



# Five years follow-up of juvenile lupus nephritis: a single-center retrospective cohort study

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**Background:** We analyze the clinical manifestations and 5 years of follow-up outcomes of children with lupus nephritis (LN) and provide a reference for clinicians.

**Methods:** The clinical data of children diagnosed with LN (n=62) from January 2012–2015 were collected and analyzed.

**Results:** The median age at the diagnosis was 12.0 years. The female to male ratio was 3.4:1. The most prevalent clinical features were mucocutaneous involvement and hematological involvement. Renal biopsy was performed on 38 patients. Class IV and class V were the most common findings. The lupus activity was improved markedly after 3 months treatment. The rate of survival was 98.3% in 5 years. The most common side effects of corticosteroid and other immunosuppressive agent drug treatment were corticosteroid-related hypertension and high intraocular pressure. The rate of cataracts, osteoporotic fracture, and visual field defects increased as the treatment progressed. Especially, the incidence of visual field defects in children is higher than adults.

**Conclusions:** The LN children showed a good prognosis. During the follow-up process, the adverse drug reactions, such as hormone-related hypertension and ocular hypertension, especially the visual field defects caused by hydroxychloroquine, cannot be excluded. However, multicenter long term follow-up studies are essential to substantiate the current data.

**Keywords:** Children; lupus nephritis; follow-up; treatment

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## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by immune inflammation. It involves multiple organs. Children with SLE are more serious than adults (1). The incidence of juvenile systemic lupus erythematosus (jSLE) is 0.4–0.6/100,000. Previous studies have shown that up to 80% of jSLE patients develop lupus nephritis (LN) (2). Moreover, significant differences are detected in the characteristics and the severity of the disease among various ethnic groups (3). A few studies focused on

the demographic characteristics, clinical manifestations, laboratory findings treatment outcomes, and follow-up of children with juvenile LN in China (4). A previous study on the research and recruitment of LN in China provides limited clinical guidance. Thus, the present study is a rare long-term follow-up study that describes the demographic, clinical features, and laboratory findings of 62 children with LN. A 5-year follow-up was conducted to provide a reference for clinicians. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-720>).

## Methods

### Participants

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (No. S-K885) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All the hospitalized children younger than 18 years old at the time of diagnosis between January 2012 and January 2015 were included in this retrospective study. Children with incomplete medical records at baseline were excluded from this study. The included children met the 1997 revised criteria of American College of Rheumatology (ACR) classification criteria of SLE and LN (5). The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) was used as a reference standard for the pathological classification of juvenile LN in the current study.

### Clinical data

The demographic, clinical, and laboratory characteristics of the patients included in this study were collected retrospectively from outpatient medical records, hospitalized medical records, or telephone questionnaires at baseline, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years. The clinical data included general parameters, such as gender, age of onset, type of renal pathology, and system of involvement. The laboratory measurements included white blood cell (WBC), platelet count (PLT), hemoglobin (Hb), erythrocyte sedimentation rate (ESR), serum creatinine, urea nitrogen, 24-hour urinary protein (24h-UP), serum C3 and C4 levels, and autoantibodies such as antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) levels, and systemic lupus erythematosus disease activity index (SLEDAI).

### Definitions

Complete remission: The laboratory results, including blood cell count, renal function, albumin, serum Complement 3 (C3) and Complement 4 (C4), erythrocyte sedimentation rate (ESR), and 24h-UP <150 mg, were normal. Partial remission should meet all following criteria: (I) urinary protein decreased by  $\geq 50\%$ , 24h-UP <3,500 mg; (II) serum creatinine and urinary protein/creatinine improved by 50%; (III) improved serum creatinine, urine protein/

creatinine <1.0, and all other laboratory tests are improved than the baseline. Remission rate = complete remission (%) + partial remission (%). Active disease: Persistent low serum complement levels, persistent thrombocytopenia or anemia, deterioration of renal function, persistent or increase in proteinuria, or appearance of new manifestations (6-8). Recurrence: During the treatment, the SLEDAI is increased by  $\geq 6$  during any 3–9 months (9,10). Lost to follow-up: children, who did not follow-up in the outpatient department or in the hospital, and it was confirmed repeatedly by phone that the child still could not be reached. Treatment adverse effects: the sepsis in this study included only the sepsis with positivity for peripheral blood culture. The mucocutaneous clinical features include rash, photosensitivity, alopecia, oral ulcers, and Raynaud's phenomenon, while the musculoskeletal manifestations are arthralgia or arthritis, myalgia or myositis (11-14).

### Statistical analysis

The characteristics were summarized using descriptive statistics. The data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) for normally distributed continuous variables or median (Q1, Q3) for continuous variables that do not conform to the normal distribution. The ratio is expressed as a percentage (%). Herein, we used the Bland method (15) to compare the data in the literature. SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) was used to compare the differences between the two groups using *t*-test or Mann-Whitney U test. The ratio was measured by  $\chi^2$  test.  $P < 0.05$  was considered statistically significant.

## Results

### Demographic data and clinical characteristics at baseline

A total of 62 patients, including 48 females and 14 males, were recruited in this study. The female to male ratio was 3.4:1. The median age at onset was 10.0 (range, 8.1–12.3) years. The median age at the diagnosis was 12.0 (range, 9.4–13.0) years. The time from onset to diagnosis was 0.3 (range, 0.1–2.0) years. In the cohort, 8/62 (12.9%) patients had a family history of autoimmune disease.

This study showed that the mucocutaneous tissue (75.8%) and blood (62.9%) involved in the disease, while the incidence of neuropsychiatric, musculoskeletal, and cardiorespiratory involvement was 35.5%, 37.1%, and 9.7%, respectively (shown in *Table 1*).

**Table 1** Characteristics of the juvenile LN patients

Parameter	N=62
<b>Demographic features</b>	
Age at disease onset, years (median, Q1, Q3)	10.0 (8.1, 12.3)
Age at diagnosis, years (median, Q1, Q3)	12.0 (9.4, 13.0)
The duration from onset till diagnosis (median, Q1, Q3)	0.3 (0.1, 2.0)
Sex (female/%)	48 (77.4%)
*Family history of autoimmunity	8 (12.9%)
<b>#Clinical features</b>	
Mucocutaneous	47 (75.8%)
Musculoskeletal	23 (37.1%)
Hematological involvement	39 (62.9%)
Neuropsychiatric involvement	22 (35.5%)
Cardiorespiratory involvement	6 (9.7%)
Kidney involvement	62 (100.0%)
Patients with renal biopsy	38 (61.3%)
I	1 (2.6%)
II	2 (5.3%)
III	6 (15.8%)
IV	16 (42.1%)
V	7 (18.4%)
VI	0 (0.0%)
III+V	1 (2.6%)
IV+V	5 (13.6%)

Q1, first quartile; Q3, third quartile. \*, family history of autoimmunity included type 1 diabetes, SLE, thyroid disease, rheumatoid arthritis and connective tissue disease (7). #, the clinical feature of mucocutaneous include rash, photosensitivity, alopecia, oral ulcers, and Raynaud's phenomenon. Musculoskeletal manifestations are arthralgia or arthritis, myalgia or myositis (15).

### Results of renal biopsy

Among the 62 LN children, 38 (61.3%) underwent renal biopsy, while the remaining 24 patients without renal biopsy were unable to cooperate due to their young age or had contraindications or their parents were concerned about the risk. Class IV and V were the most common findings on renal biopsy, and the ratio was 42.1% and 18.4%,

respectively. The ratio of Class III and IV+V was 15.8% and 13.6%, respectively. The patients in this study had fewer type I, II, and III+V stages, while no class VI was detected in our patients (shown in *Table 1*).

### Laboratory findings

Clinical data from 62, 48, 45, 47, 43, 43, 38, 29 cases of children were collected at the time of onset, 3 months, 6 months, 12 months, 2 years, 3 years, 4 years, and 5 years, respectively, while the data were not collected from 2 patients lost to follow-up. The number of telephone follow-up cases at each time point were 0 (0%), 14 (22.6%), 15 (25.0%), 13 (21.6%), 17 (28.3%), 17 (28.3%), 22 (36.7%), and 31 (51.7%), respectively.

The laboratory data for WBC, PLT, Hb, 24h-UP, and ESR are listed in *Table 2*. The positive rates of ANA and anti-dsDNA antibodies were 100.0% and 70.8%, respectively. The low C3 and C4 rates were 83.9% and 77.4%, respectively. The positive rates of anti-Sm antibody, anti-SSA antibody, and anti-SSB antibody were 27.4%, 43.5%, and 16.1%, respectively. All children were not tested for antiphospholipid antibodies. The positive rates of anti-cardiolipin antibody (ACL), anti- $\beta$ 2 glycoprotein 1 antibody ( $\beta$ 2GPI), and lupus anticoagulant (LA) were 7.4%, 3.7%, and 22.2%, respectively.

After 3 months of treatment, WBC, Hb, and PLT were higher than that before the treatment. PLT and Hb were increased at 6 months as compared to that at 3 months, while WBC was decreased slightly, and the 24h-UP decreased significantly at 3 and 6 months. Urea nitrogen and ESR were reduced significantly compared to the baseline, and the rates of low C3 and C4 and anti-dsDNA antibody decreased significantly at 3 months (shown in *Table 3*).

### Medication data

All the patients received oral corticosteroid treatment (n=62, 100%), and in the majority of the patients, it was combined with hydroxychloroquine (HCQ) (n=52, 83.9%). The frequency of pulse corticosteroid and cyclophosphamide was 72.6% (n=45) and 75.8% (n=47), respectively. Mycophenolate mofetil (MMF) was the most frequently used agent for lupus nephritis (n=42, 67.7%), followed by cyclosporine (n=11, 17.7%). Three (4.8%) patients in the cohort used tacrolimus, while leflunomide was used in 7 (11.3%) children. One patient was treated with methotrexate because of chronic arthritis, and 6 recurrent

**Table 2** Laboratory findings of juvenile LN at baseline

Parameter	At baseline (N=62)
WBC ( $\times 10^9/L$ ) (median, Q1, Q3)	6.5 (2.8, 8.9)
Hemoglobin (g/L)	102.4 $\pm$ 19.8
Platelet ( $\times 10^9/L$ ) (median, Q1, Q3)	168 [94, 267]
24-h urinary proteins (g/day) (median, Q1, Q3)	1.7 (0.9, 6.1)
Serum creatinine (mmol/L) (median, Q1, Q3)	57.0 (48.0, 79.0)
Blood urea nitrogen (mmol/L) (median, Q1, Q3)	7.5 (4.9, 11.3)
Erythrocyte sedimentation rate (mm/h) (median, Q1, Q3)	36 [21, 73]
Low C3 level, n (%)	52 (83.9)
Low C4 level, n (%)	48 (77.4)
Antinuclear antibody positivity, n (%)	62 (100.0)
Anti-dsDNA positivity, n (%)	44 (70.8)
Anticardiolipin antibody positivity, n (%) (N=54)	4 (7.4)
Anti $\beta 2$ glycoprotein 1 positivity, n (%) (N=54)	2 (3.7)
Lupus anticoagulant positivity, n (%) (N=54)	12 (22.2)
Anti-Sm antibody positivity, n (%)	17 (27.4)
Anti-SSA antibody positivity, n (%)	27 (43.5)
Anti-SSB antibody positivity, n (%)	10 (16.1)

N, n, number; Q1, first quartile; Q3, third quartile; WBC, white blood cell; C3, Complement 3; C4, Complement 4; Anti-dsDNA, anti-double stranded DNA.

patients were treated with rituximab, while one was treated with the JAK-STAT signaling pathway-targeted drug tofacitinib (shown in *Table 4*).

### Follow-up outcome

After 3 months of treatment, 49/62 children were relieved, and the remission rate was 79.0%. At 6 months, 2 patients were lost to follow-up, 53 were relieved, 6 retained the active disease, and 1 patient died of renal failure at 5 months. The remission rate was 88.3%, and the mortality rate was 1.7%. After 1 year of treatment, 58 patients were relieved, 1 patient was still in the active state, and 1 patient showed a relapse; the remission rate was 96.7%, and the recurrence rate was 10.2%. The follow-up data are presented in *Table 3*. At 5 years, 4 patients discontinued medical treatment, 20 patients relapsed, and 1 patient died; the recurrence rate was 33.3%, and the mortality rate was 1.7%.

### Treatment of adverse effects

The most common side effects of drug treatment were corticosteroid-related hypertension (54.8%) and corticosteroid-related high intraocular pressure (38.7%) at 3 months. Four patients had visual field defects (6.5%) due to hydroxychloroquine, 2 patients had sepsis (3.2%), and 3 patients had cataracts (4.8%). After 1 year of treatment, one child presented osteoporotic fracture, and the occurrence ratio was 1.7%. All the follow-up data are presented in *Table 3*. At 5 years, 65.0% of the children exhibited corticosteroid-related hypertension, 53.3% of the patients had high intraocular pressure, and 5.0% of the patients had sepsis. Moreover, 16.7% of the patients had cataract, and 16.7% had visual field defects. About half of the children developed corticosteroid-related hypertension and high intraocular pressure after ingesting glucocorticoid. The rate of cataract, osteoporotic fracture, and visual field defects was increased with the treatment progress.

### Discussion

The gender of the LN children in the current study is consistent with the LN cohort study in Japanese and UK children (6,16), and the proportion of female children is about 80%. The median age of diagnosis was 12-years-old. The studies in the UK and Japan reported that the average age at the time of diagnosis was 12.3 and 13 years old. Based on the data reported in the literature, we use the Bland method (15) to compare the two datasets and did not find any significant difference in these cohorts. The time from the onset to diagnosis is 0.3 (0.1–2.0) years, which is consistent with the results of the study on jSLE from Turkey (14,17). About 12.9% of the children in the current study have a family history of autoimmune diseases. Thus, it was shown that about 10% of SLE patients have a family history, which was consistent with the current findings (18).

In our LN cohort, mucocutaneous and blood were involved, and 35.5% of the children had neuropsychiatric symptoms. This higher incidence as compared to that in the UK could be related to the high incidence of the nervous system affecting the Asian population (19,20). Reportedly, the incidence of neuropsychiatric involvement was 7.7–45%. Also, the inconsistent diagnostic criteria for neuropsychiatric lupus is a major cause of the difference (21,22). In this study, musculoskeletal involvement was detected in 23/62 (37.1%) children. In addition, arthritis is common in SLE and is one of the diagnostic criteria. Unlike juvenile idiopathic

**Table 3** Five-year follow-up data of juvenile LN

Laboratory and clinical results	At baseline (N=62)	3 months (N=60)	6 months (N=60)	12 months (N=60)	2 years (N=60)	3 years (N=60)	4 years (N=60)	5 years (N=60)
WBC ( $\times 10^9/L$ ) (median, Q1, Q3)	6.5 (2.8, 8.9)	9.3 (6.1, 10.8)	7.6 (6.5, 9.8)	6.4 (4.8, 8.1)	7.1 (5.9, 9.4)	6.4 (5.1, 8.0)	6.9 (6.0, 8.1)	6.4 (5.0, 7.9)
Hemoglobin (g/L)	102 $\pm$ 19.8	127 $\pm$ 14.6	134 $\pm$ 12.3	129 $\pm$ 14.6	129 $\pm$ 14.7	132 $\pm$ 14.5	134 $\pm$ 13.9	132 $\pm$ 21.2
Platelet ( $\times 10^9/L$ ) (median, Q1, Q3)	168 [94, 267]	225 [207, 294]	275 [224, 337]	269 [218, 332]	273 [212, 324]	265 [213, 321]	262 [202, 316]	299 [224, 335]
24-h urinary proteins (g/day) (median, Q1, Q3)	1.7 (0.9, 6.1)	0.6 (0.2, 1.9)	0.1 (0.1, 0.4)	0.1 (0.1, 0.1)	0.04 (0.01, 0.1)	0.01 (0.0, 0.1)	0.01 (0.0, 0.3)	0.01 (0.0, 0.4)
Serum creatinine (mmol/L) (median, Q1, Q3)	57.0 (48.0, 79.0)	48.0 (40.0, 57.0)	52.0 (41.0, 63.0)	49.0 (38.0, 60.0)	53.0 (40.0, 59.0)	52.0 (45.0, 64.0)	53.0 (42.0, 62.0)	54.0 (45.0, 68.0)
Blood urea nitrogen (mmol/L) (median, Q1, Q3)	7.5 (4.9, 11.3)	5.4 (3.8, 7.2)	4.2 (3.3, 5.7)	4.3 (3.2, 5.5)	4.3 (3.5, 5.5)	4.7 (4.0, 5.5)	4.5 (3.5, 5.5)	4.6 (3.5, 5.8)
Erythrocyte sedimentation rate (mm/h) (median, Q1, Q3)	36 [21, 73]	17 [9, 27]	11 [7, 18]	9 [5, 18]	9 [3, 18]	9 [4, 19]	9 [6, 21]	9 [2, 16]
Low C3 level, n (%)	52/62 (83.9)	7/48 (14.5)	4/45 (8.9)	5/47 (10.6)	2/43 (4.7)	5/43 (11.6)	7/38 (18.4)	8/29 (27.6)
Low C4 level, n (%)	48/62 (77.4)	16/48 (33.3)	6/45 (13.3)	9/47 (19.1)	7/43 (16.3)	8/43 (18.6)	9/38 (23.7)	10/29 (34.5)
Anti-dsDNA positivity, n (%)	44/62 (70.8)	16/48 (33.3)	17/45 (37.8)	12/47 (25.5)	15/43 (34.9)	16/43 (37.2)	16/38 (42.1)	16/29 (55.2)
Outcome, n (%)								
SLEDAI	22 [18, 25]	8 [4, 10]	4 [3, 8]	4 [0, 5]	2 [0, 4]	2 [0, 4]	2 [0, 6]	2 [0, 8]
Active disease	–	13 (21.0)	6 (10)	1 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)
Cumulative recurrence	–	0 (0)	0 (0)	1 (1.7)	4 (6.6)	8 (13.3)	13 (21.7)	20 (33.3)
Remission	–	49 (79.0)	53 (88.3)	58 (96.7)	55 (91.7)	51 (82.3)	46 (76.7)	39 (65.0)
Therapy discontinued	–	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (4.8)
Death	–	0 (0)	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)
Lost follow up	–	0 (0)	2 (3.2)	2 (3.2)	2 (3.2)	2 (3.2)	2 (3.2)	2 (3.2)
Treatment adverse effects, n (%)								
Osteoporotic fracture	–	0 (0)	0 (0)	1 (1.7)	1 (1.7)	2 (3.3)	2 (3.3)	2 (3.3)
Corticosteroid related hypertension	–	34 (54.8)	36 (60.0)	38 (63.3)	38 (63.3)	38 (63.3)	39 (65.0)	39 (65.0)
Septicemia	–	2 (3.2)	2 (3.3)	2 (3.3)	3 (5.0)	3 (5.0)	3 (5.0)	3 (5.0)
Cataract	–	3 (4.8)	5 (8.3)	5 (8.3)	6 (10.0)	10 (16.7)	10 (16.7)	10 (16.7)
HCQ-related visual field defect	–	4 (6.5)	6 (10.0)	8 (13.3)	8 (13.3)	9 (15.0)	9 (15.0)	10 (16.7)
High intraocular pressure	–	24 (38.7)	26 (43.4)	28 (46.7)	28 (46.7)	30 (50.0)	32 (53.3)	32 (53.3)

N, number; Q1, first quartile; Q3, third quartile; WBC, white blood cell; C3, complement 3; C4, complement 4; anti-dsDNA, anti-double stranded DNA; SLEDAI, systemic lupus erythematosus disease activity index; HCQ, hydroxychloroquine.



**Table 4** Medication data of juvenile LN patients

Medication	Initial treatment (n=62), n (%)		Induced therapy after relapse (n=20), n (%)
	Induced therapy	Maintenance treatment	
Corticosteroid	62 (100.0)	62 (100.0)	20 (100.0)
Oral corticosteroid	17 (27.4)	62 (100.0)	14 (70.0)
Methylprednisolone pulse therapy	45 (72.6)	0 (0.0)	6 (30.0)
Cyclophosphamide pulse therapy	47 (75.8)	0 (0.0)	7 (35.0)
Mycophenolate mofetil	7 (11.3)	42 (67.7)	6 (30.0)
Cyclosporine	3 (4.8)	11 (17.7)	3 (15.0)
Tacrolimus	1 (1.6)	3 (4.8)	2 (10.0)
Hydroxychloroquine	52 (83.9)	46 (74.2)	–
Leflunomide	7 (11.3)	7 (11.3)	–
Methotrexate	1 (1.6)	1(1.6)	–
Rituximab	0 (0.0)	0 (0.0)	6 (30.0)
Tofacitinib	0 (0.0)	0 (0.0)	1 (5.0)

arthritis, SLE arthritis is non-invasive 14% incidence in Asian children (23). Another study reported that the incidence of arthritis in SLE could be about 85.7% (24), and most of the cases were acute arthritis. Conversely, chronic arthritis is rare in SLE children, with the prevalence is 2.6% (25). In this study, 1 patient had chronic arthritis that was treated with methotrexate. Cardiopulmonary involvement in children with LN accounted for 9.7% of the cases, mainly including interstitial pneumonia and myocarditis, while pericardial effusion was not included in the scope of cardiac involvement. The proportion of these systems was consistent with that reported previously (24,26). The above clinical manifestations suggested that the clinical manifestations are diverse in different races and populations. These differences were closely related to genetics, environment, and sample size.

The rate of renal biopsy in this study was 61.3%. Many children had clear renal biopsy contraindications in our study. Some children had been treated without renal biopsy in other hospitals. Concurrently, parents were concerned about the risk of renal biopsy and refused it. The criteria for renal biopsy in our institute are as follows: (I) 24h-UP >150 mg; (II) have not been treated by using glucocorticoids and immunosuppressants; (III) usually, the age of children is more than 8 years old, and they can follow doctors' instructions, because our institute has not carried out renal biopsy technique for children under general anesthesia; (IV)

The children and their parents agree to renal biopsy. These are the reasons for the low renal penetration rate in this study. Class IV and V LN were the most common findings, which were consistent with the literature reports.

ANA and anti-dsDNA antibody were detected in 62 patients, with positive rates of 100.0% and 70.8%, respectively. This phenomenon was consistent with the positive rate of jSLE reported by another center in China. The positive rates of ANA and anti-dsDNA antibody were 97.62% and 70%, respectively (27). In this study, the proportion of low complement C3 and C4 was 83.9% and 77.4%, respectively. The antibodies with high positive rates also included anti-SSA antibodies (43.5%) and anti-Sm antibodies (27.4%). The cohort consisted of 28 patients with positive SSA antibodies and/or SSB antibodies, and 10 patients were diagnosed with secondary Sjögren's syndrome. Next, 54/62 children were tested for antiphospholipid antibodies. The rate of ACL-positive was 7.4%,  $\beta$ 2GP1-positive was 3.7%, and LA-positive was 22.2%. Of the 14 patients, who were positive for antiphospholipid antibody, 1 had abnormal coagulopathy, and 1 had cerebral infarction. During the follow-up period, arteriovenous thrombosis was not detected in the other children.

At the baseline, blood tests of children indicated a decrease in WBCs or Hb or PLT because of the hematological involvement. Children usually had increased

ESR and elevated urinary protein. After treatment, the laboratory test results showed a gradual return to the normal at 3 months.

All patients in our center received oral corticosteroid treatment, and 83.9% of them received corticosteroid combined with HCQ. For patients with pathological renal Class I and II without neuropsychiatric involvement, prednisone, and MMF were administered. Intravenous infusion of methylprednisolone and cyclophosphamide for children with Class III and IV were used as induction treatment, and MMF was used as the maintenance treatment after cyclophosphamide. We usually use pulse corticosteroid and cyclophosphamide for induction therapy. Intravenous injection of methylprednisolone 15–30 mg/(kg·d), the maximum amount of 500 mg/d, for 3 days, once a week, continuous use for 2 weeks and intravenous cyclophosphamide pulse therapy every 2 weeks, every time continuous 2 days, 8–12 mg/(kg·d), for 3 months, the maximum daily dose is 1g. And changed to monthly cyclophosphamide pulse treatment for another 3 months. The maintenance treatment is followed by sequential MMF [20–30 mg/(kg·d)]. Oral prednisone for 6 to 8 weeks, gradually reduce the dose according to the therapeutic effect, until it reaches a maintenance dose of 5–10 mg/d. In the case of children with Class V, cyclosporine or tacrolimus was used. Other immunosuppressive agents, such as rituximab, were often used for relapse treatment. In the present study, one child showed active disease after one recurrence; importantly, rituximab and other immunosuppressive agents could not control his proteinuria, and hence, tofacitinib, a JAK inhibitor, was administered for the treatment. Some studies have shown that the JAK/STAT pathway is essential for resisting infection and maintaining immune tolerance (28). Several studies have shown that this signaling pathway is involved in the pathogenesis of SLE and tofacitinib reduces proteinuria in mice SLE model and improves their survival rate (29). However, the child developed severe sepsis after using the drug, and proteinuria had not been controlled effectively. Currently, the child is treated with cyclophosphamide, albeit the proteinuria is not yet relieved.

After treatment, the remission rate reached 79.0% at 3 months and increased at 6 months. The majority of children could achieve remission at 1 year. One patient had recurrence at 1 year, which increased over time. After 5 years of follow-up, the recurrence rate was noted to be 33.3%. Some patients relapsed more than one time. Although no obvious cause of recurrence was identified, it could be

ascribed to infection and sun exposure. One patient died of renal failure at 5 months after the onset. The current study showed that the survival rate at 5 years was 98.3%. Another study reported that the 3- and 5-year survival rates of children with LN are 93.59% and 87.80%, respectively (4).

Glucocorticoids and immunosuppressant effectuate adverse effects while relieving the disease. This study showed that about half of the children had hypertension or high intraocular pressure after taking glucocorticoids. With prolonged medication, some children exhibited osteoporosis and also fragility-related fractures. Two patients developed spinal compression fractures at 3 years post-drug treatment. At the same time, the incidence of cataracts increased with the prolonged period of administering glucocorticoids. At 5 years follow-up, 16.7% of the children had cataracts. This study showed that 5.0% of the children developed severe sepsis during treatment. A single-center cohort study found that 35/87 patients with SLE had at least one infection, and one of the risk factors associated with infection was oral or intravenous glucocorticoids and intravenous cyclophosphamide (30). HCQ is safe and effective for SLE patients. About 83.9% of the children were treated with HCQ in this study. However, the main adverse effect was retinopathy. In addition, visual field defects might occur after 3 months of HCQ treatment. As the treatment progresses, the incidence of visual field defects increased gradually, and the incidence of visual field defects was 16.7% at 5 years. A systematic review found that the incidence of retinopathy in patients treated with HCQ for about 10 years was only 0.1% (31). In the present study, the high incidence of visual field defects might be related to the young age. China's Rheumatology Association recommends that patients with high-risk factors for retinopathy should undergo an eye exam once a year during the treatment (32). In order to avoid the adverse consequences, we recommend that children who receive HCQ have an eye exam at least half a year.

This study describes the demographic data, clinical features, and laboratory findings of 62 children with LN. A 5-year follow-up provided a reference for the clinicians. However, there are still deficiencies in this study. This was a single-center retrospective clinical study, and the loss to follow-up may have some bias. Therefore, a multicenter, long-term follow-up study is essential to obtain reliable data.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (No. S-K885) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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