ISSN: 2582-6751
Journal of Clinical Medical Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Research Article

Histopathological Pattern of Lupus Nephritis for Implication to Treatment in a Tertiary Care Hospital, Dhaka, Bangladesh

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Citation: Hossain MT, et al. Histopathological Pattern of Lupus Nephritis for Implication to Treatment in a Tertiary Care Hospital, Dhaka, Bangladesh. Jour Clin Med Res. 2025;6(1):1-9.

https://doi.org/10.46889/JCMR.2025.6106

Received Date: 06-01-2025

Accepted Date: 24-02-2025

Published Date: 03-03-2025

Abstract

Background: Lupus Nephritis (LN) is one of the more common and serious manifestations of Systemic Lupus Erythematosus (SLE). It is regarded as both a strong predictor and a leading cause for morbidity and mortality amongst those who suffer from the disease.

Objectives: To observe the variable histopathological patterns of lupus nephritis by renal biopsy and to observe whether American College of Rheumatology (ACR) guidelines are being followed during treating the LN patients or not.

Patients and Methods: The charts of 30 consecutive patients with biopsy proven lupus nephritis admitted into Dhaka Medical College Hospital from January 2014 to June 2014 were studied. Patient with SLE without evidence of LN (defined by proteinuria more than 0.5 gm/24 hours and/or haematuria, cellular casts) were excluded.

Result: The mean age of was 26.63 ± 9.73 SD years and male:female ratio was 0.15. There were ANA positive 100% , Anti-ds DNA positive 83.3% and all the patients (100%) had low complement (C3 and C4) level.Percutaneous renal biopsy showed predominant types of lupus nephritis was Class IV (33.3%), then Class III (26.7%). Mean Activity Index (AI) 7.83 ± 2.52 and Chronicity Index (CI) 1.4 ± 1.9. In management of 76.67% received intravenous pulse methylprednisolone, 63.3% received intravenous pulse high-dose cyclophosphamide and 16.67% received Mycophenolate Mofetil (MMF).

Conclusions: In spite of MMF's more safety profile, Cyclophosphamide was generally used as a first line agent in this study for financial constance. Though the induction regimen of Cyclophosphamide used in DMCH was similar to ACR guideline, but the maintenance regimen was not followed by ACR guideline which was consistent with the KDIGO (Kidney Disease Improving Global Outcomes) guideline. But the regimen of MMF and glucocorticoids used in management of LN patients was similar to ACR guideline, 2012.

Keywords: Histopathologist; Lupus Nephritis; Implication; Bangladesh

Introduction

Systemic Lupus Erythematosus (SLE) is considered to be a prototypic autoimmune disease, characterized by involvement of multiple organs including joints, skin, central nervous system, lungs, kidneys, gastrointestinal tracts, cardiovascular system and bone marrow, accompanied by multiple laboratory abnormalities and frequent exacerbation [1]. The overall incidence rates of SLE ranges from approximately 1.8 to 7.6 per 100,000 persons/year and prevalence rates generally range from 20-70 per 100,000 [2]. The histopathology of Lupus Nephritis (LN) is extremely pleomorphic. The introduction of renal biopsy in the 1950s, the application of immunoflurescence and electron microscopic techniques in the 1960s and increasing knowledge about mechanisms of immune – mediated glomerular injury derived from experimental studies on serum sickness and other models formed the basis of the recognition and classification of the various patterns of renal injury in SLE [3,4]. As early as 1964, focal

segmental glomerulonephritis, diffuse proliferative glomerulonephritis and membranous glomerulopathy were recognised as seperate entities, followed by the identification of mesangial lesions in the 1970s. Survival of patients with SLE has improved remarkably over past decades. Earlier diagnosis, awareness of the vascular risk factors such as hypertension, nephritic syndrome, antiphospholipid syndrome and better approaches to treatment have undoubtly contributed to the improved prognosis of SLE [5]. The first World Health Organization (WHO) classification was formulated by Pirani and Pollak in Buffalo, New York in 1974 and was first used in publications in 1975 and 1978 (Table 1) [4,6]. The classification addressed glomerular lesions only. Class-I was applied to renal biopsies showing no detectable glomerular abnormalities by light, flurescence or electron microscopy. Class-II was defined as purely mesangial immune deposition and was subdivided into two subclasses depending on whether mesangial hypercellularity was present. Class-III lesions were defined as proliferative glomerulonephritis affecting fewer than 50% of the glomeruli (i.e., focal), whereas class-IV was defined as proliferative glomerulonephritis affecting more than 50% of the glomeruli (i.e., diffuse). The diagnosis of SLE is often clinically established by the presence of certain clinical and laboratory features defined by the 1997 modified American Rheumatism Association (ARA) criteria. Development of 4 out of 11 criteria over a lifetime gives a 96% sensitivity and specificity for SLE [7]. Kidney is a major target organ in upto 60% of patients with SLE, with 25-50% presenting with kidney involvement already at the time of lupus diagnosis [8]. Lupus Nephritis (LN) is regarded as both a strong predictor and a leading cause for morbidity and mortality amongst those who suffer from the disease. The presentation of LN is highly variable, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis with haematuria and red cell casts. Generally renal involvement tends to occur within the first 2 years of SLE with its frequency decreasing significantly after the first 5 years of disease [7,8]. Several studies have illustrated the lack of reliability of diagnoses rendered on the basis of clinical features alone. Therefore, making a diagnosis on clinical grounds alone is problematic and risky, underscoring the need for renal biopsy to see the histopathological pattern and to guide therapeutic decision. As the therapeutic armamentarium for LN expands, it becomes even more imperative that the correct diagnosis be made prior to instituting therapy [3,8]. Making a diagnosis of SLE is usually not a challenging problem. In addition to clinical criteria, several serological tests for SLE, including the anti-nuclear antibody and anti-double-stranded DNA antibody assays, antibodies to anti-Sm, anti-Ro and anti-La, as well as complement assays are available as confirmatory tests. However, once a diagnosis of SLE has been made, staging the renal involvement and judging the degree of activity requires the use of a histological classification. The World Health Organization (WHO) classification and more recently the International Society of Nephrology/ Renal Pathology Society (ISN/ RPS) classification, have captured this histological heterogenicity and are widely utilized in managing patients. The main purpose of classifying lupus nephritis is to make sure that the type of treatment recommended matches the severity of disease and that information about short and long-term prognosis guides both the duration and intensity of treatment. Treatment strategies will differ based on biopsy findings [3,9].

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Methodology

Type of Study

It was a cross-sectional observational study.

Place of Study

Department of Medicine and Department of Nephrology, Dhaka Medical College Hospital, Dhaka, Bangladesh.

Period of Study

From January 2014 to June 2014.

Study Population

30 cases, who were diagnosed clinically as Lupus Nephritis on the basis of ACR criteria, irrespective of age and sex were studied with subsequent renal biopsy and histopathology.

Inclusion Criteria

1. SLE patients (fulfilled at least four out of eleven ACR revised classification criteria for SLE) having proteinuria (>0.5 gm/day or 3+), haematuria or cellular casts (red cell, granular or tubular)
2. Lupus Nephritis patients age >12 years and who had no contraindication for renal biopsy
3. Lupus Nephritis patients who had no contraindication to steroid or cytotoxics

Exclusion Criteria

1. SLE patients who did not fulfill the ACR criteria of renal involvement
2. Lupus Nephritis patients who had containdication to renal biopsy
3. LN patients contraindicated to steroid or cytotoxics
4. LN patients who did not give consent
5. Pregnant LN patient

Operational Definitions

1. *Systemic Lupus Erytheatosus (SLE) :* According to American College of Rheumatology(ACR) revised classification criteria, development of 4 out of 11 criteria over a lifetime of a patient will be level as Systemic Lupus Erytheatosus (SLE).
2. *Lupus Nephritis (LN) :* LN is defined as clinical and laboratory manifestations that meets ACR criteria (persistent proteinuria >0.5 gm/day or greater than 3+ by dipstick and/or cellular casts including red blood cells, haemoglobin, granular, tubular or mixed). A review of the ACR criteria has recommended that a spot urine protein/ creatinine ratio of >0.5 can be substituted for the 24- hour protein measurement and active urinary sediment (>5 RBCs/hpf, >5 WBCs/hpf in the absence of infection or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts

Sample Size

Formula,

$$n=Z^2pq/e^2.$$

According this prevalence the sample size was 45, as time was limited, here 30 cases who were diagnosed clinically as lupus nephritis on the basis of ACR criteria, with subsequent renal biopsy and histopathology and who fufilled the inclusion and exclusion criteria admitted into Dhaka Medical College Hospital from January 2014 to June 2014 were studied.

Data Collection

After getting admission into DMCH suspected lupus patient was seen by unit doctor, after doing urine analysis if there was proteinuria(>0.5 gm/day or 3+), haematuria or cellular casts present and level as lupus nephritis immediately informed me through cell phone. I was then reevaluate the case, discuss with my co-guide and collect clinical and laboratory data and was recorded them as suspected lupus nephritis on a structured form on admission. Patient was assessed daily during hospital stay to avoid inter-observer variation. Clinical assessment included recording of presenting symptoms and their duration, pre-biopsy blood pressure, history of diabetes and/or hypertension and laboratory variables included pre-biopsy hematocrit, platelet count, blood urea nitrogen, serum creatinine, albumin, ESR, proteinuria, blood grouping and Rh-typing, HBsAg and Anti-HCV were recorded. Biopsying the kidney was an invasive procedure and associated with several potential risks. Bleeding, the most serious of these complications, sometimes required blood transfusion. Other risks include patient discomfort, infection was managed.

Each subject or gurdian were informed of the aims, methods, anticipated benefits and potential hazards or risks of the study. After that informed written consent was taken from every subject or gurdian of the patient. In the event of a case less than 18 years,consent was obtained from the eligible gurdians. The patient who were not fit for renal biopsy or who did not give consent, excluded from the study. Then patient underwent percutaneous renal biopsy under ultrasound guidence by fellow doctor or postgraduate doctor or MD(Nephrology) part-III students at Nephrology department, DMCH and with all aseptic precautions specimen was collected in a container with 10% formalin for light microscopy and was preserved in normal saline for Direct Immunoflurescence(DIF) microscopy and was sent to department of Pathology of Bangabandhu Sheikh Mujib Medical University(BSMMU), Dhaka. After renal biopsy, each patient was observed for at least 24 hours in the hospital. The histopathology and immunoflurescence reports ware collected and analyzed and then patients were classified by International Society of Nephrology (ISN) / Renal Pathology Society (RPS) Classification of LN,2003 and treated at Nephrology department by respected physicians.

I recorded the basic demographic data such as name, age, gender, occupation, residence and then recorded the histopathological patterns of lupus nephritis and treatment options which were given by department of Nephrology, DMCH. Then I assessed the compliance with ACR recommendations, 2012 with direct supervision of my co-guide and guide. The outcome of hospital stay was also recorded as cured, improved or death.

Data Analysis

Data was processed and analysed using computer software Statistical Package for Social Sciences, SPSS 16.0 Chicago-Illionois for windows. The test statistics used were descriptive statistics and Chi-square (x^2) and Student's t-Test. Level of significance was set at 0.05 and $p<0.05$ was considered statistically significant.

Results

A total of 30 cases of histological proven lupus nephritis were included in the present study. All were analysed and presented in tabulated form.

Population Characteristics: The mean age of the study patient was 26.63 ± 9.733 SD years (range: 12 to 60 years). The age distribution (Table 1) of patients at the time of kidney biopsy were as follows: 30% from 11 to 20 years, 43.3% from 21 to 30 years, 23.3% from 31 to 40 years, 3.3% from 41 to 60 years. There were 4 (13.3%) males and 26 (86.7%) females, with a male: female ratio of 0.15 (Table 2).

Laboratory Abnormalities: Table 3 shows the laboratory abnormalities of the present study patients. At the time of renal biopsy 18 patients (60%) were anaemic, 19 patients (63.3%) had microscopic haematuria and 7 patients (23.3%) had nephrotic syndrome. Renal function was impaired in 15 patients (50%) with mild renal failure (GFR <90 ml/min) in 8 cases (26.7%), moderate to severe renal impairment (GFR <60 ml/min) in 7 cases (23.3%). Proteinuria greater than 0.5 gm per 24 hours was noticed in all patients and among them 7 patients (23.3%) had nephritic range proteinuria. The other abnormalities leucopenia 3.3%, thrombocytopenia 10%, cellular (RBC) casts in urine 36.7%, raised ESR (>60 mm at the end of first hour) 46.7%.

On serological test, all patients (100%) had a positive ANA, 25 patients (83.3%) had a positive anti-ds DNA, all the patients (100%) had low complement (C3 and C4) level and 8 patients (26.7%) had positive antiphospholipid antibodies.

Histological types and treatment of Lupus Nephritis: Percutaneous renal biopsy was performed in all patients and showed the following results (Table 4): Class I- 1 patient (3.3%), Class II- 5 patients (16.7%), Class III- 8 patients (26.7%), Class IV- 10 patients (33.3%), Class V- 4 patients (13.3%), Class VI- 2 patients (6.7%). Mean Activity Index (AI) of renal histology were 7.83 ± 2.52 and Chronicity Index (CI) of renal histology were 1.4 ± 1.9 (Table 5,6).

In management of lupus nephritis 6 patients (20%) were in class I and II and they did not received any Pulse steroids or any immunosuppressives, they received oral steroids, hydroxychloroquine and renoprotective agents like angiotensin converting enzyme inhibitors. Among the study patients, 23 patients (76.67%) received intravenous pulse methylprednisolone daily for 3 days, 19 patients (63.3%) received monthly intravenous high-dose cyclophosphamide, 5 patients (16.67%) received oral mycophenolate mofetil. During maintenance phase 2 patients (6.7%) received oral azathioprine.

Age in Years	Number of Cases	Percentage
11-20	9	30
21-30	13	43.3
31-40	7	23.3
41-60	1	3.3
Total	30	100

Table 1: Age distribution of the study patients (n=30).

Sex	Number of Cases	Percentage
Male	4	13.3
Female	26	86.7
Total	30	100

Table 2: Sex distribution of the study patients.

Name of Test	No. of Patients	Percentage
Haematological		
• Anaemia	• 18	• 60
• Leukopenia	• 1	• 3.3
• Thrombocytopenia	• 3	• 10
• Raised CRP (>6)	• 2	• 6.7
• Raised ESR(>60)	• 14	• 46.7
Renal		
• Cellular cast	• 11	• 36.7
• Microscopic Haematuria	• 19	• 63.3
• Proteinuria	• 7	• 23.3
• Mild renal impairment **(**GFR<90-60 ml/min)	• 8	• 26.7
• Moderate to severe renal impairment (GFR<60 ml/min)	• 7	• 23.3
Immunological		
• ANA (positive)	• 30	• 100
• Anti-ds DNA (positive)	• 25	• 83.3
• Antiphospholipid antibody	• 8	• 26.7
• Low complement (C_3, C_4)	• 30	• 100
CRP: C-Reactive Protein;ESR: Erythrocyte Sedimentation Rate;GFR: Glomerular Filtration Rate;ANA: Anti-nuclear Antibody;Anti-ds DNA: Anti Double Stranded DNA		

Table 3: Frequency of main laboratory abnormalities.

Histological Types	No. of Patients	Percentage
Class I	1	3.3
Class II	5	16.7
Class III	8	26.7
Class IV	10	33.3
Class V	4	13.3
Class VI	2	6.7
Total	30	100

Table 4: Histological classification of lupus nephritis.

Index	Histolological Classification of Lupus Nephritis						Total (n=30)	P-value
	Class I (n=1)	Class II (n=5)	Class III (n=8)	Class IV (n=10)	Class V (n=4)	Class VI (n=2)		
Activity Index (AI)	6.0	7.8±1.64	6.63±2.13	9.0±1.41	10.5±1.73	7.1±2.5	7.83±2.52	V,VI :0.004 III,IV:0.019
Chronicity Index (CI)	00	00	0.38±1.06	1.5±1.58	3.0±00	6.0±00	1.4±1.9	V,VI:0.025

Table 5: Comparing of activity and chronicity index of renal histology in lupus nephritis.

Histological Types	No. of Pts.	I/V Methyl Prednisolone	CYC	MMF	Maintenance Therapy / Others
Class I	1	X	X	X	GC+HCQ + ACEI
Class II	5	X	X	X	GC+HCQ + ACEI
Class III	8	8	7	1	CYC + GC or MMF/AZA + GC
Class IV	10	10	9	1	CYC + GC or MMF/AZA + GC
Class V	4	4	2	2	CYC + GC or MMF/AZA + GC
ClassV I	2	1	1	1	RRT+ GC
Total	30	23	19	5	
Percentage	100	76.67	63.3	16.67	
HCQ: Hydroxychloroquine;ACEI: Angiotensin Converting Enzyme Inhibitor;CYC: Cyclophosphamide;MMF: Mycofenolate Mofetil;AZA: Azathioprine;GC: Glucocorticoids (oral);RRT: Renal Replacement Therapy;I/V: Intravenous					

Table 6: Histological types and treatment options.

A total of 30 cases of histological proven lupus nephritis were included in the present study. The mean age of the study patient was 26.63 ± 9.733 SD years with a male:female ratio of 0.15. Serologically, all patients had a positive ANA and low complement (C3 and C4) level, 83.3% had a positive anti-ds DNA and 26.7% had positive antiphospholipid antibodies. Percutaneous renal biopsy was performed in all patients and showed that 3.3% patient in class I, 16.7% patient in class II, 26.7% patient in class III, 33.3% patient in class IV, 13.3% patient in class V, 6.7% patient in class VI. Mean Activity Index (AI) of renal histology were 7.83 ± 2.52 and Chronicity Index (CI) of renal histology were 1.4 ± 1.9. In management of lupus nephritis 6 patients (20%) were in class I and II and they did not received any Pulse steroids or any immunosuppressives, they received oral steroids, hydroxychloroquine and renoprotective agents like angiotensin converting enzyme inhibitors. Among the study patients, 23 patients (76.67%) received intravenous pulse methylprednisolone daily for 3 days, 19 patients (63.3%) received monthly intravenous high-dose cyclophosphamide, 5 patients (16.67%) received oral mycophenolate mofetil. During maintenance phase 2 patients (6.7%) received oral azathioprine.

Discussion

Renal involvement is common in Systemic Lupus Erythematosus (SLE) and often determines the course of the disease. The glomerular lesion that frequently accompany SLE have been the subject of intense investigation by clinicians and pathologists for nearly a half of century. These efforts have generated numerous attempts to classify and categorize the pathological features of lupus nephritis. After several revisions of WHO classification of lupus nephritis, the recent ISN/RPS 2004 classification aims to enhance the quality of communication among renal pathologists, clinical nephrologists and rheumatologists regarding pathological findings in lupus nephritis [10,11]. American College of Rheumatology (ACR) guidelines recommended for management of lupus nephritis consisted of pulse glucocorticoids followed by high-dose daily glucocorticoids in addition to an immunosuppressive medication. Many clinical trials of glucocorticoids plus immunosuppressive interventions have been published. Therefore, the ACR determined that a new set of management recommendations which published on February 2012 [12,13]. The mean age and sex ratio of lupus nephritis in present study was similar to most of the studies show that SLE with or without renal localization is mainly a disease of the young women [14,15]. Anaemia was more common finding in the present study than other studies.15,16 Proteinuria was the main mode of expression of LN and was found in all patients, highest protein excretion was found in class VI, in contrast other study was reported highest protein excretion was found in class V [16]. Proteinuria ≥ 3.5 gm/ day was detected in 23.3% in the present study, similar to other study [17]. In the present study, 16.7% of patients had gross haematuria and 63.3% had microscopic haematuria, which was similar to those reported by some authors [17,18]. Cellular cast (RBC) was present in 36.7% patient in the present study. In other studies, cellular casts (RBC) were detected in 20.5% and 31% of LN [18,19]. In the present study, 83.3% of patient had Anti-ds DNA positive which was consistent to those

reported to some authors [18,19]. Many studies have demonstrated that elevated Anti-ds DNA level is a risk factor for development of LN. 19,20 All patients of present study had low complement (C3 and C4) level, but 73% patients had low C3 level was reported from Burling, et al., in the present study, no significant correlation was found between serological findings and classes of LN [20,21]. However, Mok, et al., found that serum level of C3, C4 and Anti-dsDNA significantly correlated with the classes of LN [22,23]. The frequency of different renal pathological classes of lupus nephritis varies in different series. In present study ,most cases were in class IV (33.3%),then in class III (26.7%) which correlates with most of the other studies [16,17,20]. But in some studies the class III was more frequent than other classes [23]. In management of lupus nephritis the immunosuppressive therapy was divided into an induction phase which targets at reducing inflammation and glomerular injury and a maintenance phase that aims to reduce the long term risk of renal flares and renal function decline. In present study, milder forms of LN (ISN/RPS Class I, II) was 20% of cases, managed by corticosteroids which consistent with Mok [22,23]. But in some studies, azathioprine added as a corticosteroid sparing agent [23]. Proliferative lupus nephritis (Class III and IV or mixed III/V and IV/V) and more serious class V (nephrotic range of proteinuria) LN patients were managed with more aggressive induction regimens consisting of corticosteroids and immunosuppressive agents. In this study, 23 patients (76.67%) managed with intravenous pulse methylprednisolone daily for 3 days followed by oral steroid 0.5-1 mg/kg/day which follow the American College of Rheumatology (ACR) guideline, 2012. In the study, 19 patients (63.3%) received high-dose cyclophosphamide 500-1000 mg/m^2 body surface area I/V monthly for 6 months followed by maintenance therapy with I/V cyclophosphamide every 3 months for additional one and half years, which consistent with the KDIGO (Kidney Disease Improving Global Outcomes) guideline, not ACR guideline [24]. In ACR guideline same induction therapy followed by maintenance with MMF 1-2 gm/day or AZA 2 mg/kg/day. This study 5 patients (16.67%) treated with oral MMF 2 gm/day for 6 months followed by maintenance with MMF 1-2 gm/day or AZA 2 mg/kg/day, which consistent with the ACR guideline [12,25]. In this study 1 patient (3.33%) of advanced sclerosing LN with ESRD was treated with renal replacement therapy. Cyclophosphamide toxicity is especially relevant in women of childbearing age, where the risk of gonadal failure is not insignificant. Infectious complications are of particular concern, with high mortality rates seen in some clinical studies [25,26]. This study was done on a small number of population, but it suggests some meaningful correlation between histological pattern and treatment of lupus nephritis. Treatment strategies will differ based on biopsy findings. For patients with class I and II histologic pattern, management with renoprotective measures is warranted. These include strict blood pressure control, preferably with blockade of renin-angiotensin system, avoiding nephrotoxins and the cessation of smoking. More recently, Mycophenolate Mofetil (MMF) has demonstrated equal, if no better, efficacy vs cyclophosphamide in remission induction and maintenance. With its better toxicity and safety profile, MMF's popularity as a primary therapy in combination with glucocorticoid therapy is growing. The addition of immunosuppressive drugs may affect long-term renal survival, reduce the risk of complications and prevent relapse. Renal replacement is the treatment of choice in lupus patients with ESRD.

Conclusion

This study was done in a tertiary care hospital, Dhaka Medical College Hospital where maximum population are poor and come from low socioeconomic condition. Intravenous Cyclophosphamide is much cheaper than oral Mycophenolate Mofetil (MMF) and its dose is single monthly whereas MMF is given daily. Thats why, in spite of MMF's more safety profile, Cyclophosphamide is generally used as a first line agent in this study for financial constance. But the regimen of Cyclophosphamide used in DMCH is not followed by American College of Rheumatology (ACR) guideline, 2012. In the study, maximum patients received high-dose cyclophosphamide 500-1000 mg/m^2 body surface area I/V monthly for 6 months as induction therapy followed by maintenance therapy with I/V cyclophosphamide every 3 months for additional one and half years, which consistent with the KDIGO (Kidney Disease Improving Global Outcomes) guideline, not ACR guideline .In ACR guideline same induction therapy followed by maintenance with MMF 1-2 gm/day or Azathioprine (AZA) 2mg/kg/day. In this study, some patients treated with oral MMF 2 gm/day for 6 months followed by maintenance with MMF 1-2 gm/day or AZA 2 mg/kg/day, which consistent with the ACR guideline. Also, the regimen of glucocorticoids used in management of LN patients with intravenous pulse methylprednisolone daily for 3 days followed by oral steroid 0.5-1 mg/kg/day consistent with ACR guideline, 2012.

Recommendation

Renal biopsy plays an important role in the diagnosis and staging of lupus nephritis. The main purpose of classifying lupus nephritis is to make sure that the type of treatment recommended matches the severity of disease and that information about short and long-term prognosis guides both the duration and intensity of treatment. There was some limitations like small sample size due to short duration of time, but findings of this study will help to future studies for better management of the patient of

lupus nephritis.

Conflict of Interest
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Acknowledgement
Acknowledge those who provided support during the study.

Consent to Participate
Informed consent was obtained from each participant prior to specimen collection.

Financial Disclosure
This research did not receive any grant from funding agencies in the public, commercial or not-for-profit sectors.

Data Availability
Data is available for the journal. Informed consents were not necessary for this paper.

Author's Contribution
The authors contributed equally.

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