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RESEARCH ARTICLE
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THE PREVALENCE OF DIFFERENT CLASSES OF LUPUS NEPHRITIS BASED ON ISN/RPN 2003 CLASSIFICATION SYSTEM KEEPING RENAL BIOPSY AS STANDARD FOR DIAGNOSIS

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Abstract:
Background: The most common symptom of systematic lupus erythematosus (SLE) is lupus nephritis (LN), with an incidence of 50–70%. Kidney biopsy, which enables histology-based classification in accordance with World Health Organization (WHO) standards declared in 1982, is the main method used to examine LN. This study aimed to classify LN according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system and determine the prevalence of different classes.
Methods: The Nephrology Department at a tertiary care hospital in Islamabad, Pakistan, conducted a retrospective observational study between February 2012 and April 2018. The study included adult

participants (age > 18 years) with a confirmed diagnosis of lupus nephritis and individuals who had undergone renal biopsy. Patient data were obtained from hospital records and analyzed thoroughly.
Results: A total of 256 biopsies were examined, and 40 cases of LN were confirmed. It is more prevalent in females (7:1), with class IV having the highest incidence rate. There was no statistically significant link between LN and urea, but proteinuria and creatinine values were significant.
Conclusion: It is essential to promptly recognize renal failure in SLE patients. Lupus nephritis can be diagnosed and treated using a kidney biopsy.

Keyword: Lupus Nephritis, SLE, Renal biopsy, ISN/RPS 2003, Serum urea, Proteinuria

Background

Lupus nephritis (LN), which affects fifty to seventy percent of patients with systemic lupus erythematosus (SLE), is a common symptom of the disease. The morbidity and mortality rates associated with LN are strongly affected by SLE. The course of lupus nephritis varies greatly, from preclinical disease in a small percentage of individuals to rapid succession to end stage renal disease (ESRD). It can be difficult to determine the precise histopathology and injury based solely on the clinical characteristics. However, some histological and clinical characteristics have been found to be good predictors of poor renal survival (1). Renal biopsy is regarded as a major diagnostic method for LN and is an essential tool for the diagnosis of this condition. After the biopsy technique, the tissue samples were examined using several consecutive procedures, including immunofluorescence (IF), light microscopy (LM), and electron microscopy. These methods allow for the analysis of specific kidney tissue features, such as cell structure and presence of immune deposits. In the majority of cases, lupus nephritis can only be conclusively diagnosed through a renal biopsy (2).
Lupus nephritis (LN) is distributed into several classes according to histopathology of renal biopsy. In 1982, the World Health Organization (WHO) created the first classification system. In 2003, this categorization was changed as a result of cooperation between the International Society of Nephrology (ISN) and Renal Pathology Society (RPS), known as the ISN/RPS classification (3). The updated classification system consists of six primary classes (Classes I-VI), each of which is further divided into subclasses. The presence of nephritic-range proteinuria at the time of presentation, low glomerular filtration rate (GFR), persistently elevated blood pressure, and anti-dsDNA antibodies are among the clinical characteristics of lupus nephritis (LN) and have been identified as predictive indicators of poor renal outcomes. However, the histological characteristics observed in renal biopsies, such as the existence of interstitial fibrosis, are the most important indicators of kidney injury (4). The aforementioned study set out to ascertain the frequency of various LN classes conforming to the International Society of Nephrology and Renal Pathology Society's (ISN/RPS) 2003 categorization scheme at the Pakistan Institute of Medical Sciences, a tertiary care facility in Islamabad, between February 2012 and April 2018. The study includes the analysis of kidney biopsies performed there during those dates.

Methods

This retrospective observational study was conducted at the nephrology department of the Pakistan Institute of Medical Sciences (PIMS) in Islamabad, Pakistan, a tertiary care hospital. The time span, including the follow-up period, was between February 2012 and April 2018. The hospital's ethical review board granted approval for the study and the patient was diagnosed with lupus nephritis through renal biopsy findings. Data for this study were retrieved from hospital records. When a biopsy specimen was deemed insufficient for analysis, the case was excluded from the study.
Following renal biopsy, two biopsy samples were taken and sent to the laboratory for analysis. The processing of the biopsy samples in the laboratory was performed according to established procedures. Each biopsy sample was examined using immunofluorescence and light microscopy. However, because electron microscopy was not available at the hospital, it could not be used. According to the International Society of Nephrology/Renal Pathology Society's (ISN/RPS) 2003 classification

system, lupus nephritis cases were categorized into one of the specified classifications; ISN/RPS's (2003) classification of LN (5) [Table 1]. The data was first gathered on an excel spread sheet and then transferred to SPSS version 25.0. Descriptive statistics (frequencies and percentages) were tabulated. Chi-square test and univariate regression analysis was applied to establish association. A p-value of less than 0.05 is considered significant.

Results

Data from 254 patients was examined for lupus nephritis. Among them, this review incorporated 40 patients with confirmed lupus nephritis (LN) validated through biopsy. The average age of study participants was 36.9 ± 4.4 years. The fundamental characteristics of these LN patients expressed at the time of biopsy are succinctly outlined in table along with the prevalence of LN [Table2]

The condition primarily affected females, with a female-to-male ratio of 7:1. Upon histopathological examination of renal biopsies, the most prevalent class of LN observed was class IV, accounting for 42.5% of the cases. Among class IV, subclass IV-S was the most prevalent. Class V was the second most frequent class, accounting for 25% of the cases, while Classes II and III were the least prevalent, accounting for 17.5% and 12.5% of the cases, respectively.

Proteinuria, Creatinine, and Urea (g/dl) values were used as continuous variables [Figure1]. The variables "Proteinuria, Creatinine, and Urea" were separated into two groups based on the median cut-off point value. Statistical analyses were performed on the grouped variables. Statistical tests (chi-square and univariate) revealed a strong association between the classes of LN and 24-hour urinary protein levels and serum creatinine levels [Table 3]. However, no significant correlation was observed between the LN class and serum urea levels. Kruskal-Wallis Test for Independent Samples confirmed the same association [Figure 2].

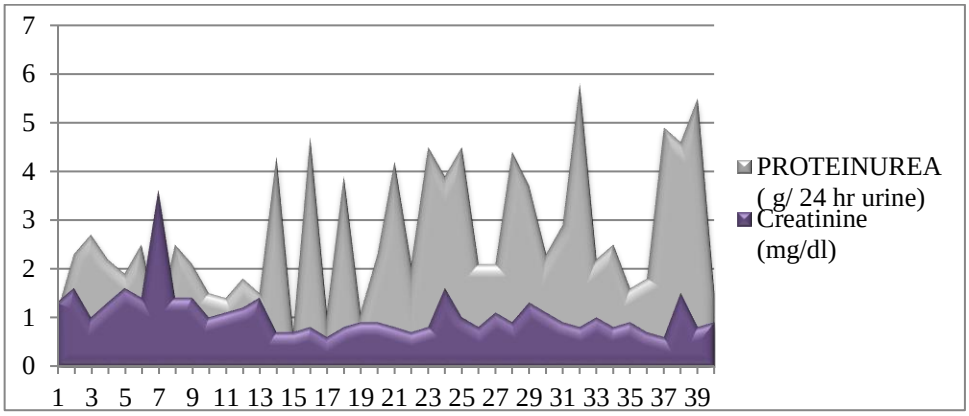
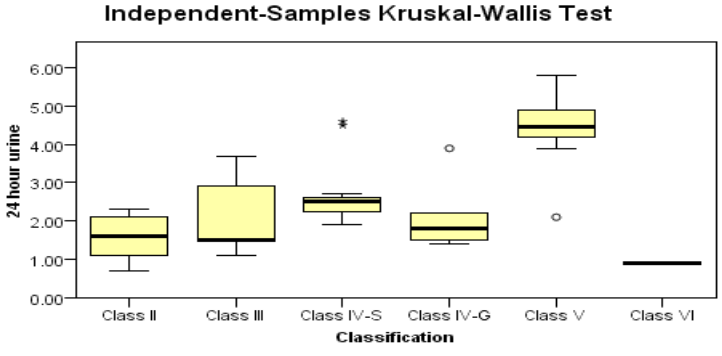
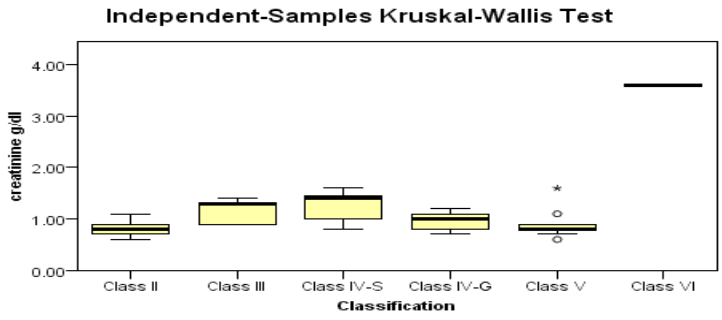


Figure 1: Proteinuria (range: 0.7 – 5.8 g/24 hour urine) and creatinine (range: 0.6 – 3.6 mg/dL)



(a)



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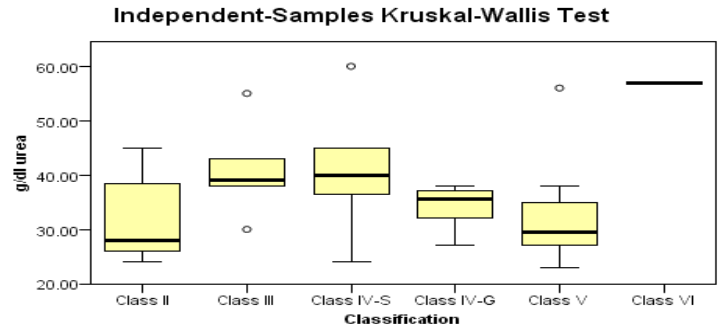

(c)

Figure 2: Kruskal-Wallis Test for Independent Samples (a) Proteinuria (range: 0.7 – 5.8 g/24 hour urine), (b) Creatinine (range: 0.6 – 3.6 mg/dL), (c) Urea (range: 23 – 60 mg/dL)

Table 1: Classification of Lupus Nephritis (LN)

Class I	Minimum Glomerular Infection	
Class II	Proliferative Glomerular Nephritis	
Class III	Localized lupus nephritis LN (involving less than 50% glomeruli)	Active/acute lesion Acute and chronic lesion Chronic lesion
Class IV IV-S: Segmental IV-G: Global	Diffused lesion (involving more than 50% glomeruli)	Active/acute lesion Acute and chronic lesion Chronic lesion
Class V	Lupus nephritis membranous	
Class VI	Advanced generalised sclerosis (> 90% involvement of glomeruli)	No active/acute lesion Chronic lesion

Table 2: Descriptive statistics

Variable	Mean	Median	SD
Proteinuria	2.74	2.3	1.4
Creatinine	1.09	0.95	0.50
Urea	36.45	36.5	9.5
Age	36.85	37	4.4
Variable		*N	%age
Gender	Male	5	12.5
	Female	35	87.5
Lupus Nephritis (LN) Classification (Prevalence of classes of LN)	Class II	7	17.5
	Class III	5	12.5
	Class IV-S	11	27.5
	Class IV-G	6	15.0
	Class V	10	25.0
	Class VI	1	2.5
Indication for Biopsy	Proteinurea	37	92.5
	Unexplained Renal Failure	1	2.5
	Proteinurea+ Hematurea	2	5.0

*N: Total number/frequency of LN cases (40), %age: Percentage, Proteinuria (protein in g/24 hours urine), Creatinine (mg/dl) and Urea (g/dl), *Class IV-S: Segmental, Class IV-G: Global, SD: standard deviation

Table 3: Association of Proteinuria, Creatinine and Urea with Prevalence of Lupus nephritis (Chi-square test)

	Proteinuria		Creatinine		Urea	
	1= < 2.3	2= >2.3	1= <0.95	2= >0.95	1= <36.5	2= >36.5
Class II	7	0	6	1	5	2
Class III	3	2	2	3	1	4
Class IV-S	5	6	2	9	3	8
Class IV-G	5	1	2	4	3	3
Class V	1	9	8	2	8	2
Class VI	1	0	0	1	0	1
TOTAL	22	18	20	20	20	20
Chi-square p-value	0.004		0.019		0.076	
Univariate Analysis p-value	0.000		0.036		0.334	

*Class IV-S: Segmental, Class IV-G: Global, The continuous variables i;e Proteinuria g/24 hours urine, Creatinine (mg/dl) and Urea (g/dl) are transformed into categorical variables using median value as cut point

Discussion

Systemic Lupus Erythematous is an autoimmune disorder that involves multiple organs and is characterized by a series of complicated symptoms. It is distinguished by the development of immune complexes and presence of various laboratory abnormalities. The clinical course of SLE is characterized by frequent relapses. Renal involvement is common and serves as a negative prognostic indicator for disease progression. Approximately 50-70 patients with SLE experience certain types of lupus nephritis (LN) that primarily manifest as glomerulonephritis. Lupus nephritis (LN) is an important contributor to mortality and morbidity associated with systemic lupus. The course of LN is exceptionally diverse, with some patients experiencing subclinical manifestations, while others develop end-stage renal disease (ESRD) very rapidly. It can be difficult to predict histopathology based purely on clinical characteristics. Certain clinical and histological parameters are associated with poor prognosis in terms of renal survival. Renal biopsy is regarded as a primary diagnostic tool, and the specimens are examined using immunofluorescence or under electron microscope and light microscope (6).

The assessment of glomerular composition in terms of active and sclerotic lesions serves as a metric for gauging the extent of fibrinoid necrosis and cellular crescents within the glomeruli. Moreover this evaluation provides nuanced classification encompassing varying degrees of tubular atrophy, interstitial inflammation and fibrosis ranging from mild to moderate and culminating severe manifestations (7). Thirty-five of the 40 patients assessed in our study were female, with a female-to-male ratio of 7:1. These results support earlier research findings that this condition is more common in women (8–13).

Our study exhibited that the most prevalent type of lupus nephritis identified through renal biopsy is class IV accounting for 42.5% of the cases, followed by class V in 25% of the cases. These findings are consistent with the study by Satish et al., which similarly identified class IV as the most prevalent, albeit at a higher frequency of 55.4% than our study (14). Class IV was found to be the most prevalent (48%), followed by class V (19.9%), and class II (19.57%) in a different study comprising 373 individuals (15). In a different study of 99 LN patients, the prevalence rates for each category were as follows: class I (3%), class II (13%), class III (9%), class IVS (20%), class IVG (46%), class V (8%), and class VI (1%) (16).

Likewise, research on the Pakistani population revealed that class IV was the most prevalent lesion in LN based on renal histology (17). Almost 40 percent of patients with this type of LN either died or lost kidney function within five years of diagnosis, as was the case in earlier studies, where the majority of study participants exhibited class IV LN (6). Given its seriousness, LN is a significant renal disease consequence of SLE (18).

Significant variations exist in the clinical progression of glomerular disease (18–20). The prognosis and treatment of the disease are influenced by both clinicopathological factors (18–21). A notable alteration in class IV LN is diffuse proliferative glomerulonephritis, which can affect the glomerular tuft segmentally or globally.

According to previous studies, patients with global involvement (class IVG) typically have less favourable outcomes. Since the majority of our patients had class IVG, they were at a high risk of developing complications and needed quick and forceful care (11,22).
Most of our patients had class IV-S, so they were at a high risk of complications. Early and aggressive management is warranted in these patients. Impaired renal function and proteinuria were identified as important clinical characteristics of our patients. However, no correlation was found between the class of LN and serum urea; instead, the class of LN showed a statistically significant association with proteinuria.

Proteinuria is a crucial diagnostic indicator for LN, as noted in a previous study (23). Proteinuria is indicator of vascular inflammation in chronic renal disease (24) and an elevated serum creatinine exhibits worsening of renal disease (25). The patients developing a protein to creatinine ratio of more than 5 g/g are at risk (26). Changes in proteins linked to LN are related to renal flare (27). Class III and IV exhibit poor prognosis (28). During treatment of SLE, proteinuria can predict disease progression to End Stage Renal Disease (29,30). Renal biopsy can be declined in cases where proteinuria can accurately predict changes in kidney dysfunction (especially in case of treatment with corticosteroids) (28). To obtain better results, intensive treatment is necessary for individuals within class IV who exhibit elevated levels of proteinuria and compromised baseline renal function (31).

Conclusion

Early detection of renal dysfunction is crucial in systemic lupus erythematosus (SLE). The identification and treatment of lupus nephritis rely heavily on renal biopsy. Class IV is the most prevalent histological class observed in biopsies of patients with SLE at our hospital. Additionally, there is a connection between proteinuria and certain types of lupus nephritis.

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