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Long-term renal survival of paediatric patients with lupus nephritis

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ABSTRACT

Background. Childhood-onset systemic lupus erythematosus (SLE) is more severe than adult-onset disease, including more frequent kidney involvement. This study aimed to investigate baseline clinical features, treatment modalities and short- and long-term renal outcomes of paediatric patients with lupus nephritis (LN).

Materials and methods. This study enrolled 53 LN patients out of 102 childhood-onset SLE patients followed at Hacettepe University between 2000 and 2020. The demographic and clinical data were reviewed retrospectively from the medical charts and electronic records. All SLE patients with renal involvement underwent renal biopsy either at the time of diagnosis or during follow-up.

Results. The median age at onset of SLE was 13.3 years [interquartile range (IQR) 10.4–15.8]. The median follow-up duration was 43.1 months (IQR 24.3–69.3). Of the 102 SLE patients, 53 (52%) had LN. The most frequent histopathological class was Class IV LN (54.7%), followed by Class III (22.6%). The proportion of patients who achieved either complete or partial remission was 77.3% and 73% at 6 and 12 months, respectively. In the overall LN cohort, 5- and 10-year renal survival rates were 92% and 85.7%, respectively. The remission rate at Month 6 was significantly higher in mycophenolate mofetil (MMF)- and cyclophosphamide (CYC)-treated groups than other combination therapies ($P = 0.02$). Although no difference was found between the CYC and MMF response rates ($P = 0.57$) in proliferative LN (Classes III and IV), the majority of Class IV patients (79%) received CYC as induction therapy. There was no difference between the response rates in any treatment regimens at Month 12 ($P = 0.56$). In the multivariate analysis, male gender, requiring dialysis at the time of LN diagnosis and failure to achieve remission at 6 and 12 months were found to be associated with poor renal outcome.

Conclusions. Our study demonstrated that male gender, failure to achieve remission at 6 and 12 months and requiring dialysis at the time of diagnosis were the best predictors of poor renal outcome. Therefore appropriate and aggressive management of paediatric LN is essential to achieve and maintain remission.

Keywords: childhood-onset systemic lupus erythematosus, cyclophosphamide, lupus nephritis, mycophenolate mofetil, renal outcome

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic complicated multisystem autoimmune disease with a wide range of clinical manifestations. SLE presents during childhood in 15–20% of cases [1, 2]. Childhood-onset SLE is characterized by a more active disease course and more frequent renal involvement compared with adult-onset SLE [3]. Lupus nephritis (LN) is a major cause of mortality and morbidity both in adult and paediatric patients [4]. Renal involvement has been reported to occur in 25–80% of paediatric SLE patients, either as an initial presentation or later in the disease course [2, 5]. The overall mortality rate of SLE patients with and without LN is 2.4- and 6.8-fold higher, respectively, than that of the general population [6–8].

In recent years there have been significant improvements in the diagnosis and treatment protocols for LN. Five-year survival rates of patients with LN, which was 50% in the 1960s, increased to 80% in the 1990s [9, 10]. However, the rate of renal remission is still suboptimal [11]. Based on adult studies, 10–30% of patients with active LN progress to end-stage renal disease (ESRD) [8, 12, 13]. In contrast to adult LN, the data

regarding long-term prognosis of paediatric LN are still very limited. Since the progress of LN is more aggressive in childhood, it is crucial to predict poor renal outcomes in paediatric patients. An insufficient renal response to induction therapy is considered a leading cause of relapses and poor prognosis [14, 15]. The Euro-LN trial demonstrated that the renal response after 6 and 12 months of treatment predicted long-term renal outcomes [16].

The aim of this study was to investigate the baseline clinical features, treatment modalities and short- and long-term renal outcomes of paediatric patients with LN and predict the risk factors for poor renal prognosis.

MATERIALS AND METHODS

Patients

This study enrolled 102 SLE patients followed at Hacettepe University School of Medicine, Departments of Pediatric Nephrology and Rheumatology between 2000 and 2020. The inclusion criteria were fulfilment of Systemic Lupus International Classification Collaborating Clinics classification criteria [17] and age of disease onset <18 years. Those who had no baseline information in the hospital medical records and had a follow-up duration <6 months were excluded. All SLE patients with renal involvement underwent renal biopsy either at the time of diagnosis or during follow-up.

Clinical and laboratory information and disease activity index

The demographic data and clinical manifestations, laboratory values, disease activity indices and treatment regimens at the time of SLE and LN diagnosis were reviewed retrospectively from the medical charts and electronic records. Visits were scheduled quarterly or more frequently, if medically necessary. Antinuclear antibody (ANA) was measured by indirect immunofluorescence and a titre ≥1:80 was considered positive. Anti-double-stranded DNA (anti-dsDNA) antibody was measured by enzyme-linked immunosorbent assay. C3 and C4 levels were examined by nephelometry and normal values were 79–152 mg/dL and 16–38 mg/dL, respectively. Glomerular infiltration rate (GFR) was estimated using the Schwartz formula [18]. Hypertension was defined as systolic or diastolic blood pressure ≥95th percentile for age, height and sex [19]. Disease activity at the time of SLE and LN diagnosis was accessed by the SLE Disease Activity Index (SLEDAI). Patients with evidence of renal involvement (haematuria, proteinuria or both), an unexplained abnormal serum creatinine level and GFR ≤90 mL/min/1.73 m^2 underwent renal biopsy. Renal pathology was classified according to the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) 2003 classification criteria for LN [20].

Treatment regimens

The treatment for proliferative LN (Classes III and IV) consisted of two phases: induction and maintenance. For most of the patients, our induction therapy consisted of intravenous pulse methylprednisolone (MPZ) at a dose of 10–30 mg/kg (maximum 1 g/day, three doses given monthly) for three to six doses and oral prednisolone 0.5–1 mg/kg/day between MPZ courses. Intravenous MPZ was either combined with mycophenolate mofetil (MMF) given orally at a dose of 1200 mg/m^2/day in two divided doses or intravenous cyclophosphamide (CYC) given monthly at a dose of 500–1000 mg/m^2/day (maximum 750 mg/dose) for three to six doses. Oral CYC was given at doses of 1–2 mg/kg/day. Rituximab (RTX) was given at a dose of 375 mg/m^2 for four weekly doses. As for maintenance immunosuppression, prednisolone, MMF and azathioprine (AZA) 1–3 mg/kg/day (maximum 150 mg/day) were given. Cyclosporine was started at a dose of 3–6 mg/kg/day. Trough levels were maintained at 50–100 μg/L. For the patients with Classes II, V and VI LN, pulse/oral MPZ, AZA, MMF and/or CYS were given. Hydroxychloroquine was given to all SLE patients. Also, all LN patients received angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers.

Outcome definition

Response status was assessed as complete remission (CR) or partial remission (PR). CR was defined as normal renal function (GFR >90 mL/min/1.73 m^2) and proteinuria <0.5 g/day or urine protein:creatinine ratio (UPCR) <0.5 in at least two consecutive measurements or subsequent visits. PR was defined as stable renal function and a reduction of proteinuria of >50% from baseline [21]. Renal relapse was defined as an increase of >50% in proteinuria and/or a decrease in GFR >25% from baseline [22]. Chronic kidney disease (CKD) was diagnosed in patients with a GFR <90 mL/min/m^2 or increased serum creatinine persisting for at least 3 months. ESRD was defined as a GFR <15 mL/min/m^2 or either the need for renal transplantation or long-term dialysis. We evaluated the risk factors for poor renal outcomes (GFR <60 mL/min and/or persistent dialysis).

Statistical analysis

For normally distributed variables (mean ± SD), the association between groups was analysed by Student's *t*-test. The Mann–Whitney *U*-test was used for those with non-normal distribution [median (25th–75th percentile)]. Characteristics were analysed by the Pearson chi-squared test, Fisher's exact test and Wilcoxon rank-sum test, as appropriate. Kaplan–Meier curves were plotted to determine the relapse-free survival between the different treatment modalities and were compared using the log-rank test. Time to first renal flare was calculated for patients who reached this endpoint. The remaining patients were censored at the last follow-up or at the time of CKD. Risk factors for poor renal outcomes were determined by Cox regression analysis and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). A P-value <0.05 was considered statistically significant. SPSS Statistics version 23.0 (IBM, Armonk, NY, USA) was used for statistical analysis. The study was approved by the institutional ethics committee of Hacettepe University. Written informed consent was obtained from the patients and parents of all patients.

Table 1. Baseline characteristics of all patients at the time of SLE diagnosis ($N = 102$)

Characteristics	Values
Age at SLE diagnosis (years), median (IQR)	13.3 (10.4–15.8)
Cutaneous involvement, *n* (%)	71 (69.6)
Malar rash	62 (60.8)
Discoid rash	12 (11.8)
Photosensitivity, *n* (%)	45 (44.1)
Oral/nasal ulceration, *n* (%)	25 (24.5)
Synovitis including two or more joints, *n* (%)	47 (46.1)
Serositis, *n* (%)	17 (16.7)
Renal disorder, *n* (%)	43 (42.2)
Neurologic disorder, *n* (%)	15 (14.7)
Haematologic disorder, *n* (%)	64 (62.7)
Haemolytic anaemia	18 (17.6)
Leucopenia <4000/mm^3	34 (33.3)
Lymphopenia <1500 mm^3	38 (37.3)
Thrombocytopenia <150 000/mm^3	40 (39.2)
ANA positivity, *n* (%)	102 (100)
Anti-dsDNA positivity, *n* (%)	76 (74.5)
ENA positivity, *n* (%)	21 (20.6)
Antiphospholipid positivity, *n* (%)	35 (34.3)
Lupus anticoagulant positivity, *n* (%)	21 (20.6)
Anticardiolipin IgM, *n* (%)	16 (15.7)
Anticardiolipin IgG, *n* (%)	15 (14.7)
Anti-β2 glycoprotein I IgM, *n* (%)[a]	13 (20.6)
Anti-β2 glycoprotein IgG, *n* (%)[a]	6 (9.5)
Low complement, *n* (%)	84 (82.4)
C3 (mg/dl), median (IQR)	63 (37.2–79.7)
C4 (mg/dl), median (IQR)	10 (5.0–15.0)
Leucocyte (per mm^3), median (IQR)	5300 (3700–8700)
Lymphocyte (per mm^3), median (IQR)	1500 (1000–2200)
Platelet (per mm^3), median (IQR)	183 000 (126 000–283 000)
Haemoglobin (g/dL), median (IQR)	11.1 (9.8–13)
Albumin (g/dL), median (IQR)	3.8 (3.4–4.3)
Creatinine (mg/dL), median (IQR)	0.57 (0.4–0.7)
Direct Coombs positivity, *n* (%)	19 (18.6)
Sedimentation (mm/h), median (IQR)	24 (11.75–41.50)
SLEDAI score, median (IQR)	10 (7.8–16)

[a]$n = 63$.
ENA, extractable nuclear antigen antibody.

RESULTS

Patients' characteristics

Of the 102 patients diagnosed with childhood-onset SLE, 33.3% ($n = 37$) were <12 years of age and the median age at onset of SLE was 13.3 years [interquartile range (IQR) 10.4–15.8]. The female:male ratio was 2.7:1. The median follow-up duration was 43.1 months (IQR 24.3–69.3). At the time of SLE diagnosis, the most common manifestation was cutaneous involvement (69.6%), followed by haematologic disorder (62.7%) and renal disorder (42.2%) disease (Table 1). In the presented cohort, 74% of the patients had elevated anti-dsDNA antibody levels and 78.4% had decreased C3 and/or C4 levels. The median SLEDAI score at the time of SLE diagnosis was 10 (IQR 7.75–16). Other demographic and clinical features of the SLE patients are summarized in Table 1.

Renal involvement

There were 53 patients (52%) with LN. Among them, LN was present at presentation in 34 (64.2%) patients, whereas 19 patients (35.8%) developed LN during follow-up. The median age of LN diagnosis was 13.1 years (IQR 10.8–15.5). For patients who developed LN during follow-up, the median duration from SLE diagnosis to LN diagnosis was 18.5 months (IQR 2.9–34.1). Sixteen patients (30%) had hypertension. At the time of LN diagnosis, proteinuria was the most common urinary abnormality in 51 (96.2%) children and 17 (33.3%) of them were in the nephrotic range (15 had nephrotic syndrome). Microscopic haematuria was present in 33 (62.2%) patients. The median GFR at the time of LN diagnosis was 135 mL/min/1.73 m^2 (IQR 105–178). Among all LN patients, 18.9% ($n = 10$) presented with a GFR <90 mL/min/1.73 m^2, 5.7% ($n = 3$) with a GFR of 60–89 mL/min/1.73 m^2, 5.7% ($n = 3$) with a GFR of 30–59 mL/min/1.73 m^2 and 7.5% ($n = 4$) with a GFR <30 mL/min/1.73 m^2. An elevated serum creatinine level was noted in 11 patients (10.8%) and 6 of them had oliguria.

The most frequent histopathological class was Class IV LN [29 children (54.7%)] followed by Class III [12 patients (22.6%)]. The number of children with Classes II, V and VI nephritis was 9, 2 and 1, respectively. The median SLEDAI score at the time of LN diagnosis was 21 (IQR 14–27.5). We compared the characteristics of LN patients according to the timing of LN diagnosis. Patients diagnosed with SLE and LN simultaneously had a significantly lower GFR at LN diagnosis ($P = 0.03$) and a higher rate of arthritis ($P = 0.04$) when compared with patients who developed LN during follow-up (Table 2).

Immunosuppressive treatment

Among 41 patients with proliferative LN (Classes III and IV) at induction, 22 (53.7%; 2 patients with Class III and 20 patients with Class IV) patients received pulse MPZ (3–6 doses) + CYC (3–6 doses). In contrast, 10 patients (24.4%; 7 patients with Class III and 3 patients with Class IV) received pulse MPZ (one to four doses) and MMF and 9 (21.9%) patients received other combination therapies including RTX ($n = 3$), oral CYC ($n = 5$) and AZA ($n = 1$). As for maintenance immunosuppression, 13 patients (31.7%) were on prednisolone + AZA, 22 patients (53.7%) on prednisolone + MMF, 3 patients (7.3%) on only prednisolone and 1 patient (2.4%) on prednisolone + cyclosporine. Two patients were lost to follow-up after induction treatment. Among patients with non-proliferative LN [Class V ($n = 2$), Class II ($n = 9$)], five patients received pulse MPZ (1–4 doses) + AZA, one patient received prednisolone + MMF, one patient received prednisolone + oral CYC and four patients received prednisolone alone. The most common maintenance therapy was prednisolone + AZA ($n = 5$), followed by prednisolone alone ($n = 4$) and prednisolone + MMF ($n = 2$) (Table 3).

Short-term renal outcomes at 6 and 12 months after induction treatment

In our LN cohort (Classes II–VI), the proportion of patients who achieved either CR or PR was 77.3% and 73% at 6 and 12 months, respectively. There was no difference between the response rates of MMF and CYC and other combination treatment groups at 6 months ($P = 0.05$) and 12 months ($P = 0.71$)

Table 2. Comparison of demographic and clinical characteristics of LN patients based on the time of renal involvement

Characteristics	All LN patients ($n = 53$)	Simultaneous diagnosis of LN and SLE ($n = 32$)	LN diagnosis after SLE diagnosis ($n = 21$)	P-value
SLE diagnosis before 12 years, *n* (%)	21 (39.6)	15 (46.9)	6 (28.6)	0.18
Age at LN onset, median (IQR)	13.1 (10.8–15.5)	12.11 (10.33–14.39)	13.83 (12.53–15.70)	0.15
Malar rash, *n* (%)	28 (52.8)	17 (53.1)	11 (52.4)	0.96
Photosensitivity, *n* (%)	16 (30.2)	11 (34.4)	5 (23.8)	0.41
Discoid rash, *n* (%)	6 (11.3)	3 (9.4)	3 (14.3)	0.67
Oral/nasal ulceration, *n* (%)	5 (9.4)	1 (3.1)	4 (19)	0.07
Arthritis, *n* (%)	**27 (50.9)**	**20 (62.5)**	**7 (33.3)**	**0.04**
Serositis, *n* (%)	14 (26.4)	9 (28.1)	5 (23.8)	0.73
Neurologic disorder, *n* (%)	11 (20.8)	6 (18.8)	5 (23.8)	0.66
Haematologic disorder, *n* (%)	35 (66)	22 (68.8)	13 (61.9)	0.61
Anaemia, *n* (%)	29 (54.7)	18 (56.3)	11 (52.4)	0.78
Leucopenia, *n* (%)	19 (35.8)	11 (34.4)	8 (38.1)	0.78
Lymphopenia, *n* (%)	26 (52)	15 (48.8)	11(57.9)	0.51
Thrombocytopenia, *n* (%)	16 (30.2)	11 (34.4)	5 (23.8)	0.41
Anti-dsDNA positivity, *n* (%)	45 (84.9)	27 (84.4)	18 (85.7)	0.89
Low complement, *n* (%)	50 (94.3)	30 (93.8)	20 (95.2)	0.82
C3, median (IQR)	40.2 (27.5–61.8)	39 (25.8–61.85)	43 (35–60)	0.48
C4, median (IQR)	5.6 (4–10)	5.4 (3.87–7.60)	6.70 (4.10–10)	0.36
Proteinuria, *n* (%)	51 (96.2)	30 (93.8)	21 (100)	0.51
UPCR (mg/mg), median (IQR)	1.12 (0.59–3.0)	1.12 (0.56–1.80)	1.12 (0.64–3.00)	0.91
24 h urine protein, (mg/day) median (IQR)	742 (455–2415)	1020 (450–2450)	680 (480–1273)	0.45
Microscopic haematuria, *n* (%)	33 (64.7)	19 (63.3)	14 (66.7)	0.81
Oliguria, *n* (%)	6 (11.5)	4 (12.9)	2 (9.5)	0.71
Nephrotic syndrome, *n* (%)	15 (29.4)	10 (33.3)	5 (23.8)	0.46
Hypertension, *n* (%)	16 (31.4)	12 (42.9)	4 (19)	0.11
GFR (mL/min/1.73 m^2), median (IQR)	**130 (103–170)**	**110 (89.50–157)**	**147(126–178)**	**0.03**
Creatinine (mg/dL), median (IQR)	0.59 (0.41–0.77)	0.61 (0.41–0.81)	0.51 (0.46–0.69)	0.47
Albumin (g/dL), median (IQR)	3.4 (2.6–3.8)	3.22 (2.56–3.80)	3.54 (2.90–3.80)	0.28
SLEDAI score at LN diagnosis, median (IQR)	21 (IQR 14–27.5)	20 (14–27)	11 (9–16)	0.77
GFR <90 mL/min/1.73 m^2, *n* (%)	13 (24.5)	10 (31.3)	3 (14.3)	0.16

Statistically significant parameters are presented in bold.

(Figure 1A and B). At 6 months, 22.6% of patients were classified as non-responders, and the proportion of those decreased to 20.8% at 12 months. Overall, 9.4% experienced at least one renal flare during the first year.

Among patients with proliferative LN (Classes III–IV), CR and PR rates were 78.1% and 75.7% at 6 and 12 months, respectively. Although the remission rate at 6 months was significantly higher in the MMF- and CYC-treated groups than other combination therapies (P = 0.02), no difference was found between the CYC and MMF response rates (P = 0.57), but CYC was mostly (79%) given to Class IV patients as induction therapy. There was no difference between the response rates in any treatment regimens at 12 months (P = 0.56) (Figure 1C and D).

Long-term renal outcomes and prognosis

The median follow-up of LN patients was 47.7 months (IQR 25.4–78). In the entire LN cohort, 5- and 10-year renal survival rates were 92% and 85.7%, respectively. In the proliferative LN group, the 5- and 10-year renal survival rates were 90.5% and 75%, respectively. We also evaluated the CR, PR and flare rates every year for 10 years after the induction treatment to determine the maintenance of the remission state. After induction we were able to follow-up 47, 41, 36, 28, 25, 22, 18, 12, 11 and 7 patients for each year after the diagnosis to 10 years of follow-up, respectively (Figure 2A). The remission rates (either CR or PR) at 2, 4, 6, 8 and 10 years were 82.9%, 78.6%, 77.3%, 66.7% and 85.7%, respectively. Ten-year renal outcome of Classes III–IV LN patients are shown in Figure 2B. During follow-up, 6 patients (11.3%) were non-responsive to the treatment and 13 patients (24.5%) experienced at least one renal relapse after achieving PR or CR. There was no significant difference in relapse rates between patients treated with CYC (22.7%) and MMF (27.3%) and other combination therapies (25.0%) (P = 0.99). Repeat renal biopsy was performed in 12 patients and a third renal biopsy was performed in 4 patients. The median time to first relapse was 26 months (IQR 12.1–42.7). In patients who received CYC + MPZ as induction treatment, the median time to first relapse was longer [15.0 months (IQR 8.5–21.5)] than in patients treated with MMF + MPZ [12.1 months (IQR 5.3–18.9)]. However, it did not reach statistical significance (P = 0.68) (Figure 3).

LN patients who attained CR at 6 months after induction treatment had better renal survival compared with patients who did not (P < 0.001) (Figures 4 and 5). After a median follow-up of 54.5 mopnths (IQR 11.7–104.1), six patients developed CKD and four of them were diagnosed with ESRD. All patients with

Table 3. Immunosuppressive treatment of LN patients based on their renal severity

Treatment		Proliferative LN ($n=41$)			Non-proliferative LN ($n=12$)		
		Class III ($n=12$), n	Class IV ($n=29$), n	Total ($n=41$), n (%)	Class II ($n=9$), n	Class V ($n=2$), n	Total ($n=11$), n (%)
Induction therapy	Pulse MPZ + CYC	2	20	22 (53.7)	–	–	–
	Pulse MPZ + MMF	7	3	10 (24.4)	1	–	1 (9)
	Pulse MPZ + AZA	1	–	1 (2.4)	3	2	5 (45.4)
	Pulse MPZ + oral CYC	2	3	5 (12.1)	1		1 (9)
	Pulse MPZ + RTX	–	3	3 (7.3)	4	–	4 (36.3)
	Prednisolone alone	3	–	3 (7.3)	–	–	–
Maintenance therapy	Prednisolone + AZA	4	9	13 (31.7)	3	2	5 (45.4)
	Prednisolone + MMF	6	16	22 (53.7)	2	–	2 (18.1)
	Prednisolone + CsA	0	1	1 (2.4)	–	–	–
	Prednisolone alone	2	1	3 (7.3)	4	–	4 (36.3)
	Lost to follow–up	0	2	2 (4.8)	–	–	–

CsA, cyclosporine A.

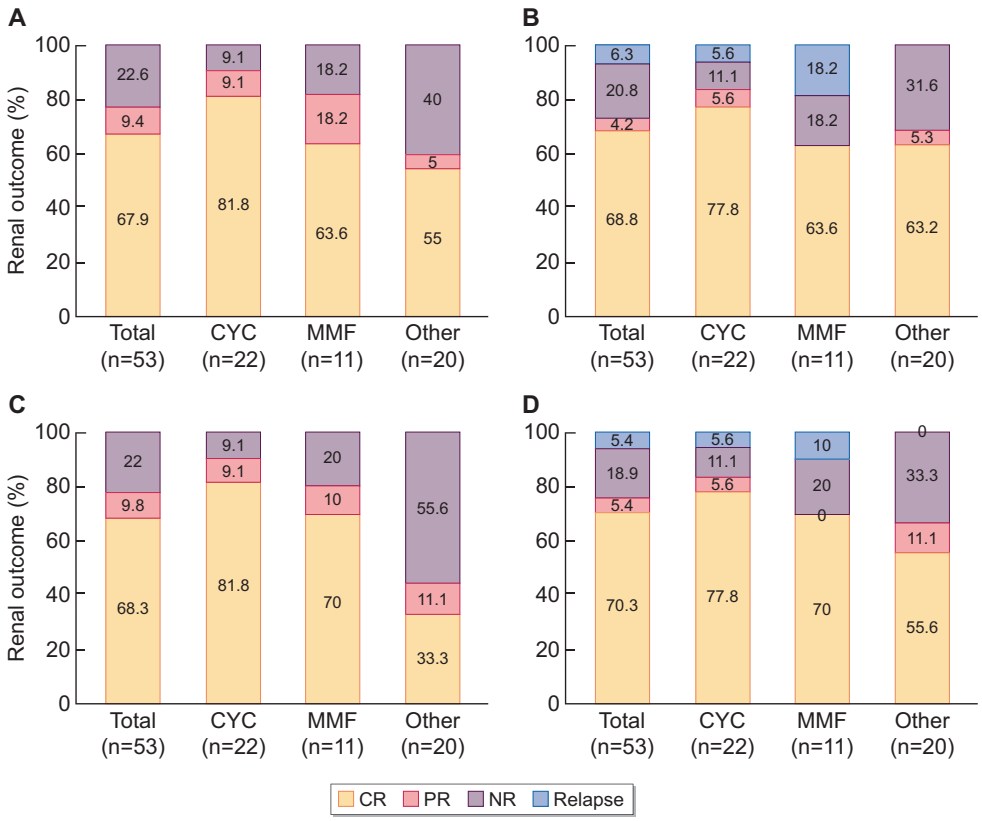

FIGURE 1: Renal outcomes of LN patients. (A) Renal outcome (%) at 6 months for all LN patients (P = 0.053). (B) Renal outcome (%) at 12 months for all LN patients (P = 0.71). (C) Renal outcome (%) at 6 months for LN patients with Classes III and IV. The remission rate at 6 months was significantly higher in the MMF- and CYC-treated groups than other combination therapies (P = 0.02). (D) Renal outcome (%) at 12 months for LN patients with Classes III and IV (P = 0.56). NR, non-response.

ESRD were Class IV LN. One patient received a living related renal transplant from her father; however, she experienced rejection and required dialysis. Three patients with LN died. One patient died after the development of acute myeloid leukaemia and infection when she was in PR. The other patient died after reaching ESRD. A third LN patient died after haematopoietic stem cell transplantation (Ikaros gene defect).

Risk factors associated with poor renal outcome

We created a multivariate model based on the possible predictors of poor renal outcome among Class III and IV LN patients. Male gender [HR 8.41 (1.79–39.47), P = 0.007], requiring dialysis at the time of LN diagnosis [HR 6.48 (1.78–22.68), P = 0.023] and not attaining remission at 6 months [HR 8.6 (1.65–44.91), P = 0.010] and 12 months [HR 13.82 (1.68–

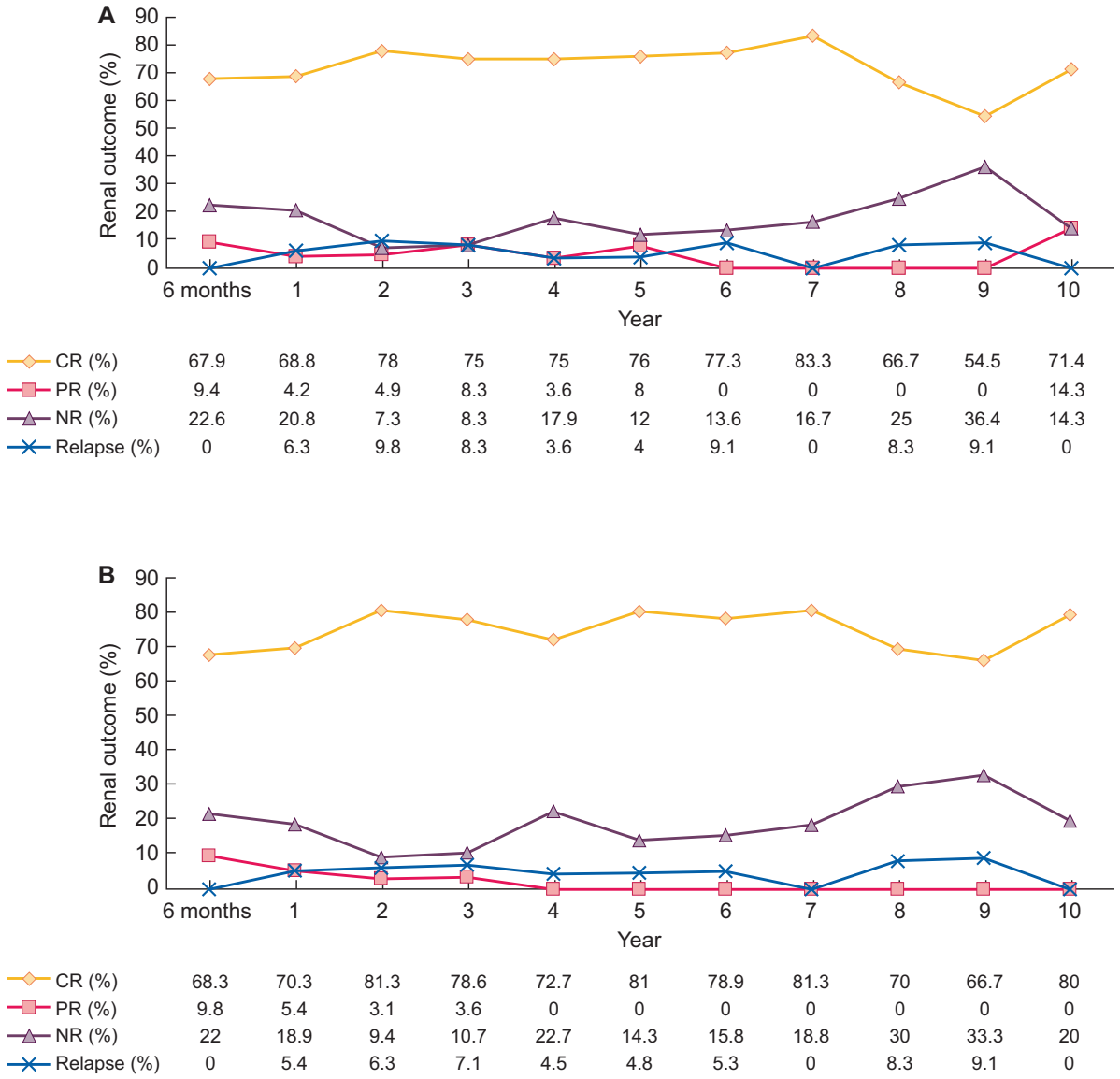

FIGURE 2: (A) 10-year renal outcome rates in the whole LN group ($n = 53$). (B) 10-year renal outcome rates in the Classes III and IV LN group ($n = 41$).

113.49), P = 0.014] were found to be associated with poor renal outcome (Table 4). For the SLEDAI at the time of LN, although the HR showed a positive association with poor renal outcome, the statistical significance was only borderline [HR 1.09 (0.99–1.19), P = 0.054].

Long-term complications

The median height standard deviation score (SDS) at the time of LN diagnosis and the last visit was −0.38 (IQR −1.65–0.01) and −0.22 (IQR −1.82 to −0.05), respectively. The median BMI SDS at the time of LN diagnosis and the last visit was −0.17 (IQR −0.91–1.09) and 0.68 (IQR −0.03–1.4), respectively. Both height SDS (P = 0.04) and BMI SDS (P = 0.002) were statistically greater at the last visit compared with at diagnosis. After excluding three LN patients who died, among 50 LN patients, 1 patient developed amenorrhea (2%), 1 patient developed cataracts (2%) and 8 patients developed osteoporosis (16%) during follow-up.

DISCUSSION

In this study we reported a large paediatric cohort of LN, followed for a median period of 47.7 months, with 10 years of renal survival outcomes. In patients with proliferative LN, the response rates at 6 and 12 months were similar in patients who received MMF or CYC as induction treatment, but the majority of the Class IV patients received CYC. The time to first relapse was slightly longer in the CYC group, but the difference was not statistically significant, and relapse rates during follow-up were also similar in the two groups. Male gender, requiring dialysis at the time of LN diagnosis and failure to achieve remission at 6 and 12 months was found to be associated with poor renal outcome. The risk of poor renal outcome was 8.6 and 13.8 times the risk for those who did not attain remission at 6 and 12 months, respectively. Supporting this, our LN patients who attained CR at 6 months after induction treatment had a better renal survival rate compared with patients who did not (P < 0.001).

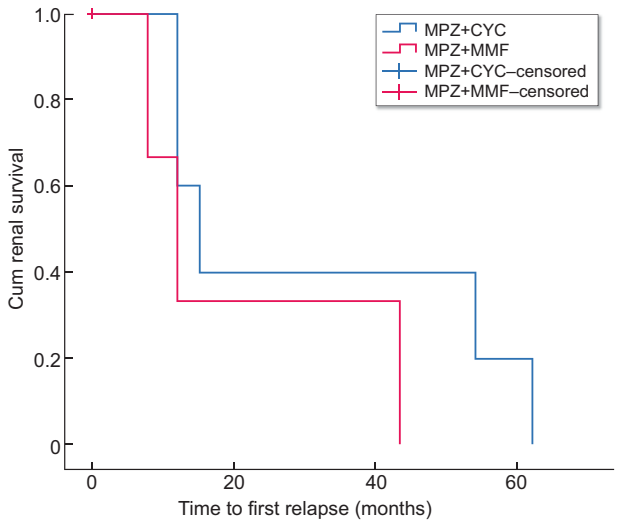

FIGURE 3: Time to first relapse of LN patients who received CYC or MMF as induction treatment (P = 0.681).

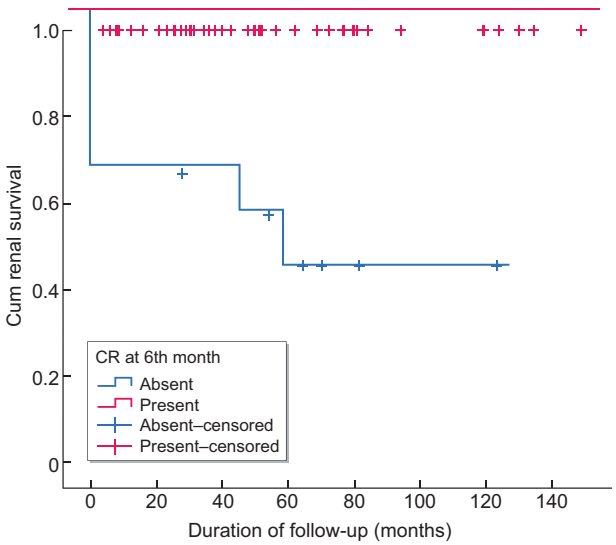

FIGURE 4: Renal survival of LN patients with and without CR at 6 months (P < 0.001).

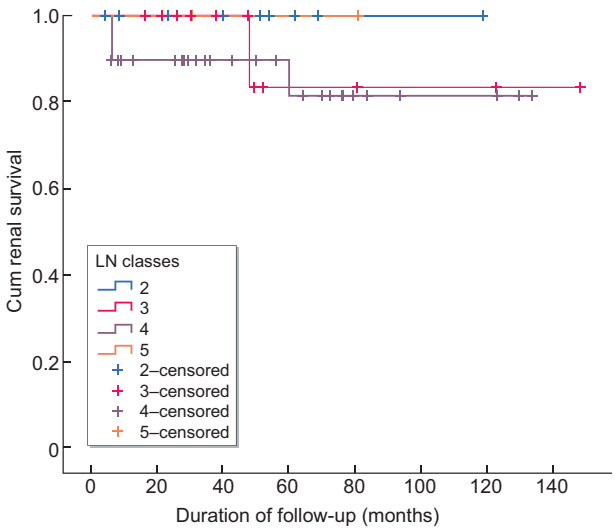

FIGURE 5: Time to CKD (GFR <60 mL/min and/or persistent dialysis) was not statistically different between the LN classes (P = 0.664).

We present the baseline characteristics of 102 SLE patients where 52% of them had LN proven with renal biopsy. The diagnosis of LN was simultaneous with SLE in 64.2% of patients. It is unclear whether the time of the onset of LN affects the treatment response and long-term prognosis of SLE patients. In a retrospective review of 66 adult patients with proliferative LN, simultaneous diagnosis of SLE and LN was associated with poor renal survival [23]. In contrast, a recent report showed no difference in severity or prognosis between early- and late-onset adult LN patients [24]. In this study, paediatric patients diagnosed with SLE and LN simultaneously had a reduced GFR compared with patients developing renal involvement during follow-up. Compatible with the literature, Class IV LN was the most common histopathologic ISN/RPS type in our cohort (54.7%) and was associated with the worst kidney prognosis. The frequency of Class IV LN, which was reported in previous pediatric SLE-based studies, varied between 42% and 67.3% [25–28]. In our cohort, all patients who developed CKD were Class IV LN, which showed poor prognosis despite intensive immunosuppressive therapy.

In 2017, the SHARE initiative recommended both CYC and MMF as the initial regimen for proliferative LN in paediatric patients. In paediatric LN there are no randomized controlled trials comparing induction treatment regimens. However, many observational cohort studies and case reports provide treatment outcomes for Class III/IV LN. Several studies have compared renal outcomes in paediatric patients with proliferative LN receiving CYC or MMF induction therapy and no significant differences were noted [29–31]. In the literature, there are other studies that show the superiority of MMF as an induction treatment. Zhang *et al.* [32] studied the renal outcome of

Table 4. Cox regression analysis for poor renal outcome among LN patients with Classes III and IV

Variables	HR (95% CI)	P-value
Male gender	8.41 (1.79–39.47)	**0.007**
SLE diagnosis before 12-year-old age	0.34 (0.10–1.13)	0.79
Serositis at the time of LN diadnosis	2.6 (0.47–14.32)	0.272
Neurological involvement at the time of LN diagnosis	1.18 (0.13–10.13)	0.874
GFR <60 mL/min at the time of LN diagnosis	0.15 (0.04–6.82)	0.337
Hypoalbuminaemia at the time of LN diagnosis	0.67 (0.18–2.47)	0.552
Dialysis at the time of LN diagnosis	6.48 (1.78–22.68)	**0.023**
Hypertension at the time of LN diagnosis	0.36 (0.09–1.44)	0.150
SLEDAI at the time of LN diagnosis	1.09 (0.99–1.19)	**0.054**
Anti-phospholipid positivity at the time of LN diagnosis	1.36 (0.40–4.61)	0.612
Increased creatinine at the time of LN diagnosis	1.94 (0.17–22.34)	0.592
Renal relapse	0.81 (0.20–3.34)	0.781
Thrombocytopenia at the time of LN diagnosis	3.56 (0.86–14.74)	0.079
No response at 6 months	8.6 (1.65–44.91)	**0.010**
No response at 12th months	13.82 (1.68–113.49)	**0.014**

Statistically sugnificant values are presented in bold.

Chinese paediatric LN patients. They showed that induction treatment with MMF was associated with a lower risk of renal flare on multivariate analysis. The majority of our Class III and IV LN patients received CYC (53.7%) or MMF (21.9%) as induction treatment. We did not find any difference between the CYC and MMF response rates after 6 months of treatment ($P = 0.57$). Twelve months of CR or PR rates were also not different in the two treatment regimens ($P = 0.564$). Although time to first flare was slightly longer in the CYC group, it did not reach statistical significance.

We evaluated the response rates at 6 and 12 months after induction treatment. In patients with proliferative LN, the proportion of patients who achieved either CR or PR was 78.1% and 75.7% at 6 and 12 months, respectively. CR at 6 and 12 months was achieved in 68.3% and 70.3% of those, respectively. Our 6- and 12-month CR rates were better than in many reports on paediatric patients with proliferative LN [27, 29, 30, 33]. Wu *et al.* [27] reported that 67% of patients with proliferative LN met the criteria of CR within 6 months after induction treatment. In a retrospective study of 191 paediatric patients with Class III LN, at 6 months, no patient had achieved CR in the CYC group while 57% were in PR. In the MMF group, 66% had achieved CR [29]. In a German registry study, which included 79 children with juvenile proliferative LN, the CR rate at 12 months was 38% [31]. There are also two paediatric studies that reported outcomes for CR rates at 12 months similar to those in this study [34, 35].

Predictors of renal survival and/or actuarial survival have also been studied in the literature. Singh *et al.* [36] evaluated 53 patients with LN. They found that on univariate analysis, only baseline serum creatinine and serious infection were statistically significant predictors of time to death [36]. Consistent with previous studies, male gender, requiring dialysis at the time of LN diagnosis and not attaining remission at 6 and 12 months following induction therapy was found to be associated with a poor prognosis [25, 27, 37, 38].

In the adult series, 25–30% of patients with proliferative LN developed ESRD within 20 years of follow-up [12, 39]. The data regarding long-term follow-up outcomes in paediatric SLE are limited. However, in the last decades, improving outcomes have also been observed in paediatric LN similar to adult LN [5, 40]. In 1968, 5- and 10-year survival rates of LN were reported to be <50% [40]. Between 1977 and 1991, the 5-year overall survival rate of paediatric SLE was reported as 76.3% [41]. We found the 5- and 10-year renal survival rates in the proliferative LN group to be 90.5% and 75%, respectively. In our study, the survival of different LN classes seems to be comparable. However, intense immunosuppressive treatment was given to Class III and IV patients. The multidisciplinary follow-up of these patients may have contributed to the good outcome in our series.

The strength of our study is that it provides a long-term renal outcome in paediatric LN patients. However, the study has some limitations. The number of patients was relatively limited and the study had a retrospective design. Another limitation is that the treatment regimens in our cohort were not entirely standardized in the patients with a long period of follow-up. Finally, there was a bias to start CYC for patients with a more severe renal presentation. Although MMF and CYC seem comparable in terms of efficacy, as we mentioned above, the majority of Class IV LN patients received CYC at induction.

In conclusion, our study demonstrated that male gender, failure to achieve remission within 1 year after induction treatment and requiring dialysis at the time of diagnosis were the best predictors of poor renal outcome. Therefore prompt recognition and aggressive management of paediatric LN are essential to achieve and maintain remission.

CONFLICT OF INTEREST STATEMENT

None declared.

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