

Clinical and biochemical manifestations of systemic lupus erythematosus at first diagnosis within Chinese patients

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Abstract

Background: The objective of this paper was to describe the first symptoms associated with systemic lupus erythematosus (SLE), including clinical manifestations, laboratory findings, prognoses, differences between men and women at the time of first diagnosis of SLE.

Methods : We enrolled 223 patients with initial diagnosis of SLE. Their initial symptoms, demographic, clinical and laboratory data, prognoses and causes of death were analyzed retrospectively. Clinical manifestations and laboratory profiles were compared between male and female patients.

Results: Compared with female patients, male patients had an earlier age of onset, a higher incidence of neuropsychiatric involvements, a lower incidence of leukocytopenia , and a higher score of SLE Disease Activity Index (SLEDAI) at diagnosis. Fever and malar rash were most frequent presentations at onset of SLE. The most common clinical manifestation at first diagnosis was fever, followed by arthralgia, malar rash, Raynaud ' s phenomenon, arthritis. The liver function abnormalities included increased ALT,AST,ALP and γ -GGT. ANA were found in 100% of patients, followed by anti-dsDNA(LIA) in 72.1%, anti-Ro60 in 67.8%, anti-Ro52 in 62.3%, anti-nucleosomes in 55.7%.

Conclusions: We identified clinical and serological manifestations of Chinese SLE patients at first diagnosis. Male patients showed a distinctive manifestation including younger age of onset, a higher incidence of CNS manifestations, a higher score of SLEDAI compared to females.

Background

Systemic lupus erythematosus(SLE) is a chronic autoimmune disease involving various organs and systems. Management of SLE is vastly complicated owing to the considerable variabilities in the clinical and laboratory manifestations, disease courses, and prognoses, particularly on the grounds of sex¹. Accordingly, the timely diagnosis of patients with SLE is often delayed^{2, 3}. The care of SLE patients also has its challenges owing to the considerable sex-specific variabilities in the clinical and laboratory. Especially, a notable impact upon woman of childbearing age are most susceptible^{1, 4}.

Ninety-three percent of SLE patients survive over 5 years from diagnosis⁵, of which infection, lupus encephalopathy, atherosclerosis and pulmonary hypertension are the most frequent causes of death^{6, 7}. Few studies, however, have reported on the cause of death in SLE patients followed up from their initial diagnoses. To the contrary, research on the clinical and biochemical features accumulating over the course of diseases are abundant^{1, 8, 9}. Whilst a snapshot of the clinical and biochemical manifestations at onset of SLE has been described¹⁰, no studies have yet reported on a cohort of Chinese SLE patients.

The present study was aimed to outline the clinical and biochemical manifestations first diagnosis of Chinese patients with SLE, which deepened our understanding on the prognosis. We also compared the differences in these parameters between male and female patients.

Methods

Patients

A cohort of 223 patients suffered from SLE with the first diagnosis, attending the department of rheumatology and immunology of first affiliated hospital to Bengbu medical college between January 2012 and December 2015, were enrolled and retrospectively analyzed. All patients were fulfilled the American College of Rheumatology revised classification criteria for SLE in 1997¹¹. Patients' medical records were collected, of which the following data were extracted—sex; the first clinical symptoms associated with SLE; age at disease onset defined as age when symptoms were first presented; age at the time of first diagnosis of SLE, duration between the presentation of clinical symptoms associated with the onset of SLE and the formal diagnosis of SLE; organ involvements; concomitant diseases(s); SLE Disease Activity Index(SLEDAI) score; clinical and laboratory manifestations; causes of death.

Clinical outcomes

The clinical manifestations included: fatigue; fever; arthritis; arthralgia; malar rash; discoid rash; alopecia; photosensitivity; oral ulcer; raynaud's phenomenon; vasculitis of hands; limbs rash and organ involvements of cardiac, lung, hematologic, renal, digestive and central nervous systems. Fever was considered when body temperature was $\geq 37.3^{\circ}\text{C}$ without other causes.

Biochemical outcomes

The standard hematological, renal, hepatic, urinary and immunological profiles were determined. The abnormal threshold of each parameter were as following. Hematological: leucopenia , white blood cell count $\leq 4 \times 10^9/\text{l}$; lymphopenia, lymphocyte count $\leq 1.5 \times 10^9/\text{l}$; hypoeosinophilia, eosinophil count $\leq 0.02 \times 10^9/\text{l}$; mononucleosis, monocytes $\leq 0.9 \times 10^9/\text{l}$; monocytopenia, monocyte count $\leq 0.08 \times 10^9/\text{l}$; anemia, hemoglobin $\leq 120 \text{ g/l}$;

thrombocytopenia, platelet count $\leq 100 \times 10^9/l$; Hemolytic anemia was considered if direct Coomb's test was positive; elevated erythrocyte sedimentation rate (ESR), ≥ 25 mm at 1 hour.

Hepatic/digestive: increased alanine aminotransferase (ALT), ≥ 45 u/l; elevated aspartate aminotransferase (AST), ≥ 40 u/l; elevated alkaline phosphatase (ALP), ≥ 100 u/l, elevated γ -glutamyltransferase (γ -GGT), ≥ 45 u/l; low albumin (ALB), ≤ 40 g/l; elevated globulin (GLB), ≥ 40 g/l; elevated total bilirubin (TBIL), ≥ 22 μ mol/l excluding hemolytic anemia.

Immunological: normal C-reactive protein (CRP), ≤ 6 mg/l; normal values for IgG, 7-16 g/l; IgA, 0.4-2.8 g/l; IgM, 0.7-3.0 g/l; C3, 0.88-2.01 g/l; C4, 0.16-0.47 g/l. The autoantibodies were also determined in addition to the generic immunological markers. ANA was examined by indirect immunofluorescence with HEp-2 cells as substrate. Anti-dsDNA was also detected by indirect immunofluorescence technique using Crithidia luciliae as substrate or with line immuno assay (LIA). The anti-extractable nuclear antigens (anti-nucleosomes, anti-histones, anti-Sm, anti-U1snRNP, anti-SSA/Ro60, anti-SSA/Ro52, anti-SSB, anti-Scl-70, anti-ribosomal P0, anti-centromere) were determined by the line immunoassay (Germany). Rheumatoid Factor (RF-IgM), anti-cardiolipin (aCL IgG), anti- β 2 glycoprotein 1 (anti- β 2GP1-IgG), anti-cyclic citrullinated peptide (anti-CCP), anti-anproteinase 3 (anti-PR3), anti-myeloperoxidase (anti-MPO) were measured by enzyme-linked immunosorbent assay (ELISA).

Renal: Lupus nephritis was defined if proteinuria ≥ 0.5 g/day or if cellular cast or serum creatinine ≥ 104 μ mol/l.

Urinary: urine was analyzed over 24 hours, with proteinuria diagnosis if protein excretion ≥ 0.5 or $\geq 3+$, leucocyturia if leukocytes ≥ 28 / μ l excluding infection, and hematuria if red blood cells ≥ 10 / μ l or ≥ 17 / μ l for males and females, respectively (excluding infection or stone).

Neuropsychiatric SLE were diagnosed in accordance with the American College of Rheumatology nomenclature¹². Pulmonary arterial hypertension (PAH) was diagnosed if systolic PAP ≥ 40 mmHg according to an echocardiography.

Statistical Analysis

All Statistical analyses were undertaken within SPSS [version 21.09 IBM]. Continuous data are expressed as means \pm standard deviation (SD) and analyzed with student's t test. Categorical data were expressed as the frequency (n) and percentage, and analyzed with the Chi-squared and Fisher exact test. Odds ratio (OR) and 95% confidence interval (CI)

were determined using the Chi-squared test. A p value ≤ 0.05 was considered statistically significant .

Results

Clinical symptoms associated with the onset of SLE

We studied the clinical symptoms that presented at first diagnosis of SLE within a cohort of 223 Chinese patients (Table 1). Within this cohort, 213 patients were female (95.5%) and 10 patients were male (4.5%). There were 21.3 SLE incidences in females for every 1 on male case. The mean age at onset of SLE was significantly lower within males (24.50 ± 7.80) than females (33.80 ± 13.13 ; $P = 0.004$). Furthermore, the mean age at first diagnosis of SLE was markedly lower within males (25.00 ± 8.00) than females (34.57 ± 13.50 ; $P = 0.004$). The duration from the onset of symptoms to a diagnosis was 10.89 ± 26.21 months, and the sex-specific differences were not considered significant. A malar rash (17.9%), fever (17.9%), arthralgia (17.5%), arthritis (9.4%), and renal (9.4%) and hematological involvement (thrombocytopenia, hemolytic anemia, lymphadenopathy and leucopenia combined) were the most common symptoms presented at the onset of SLE, whereas deep vein thrombosis in the right lower extremity (0.4%) and renal vein thrombosis (0.4%) were the least common ones.

Clinical manifestations at first diagnosis of SLE

Clinical manifestations presented at the time of first diagnosis of SLE were noted (Table 2). Fever was the most common clinical manifestation at the first diagnosis of SLE, occurring 44.4% of 223 Chinese patients, with 10.3% of the total cohort having a fever of $37.3-38.0^\circ\text{C}$, 17.5% a fever of $38.1-39.0^\circ\text{C}$, and 7.2% with a severe of $>39.1^\circ\text{C}$. Arthralgia (42.2 %) and malar rash (35.9) were the most common symptoms, followed by Raynaud's phenomenon (16.1%), arthritis (15.2%), and alopecia (14.8%). The prevalence of myocardium involvements (10.8%), photosensitivity (10.3%), pericarditis (9.4%), pleuritis (9.0%), dry mouth (9.0%), limb rashes (8.5%), and oral ulcers (7.2%) were also particularly noticeable. There was no significant differences in the prevalence of clinical manifestations within males and females, aside from vasculitis of the hands and neuropsychiatric symptoms, which were significantly more prevalent within male SLE patients than female counterparts ($P = 0.034$ and 0.001 , respectively). Discoid rash (0.4%) and acute pancreatitis (0.4%) were particularly rare in SLE patients at first diagnosis. Pulmonary hypertension and intestinal pseudo-obstruction (IPO) were also noted within SLE patients at the time of

diagnosis. Disease activity was evaluated by SLEDAI scoring, with a significantly lower score in females than males ($P=0.048$).

Laboratory findings at the time of first diagnosis of SLE

In addition to clinical manifestations, an array of laboratory tests pertaining to 51 indices of hematological, hepatic, digestive, immunological, renal, and urinary profiles were determined at the time of first diagnosis of SLE (Table 2). Hematologic abnormalities were noted within the majority of SLE patients at the time of first diagnosis. Anemia was the most common hematological manifestation noted within the cohort of 223 Chinese patients (82.7%), followed by lymphopenia (72.1%), hypoeosinophilia (52.8%), leukocytopenia (45.1%), and thrombocytopenia (23.0%). Mononucleosis (8.9%) and monocytopenia (9.4%) were also observed within our cohort. There were 7 SLE patients (3.2%) with hemolytic anemia at time of their first diagnosis. The frequency of leukocytopenia within females (45.7%) was significantly higher than within males (4.1%; $P=0.021$).

The prevalence of proteinuria of >0.5 /d and $\geq 3+$ within SLE patients at the time of first diagnosis were 45.1% and 16.6%, respectively. Meanwhile, the prevalence of pyuria was 33.3%, followed by hematuria (21.3%), elevated serum creatinine (5.4%), and finally casts in urine (0.5%). There was no significant difference in the prevalence of renal involvements within males and females.

Many parameters of liver function were considered abnormal. Serum ALT, AST, ALP, γ -GGT, and GLB were elevated at first diagnosis of SLE (14.9, 16.5, 19.4, 22.0, and 29.8% prevalence, respectively). To the contrary, aberrant low serum ALB was noted in 72.9% of SLE patients at the time of their diagnosis. Elevated TBIL was relatively uncommon which was only found in 2.0% of 196 patients. There was no difference in the prevalence of abnormal liver-function tests within male and female patients of SLE (Table 2).

Inflammatory markers, most notably CRP and ESR, were detected in many SLE patients at first diagnosis (Table 2). ESR was elevated in the majority of SLE patients (78.3%), with the mean level at 55.87 ± 32.12 mm/h. The mean level of CRP was 12.10 ± 22.50 mg/L, which was abnormally elevated within 43.6% patients (excluding patients with infection(s)). There was no significant difference in the mean level and prevalence of ESR and CRP within males and females.

Immunological features at the time of first diagnosis of SLE

In addition to the generic markers of inflammation, we also determined total immunoglobulin levels and the presence of 18 autoantibodies at SLE diagnosis (Table 3). At the time of initial diagnosis of SLE, 100% of SLE patients were tested positive for ANA, whereas 52.1% were positive for anti-dsDNA (IIF), rising to 72.1% if determination was via LIA. Anti-histones antibodies and anti-nucleosomes were positive in 55.9 and 55.7% of SLE patients sampled. Of the extractable nuclear antibodies, anti-Ro/SSA60 antibodies were the most prevalent (67.8%), followed by anti-Ro/SSA52 (62.3%), anti-U1snRNP (55.5%), anti-Sm in (55.4%), anti-ribosomal P0 (44.4%), anti-La/SSB (27.9%), anti-MPO (3.5%), anti-Scl70 (1.3%), and anti-PR3 (0). None of the SLE patients were positive for the anti-Jo1 . Rheumatoid factor was elevated in 50.5% (46/91) of SLE patients, whereas the anti-CCP antibody was present in only 4.6% of those sampled. Anti-phospholipid antibodies were observed at diagnosis in a subset of patients, including aCL(13.2%) and anti-β2GP1 (21.12%). There was no significant difference in the aforementioned autoantibodies within male and female patients. Serum IgG, IgA, and IgM were elevated in 71.0, 48.0, and 3.1% of SLE patients, respectively, and decreased in 2.4, 0.4, and 7.2%.

Causes of death

Four (1.8%) of the 223 enrolled SLE patients died during the course of the study; the causes of which are presented in Table 4. Three patients succumbed to complications associated with active SLE, whereas the other one patient died from pulmonary hypertension and cardiac failure. The duration between diagnosis and SLE-rated deaths were < 6 months. There was no difference in death prevalence between men and women (Table 2).

The relation of autoantibodies and NPSLE, lupus nephritis at the time of first diagnosis of SLE.

Neuropsychiatric and renal involvements were associated with a worse prognosis^{13, 14}, and as such we analyzed that the correlation between the presence of autoantibodies at the time of first SLE diagnosis and neuropsychiatric systemic lupus erythematosus (NPSLE) or lupus nephritis. Overall, the vast number of autoantibodies determined had no significant correlations with NPSLE or lupus nephritis. Anti-U1snRNP, however, was negative indicator for NPSLE (OR=0.187; $P=0.047$), and anti-Ro/SSA52 antibody was associated with lupus nephritis (OR=2.424; $P=0.006$).

Discussion

In the present study, there were ~21 incidences of SLE in females per male at the time of first diagnosis, which differed somewhat from the ~10 female to 1 male case reported elsewhere^{1, 9, 15-17}. On the other hand, three studies observed an approximate 18 to 23 SLE diagnoses within female for every male diagnosis.^{18, 19} The mean age at the onset of SLE was 34.14 ± 13.07 , which was in accordance with previous studies^{9, 10}. Furthermore, in consolidation with previous studies, the average age at onset of SLE was younger in men than in women of our cohort¹. The mean duration between the onset of symptoms associated with SLE and diagnoses was longer than data reported within other studies^{1, 9, 20}.

The most frequent manifestations at onset of SLE are typically of musculoskeletal or mucocutaneous involvements¹. In juvenile SLE, pallor and fever tend to present first²¹. Within our cohort, malar rash and fever were the most common initial presentations (17.9%), followed by arthralgia (17.5%), arthritis (9.4%), and renal involvements (9.4%). The prevalence of fever at onset of SLE is highly discrepant within the literature, with the percentage of male and female SLE patients being 41.5% in men and 43.9% in women²⁰, whilst Choi et al. observed fever within 28% of patients at the onset of SLE (28%)¹⁰. Fever may develop within SLE patients due to an immunological response to active disease or infection, or as part of bodily reactions to the treatment. 44.4% of cohort had fever at the time of SLE diagnosis, which may attribute to the underlying disease activities. By temperature, a moderate fever was most frequent (38.1-39°C), followed by mild (37.3-38°C) and severe (>39°C) fever. Though, it should be noted that it was not possible to determine all fevers, which may have skewed the results in a manner unseen thus far.

Arthritis or arthralgia are common presentations at diagnosis of SLE¹⁰ and late-onset lupus^{22, 23}. But the occurrence rate of arthritis and arthralgia in our patients was less than that was reported in the aforementioned studies. Cutaneous involvement is also frequently reported in SLE patients, of which malar rash and photosensitivity are the most common¹. Our study showed that malar rash was frequent cutaneous manifestations at time of SLE diagnosis, followed by Raynaud's phenomenon and alopecia, whilst discoid rash was rare. Less than 20% of SLE patients were reported to have pericarditis at first diagnosis^{9, 23}. Myocarditis had also been observed in patients at diagnosis of SLE²³, the prevalence of which was similar with our cohort. Pulmonary involvement, pleuritis, ILD, and pulmonary hypertension were observed within our patients, as also described by Catoggio et al²³.

Hematological abnormalities are commonly observed within SLE patients. Aleem et al. previously observed anemia, lymphopenia and leukopenia at time of diagnosis within 63%,

40%, and 30% of SLE patients, respectively²⁴. Our study showed that 82.7% of Chinese patients with a first diagnosis of SLE had anemia, whilst 72.1% had lymphopenia and 52.8% had hypoeosinophilia. Mononucleosis or monocytopenia was presented around 9% of our patients. The occurrence of thrombocytopenia was not less common, and 23% patients presented thrombocytopenia. Renal involvements are commonly reported at initial diagnosis of SLE, such as renal lesions, proteinuria, hematuria, pyuria, and elevated serum creatinine¹⁰. Proteinuria, defined as the urinary excretion of > 0.5 grams protein per day, was the most common disorder within the present cohort. Of the renal abnormalities, 45.1% of patients had pyuria and hematuria, whilst casts in urine were rare.

Liver biochemical abnormalities in patients with SLE are typically attributed to obesity, hypertension, and the hepatotoxic effects of therapeutic medication²⁵. But it may also be due to the autoimmunity inherent to SLE²⁶. Our study showed that elevated serum ALT, AST, ALP, and γ -GGT were presented within 14.9, 16.5, 19.4, 22% of the present cohort, respectively. We had strong confidence that, since infection and drug confounders were excluded, these abnormalities were solely due to SLE. Elevated TBIL resulting from SLE was rare in our patients. Elsewhere, the prevalence of neuropsychiatric SLE (NPSLE) reportedly ranged from 21% to 95% in SLE patients²⁷, but we found, by contrast, a prevalence of 4.5% in our study.

Eudy et al. observed that elevated CRP was associated with a greater prevalence of flares in SLE patients, and may therefore be predictive for disease activity²⁸. The prevalence of elevated CRP was 43.6% in our cohort. Raised ESR is also associated with disease activity and organ-specific activity in SLE²⁹, and is particularly common within SLE patients (~79%) at the time of diagnosis²⁴. The prevalence of elevated ESR was 78.3% within the present study. The mean SLEDAI score of disease severity was 9.53, which was classified as a moderate activity³⁰. Complement levels below the normal limit are common at diagnosis of SLE. Choi et al. found that the prevalence of low serum C3 and C4 was 74.6% and 46.3% at diagnosis of SLE, respectively¹⁰. Aleem et al., meanwhile, reported that the prevalence of low serum C3 and C4 within SLE patients at initial diagnosis were 45.4% and 42.2%, respectively²¹. By comparison, our results showed that the prevalence of low serum C3 and C4 within SLE patients at initial diagnosis were much higher at 93.3% and 88.0%, respectively. We observed that increased IgG and IgA were common. Decreased IgG and IgA were less common. But decreased or increased IgM was totally less common.

Our data were strongly associated ANA with the diagnosis of SLE (100% prevalence); data of which were supported by Choi et al., who reported that 93% of patients were positive for ANA at the onset of SLE¹⁰. We also found that >50% of patients had positivity

for the anti-nucleosomes, anti-Sm and anti-U1snRNP. The positivity of anti-dsDNA was variable and highly dependent upon the detection method used. Anti-Ro52 and anti-Ro60 were frequent in 62.3% and 67.8% of SLE patients, respectively. Only Choi et al. reported the presence of anti-Ro52 at diagnosis of SLE¹⁰.

The primary causes of death in SLE patients have changed over time. Whilst lupus activity has decreased over time, co-mortality from infections are now most common within SLE patients⁷. Our data showed that the primary cause of death within SLE was lupus activity. Anti-ds-DNA and anti-nucleosome play a major role in the pathogenesis of lupus nephritis³¹, but our results showed that anti-Ro52 also correlated with LN. Furthermore, anti-U1RNP in cerebrospinal fluid (CSF) is typically associated with NPSLE³², whereas we found that anti-U1snRNP in serum was associated with NPSLE.

Whilst male patients tend to develop identical clinical and biochemical manifestations of SLE compared with female patients, males tend to exhibit a higher renal involvement, pleuritis and serositis, thrombocytopenia¹⁷. Furthermore, our data showed that SLE onsets at a younger age within males, and, at diagnosis, tended to have a higher prevalence of vasculitis of the hands, CNS manifestations, a lower rate of leukocytopenia, and a higher SLEDAI score compared to women. Hematuria was higher in men, but not statistically significant.

The present study outlined the clinical manifestations and laboratory features, and their relative prevalence within 223 Chinese patients, at diagnosis of SLE. We acknowledge that there are many limitations of this study, including the limited number of patients, and of males in particular. Additionally, this was performed in a single center. A larger-scale, multicenter study is needed to clarify the features of Chinese patients at initial diagnosis of SLE.

Conclusions

We identified that fever and malar rash were the most common first symptoms associated with SLE; that fever, arthralgia and malar rash were the most frequent clinical manifestations within SLE at the time of first diagnosis; that the cause of death in SLE patients at diagnosis was lupus activity; that male patients had a higher score of SLEDAI and a lower incidence of leukocytopenia.

Abbreviations

aCL:	anticardiolipin
ALB:	albumin
ALP:	alkaline phosphatase
AST:	aspartate aminotransferase
C3 :	complement 3
C4 :	complement 4
CCP:	cyclic citrullinated peptide
CNS:	central nervous system
dsDNA:	double-stranded DNA
GPI:	glycoprotein I
GLB:	globulin
HbsAb:	hepatitis B surface antibody
IgM:	immunoglobulin M
IgA:	immunoglobulin A
IgG:	immunoglobulin G
IIF:	indirect immunofluorescence
IPO:	intestinalpseudo-obstruction
LN:	lupus nephritis
MPO:	myeloperoxidase
PBC:	primary biliary cirrhosis
PR3:	antiproteinase 3
Sm:	smith
SSA:	Sjögren syndrome antigen A
RA:	rheumatoid arthritis
RF:	rheumatoid factor
Scl:	scleroderma
SLE:	systemic lupus erythematosus
SLEDAI:	systemic lupus erythematosus disease activity index
SSB:	Sjögren syndrome antigen B
TBIL:	total bilirubin
TTP:	thrombotic thrombocytopenic purpura
U1snRNP:	U1 small nuclear ribonucleoprotein
γ-GGT:	γ-glutamyltransferase

Declarations

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Authors' contributions

CH Xie designed the study and wrote the manuscript. LL Zhang, YY Wang, ZJ Li, LJ Chen, P Zhao, C Jiang, XY Fan and JQ Li collected the data. All authors read and approved the manuscript.

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Availability of data and materials

The data are owned by Changhao Xie. All data are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the institutional review board of the first affiliated hospital to Bengbu Medical college. The study was only involved with the review of medical records and therefore the written informed consent was not required.

Consent for publication

Not applicable

Competing interests

The Authors declares that there is no conflict of interest.

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Tables

Table 1

Variable	All(n=223)	Female(n = 213)	Male(n = 10)	<i>P</i> value
Gender, n(%)	223 (100)	213 (95.5)	10 (4.5)	
Age at onset of SLE, years	33.38±13.07	33.80±13.13	24.50±7.80	0.004
Age at first diagnosis of SLE, years	34.14±13.43	34.57±13.50	25.00±8.00	0.004
Time of onset to diagnosis, months	10.89±26.21	11.06±26.77	7.30±7.43	0.658
Malar rash	40(17.9)	36(16.9)	4	
Arthralgia	39(17.5)	37(17.4)	2	
Arthritis	21(9.4)	21(9.9)	0	
Fever, n(%)	40(17.9)	38(17.8)	2	
Raynaud's phenomenon	8(3.6)	7(3.3)	1	
Renal involvement	21(9.4)	21(9.9)	0	
Limb rash	8(3.6)	8 (3.8)	0	
Intestinal pseudo-obstruction	6(2.7)	6(2.8)	0	
Myocardium involvement	8(3.6)	8(3.8)	0	
Thrombocytopenia	8(3.6)	8(3.8)	0	
Hemolytic anemia	4(1.8)	4(1.9)		
Lymphadenopathy	1(0.4)	1(0.5)	0	
Leucopenia	1(0.4)	1(0.5)	0	
Pleural effusion	4(1.8)	4(1.9)	0	
Alopecia	2(0.9)	2(0.9)	0	
Hepatic cirrhosis(including 1 PBC)	2(0.9)	2(0.9)	0	
Fatigue	4(1.8)	4(1.9)	0	
Neuropsychiatric disorder	2(0.9)	1(0.5)	1	
DVT in right lower extremity	1(0.4)	1(0.5)	0	
Left renal vein thrombosis	1(0.4)	1 (0.5)	0	
Hands and feet swelling	2(0.9)	2(0.9)	0	

Table 2

Variable	All(n=223)	Female(n = 213)	Male(n =10)	P value
Fatigue	12(5.4%)	12(5.6%)	0(0)	1
^a Fever	99(44.4)	94(44.1)	5(50)	0.715
37.3-38.0°C	23(10.3)	22(10.3)	1(10)	0.718
38.1-39°C	39(17.5)	37(17.4)	2(20)	
>39.1°C	16(7.2)	16(7.5)	0(0)	
Unknown	21(9.4)	19(8.9)	2(20)	
Arthritis	34(15.2)	33(15.5)	1(10)	0.982
Arthralgia	94(42.2)	91(42.7)	3(30)	0.639
Malar rash	80(35.9)	74(34.7)	6(60)	0.197
Discoid rash	1(0.4)	1(0.5)	0(0)	1
Alopecia	33(14.8)	31(14.6)	2(20)	0.985
Photosensitivity	23(10.3)	21(9.9)	2(20)	0.618
Oral ulcer	16(7.2)	16(7.5)	0(0)	1
Raynaud's phenomenon	36(16.1)	34(16)	2(20)	1
Vasculitis of hands	7(3.1)	5(2.4)	2(20)	0.034
Limb rash	19(8.5)	18(8.5)	1(10)	1
Cardiac involvement				
Pericarditis	21(9.4)	20(9.4)	1(10)	1
Myocardium involvement	24(10.8)	24(11.3)	0(0)	0.606
Lung involvement				
Pleuritis	20(9.0)	20(9.4)	0(0)	0.605
ILD	9(4.0)	9(4.2)	0(0)	1
Pulmonary hypertension	7(3.1)	7(3.3)	0(0)	1
Hematologic involvement				
Leukocytopenia	98/217(45.1)	95/208(45.7)	3/9(4.1)	0.021
Lymphopenia	140/194(72.1)	136/187(92.7)	4/7(57.1)	0.547
Hypoeosinophilia	93/176(52.8)	90/169(53.3)	3/7(42.9)	0.878
Anemia	178/215(82.7)	170/205(82.9)	8(80)	0.811
Hemolytic anemia	7(3.2)	7(3.3)	0(0)	1
Mononucleosis	17/190(8.9)	16/183(8.7)	1/7(14.3)	0.778
Monocytopenia	18/190(9.4)	17/183(9.3)	1/7(14.3)	
Thrombocytopenia	50/217(23.0)	46/207(22.2)	4(40)	0.117
Purpura	6(2.7)	6(2.8)	0(0)	1
Renal involvement				
Proteinuria(>0.5g/d)	79/175(45.1)	75/167(44.9)	4/8(50)	1
Proteinuria(≥3g/d)	34/204(16.6)	31/195(15.9)	3/9(33.3)	0.174
Hematuria	40/187(21.3)	58/158(32.2)	4/6(66.7)	0.097
Pyuria	62/186(33.3)	39/181(21.5)	1/6(16.7)	1
Elevated serum creatinine	11/202(5.4)	11/196(5.6)	0(0)	1
Casts in urine	1/188(0.5)	1/182(0.5)	0(0)	1
Digestive system				
Increased ALT	32/214(14.9)	29/205(14.1)	3/9(33.3)	0.270
Elevated AST	35/212(16.5)	33/203(16.)	2/9(22.2)	0.990
Elevated ALP	40/206(19.4)	40/199(20.1)	0/7(0)	0.350
Elevated γ -GGT	45/204(22.0)	44/197(22.3)	1/7(14.3)	0.967
Low ALB	154/211(72.9)	149/203(73.4)	5/8(62.5)	0.496
Elevated GLB	62/208(29.8)	60/201(29.9)	2/7(28.6)	1.000
^b Elevated TBIL	4/196(2.0)	3/189(1.6)	1/7(14.3)	0.331
IPO	6(2.7)	6(2.8)	0(0)	1.000
Acute pancreatitis	1(0.4)	1(0.5)	0(0)	1.000
CNS involvement	10(4.5)	7(3.3)	3(30)	0.001

Dry eye	10(4.5)	10(4.7)	0(0)	1.000
Dry mouth	20(9.0)	20(9.4)	0(0)	0.605
^a Mean ESR(mm/hr)	55.87±32.12	56.39±32.36	43.50±24.39	0.337
^a ESR (>25mm/hr)	116/148(78.3)	111/142(78.2)	5/6(83.3)	1
Mean CRP (mg/L)	12.10±22.50	11.83±22.67	20.69±15.53	0.388
CRP (6mg/L)	82/188(43.6)	78/183(42.6)	4/5(80)	0.228
SLEDAI(n=195)	9.53±4.92	9.39±4.89	13.14±4.56	0.048
Death	4(1.8)	3(1.4)	1(10)	0.434
Concomitant disease				
RA	2(0.9)	2(0.9)	0(0)	1.000
PBC	1(0.4)	1(0.5)	0(0)	1.000
Hypothyroidism	4(1.8)	4(1.9)	0(0)	1.000
Pregnancy	7(3.1)			
HbsAb	79/123 (64.2)	78/119(65.5)	1/4(25)	0.257

Table 3

Variable	ALL(n=223)	Female(n=213)	Male(n=10)	Pvalue
Elevated RF	46/91(50.5)	42/87(48.3)	4/4(100)	0.117
Elevated anti-CCP	2/43(4.6)	2/40(5.0)	0/3(0)	1
IgG(g/L)	20.23±7.46	20.31±7.50	18.38±6.57	0.476
Decreased IgG	5/207(2.4)	4/199(2)	1/8(12.5)	0.166
Elevated IgG	147/207(71.0)	142/199(71.4)	5/8(62.5)	
IgA(g/L)	2.95±1.36	2.66±1.38	2.96±0.89	0.542
Decreased IgA	1/200(0.4)	1/192(0.5)	0/8(0)	0.396
Elevated IgA	96/200(48.0)	94/192(49)	2/8(25)	
IgM(g/L)	1.34±0.62	1.35±0.62	1.06±0.35	0.235
Decreased IgM	14/192(7.2)	14/185(7.6)	0/7(0)	0.655
Elevated IgM	6/192(3.1)	6/185(3.2)	0/7(0)	
C3(g/L)	0.48±0.22	0.48±0.22	0.47±0.23	0.936
Low C3	195/209(93.3)	187/200(93.5)	8/9(88.9)	1.000
C4 (g/L)	0.08±0.09	0.08±0.09	0.10±0.08	0.684
Low C4	184/209(88.0)	177/200(88.5)	7/9(77.8)	0.657
Anti-dsDNA (LIA)	158/219(72.1)	152/209(72.7)	6/10(60)	0.606
Anti-histones	122/218(55.9)	117/208(56.3)	5/10(50)	0.697
Anti-nucleosomes	122/219(55.7)	117/209(56.0)	5/10(50)	0.963
Anti-Sm	122/220(55.4)	116/210(55.2)	6/10(60)	1.000
Anti-U1snRNP	121/218(55.5)	114/208(54.8)	7/10(70)	0.536
Anti-ribosomal P0	97/218(44.4)	91/208(43.8)	6/10(60)	0.494
Anti-Ro/SSA52	136/218(62.3)	130/208(62.5)	6/10(60)	1.000
Anti-Ro/SSA60	148/218(67.8)	141/208(67.8)	7/10(70)	1.000
Anti-La/SSB	61/218(27.9)	58/208(27.9)	3/10(30)	1.000
Anti-centromere	13/219(5.9)	13/209(6.2)	0	1.000
Anti-Jo1	0/219(0)	0	0	
Anti-Scl70	3/218(1.3)	3/208(1.4)	0	1.000
Anti-nuclear(IIF)	207/207(100)	197/197(100)	10(100)	
Anti-dsDNA(IIF)	99/190(52.1)	93/180(51.7)	6(60)	0.851
Elevated aCL	7/53(13.2)	7/50(14.0)	0	1.000
Elevated anti-β2-GPI	11/52(21.15)	11/49(22.4)	0/3(0)	1.000
Anti-PR3	0/55(0)	0	0	
Anti-MPO	2/56(3.5)	1/53(1.9)	1/3(33.3)	0.209

Table 4

Sex	Age at onset (years)	Months between onset and death	Clinical outcomes	Biochemical outcomes	Cause(s) of death
Male	25	6	NPSLE, purpura, malar rash, alopecia,	platelet $12 \times 10^9/l$, positive	NPSLE, Thrombocytopenia
Female	28	0.5	Vasculitis of hands fever, pleuritis, IPO, LN, NPSLE, acute pancreatitis	anti-u1RNP, anti-SSA60, anti-SSB positive anti-dsDNA, anti-histone, anti-SSA52, anti-SSA60, anti-SSB, anti-nucleosome, leukocytopenia	IPO acute pancreatitis, infection
Female	25	36	pericarditis, pulmonary hypertension, cardiac failure,	positive anti-SmD1, anti-u1RNP, anti-SSA52, anti-SSA60, anti-SSB	pulmonary hypertension, cardiac failure
Female	47	1	half a month after pregnancy TTP (thrombocytopenia, headache and coma)	positive anti-dsDNA, anti-U1RNP, anti-SSB, platelet $8 \times 10^9/l$	TTP

Table 5

Autoantibody	NPSLE OR(95%CI)	Pvalue	Lupus nephritis OR(95%CI)	Pvalue
Anti-dsDNA (LIA)	0.563(0.153-2.067)	0.606	1.628(0.816-3.250)	0.165
Anti-histones	0.778(0.219-2.768)	0.697	1.321(0.720-2.424)	0.369
Anti-nucleosomes	0.786(0.221-2.798)	0.710	1.614(0.879-2.966)	0.121
Anti-Sm	0.328(0.082-1.302)	0.183	1.119(0.616-2.033)	0.773
Anti-U1snRNP	0.187(0.039-0.902)	0.047	1.207(0.664-2.194)	0.537
Anti-ribosomal P0	0.520(0.131-2.066)	0.536	1.064(0.554-1.822)	0.989
Anti-Ro/SSA52	2.500(0.518-12.070)	0.399	2.424(1.272-4.601)	0.006
Anti-Ro/SSA60	1.943(0.402-9.398)	0.622	0.874(0.456-1.673)	0.683
Anti-SSB	2.714(0.757-9.732)	0.112	0.863(0.448-1.665)	0.661
Anti-centromere	1.824(0.213-15.606)	1.000	0.681(0.203-2.286)	0.74
Anti-dsDNA(IIF)	0.724(0.188-2.785)	0.897	0.715(0.225-2.280)	0.570
Elevated aCL	0.851(0.755-0.959)	0.582	0.347(0.036-3.373)	0.344
Elevated anti-β2-GPI	0.720(0.075-6.889)	1.000	1.278(0.301-5.420)	0.726

