

# Assessing kidney outcomes in childhood-onset lupus nephritis: role of National Institutes of Health-modified histological indices

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**Background:** Childhood-onset lupus nephritis (cLN) is an aggressive disease. Although histological class has historically guided its treatment, its prognostic value remains limited. Although the National Institutes of Health (NIH)-modified activity index (AI) and chronicity index (CI) incorporate glomerular and tubulointerstitial changes and may provide better prognostic insight, their utility in cLN is not well established.

**Purpose:** Here we aimed to assess the utility of the NIH-modified AI and CI for predicting kidney outcomes and identify histopathological features and treatment-related factors associated with the development of kidney function impairment in cLN.

**Methods:** We retrospectively analyzed 60 children with biopsy-proven proliferative lupus nephritis. Their baseline clinical and histological features, treatments, and outcomes were assessed. The association between AI and CI scores, along with individual histological components, and kidney function impairment, defined as an estimated glomerular filtration rate < 90 mL/min/1.73 m<sup>2</sup> sustained for ≥3 months, was evaluated.

**Results:** Over a median follow-up of 55.5 months, 30% of patients developed kidney function impairment. AI scores and glomerular lesions did not differ significantly between patients with and without kidney function impairment. However, the CI scores were significantly higher in patients who developed kidney function impairment, with tubular atrophy and interstitial fibrosis being the most predictive components. On a multivariate analysis, tubular atrophy was an independent predictor of kidney function impairment (hazard ratio [HR], 17.74; 95% confidence interval [CI], 1.94–162.5;  $P=0.01$ ). Use of mycophenolate mofetil (MMF) as maintenance therapy was associated with a reduced risk of kidney function impairment (HR, 0.09; 95% CI, 0.02–0.47;  $P=0.003$ ).

**Conclusion:** Chronic tubulointerstitial changes, particularly tubular atrophy, are a stronger predictor of long-term kidney function than glomerular findings or AI scores. These findings highlight the prognostic value of NIH-modified CI and the importance of MMF in maintenance therapy. The early identification of chronic lesions on biopsy may guide therapeutic decisions aimed at preserving kidney function and improving long-term outcomes in patients with cLN.

**Key words:** Chronicity index, Kidney failure, Lupus nephritis, Mycophenolic acid, Tubulointerstitial fibrosis

## Key message

**Question:** In children with proliferative lupus nephritis, do National Institutes of Health-modified indices and treatment choices predict long-term kidney function?

**Finding:** Higher chronicity index scores, especially tubular atrophy and interstitial fibrosis, predicted kidney impairment. Additionally, the use of mycophenolate mofetil (MMF) for maintenance therapy was associated with a lower risk of kidney function decline.

**Meaning:** The early recognition of chronic lesions and MMF-based maintenance therapy may improve kidney outcomes in childhood-onset lupus nephritis.

## Introduction

Systemic lupus erythematosus (SLE) is a chronic, life-threatening autoimmune disease characterized by systemic inflammation and the production of pathogenic autoantibodies, leading to multisystem organ involvement. Approximately one in 5 patients with SLE experience disease onset before the age of 18 years, a form referred to

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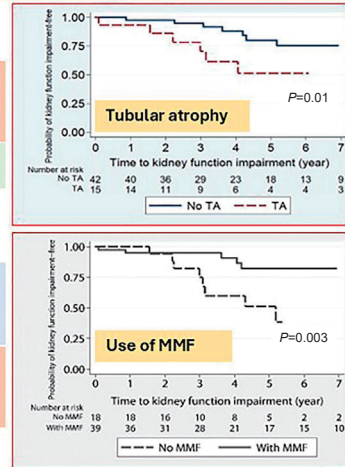
**60 Children with  
proliferative lupus nephritis**

**Median follow-up - 55.5 months**



**18 Patients (30%) developed  
kidney function impairment**

**Risk factor – Tubular atrophy  
Protective factor – Use of MMF**



**Graphic abstract.** Overview of study design and results. NIH, National Institutes of Health; MMF, mycophenolate mofetil; TA, tubular atrophy.

as childhood-onset SLE.<sup>1,2</sup> Compared to adults, children with SLE often exhibit a more severe disease course, with increased morbidity and mortality.<sup>3,4</sup>

Among the various manifestations of SLE, lupus nephritis (LN)—an immune complex-mediated glomerulonephritis—represents one of the most serious complications. LN affects 60%–80% of children with SLE, with a predominance of proliferative forms (class III/IV/mixed).<sup>5</sup> Proliferative LN is a leading cause of chronic kidney disease (CKD) in the pediatric population.<sup>6</sup> Early identification of patients at risk for adverse kidney outcomes is essential for tailoring therapeutic interventions and improving long-term prognosis.

Kidney biopsy remains the definitive method for diagnosing and classifying LN, providing essential histopathological information to guide treatment decisions. The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system primarily focuses on glomerular involvement. The ISN/RPS classification does not fully capture the spectrum of histological changes, particularly tubulointerstitial and vascular lesions.<sup>7</sup> To address this limitation, the National Institutes of Health (NIH) proposed a semiquantitative scoring system incorporating an activity index (AI) and a chronicity index (CI), which evaluates the extent of active inflammation and chronic, irreversible damage, respectively.<sup>8</sup> A modified version of this scoring system further refines the assessment by including detailed evaluation of glomerular, tubular, and interstitial components.<sup>9</sup>

Although the prognostic utility of the NIH-modified indices has been demonstrated in adult patients with LN,<sup>10-12</sup>

evidence supporting their application in pediatric populations remains limited.<sup>13</sup> In children, disease chronicity and regenerative capacity may differ from adults, potentially altering the relationship between histological findings and long-term outcomes. Elucidating the predictive value of AI and CI in childhood-onset LN (cLN) could therefore enhance risk stratification and inform more effective treatment strategies for this population.

The objective of this study was to assess the clinical utility of the NIH-modified AI and CI in predicting kidney outcomes in children with biopsy-confirmed proliferative LN. Additionally, we aimed to identify specific histopathological features and treatment-related factors associated with the development of kidney function impairment in cLN.

## Methods

### 1. Study design and population

This retrospective cohort study was conducted at a single university-affiliated tertiary care center. Medical records of patients under 18 years of age who had biopsy-confirmed LN between 2018 and 2024 were reviewed. This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (No. 0753/64).

Inclusion criteria were as follows: (1) histological diagnosis of LN class III, IV, or mixed class (III+V or IV+V); (2) kidney biopsy specimen containing at least 10 glomeruli; and (3) a minimum follow-up duration of 1-year postbiopsy.

## 2. Clinical and laboratory assessment

Demographic, clinical, and laboratory data were collected from the time of kidney biopsy through the last follow-up visit. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K).<sup>14</sup> Hypertension was defined as systolic and/or diastolic blood pressure  $\geq$  the 95th percentile for age, sex, and height or the use of antihypertensive medication.<sup>15</sup> Hematuria was defined as the presence of  $>5$  red blood cells per high-power field and/or erythrocyte casts in the urine.<sup>16</sup> Proteinuria was quantified using the urine protein-to-creatinine ratio (UPCR), with values  $>0.5$  mg/mg considered abnormal.<sup>5</sup> Nephrotic syndrome was defined as UPCR  $>2.0$  mg/mg in the presence of hypoalbuminemia.<sup>5</sup>

Acute kidney injury (AKI) was classified based on the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines.<sup>17</sup> Baseline serum creatinine was defined as the lowest recorded value within 3 months prior to presentation.<sup>18</sup> For patients lacking baseline measurements, estimated baseline creatinine was calculated using the Hoste equation.<sup>19</sup>

For CKD evaluation, estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula for patients  $\leq 18$  years old<sup>20</sup> and the CKD-EPI (epidemiology collaboration) creatinine equation for those  $>18$  years.<sup>21</sup> The most recent serum creatinine values were used for evaluating long-term kidney function.

## 3. Histopathological assessment

Histopathological evaluations of kidney biopsy specimens were conducted by certified renal pathologists at the institution. Kidney biopsies were analyzed using light microscopy, immunofluorescence, and electron microscopy. All specimens were classified according to the 2003 ISN/RPS classification for LN.<sup>7</sup> The modified NIH indices were calculated using a semiquantitative scoring system as previously described.<sup>8</sup>

The AI includes 6 components: endocapillary hypercellularity, neutrophil infiltration/karyorrhexis, fibrinoid necrosis, hyaline deposits, cellular/fibrocellular crescents, and interstitial inflammation. Each component is scored from 0 to 3 based on lesion extent, with fibrinoid necrosis and crescents weighted by a factor of two, yielding a total AI ranging from 0 to 24. The CI includes 4 components: total glomerulosclerosis, fibrous crescents, tubular atrophy (TA), and interstitial fibrosis. Each is scored on a 0–3 scale, yielding a total CI ranging from 0 to 12.

## 4. Treatment regimen

Treatment strategies were individualized based on clinical presentation and histologic classification. All patients

received induction therapy consisting of high-dose corticosteroids, either 3 pulses of intravenous methylprednisolone (30 mg/kg/dose, maximum 1,000 mg) or high-dose oral prednisolone (2 mg/kg/day, maximum 60 mg/day), followed by a tapering schedule.

All patients also received adjunctive immunosuppressive therapy with either intravenous cyclophosphamide or oral mycophenolate mofetil. The choice of immunosuppressive agent, as well as the use of adjunct therapies such as antimalarial drugs or renin-angiotensin-aldosterone system inhibitors, was at the discretion of the treating physician.

Patients were monitored monthly during the first month, every 2–3 months during the first year, and every 3–4 months thereafter. At each visit, clinical, laboratory, and treatment data were documented.

## 5. Outcome definitions

Patients were followed until transfer to adult care, death, or December 2024. The primary outcome was progression to kidney function impairment, defined as a sustained eGFR  $<90$  mL/min/1.73 m<sup>2</sup> for at least 3 months, confirmed by 2 or more measurements.<sup>22</sup>

Complete remission (CR) was defined as a reduction in UPCR to  $<0.5$  mg/mg accompanied by stable or improved kidney function (within  $\pm 10\%$ – $15\%$  of baseline). Partial remission (PR) was defined as a  $\geq 50\%$  reduction in proteinuria to  $<3$  mg/mg, with stable or improved kidney function.<sup>23</sup> The response to initial induction treatment was assessed based on the remission status at the end of the induction phase.

## 6. Statistical analysis

Data analyses were performed using Stata 14 (StataCorp., TX). A 2-sided  $P < 0.05$  was considered statistically significant. Continuous variables were summarized as medians with interquartile ranges, and group comparisons were conducted using the Mann-Whitney  $U$  test. Categorical variables were compared using either the chi-squared test or Fisher exact test, as appropriate.

Kaplan-Meier curves were generated to estimate the time to kidney function impairment, with subgroup differences assessed using the log-rank test. Cox proportional hazards regression was used to identify predictors of kidney function impairment, and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Variables significantly associated with kidney function impairment in univariate analysis, along with clinically relevant covariates reflecting disease severity (e.g., histologic class IV, eGFR at kidney biopsy, AKI at biopsy, and interstitial fibrosis), were simultaneously entered into the multivariable model. This approach was chosen to reduce residual confounding and address potential treatment

allocation bias, particularly the concern that MMF may have been preferentially prescribed to patients with milder disease.

Remission status was not included in the multivariable analysis due to definitional overlap. In patients with previously normal kidney function, failure of eGFR to return to baseline was a criterion for both kidney function impairment and non-CR, resulting in a high correlation between these variables. This dependency precluded the use of CR as an independent predictor of kidney function impairment. Model fit was assessed using likelihood ratio chi-square tests, and interaction terms were examined to evaluate potential effect modification.

## Results

### 1. Patient characteristics at kidney biopsy

A total of 60 patients were included in the study, of whom 52 (86.7%) were female. All clinical and laboratory variables at kidney biopsy were available for all patients, with no missing data (Table 1).

The median age at kidney biopsy was 12.7 years (10.8–14.0). The median interval from the diagnosis of LN to kidney biopsy was 30 (19–90) days, and the SLEDAI-2K score was 16 (13.5–20). The median levels of serum C3 and C4 were 41 (30–62) and 7.4 (4.0–10.8) mg/dL, respectively.

The median serum creatinine level was 0.7 (0.6–1.1) mg/dL, and the eGFR was 89 (49–110) mL/min/1.73 m<sup>2</sup>.

AKI was present in 24 patients (40%). All patients had proteinuria, with a median UPCR of 4.1 (2.1–7.0) mg/mg of creatinine. Nephrotic syndrome was present in 25 patients (41.7%). Hematuria was noted in 42 patients (70.0%), and hypertension was observed in 40 patients (66.7%).

### 2. Histological findings

Histological findings of kidney biopsy are presented in Table 2. The median number of glomeruli per biopsy was 28 (18–36). Pure proliferative LN (class III or IV) was identified in 47 patients (78.3%). The median AI was 3 (2–7). The most frequent AI component was endocapillary hypercellularity (51 patients, 85.0%), followed by cellular/fibrocellular crescents (30 patients, 50.0%). Interstitial inflammation was observed in 25 patients (41.7%).

The median CI was 1 (0–2.5). Glomerulosclerosis was the most common chronic lesion, found in 32 patients (53.3%). TA and interstitial fibrosis were noted in 18 patients (30.0%) and 13 patients (21.7%), respectively, and predominantly mild in severity.

### 3. Therapeutic data

Therapeutic regimens are summarized in Table 3. Hydroxychloroquine was administered to all patients. All patients received corticosteroids for induction, including pulse methylprednisolone in 26 patients (43.3%) and oral prednisolone in the remaining cases. Adjuvant induction immunosuppressive therapy included cyclophosphamide in 34 patients (56.7%) and mycophenolate mofetil in 26

**Table 1. Clinical characteristics of renal biopsies collected from patients with childhood-onset lupus nephritis**

Characteristics	Total (N=60)	KFI (N=18, 30%)	No-KFI (N=42, 70%)	P value
Female sex	52 (86.7)	16 (88.9)	36 (85.7)	0.55
Age (yr)	12.7 (10.8–14.0)	12.4 (10.6–13.8)	12.7 (11.0–14.0)	0.52
Time from LN to kidney biopsy (day)	30 (19–90)	38 (10–188)	30.5 (21–77)	0.87
SLEDAI-2K	16 (13.5–20.0)	16 (14–19)	16.5 (12–21)	0.76
Serum C3 (mg/dL)	41 (30–62)	38 (27–62)	44 (30–65)	0.37
Serum C4 (mg/dL)	7.4 (4.0–10.8)	5.0 (4.0–9.6)	8.0 (3.7–12.1)	0.20
Anti-dsDNA positivity	46 (76.7)	14 (77.8)	32 (76.2)	0.71
Hemoglobin (g/dL)	10.3 (8.7–11.5)	9.7 (8.7–11.7)	10.3 (8.7–11.3)	0.79
White blood cell count ( $\times 10^3/\text{mm}^3$ )	7.3 (4.4–12.0)	7.3 (5.3–10.9)	7.3 (4.2–12.2)	0.91
Platelet count ( $\times 10^3/\text{mm}^3$ )	287 (162–336)	261 (142–322)	287 (178–352)	0.52
Serum creatinine (mg/dL)	0.7 (0.6–1.1)	0.7 (0.6–1.5)	0.7 (0.5–0.8)	0.06
eGFR (mL/min/1.73 m <sup>2</sup> )	89 (49–110)	76 (43–95)	98 (69–119)	<b>0.03</b>
AKI	24 (40.0)	11 (61.1)	13 (31.0)	<b>0.03</b>
Serum albumin (g/dL)	3.0 (2.4–3.2)	3.1 (2.5–3.4)	2.9 (2.2–3.2)	0.28
UPCR (mg/mg of creatinine)	4.1 (2.1–7.0)	4.2 (2.2–5.7)	4.1 (2.0–7.1)	0.91
Nephrotic syndrome	25 (41.7)	7 (38.9)	18 (42.9)	0.78
Hematuria	42 (70.0)	13 (72.2)	29 (69.0)	1.00
Hypertension	40 (66.7)	13 (72.2)	27 (64.3)	0.55

Values are presented as number (%) or median (interquartile range).

KFI, kidney function impairment; LN, lupus nephritis; C3, complement C3; C4, complement C4; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index 2000; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; UPCR, urine protein-to-creatinine ratio.

Boldface indicates a statistically significant difference with  $P < 0.05$ .

(43.3%).

Four patients (6.7%) received only low-dose prednisolone as maintenance therapy. Maintenance therapy consisted of low-dose prednisolone in combination with cyclophosphamide, mycophenolate, or cyclosporine in 56 patients (93.3%). Renin-angiotensin-aldosterone system inhibitors were also prescribed in 56 patients (93.3%).

#### 4. Clinical outcomes

At last follow-up, the median patient age was 17.0 (15.8–19.3) years. Over a median follow-up period of 55.5 (36.1–75.3) months, 18 patients (30%) developed kidney function impairment, distributed across CKD stages 2 (n=9), 3 (n=3), 4 (n=3), and 5 (n=3). Three patients had kidney function impairment at the time of biopsy and did not experience recovery of kidney function. The Kaplan-Meier curve for kidney function impairment is shown in Fig. 1A. The

**Table 2. Histological findings of patients with childhood-onset lupus nephritis**

Findings	Total (N=60)	KFI (N=18, 30%)	No-KFI (N =42, 70%)	P value
No. of glomeruli	28 (18–36)	28 (22–30)	28 (18–42)	0.67
Histologic class				0.16
III	19 (31.7)	8 (44.4)	11 (26.2)	
IV	28 (46.7)	9 (50.0)	19 (45.2)	
Mixed (III+V/IV+V)	13 (21.7)	1 (5.6)	12 (28.6)	
Activity index	3 (2–7)	3.5 (1–10)	3 (2–7)	0.97
Endocapillary hypercellularity <sup>a)</sup>	51 (85.0)	14 (77.8)	37 (88.1)	0.43
Neutrophil infiltration <sup>a)</sup>	26 (43.3)	6 (33.3)	20 (47.6)	0.31
Hyaline deposits <sup>a)</sup>	16 (26.7)	6 (33.3)	10 (23.8)	0.45
Cellular/fibrocellular crescents <sup>a)</sup>	30 (50.0)	9 (50.0)	21 (50.0)	1.00
Fibrinoid necrosis <sup>a)</sup>	6 (10.0)	2 (11.1)	4 (9.5)	1.00
Interstitial inflammation <sup>a)</sup>	25 (41.7)	10 (55.6)	15 (35.7)	0.17
Chronicity index	1 (0–2.5)	3 (1–4)	1 (0–1)	<b>&lt;0.001</b>
Glomerulosclerosis <sup>a)</sup>	32 (53.3)	13 (72.2)	19 (45.2)	0.09
Fibrous crescents <sup>a)</sup>	11 (18.3)	5 (27.8)	6 (14.3)	0.28
Tubular atrophy <sup>a)</sup>	18 (30.0)	11 (61.1)	7 (16.7)	<b>0.001</b>
Mild	16	9	7	
Moderate	1	1	0	
Severe	1	1	0	
Interstitial fibrosis <sup>a)</sup>	13 (21.7)	9 (50.0)	4 (9.5)	<b>0.001</b>
Mild	11	7	4	
Moderate	1	1	0	
Severe	1	1	0	

Values are presented as median (interquartile range) or number (%).

KFI, kidney function impairment.

<sup>a)</sup>Variables were categorized as absent or present.

Boldface indicates a statistically significant difference with  $P < 0.05$ .

**Table 3. Therapeutic data of patients with childhood-onset lupus nephritis**

Variable	Total (N=60)	KFI (N=18, 30%)	No-KFI (N =42, 70%)	P value
RAASi	56 (93.3)	17 (94.4)	39 (92.9)	1.00
Induction corticosteroids				0.09
Pulse methylprednisolone	26 (43.3)	11 (61.1)	15 (35.7)	
Oral prednisolone	34 (56.7)	7 (38.9)	27 (64.30)	
Induction immunosuppressants				0.16
Cyclophosphamide	34 (56.7)	13 (72.2)	21 (50.0)	
Mycophenolate	26 (43.3)	5 (27.8)	21 (50.0)	
Maintenance immunosuppressants				
Cyclophosphamide	23 (38.3)	10 (55.6)	13 (31.0)	0.07
Mycophenolate	40 (66.7)	8 (44.4)	32 (76.2)	<b>0.02</b>
Cyclosporine	11 (18.3)	6 (33.3)	5 (11.9)	0.07

Values are presented as number (%).

KFI, kidney function impairment; RAASi, renin-angiotensin-aldosterone system inhibitor.

Boldface indicates a statistically significant difference with  $P < 0.05$ .

kidney function impairment-free survival rates (95% CI) at 1, 3, and 5 years were 91.6% (81.0%–96.4%), 83.7% (70.9%–91.2%), and 68.0% (51.9%–79.7%), respectively. Four patients (6.7%) died during follow-up; all had developed kidney function impairment.

CR was achieved in 51 patients (85.0%) at a median of 9.2 (4.7–21.5) months. Of these, 23 (38.3%) achieved CR within 6 months and 14 (23.3%) between 6 and 12 months. Among the 9 patients who did not achieve CR, 4 achieved PR. The Kaplan-Meier curve for CR is presented in Fig. 2. The CR rates (95% CI) at 6 and 12 months were 38.3% (27.4%–51.8%) and 61.7% (49.7%–73.8%), respectively.

### 5. Factors associated with kidney function impairment

Baseline clinical characteristics—including sex, age, time from LN diagnosis to biopsy, SLEDAI score, complement levels (C3, C4), anti-dsDNA positivity, serum albumin, proteinuria, hematuria, hypertension, hemoglobin, white blood cell count, and platelet count—did not differ significantly between patients with and without kidney function impairment (Table 1). However, patients who developed kidney function impairment had significantly lower eGFR at baseline ( $67.6 \pm 32.5$  vs.  $92.3 \pm 44.8$  mL/min/1.73 m<sup>2</sup>,  $P=0.04$ ) and a higher incidence of AKI at biopsy (61.1% vs. 31.0%,  $P=0.03$ ).

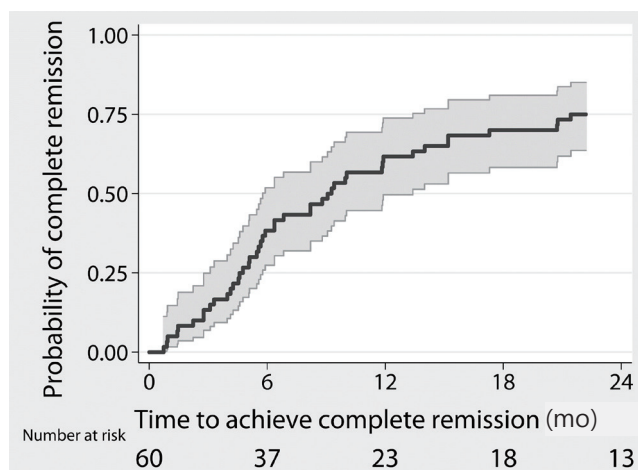
The histological class did not differ significantly between groups. After reclassifying mixed classes III+V as class III and IV+V as class IV, the proportion of patients who developed kidney function impairment did not differ significantly between class III (25.0%,  $n=9/36$ ) and class IV (37.5%,  $n=9/24$ ) ( $P=0.30$ ). However, CR at the end of induction therapy was significantly more frequent in class III (50.0%,  $n=18/36$ ) than class IV (37.5%,  $n=9/24$ ) ( $P=0.02$ ).

The number of glomeruli and AI were similar between groups, and no AI component was significantly associated with kidney function impairment. In contrast, the CI was significantly higher in patients who developed kidney function impairment (median 3 [1–4] vs. 1 [0–1],  $P<0.001$ ), with TA and interstitial fibrosis being the most strongly

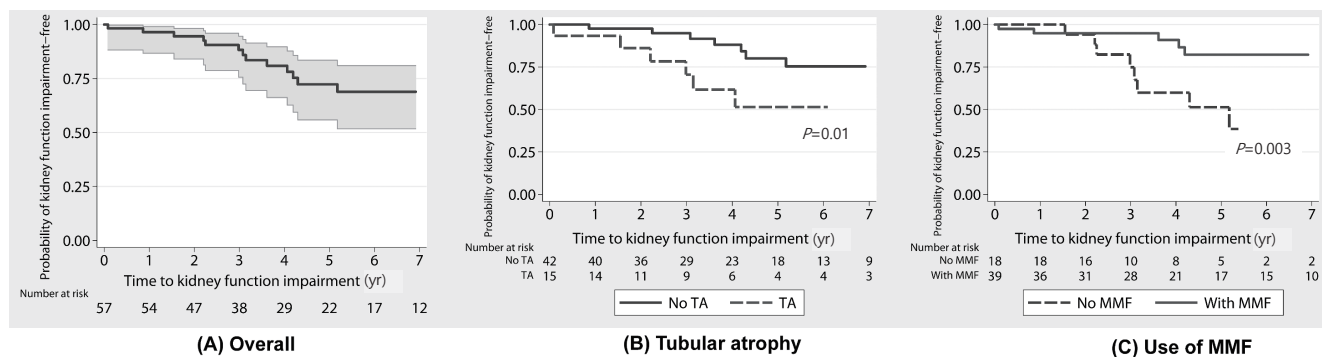
associated components (Table 2).

No significant differences were observed in induction therapy between groups. However, use of MMF for maintenance therapy was significantly lower among those who developed kidney function impairment (44.4% vs. 76.2%,  $P=0.02$ ) (Table 3). To address potential treatment selection bias, we performed a subgroup analysis comparing patients who received MMF vs. non-MMF maintenance therapy (Supplementary Table 1). Apart from significantly lower eGFR at biopsy in the non-MMF group than in the MMF group (83 [36–91] mL/min/1.73 m<sup>2</sup> vs. 102 [79–119] mL/min/1.73 m<sup>2</sup>, respectively;  $P=0.008$ ). No significant differences were observed in CI score, TA, interstitial fibrosis, SLEDAI-2K, or the prevalence of AKI at biopsy.

Six variables were included in Cox regression analysis: histologic class IV, eGFR at biopsy, AKI at biopsy, presence of TA, presence of interstitial fibrosis, and MMF use for maintenance therapy (Table 4). In univariate analysis, the presence of TA was associated with more than a threefold increased hazard of developing kidney function impairment (HR, 3.39, 95% CI, 1.19–9.64;  $P=0.02$ ), while MMF use was associated with a 75% reduction in risk (HR,



**Fig. 2.** Probability of complete remission in childhood-onset lupus nephritis.



**Fig. 1.** Probability of kidney function impairment-free in childhood-onset lupus nephritis: overall (A), stratified by the presence of tubular atrophy (TA) (B), and stratified by the use of mycophenolate mofetil (MMF) as maintenance therapy (C).

**Table 4. Cox proportional hazards models for the risk of developing kidney function impairment in patients with childhood-onset lupus nephritis**

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	aHR	95% CI	P value
Histologic class IV	1.35	0.49–3.73	0.57	1.01	0.25–4.03	0.99
eGFR at kidney biopsy	0.99	0.98–1.00	0.40	1.02	0.99–1.04	0.20
AKI at kidney biopsy	1.96	0.71–5.42	0.20	6.10	0.90–41.51	0.07
Presence of tubular atrophy	3.39	1.19–9.64	<b>0.02</b>	17.74	1.94–162.5	<b>0.01</b>
Presence of interstitial fibrosis	2.62	0.88–7.78	0.08	0.23	0.02–2.62	0.24
MMF as maintenance therapy	0.25	0.08–0.76	<b>0.02</b>	0.09	0.02–0.47	<b>0.003</b>

HR, hazard ratio; aHR, adjusted HR; CI, confidence interval; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; MMF, mycophenolate mofetil. Boldface indicates a statistically significant difference with  $P < 0.05$ .

0.25; 95% CI, 0.08–0.76;  $P = 0.02$ ).

In multivariate Cox regression, both TA and MMF use remained independently associated with kidney function impairment. Specifically, patients with TA had over an 18-fold increased risk of kidney function impairment (HR, 17.74; 95% CI, 1.94–162.5;  $P = 0.01$ ). Conversely, MMF use for maintenance therapy was associated with an 91% lower risk of kidney function impairment (HR, 0.09; 95% CI, 0.02–0.47;  $P = 0.003$ ), underscoring its potential protective role. Model fit was supported by a significant likelihood ratio test ( $P < 0.001$ ), and no significant effect modification was detected among included covariates (Fig. 1B and C).

## Discussion

Kidney involvement is common in children with SLE and often follows a more severe clinical course compared to adult-onset disease.<sup>4,24</sup> Kidney biopsy plays a critical role in confirming the diagnosis of LN, informing treatment decisions, and offering prognostic insight. In our study, 30% of patients developed kidney function impairment during follow-up, underscoring the aggressive nature of kidney involvement in cLN. Notably, differences in histologic LN class III versus IV—focused primarily on glomerular involvement—were not associated with kidney outcomes in our cohort. Although long-term kidney outcomes may not differ markedly between class III and class IV, patients with class III lesions may have a more favorable early treatment response as CR to induction therapy was significantly more frequent in class III.

Given that the tubules and interstitium constitute most of the renal parenchyma, injury in these compartments may be predictive of long-term kidney function. The NIH-modified classification incorporates pathology from all compartments of the nephron and provides composite scores for AI and CI.<sup>8</sup> Our study aimed to evaluate the prognostic value of these indices in cLN.

We observed that glomerular lesions—both acute and chronic—did not significantly differ between patients with

and without kidney function impairment. This supports previous research indicating that setting a new threshold (such as  $>10\%$ ) for glomerular involvement may improve the prognostic utility of histologic scores in cLN.<sup>25</sup>

Conversely, we found that CI scores were significantly higher in patients who progressed to kidney function impairment, with TA and interstitial fibrosis being the key histologic components associated with poor outcomes. Tubulointerstitial lesions are increasingly recognized as more predictive of long-term kidney function in LN than glomerular changes.<sup>10,11</sup> In our cohort, TA was associated with over a fivefold increased risk of developing kidney function impairment, underscoring its strong prognostic value. This finding suggests that tubulointerstitial injury—possibly sustained by subclinical inflammation or persistent proteinuria—may contribute to chronic glomerular filtration rate decline, even in the absence of active glomerular inflammation. The strength of this association highlights the need to prioritize tubulointerstitial findings when assessing histologic severity and prognosis in pediatric LN.

In addition, the use of MMF as maintenance therapy was independently associated with a markedly reduced risk of kidney function impairment. MMF exerts its immunosuppressive effects by inhibiting *de novo* purine synthesis in lymphocytes and possesses direct anti-fibrotic properties. Experimental studies have demonstrated that MMF suppresses profibrotic cytokines like transforming growth factor- $\beta$ , inhibits myofibroblast proliferation, and reduces collagen deposition in kidney tissue.<sup>26,27</sup> These mechanisms may specifically counteract the development of chronic tubulointerstitial lesions—the key histologic predictors of kidney function impairment in our study—and thus may help preserve long-term renal function in cLN.

The finding that MMF use as maintenance therapy was associated with a 91% lower risk of progression to kidney function impairment is clinically important, particularly during the maintenance phase when subclinical autoimmunity and low-grade inflammation may continue to promote chronic damage.<sup>28</sup> Nevertheless, treatment

allocation in our study was based on physician discretion and may have influenced the outcomes, particularly as patients with lower baseline kidney function were less likely to receive MMF. Therefore, the apparent protective effect of MMF during the maintenance phase must be interpreted with caution.

Participants in our study exhibited high disease activity at biopsy, as indicated by elevated SLEDAI-2K scores and high rates of nephrotic syndrome and AKI. While AKI was more common in those who developed kidney function impairment, it did not independently predict long-term outcomes. This may reflect the reversibility of acute lesions with effective induction immunosuppressive treatments including the use of cyclophosphamide or MMF. Importantly, induction immunosuppressive regimens did not differ significantly between groups, further highlighting the importance of the maintenance phase in determining long-term kidney outcomes.

The observed mortality rate of 6.7%, with all deaths occurring in patients who had developed kidney function impairment, emphasizes the need for early identification of at-risk patients and the implementation of targeted strategies to prevent irreversible kidney damage.

This study has several limitations. It was conducted at a single tertiary care center with a relatively small sample size when comparing to studies in adult patients with LN. Although we used standardized NIH-modified indices for histological assessment, potential interobserver variability remains a concern, which may limit the generalizability of findings. Additionally, detailed information on vascular lesions in the kidney histology was limited.

Treatment allocation in our study was nonrandomized and we cannot completely rule out treatment selection bias since patients with lower baseline kidney function were less likely to receive MMF. While multivariable Cox regression adjusted for eGFR and other confounders confirmed the independent association of MMF with reduced kidney impairment risk, residual confounding due to the retrospective design remains possible. A prospective, randomized study with a larger cohort is needed to confirm its benefits in pediatric LN.

The timing of kidney biopsy can significantly impact both histological findings and clinical outcomes. In our cohort, most patients underwent biopsy early, with 50% biopsied within one month and 75% within 3 months of LN diagnosis. Despite this early evaluation, chronic lesions were present in a substantial proportion of patients, although they were generally mild. While childhood-onset LN often presents abruptly, some cases may follow a subclinical or "silent" course, potentially delaying diagnosis and treatment.<sup>29-31</sup> Nevertheless, even mild chronic changes were associated with worse kidney outcomes.

Previous studies have established the absence of CR as a significant predictor of adverse kidney outcomes.<sup>1)</sup> Another limitation involves the definitional overlap between CR and kidney function impairment. Specifically, the failure of eGFR to return to baseline was used as a component in defining both non-CR and kidney function impairment in children with initially normal kidney function. This overlap introduced a dependency that could confound statistical analyses. As such, we did not include CR status as a covariate in the multivariable model evaluating predictors of kidney function impairment, to avoid circular reasoning and ensure analytic validity.

Finally, the retrospective nature of the study limited our ability to assess important confounders such as treatment adherence, LN flare frequency, cumulative AKI episodes, and exposure to nephrotoxic agents—all of which may influence kidney outcomes.

Our findings reinforce existing guidelines that recommend MMF as a preferred agent for maintenance therapy in LN.<sup>23)</sup> In pediatric populations, preserving kidney function is particularly crucial, as these patients face decades of potential disease burden. Early identification of chronic tubulointerstitial lesions may help guide personalized treatment strategies aimed at halting progression before irreversible damage occurs.

In conclusion, our study emphasizes the prognostic importance of chronic histologic lesions—especially TA—in predicting long-term kidney outcomes in childhood-onset LN. The NIH-modified CI appears to offer greater prognostic value than the AI in this setting. Furthermore, maintenance therapy with MMF may be beneficial in preserving kidney function.

## Footnotes

Supplementary material: Supplementary Table 1 is available at <https://doi.org/10.3345/cep.2025.01277>.

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