

Clinicopathological Features of Kidney Biopsy Samples in Patients with Lupus Nephritis in Iran

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ABSTRACT

Background and Aim: Systemic lupus erythematosus is a chronic autoimmune disease that is more common in women and has recently increased in prevalence. One of its complications is lupus nephritis, which occurs in 50% of patients. This study was conducted with the aim of investigating the clinical pathology of kidneys of patients with systemic lupus erythematosus and patients with systemic lupus erythematosus who underwent kidney biopsy between 2015 and 2023. **Methods:** 116 patients were included in the study. Most of the patients were in the age group of 20 to 40 years and most of them were women. The most common class of involvement was class IV, and the highest activity index and chronic index were also recorded in this class. **Results:** There was a significant relationship between lupus nephritis class and hematuria. The serum creatinine of patients had a significant relationship with the class of lupus nephritis, and the highest level of creatinine was in class VI and the lowest level was in class II. All patients in our study had proteinuria and it was significantly related to the class of lupus nephritis, and the highest level of proteinuria was in class VI and the lowest in class II. All classes of lupus nephritis showed a decrease in C3 compared to the normal range. C4 and CH50 had a significant relationship with the class of lupus nephritis. Anemia was significantly related to the class of lupus nephritis, and the highest prevalence of anemia was in class IV. **Conclusion:** Most patients were women aged 20-40 years. Class IV was the most common type of lupus nephritis and showed the highest activity and chronicity indices. Lupus nephritis class demonstrated significant relationships with hematuria, serum creatinine, proteinuria, complement levels, and anemia. The highest creatinine and proteinuria levels were observed in class VI, while the greatest prevalence of anemia and the greatest decrease in C3 were seen in class IV.

Keywords: Systemic lupus erythematosus, Clinicopathological, Lupus nephritis.

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects women of all ages and races more than men and usually occurs in older men.^[1] Its prevalence is highest among blacks and less among whites.^[2] The prevalence of systemic lupus erythematosus appears to be increasing over time.^[3] Despite the progress in treatment, the mortality of patients with systemic lupus erythematosus, which is caused by kidney, cardiovascular and infectious diseases, is increasing.^[4] The risk of myocardial infarction and cardiac death is higher in patients with Lupus Nephritis (LN) than in patients with systemic lupus erythematosus without LN.^[5] Kidney involvement occurs in about 50% of patients with systemic lupus erythematosus and about 10% of people eventually develop End-Stage Renal Disease

(ESRD).^[6] Renal biopsy is usually performed in the presence of at least one of the following, including urine protein greater than 500 mg/24 hr, active urinary sodium with persistent hematuria, and an unexplained increase in serum creatinine.^[7] There are different types of lupus nephritis, including class I (minimum mesangial lupus nephritis), class II (proliferative mesangial lupus nephritis), class III (focal lupus nephritis), class IV (diffuse lupus nephritis), and class V (membranous lupus nephritis) and class VI (advanced sclerosing nephritis) is divided.^[8] In the last 5 decades, the most common classes of lupus nephritis were class IV (50%), class III (25%) and class V (20%) and the prevalence of mixed forms included III+IV and IV+V.^[9] The most common type of lupus nephritis is class IV, and there is a strong relationship between Activity Index (AI) and 24-hr urine protein, serum C3, serum albumin, urinalysis, and platelets.^[10] Elevated serum creatinine and BUN are more common in lupus nephritis patients with interstitial tubule damage other than tubular degeneration and interstitial tubule inflammation may initiate chronic kidney injury and predict treatment response.^[11] Lupus nephritis patients with proliferative nephritis have symptoms



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such as high blood pressure, more frequent proteinuria, increased urinary red blood cells, decreased hemoglobin, and C3 supplement use.^[12] Treatment of lupus nephritis usually includes immunosuppressive therapy, usually with mycophenolate mofetil or cyclophosphamide, and with glucocorticoids, although these treatments are not uniformly effective.^[13] Despite increased knowledge about disease pathogenesis and improved treatment options, lupus nephritis remains an important cause of morbidity and mortality among patients with SLE. Knowledge of the clinical and pathological status of patients with systemic lupus erythematosus in each region is useful for future planning in the management of these patients' condition.^[14] In this study, the clinicopathology of kidney biopsy samples in lupus patients referred to the Pathology Department of Shahid Sadoughi Hospital in Yazd from 2016 to 2024 was examined.

MATERIALS AND METHODS

All patients with systemic lupus erythematosus referred to Shahid Sadoughi Hospital in Yazd from 2016 to 2023 were examined. After confirmation in the pathology department, the patients were examined in terms of the following variables using the hospital's computerized clinical database: age, gender, pathological diagnosis (lupus nephritis class, activity index and chronic index), serum creatinine, hematuria, proteinuria, C3, C4, CH50 and anemia. Patients who were not examined for the above cases or did not have enough sample size or had non-diagnostic pathology reports were excluded from the study. Finally, considering the inclusion and exclusion criteria, 116 patients were examined.

Ethic Issues

This research followed the principles of the Declaration of Helsinki. Informed consent was obtained and the research was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences in Yazd.

Statistical Analysis of Data

All continuous values were expressed as mean \pm standard deviation and categorical variables were expressed as percentages. Student's *t*-test was used to compare the mean difference of continuous variables in two groups. Pearson's correlation test and chi-square were used to compare frequency variables and correlation between different variables. After collecting the data,

statistical analysis was done with SPSS version 24 software and the final results were extracted.

RESULTS

In this study, we recorded a total of 116 biopsies from LN patients. Out of 116 patients, 101 (87.1%) were women and 15 (12.9%) were men, with a female-to-male ratio of 6.7:1. The average age of all patients was 33.7 ± 9.4 years and the most common age range in all classes was 20-40 years (68.1%) (Table 1). As shown in Table 2, the distribution of kidney biopsies according to the 2003 ISN/RPS classification, it is clear that most of the cases belong to class III and IV. Table 3 shows the relationship of various factors including age, sex, hematuria, creatinine concentration, urine protein and anemia with different classes of lupus nephritis. 90 patients (77.6%) had hematuria and 26 patients (22.4%) did not have hematuria. There was a significant relationship between the class of lupus nephritis and hematuria ($P=0.01$), which had the highest prevalence in class III and the lowest prevalence in other cases. The range serum creatinine at the time of biopsy was 1.05 to 7.9 mg/dl and there was a significant relationship between lupus nephritis class and serum creatinine ($P<0.05$), so that the highest creatinine values were in class VI with an average of 7.96 mg/dL and the lowest creatinine values were in class II with an average of 1.05 mg/dL was seen. The range 24 hr urine protein excretion was 822 to 1967. All patients had proteinuria, and the average 24-hr urine protein content of the patients was 1175.8-1588.68 mg; There was a significant relation between the class of lupus nephritis and the amount of proteinuria ($P=0.03$), so that the highest values of proteinuria were in class VI and the lowest in class II. However, no significant relationship was observed between the intensity of proteinuria and class of lupus nephritis. We also investigated the patients in terms of the presence of anemia and there was a significant relation between the class of lupus nephritis and anemia ($P=0.04$) and the highest amount of anemia was seen to class IV. The average level of C3 of patients in all classes of lupus nephritis was decreased compared to the normal range and the highest decrease was seen in class IV. There was no significant relationship between lupus nephritis classes and C3 level ($P=0.06$). There was a significant relationship between the class of lupus nephritis and the average C4 ($P=0.04$) and the average blood C4 of patients in class II lupus nephritis was 12.2, in class III 20.1, in class IV 14.9, in class V 18.7 and in class VI 11.4. The average CH50 in patients was 65.9 and there

Table 1: Frequency and percentage of gender and age range of studied patients.

		Frequency	Percent
Sex	Female	101	87.1
	Male	15	12.9
Age	<20	8	6.9
	20-40	79	68.1
	>40	29	25

was a significant relationship between lupus nephritis classes and CH50 level ($P=0.007$), so that the highest CH50 levels were 86 in class III and 76 in class II. Between classes of lupus nephritis and activity index, classes III and IV of lupus nephritis had a higher activity index. Also, there was a significant relationship between proliferative and non-proliferative involvement and hematuria ($P=0.03$), so that the highest percentage of hematuria was observed in proliferative cases (84%) (Table 4).

DISCUSSION

In our study, patients with systemic lupus erythematosus who underwent kidney biopsy from 2015 to 2023 were investigated. As expected, the majority of patients were women, so that the percentage of women in this study was reported as 87%. The largest number of patients with this disease were in the age range

Table 2: Frequency and percent distribution of lupus nephritis classes.

ISN/RPS classes	Frequency	Percent
I	1	0.9
II	14	12.1
III	25	21.6
IV	50	43.1
V	12	10.3
VI	3	2.6
other	11	9.5

ISN/RPS: International Society of Nephrology / Renal Pathology Society.

between 20 and 40 years, which included 68% of the patients which is consistent with similar studies.^[15] According to the studies and surveys conducted at the global level, the overall affection rate for women is 6.3 per million people per year and about four times that of men.^[16] Therefore, the gender ratio in our regional study is also close to this ratio. The gender distribution is also biased in favor of females, as is well established in almost all previous studies on LN, and in a study from neighboring province in Iran.^[17] The results of this study showed that the highest prevalence rate of lupus nephritis includes classes III and IV, and these two classes include 60% of patients in total. Nasri et al.'s study showed that nearly 70% of patients were in classes III and IV of lupus nephritis.^[18] Creatinine level is one of the factors that are checked in lupus nephritis patients. In this study, the highest level of serum creatinine was observed in class VI, and apparently there is a direct relationship between creatinine and the class of the disease, and its level is higher in the higher class. In the study of Shariati Sarabi et al., patients with higher International Society of Nephrology and Renal Pathology (ISN/RPS) classes had longer disease duration and higher BUN and serum creatinine values, and patients with chronic lesions had higher serum creatinine.^[19] In our study, there was also a significant relationship between lupus nephritis class and serum creatinine (highest values in class VI). In one study, it was found that high serum creatinine was more common in patients with lupus nephritis with tubulointerstitial injury and interstitial tubulo-inflammation may initiate chronic kidney injury and predict treatment response.^[20] Anemia is a common clinical finding in end-stage

Table 3: Relationship of various factors including age, sex, hematuria, creatinine concentration, urine protein and anemia with different classes of lupus nephritis.

		Class I	Class II	Class III	Class IV	Class V	Class VI	other	P value
Age	<20	0	14.3%	4.0%	10.0%	0.0%	0.0%	0.0%	
	20-40	100%	71.4%	60.0%	74.0%	66.7%	66.7%	54.5%	
	>40	0%	14.3%	36.0%	16.0%	33.3%	33.3%	45.5%	
Sex	Female	100%	85.7%	84.0%	88.0%	83.3%	66.7%	100.0%	
	Male	0%	14.3%	16.0%	12.0%	16.7%	33.3%	0.0%	
Hematuria	+	100%	50.0%	72.0%	90.0%	58.3%	100.0%	81.8%	0.01
	-	0%	50.0%	28.0%	10.0%	41.7%	0.0%	18.2%	
Mean of creatinine		1.4±0.3	1±0.5	2.2±0.3	1.52±0.1	1.52±0.5	7.96±1.7	1.53±0.8	<0.05
Mean of protein of urine 24h		1258±120	822±69	1349±113	1814±128	1891±121	1967±837	1676±929	0.03
Intensity of urine protein	150-1000	0%	69.2%	45.8%	30.0%	25.0%	33.3%	27.3%	>0.05
	1000-3000	100%	30.8%	41.7%	56.0%	58.3%	66.7%	63.6%	
	>3000	0%	0.0%	12.5%	14.0%	16.7%	0.0%	9.1%	
Anemia	+	0%	85.7%	88.0%	90.0%	58.3%	66.7%	63.6%	0.04
	-	100%	14.3%	12.0%	10.0%	41.7%	33.3%	36.4%	

Values are reported as numbers (percentages). P-value is obtained from Fisher's Exact Test and Chi squared test.

Table 4: Relationship between of C3, C4 and CH50 with different classes of lupus nephritis.

		Class I	Class II	Class III	Class IV	Class V	Class VI	Other	P
Mean of C ₃		51±17	67.7±5	84.4±42	61±36	70.4±49	62±1	94.8±29	0.06
	<90	100%	71.4%	64.0%	84.0%	66.7%	100.0%	45.5%	
	90-180	0%	28.6%	36.0%	16.0%	33.3%	0.0%	54.5%	
Mean of C ₄		6.2±1	12.2±2.7	20.1±4.5	14.9±3	18.7±4	11.4±3.1	27.8±3	0.04
	<10	100%	50.0%	20.0%	36.0%	25.0%	33.3%	9.1%	
	10-40	0.0%	50.0%	68.0%	62.0%	66.7%	66.7%	72.7%	
	>40	0.0%	0.0%	12.0%	2.0%	8.3%	0.0%	18.2%	
Mean CH50		123±22	76±29.7	86±23.2	54.4±6.70	68.6±6.4	61.6±9.2	53±9.4	0.007

Values are reported as numbers (percentages). P-value is obtained from Fisher's Exact Test and Chi squared test.

renal failure. In our study, there was also a significant relationship between lupus nephritis class and anemia (highest prevalence in class IV). In SLE, there is an association between the level of inflammatory cytokines and intensity of anemia. Inflammatory cytokines inhibit erythropoietin production and erythroid progenitor cells proliferation. In severe cases, inflammatory cytokines lead to myelofibrosis. Renal parenchymal infiltration by inflammatory cells could directly inhibit renal erythropoietin production.^[21] In the study of Alam et al., out of 340 patients examined, most patients had class IV renal involvement (71.9%), arthralgia (47.1% of cases) and anemia (60.3% of cases) was the most common symptom among patients.^[22] In our study, there was no significant relationship between C3 level and class of lupus nephritis and in most classes of lupus nephritis examined, the level of C3 decreased and the greatest was in class I. The concentration of c4 in this study showed a decrease compared to the normal state. Past studies have also shown that the thickness of C3 and C4 decreases in lupus nephritis patients.^[23] Also, there was a significant relationship between C4 level and lupus nephritis class. In the study by Satirapoj et al., patients with class IV had significantly higher rates of microscopic hematuria, proteinuria, hypertension, renal dysfunction, anemia, hypoalbuminuria, and anti-dsDNA antibodies.^[24] All these results were related to high activity and chronic indicators of lupus pathology. A significant relationship between lupus nephritis and CH50 was observed in our study, and there was also a significant relationship between CH50 and the class of lupus nephritis. In our study, there was a significant relationship between the class of lupus nephritis and hematuria (highest prevalence in class IV).

CONCLUSION

In this study, it was found that most of the patients were in the age group of 20 to 40 years and most of them were women. The most common class observed was class IV, and there was a significant

relationship between the class of lupus nephritis and hematuria. Serum creatinine of patients had a significant relationship with class of lupus nephritis and the highest level of creatinine was observed in class VI. All patients in our study had proteinuria and there was a significant correlation with lupus nephritis class. All classes of lupus nephritis showed a decrease in C3 compared to the normal range. C4 had a significant relationship with the class of lupus nephritis, so that the highest levels were recorded in class III and the lowest level in class VI. CH50 had a significant relationship with the class of lupus nephritis, and the strongest decrease was observed in class IV and the lowest decrease was observed in class III and II. Anemia was significantly related to the class of lupus nephritis, and the highest prevalence of anemia was observed in class IV.

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None.

ABBREVIATIONS

SLE: Systemic Lupus Erythematosus; **LN:** Lupus Nephritis; **ESRD:** End-Stage Renal Disease; **AI:** Activity Index; **BUN:** Blood Urea Nitrogen; **ISN/RPS:** International Society of Nephrology/ Renal Pathology Society.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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