Original Article

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Clinical Presentation and Biochemical Parameters of Childhood Lupus Nephritis and Its Correlation with Underlying Renal Histopathology: A Cross-sectional Study

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ABSTRACT

Background: *Lupus nephritis is a major concern in patients with systemic lupus erythematosus. Clinical presentation and biochemical parameters are usually correlated with histopathological classes of lupus nephritis; however, patients with mild clinical features may have moderate to severe glomerular injury, while severe presentations may sometimes show less severe damage. The aim of this study was to assess clinical presentation and biochemical parameters of childhood lupus nephritis and their correlation with renal histopathology.* ***Methods & Materials:*** *This cross-sectional observational study was conducted in the Department of Pediatric Nephrology, Bangladesh Shishu Hospital & Institute (BSH&I), from October 2022 to March 2024. A total of 44 children aged 4–18 years who fulfilled the 2019 ACR/EULAR criteria.* ***Results:*** *Among 44 participants, mean age was 10.6 years with a female-to-male ratio of 3.4:1. About 81.81% had nephritis with systemic features and 18.19% had isolated lupus nephritis. Class IV was the most common histopathological class (32%). Proteinuria was present in 97.3%, of whom 56.8% had nephrotic-range proteinuria. Other findings included hematuria, anasarca, hypertension, and acute kidney failure. Anasarca, nephrotic-range proteinuria, acute kidney failure, reduced eGFR, increased spot uPCR, hypoalbuminemia, SLEDAI, and renal SLEDAI were significantly higher in Class IV LN. However, 18.18% of Class II LN also had nephrotic-range proteinuria. Non-nephrotic proteinuria was significantly higher in Class II LN (p=0.005), but was also seen in 22.22% of Class III, 14.28% of Class IV, and 33.33% of Class V LN.* ***Conclusion:*** *Clinical and biochemical severity is greater in advanced lupus nephritis, especially Class IV LN.*

Keywords: *Systemic Lupus Erythromatosus, Lupus Nephritis, Clinical presentation, Biochemical parameters, Renal histopathology.*

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder that causes inflammation in connective tissue, leading to symptoms that affect multiple systems in the body, including joints, skin, kidneys, heart, lungs, and the nervous system[1].

Childhood onset systemic lupus erythematosus (SLE) accounts for 10-20% of all SLE cases. The worldwide incidence of SLE ranges from 0.3 to 2.5 per 100,000 while prevalence ranges from 1.89 to 25.7 per 100,000 [2]. Females have a higher incidence rate of childhood SLE with a female to male ratio of 4:3, which increases to 9:1 during the reproductive period[3].

Renal involvement is a major concern in patients with Systemic Lupus Erythematosus SLE), accounting for 65% of cases[4]. Interestingly, studies have shown that childhood SLE is associated with a higher prevalence of renal involvement than adult-onset SLE [5,6]. Lupus nephritis is a significant cause of morbidity, mortality, and increased healthcare costs, with 10-30% of patients ultimately progressing to end-stage kidney disease within 15 yrs of diagnosis [7]. The clinical presentation of lupus nephritis can range from minimal proteinuria to rapidly progressive glomerulonephritis [8].

Renal biopsy is the most reliable method for diagnosing lupus nephritis [9]. The International Society of Nephrology/Renal Pathology Society (ISN/RPS) issued a classification in 2003, which includes six types of nephritis determined by light, electronic and immunofluorescence microscopy findings [10]. There are six classes, and class I or II is considered as moderate SLE, while class III and onwards are categorized as severe SLE.

It is important to conduct careful screening tests for patients with lupus nephritis, as many may not exhibit any obvious symptoms of urinary abnormalities [11].

According to the American College of Rheumatology 2012 guidelines, a renal biopsy may be recommended if the patient has 24-hour proteinuria levels exceeding 1gm/m^2/24hrs or if urinary spot PCR levels are higher than 1mg/mg. Additionally, a biopsy may be necessary if the patient has 24-hour proteinuria levels above 0.5gm/m^2/24hrs, along with hematuria ≥5/HPF or cellular casts, or if there is an increase in serum creatinine levels without any compelling alternative causes, such as sepsis, hypovolemia, or medication [12].

Clinical presentation and biochemical parameters such as proteinuria, hematuria, hypertension, serum creatinine, and glomerular filtration rate are often correlated with the

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histopathological classes of lupus nephritis (LN). Studies have shown that Class IV LN is associated with more severe clinical manifestations and poorer outcomes. Significant correlations between proteinuria and histopathological classes have also been reported, while hematuria and pyuria showed no such association. Edema, nephrotic-range proteinuria, hypertension, renal impairment, elevated creatinine, and increased proteinuria have been linked to advanced classes of LN [13]. Patients with Class I–II LN usually present with mild proteinuria or hematuria, whereas Class III–IV LN commonly manifests with hypertension, nephritic urine sediment, and nephrotic-range proteinuria [14].

However, clinical severity does not always reflect histopathological damage. Some patients with mild clinical features may have severe nephritis, while severe clinical presentations may correspond to less severe pathology [15-18]. Therefore, this study aimed to evaluate the relationship between clinical severity and histopathological classes of childhood lupus nephritis.

METHODS & MATERIALS

This cross-sectional observational study was conducted in the Department of Pediatric Nephrology, Bangladesh Shishu Hospital & Institute (BSH&I), from October 2022 to March 2024. A total of 44 children aged 4–18 years who fulfilled the 2019 ACR/EULAR criteria for systemic lupus erythematosus (SLE) and underwent renal biopsy for lupus nephritis (LN) were included using non-probability convenient purposive sampling. Patients with insufficient glomeruli in biopsy specimens were excluded. Data were collected using a structured questionnaire through interviews with parents or legal guardians and review of clinical records. Demographic variables included age, gender, duration of renal involvement, and time of onset of nephritis from initial symptoms. Clinical variables included anasarca, proteinuria, hematuria, acute kidney failure, and hypertension, while biochemical parameters included serum albumin, serum creatinine, estimated glomerular filtration rate (eGFR), spot urinary protein-creatinine ratio (uPCR), urine RBC, urine WBC, and urinary casts. Disease activity was assessed using SELENA-SLEDAI and renal SLEDAI scores. Laboratory investigations included complete blood count, urine routine examination, serum albumin, serum creatinine, complement levels, ANA, and anti-dsDNA antibodies. eGFR was calculated using the modified Schwartz formula. Ultrasound-guided percutaneous renal biopsy was performed according to standard procedures, and histopathological classification was done according to the ISN/RPS 2003 classification of lupus nephritis. Renal tissue specimens were evaluated by light microscopy and immunofluorescence microscopy at Bangabandhu Sheikh Mujib Medical University. Ethical approval was obtained from the Ethical Review Committee of BSH&I, and informed written consent was obtained from parents or legal guardians. Data were analyzed using IBM SPSS version 25. Qualitative variables were expressed as frequency and percentage, and quantitative variables as mean ± SD. ANOVA with Tukey HSD post hoc test and Pearson's chi-square test were applied, with $p<0.05$ considered statistically significant.

RESULTS

Table I showed baseline characteristics of the patients. Mean age of the patient was 10.6±2.4 years. Most of the patient were female (77.3%) with female to male ratio 3.4:1. Average duration of the nephritis was 34.9±12.9 days and time of onset of nephritis ranged from 10 days to 5 years with mean duration 6.4 months. 81.81% had systemic manifestation along with Lupus Nephritis while, 18.19% showed isolated Lupus Nephritis manifestations. Baseline eGFR was 73.33±32.30 ml/min/m2.

Table I: Baseline Characteristics of the study subjects. (*n*=44).

Parameters		Frequency (n)	Percentage (%)	Mean (SD)
Age (4yrs- 16yrs)				10.6 ±2.4
Gender	Male	10	22.7%	
	Female	34	77.3%	
Presentation	Isolated nephritis	8	18.19%	
	Along with systemic features	36	81.81	
Duration of Nephritis (Days)				34.9 ±12.9
Time of onset of Nephritis from initial symptoms (months)				6.4±12.92
eGFR				73.33 ± 32.30

Result expressed as percentage and mean±SD.

Table II showed Among renal manifestation of the Lupus Nephritis, Proteinuria (both non-nephrotic and nephrotic range) was the most common manifestations (97.73%) among them 56.8% had nephrotic range followed by hematuria (79.6%), anasarca (54.54%). hypertension (52.3%) and acute kidney failure (20.5%).

Table II: Renal manifestations of the study subjects. (*n*=44)

Renal Manifestations		Frequency (n=44)	Percentage (%)
Anasarca		24	54.54
Hematuria	Gross	19	43.2
	Microscopic	16	36.4
Proteinuria	Non nephrotic range	18	40.9
	Nephrotic range	25	56.8
Acute kidney failure		9	20.5
Hypertension		23	52.3

Result expressed as percentage.

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Table III showed mean albumin was 20.5g/L, S. creatinine 1.6mg/dl, eGFR 73.3ml/m^2/min. 97.3% patient had sopt PCR >0.2 among them 56.8% had >2 spot PCR, 47.7% had reduced eGFR (<90ml/min/1.73m^2) among them 20.5% had eGFR <35ml/min/1.73m^2, 95.45% had low C3, 75% had low C4 and 93.2% had both positive ANA & Anti-dsDNA.

Table III: Baseline Biochemical and Immunological Parameters of the study subjects (*n*=44).

Biochemical Parameters		Number	Percent (%)	Mean	SD
S.Albumin (gm/L)				20.5	8.163
Spot Urinary Protein creatinine ratio	<0.5	1	2.3		
	0.5-1	11	25		
	1-2	7	15.9		
	>2	25	56.8		
Urine RBC (>5/hpf)		35	79.54		
S. Creatinine (mg/dl)				1.6	2.679
Estimat ed GFR	>90ml/min/1.73m^2	23	52.23		
	35-90ml/min/1.73m^2	12	27.27		
	<35 ml/min/1.73m^2	9	20.5		
Low C3		42	95.45		
Low C4		33	75		
ANA (+ve)		41	93.2		
Anti-dsDNA (+ve)		41	93.2		

Results expressed as percentage and mean±SD.

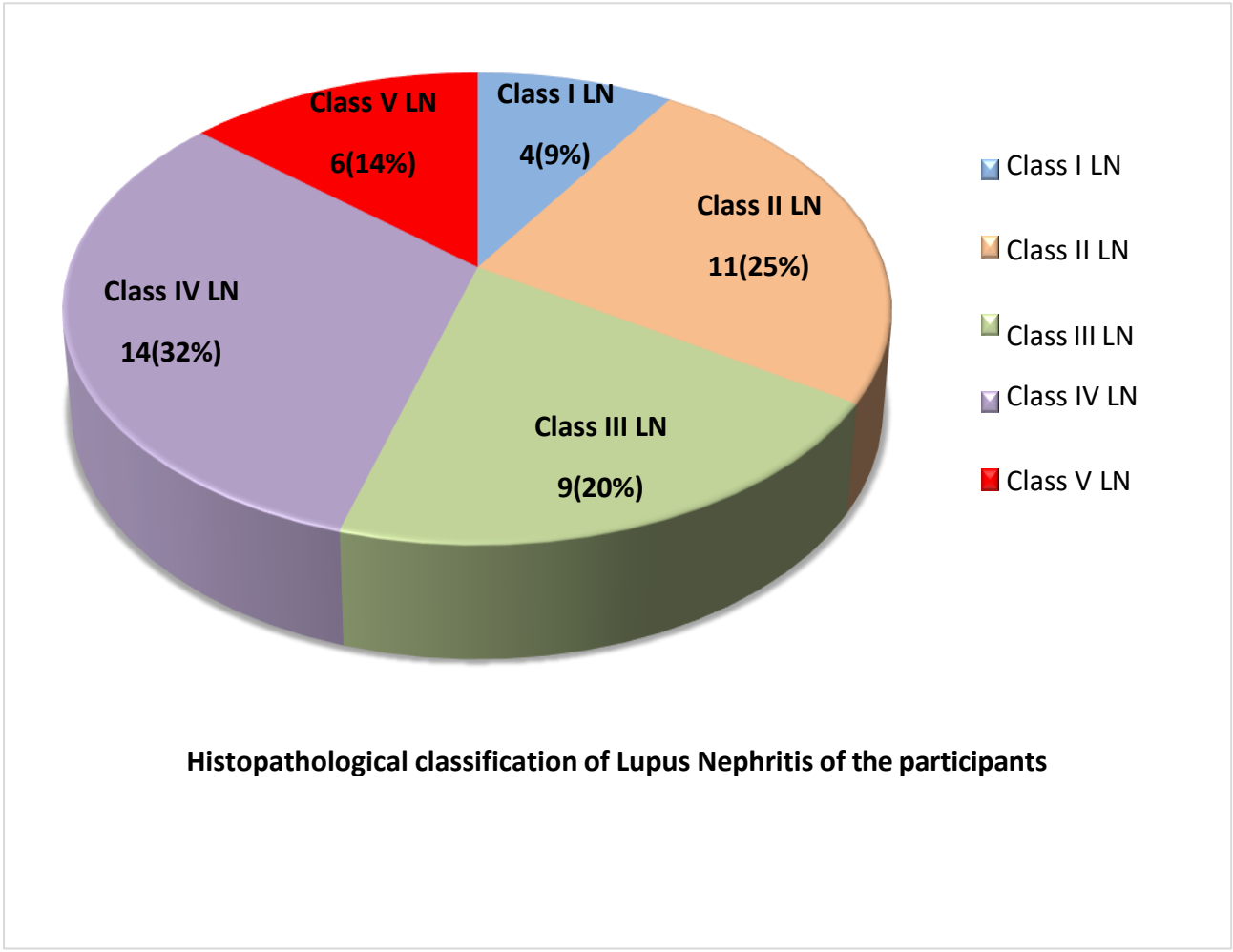

Figure 1: Frequency distribution of histopathological classes of Lupus Nephritis. (*n*=44).

Figure 1 showed Class IV lupus nephritis was the most common, representing 32% patients, followed by Class II (25%), Class III (20%), Class V (14%), and Class I (9%).

Table IV showed Non-nephrotic range proteinuria were more in class II LN but 22.22% of Class III LN, 14.28% of class IV LN and 33.33% of class V LN had non-nephrotic range proteinuria. Anasarca, nephrotic range proteinuria, acute kidney failure were significantly highest in class IV LN but

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18.18% of class II LN had nephrotic range proteinuria. There was no significant difference of hematuria and hypertension between classes of LN.

Table IV: Clinical presentation of Lupus Nephritis according to histopathological classes.

Variables	Total (n=44)	Class I (n=4)	Class II (n=11)	Class III (n=9)	Class IV (n=14)	Class V (n=6)	P value
Anasarca	24 (54.54%)	0 (0.0%)	2 (18.18%)	6 (66.67%)	12 (85.71%)*	4 (66.7%)	0.003
Nephrotic range proteinuria in urine dipstick	25 (56.8%)	0 (0.0%)	2 (18.18%)	7 (77.78%)	12 (85.71%)*	4 (66.67%)	0.003
Non nephritic range proteinuria in urine dipstick	18 (40.9%)	03 (75.0%)	9 (81.81%)**	3 (22.22%)	2 (14.28%)	2 (33.33%)	0.005
Hypertension	23 (52.3%)	1 (25.0%)	2 (18.18%)	6 (66.67%)	10 (71.42%)	4 (66.67%)	0.082
Acute kidney failure	9 (20.5%)	0 (0.0%)	0 (0.0%)	1 (11.11%)	6 (42.85%)***	2 (33.33%)	0.01
Haematuria in urine dipstick	35 (79.6%)	3 (75.0%)	8 (72%)	7 (77.8%)	13 (92.9%)	4 (66.7%)	0.641

**p value <0.05 versus class II*
*** p value<0.05 versus class III, IV or V*
**** p value <0.05 versus class III*
P value<0.05 considered as significant which reached from pearson chi-square test.

Table V showed there was a significant difference in eGFR (p = .022), spot urinary protein creatinine ratio (p = .003), serum albumin levels (p = .004) and serum C4 levels be (p = .011) and SLEDAI scores (p < .001) between classes but no significant difference found in serum C3 levels (p = .129) and class IV had highest significant level compared with other groups.

Table V: Biochemical variables of lupus nephritis patients according to histopathological classes.

Renal Parameters	Class I (n=4)	Class II (n=11)	Class III (n=9)	Class IV (n=14)	Class V (n=6)	p value
eGFR (Mean±SD)	92.35±11.9	95.62±23.729	68.19±30.73	57.63±26.60*	63.78±46.672	0.022
Spot PCR (Mean± SD)	0.79±0.738	3.29±3.178	8.18±7.31	12.15±6.784*	8.384±6.3	0.003
S. Albumin (Mean±SD)	28.18±12.677	23.84±7.166	23.28±4.533	14.68±5.884**	18.62±8.1	0.004
C3mg/dl (Mean±SD)	0.53±0.226	0.48±0.269	0.34±0.1853	0.29±0.169	0.32±0.20	0.129
C4mg/dl (Mean±SD)	0.08±0.039	0.27±0.284	0.06±0025	0.05±0.027***	0.11±0.12	0.011
ANA (%positive)	3 (75.0%)	10 (90.9%)	8 (88.9%)	14 (100%)	6 (100%)	0.42
Anti-DNA (%positive)	3 (75.0%)	10 (90.9%)	8 (88.9%)	14 (100%)	6 (100%)	0.42
SLEDAI Score (Mean±SD)	7.8±1.57	11.7±5.85	14.6±4.50	18.0±5.34****	13.1±3.35	<0.001

p value <0.05 = significant, p value reached from two way ANOVA test followed by Tukey HSD post hoc analysis
** p<0.05 compared with class I or II*
****p<0.05 compared with class I, II or III*
*****p<0.05 compared with class II or V*
***** p< 0.05 compared with class I or II*

Table VI showed Proteinuria (>0.5gm/24hra) observed in 97.7% of cases. Haematuria, another common renal manifestation, was present in 79.5% of cases Urine white blood cells (WBCs) were detected in 15.9% of cases and urinary casts were observed in 31.8% of cases, both of which had significant difference between classes of LN. No significant difference of proteinuria and hematuria among different classes of LN. Moreover, the Renal SLE Disease Activity Index (SLEDAI) scores varied across different classes of lupus nephritis. Class III, IV and V lupus nephritis exhibited the highest mean scores, reflecting increased disease activity in these groups. There was a significant difference in Renal SLEDAI scores between groups (p < .001), class IV had significantly highest Renal SLEDAI compared with class I, II, III and V (p<0.05).

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Table VI: Renal SLEDAI of Lupus Nephritis patients according to histopathological classes.

Variables	Total (N=44)	Class I (n=4)	Class II (n=11)	Class III (n=9)	Class IV (n=14)	Class V (n=6)	P value
Proteinuria (Spot PCR >0.5)	43 (97.7%)	3 (75.0%)	11 (100%)	9 (100%)	14 (100%)	6 (100%)	0.526
Haematuria (>5/HPF)	35 (79.5%)	3 (75.0%)	8 (72%)	7 (77.8%)	13 (92.9%)	4 (66.7%)	0.641
Urine WBC (>5/HPF)	7 (15.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (42.9%)	1 (16.7%)	0.016
Casts	14 (31.8%)	0 (0.0%)	0 (0.0%)	3 (33.0%)	8 (57.1%)	3 (50.0%)	0.017
Renal SLEDAI	8.18 ±3.655	4.00 ±0.000	5.82 ±2.089	8.0 ±3.464	11.43* ±3.081	8.00 ±2.530	<0.001

** p<0.05 compared with class I, II, III and V by post hoc analysis done by Tukey HSD.*
p <0.05 = significant, p value reached from ANOVA for mean and chi-square for percentage.

DISCUSSION

Renal involvement is common in systemic lupus erythromatosus and often determines the course of the disease. The purpose of this study was to evaluate the main clinical presentation and biochemical parameters of lupus nephritis and to explore relationship between the clinical and histopathological classes of lupus nephritis in children of Bangladesh. Here, out of 44 study participants, age and sex distribution were similar to Chowdhury et al. and Mina et al. [3,19]. About 81.81% patient exhibited nephritis along with systemic presentations but 18.19% showed isolated lupus nephritis. Most of the patients of isolated lupus nephritis, had nephrotic syndrome with atypical presentations with hypocomplementemia and both ANA & Anti-dsDNA positivity, one patient had persistent hematuria with hypertension.

Among distribution of histopathological classes, Class IV lupus nephritis was the most common, representing 32% of patients, followed by Class II (25%), Class III (20%), Class V (14%), and Class I (9%) similar to as study by Devadass et al[20].

Proteinuria is the main characteristic of lupus nephritis. According to Almaani et al., 100% of lupus nephritis patients have proteinuria, with 50% of them having nephrotic range proteinuria [21]. This finding was similar to this study, which reported that 97.3% of patients have proteinuria, with 56.8% of them having nephrotic range proteinuria and 40.9% had non-nephrotic range proteinuria. One patient had no proteinuria but had persistent hematuria with hypertension along with other manifestations of SLE.

There is a believe that severe histological lesions are associated with high levels of proteinuria and vice versa. In this study, highest protein excretion was found in class IV LN but was not significantly differ with class V LN.

In this study, it was found that Anasarca, Nephrotic range proteinuria, Acute Kidney Failure, SLEDAI and renal SLEDAI score were significantly highest in class IV lupus nephritis (p<0.05) but 18.18% of class II Lupus nephritis present with nephrotic range proteinuria. High proteinuria in class II LN may be related to podocytopathy since histological changes are not severe enough to explain the degree of proteinuria. Chouhani et al., showed 35% of class II LN had nephrotic range proteinuria [22]. Non-nephrotic range proteinuria was significantly more in class II LN, but it is important to note that 22.22% class III LN, 14.28% class IV LN and 33.33% class V LN presented with non-nephrotic range proteinuria but the difference was not significant. No significant difference found in hematuria and hypertension between classes of lupus nephritis but 66.7% of class V lupus nephritis had hematuria which had no appropriate explanation, it might be due to associated glomerulosclerosis or had mixed classes.

Mean baseline eGFR was 73.33ml/min/1.73m^2, mean serum creatinine was 1.6mg/dl and mean serum albumin was 20.5 ± 8.16g/L. In this study, Average duration of the nephritis was 34.9 days and time of onset of nephritis ranged from 10 days to 5 years. This study showed that mean eGFR, serum albumin level and serum C4 were significantly low while spot urinary PCR was significantly high in class IV lupus nephritis group whereas C3 level had no significant difference. This results are similar to the studies conducted by Charaya et al., and Ismail et al., where they found class IV lupus nephritis had more aggressive presentations [13,23].

The exception of this study (non nephrotic range proteinuria in class III, IV and V) was consistent with Fulgeri et al., and Baqui et al, [15,18].

Among Renal SLEDAI, Proteinuria (Spot PCR>0.5mg/mg) and Hematuria (Urine RBC>5/hpf) had no significant differences between classes of lupus nephritis but Pyuria (urinary WBC >5/HPF) and Urinary casts were high in class IV Lupus Nephritis (p=0.016 and p=0.017 respectively).

LIMITATIONS

Histopathological slides were analyzed by different histopathologists, which increases the likelihood of varying opinions. Inhomogeneous and limited number of sample in different groups.

RECOMMENDATIONS

Future studies are needed to reflect the actual scenario of lupus nephritis classes in mild presentations using a prospective, longitudinal design on a multicenter basis and a large sample.

CONCLUSION

This study results concluded that, the majority of cases of class IV lupus nephritis are associated with severe clinical symptoms like anasarca, nephrotic-range proteinuria, and acute kidney failure, as well as biochemical changes such as increased spot urinary protein creatinine ratio, hypoalbuminemia, and reduced eGFR. However, a few cases of class II lupus nephritis have shown severe symptoms, while some cases of class IV lupus nephritis have shown minimal clinical symptoms. There is a consistent relationship between clinical and biochemical parameters and the histopathological classes of lupus nephritis, but there are some non-significant exceptions.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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