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Long-Term Outcomes of Children and Adolescents With Biopsy-Proven Childhood-Onset Lupus Nephritis

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Introduction: Long-term data pertaining to childhood-onset lupus nephritis (cLN) remain extremely scarce.

Methods: We conducted a retrospective cohort study of biopsy-proven cLN with onset age $\leq$18 years diagnosed from 2001 to 2020 to ascertain the long-term patient and kidney survival rates, and the incidence of advanced chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] $<$60 ml/min per 1.73 m^2).

Results: A total of 92 subjects (78 female; age 13.7 $\pm$ 3.3 years; all Chinese) were included, with follow-up duration of 10.3 years (interquartile range, 5.8–15.9). Of these, 83 children (90%) had proliferative lupus nephritis (LN) (Class III/IV $\pm$ V). Mycophenolate was used for induction in 36%, whereas 34% received cyclophosphamide (CYC); 55% received mycophenolate as maintenance immunosuppression. The rates of complete remission (CR) and partial remission (PR) at 6 months and 12 months, respectively, were 65% and 20% and 78% and 8%. Two patients died (mortality rate 2.1/1000 patient-years), with a standardized mortality ratio of 22.3. Three patients (3.2%) developed end-stage kidney disease (ESKD), and advanced CKD occurred in 5 patients (5.4%). Survival rates without advanced CKD, ESKD, or death were 96.7%, 94.2%, 92.7%, 83.2% and 83.2% at 1 year, 5 years, 10 years, 15 years, and 20 years, respectively. Multivariate analysis revealed that severe kidney failure necessitating dialysis at presentation (adjusted hazard ratio 37.7, 95% confidence interval [CI] 4.0–355.6, $P = 0.002$), nonresponse (NR) after 12 months of treatment (adjusted hazard ratio 11.2, 95% CI 2.3–54.9, $P = 0.003$), and multiple nephritis flares (adjusted hazard ratio 2.6, 95% CI 1.1–6.2, $P = 0.03$) were predictive of advanced CKD, ESKD, or death. Other adverse outcomes included infections (2.9 episodes/100 patient-years), osteopenia (32%), hypertension (17%), short stature (14%), and avascular necrosis (7%).

Conclusion: The long-term outcomes of cLN appeared to have improved in the present era with effective immunosuppression, cautious drug tapering, and assurance of medication adherence. There is still an unacceptably high prevalence of adverse outcomes.

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Systemic lupus erythematosus (SLE) is a multisystem, lifelong autoimmune disease. Approximately 10% to 20% of patients present with SLE during childhood.[1]

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The incidence of SLE and LN differ considerably across regions and is more prevalent among Asians. Childhood-onset SLE is known to have a high frequency of LN, with a cumulative incidence of 35.6% in a recent large US study.[1,2] Early diagnosis and treatment is important because LN can lead to the development of CKD, ESKD, and mortality.[3–5]

Despite the availability of effective immunosuppressive therapies, treatment response in cLN remains suboptimal, with 50% to 78% patients in full remission at 24 months based on various criteria for response.[6] Improvement in survivals have also plateaued in past

decades,[5] and up to 9% and 14% of children with cLN died or developed ESKD during the course of illness, respectively.[7-9] CKD progression and ESKD, together with complications in various organs, are major challenges in the long-term management of patients who transitioned to adulthood.[7]

Outcome data specific to cLN, however, remain extremely scarce.[8,10-14] In particular, all of these studies were limited by follow-up duration of <5 years to 6 years.[8,10-13] This study aims to examine the long-term clinical outcomes in patients with cLN over a 20-year period in the present era.

METHODS

The Pediatric Nephrology Center of Hong Kong Children's Hospital, formerly located at Princess Margaret Hospital, Hong Kong, is the only designated site offering maintenance kidney replacement therapy (KRT) (dialysis and kidney transplantation) to children in Hong Kong and serves as territory-wide pediatric nephrology referral center. We conducted a retrospective cohort study of children with biopsy-proven LN and disease onset at age ≤ 18 years, who presented between January 1, 2001, and December 31, 2020. Patients without histologic confirmation of diagnosis, and those with follow-up shorter than 1 year, were excluded. The cutoff date for data retrieval was set at April 1, 2022. The diagnosis of SLE was based on the American College of Rheumatology classification.[15] Histology was classified according to the 1982 World Health Organization classification for LN and the International Society of Nephrology/Renal Pathology Society classification before and after 2004, respectively.[16,17] Anonymized data on patient demographics, treatment regimens, laboratory parameters, and patient and kidney survival outcomes were reviewed. The study was performed according to the Declaration of Helsinki and was approved by the institutional review board of the Hong Kong Children's Hospital, Hospital Authority, Hong Kong (HKCH-REC-2021-024).

Treatment of cLN was standardized and included initial therapy with heavy immunosuppression followed by low-dose maintenance.[18] Patients with proliferative LN (class III, focal proliferative, and class IV, diffuse proliferative) were given high-dose corticosteroids in combination with CYC or mycophenolate mofetil (MMF) as initial therapy, followed by low-dose prednisolone and azathioprine (AZA) or MMF as maintenance. At treatment initiation, high-dose oral corticosteroid (0.8–1 mg/kg per day) was given, with or without intravenous pulse methylprednisolone (10–30 mg/kg per dose for 3 doses, maximum 1 g/dose). Prednisolone was then gradually tapered to 10 mg/d (or 0.3 mg/kg per day in young children) by 4 months after treatment initiation. Whereas CYC was the predominant initial therapy during the first treatment decade (2001–2010), MMF became the standard induction in the second decade (2011–2020) and CYC was reserved for patients with crescentic lesions in >25% of glomeruli on kidney biopsy, significant renal impairment (eGFR <30–40 ml/min per 1.73 m^2) or concomitant life-threatening extrarenal manifestations (e.g., cerebral involvement). CYC was mostly administered intravenously, according to the National Institutes of Health (0.5–1 g/m^2 monthly for 6 months) or Euro-Lupus (500 mg every 2 weeks for 3 months) regimens. Oral CYC, if used, was given at 2 to 3 mg/kg daily for 6 months. Dosing for MMF during initial treatment was 1200 mg/m^2 per day and AZA was given at 1.5−2 mg/kg per day. During the maintenance phase, corticosteroid was tapered to 3 to 5 mg/d and MMF to 600 to 900 mg/m^2 per day. Immunosuppression was continued for at least 3 years until young adulthood. Mixed class III + V or class IV + V LN were treated as proliferative LN. Class V (membranous) LN was treated with corticosteroid and MMF. Triple therapy with corticosteroid, MMF, and calcineurin inhibitors or adjunctive therapies (e.g., anti-CD20 and plasma exchange) were offered in selected patients who were refractory to first-line therapy. Antimalarials, statins, and/or renin-angiotensin-aldosterone-system inhibitors were used in most patients unless contraindicated. Medication adherence was checked, documented, and counseled by attending physicians at each medical visit. Nonadherence with medication was self-reported and defined as <80% of prescribed medications were taken by the patients between the consecutive clinic visits.[19]

Patients were followed weekly initially with follow-up interval gradually increasing to every 8 weeks in stable subjects. Clinical parameters, urinalysis, complete blood count, renal biochemistry, anti–double-stranded DNA (anti-dsDNA) antibodies titers, and complement 3 levels were determined at each visit. Urine protein-to-creatinine ratios (UPCRs) were quantified at most visits. eGFR was calculated on the basis of serum creatinine, in reference to the Revised Bedside Schwartz Formula for patients younger than 18 years, and the CKD-Epidemiology Collaboration 2021 Race-free eGFR calculation in those older than 18 years.[20,21] Age groups were defined as age at LN diagnosis as children (<12 years) and adolescents (12–18 years).

Primary outcomes included patient survival, renal survival, and a composite outcome of advanced CKD

(stage 3–5, eGFR <60 ml/min per 1.73 m^2), ESKD requiring maintenance KRT, and/or mortality. Renal survival was defined as survival independent of KRT. Patients were censored at last follow-up. Secondary outcomes included disease remission at 6 months and 12 months after treatment, renal relapse, complications, and eGFR, UPCR, and CKD staging at last follow-up. CR was defined as sustained UPCR <0.5 mg/mg on an early morning urine.[18] PR was reduction in UPCR by ≥50% and <3 mg/mg.[18] Both CR and PR also required improvement or stabilization of kidney function (eGFR decrease of <15% at 6 months or 12 months compared with baseline). Patients who did not attain CR and PR at the given time points were defined as NR. Renal relapse was defined as a UPCR value >1 mg/mg in patients with proteinuria <0.5 mg/mg, or increase in UPCR by 1 mg/mg or more in patients with proteinuria above 0.5 mg/mg, and/or increase in serum creatinine, supported by either serologic activity or repeat kidney biopsy.[22] Complications evaluated included infection, hypertension, diabetes mellitus, malignancy, short stature, decreased bone mineral density, and avascular necrosis. Hypertension was defined as blood pressure ≥95th percentile for age and height in children aged <13 years, or ≥130/80 mm Hg in those aged >13 years.[23] Short stature was defined as height ≤−2 SD for age and sex, according to published local reference.[24] Decreased bone mineral density was detected by bone densitometry, on the basis of the International Society of Clinical Densitometry definition.[25] Avascular necrosis was diagnosed by magnetic resonance study when clinically indicated.

Statistical Analysis

IBM SPSS statistics version 26 software was used for statistical analysis. Descriptive statistics were used for demographic data as appropriate. Baseline demographics, laboratory data, and treatment regimens were compared between the 2 eras using Fisher exact test for the categorical variables and independent-samples t test for parametric and Mann-Whitney U test for nonparametric continuous data. Kaplan-Meier method of survival analysis was used to generate the survival curve and survival pattern for patient and kidney survivals. Log-rank test and Breslow test were used to detect any significant difference in survival rates between each factor. Cox regression analysis was used to detect the hazard ratios and the independent effect of each significant factor on the composite outcome. Crude mortality rate was expressed as deaths per 1000 patient-years, and standardized mortality ratios were calculated. We adopted the population in 2010 (both sexes and ages) as the standard population to calculate the standardized mortality ratios, based on data obtained from the Census and Statistics Department of Hong Kong. A P value < 0.05 in 2 tails was treated as significant in all tests.

RESULTS

A total of 130 patients with childhood-onset SLE were identified, of whom 96 had biopsy-proven LN. After excluding 4 patients who had inadequate follow-up, 92 children (female, $n = 78$) were included in the data analysis (Table 1). The age at cLN diagnosis was 13.7 ± 3.3 years, and the median follow-up duration was 10.3 years (interquartile range, 5.8–15.9) (total 945.9 patient-years). Five patients (5.4%) were lost to follow-up. Seventy-three children (79.3%) presented with LN, whereas 19 patients developed kidney involvement following an initial diagnosis of childhood-onset SLE. The most frequent renal presentation was acute nephritic syndrome (40.2%), and 7 patients required KRT. Eighty-three children (90.2%) had proliferative LN.

Therapy and Treatment Response

All patients received corticosteroids. Thirty-three patients (35.9%) received MMF both as initial (induction) and maintenance therapy. Seventeen patients (18.5%) received sequential immunosuppressive regimen with CYC as initial therapy followed by MMF maintenance (Table 1). There was a significant change in the choice of immunosuppressant over the past 2 decades ($P <$ 0.001). During the first decade, more patients received CYC (53.8%) and AZA (28.2%) as induction, and 66.7% patients received AZA as maintenance. In contrast, MMF was used more frequently in the second decade both as initial (64.2% vs. 7.7%) and maintenance (77.4% vs. 25.6%) therapies. Fifteen patients (16.3%) reported documented medication nonadherence during the observation period. Fifteen and 9 patients were taken off from steroid and steroid-sparing agent 9.1 ± 4.9 years and 8.9 ± 6.2 years after initiation of maintenance immunosuppression, respectively. Only 2 of these patients were completely withdrawn from immunosuppression.

The overall rates of CR/PR/NR at 6 months and 12 months were 65.2%/19.6%/15.2% and 78.3%/7.6%/14.1%, respectively (Table 2). These remission rates were not different between the 2 treatment decades (6-month CR/PR/NR during decade 1 vs. decade 2: 69.2%/10.3%/20.5% vs. 62.3%/26.4%11.3%, $P = 0.11$; 12-month CR/PR/NR during decade 1 vs. decade 2: 79.5%/5.1%/15.4% vs. 77.4%/9.4%/13.2%, $P =$ 0.86). Thirty-seven patients (40.2%) developed kidney flares during follow-up, and 17 (18.5%) had more than 1 flare. There were 63 episodes of kidney flares, with the first renal flare occurring at 4.9 ± 3.7 years after the

Table 1. Baseline characteristics of 92 children with biopsy-proven lupus nephritis

Characteristics	All (n = 92) Mean/Median/N	SD/IQR/%
Age at SLE diagnosis, yr	13.1	3.2
Age at LN diagnosis, yr	13.7	3.3
Gender		
Male	14	15.2%
Female	78	84.8%
Renal manifestations at presentation		
Proteinuria	23	25.0%
Nephrotic syndrome	25	27.1%
Nephritic syndrome	37	40.2%
AKI requiring acute dialysis	7	7.6%
SLE-DAI score	17.6	6.6
Laboratory parameters at presentation		
Serum creatinine, μmol/l	57	(45–79)
eGFR, ml/min per 1.73 m^2	94.3	40.4
Urine protein-to-creatinine ratio, mg/mg	4.0	5.5
Anti-dsDNA antibodies[a], IU/ml	229.5	154.3
Complement 3[b], g/l	0.4	0.2
Histologic classifications		
III	20	21.7%
IV	43	46.7%
V	8	8.7%
III/IV + V	20	21.7%
Lupus podocytopathy	1	1.1%
Therapy		
Corticosteroids	92	100%
Intravenous pulse methylprednisolone	61	66.3%
Initial-maintenance therapy		
MMF-MMF	33	35.9%
CTX-MMF	17	18.5%
CTX-AZA	14	15.2%
AZA-AZA	15	16.3%
Triple therapy[c]	6	6.5%
Others[d]	7	7.6%
Adjunctive therapy		
Rituximab	6	6.5%
Therapeutic plasma exchange	4	4.3%
Antimalarials	64	69.6%

AKI, acute kidney injury; AZA, azathioprine; CNI, calcineurin inhibitor; CTX, cyclophosphamide; DAI, disease activity index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LN, lupus nephritis; MMF, mycophenolate mofetel; SLE, systemic lupus erythematosus.
[a]Anti-dsDNA antibodies, Ref < 55 IU/ml.
[b]Complement 3, Ref < 0.9 g/l.
[c]Triple therapy included use of CNIs in addition to corticosteroid and MMF (cyclosporin A, n = 3, and tacrolimus, n = 3).
[d]Other therapy included corticosteroid monotherapy (n = 3), CTX-CTX (n = 2), AZA-CNI (n = 1). One patient died during initial therapy and thus no information on maintenance therapy.

Table 2. Clinical outcomes of childhood-onset lupus nephritis following treatments

Outcomes	All (n = 92) Mean/N	SD/%
Remission at 6 mo		
Complete response	60	65.2%
Partial response	18	19.6%
Nonresponse	14	15.2%
Remission at 12 mo		
Complete remission	72	78.3%
Partial remission	7	7.6%
Nonresponse	13	14.1%
Renal relapse		
No relapse	55	59.8%
One episode of relapse	20	21.7%
>1 episode of relapse	17	18.5%
Death	2	2.2%
Development of CKD		
No CKD	79	85.9%
Stage 2	5	5.4%
Stage 3	1	1.1%
Stage 4	4	4.3%
Stage 5D	3	3.3%
Renal parameters at last follow-up		
Serum creatinine, μmol/l	69.6	43.8
eGFR, ml/min per 1.73 m^2	112.5	28.9
Urine protein-to-creatinine ratio, mg/mg	0.3	0.8

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

initial episode of LN. Whereas 1 flare occurred in a patient who was completely withdrawn from maintenance immunosuppression following transition to adult care, 5 episodes occurred in patients receiving low-dose steroid alone and in 4 episodes in patients with steroid-sparing agent only. The most common maintenance immunosuppression being used at the time of the 63 relapse episodes was prednisolone (n = 57, 90.1%) and MMF (n = 38, 60.3%), followed by AZA (n = 16, 25.4%), calcineurin inhibitors (n = 10, 15.9%) and CYC (n = 1, 1.6%). There were 47 episodes of extrarenal flares (mucocutaneous: n = 20, 42.6%; musculoskeletal: n = 11, 23.4%; hematological: n = 9, 19.1%; central nervous system: n = 5, 10.6%; cardiovascular: n = 3, 6.4%; gastrointestinal: n = 3, 6.4%; ophthalmologic: n = 3, 6.4%). The renal and extrarenal relapse rates were 6.7 and 5.0 relapses per 100-patient-years, respectively.

Patient and Kidney Survival

There were 2 deaths (2.2%), translating to a crude mortality rate of 2.1 deaths per 1000 patient-years (95% CI, 0.3–7.6) and a standardized mortality rate of 22.3 (95% CI, 6.6–38.1). Overall patient survival rate was 98.9% at 1 year, 5 years, and 10 years and 95.9% at 15 years and 20 years (Figure 1a). One patient died from culture-negative pneumonia, 13.6 years after initial diagnosis. The other patient died 40 days after presentation because of active and severe lupus with macrophage activation syndrome and cerebral involvement.

Three patients (3.3%) developed ESKD, and all of them experienced kidney flare(s). Kidney survival rate was 98.9%, 96.4%, 94.6%, 91.5%, and 91.5% at 1 year, 5 years, 10 years, 15 years, and 20 years, respectively (Figure 1a). Two patients progressed from CKD, whereas another initiated KRT following a severe

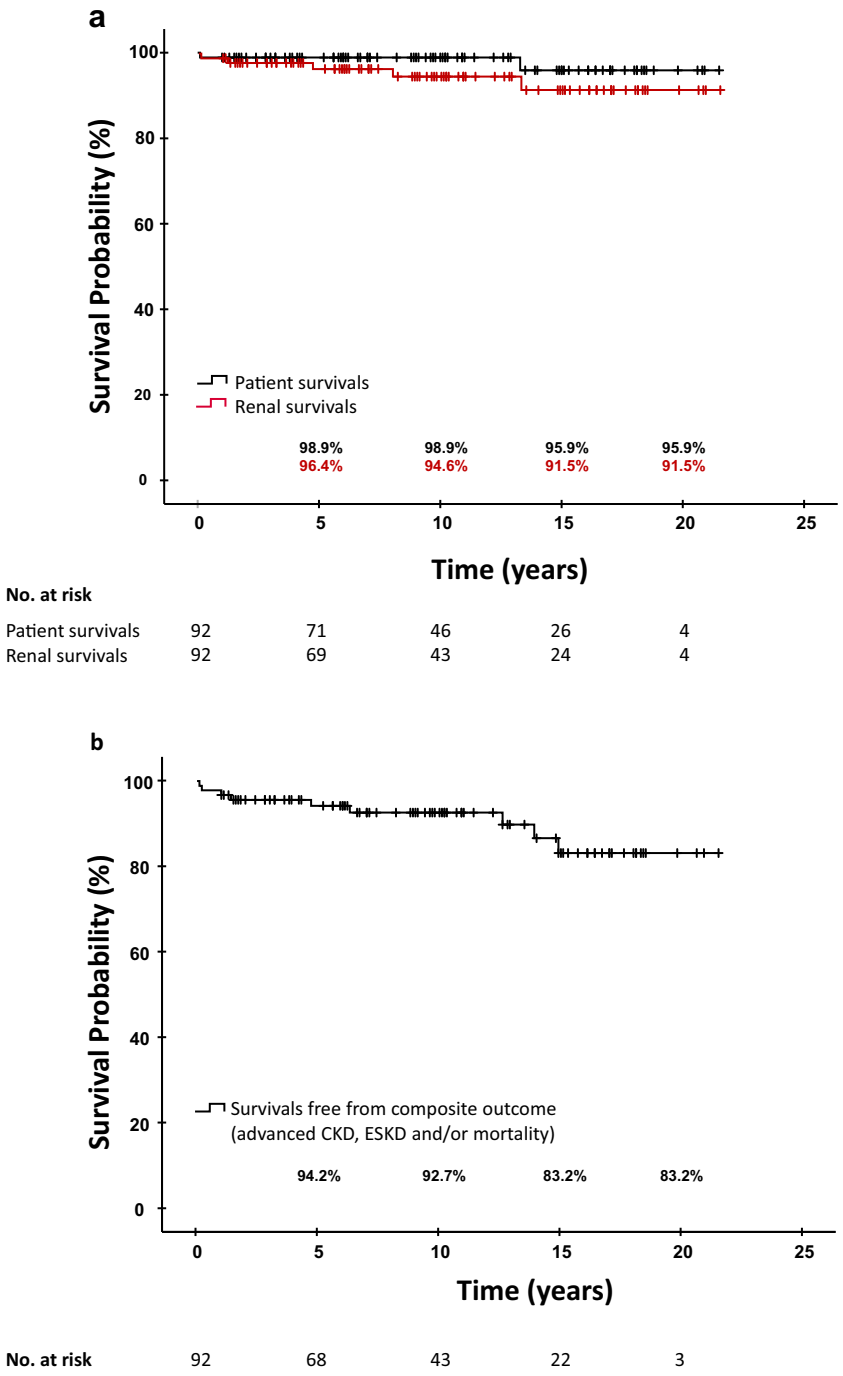

Figure 1. (a) Kaplan-Meier plot of patient and renal survivals in 92 patients with childhood-onset lupus nephritis. (b) Kaplan-Meier plot of the composite outcome including advanced chronic kidney disease (stage 3–5), ESKD, and deaths in 92 patients with childhood-onset lupus nephritis. CKD, chronic kidney disease; ESKD, end-stage kidney disease.

renal relapse. One patient received peritoneal dialysis, 1 received hemodialysis, and 1 received a transplant but returned to hemodialysis following graft failure because of compliance issues.

Composite Outcome

Five additional patients (5%) developed advanced CKD (stage 3–5) during follow-up. The rate of survival free from the composite outcome of advanced CKD/ESKD/death was 96.7%, 94.2%, 92.7%, 83.2%, and 83.2% at 1 year, 5 years, 10 years, 15 years, and 20 years, respectively (Figure 1b). Development of advanced CKD/ESKD/death was associated with need for KRT at presentation, nonremission at 6 months or 12 months after treatment, an increasing number of renal flares, UPCR >1 mg/mg at 1 year after treatment, and documented medication nonadherence (Figure 2a–c and Figure 3a–c), but not with age and decades at LN diagnosis, gender, baseline UPCR, and anti-dsDNA/complement 3 levels or immunosuppressants used. Proliferative LN by itself

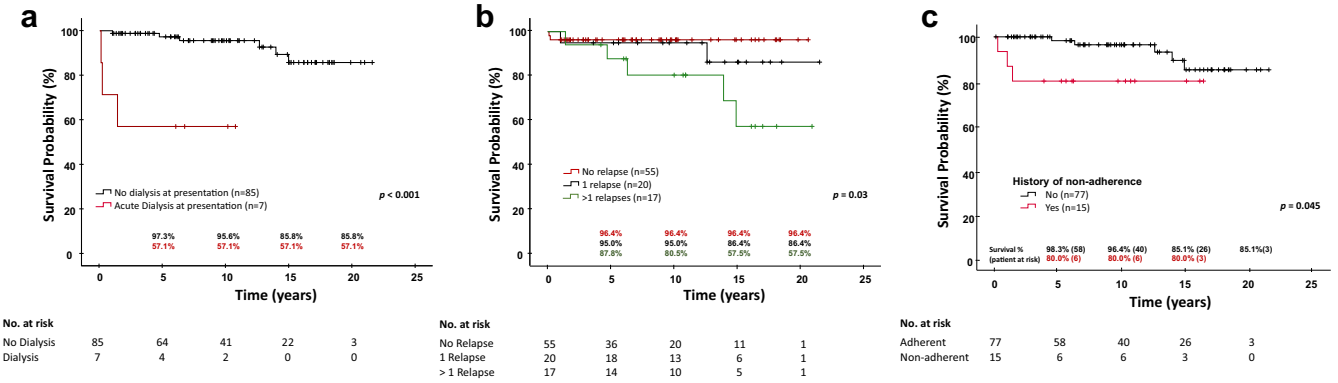

Figure 2. Kaplan-Meier plot of the composite outcome including advanced chronic kidney disease (stage 3–5), ESKD, and deaths in 92 patients by (a) need of acute dialysis at presentation, (b) number of renal relapse, and (c) medication adherence.

was also not a significant risk factor ($P = 0.4$). Multivariate analysis showed that severe kidney injury that necessitated KRT at presentation, NR at 12 months, and increasing number of kidney flares were significant risk factors for developing advanced CKD/ESKD/death (Table 3).

Adverse Events

Fifteen patients (16.3%) developed a total of 27 infectious episodes that necessitated hospitalization, conferring to an infection rate of 2.9 episodes per 100 patient-years. Five infections (18.5%) occurred within 1 year after presentation. Eight infectious episodes occurred in 4 patients with CKD or ESKD. One patient on peritoneal dialysis had 5 episodes of infection, including cytomegalovirus pneumonitis, *Pneumocystis jirovecii* pneumonia, *Citrobacter* peritonitis and talaromycosis. Details of the timing and types of infections are summarized in Tables 4 and 5). One patient without prior CYC exposure developed bilateral renal cell carcinoma complicating acquired cystic kidney disease after ESKD. Sixteen patients (17.3%) had hypertension, and 7 of the 16 patients had CKD. Seventeen of 53 patients (32.1%) had decreased bone mineral density at a median of 2.3 years (interquartile range, 1.0–4.7) after treatment initiation, and in 1 patient, the diagnosis of osteoporosis was established. Avascular necrosis occurred in 6 patients (6.5%) and was detected following 2.7 years (interquartile range, 1.8–3.6) of steroid exposure. Hips were involved in all patients (bilateral, $n = 3$; unilateral, $n = 3$), and 1 patient also developed avascular necrosis over bilateral knees. Thirteen patients (14.1%) had short stature with height ≤ -2 SD for age and sex. Table 4 summarizes the treatment-associated complications in our cohort.

DISCUSSION

Our study reports the longest follow-up data to date on cLN and shows that patient and kidney survival in cLN seemed to have improved in the present era, probably attributed to effective treatment of active disease, efficacious long-term maintenance immunosuppression, and increased awareness of medication adherence. The

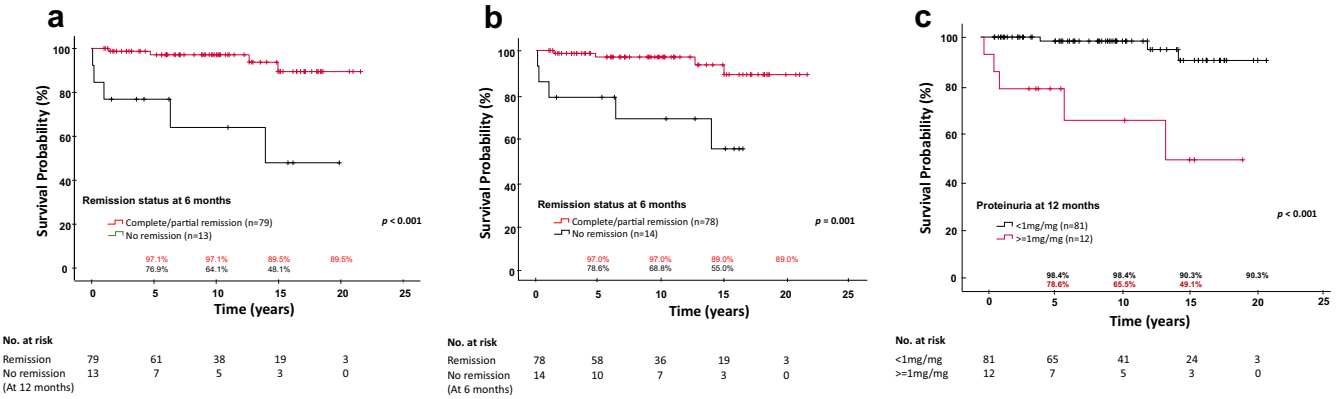

Figure 3. Kaplan-Meier plot of the composite outcome including advanced chronic kidney disease (stage 3–5), ESKD, and deaths in 92 patients by (a) remission status at 12-month posttreatment, (b) remission status at 6-month posttreatment, and (c) proteinuria >1 mg/mg at 12-month posttreatment.

Table 3. Risk factors for the composite outcome of advanced chronic kidney disease, end-stage kidney disease and/or death in 92 children with childhood-onset lupus nephritis

	Univariate analysis		Multivariate analysis	
Variables	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**[a]
Acute dialysis at presentation		<0.001		0.002
No	1.0 [Ref]		1.0 [Ref]	
Yes	15.64 (3.14–77.80)		37.67 (3.99–355.56)	
Remission at 12 mo				
Complete/partial remission	1.0 [Ref]		1.0 [Ref]	
Nonresponse	9.08 (2.43–33.89)	0.001	11.15 (2.26–54.92)	0.003
Number of renal relapses	2.61 (1.15–5.93)	0.02	2.62 (1.11–6.20)	0.03
Medication nonadherence		0.04		0.75
No	1.0 [Ref]		1.0 [Ref]	
Yes	3.91 (1.02–16.52)		1.32 (0.23–7.48)	

CI, confidence interval.
[a]Adjusted for age and gender.

overall mortality (2%), though appearing relatively favorable compared with 6% to 9% in other pediatric cohorts,[8,9] was still 22 times higher than that in age-matched and sex-matched healthy children. Approximately 8% of patients with cLN developed advanced CKD and/or ESKD. Severe initial presentation, NR to initial therapy, and kidney flares were important predictors of adverse outcomes. Finally, early and late treatment–related complications such as infection, short stature, and avascular necrosis could occur in a subset of patients.

Despite a dramatic improvement in survival rates, children and adults with LN are still associated with significantly increased mortality, with infection being the leading cause of death.[9,26] Even in the more recent era, cLN-associated mortality remains as high as 6% to 9%, with a 5-year patient survival rate down to 86.5%.[8,9] In the adult population, 5-year and 10-year patient survival rates in LN range from 80% to 99% and from 75% to 98%, respectively.[2,27-29] Compared with previous literature, our cohort reported an impressive patient survival rate of 98.9% at 10 years with only 2 mortalities. Apart from effective immunosuppression, this better outcome is partly explained by a robust public health care system that facilitates timely access to medical care and treatment equity in children. Both episodes were unrelated to ESKD but secondary to infection or extrarenal manifestation. This highlights the importance of ensuring a delicate balance in immunosuppression associated with inadequate disease control and fatal infective complications. Notwithstanding, patients reaching ESKD are at higher risk of death,[3] emphasizing the importance of slowing kidney progression by effective immunosuppressive treatments.

The renal outcomes in this cohort were promising, with 5.4% and 3.3% children developed advanced CKD and ESKD, respectively. There is little information on the prevalence rate of CKD among patients with cLN. In the UK Juvenile-onset Systemic Lupus Erythematosus (JSLE) Cohort study, 3.8% of 399 children

Table 4. Incidence and onset time for complications in 92 patients with childhood-onset lupus nephritis

Adverse events	**Incidence, *n* (%)**	**Median onset time (interquartile range), yr**
Infections		
Early (< 1 yr), episodes per 100 patient-yrs	5.5	0.14 (0.13–0.19)
Late (>1 yr), episodes per 100 patient-yrs	2.6	6.1 (4.5–9.3)
Hypertension	16 (17.4)	5.9 (0.7–11.7)
Diabetes mellitus	9 (0)	-
Cardiovascular disease[a]	2 (2.2)	10.4
Malignancy	1 (1.1)	30.0
Short stature	13 (14.1)	-
Decreased bone mineral density	17[b] (32.1)	2.3 (1.0–4.7)
Avascular necrosis	6 (6.5)	2.7 (1.8–3.6)

[a]One patient had dilated cardiomyopathy and another had pulmonary hypertension.
[b]53 patients performed dual energy X-ray absorptiometry scan.

Table 5. Details of infections requiring hospitalization

Infective episodes	**Number**
Upper respiratory infection[a]	6
Herpes zoster[b]	5
Gastroenteritis	3
Bacteremia	2
Cutaneous infection	2
Pneumonia	1
Citrobacter peritonitis	1
Opportunistic infection	
Cytomegalovirus pneumonitis[c]	1
Pneumocystis Jiroveci pneumonia[c]	1
Tuberculosis meningitis	1
Talaromycosis[c]	1
Others[d]	3

[a]Three patients had influenza infections.
[b]One patient had disseminated herpes zoster.
[c]One patient with end-stage kidney disease on maintenance dialysis.
[d]One patient had herpes simplex stomatitis, and another had 2 episodes of clinical sepsis.

developed CKD stage 2 to 5 and only 1.5% patients had advanced CKD.[5] In contrast, 11% of Turkish children and 6.7% of adults with LN developed advanced CKD.[8,30] The rates of ESKD in cLN vary considerably between centers, ranging from 1% to 14%.[7,8,10,11,13] These depend on treatment eras, follow-up duration, referral threshold, and patient factors such as ethnicity.

In this study, severe presentation, remission status at 1 year, and renal relapse were independent predictors of renal outcomes. It is not unanticipated to observe that renal impairment and need for acute KRT at presentation, both being indicators for severe nephritis, are strong predictors of poor long-term renal outcomes. Indeed, the favorable long-term outcomes in our cohort are contributed by the higher remission rate (CR and PR rates of 86%) compared with other pediatric cohorts,[6,8] which mirrors the satisfactory response to immunosuppression described among East Asian Children and Chinese adult patients with LN.[6,31] On the contrary, children who failed to respond to immunosuppression had an 8-fold risk of developing advanced CKD or ESKD, or death, likely because of ongoing inflammation and consequently multiorgan damage. In concurrence with our data, the benefits of standard therapies have plateaued over the past 2 decades.[26,32] The use of rituximab in LN remains controversial as compared with other pediatric glomerular conditions.[33–36] Newly approved treatments for LN such as belimumab and voclosporin may offer new hope to managing cLN. Unfortunately, none of these recent clinical trials have involved children with severe LN, and this calls for initiatives to involve pediatric populations in future drug development programs.

Renal relapse is associated with cumulative kidney damage and is prevalent among adolescent patients with LN.[9] Our data showed that each episode of kidney flare would double the risk of developing adverse outcomes and that all 3 patients who reached ESKD experienced renal relapse. Importantly, 60% of our patients did not experience any kidney flare throughout the 10-year observation period. In comparison, only 40% children remained in stable remission after 24 months of follow-up in a large international pediatric cohort.[6] We postulate that the policy of very long-term, low-dose immunosuppression and cautious withdrawal in selected patients may account for the low relapse rate. In addition, our data showed that medication nonadherence was associated with adverse long-term prognosis. Only 16% of our patients had nonadherence issue, compared with 64% among adult patients with LN,[37] likely attributed to active family involvement and the regular adherence check and drug counseling during clinic visits. Both long-term immunosuppression therapy and favorable medication adherence effectively prevent disease relapses and in turn improve treatment outcomes.

The use of intense or prolonged immunosuppression should be justified and is associated with treatment-associated complications, such as life-threatening infections, cardiovascular disease, infertility, short stature, avascular necrosis, and malignancy.[38] These data are extremely limited in children. In our study, infection was the most common complication but was only found in 16% of patients, compared with a German pediatric cohort among whom 23% developed infection.[14] Infections requiring hospitalization were mostly mild to moderate; however, lethal and opportunistic infections did occur, especially among those with CKD. This underscores the importance of judicious use of immunosuppression and appropriate prophylaxis for infections. Although a significant proportion of patients developed steroid toxicity including short stature (14%), osteopenia (32%), and avascular necrosis (7%), similar incidence (growth failure, 16%; osteopenia, 41%; avascular necrosis, 10.2%) was reported in other pediatric cohorts.[38,39] Although studies in other ethnic groups of childhood-onset SLE have reported increased cardiovascular events in children,[7] this was not observed in our cohort. The patient with bilateral renal cell carcinoma was likely attributed to acquired cystic kidney disease after reaching ESKD[40,41] and was not related to prior cytotoxic exposures.

One limitation of this study is the changing choice of immunosuppressants throughout different treatment eras, which may confound the long-term outcomes. Furthermore, our study is not designed to evaluate the treatment effect of immunosuppressive therapy because of possible indication bias. Nonadherence to medication is self-reported and could be underreported in this context. Similarly, complications such as avascular necrosis may also be underreported because investigations were only offered if clinically indicated. Our study was performed in a single center, which may limit its generalizability. In particular, all our patients were Chinese, where ethnicity impact on treatment outcomes and East Asian children were reported to have superior remission rates than patients of other ethnicities.[6] Nevertheless, our study includes a relatively large pediatric cohort with a long observation period, with minimal loss to follow-up and missing data. Thus, our cohort represents real-world data on the important long-term outcomes of cLN.

In conclusion, children with LN show fairly promising long-term patient and renal survival rates when treated with long-term effective immunosuppression and measures to ensure medication adherence. Predictors for poor outcomes include severe nephritis at presentation, suboptimal treatment response, and

kidney flares. Significant complications, especially infections and steroid toxicities, can occur in a subset of patients but are comparable to other pediatric cohorts.

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

EY-hC and DY-hY designed the study, drafted the manuscript, and were responsible for the data integrity and analysis results. WH-sW and W-tW provided statistical support and critically reviewed the manuscript. All authors provided significant inputs for data collection, intellectual content, results interpretation, and manuscript development and final approval.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Statement.

REFERENCES

1. Hersh AO, von Scheven E, Yazdany J, et al. Differences in long-term disease activity and treatment of adult patients with childhood- and adult-onset systemic lupus erythematosus. *Arthritis Rheum*. 2009;61:13–20. https://doi.org/10.1002/art.24091
2. Wenderfer SE, Chang JC, Davies AG, et al. Using a multi-institutional pediatric learning health system to identify systemic lupus erythematosus and lupus nephritis: development and validation of computable phenotypes. *Clin J Am Soc Nephrol*. 2022;17:65–74. https://doi.org/10.2215/CJN.07810621
3. Yap DY, Tang CS, Ma MK, et al. Survival analysis and causes of mortality in patients with lupus nephritis. *Nephrol Dial Transplant*. 2012;27:3248–3254. https://doi.org/10.1093/ndt/gfs073
4. Chan EYH, Yap DYH, Wong WHS, et al. Demographics and long-term outcomes of children with end-stage kidney disease: a 20-year territory-wide study. *Nephrol (Carlton)*. 2022;27:171–180. https://doi.org/10.1111/nep.14007
5. Oni L, Wright RD, Marks S, et al. Kidney outcomes for children with lupus nephritis. *Pediatr Nephrol*. 2021;36:1377–1385. https://doi.org/10.1007/s00467-020-04686-1
6. De Mutiis C, Wenderfer SE, Orjuela A, et al. Defining renal remission in an international cohort of 248 children and adolescents with lupus nephritis. *Rheumatol (Oxf Engl)*. 2021;61:2563–2571. https://doi.org/10.1093/rheumatology/keab746
7. Groot N, Shaikhani D, Teng Y, et al. Long-term clinical outcomes in a cohort of adults with childhood-onset systemic lupus erythematosus. *Arthritis Rheumatol*. 2019;71:290–301. https://doi.org/10.1002/art.40697
8. Demir S, Gülhan B, Özen S, et al. Long-term renal survival of paediatric patients with lupus nephritis. *Nephrol Dial Transplant*. 2021;37:1069–1077. https://doi.org/10.1093/ndt/gfab152
9. Qiu S, Zhang H, Yu S, et al. Clinical manifestations, prognosis, and treat-to-target assessment of pediatric lupus nephritis. *Pediatr Nephrol*. 2022;37:367–376. https://doi.org/10.1007/s00467-021-05164-y
10. Wong S-N, Tse K-C, Lee T-L, et al. Lupus nephritis in Chinese children–a territory-wide cohort study in Hong Kong. *Pediatr Nephrol*. 2006;21:1104–1112. https://doi.org/10.1007/s00467-006-0052-3
11. Hari P, Bagga A, Mahajan P, Dinda A. Outcome of lupus nephritis in Indian children. *Lupus*. 2009;18:348–354. https://doi.org/10.1177/0961203308097570
12. Srivastava P, Abujam B, Misra R, et al. Outcome of lupus nephritis in childhood onset SLE in North and Central India: single-centre experience over 25 years. *Lupus*. 2016;25:547–557. https://doi.org/10.1177/0961203315619031
13. Vachvanichsanong P, Dissaneewate P, McNeil E. Diffuse proliferative glomerulonephritis does not determine the worst outcome in childhood-onset lupus nephritis: a 23-year experience in a single centre. *Nephrol Dial Transplant*. 2009;24:2729–2734. https://doi.org/10.1093/ndt/gfp173
14. Suhlrie A, Hennies I, Gellermann J, et al. Twelve-month outcome in juvenile proliferative lupus nephritis: results of the German registry study. *Pediatr Nephrol*. 2020;35:1235–1246. https://doi.org/10.1007/s00467-020-04501-x
15. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982;25:1271–1277. https://doi.org/10.1002/art.1780251101
16. Weening JJ, D'agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int*. 2004;65:521–530. https://doi.org/10.1111/j.1523-1755.2004.00443.x
17. Markowitz GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. *Kidney Int*. 2007;71:491–495. https://doi.org/10.1038/sj.ki.5002118
18. Rovin BH, Adler SG, Barratt J. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100:S1–S276. https://doi.org/10.1016/j.kint.2021.05.021
19. Costedoat-Chalumeau N, Tamirou F, Piette J-C. Treatment adherence in systemic lupus erythematosus and rheumatoid arthritis: time to focus on this important issue. *Rheumatol (Oxf Engl)*. 2018;57:1507–1509. https://doi.org/10.1093/rheumatology/kex337
20. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20:629–637. https://doi.org/10.1681/ASN.2008030287
21. Miller WG, Kaufman HW, Levey AS, et al. National Kidney Foundation Laboratory Engagement Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimated glomerular filtration rate: practical guidance for clinical laboratories. *Clin Chem*. 2022;68:511–520. https://doi.org/10.1093/clinchem/hvab278
22. Yap DY, Tang C, Ma MK, et al. Longterm data on disease flares in patients with proliferative lupus nephritis in recent years. *J Rheumatol*. 2017;44:1375–1383. https://doi.org/10.3899/jrheum.170226
23. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140:e20171904. https://doi.org/10.1542/peds.2017-1904
24. Leung S. Standards for the anthropometric assessment of nutritional status of Hong Kong children. *HK J Paediatr*. 1995;12:5–15.

25. Lewiecki EM, Binkley N, Morgan SL, et al. Best practices for dual-energy X-ray absorptiometry measurement and reporting: International Society for Clinical Densitometry Guidance. *J Clin Densitom*. 2016;19:127–140. https://doi.org/10.1016/j.jocd.2016.03.003
26. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015: a systematic review and Bayesian meta-analysis. *Arthritis Rheumatol*. 2016;68:1432–1441. https://doi.org/10.1002/art.39594
27. Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. *Am J Kidney Dis*. 2000;35:904–914. https://doi.org/10.1016/s0272-6386(00)70262-9
28. Ichinose K, Kitamura M, Sato S, et al. Factors predictive of long-term mortality in lupus nephritis: a multicenter retrospective study of a Japanese cohort. *Lupus*. 2019;28:295–303. https://doi.org/10.1177/0961203319826690
29. Zheng Z, Zhang L, Liu W, et al. Predictors of survival in Chinese patients with lupus nephritis. *Lupus*. 2012;21:1049–1056. https://doi.org/10.1177/0961203312445230
30. Mageau A, Timsit J-F, Perrozziello A, et al. The burden of chronic kidney disease in systemic lupus erythematosus: a nationwide epidemiologic study. *Autoimmun Rev*. 2019;18:733–737. https://doi.org/10.1016/j.autrev.2019.05.011
31. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Eng J Med*. 2000;343:1156–1162. https://doi.org/10.1056/NEJM200010193431604
32. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol*. 2009;20:1103–1112. https://doi.org/10.1681/ASN.2008101028
33. Chan EY, Yu ELM, Angeletti A, et al. Long-term efficacy and safety of repeated rituximab to maintain remission in idiopathic childhood nephrotic syndrome: an international study. *J Am Soc Nephrol*. 2022;33:1193–1207. https://doi.org/10.1681/ASN.2021111472
34. Chan EY-h, Tullus K. Rituximab in children with steroid sensitive nephrotic syndrome: in quest of the optimal regimen. *Pediatr Nephrol*. 2021;36:1397–1405. https://doi.org/10.1007/s00467-020-04609-0
35. Marlais M, Wlodkowski T, Printza N, et al. Clinical factors and adverse kidney outcomes in children with antineutrophil cytoplasmic antibody-associated glomerulonephritis. *Am J Kidney Dis*. 2022. https://doi.org/10.1053/j.ajkd.2022.05.013. Published online July 8.
36. Chan EY, Webb H, Yu E, et al. Both the rituximab dose and maintenance immunosuppression in steroid-dependent/frequently relapsing nephrotic syndrome have important effects on outcomes. *Kidney Int*. 2020;97:393–401. https://doi.org/10.1016/j.kint.2019.09.033
37. Prados-Moreno S, Sabio JM, Pérez-Mármol JM, Navarrete-Navarrete N, Peralta-Ramírez MI. Adherence to treatment in patients with systemic lupus erythematosus. *Med Clin (Barc)*. 2018;150:8–15. https://doi.org/10.1016/j.medcli.2017.05.035
38. Sit JK, Chan WK. Risk factors for damage in childhood-onset systemic lupus erythematosus in Asians: a case control study. *Pediatr Rheumatol Online J*. 2018;16:1–11. https://doi.org/10.1186/s12969-018-0271-8
39. Lilleby V, Lien G, Frey Frøslie K, et al. Frequency of osteopenia in children and young adults with childhood-onset systemic lupus erythematosus. *Arthritis Rheum*. 2005;52:2051–2059. https://doi.org/10.1002/art.21115
40. Chan EY, Warady BA. Acquired cystic kidney disease: an under-recognized condition in children with end-stage renal disease. *Pediatr Nephrol*. 2018;33:41–51. https://doi.org/10.1007/s00467-017-3649-9
41. Chan EYH, Warady BA. Acquired cystic kidney disease. In: Warady BA, Schaefer F, Alexander SR, eds. *Pediatric Dialysis Case Studies*. Springer; 2017:335–341.