Diffuse proliferative glomerulonephritis does not determine the worst outcome in childhood-onset lupus nephritis: a 23-year experience in a single centre

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Abstract
Introduction. Lupus nephritis (LN) is the major indicator of morbidity and mortality in systemic lupus erythematosus (SLE). Many studies have found a significantly worse patient survival rate in patients with LN class IV than patients with other LN classes.

Objective. The aim was to describe the severity and outcomes of LN in a group of Thai children.

Methods. We retrospectively reviewed the patient files of children diagnosed with SLE aged ≤18 years in Songklanagarind Hospital, Southern Thailand, from 1985 to 2007.

Results. Of 216 SLE patients, 180 had renal biopsy results, and the others were excluded from analysis. There were 33 males and 147 females, average age 11.8 ± 2.6 years (range 3.6–18.0), with a median follow-up period of 3.9 years (range 9 days to 19.4 years). Using the WHO LN classification, there were 9, 55, 5, 94 and 14 patients of classes I–V, respectively, as well as 2 with end-stage renal disease and 1 with IgM nephropathy. The mortality rate was 23% (42/180). Patients with LN class II had a similar renal and patient survival compared to patients with LN class IV (P = 0.3 and 0.2, respectively). Cox proportional hazard regression analysis in 177 patients (3 patients who had a renal biopsy result outside the WHO classification were omitted) showed that gender was an independent risk factor for survival. Males had 2.6 times the hazard rate compared to females (95% CI 1.2–5.7, P = 0.03), but LN classification, age and timing of the renal biopsy were not significant.

Conclusion. Renal and patient survival in LN classes II and IV were similar. Gender was the only independent risk factor of mortality, with males at greater risk than females.

Keywords: diffuse proliferative glomerulonephritis; lupus nephritis; renal failure; systemic lupus erythematosus (SLE)

Introduction
Lupus nephritis (LN) is detected at presentation of systemic lupus erythematosus (SLE) in 25–50% of patients. However, LN may develop after initial presentation in up to 60% of adults and 80% of children [1,2]. LN is known to be the major indicator of morbidity and mortality in SLE, and its histopathological classification determines the prognosis. SLE is relatively rare in children compared to adults; however, LN is more common and more severe in children [1,3–5]. Multiple immunosuppressive drugs have been trialled in search of the most efficacious treatment for this debilitating illness; however, all current regimes used to treat LN have serious consequences, particularly serious infection. Both LN itself and the consequences of its treatment cause significant morbidity, including mortality due to chronic kidney disease (CKD) or infection.

Many studies have been undertaken to determine the most efficacious dosage, type and intensity of immunosuppressive drugs to achieve the optimal renal survival with minimal adverse effects, but to date a satisfactorily


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Multivariate analysis using the Cox proportional hazard regression was used to determine risk factors for overall survival. P-values <0.05 were considered statistically significant.

Results

There were 216 children treated at our institution for SLE during the study period. Of these, 182 (84%) had a renal biopsy performed. In two children, the tissue from the biopsy was insufficient for diagnosis; one child died soon after his first and only biopsy, while the parents of the other refused to allow a second biopsy. These two patients were therefore excluded from the study, leaving 180 (83%) patients for analysis.

There were 33 boys (18.4%) and 147 girls (81.6%), average age 11.8 ± 2.6 years (range 3.6–18.0). The median period from SLE diagnosis to the first renal biopsy was 18 days (range 0 days to 6.2 years). The median follow-up period was 3.9 years (range 9 days to 19.4 years). Table 1 shows the results of the renal biopsies. From the first biopsy, the number of glomerulonephritis classes I–V patients, based on WHO classifications, was 10, 81, 67 and 15, respectively. Two patients had end-stage renal disease (ESRD), while one had IgM nephropathy. Sixty-one patients had a second biopsy, following which 41 were changed to another class, including 23 out of 35 LN class II changed to LN class IV, and 9 out of 21 LN class IV changed to LN class II, 2 to LN class V and 1 to ESRD (Table 1). Finally, by using the most severe LN class, classes I–V were changed to 9, 55, 5, 94 and 14, respectively.

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>LN I</th>
<th>LN II</th>
<th>LN III</th>
<th>LN IV</th>
<th>LN V</th>
<th>ESRD</th>
<th>IgM</th>
<th>TIN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>First biopsy</td>
<td>10</td>
<td>81</td>
<td>4</td>
<td>67</td>
<td>15</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>180</td>
</tr>
<tr>
<td>Second biopsy</td>
<td>0</td>
<td>20</td>
<td>1</td>
<td>34</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>61</td>
</tr>
<tr>
<td>Third biopsy</td>
<td>1</td>
<td>7</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Fourth biopsy</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Most severe LN class</td>
<td>9</td>
<td>55</td>
<td>5</td>
<td>94</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>180</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>1 (11.1%)</td>
<td>7 (12.7%)</td>
<td>3 (60.0%)</td>
<td>25 (26.6%)</td>
<td>3 (21.4%)</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>0 (42)</td>
<td>23.3%</td>
</tr>
</tbody>
</table>

Table 1. Renal biopsy results and mortality rates by histopathology results in 180 SLE patients with one to four biopsies, and medication status of 94 patients still on follow-up at the time of study

With other immunosuppressive drug
<table>
<thead>
<tr>
<th>Medication status at last follow-up</th>
<th>Free of medication</th>
<th>Prednisolone only</th>
<th>Azathioprine</th>
<th>IV cyclophosphamide</th>
<th>Oral cyclophosphamide</th>
<th>Mycophenolate mofetil</th>
</tr>
</thead>
<tbody>
<tr>
<td>With other immunosuppressive drug</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>11</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Prednisolone only</td>
<td>5</td>
<td>20</td>
<td>1</td>
<td>16</td>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>Orally cyclophosphamide</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IV cyclophosphamide</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

LN, lupus nephritis; ESRD, end-stage renal disease; IgM, Immunoglobulin M nephropathy; TIN, tubulointerstitial nephritis.

The morphological classification of LN followed the World Health Organization (WHO) system [7]. Due to the small study sample, we defined class I as normal glomeruli and classes II–VI as mesangial proliferative, focal segmental, diffuse proliferative, membranous and advanced sclerosing glomerulonephritis, respectively.

A follow-up biopsy was performed (1) when there was evidence of progressive nephritis, (2) deterioration of renal function, (3) a flare-up of proliferative glomerulonephritis, respectively.

Table 1 shows the results of the renal biopsies. From the first biopsy, the number of glomerulonephritis classes I–V patients, based on WHO classifications, was 10, 81, 67 and 15, respectively. Two patients had end-stage renal disease (ESRD), while one had IgM nephropathy. Sixty-one patients had a second biopsy, following which 41 were changed to another class, including 23 out of 35 LN class II changed to LN class IV, and 9 out of 21 LN class IV changed to LN class II, 2 to LN class V and 1 to ESRD (Table 1). Finally, by using the most severe LN class, classes I–V were changed to 9, 55, 5, 94 and 14, respectively.

Table 1. Renal biopsy results and mortality rates by histopathology results in 180 SLE patients with one to four biopsies, and medication status of 94 patients still on follow-up at the time of study

<table>
<thead>
<tr>
<th>Patients and methods</th>
</tr>
</thead>
</table>
| We retrospectively reviewed the medical records of patients aged <18 years who fulfilled the 1997 updating the American College of Rheumatology revised criteria for the classification of SLE [6] and who had a renal biopsy performed, who had been treated at the Pediatrics Department of Songklanagarind Hospital, Southern Thailand, between February 1985 and December 2007. The age at diagnosis of the patients who were referred to us was determined from the date of their first visit to our institution. We divided the age of the patients into four age groups, <9 years, >9–12 years, >12–14 years and >14 years, in order to create roughly equal-sized groups. Patients who did not have a renal biopsy were excluded from the analysis.

The overall mortality rate was 23% (42/180). Figure 1A shows the Kaplan–Meier survival curve for overall patient survival. The survival rates at 2, 5, 10 and 15 years were 91%, 77%, 65% and 53%, respectively. The mortality rate of patients at last follow-up was 42% (42/180), and the median period from SLE diagnosis to the first renal biopsy was 18 days (range 0 days to 6.2 years). The median follow-up period was 3.9 years (range 9 days to 19.4 years). Table 1 shows the results of the renal biopsies. From the first biopsy, the number of glomerulonephritis classes I–V patients, based on WHO classifications, was 10, 81, 67 and 15, respectively. Two patients had end-stage renal disease (ESRD), while one had IgM nephropathy. Sixty-one patients had a second biopsy, following which 41 were changed to another class, including 23 out of 35 LN class II changed to LN class IV, and 9 out of 21 LN class IV changed to LN class II, 2 to LN class V and 1 to ESRD (Table 1). Finally, by using the most severe LN class, classes I–V were changed to 9, 55, 5, 94 and 14, respectively.

Males and females had a similar age distribution, interval from diagnosis to biopsy, LN classification and outcome, but the median follow-up time in girls was significantly longer than that in boys (4.3 versus 2.2 years, P = 0.03) (Table 2). There were no differences of LN classification (P = 0.8) or mortality (P = 0.7) between age groups.

The overall mortality rate was 23% (42/180). Figure 1A shows the Kaplan–Meier survival curve for overall patient survival. The survival rates at 2, 5, 10 and 15 years were 91%, 77%, 65% and 53%, respectively. The mortality rate of patients at last follow-up was 42% (42/180), and the median period from SLE diagnosis to the first renal biopsy was 18 days (range 0 days to 6.2 years). The median follow-up period was 3.9 years (range 9 days to 19.4 years).
rates were similar between genders (males = 30.3% versus females = 21.8%, \( P = 0.4 \)) (Table 2); males had a significantly worse survival at all points evaluated (\( P = 0.04 \)), the rates at 2, 5, 10 and 15 years being 86% versus 92%, 57% versus 81%, 47% versus 68% and 47% versus 54%, respectively (Figure 1B). Table 1 shows the mortality rates of patients by renal histopathology. Patients who had LN classes II and IV had survival rates at 2, 5, 10 and 15 years being 86% versus 92%, 90% versus 72%, respectively. Patients with LN class II had a similar renal survival rate to patients with LN class IV (\( P = 0.3 \)).

Table 3 gives the Cox proportional hazard regression analysis in 177 patients (three patients who had a renal biopsy result outside the WHO classification were omitted), showing that gender was the only independent risk factor for survival. Males had 2.6 times the hazard rate compared to females (95% CI 1.2–5.7, \( P = 0.03 \)), but LN classification, age and timing of renal biopsy were not significant.

A total of 138 patients were alive at the time of analysis, of whom 94 were still coming for follow-up visits (16 were lost to follow-up, 28 had been referred elsewhere). Of these, 20 were free of medication and 74 were on prednisolone; 44 of these 74 were on prednisolone alone and 30 needed additional immunosuppressive drugs (Table 1).

### Discussion

Our study of a group of Thai children with SLE showed more prevalence of WHO class II LN in SLE patients at the first renal biopsy than other studies [9–11]. This is likely because in our institution, we perform a renal biopsy on most SLE patients, whether or not the LN is clinically confirmed, in order to determine the renal histopathology in these patients. In the study period, the patients who did not have a renal biopsy were those who were either very sick and subsequently died before the biopsy was performed, refused or had strong contraindications. In the patients of this study, 84% had a renal biopsy, and from the initial results, half of them (51%) had normal renal histology (LN class I) or only mild nephritis (LN class II). There have been many other studies examining LN and SLE as in ours, and in most, a renal biopsy was performed only if clinical nephritis was present, which explains why LN class IV histopathology was more common in those studies than in our study [11–15]. One earlier report on SLE in adults had results from a renal biopsy performed in 25 patients who, although urinalysis and serum creatinine were normal, showed 17 normal renal histologies, 5 with mesangial glomerulonephritis, 2 with focal proliferative nephritis and 1 with isolated interstitial nephritis; however, altogether LN class IV was still predominated [16].

In the patients of our study, a follow-up renal biopsy had been performed when indicated, with the maximum being four biopsies. We found that 1 in LN class I, 23 in LN class II and 1 in LN class V had progressed to LN class IV at the second biopsy, and 2 in LN class II had progressed to LN class IV at the third biopsy, and therefore the final LN class IV figure became 52% (94/180) and the most common renal histopathology. This finding indicates that an early renal biopsy does not always show the full magnitude of renal involvement, and if the nephritis is progressive, a repeat biopsy should be performed.

Delayed renal biopsy after clinical LN presentation has been reported as one of the risk factors of renal survival [17]. Our study showed that in our institution, we had performed renal biopsies very early, in 65% of patients within 1 month and in 82% within 3 months; as noted earlier, it is our policy...
Fig. 1. (A) Overall patient survival rate (n = 180 patients) and number of patients at risk during each time period; (B) patient survival rate (n = 180 patients) by sex, and number of patients at risk during each time period; (C) patient survival rate (n = 149 patients) by most severe renal histopathology (LN classes II versus IV), and number of patients at risk during each time period; (D) overall renal survival rate (n = 180 patients), and number of patients at risk during each time period; and (E) renal survival (n = 149 patients) by most severe renal histopathology (LN classes II versus IV), and number of patients at risk during each time period. CI: confidence interval; N at risk: numbers at risk.
to obtain a renal biopsy in all SLE patients with no actual contraindications. However, in our study, the interval from diagnosis and renal biopsy was not a risk factor for survival.

A delayed renal biopsy leads to the delayed administration of aggressive immunosuppressive drugs, since such administration is based on renal histopathology; thus, delayed commencement of appropriate treatment could be a risk factor, rather than the delayed renal biopsy itself.

A report from Japan including both children and adult patients showed that males had significantly worse survival than females (HR = 3.64, 95% CI 1.89–6.98) and age at diagnosis had no effect on renal survival, both of which were comparable to our study [18].

LN is more common in childhood onset SLE, and the clinical manifestation of nephritis varies from mild to the maximum of ESRD [11]. In one study, nephrotic syndrome at presentation did not predict renal survival while LN WHO class IV, hypertension and the presence of renal insufficiency predicted a worse outcome [19]. A study from Hong Kong showed that LN patients who had hypertension, nephrotic syndrome, glomerular filtration rate <50 ml/min, incomplete remission in the first year or diffuse proliferative glomerulonephritis had a significantly less favourable renal survival rate. In another study involving 34 children, histopathology was an independent risk factor determining the prognosis of renal and overall patient survival [14]. In our study, we did not evaluate the clinical manifestations of nephritis but instead histopathology, which was not found to be an independent risk factor.

In a report on 167 SLE children, Yang et al. [20] found that the 5-year renal and patient survival rates were 93% and 91%, respectively, while the 5-year renal and patient survival rates in patients with LN class IV specifically were 88% and 82%, respectively. Our study showed patient survival rates for classes II and IV at 5 years of 87% and 75%, respectively, and renal survival for classes II and IV at 5 years of 90% and 93%, respectively. One explanation for the lower patient survival in our study would probably be that during the study period, we did not perform renal replacement therapy in patients with ESRD.

LN is treatable but not curable. The histopathology can become either better or worse, as our study showed with the changes of renal histopathology in several patients at a follow-up repeat renal biopsy. At the conclusion of our study, only 20/94 patients were free of medication, with two who had been treated for >10 years and eventually developed CKD.

In our study, there was no statistically significant difference in patient survival between patients with LN classes II and IV, although most other studies have found a significantly worse patient survival rate in patients with LN class IV than patients with other LN classes [9,20–23]. This may reflect that our therapy regime in patients with LN IV provided a good result, lifting the patient survival of this class up to the same level as patients with LN II. Although it is possible that our treatment of class II patients was not aggressive enough, we feel that the reason for this better outcome of class IV patients is that our treatment of patients with class IV was more aggressive than that in class II, thus improving the outcome of this group. In future, we may choose to treat patients with LN class II similarly to those with class IV in order to try to improve their outcomes; however, we must emphasize that the treatment regimens given to patients in our retrospective study were quite varied, reflecting a wide variation in the clinical disease over their whole treatment period.

SLE has been a challenging disease for a long time both in terms of diagnosis and treatment modalities. Diagnosis is usually delayed due to late manifestation of symptoms. Although many treatment protocols have been tried, no optimal treatment has yet been found.

### Conclusion

LN, one of the most serious organ involvement conditions in SLE, will often develop later or progress from the first presentation. A repeat renal biopsy is required when indicated to re-evaluate the severity of the disease and the mode of therapy. In our study, LN WHO class IV was the most...
common renal histopathology. Unlike most other studies, our aggressive immunosuppression appeared to minimize the different prognoses between LN classes II and IV. Male gender was the only independent risk factor of mortality.

Conflict of interest statement. None declared.

References

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Medullary sponge kidney associated with primary distal renal tubular acidosis and mutations of the H+-ATPase genes

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Abstract
Background. Medullary sponge kidney (MSK) is a rare congenital disease characterized by diffuse ectasia or dilation of precalceal collecting tubules. Although its pathogenesis is unknown, the association with various congenital diseases suggests that it could be a developmental disorder. In addition to the typical clinical features of nephrolithiasis and urolithiasis, patients with MSK show tubular

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