Long-term outcomes and associated prognostic risk factors of childhood-onset lupus nephritis

Eujin Park¹, Jiwon Jung², Jeeseu Min³, Hyeonju Lee³, Min Ji Park⁴, Ji Yeon Song⁵, Ji Hyun Kim⁶, Kyung Mi Jang⁷, Eun Mi Yang⁸, Yo Han Ahn⁹, Min Hyun Cho¹, Joo Hoon Lee², Young Seo Park¹, Soon Chul Kim¹¹, Se Jin Park¹², Jung Won Lee¹³, Kee Hyuck Kim¹⁴, Ki Soo Pai¹⁵, Hee Gyung Kang³,⁹,¹⁰, Seong Heon Kim³,¹⁰

¹Department of Pediatrics, Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea
²Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Republic of Korea
³Department of Pediatrics, Seoul National University Children's Hospital, Seoul, Republic of Korea
⁴Department of Pediatrics, Kyungpook National University School of Medicine, Daegu, Republic of Korea
⁵Department of Pediatrics, Pusan National University Children's Hospital, Yangsan, Republic of Korea
⁶Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
⁷Department of Pediatrics, Yeungnam University College of Medicine, Yeungnam University Hospital, Daegu, Republic of Korea
⁸Department of Pediatrics, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea
⁹Kidney Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul, Republic of Korea
¹⁰Department of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea
¹¹Department of Pediatrics, Jeonbuk National University Hospital, Jeonbuk National University Medical School, Jeonju, Republic of Korea
¹²Department of Pediatrics, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon, Republic of Korea
¹³Department of Pediatrics, Ewha Womans University Seoul Hospital, Seoul, Republic of Korea
¹⁴Department of Pediatrics, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea
¹⁵Department of Pediatrics, Ajou University School of Medicine, Suwon, Republic of Korea

Background: This study investigated the clinical characteristics and kidney outcomes of childhood-onset lupus nephritis (LN), and risk factors associated with prognosis.

Methods: We enrolled 216 patients with histologically diagnosed LN during childhood. The Korean Society of Pediatric Nephrology organized a retrospective cohort study of childhood-onset LN in 13 major pediatric nephrology centers in South Korea.

Results: The mean age at kidney biopsy was 13.2 ± 3.2 years. The main forms of presentation were nephrotic syndrome and/or hematuria in 152 patients (70.4%), and the most common histological finding was World Health Organization (WHO) class IV in 138 patients (63.9%), followed by WHO class III in 34 patients (15.7%). In the outcome analysis, the mean follow-up period of the patients was 7.8 ± 5.1 years. At last follow-up, 32 patients (14.8%) developed advanced chronic kidney disease (CKD). Male sex and failure to achieve remission at 12 months of treatment were significant risk factors for developing advanced CKD (hazard ratio of 2.57 and 2.29, respectively).

Conclusion: Our study demonstrated the clinical characteristics and long-term outcomes of patients with childhood-onset LN. Male sex and failure to achieve remission in the first year of treatment were predictive of advanced CKD. Therefore, prompt awareness and close monitoring of these high-risk patients are needed, which may further improve the prognosis of children with LN.

Keywords: Chronic renal insufficiency, Lupus nephritis, Pediatrics, Prognosis

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Correspondence: Seong Heon Kim
Department of Pediatrics, Seoul National University Children's Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
E-mail: kimsh22@snu.ac.kr
ORCID: https://orcid.org/0000-0001-8003-3010

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Introduction

Lupus nephritis (LN) is one of the most serious complications of systemic lupus erythematosus (SLE), characterized by disorders of innate and adaptive immunities, resulting in immune complex deposition in the affected kidney, eventually leading to chronic irreversible kidney damage [1–3]. Although the therapeutic management of LN has improved patient and kidney survival over the past few decades, the prognosis of LN is highly variable, and efforts have been made to identify factors predicting kidney outcomes [4–9]. Race, sex, presence or lack of specific autoantibodies, kidney function at diagnosis, certain histopathologic findings, nephritic flares, and treatment response may influence the prognosis of LN [4,6,10–14]. Among them, treatment response and histological findings of proliferative LN have been consistently reported to be related to kidney outcomes in pediatric LN patients, but the influence of other factors on prognosis remains controversial [15–20].

Furthermore, because childhood-onset LN is extremely rare, little is known about the clinical characteristics, kidney outcomes, and prognostic factors in this population. Our goals were to analyze the clinical features and course of childhood-onset LN and determine predictive factors for poor kidney prognosis.

Methods

Participants

The Korean Society of Pediatric Nephrology organized a retrospective cohort study of childhood-onset LN in 13 major pediatric nephrology centers in South Korea. The cohort included patients diagnosed with LN before the age of 18 years from 2000 to 2020. This study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Hospital (No. 2103-067-1203). Patients registered in the cohort were histologically diagnosed by percutaneous kidney biopsy and classified according to the World Health Organization classification [21]. Demographic data, clinical characteristics, laboratory values at the time of diagnosis, and kidney outcomes of the patients during visits were reviewed retrospectively from electronic medical records. Patients who could not be followed for at least 12 months to assess treatment response were excluded from the study.

Laboratory methods

The glomerular filtration rate (GFR) was estimated using Schwartz’s formula [22]. Complement 3 (C3) and complement 4 (C4) levels were measured using nephelometry. Anti–double-stranded DNA (anti-dsDNA) antibody was measured using qualitative fluoroenzyme immunoassay.

Definitions

Azotemia was defined as an estimated GFR (eGFR) below 90 mL/min/1.73 m². When classifying a patient’s response to treatment, complete remission (CR) was defined as stable serum creatinine and reduction of proteinuria to <0.5 g/day in at least two consecutive measurements or subsequent visits, partial remission (PR) was defined as a reduction of proteinuria to 0.5–3.0 g/day or a decrease >50% from baseline, and resistant was defined as failure to achieve PR or CR [21]. In the outcome analysis, advanced chronic kidney disease (CKD) was defined as confirmed stages 3, 4, and 5 of CKD classification [21].

Statistical analysis

Qualitative variables are described as percentages. Continuous variables are presented as means and standard deviations. The chi-square tests were used to investigate the association between qualitative variables, and the Mann-Whitney U tests were used to compare differences between two independent groups on a continuous scale. Cox proportional-hazards regression analysis was used to detect the HRs and the independent effect of each clinical factor on the composite outcome (risk of developing advanced CKD by 10 years). In the analysis, male sex, azotemia at onset, proliferative LN, and failure to achieve remission at 12 months of treatment were considered as clinical risk factors for advanced CKD. Potential confounders were checked a priori using directed acyclic graphs (Supplementary Figure 1, available online) [23]. Statistical significance was set at p < 0.05. Statistical analysis was performed using IBM SPSS for Windows version 26.0 (IBP Corp.).
Results

Clinical characteristics of the cohort

We analyzed the records of 216 patients enrolled in this cohort. The mean age at the onset of nephropathy was 13.2 ± 3.22 years, and 59 patients (27.3%) were male. Of these, 32 patients (14.8%) were previously diagnosed with SLE. The main forms of presentation were nephrotic syndrome with or without hematuria in 152 patients (70.4%), followed by proteinuria with or without hematuria in 46 patients (21.3%). Eighteen patients (8.3%) presented with isolated hematuria. At the onset of nephropathy, 110 patients (50.9%) had normal kidney function, and 106 patients (49.1%) had azotemia. The most common histological finding was World Health Organization (WHO) class IV in 138 patients (63.9%), followed by WHO class III in 34 patients (15.7%), and WHO class V in 24 patients (11.1%). Laboratory tests revealed that C3 levels were lower in 194 patients (89.8%), and C4 levels were lower in 171 patients (79.2%). High anti-dsDNA levels were observed in 154 patients (71.3%). The proportion of azotemia at the onset of LN was significantly higher in male patients than in females (p = 0.03) (Table 1).

Treatment responses of the cohort

All patients received corticosteroids. Forty-six (21.3%) and 91 patients (42.1%) received mycophenolate mofetil (MMF) and cyclophosphamide (CPM), respectively, while 25 patients (11.6%) sequentially switched from CPM to MMF as induction therapy. MMF has been currently more frequently used than before (39.4% vs. 22.6%, p = 0.01) as induction therapy in patients diagnosed with LN since 2010.

Patients were classified into proliferative and nonproliferative LN based on histological findings and kidney outcomes were analyzed at 6 and 12 months after treatment. Of 172 patients with proliferative LN, 113 (65.7%) achieved CR after 6 months of induction treatment, and 135 (78.5%) achieved CR after 12 months. In addition, out of 44 patients with nonproliferative LN, 38 (86.4%) achieved CR after 6 months of induction treatment, and 36 (81.8%) maintained CR after 12 months.

### Table 1. Patients' characteristics at the onset of lupus nephritis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>157</td>
<td>59</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Onset age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Previous diagnosis of SLE, &gt;3 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diagnosed before 2010</td>
<td></td>
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<tr>
<td>Presenting symptom</td>
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<tr>
<td>Isolated hematuria</td>
<td></td>
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<tr>
<td>Proteinuria and/or hematuria</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Nephrotic syndrome and/or hematuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kidney function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azotemia (eGFR below 90 mL/min/1.73 m²)</td>
<td>70 (44.6)</td>
<td>36 (61.0)</td>
<td>106 (49.1)</td>
<td>0.03&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Laboratory findings at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low C3</td>
<td>143 (91.1)</td>
<td>51 (86.4)</td>
<td>194 (89.8)</td>
<td>0.32&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low C4</td>
<td>127 (80.9)</td>
<td>44 (74.6)</td>
<td>171 (79.2)</td>
<td>0.31&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>High anti-dsDNA titer (&gt;60 IU/mL)</td>
<td>110 (70.1)</td>
<td>44 (74.6)</td>
<td>154 (71.3)</td>
<td>0.51&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Presence of anti-phospholipid Abs</td>
<td>88 (56.1)</td>
<td>32 (54.2)</td>
<td>120 (55.6)</td>
<td>0.81&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO class III</td>
<td>25 (15.9)</td>
<td>9 (15.3)</td>
<td>34 (15.7)</td>
<td>0.42&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>WHO class IV</td>
<td>96 (61.1)</td>
<td>42 (71.2)</td>
<td>138 (63.9)</td>
<td></td>
</tr>
<tr>
<td>WHO class V</td>
<td>18 (11.5)</td>
<td>6 (10.2)</td>
<td>24 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, or number (%).

Ab, antibody; C3, complement 3; C4, complement 4; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; SLE, systemic lupus erythematosus; WHO, World Health Organization.

<sup>a</sup>Mann-Whitney U test, <sup>b</sup>chi-square test.
CR after 12 months. By comparing induction treatment in male than in females, the proportion of CR after 6 and 12 months in proliferative LN and CR after 12 months in non-proliferative LN were all higher in females than in males; although, there were no statistically significant differences (Table 2).

Kidney outcomes of the cohort

In the kidney outcome analysis, the mean follow-up period of the patients was 7.8 ± 5.11 years. At the last follow-up visit, 18 patients (8.3%) progressed to CKD stage 5, 14 patients (6.5%) progressed to CKD stages 3 and 4, while 184 patients (85.2%) remained in CKD stages 1 and 2. When comparing males and females, there was no significant difference in the follow-up period, but males had higher rates of advanced CKD than females (Table 3). Patients who progressed to advanced CKD at the last follow-up reached that status within a mean of 6.7 ± 3.63 years after diagnosis, and there was a significant difference in the follow-up period between patients with advanced and non-advanced CKD (10.9 ± 7.11 vs. 7.3 ± 4.49, p = 0.01). There were six deaths (2.8%) due to severe anemia, pancreatitis, liver failure, cerebral infarction, myocardial infarction, and cardiomyopathy caused by active and severe SLE.

We conducted a Cox proportional-hazards regression analysis to explore the independent risk factors for developing advanced CKD by 10 years. In the adjusted model, there was an increased risk of developing advanced CKD in males (hazard ratio [HR], 2.566; 95% confidence interval [CI], 1.149–5.733; p = 0.02) and in patients who failed to achieve CR at 12 months of treatment (HR, 2.29; 95% CI, 1.06–4.94; p = 0.04) (Table 4). Development of advanced CKD was not associated with other clinical factors (azotemia at onset and proliferative LN).

Discussion

To date, this is the largest multicenter study of childhood-onset LNs in South Korea and the study comprehensively shows clinicopathological characteristics, treatment responses, kidney outcomes, and risk factors associated with the development of advanced CKD in childhood-onset LNs. We attempted to collect long-term data with a

<table>
<thead>
<tr>
<th>Table 2. Treatment responses of patients at 6 and 12 months of treatment</th>
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<tr>
<td>After treatment</td>
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<tr>
<td>At 6 mo</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR/R</td>
</tr>
<tr>
<td>At 12 mo</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR/R</td>
</tr>
</tbody>
</table>

Data are expressed as number (%). CR, complete remission; PR, partial remission; R, resistant. aChi-square test.

<table>
<thead>
<tr>
<th>Table 3. Kidney outcomes of patients at last follow-up</th>
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<tbody>
<tr>
<td>Kidney outcome</td>
</tr>
<tr>
<td>Total follow-up period (yr)</td>
</tr>
<tr>
<td>Total time on immunosuppressant (yr)</td>
</tr>
<tr>
<td>CKD stages 1 and 2</td>
</tr>
<tr>
<td>CKD stages 3 and 4</td>
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<tr>
<td>CKD stage 5</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or number (%). CRD, chronic renal disease. aMann-Whitney U test, bchi-square test.
A retrospective multicenter study involving 13 major pediatric nephrology centers across South Korea. For the clinical characteristics, the cohort mainly presented as nephrotic syndrome and WHO class IV being the most common form, and these have similarly been reported in previous pediatric LN studies [2,17,19]. In this study, nonproliferative LN patients showed better treatment responses than proliferative LN patients, and approximately 15% of the patients developed advanced CKD at the last follow-up. These results are comparable to recent pediatric LN cohorts where overall CR rates at 12 to 24 months ranged from 53.3% to 78.3% and rates of progression to advanced CKD at the last follow-up ranged from 8.7% to 28.8% [17–19].

The risk of kidney function deterioration in pediatric LN patients has been strongly associated with the histological findings of proliferative LN and poor treatment response [4,17–20]. In this study, failure to achieve remission in the first year was an independent risk factor for developing advanced CKD in childhood-onset LN, whereas the histological finding of proliferative LN was not associated with the development of advanced CKD. Although it is difficult to clearly explain why the results of the study differ from those of previous studies, it is possible that active and effective treatments have been implemented in proliferative LN patients as awareness of these high-risk patients increased [5,9].

In addition, male was also an independent risk factor for progression to advanced CKD in this study. Till date, there have been conflicting reports when kidney prognosis between males and females among LN and SLE patients are compared [24–27]. Moreover, data on pediatric LN are limited, and there are few data on the effect of sex on the outcome of childhood-onset LN. A recent pediatric LN cohort study from Turkey (10 males) reported results similar to those of the present study. In this study, male sex was a predictor of poor kidney outcome [15]. Data from India (13 males) and South Korea (22 males) identified male sex as a significant risk factor for predicting kidney failure in childhood LN in the multivariable analysis [17,28]. However, these results could not be confirmed in pediatric LN cohort studies that enrolled a relatively large number of patients with LN. The Italian Collaborative Study reported the results of analyzing data from 161 pediatric LN patients (39 males). They could not find any statistical significance between sex and progression to kidney failure, although male sex was associated with a higher risk of nephritic flares [18]. A retrospective cohort of 92 pediatric LNs from Hong Kong (14 males) showed no association between the development of advanced CKD and sex [19]. Although these pediatric LN cohort studies have the advantage of including a larger number of total LN patients than previous studies, they still have limitations such as the small number of male patients included or the short follow-up period. As the pathogenesis of LN is widely heterogeneous, it is possible that some regional or ethnic factors other than sex may have played a role [29–32]. Therefore, more studies on the prognostic factors of pediatric LN are needed to better identify high-risk groups and further improve kidney outcomes.

Our study expands on the results of recent pediatric LN cohort studies on the effects of male sex and treatment responses on kidney prognosis but best reflects the homogeneity of ethnic and sociodemographic characteristics of South Korea. While this study has the strength of including a large number of pediatric LN patients and providing a relatively longer follow-up period, it also has some limitations. This was a retrospective multicenter cohort study, and it is inevitable that some information would be missing. Data were unavailable on frequent nephritis flares and specific autoantibodies, a powerful predictor of prognosis in LN patients. We were also unable to analyze data on cumulative doses of immunosuppressive drugs such as steroids. Although we classified the renal histology according to the WHO classification, we did not analyze the information related to activity or chronicity. Finally, we used an

| Table 4. Risk for developing advanced chronic kidney disease |
|-----------------|------------------|-----------------|
| Variable        | Cox proportional hazard model | p-value |
| Male            | Unadjusted       | Adjusted*       | Unadjusted | Adjusted* |
|                 | HR (95% CI)      | HR (95% CI)     |             | HR (95% CI) |
| Male            |                   |                 |             |             |
| Unadjusted      | 2.47 (1.21–5.03)  | 2.57 (1.15–5.73) | 0.01        | 0.02        |
| Adjusted*       | 3.31 (1.98–4.13)  | 2.29 (1.06–4.94) | 0.07        | 0.04        |

CI, confidence interval; CR, complete remission; HR, relative hazards ratio.

*Adjusted for onset age, azotemia at onset, proliferative lupus nephritis, and treatment response at 12 months.

*Adjusted for onset age, sex, azotemia at onset, and proliferative lupus nephritis.
intermediate measure of outcome (advanced CKD) rather than a hard point (kidney failure or death) for outcome analysis. Further studies in a prospective pediatric LN cohort collecting a large number of male patients and all possible clinical risk factors related to kidney prognosis and providing a longer follow-up period are needed.

In summary, our cohort showed that childhood-onset LN commonly presents as nephrotic syndrome, with WHO class IV being the most common form, and approximately 15% of the patients developed advanced CKD. Male sex and failure to achieve remission in the first year were independently associated with the development of advanced CKD. In order to establish appropriate treatment and follow-up plans for children with LNs, timely evaluation and close monitoring of these high-risk patients are required.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors’ contributions

Conceptualization: EP, SHK
Data curation: JJ, JM, HL, MJP, JYS, JHK, KMJ, EMY, SCK, SJP, JWL, KHK, KSP, YSP
Funding acquisition: SHK
Formal analysis: EP
Supervision: YHA, MHC, JHL, HGK
Writing-original draft: EP, SHK
Writing-review & editing: EP, SHK
All authors read and approved the final manuscript.

ORCID

Eujin Park, https://orcid.org/0000-0002-4413-468X
Jiwon Jung, https://orcid.org/0000-0001-5358-7966
Jeesu Min, https://orcid.org/0000-0003-1535-7769
Hyeonju Lee, https://orcid.org/0000-0003-0457-635X
Min Ji Park, https://orcid.org/0000-0002-3485-5598
Ji Yeon Song, https://orcid.org/0000-0002-9665-4717
Ji Hyun Kim, https://orcid.org/0000-0001-8477-0157
Kyung Mi Jang, https://orcid.org/0000-0002-2226-9268
Eun Mi Yang, https://orcid.org/0000-0001-9410-5855
Yo Han Ahn, https://orcid.org/0000-0002-8185-4408
Min Hyun Cho, https://orcid.org/0000-0002-7965-7587
Joo Hoon Lee, https://orcid.org/0000-0001-8010-3605
Young Seo Park, https://orcid.org/0000-0001-7653-2036
Soon Chul Kim, https://orcid.org/0000-0002-5947-4599
Se Jin Park, https://orcid.org/0000-0002-7650-5393
Jung Won Lee, https://orcid.org/0000-0003-1846-3153
Kee Hyuck Kim, https://orcid.org/0000-0003-4720-6455
Kí Soo Pai, https://orcid.org/0000-0003-0373-4336
Hee Gyung Kang, https://orcid.org/0000-0001-8323-5320
Seong Heon Kim, https://orcid.org/0000-0001-8003-3010

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