Sex differences in systemic lupus erythematosus (SLE): an inception cohort of the Chinese SLE Treatment and Research Group (CSTAR) registry XVII

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Abstract

Background: The onset and clinical presentation of systemic lupus erythematosus (SLE) are sex-related. Few studies have investigated the distinctions in clinical characteristics and treatment preferences in male and female SLE patients in the initial cohort. This study aimed to improve the understanding of Chinese SLE patients by characterizing the different sexes of SLE patients in the inception cohort.

Methods: Based on the initial patient cohort established by the Chinese SLE Treatment and Research Group, a total of 8713 patients (795 men and 7918 women) with newly diagnosed SLE were enrolled between April 2009 and March 2021. Of these, 2900 patients (347 men and 2553 women) were eligible for lupus nephritis (LN). A cross-sectional analysis of the baseline demographic characteristics, clinical manifestations, laboratory parameters, organ damage, initial treatment regimens, and renal pathology classification was performed according to sex.

Results: In the SLE group, as compared to female patients, male patients had a later age of onset (male *vs.* female: 37.0 ± 15.8 years *vs.* 35.1 ± 13.7 years, $P = 0.006$) and a higher SLE International Collaborative Clinic/American College of Rheumatology damage index score (male *vs.* female: 0.47 ± 1.13 *vs.* 0.34 ± 0.81, $P = 0.015$), LN (male *vs.* female: 43.6% *vs.* 32.2%, $P < 0.001$), fever (male *vs.* female: 18.0% *vs.* 14.6%, $P = 0.010$), thrombocytopenia (male *vs.* female: 21.4% *vs.* 18.5%, $P = 0.050$), serositis (male *vs.* female: 14.7% *vs.* 11.7%, $P = 0.013$), renal damage (male *vs.* female: 11.1% *vs.* 7.4%, $P < 0.001$), and treatment with cyclophosphamide (CYC) ($P < 0.001$). The frequency of leukopenia (male *vs.* female: 20.5% *vs.* 25.4%, $P = 0.002$) and arthritis (male *vs.* female: 22.0% *vs.* 29.9%, $P < 0.001$) was less in male patients with SLE. In LN, no differences were observed in disease duration, SLE Disease Activity Index score, renal biopsy pathological typing, or 24-h urine protein quantification among the sexes. In comparisons with female patients with LN, male patients had later onset ages ($P = 0.026$), high serum creatinine ($P < 0.001$), higher end-stage renal failure rates ($P = 0.002$), musculoskeletal damage ($P = 0.023$), cardiovascular impairment ($P = 0.009$), and CYC use ($P = 0.001$); while leukopenia ($P = 0.017$), arthritis ($P = 0.014$), and mycophenolate usage ($P = 0.013$) rates were lower.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002360

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Chinese Medical Journal 2022;135(18)
Received: 09-02-2022; **Online:** 20-10-2022 **Edited by:** Lishao Guo

Conclusions: Male SLE patients had more severe organ damage and a higher LN incidence compared with female SLE patients; therefore, they may require more aggressive initial treatment compared to female patients.
Keywords: Systemic lupus erythematosus; Lupus nephritis; Sex; End-stage renal disease; Sex differences

Introduction

Systemic lupus erythematosus (SLE), an autoimmune disease with unknown etiology that is typified by seropositivity for multiple autoantibodies and systemic involvement, is prevalent among women of reproductive age.[1,2] Lupus nephritis (LN) is a severe, inflammatory renal condition involving kidney damage due to SLE.[3] Varying degrees of LN occur in >60% of SLE patients.[4,5] Approximately 10% to 30% of patients progress to end-stage renal disease (ESRD) in the first 15 years after LN diagnosis. LN, infection, and lupus encephalopathy cumulatively form the critical etiological axis of death among Chinese SLE patients.[6,7] Notably, the LN patient's 10-year survival rate improves to 95% from 46%, provided that disease remission is tremendously achieved in recent years.[8]

Over recent decades, numerous cohort studies have shown that multiple genetic, hormonal, and environmental factors affect the development and nature of SLE.[9-11] Differences in the clinical presentation and severity of SLE in male and female patients have been increasingly reported in the relevant literature.[12-14] However, the conclusions are often inconsistent due to differences between the studies in terms of race, disease onset, follow-up duration, and sample size.

Currently, limited epidemiological data are available regarding men with SLE and LN in the Chinese population; however, few studies have assessed inception cohorts of different sexes. Since its establishment in 2009, the Chinese SLE Treatment and Research Group (CSTAR) has registered >30,000 SLE patients online and, being the largest multicenter data platform in China; it has now published a series of studies on the clinical manifestations of SLE, including those associated with sex, family history, and pulmonary arterial hypertension.[15-17] Based on the results of the CSTAR cohort studies and previously published relevant studies, this study aims to improve the understanding of SLE and LN in China and determine the clinical features of LN from the analysis of the clinical characteristics and initial treatment options of newly diagnosed SLE and LN patients of different sexes.

Methods

Ethical approval

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (No. JS-2038), which was the lead research site. All patients had signed informed consent themselves or through their legal guardians before being registered.

Patient recruitment

Based on data accumulated in the CSTAR online registry, we collected the data of patients with SLE who were registered in 286 centers in China between April 2009 and March 2021 and met the criteria of having complete baseline information and having completed registration within 3 months of diagnosis. Patients included met the criteria for SLE classification established by the American College of Rheumatology (ACR) in 1997[18] or the 2012 Systemic Lupus International Collaborating Clinics (SLICC)/ACR[19] or the 2019 European League Against Rheumatism/ACR.[20] LN was defined as meeting the "renal disease" entry in the three SLE classification criteria described above. "Newly diagnosed SLE or LN" was defined as SLE or LN with a diagnosis to registration interval of <3 months.

Data collection

Data collection included: demographic characteristics, clinical presentation, laboratory parameters, renal pathology, and therapeutics. We collected baseline registry data from the patients who met the definition of "newly diagnosed SLE or LN" (<3 months between the diagnosis of SLE or LN and registration). Regarding data collection on organ damage, at the time of entering baseline data, the disease duration of some patients was >6 months. We collected entries for organ damage recorded at baseline that were verified to actually exist and that met the SLICC definition and criteria for organ damage (especially entries in which the damage needed to last >6 months), the data that met these requirements were collected and analyzed. The demographic variables included were sex, age of disease onset, confirmation of diagnosis time, registration time, and course of disease (time from the appearance of clinical symptoms to a definitive diagnosis). Clinical manifestations included fever (SLE activity-induced fever rather than infection-induced), LN, myositis, mucocutaneous lesions, arthritis, vasculitis, serositis, leukocytopenia, thrombocytopenia, and neuropsychiatric lupus. Systemic manifestations were evaluated based on the SLE Disease Activity Index (SLEDAI)-2K.[21] Laboratory indicators hypocomplementemia, anti-double-stranded deoxyribonucleic acid (DNA), anti-ribonucleoprotein, anti-Smith, anti-Sjögren's syndrome-related antigen A (SSA), antinuclear antibody, anti-Sjögren's syndrome-related antigen B (SSB), and antiphospholipid antibody (APL). SLE impairment indicators were measured using the SLICC/ACR damage index (SDI) score for analysis.[22] Patients were classified according to the SDI score as without organ damage (SDI score = 0) or with organ damage (SDI score ≥1). Clinical features, which are relevant to patients with LN, included anemia, hypoalbuminemia, serum creatinine, hematuria, 24-h urine protein quantification (24h-UP), glomerular filtration rate (GFR, calculated by Cockcroft-Gault formula), and kidney pathology type on biopsy. Based on the International Society of Pathology/Renal Pathology Society classification of LN, formulated in 2003[23] and revised in 2018,[24] the LN pathological type

was classified as follows: class I, minimal mesangial; class II, mesangial proliferative; class III, focal; class IV, diffuse; class V, membranous; class VI, advanced sclerosing; and class III and V or class IV and V, combined membranous and proliferative.

Statistical analysis

Continuous variables are calculated and shown by mean ± standard deviation (SD) for normal distribution, while categorical variables are assessed and presented as numbers (*n*) and percentages (%). The differences in socio-demographic and clinical characteristics, organ damage, and therapeutic regimens between different sexes were compared with the analysis of the Student's *t*-test for continuous variables in terms of the normal distribution; variables that do not conform to the normal distribution are tested using the Mann–Whitney test. Chi-squared tests were used to assess categorical variables. All the tests were two-tailed, and *P* values <0.05 indicated significant results. SPSS 23.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analysis.

Results

Demographics

Of the 8713 newly diagnosed patients with SLE in our cohort, 795 were men (incidence: 9.1%) and 7918 were women (incidence: 90.9%), of whom 2900 SLE patients met the diagnostic criteria for LN, including 347 (12.0%) men and 2553 (88.0%) women, with a male: female ratio of 1:7.3. For both sexes, the age of onset was 37.0 ± 15.8 years (male) and 35.1 ± 13.7 years (female, $P = 0.006$) in the SLE group, 37.3 ± 16.1 years (male) and 35.0 ± 13.9 years (female, $P = 0.026$) in the LN group, respectively, with statistical significance of all these values.

The sex difference was not statistically significant in terms of the disease course as well as the SLEDAI score. The mean SLICC/ACR organ damage scores were higher for men than for women in the SLE group (0.47 ± 1.13 *vs.* 0.34 ± 0.81, $P = 0.015$), while in the LN group, the sex difference was not statistically significant (0.74 ± 1.49 *vs.* 0.55 ± 1.02, $P = 0.355$; Tables 1 and 2).

Clinical manifestations and laboratory tests of SLE in different sexes

Mucocutaneous involvement accounted for 39.2% ($n = 3413$) and was presented as the predominant organ-system involvement for SLE, followed by renal (33.3%; $n = 2900$), arthritis (29.2%; $n = 2545$), leukopenia (25.0%; $n = 2175$), and thrombocytopenia (18.8%; $n = 1638$). A univariate analysis revealed that male patients with SLE were more frequently presented with LN (43.6% *vs.* 32.2%, $P < 0.001$), fever (18.0% *vs.* 14.6%, $P = 0.010$), thrombocytopenia (21.4% *vs.* 18.5%, $P = 0.050$), and serositis (14.7% *vs.* 11.7%, $P = 0.013$), while less frequently presented with leukopenia (20.5% *vs.* 25.4%, $P = 0.002$) and arthritis (22.0% *vs.* 29.9%, $P < 0.001$; Table 1).

Clinical manifestations, laboratory tests, and pathological classification of LN in different sexes

Of the 2900 LN patients, 1172 (40.4%) had mucocutaneous involvement at presentation, 777 (26.8%) had arthritis, 754 (26.0%) had leukopenia, 674 (23.2%) had thrombocytopenia, and 558 (19.2%) had serositis. LN was less frequently presented with leukocytopenia (20.7% *vs.* 26.7%, $P = 0.017$) and arthritis (21.3% *vs.* 27.5%, $P = 0.014$) in male patients compared with that of female patients [Table 2]. Serum creatinine levels were significantly higher in the male LN group compared with the female LN group (97.4 ± 68.4 μmol/L *vs.* 80.1 ± 69.1 μmol/L, $P < 0.001$). The 24-UP, creatinine clearance, and hypoalbuminemia showed no difference between the sexes (*P* values of 0.647, 0.279, and 0.267, respectively). Overall, 482 patients with LN underwent renal biopsy (renal biopsy rate = 16.6%), of whom 264 had definite documented LN pathology type (33 men and 231 women). The proportions of male and female patients according to different pathological LN renal biopsy classification types were: in the male group, 15 (45.5%) were type IV or IV + V, 8 (24.2%) were type I or II, and 5 (15.2%) were in both class III or III + V and class V; in the female group, 105 (45.5%) were class IV or IV + V, 52 (22.5%) were class III or III + V, 39 (16.9%) were class V, and 33 (14.3%) were class I or II. The pathological classification of LN patients did not differ between the sexes ($P = 0.457$; Table 3).

Organ damage in different sexes

Of 8713 SLE patients, 7809 had organ damage (721 men and 7088 women). The most frequent types of organ damage were renal (7.8%; $n = 606$), skin (4.2%; $n = 329$), and pulmonary (4.1%; $n = 320$). The incidences of renal damage (11.1% *vs.* 7.4%, $P < 0.001$), cardiovascular events (3.1% *vs.* 1.7%, $P = 0.009$), peripheral vascular damage (2.4% *vs.* 0.8%, $P < 0.001$), and diabetes mellitus (1.1% *vs.* 0.5%, $P = 0.047$) had significantly increased in men than in women with SLE [Table 4].

Of the 2900 LN patients, the most frequent types of organ damage were renal (20.8%; $n = 543$), followed by pulmonary (5.1%; $n = 134$) and skin (4.7%; $n = 122$). The male LN group had higher rates of musculoskeletal damage (6.9% *vs.* 4.1%, $P = 0.023$), cardiovascular events (5.3% *vs.* 2.7%, $P = 0.009$), and peripheral vascular damage (3.8% *vs.* 1.2%, $P < 0.001$) compared with female LN group. The GFR < 50% or end-stage renal failure was significantly higher in men with LN than in women with LN (6.9% *vs.* 3.4%, $P = 0.002$), while the rate of 24h-UP ≥3.5 g did not differ between the sexes ($P = 0.515$; Table 5).

Treatment of immunosuppressants in different sexes

The rates of glucocorticoid application (including methylprednisolone pulses) between the sexes in either the SLE or LN groups had no significant differences. The glucocorticoid dosage (equivalent dose of prednisone) was higher in male patients than in female patients in both the SLE and LN groups, and the differences were

Table 1: Clinical characteristics and initial treatment in 8713 newly diagnosed patients with SLE by sex.

Variables	Male ($N = 795$)	Female ($N = 7918$)	$t/Z/\chi^2$	P value
Characteristics				
Age at onset (years), mean ± SD	37.0 ± 15.8	35.1 ± 13.7	−2.745†	0.006
Course of disease (months), median (Q1–Q3)	3.00 (1.00–12.00)	3.00 (1.00–13.00)	−0.339‡	0.735
SLEDAI score, mean ± SD	8.30 ± 7.24	8.29 ± 7.47	−0.342†	0.732
SDI score, mean ± SD	0.47 ± 1.13	0.34 ± 0.81	−2.436‡	0.015
Clinical manifestation, *n* (%)				
Renal disease	347 (43.6)	2553 (32.2)	42.318*	<0.001
Fever	143 (18.0)	1155 (14.6)	6.589*	0.010
Vasculitis	48 (6.0)	461 (5.8)	0.061*	0.805
Myositis	16 (2.0)	203 (2.6)	0.896*	0.344
Thrombocytopenia	170 (21.4)	1468 (18.5)	3.827*	0.050
Leukopenia	163 (20.5)	2012 (25.4)	9.288*	0.002
Neuropsychiatric lupus	52 (6.5)	487 (6.2)	0.190*	0.663
Mucocutaneous	289 (36.4)	3124 (39.5)	2.918*	0.088
Arthritis	175 (22.0)	2370 (29.9)	21.912*	<0.001
Serositis	117 (14.7)	927 (11.7)	6.204*	0.013
Hypocomplementemia	454 (57.1)	4544 (57.4)	0.023*	0.878
Autoantibody–positive, *n* (%)				
ANA	769 (96.7)	7566 (95.6)	2.404*	0.121
Anti-dsDNA	347 (43.6)	3699 (46.7)	2.735*	0.098
Anti-Sm	331 (41.6)	3471 (43.8)	1.424*	0.233
Anti-RNP	265 (33.3)	2760 (19.3)	0.740*	0.390
Anti-SSA	320 (40.3)	4242 (53.6)	51.406*	<0.001
Anti-SSB	107 (13.5)	1614 (20.4)	21.927*	<0.001
APLs	204 (25.7)	1859 (23.5)	1.904*	0.168
Therapeutic regimen				
Prednisone, *n* (%)	700 (88.1)	6819 (86.1)	2.276*	0.131
Methylprednisolone pulses, *n* (%)	46 (5.8)	416 (5.3)	0.408*	0.523
Dosage of prednisolone (mg/day), mean ± SD	48.6 ± 32.6	43.2 ± 29.8	−4.193‡	<0.001
HCQ, *n* (%)	545 (68.6)	5659 (71.5)	2.997*	0.083
CYC, *n* (%)	186 (23.4)	1276 (16.1)	27.428*	<0.001
MMF, *n* (%)	93 (11.7)	1123 (14.2)	3.714*	0.054
CNIs, *n* (%)	68 (8.6)	673 (8.5)	0.003*	0.959

* χ^2 values. † t values. ‡ Z values. Values are presented as mean ± SD, *n* (%), median (Q1–Q3). ANA: Antinuclear antibody; APLs: Antiphospholipid antibodies; CNIs: Calcineurin inhibitors; CYC: Cyclophosphamide; dsDNA: Double-stranded DNA; HCQ: Hydroxychloroquine; MMF: Mycophenolate mofetil; RNP: Ribonucleoprotein; rRNP: Ribosomal RNA protein; SD: Standard deviation; SDI: SLICC/ACR damage index; SLE: Systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; SLICC/ACR: SLE International Collaborative Clinic/American College of Rheumatology; Sm: Smith; SSA: Sjögren's syndrome-related antigen A; SSB: Sjögren's syndrome-related antigen B.

statistically significant (SLE group: 48.6 ± 32.6 mg/day *vs.* 43.2 ± 29.8 mg/day, $P < 0.001$; LN group: 55.3 ± 32.5 mg/day *vs.* 51.0 ± 30.7 mg/day, $P = 0.024$; Tables 1 and 2). The application of cyclophosphamide (CYC) was significantly higher in men compared with women in both the SLE and LN groups (SLE group: 23.4% *vs.* 16.1%, $P < 0.001$; LN group: 34.6% *vs.* 25.9%, $P = 0.001$). In the LN group, mycophenolate mofetil was used more frequently in women than that in men, while the application of hydroxychloroquine, calcineurin inhibitors, or biological agents (CD20 or belimumab) did not differ between sexes [Tables 1 and 2].

Discussion

To date, the present study is the largest inception cohort study comparing the characteristics of patients with SLE and LN by sex. Previously, the impact of sex on the phenotypes and long-term outcomes for Chinese SLE patients were preliminarily described through the CSTAR registry studies.[16,25,26] In the present study, we documented the clinical features, laboratory characteristics, and initial treatment regimen of patients newly diagnosed with SLE and LN according to sex. Further, we described the pathology and organ damage in these patients with LN according to sex. Our results may help to understand the characteristics of SLE at its onset and its original disease phenotype, and therefore, can be considered as a guide to its treatment and prognosis.

In this inception cohort, males accounted for 9.1% of total SLE, with a ratio of 1:10 (men:women), but this ratio dropped to 1:7.4 when LN was present. The prevalence of LN in this cohort was 33.3%, which is lower than that reported in the CSTAR cohort in 2013 (47.4%).[16] This difference has been attributed to the relatively low rate of kidney involvement at the time of SLE diagnosis in this inception cohort. The low rate of renal biopsy for LN

Table 2: Clinical characteristics and initial treatment in 2900 newly diagnosed patients with LN by sex.

Variables	Total ($N = 2900$)	Male ($N = 347$)	Female ($N = 2553$)	$t/Z/\chi^2$	*P* value
Characteristics					
Age at onset (years), mean ± SD	35.3 ± 14.2	37.3 ± 16.1	35.0 ± 13.9	−2.222†	0.026
Course of disease (months), median (Q1–Q3)	3.00 (1.00–12.00)	3.00 (1.00–10.00)	3.00 (1.00–12.00)	−0.157‡	0.875
SLEDAI score, mean ± SD	11.7 ± 8.5	11.2 ± 8.1	11.7 ± 8.5	−1.228†	0.219
SDI score, mean ± SD	0.57 ± 1.09	0.74 ± 1.49	0.55 ± 1.02	−0.924‡	0.355
Clinical manifestation, *n* (%)					
Fever (non-infection)	491 (16.9)	62 (17.9)	429 (16.8)	0.246*	0.620
Vasculitis	198 (6.8)	22 (6.3)	176 (6.9)	0.147*	0.701
Myositis	97 (3.3)	9 (2.6)	88 (3.4)	0.688*	0.407
Thrombocytopenia	674 (23.2)	84 (24.2)	590 (23.1)	0.206*	0.650
Leukocytopenia	754 (26.0)	72 (20.7)	682 (26.7)	5.648*	0.017
Neuropsychiatric lupus	221 (7.6)	29 (8.4)	192 (7.5)	0.304*	0.581
Mucocutaneous	1172 (40.4)	125 (36.0)	1047 (41.0)	3.156*	0.076
Arthritis	777 (26.8)	74 (21.3)	703 (27.5)	6.007*	0.014
Serositis	558 (19.2)	67 (19.3)	491 (19.2)	0.001*	0.973
Hypocomplementemia	1914 (66.0)	222 (64.0)	1692 (66.3)	0.719*	0.397
Autoantibody–positive, *n* (%)					
ANA	2795 (96.4)	338 (97.4)	2466 (96.6)	0.633*	0.426
Anti-dsDNA	1579 (54.4)	181 (52.2)	1398 (54.8)	0.831*	0.362
Anti-Sm	1329 (45.8)	153 (44.1)	1127 (44.1)	0.000*	0.985
Anti-RNP	969 (33.4)	109 (31.4)	873 (34.2)	1.056*	0.304
Anti-SSA	1554 (53.6)	152 (43.8)	1426 (55.9)	17.877*	<0.001
Anti-SSB	583 (20.1)	54 (15.6)	538 (21.1)	5.711*	0.017
APLs	724 (25.0)	97 (28.0)	627 (24.6)	1.879*	0.170
Therapeutic regimen, *n* (%)					
Prednisone, *n* (%)	2630 (90.7)	315 (90.8)	2315 (90.7)	0.004*	0.952
Methylprednisolone pulses, *n* (%)	265 (9.1)	34 (9.8)	232 (9.1)	0.185*	0.667
Dosage of prednisolone (mg/day), mean ± SD	–	55.3 ± 32.5	51.0 ± 30.7	−2.249†	0.024
HCQ, *n* (%)	1956 (67.4)	223 (64.3)	1733 (67.9)	1.819*	0.177
CYC, *n* (%)	782 (27.0)	120 (34.6)	662 (25.9)	11.611*	0.001
MMF, *n* (%)	626 (21.6)	57 (16.4)	569 (22.3)	6.199*	0.013
CNIs, *n* (%)	263 (9.1)	29 (8.4)	234 (9.2)	0.242*	0.623

* χ^2 values. † *t* values. ‡ *Z* values. ANA: Antinuclear antibody; APLs: Antiphospholipid antibodies; CNIs: Calcineurin inhibitors; CYC: Cyclophosphamide; dsDNA: Double-stranded DNA; HCQ: Hydroxychloroquine; LN: Lupus nephritis; MMF: Mycophenolate mofetil; RNP: Ribonucleoprotein; rRNP: Ribosomal RNA protein; SD: Standard deviation; SDI: SLICC/ACR damage index; SLE: Systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; SLICC/ACR: SLE International Collaborative Clinic/American College of Rheumatology; Sm: Smith; SSA: Sjögren's syndrome-related antigen A; SSB: Sjögren's syndrome-related antigen B.

Table 3: Renal manifestations of newly diagnosed patients with LN by sex.

Variables	Male ($N = 347$)	Female ($N = 2553$)	$t/Z/\chi^2$	*P* value
Anemia (%)	58.1	59.4	0.226*	0.635
Hypoalbuminemia (<35 g/L) (%)	68.0	71.3	1.231*	0.267
Hematuria (%)	45.4	46.9	0.198*	0.656
Serum creatinine (μmol/L), mean ± SD	97.4 ± 68.4	80.1 ± 69.1	3.79†	<0.001
GFR (mL/min), mean ± SD	100.6 ± 45.7	96.8 ± 44.1	1.084†	0.279
24h-UP (g/L), median (range)	1.60 (0.65–3.71)	1.45 (0.65–3.40)	−0.458‡	0.647
LN pathological classification, *n* (%)	$N = 33$	$N = 231$	2.600*	0.457
Class I or II	8 (24.2)	33 (14.3)		
Class III or III + V	5 (15.2)	52 (22.5)		
Class IV or IV + V	15 (45.5)	105 (45.5)		
Class V	5 (15.2)	39 (16.9)		

* χ^2 values. † *t* values. ‡ *Z* values. 24h-UP: 24-h urine protein quantification; GFR: Glomerular filtration rate; LN: lupus nephritis; SD: Standard deviation.

Table 4: Comparison of organ damage in 7809 patients with SLE by sex, *n* (%).

System/organ damage	Total (*N* = 7809)	Male (*N* = 721)	Female (*N* = 7088)	χ^2	*P* value
SLICC/ACR ≥1	1750 (22.4)	185 (25.7)	1565 (22.1)	4.822	0.028
Ocular	109 (1.4)	13 (1.8)	96 (1.4)	0.957	0.328
Neuropsychiatric	260 (3.3)	32 (4.4)	228 (3.2)	3.034	0.082
Renal	606 (7.8)	80 (11.1)	526 (7.4)	12.346	<0.001
Pulmonary	320 (4.1)	36 (5.0)	284 (4.0)	7.080	0.203
Cardiovascular	142 (1.8)	22 (3.1)	120 (1.7)	6.763	0.009
Peripheral vascular	77 (1.0)	17 (2.4)	60 (0.8)	15.311	<0.001
Gastrointestinal	79 (1.0)	11 (1.5)	68 (1.0)	2.096	0.148
Musculoskeletal	282 (3.6)	34 (4.7)	248 (3.5)	2.784	0.095
Skin	329 (4.2)	29 (4.0)	300 (4.2)	0.072	0.789
Gonad	11 (0.1)	1 (0.1)	10 (0.1)	0.000	0.987
Diabetes mellitus	45 (0.6)	8 (1.1)	37 (0.5)	3.943	0.047
Malignancy	12 (0.2)	1 (0.1)	11 (0.2)	0.012	0.913

SLE: Systemic lupus erythematosus; SLICC/ACR: SLE International Collaborative Clinic/American College of Rheumatology.

Table 5: Comparison of organ damage in 2616 patients with LN by sex, *n* (%).

System/organ damage	Total (*N* = 2616)	Male (*N* = 319)	Female (*N* = 2297)	χ^2	*P* value
SLICC/ACR ≥1	890 (34.0)	112 (35.1)	778 (33.9)	0.192	0.662
Ocular	47 (1.8)	9 (2.8)	38 (1.7)	2.162	0.141
Neuropsychiatric	114 (4.4)	16 (5.0)	98 (4.3)	0.377	0.539
Renal	543 (20.8)	74 (23.2)	469 (20.4)	1.316	0.251
eGFR <50%/ERSD	99 (3.8)	22 (6.9)	77 (3.4)	9.664	0.002
24h-UP ≥3.5 g	482 (18.4)	63 (19.7)	419 (18.2)	0.424	0.515
Pulmonary	134 (5.1)	20 (6.3)	114 (5.0)	4.304	0.321
Cardiovascular	78 (3.0)	17 (5.3)	61 (2.7)	6.921	0.009
Peripheral vascular	39 (1.5)	12 (3.8)	27 (1.2)	12.758	<0.001
Gastrointestinal	39 (1.5)	7 (2.2)	32 (1.4)	1.224	0.268
Musculoskeletal	116 (4.4)	22 (6.9)	94 (4.1)	5.198	0.023
Skin	122 (4.7)	13 (4.1)	109 (4.7)	0.283	0.595
Gonad	5 (0.2)	1 (0.3)	4 (0.2)	0.285	0.593
Diabetes mellitus	22 (0.8)	5 (1.6)	17 (0.7)	2.299	0.129
Malignancy	3 (0.1)	1 (0.3)	2 (0.1)	1.253	0.263

24h-UP: 24-h urine protein quantification; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; LN: Lupus nephritis; SLE: Systemic lupus erythematosus; SLICC/ACR: SLE International Collaborative Clinic/American College of Rheumatology.

(16.6%) is because of the predominance of rheumatology departments in the participating centers in this study and it suggests that the renal manifestations of LN patients admitted by rheumatologists may not be as severe as those admitted by nephrologists. Currently, there is no substitute for renal biopsy and renal pathology type to guide the diagnosis, treatment, and assessment of prognosis in LN. Therefore, aggressive renal biopsy or even repeated renal biopsy is particularly important in the management of LN and should further attract the attention of rheumatologists.

Many recent large domestic and multinational cohort studies have presented the clinical manifestations of patients with SLE by sex,[13,14,27-33] but with inconsistent results. The results of this cohort study were similar to that of the CSTAR cohort study in terms of the higher incidences of nephritis and fever, the incidence of leukopenia, and the lower rates of arthritis among male patients with SLE in the present study.[16] Nevertheless, the CSTAR registry V study revealed that men with SLE had a higher incidence of vasculitis, neuropsychiatric lupus, and a higher SLEDAI score[16] than those of women, which was not found in this study. These differences may be associated with the population features of the present study, such as the incomplete clinical phenotype of the enrolled patients at the time of presentation and the relative mildness of SLE at presentation. It also illustrates that men with SLE have unique characteristics and manifest some atypical clinical symptoms. The higher baseline SLICC/ACR injury scores (0.47 ± 1.13) in male SLE patients suggest that the male sex may have a faster disease progression and a potentially worse prognosis.

Consistent with most studies,[12,32] men with SLE in the inception cohort had an older age of onset on average. In the Grupo Latino Americano de Estudio del Lupus Eritematoso (GLADEL) initial cohort published by Garcia *et al*[13] in 2005, the median age at onset for male SLE patients was 27 years, which was less than that observed in

our study (37.0 ± 15.8 years) and that reported in the CSTAR registry V (30.0 ± 14.5 years).[16]

Consistent with previous reports, this study found that fever,[13] thrombocytopenia, and kidney damage[14,28-30,34,35] were the most common manifestations, while arthritis[12,14,28,34,36] was less common in male SLE patients than that in female patients. In the GLADEL cohort, male SLE patients exhibited a distinctive profile with a higher incidence of low complement C3 levels, hemolytic anemia, and anti-cardiolipin antibodies-IgG, which was not observed in this study. Mok *et al*[30] reported that anti-double-stranded DNA antibodies and APL exhibited no difference between the sexes at the time of diagnosis, which is consistent with the results of our autoantibody analyses, which did not yield different results between sexes, except in terms of anti-SSA and SSB antibodies, which were higher in the women in this study. Although a few studies suggested significant differences between male and female patients with LN in terms of clinical manifestations (mucocutaneous involvement,[28,37,38] serositis,[36,39,40] and neuropsychiatric lupus erythematosus),[41] we did not find significant differences between sexes in terms of most clinical characteristics, except for leukocytopenia and arthritis.

Several studies[9,13,25,33,42-44] have reported more frequent incidences of LN among men and with higher severity than that in women; however, in this study, male and female LN patients did not show differences in the disease duration, SLEDAI scores, and having SLICC/ACR scores ≥1. These could be explained by the relatively mild disease in the initial cohort and the relatively low proportion of patients with renal involvement at diagnosis. Meanwhile, previous research indicates that sex is not the only predictor of LN.[32,45] Some clinical manifestations of LN lacked significant differences between the sexes, which may be attributed to the incomplete clinical phenotype of the patients in the initial cohort. A more aggressive disease course has been reported for male patients with LN in previous cohorts.[25,29,32,33,46] We observed no differences between sexes in the clinical manifestations of nephropathy, except for higher serum creatinine levels among men with LN than among women with LN, which is consistent with the findings published by the Peking University Hospital in its cohort study of 315 Chinese patients with LN.[29] Male patients with LN had higher serum creatinine levels than female LN patients, and this is consistent with previously published reports.[44,46-49] Tang *et al*[48] and Soni *et al*[44] reported significant differences in the renal-related manifestations in LN patients by sex; for example, differences in albumin and hemoglobin levels and 24h-UP, which were not found in our study, possibly because the patients enrolled in our cohort had a milder disease status than those enrolled in other cohorts.

The pathological differences in the presentation of nephritis between the sexes have not been elucidated. Class IV and IV + V were the major pathological types of nephritis across both sexes, which is consistent with the previous findings that the proliferative glomerulonephritis was viewed as the dominant histological finding on renal biopsy in patients with LN.[14,29,42,43,47,50,51] This study showed that renal pathological classification of LN patients did not differ significantly between sexes, which was consistent with another cohort study involving 315 patients with LN, published by Peking University Hospital.[29]

Furthermore, in the present study, organ damage in SLE was more common among men than among women. At baseline, 22.4% of patients with SLE (185 men and 1565 women) had SDI score ≥1, which is higher than the prevalence reported in CSTAR registry XI (16.5%)[25] but lower than the rate reported by Shaharir *et al*[52] for Malaysian SLE patients (41.9%) and previous studies (40%). In our initial cohort, renal and cardiovascular damages are mainly developed in male patients, which were also reported in the studies involving South Korean,[53] Malaysian,[52] and African American populations.[12] In the LN cohort, 6.9% of male patients and 3.4% of female patients had a creatinine clearance rate <50% or ESRD at the time of enrollment, suggesting that male SLE patients are susceptible to kidney damage, and patients who have kidney injuries may be more susceptible to irreversible damage to this organ.

The immunosuppressive therapy at entry revealed that CYC treatment was more commonly prescribed for men with LN and SLE than for women with SLE or LN; this is comparable to previously reported research.[25,31,54] Mycophenolate mofetil is used more commonly among female patients, which may be due to fertility considerations. Moreover, heavy organ involvement may be one of the reasons for choosing CYC to treat male patients. In our cohort, patients were rarely treated with biologic drugs such as rituximab and belimumab. We attributed this finding to the enrollment of most patients before 2019. Long-term follow-up will be necessary to evaluate more data on the application of biological agents such as belimumab in LN.

To our knowledge, this is the largest inception cohort study so far on the sex-based differences among Chinese SLE patients and we analyzed not only the sex-based differences in SLE in the initial cohort but also the gender differences in LN. Our study had some limitations. First, as a cross-sectional study, we conducted a descriptive study of the baseline data of the cohort. Second, three different SLE classification instruments were used and they are not entirely identical, which might influence the results. Third, the number of patients with renal biopsy-proven LN is insufficient. Although our study was only a descriptive analysis of the cohort at the baseline, we believe that a study based on a cross-sectional design of data from the initiation cohort may be more descriptive of the original phenotype of the disease than other cohort studies. In the future, more long-term follow-up cohort studies should be conducted based on this study to explore further differences in the long-term prognosis, conduct risk factor analysis, and analyze various maintenance therapy options for patients with SLE and LN by sex. Further, data collected of patients with SLE or LN at initial presentations can be compared with the data from the follow-up evaluations, including that of patients

without initial renal involvement, to explore the proportion of patients who develop LN during follow-up and present a risk factor analysis.

In conclusion, the present study compared sex-based differences in the clinical characteristics of newly diagnosed SLE or LN patients in a Chinese inception cohort as well as the initial treatment of these patients. The major findings included a later age of onset, a higher rate of renal, cardiovascular, and peripheral vascular damage. We also found a higher rate of initial treatment with CYC and a higher dosage of glucocorticoids were used in Chinese men with SLE or LN than in women.

Chinese men with SLE have a higher rate of fever, nephritis, serositis, and thrombocytopenia. Chinese men with LN have higher serum creatinine levels, which may lead to kidney failure, compared with women. Male patients with SLE or LN may require more aggressive initial treatment compared with female patients.

Funding

This study was supported by grants from the Chinese National Key Technology R&D Program, Ministry of Science and Technology (Nos. 2021YFC2501301-5 and 2017YFC0907601-3), Beijing Municipal Science & Technology Commission (No. Z201100005520022, 23, and 25–27), and CAMS Innovation Fund for Medical Sciences (CIFMS; 2021-I2M-1-005).

Conflicts of interest

None.

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How to cite this article: Gui Y, Bai W, Xu J, Duan X, Zhan F, Zhao C, Jiang Z, Li Z, Wu L, Liu S, Yang M, Wei W, Wang Z, Zhao J, Wang Q, Leng X, Tian X, Li M, Zhao Y, Zeng X, CSTAR co-authors. Sex differences in systemic lupus erythematosus (SLE): an inception cohort of the Chinese SLE Treatment and Research Group (CSTAR) registry XVII. Chin Med J 2022;135:2191–2199. doi: 10.1097/CM9.0000000000002360