

Chinese Systemic Lupus Erythematosus Treatment and Research Group Registry IX: Clinical Features and Survival of Childhood-Onset Systemic Lupus Erythematosus in China

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Abstract

Background: Approximately 15–20% cases of systemic lupus erythematosus (SLE) are diagnosed in children. There have been a few studies reporting the epidemiological data of pediatric-onset SLE (cSLE) in China, neither comparing the differences between cSLE and adult-onset SLE (aSLE). The aim of this study was to describe the impact of age of onset on clinical features and survival in cSLE patients in China based on the Chinese SLE Treatment and Research group (CSTAR) database.

Methods: We made a prospective study of 225 cSLE patients (aged <16 years) and 1759 patients aged 16–50 years based on CSTAR registry. We analyzed initial symptoms, clinical presentations, SLE disease activity, damages, and outcomes of cSLE, as well as compared with aSLE patients.

Results: The mean age of cSLE patients was 12.16 ± 2.92 years, with 187 (83.1%) females. Fever ($P < 0.001$) as well as mucocutaneous ($P < 0.001$) and renal ($P = 0.006$) disorders were found to be significantly more frequent in cSLE patients as initial symptoms, while muscle and joint lesions were significantly less common compared to aSLE subjects ($P < 0.001$). The cSLE patients were found to present more frequently with malar rash ($P = 0.001$; odds ratio [OR], 0.624; 95% confidence interval [CI], 0.470–0.829) but less frequently with arthritis ($P < 0.001$; OR, 2.013; 95% CI, 1.512–2.679) and serositis ($P = 0.030$; OR, 1.629; 95% CI, 1.053–2.520). There was no significant difference in SLE disease activity index scores between cSLE and aSLE groups ($P = 0.478$). Cox regression indicated that childhood onset was the risk factor for organ damage in lupus patients (hazard ratio 0.335 [0.170–0.658], $P = 0.001$). The survival curves between the cSLE and aSLE groups had no significant difference as determined by the log-rank test (0.557, $P = 0.455$).

Conclusions: cSLE in China has different clinical features and more inflammation than aSLE patients. Damage may be less in children and there is no difference in 5-year survival between cSLE and aSLE groups.

Key words: Childhood Onset; Outcomes; Systemic Lupus Erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with a broad range of clinical and serological diversity. Although the peak age of onset occurs in middle

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younger (16–50 years), approximately 15–20% patients are children or adolescents under the age of 16 years.^[1] The diagnosis of childhood-onset SLE (cSLE) ranged from 14 to 20 years was defined as 16 years old in the most studies.^[2,3]

According to the previous studies, cSLE presents vary in disease profile.^[3–7] The cSLE patients have more frequent involvement in renal, hematological system and central nervous system, as well as less pulmonary involvement and arthritis, compared with adult-onset SLE (aSLE) patients.^[2,8,9] With different evaluation method, the comparison of disease activity between early- and late-onset SLE is not certain.^[10,11] However, cSLE patients are more likely to receive intensive drug therapies and have a two-fold higher mortality rate.^[10–12]

The demographic, clinical, and laboratory features of cSLE are variable in different ethnic groups.^[1,4,13–16] Meanwhile, the data of Chinese lupus were limited due to lack of prospective multicenter studies.^[7] Chinese SLE Treatment and Research group (CSTAR) developed the first nationwide online registry of Chinese lupus. Based on the CSTAR cohort, we analyzed differences of childhood-onset and adult-onset lupus patients in disease profiles, including clinical manifestation and outcomes.

METHODS

Ethical approval

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (Beijing, China), which was the lead research site. All patients had signed informed consent themselves or through their legal guardians before being registered.

Patient recruitment

Our prospective study was based on the CSTAR online registry, which includes patients from 104 high-ranked rheumatology centers, covering 30 provinces in China. Patients were included only if they fulfilled the 1997 revised American College of Rheumatology (ACR) criteria. This online registry was launched in April 2009, and 2104 Chinese SLE patients were registered until February 2010. For this study, we focused on cSLE patients who were under 16 years of age of onset and compared them with aSLE patients whose age of onset was between 16 and 50 years.

Data collection

All CSTAR centers provided uniform evaluations and recorded data with the same protocol-directed methods. Demographic data were generally collected. Clinical data including initial and cumulative manifestations at enrollment were collected. Initial manifestations meant the manifestations that present before the first visit to a rheumatologist. Symptoms that patients had ever had until enrollment were defined as cumulative manifestations which were assessed using ACR classification criteria and the SLE disease activity index (SLEDAI). Disease damage was assessed by the Systemic Lupus International Collaborating Clinics/ACR damage index (SDI) which included 12 different organ systems (ocular, neuropsychiatric,

renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, gonad, endocrine, and malignancy). To be considered in the SDI, most items must persist for at least 6 months. The survival data of follow-up have been collected by April 2016.

Autoantibody levels were also recorded including anti-double-stranded DNA, anti-Smith, anti-SSA/Ro, anti-SSB/La, anti-ribonucleoprotein (RNP), and anti-ribosomal RNP antibodies measured at local laboratories. Antiphospholipid antibodies including anticardiolipin, lupus anticoagulant, and anti- β 2-glycoprotein-I antibodies were tested only if antiphospholipid syndrome was suspected. SLE disease activity was evaluated in all patients by SLEDAI at the time of enrollment.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD) for normal distribution or medians (interquartile ranges) for skewed distributions, while categorical variables were presented as numbers (*n*) and percentages. A Student's *t*-test was used for comparison of continuous variables, and Chi-square and Fisher's exact tests were used to compare categorical data. After adjusting for gender ratio differences, logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Kaplan-Meier survival analysis and log-rank test were used to compare outcomes. Because cause of death could not always be confidently ascribed, all-cause mortality was analyzed. All tests were two-tailed, and the level of statistical significance (*P* value) was set at 0.05. Statistical analyses were performed using SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographics

Out of 2104 patients, 1984 were <50 years old. A total of 225 patients were included in the cSLE group with an average age of 12.16 ± 2.92 years (range, 1.4–16.0 years), and 1759 patients comprised the aSLE group with an average age of 30.03 ± 8.85 years (range, 16.0–50.0 years). 83.1% were women in the cohort of cSLE patients, as well as 92.4% in aSLE group. There was no significant difference in the time to diagnosis between cSLE and aSLE group [Mann-Whitney test, *P* = 0.766; Table 1].

Clinical features

The initial manifestations reported in both groups are summarized in Table 2. Fever (*P* < 0.001) as well as mucocutaneous (*P* < 0.001) and renal (*P* = 0.006) disorders were found to be significantly more frequent in cSLE patients as initial symptoms, while muscle and joint lesions were significantly less common compared to aSLE subjects (*P* < 0.001).

A comparison of cSLE and aSLE clinical characteristics is shown in Table 2. The cSLE patients were found to present more frequently with malar rash (*P* = 0.001; OR, 0.624; 95% CI, 0.470–0.829) but less frequently with

Table 1: Demographic data of patients with different SLE onset ages

Characteristics	cSLE (n = 225)	aSLE (n = 1759)	t/Z/ χ^2	P
Female, n (%)	187 (83.1)	1625 (92.4)	21.655*	0.001
Age of onset (years), mean \pm SD	12.16 \pm 2.92	30.03 \pm 8.85	-30.049†	<0.001
Age at diagnosis (years), mean \pm SD	13.35 \pm 3.84	31.17 \pm 9.35	-27.867†	<0.001
Time to diagnosis (months), median (range)	29.70 (9.69–62.49)	16.70 (4.00–55.39)	2.164‡	0.766

* χ^2 values; †t values; ‡Z values. SD: Standard deviation; cSLE: Childhood-onset SLE; aSLE: Adult-onset SLE; SLE: Systemic lupus erythematosus.

Table 2: Clinical features of patients with different SLE onset ages

Variables	cSLE (n = 225)	aSLE (n = 1759)	t/Z/ χ^2	P
Initial manifestation				
Fever	134 (59.6)	627 (35.6)	48.234*	<0.001
Musculoskeletal	91 (40.4)	977 (55.5)	18.297*	<0.001
Mucocutaneous	149 (66.2)	941 (53.5)	13.050*	<0.001
Hemocytopenia	76 (33.8)	557 (31.7)	0.410*	0.522
Renal	75 (33.3)	437 (24.8)	7.509*	0.006
Neuropsychiatric	8 (3.6)	64 (3.6)	0.004*	0.950
Respiratory	11 (4.9)	94 (5.3)	0.082*	0.774
Clinical manifestation				
Malar rash	134 (59.6)	848 (48.2)	10.274*	0.001
Discoid lesions	11 (4.9)	97 (5.5)	0.152*	0.697
Arthritis	87 (38.7)	994 (56.5)	25.275*	<0.001
Serositis	25 (11.1)	295 (16.8)	4.724*	0.030
Renal disorder	112 (49.8)	833 (47.4)	0.405*	0.525
Neurologic disorder	11 (4.9)	88 (5.0)	0.005*	1.000
ILD	5 (2.2)	70 (4.0)	2.285	0.173
PAH	6 (2.7)	63 (3.6)	0.732*	0.388
Leukocytopenia	43 (19.1)	425 (24.2)	2.823*	0.093
Thrombocytopenia	27 (12.0)	292 (16.6)	3.129*	0.077
Hypocomplementemia	142 (63.1)	1179 (67.0)	1.375*	0.241
SLEDAI	9.39 \pm 6.89	9.74 \pm 7.07	-0.709†	0.478
Autoantibody-positive				
Anti-dsDNA	77 (34.2)	504 (28.7)	2.988*	0.084
Anti-Sm	37 (16.4)	290 (16.5)	0.045*	0.987
Anti-RNP	19 (8.4)	156 (8.9)	0.045*	0.833
Anti-SSA	48 (21.3)	428 (24.3)	0.984*	0.321
Anti-SSB	19 (8.4)	194 (11.0)	1.390*	0.238
APL	47/112 (42.0)	344/775 (44.4)	0.233*	0.629

Values are presented as mean \pm SD, n (%) or n/N (%). * χ^2 values; †t values. SD: Standard deviation; ILD: Interstitial lung disease; PAH: Pulmonary arterial hypertension; SLEDAI: SLE disease activity index; dsDNA: Double-stranded DNA; Sm: Smith; RNP: Ribonucleoprotein; SSA: Sjögren's syndrome-related antigen A; SSB: Sjögren's syndrome-related antigen B; APL: Antiphospholipid antibody; cSLE: Childhood-onset SLE; aSLE: Adult-onset SLE; SLE: Systemic lupus erythematosus.

arthritis ($P < 0.001$; OR , 2.013; 95% CI , 1.512–2.679) and serositis ($P = 0.030$; OR , 1.629; 95% CI , 1.053–2.520). There was no significant difference in SLEDAI scores between cSLE and aSLE group ($P = 0.478$).

Laboratory findings

Autoantibody profiles and percentages of patients positive for different autoantibodies are shown in Table 2. There was no significant difference in laboratory data between the two groups.

Outcomes

In cSLE group, 23 patients had damage at baseline, and at follow-up, 30 had damages including nine new damages. In aSLE group, 207 patients had damage at baseline, and

336 had damages which included 162 new damages at follow-up. After controlling the influence of gender and time from onset to diagnosis, Cox regression indicated that childhood onset was the risk factor for organ damage in lupus patients (hazard ratio [HR] 0.335 [0.170–0.658], $P = 0.001$).

Until April 2016, the follow-up data of 1409 patients were collected. The 1-, 3-, and 5-year survival rates of cSLE patients were 98.5%, 97.4%, and 97.4%, respectively. As well, the 1-, 3-, and 5-year survival rates of aSLE patients were 99.5%, 98.9%, and 97.9%, respectively. The survival curves between the cSLE and aSLE groups had no significant difference as determined by the log-rank test (0.557, $P = 0.455$).

DISCUSSION

SLE is a diverse disease varying by the age of onset.^[16,17] However, the association between age of onset and SLE in Chinese populations remains unclear. Based on the first nationwide multicenter registry,^[18-21] our study prospectively investigated the clinical characteristics and survival of cSLE patients from over 30 provinces of China and compared them with adult-onset lupus patients.

Our study showed that fever as well as mucocutaneous and renal disorders occurred more frequently in cSLE patients as initial symptoms relative to adult-onset patient group. This finding was consistent with most previous studies from Asia, Europe, and Latin America^[16,22-24] and supports the notion that cSLE is more active and associated with more inflammation than aSLE patients.^[11,25,26]

Previous studies have also reported renal involvement to be more common in cSLE patients.^[11,24] According to our data, there was a significantly higher incidence of renal involvement as an initial symptom in cSLE ($P = 0.006$) patients but not as a cumulative symptom ($P = 0.569$; OR , 0.922; 95% CI , 0.697–1.219). This is in accordance with the research from the Grupo Latino Americano de Estudio de Lupus database that found renal involvement frequency did not significantly differ between cSLE and aSLE patients.^[16] Tan *et al.*^[27] suggested that previous reports with positive renal results might be due to a referral bias since many cSLE patients were primarily diagnosed by pediatric nephrologists and not pediatric rheumatologists. Furthermore, since the gender effect was isolated in our analyses, the effect of age of onset on kidney symptoms is more accurately reflected in our study.

We found that the prevalence of neuropsychiatric involvements was not significantly different between Chinese cSLE and aSLE cohorts. Different races had conflicting results in this kind of comparing.^[5,8-10,12,16,28] Furthermore, this may due to the various definition of “neuropsychiatric.” Recently, the ACR defines 19 syndromes for neuropsychiatric SLE, which is not yet validated in pediatric patients.

The effect of onset age on SLE disease activity remains controversial. Utilizing CSTAR cohort data, we analyzed differences between cSLE and aSLE patients. Unlike previous studies,^[11] we did not detect differences in SLEDAI scores between these groups. This might reflect similarities in clinical features among these groups, except for arthritis, rash, and fever, which did not substantially contribute to the total SLEDAI score.

Long-term outcomes were evaluated by assessing organ damages and mortality rate. Our study indicated that less damages were seen in cSLE as compared to that of aSLE (HR 0.335 [0.170–0.658], $P = 0.001$). This is in accordance with previous studies^[29] and is not surprising since many items of damage were due to aging (cataracts, cardiovascular, peripheral vascular, diabetes mellitus,

and malignancy). The mortality rate was similar in our two groups. While survival rates are high in our cohort, long-term follow-up is needed.

Limitations of our study include the inability to determine all comorbidities. Given the multicenter nature of data collection, we were unable to accurately capture the exact data about all medical information. Another limitation is that our data come from a prevalent cohort but not an inception cohort. We try to eliminate this error by controlling the variable of time from onset to diagnosis in Cox regression analysis. Moreover, our cohort sample is large enough to neglect this error. We will further validate these in future study.

In conclusion, this is the largest cohort of SLE from multicenter in China, for which demographic, clinical, immunological, and outcome data are available. cSLE has more fever, mucocutaneous and renal disorders as initial symptoms and has less arthritis and serositis as cumulative symptoms than that of aSLE patients. Five-year survival rates were very high for both groups, with a younger age of lupus onset associated with a slightly lower 5-year survival. Long-term study is needed for more information.

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Conflicts of interest

There are no conflicts of interest.

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