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Original Article

Lupus Nephritis in Children: An experience in tertiary care centres

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Abstract

Lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus in children, and is a leading cause of long-term morbidity. However, local data on paediatric LN from Sri Lanka are limited. This study aimed to describe the clinicopathological characteristics, management strategies, treatment outcomes and complications of childhood LN across three tertiary care centres in Sri Lanka.

A retrospective descriptive study was conducted among children less than 16 years with biopsy-proven LN. Demographic, clinical, biochemical, histological and therapeutic data were extracted from medical records. Disease activity and chronicity indices were assessed using NIH criteria. The time taken to reach remission was analysed using the Kaplan–Meier method, and predictors of remission were evaluated using Cox proportional hazards modelling.

Thirty eight children (mean age 11.8 ± 2.6 years, 68.4% female) were included. Majority presented with proteinuria and proliferative LN was predominant (class IV: 55%; class III: 26%). Hyaline necrosis and cellular crescents were significantly associated with higher activity scores. Patients treated with cyclophosphamide (CYC) achieved remission faster than those who did not receive it ($p = 0.024$). Male sex (HR = 2.90, $p = 0.030$), a higher activity index (HR = 0.88, $p = 0.034$) and proliferative class (HR = 0.04, $p = 0.001$) were associated with delayed remission. Five patients experienced relapse during follow-up, with higher chronicity indices and more frequent tubulointerstitial damage. No deaths were recorded.

Childhood LN in Sri Lanka predominantly presented as a proliferative disease with moderate activity and low chronicity. Cyclophosphamide induction therapy was found to achieve earlier remission, while male sex, higher activity and proliferative class were found to predict a delayed remission. Although relapses occurred in a minority, the overall outcomes were favourable.

Key Words

Lupus Nephritis, children, tertiary centre experience

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease characterized by antibodies directed against self-antigens, resulting in multi-organ damage. Around 20% of cases are diagnosed during childhood [1,2] Lupus nephritis (LN) in children tends to present earlier and behaves more aggressively with higher morbidity and lower survival rate when compared to adult onset SLE [3]. Timely recognition and appropriate treatment of renal involvement are essential to prevent permanent renal damage and progression to advanced renal failure.

The diagnosis of SLE is made according to the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) criteria [4]. Kidney disease Improving Global Outcomes (KDIGO) guidelines suggested that LN should be suspected in SLE patients with proteinuria, renal dysfunction, active urinary sediments or hypertension and all cases should be confirmed by renal biopsy [5]. Renal histological examination is classified with the use of the International Society of Nephrology/Renal Pathology Society (ISN/

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RPS) scale. The ISN/RPS classification recognizes six classes of nephritis, which carry a prognostic value as they are associated with disease severity and long-term renal outcome [6]

Methodology

A retrospective descriptive study was conducted among 38 children (under 16 years) with biopsy-proven LN, diagnosed according to the ISN/RPS classification. Data were extracted from the patients' medical records. Data were analyzed using R version 4.3.2. Descriptive analyses were performed to summarize the socio-demographic, clinicopathological, serological, and treatment characteristics of the study population. Differences in distributions across subgroups were explored descriptively without inferential comparisons due to the modest sample size. The disease activity (range 0–24) and chronicity indices (range 0–12) were analyzed as continuous dependent variables using linear regression models. Initially, univariate linear regression was performed to examine associations between each independent variable and the two outcomes. Variables with a p-value < 0.20 in univariate analyses, or those considered clinically relevant based on prior evidence, were entered into the multivariable linear regression models. Results from both univariate and multivariable models were reported as β coefficients with 95% confidence intervals (CI) and corresponding p-values.

To identify factors associated with time to remission, a Cox proportional hazards regression model was used. Time to remission was defined as the duration (in weeks) from diagnosis to complete remission, as documented in follow-up clinical records. Hazard ratios (HR) with corresponding 95% CI and p-values were reported. Time-to-remission analysis was performed using the Kaplan–Meier method. Survival curves were plotted separately for patients receiving different induction Cregimens.

Results

Patient demographics and clinicopatholpgical characteristics

Table 01: Clinical, renal, histological, treatment and outcome characteristics (n=38)

Parameter	Variable	n / Mean ± SD	%
Patient Demographics			
Age	Age (years)	11.8 ± 2.6	
Gender	Female	26	68.4
	Male	12	31.6
Area of residence	Western	15	39.5
	Central	6	15.8
	Southern	0	0
	Northern	4	10.5
	North Western	4	10.5
	North Central	1	2.6
	Eastern	3	7.9
	Uva	3	7.9
	Sabaragamuwa	2	5.3
Clinical Manifestations			
Constitutional	Fever	16	42.1
Hematological	Leukopenia	8	21.1
	Thrombocyto-penia	8	21.1
	Autoimmune haemolysis	0	0.0
Neuropsychiatric	Psychosis	1	2.6
	Seizure	3	7.9
Musculoskeletal	Arthritis	14	36.8
Mucocutaneous	Alopecia	11	28.9
	Discoid lupus	3	7.9
Serosal	Pericarditis	0	0.0
	Pleural effusion	4	10.5
Biomarker Profile			
dsDNA	Anti-dsDNA positive	27	71.1
Complement	Complement C3 (mg/dL)	58.2 ± 39.0	
	Complement C4 (mg/dL)	13.7 ± 17.0	
Renal Features			
Hematuria		18	47.4
Hypertension and hypertensive encephalopathy		18	47.4
Oedema		18	47.4
Oliguria		5	13.2
Acute kidney injury		1	2.6
Proteinuria Nephrotic range proteinuria		25	65.8
Sub nephrotic range proteinuria		13	34.2
Renal class	Class II	5	13.2
	Class III	10	26.3
	Class IV	21	55.3
	Class II to V	2	5.3
Baseline UPCR (mg/mmol)		323.8 ± 230.0	
UPCR in remission (mg/mmol)		68.6 ± 110.2	
eGFR at presentation (mL/min/1.73m²)		96.7 ± 31.7	
eGFR at 1 year (mL/min/1.73m²)		124.9 ± 52.4	

Parameter	Variable	n / Mean ± SD	%
Activity index		5.5 ± 3.5	
Chronicity index		0.7 ± 1.9	
Histopathological Features			
Endocapillary hypercellularity/ proliferation		28	73.7
Hyaline necrosis with or without karyorrhexis		21	55.3
Mesangial hypercellularity/ proliferation		30	78.9
Mesangial expansion		18	47.4
Cellular crescents		4	10.5
Fibrous crescents		4	10.5
Sclerosis		3	7.9
Tubular atrophy		6	15.8
Interstitial fibrosis		8	21.1
Lymphocyte infiltration		19	50.0
Proliferative lesion		10	26.3
Treatment & Outcome			
Prednisolone (induction)		38	100.0
Cyclophosphamide (CYC) (induction)		30	78.9
Mycophenolate mofetil (MMF) (induction)		3	7.9
MMF (maintenance)		29	76.3
Azathioprine (maintenance)		4	10.5
Hydroxychloroquine (maintenance)		38	100.0
AKI requiring dialysis		1	2.6
Chronic kidney disease		0	0.0
Survived		38	100.0

All continuous variables are presented as mean ± SD; categorical variables as n (%)

Associations with activity index (AI)

Table 02: Univariate linear regression analyses for AI .

Variable	β Coefficient	95% Confidence Interval	p-value
Age (years)	0.071	-0.378 – 0.52	0.750
Sex (female)	-1.135	-3.589 – 1.32	0.355
Anti-dsDNA positive	0.283	-2.262 – 2.827	0.823
Complement C3 (mg/ dL)	-0.028	-0.057 – 0	0.052
Complement C4 (mg/ dL)	-0.062	-0.127 – 0.004	0.063
Hematuria	-0.161	-2.473 – 2.151	0.888
Hypertension / HT encephalopathy	-1.322	-3.591 – 0.947	0.245
Oedema	-2.061	-4.266 – 0.144	0.066
Proteinuria	-0.486	-2.915 – 1.942	0.687
Cyclophosphamide	1.926	-1.779 – 5.632	0.299
Endocapillary hypercellularity	1.050	-1.548 – 3.648	0.418
Mesangial hyper-cellularity	2.500	-0.203 – 5.203	0.068
Hyaline necrosis with or without karyorrhexis	3.199	1.144 – 5.254	0.003
Cellular crescents	5.059	1.707 – 8.41	0.004

Table 03: Multivariate linear regression analyses for AI .

Variable	β Coefficient	95% Confidence Interval	p-value
Age (years)	-0.30	-0.74 – 0.15	0.185
Sex (female)	-0.88	-2.97 – 1.21	0.394
Anti-dsDNA positive	0.23	-2.14 – 2.60	0.845
Complement C3 (mg/dL)	-0.00	-0.04 – 0.03	0.852
Complement C4 (mg/dL)	-0.02	-0.10 – 0.05	0.515
Oedema	-1.58	-3.50 – 0.33	0.102
Mesangial hypercellu-larity	1.34	-1.13 – 3.81	0.276
Hyaline necrosis with or without karyorrhexis	2.53	0.57 – 4.48	0.013
Cellular crescents	4.62	1.07 – 8.16	0.013

The presence of hyaline necrosis with or without karyorrhexis and cellular crescents were both significantly associated with higher AI scores in univariate analysis (Table 02). In the multivariate

analysis, presence of hyaline necrosis with or without karyorrhexis and cellular crescents were independently associated with higher AI scores (Table 03).

Associations with chronicity index (CI)

Table 04: Univariate linear regression analyses for CI .

Variable	β Coefficient	95% Confidence Interval	p-value
Age (years)	0.031	-0.216 – 0.278	0.802
Sex (female)	-0.910	-2.24 – 0.419	0.173
Anti-dsDNA positive	0.616	-0.767 – 1.999	0.372
Complement C3 (mg/dL)	-0.011	-0.027 – 0.005	0.190
Complement C4 (mg/dL)	-0.017	-0.054 – 0.021	0.374
eGFR at presentation (mL/min/1.73m²)	-0.008	-0.028 – 0.013	0.451
Baseline UPCR (mg/mmol)	0.001	-0.002 – 0.004	0.465
UPCR in remission (mg/mmol)	0.011	0.006 – 0.015	<0.001
Fibrous crescents	0.324	-1.74 – 2.388	0.752
Tubular atrophy	0.938	-0.773 – 2.648	0.274
Interstitial fibrosis	0.367	-1.184 – 1.918	0.635
Sclerosis	1.038	-1.288 – 3.364	0.371
Lymphocyte infiltration	-0.158	-1.425 – 1.11	0.802
Proliferative lesion	-0.150	-1.59 – 1.29	0.834

Univariate linear regression analyses showed that higher UPCR in remission was significantly associated with increased CI values (Table 04). In the multivariable model, after adjusting for confounders (Table 05), female sex was negatively associated with CI while PCR in remission remained positively associated.

Table 05: Multivariate linear regression analyses for CI.

Variable	β Coefficient	95% Confidence Interval	p-value
Age (years)	0.15	-0.05 – 0.34	0.131
Sex (female)	-1.01	-1.99 – -0.03	0.044
Complement C3 (mg/dL)	-0.01	-0.02 – 0.00	0.140
eGFR at presentation (mL/min/1.73m²)	-0.01	-0.03 – 0.00	0.109
UPCR in remission (mg/mmol)	0.01	0.01 – 0.02	<0.001
Tubular atrophy	0.38	-0.90 – 1.67	0.548

Time to remission by induction therapy

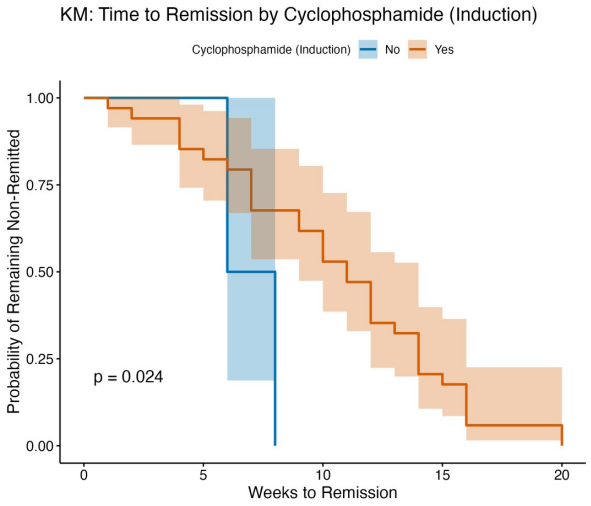

Figure 01: Kaplan–Meier survival analysis

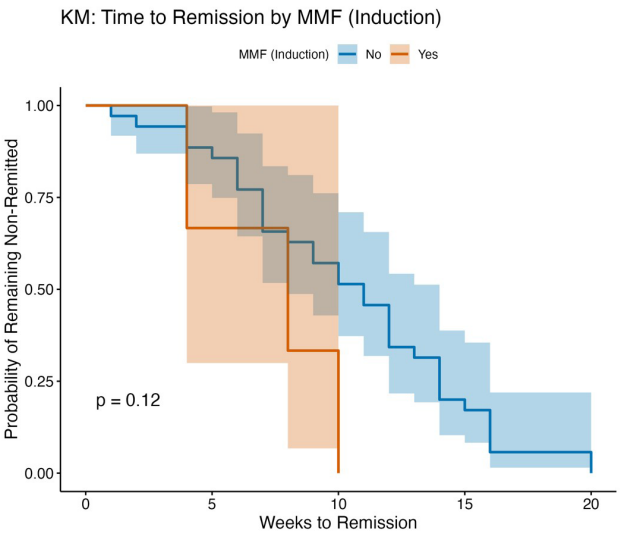

Figure 02: Kaplan - Meier survival analysis

The median time to remission was shorter among patients who received CYC. The Kaplan–Meier survival curves showed a significant difference between the two groups (p = 0.024) (Figure 01). The probability of remaining non-remitted declined more rapidly among patients treated with CYC, indicating that this group achieved remission earlier. Patients who received MMF demonstrated a shorter time to remission. However, this difference was not statistically significant (p = 0.12) (Figure 02). The probability of achieving remission increased progressively over time in both groups, with overlapping confidence intervals indicating comparable remission patterns during follow-up.

Factors associated with time to remission

Table 06: Cox proportional hazards model for time to remission

Variable	Hazard Ratio	95% CI	p value
Age (years)	1.11	0.93 – 1.34	0.246
Sex: male vs female	2.90	1.11 – 7.54	0.030
Activity Index	0.88	0.77 – 0.99	0.034
Chronicity Index	1.08	0.82 – 1.42	0.588
Proliferative vs Non-proliferative(-class)	0.04	0.01 – 0.27	0.001
eGFR at presentation (mL/min/1.73m²)	1.00	0.99 – 1.01	0.535
UPCR at baseline (mg/mmol)	1.00	1.00 – 1.00	0.075
CYC (Induction): Yes vs No	0.56	0.11 – 2.70	0.467
MMF (Induction): Yes vs No	0.10	0.01 – 1.11	0.061

In the adjusted model (Table 06), male sex, higher activity index were, proliferative class were significantly associated with time to remission.

Relapse characteristics

Table 07: Characteristics by relapse status

Variable*	Category	No relapse (n=33)	Relapse (n=5)
Patient Demographics			
Age (years)		11.7 ± 2.7	12.2 ± 2.1
Sex	Female	21 (65.6%)	4 (80.0%)
	Male	11 (34.4%)	1 (20.0%)
Renal Indices			
AI		5.4 ± 3.6	5.8 ± 3.1
CI		0.3 ± 0.6	2.8 ± 4.3
ISN/RPS class	II	5 (15.6%)	0 (0%)
	III	8 (25.0%)	2 (40.0%)
	IV	17 (53.1%)	3 (60.0%)
	Mixed (II–V)	2 (6.3%)	0 (0%)
eGFR at presentation (mL/min/1.73m²)		96.6 ± 33.4	97.0 ± 23.0
UPCR at baseline (mg/mmol)		310.8 ± 225.0	392.7 ± 266.4
Histopathological characteristics			
Tubular atrophy	No	29 (90.6%)	3 (50%)
	Yes	3 (9.4%)	3 (50%)
Interstitial fibrosis	No	26 (81.2%)	4 (66.7%)
	Yes	6 (18.8%)	2 (33.3%)
Sclerosis	No	31 (96.9%)	4 (66.7%)
	Yes	1 (3.1%)	2 (33.3%)
Treatment Characteristics			
CYC (induction)	No	4 (100%)	
	Yes	28 (82.4%)	6 (17.6%)
MMF (induction)	No	30 (85.7%)	5 (14.3%)
	Yes	2 (66.7%)	1 (33.3%)
MMF (maintenance)	No	7 (77.8%)	2 (22.2%)
	Yes	25 (86.2%)	4 (13.8%)
Azathioprine (maintenance)	No	30 (88.2%)	4 (11.8%)
	Yes	2 (50%)	2 (50%)
Hydroxychloroquine (maintenance)	No	5 (62.5%)	3 (37.5%)
	Yes	27 (90%)	(10%)

**Data are presented as mean ± SD or n (%)*

Of the 38 children with LN, five patients (13.2%) experienced at least one relapse during the follow-up period (Table 07). The mean duration to the first relapse episode was 15.8 ± 9.9 months, and the most common clinical manifestation of relapse was proteinuria.

Discussion

This multicentre Sri Lankan paediatric cohort comprised of 38 children with biopsy-proven LN. Nephrotic-range proteinuria (66%), and proliferative histology (class IV: 55%; class III: 26%) were most prevalent. Findings of oedema, hypertension, and haematuria were common at presentation. Similarly, the Indian Paediatric LN Registry reported that oedema (75%), hypertension (54%), and nephrotic-range proteinuria (68%) were prominent at diagnosis [7]. However, this cohort had a higher rate of AKI (43% vs 2.6% in present study), which suggests that they had more severe renal involvement initially [7].

The significant and independent association of hyaline necrosis and cellular crescents with higher AI agrees the findings of other studies on paediatric and adult LN [8–10]. The absence of independent associations with demographic, serological and clinical factors is consistent with other studies indicating that histological features are more effective direct predictors of renal activity than systemic or serological markers alone [8].

The significant positive correlation between higher UPCR during remission and an increased CI suggests that persistent proteinuria following initial treatment is associated with more severe, irreversible kidney damage, such as tubular atrophy, interstitial fibrosis and glomerulosclerosis [11]. The lack of significant associations between the CI and baseline UPCR, eGFR, histopathological chronic changes or serological markers denotes that these indices may reflect accumulated damage rather than the severity of the initial disease [12]a multivariate Cox proportional hazards regression analysis with cubic spline functions model and smooth curve fitting (penalized spline method. This emphasises the importance of monitoring proteinuria throughout the course of the disease rather than relying on the initial presentation alone.

The observation of CYC therapy leads to earlier remission agrees with ALMS and other studies which have demonstrated the effectiveness of both CYC and MMF in inducing remission in proliferative LN, though CYC often yields a faster early response, particularly in severe cases [13].

A higher AI was significantly associated with a lower likelihood of achieving remission. Choi et al. (2023) demonstrated that NIH-derived AI and CI were associated with treatment response and long-term prognosis in LN [10]. This supports the pathobiological rationale that more intense glomerular injury (higher activity) delays prompt remission. Additionally, the presence of proliferative forms was strongly associated with a lower risk of remission which is consistent with earlier paediatric studies [14].

The predominance of proliferative disease among relapsed and non relapsed cases aligns with global findings suggesting that class III/IV LN is more likely to exhibit recurrent activity than non-proliferative classes [15].

Limitations

Relatively small size limited the statistical power of the tests, particularly for subgroup analyses or associations. Conducting the study in only three tertiary care centres may also limit its applicability to different healthcare settings or ethnic groups. The retrospective design limits data completeness and control over data collection variables. Some clinical or laboratory details may have been missing or inconsistently recorded, which can affect the robustness of the data.

Conclusions

This study provides a comprehensive description of the clinicopathological and therapeutic profiles of paediatric LN in tertiary care settings in Sri Lanka. Most patients presented with nephrotic-range proteinuria and proliferative LN was the most prevalent form. Histopathological features were key predictors of higher disease activity whereas persistent proteinuria during remission was associated with chonic renal damage.

Although CYC permitted faster remission, it was notably delayed among males, those with high AI and proliferative LN. Relapses were less common

but more frequently ended in higher chronicity and tubulointertitial injury. These findings emphasize the importance of early diagnosis, careful monitoring of proteinuria and timely therapy to optimize renal outcomes in paediatric LN. Further longitudinal studies with larger cohorts are needed to assess long-term renal survival and refine treatment protocols for Sri Lankan children.

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