicating that close monitoring and careful treatment is needed to prevent death in these patients with cSLE.

ACKNOWLEDGMENT

We are grateful to all the study participants.

REFERENCES

1. Klein-Gitelman M, Reiff A, Silverman ED. Systemic lupus erythematosus in childhood. Rheum Dis Clin North Am 2002;28:561-77.
2. Font J, Cervera R, Espinosa G, Pallares L, Ramos-Casals M, Jimenez S, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. Ann Rheum Dis 1998;57:456-9.
3. Lee BW, Yap HK, Yip WC, Low PS, Saw AH, Tay JS, et al. A 10 year review of systemic lupus erythematosus in Singapore children. Aust Paediatr J 1987;23:163-5.
4. Tucker LB, Menon S, Schaller JG, Isenberg DA. Adult- and childhood-onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. Br J Rheumatol 1995;34:866-72.
5. Carreno L, Lopez-Longo FJ, Monteagudo I, Rodriguez-Mahou M, Bascones M, Gonzalez CM, et al. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. Lupus 1999;8:287-92.
6. Brunner HI, Gladman DD, Ibanez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Rheum 2008;58:556-62.
7. Ramirez Gomez LA, Uribe Uribe O, Osio Uribe O, Grisales Romero H, Cardiel MH, Wojdyla D, et al. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. Lupus 2008;17:596-604.
8. Mok CC, Mak A, Chu WP, To CH, Wong SN. Long-term survival of southern Chinese patients with systemic lupus erythematosus: a prospective study of all age-groups. Medicine 2005;84:218-24.
9. Tucker LB, Uribe AG, Fernandez M, Vila LM, McGwin G, Apte M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). Lupus 2008;17:314-22.
10. Joo YB, Bae SC. Assessment of clinical manifestations, disease activity and organ damage in 996 Korean patients with systemic lupus erythematosus: comparison with other Asian populations. Int J Rheum Dis 2015;18:117-28.
11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
12. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288-91.
13. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363-9.
14. Ibanez D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol 2003;30:1977-82.
15. Kim YJ, Shim JS, Choi CB, Bae SC. Mortality and incidence of malignancy in Korean patients with rheumatoid arthritis. J Rheumatol 2012;39:226-32.
16. Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. Lupus 2011;20:1345-55.

17. Barron KS, Silverman ED, Gonzales J, Reveille JD. Clinical, serologic, and immunogenetic studies in childhood-onset systemic lupus erythematosus. Arthritis Rheum 1993;36:348-54.
18. Costallat LT, Coimbra AM. Systemic lupus erythematosus: clinical and laboratory aspects related to age at disease onset. Clin Exp Rheumatol 1994;12:603-7.
19. Janwityanujit S, Totemchokchyakarn K, Verasertniyom O, Vanichapuntu M, Vatanasuk M. Age-related differences on clinical and immunological manifestations of SLE. Asian Pac J Allergy Immunol 1995;13:145-9.
20. Livingston B, Bonner A, Pope J. Differences in autoantibody profiles and disease activity and damage scores between childhood- and adult-onset systemic lupus erythematosus: a meta-analysis. Semin Arthritis Rheum 2012;42:271-80.
21. Hersh AO, von Scheven E, Yazdany J, Panopalis P, Trupin L, Julian L, et al. Differences in long-term disease activity and treatment of adult patients with childhood- and adult-onset systemic lupus erythematosus. Arthritis Rheum 2009;61:13-20.
22. Yurkovich M, Vostretsova K, Chen W, Avina-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis Care Res 2014;66:608-16.
23. Lerang K, Gilboe IM, Steinar Thelle D, Gran JT. Mortality and years of potential life loss in systemic lupus erythematosus: a population-based cohort study. Lupus 2014;23:1546-52.
24. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54:2550-7.
25. Hersh AO, Trupin L, Yazdany J, Panopalis P, Julian L, Katz P, et al. Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematosus. Arthritis Care Res 2010;62:1152-9.
26. Thomas G, Mancini J, Jourde-Chiche N, Sarlon G, Amoura Z, Harle JR, et al. Mortality associated with systemic lupus erythematosus in France assessed by multiple-cause-of-death analysis. Arthritis Rheumatol 2014;66:2503-11.
27. Harisdangkul V, Nilganuwonge S, Rockhold L. Cause of death in systemic lupus erythematosus: a pattern based on age at onset. South Med J 1987;80:1249-53.
28. Alarcon GS, McGwin G Jr., Bastian HM, Roseman J, Lisse J, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups. VII [correction of VIII]. Predictors of early mortality in the LUMINA cohort. LUMINA Study Group. Arthritis Rheum 2001;45:191-202.
29. Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine 2006;85:147-56.
30. Duran S, Apte M, Alarcon GS, Marion MC, Edberg JC, Kimberly RP, et al. Features associated with, and the impact of, hemolytic anemia in patients with systemic lupus erythematosus: LX, results from a multiethnic cohort. Arthritis Rheum 2008;59:1332-40.
31. Ruiz-Irastorza G, Egurbide MV, Martinez-Berriotxoa A, Ugalde J, Aguirre C. Antiphospholipid antibodies predict early damage in patients with systemic lupus erythematosus. Lupus 2004;13:900-5.
32. Broder A, Mowrey WB, Kim M, Murakhovskaya I, Billett H, Neugarten J, et al. Association between antiphospholipid antibodies and all-cause mortality among end-stage renal disease patients with and without SLE: a retrospective cohort study. Rheumatology 2016;55:817-25.