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Predictors of Remission in Lupus Nephritis Patients

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ABSTRACT

Background: Lupus nephritis (LN) is a common and serious manifestation of SLE, occurring in more than half of patients with SLE during their course of illness, in 10–25% of such patients, kidney disorder progresses to end-stage renal disease (ESRD).

Objective: To determine the predictors of remission in patients with biopsy-proven lupus nephritis, and to assess the long-term renal remission rate in our lupus nephritis patients.

Patients and Methods: This is a retrospective observational study carried out at the Rheumatology and Nephrology Units, Internal Medicine Department, Menoufia and Mansoura Universities Hospitals, Egypt for a 1-year duration between 1 June 2019 and 1 June 2020. A total of 60 patients with biopsy-proven LN were studied.

Results: In the current study, after six months of follow-up, about two-thirds of patients achieved remission. The urinary protein creatinine ratio (UPCR) of 4.9 g/g, systemic lupus erythematosus disease activity index (SLEDAI) of 20 and Hb of 8.8 g/dl at the third month are valuable for predicting remission at the sixth month in active lupus nephritis. On multivariate analysis, serum creatinine (SCr) at the time of diagnosis is the only independent predictor of remission (complete or partial) at 6 months. According to the receiver operating characteristic curve, the cut-off value of SCr ≤ 2.9 mg/dL with 100% specificity and 98 % sensitivity was a predictor for renal remission.

Conclusion: The UPCR of 4.9 g/g, SLEDAI of 20 and Hb of 8.8 g/dl at the third month are valuable for predicting remission at the sixth month in active lupus nephritis. Serum creatinine level ≤2.9 mg/dL at the time of diagnosis was the only independent predictor of complete remission at 6 months.

Keywords: Lupus nephritis, Predictors, Remission.

INTRODUCTION

Systemic lupus erythematosus is a chronic, multisystemic, inflammatory, autoimmune disorder characterized by the formation of autoantibodies directed against self-antigen and immune complex resulting in a wide range of clinical manifestations and target organs (kidney, lungs) damage with unpredictable flares and remissions that eventually lead to permanent injury[(1)]. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, epigenetic, ethnic, immune-regulatory, hormonal, and environmental factors[(2)]. SLE predominantly affects women, with a reported peak female-to-male ratio of 11:1 during the childbearing years[(3)].

Lupus nephritis (LN) is one of the severe manifestations of systemic lupus erythematosus (SLE) and a common cause for end-stage renal disease significantly affecting the survival of SLE patients. Generally, at least six months are needed to assess treatment responses. Failure to respond to immunosuppressive therapy can lead to a worsening of renal function. Clinical trials in LN usually use complete remission (CR) and partial remission (PR) as primary endpoints. Complete remission was defined as albumin 35 g/l, urinary protein creatinine ratio (UPCR)<0.3 g/g, a normal range of SCr or at a level increasing no more than 15% from baseline, and without lupus flares[(4)]. Partial remission was defined as albumin 30 g/l, a proteinuria > 0.3 but < 3.5 g per 24 hours or decrease 50% from baseline, a normal range of SCr or at a level increasing no more than 15% from the baseline and without lupus flares. While no remission was defined as not meeting the response criteria[(5)].

For this reason, prediction of the long-term renal outcome at the early stages of the disease is of vital importance. Thus, several studies have sought to identify early clinical features, laboratory tests, and molecular mechanisms that are associated with unfavorable renal prognosis, to optimize the surveillance and interventions in these patients[(2)]. Therefore, this study aimed to determine the predictors of remission in patients with biopsy-proven lupus nephritis, and to assess the long-term renal remission rate in our lupus nephritis patients.

PATIENTS AND METHODS

This is a retrospective observational study conducted on 60 SLE patients with lupus nephritis who were admitted to Rheumatology and Nephrology Units, Internal Medicine Department, Menoufia and

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Mansoura Universities Hospitals, Egypt during 1-year duration between 1 June 2019 and 1 June 2020.

The study included 60 SLE patients (classified according to the 1997 American College of Rheumatology[6] or Systemic Lupus Collaborating Clinics criteria[7] with biopsy-proven LN (classified according to The revised ISN/RPS 2018 histopathological classification system[8] were identified and categorized into remission (partial and complete), and no-remission.

Ethical consideration:

The study protocol was approved by the Institutional Research Board of the Faculty of Medicine, Menofuia University. The study was explained to all patients, and informed written consent was obtained from all of them before starting the study.

Inclusion Criteria: Age > 18 years and SLE patients with biopsy-proven LN.

Exclusion criteria: Severe physical disability**,** patients with uncontrolled hypertension, diabetes mellitus, or severe ischemic heart diseases, patients with mental illness, patients with overlap syndrome, and refusal to participate in the study.

All patients were subjected to the following:
Complete history taking, clinical examination, and disease activity was assessed by SLEDAI.

The Laboratory investigations were reported at the time of renal biopsy and after 1, 3, 6 months of treatment: complete blood count, serum creatinine (SCr), SLEDAI, serum albumin, C-reactive protein, urine analysis, and 24-hour urinary protein excretion, glomerular filtration rate (eGFR), C3 and C4 levels and autoantibody profile, including ANA and anti-dsDNA antibodies,

Renal biopsy:

Renal biopsy was performed for all patients fulfilling the American College of Rheumatology (ACR) criteria to confirm the diagnosis of lupus nephritis (LN) and to classify the glomerular disease by the revised International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2018 histopathological classification system[8], also LN class and activity and chronicity scores were recorded. Patients were reviewed at one month, three months, and six months for clinical assessment, renal function assessment (SCr and eGFR), assessment of proteinuria, and monitoring response to therapy**.**

Statistical analysis

The collected data were coded, processed and analyzed using IBM SPSS for Windows v24 (IBM Corp., Armonk, NY). Data were expressed as the mean ±standard deviation (SD). Qualitative data were presented as frequencies and relative percentages. Independent samples t-test was used to compare continuous variables. The chi-square test was used to assess the differences between qualitative variables. Logistic regression analysis was carried out to identify the potential predictors for renal recovery. Receiver operating characteristic (ROC) curve analysis was done to identify the cut points below which renal recovery is likely. P-values of ≤ 0.05 were considered significant.

RESULTS

In the current study, the majority of patients are female (81.7 %) and the female to male ratio is 8.2: 1. The mean age of the study population is 30.6 ±9 years while the mean age at the onset of LN is 28.7± 9.1 years. There was a significant difference between the remission group and the no-remission group regarding the family history of SLE and SLEDAI. SLEDAI was significantly lower among the remission group when compared with the no-remission group [Table 1].

Table (I): Baseline demographic and clinical characteristic of the patients in the study groups

Variables		No remission (n=16)	Partial / Complete remission (n=44)	p-value
Age (years)	Mean ±SD	31.6±8.0	30.2±9.3	0.608
Sex	Female, n (%)	13 (81.2)	36 (81.8)	1.000
	Male, n (%)	3 (18.8)	8 (18.2)	
Age at onset of SLE (years)	Mean ±SD	27.9±7.3	27.6±9.4	0.894
Age at onset of LN (years)	Mean ±SD	29.1±8.5	28.5±9.4	0.834
Duration of LN (months)	Mean ±SD	34.5±16.9	27.0±13.5	0.080
Duration of SLE (years)	Mean ±SD	3.7±1.7	3.0±1.4	0.155
SLEDAI	Mean ±SD	34.9±9.1	13.0±6.6	<0.001
Family history	- ve, n (%)	4 (25)	35 (79.5)	<0.001
	+ ve, n (%)	12(75)	9(20.5)	

In this study renal biopsies revealed that the most common class was class IV. 98.3% of patients in the study received steroids therapy in combination with other immunosuppressive drugs and 5% of cases received steroids only. The immunosuppressive regimens included mycophenolate mofetil (46.7% of cases), intravenous cyclophosphamide (41.7% of cases), cyclosporin A (CSA) (3.3% of cases) and azathioprine (AZA) (1.7% of cases). 7 patients in this study had two renal biopsies. The mean indications for repeated renal biopsy are increased proteinuria or serum creatinine or both.

The change in histopathological class was recognized, 42.9 % of cases have a different histopathological class, and also 71.4 of cases have a different treatment protocol after the second renal biopsy. 35.0% of patients needed hospitalization, renal flares occurred in 11.7% of patients. 1.7% of cases needed plasmapheresis while 25% of them needed hemodialysis. 26.7% of cases in the study didn't have remission, 73.3% achieved partial remission (31.7 %) or complete remission (41.7%), the mean Time to remission was 6 months.

There was significant difference between remission group and no-remission group regarding renal histopathological class. The lowest rate of remission was reported in class VI. Lupus nephritis activity index and lupus nephritis chronicity index were significantly lower among the remission group when compared with the no-remission group [Table 2].

Table (2): Characteristic of Renal histopathological class and treatment protocol of patients with LN who achieved remission and did not achieve remission after six months of follow up

Variables		**No remission (n=16)**	**Partial/Complete remission (n=44)**	
				p-value
Renal histopathological Class	Class II, n (%)	0 (0.0)	5(11.4)	0.06
	Class III, n (%)	1 (6.3)	13(29.5)	
	Class IV, n (%)	12 (75)	23(52.3)	
	Class V, n (%)	2(12.5)	3(6.8)	
	Class VI, n (%)	1 (6.3)	0(0.0)	
Activity index	Mean ±SD	6.6±3.4	3.8±3.2	0.005
Chronicity index	Mean ±SD	7.9±2.5	1.6±1.9	<0.001
Treatment protocol	Nil, n (%)	1 (6.3)	0 (0.0)	0.194
	Steroid only, n (%)	0 (0.0)	3 (6.8)	
	Steroid plus MMF, n (%)	7 (43.8)	21(47.7)	
	Steroid plus CYC, n (%)	7 (43.8)	18 (40.9)	
	Steroid plus CSA, n (%)	0 (0.0)	2 (4.5)	
	Steroid plus AZA, n (%)	1 (6.3)	0 (0.0)	
Re-biopsy	Not needed, n (%)	9 (56.2)	44 (100)	<0.001
	Done, n (%)	7 (43.8)	0 (0.0)	

MMF: Mycophenolate Mofetil, CYC: Cyclophosphamide, CSA: Cyclosporin, AZA: Azathioprine

The Platelet's count, hemoglobin, WBC, C3, C4, and albumin levels were significantly higher in the remission group than in the no-remission group at months 1, 3, and 6. While, serum creatinine levels, UPCR were significantly lower in the remission group than in the non-remission group at diagnosis, 1, 3 and 6 months. Also, Urinary RBCs were significantly lower in the remission group than in the non-remission group at diagnosis and 6 months after treatment. While, eGFR was significantly higher in the remission group than in the non-remission group at diagnosis and 6 months after treatment [Table 3].

Table (3): Laboratory characteristics of patients with LN who achieved remission and those who did not achieve remission after six months of follow-up

Variable	No remission (n=16)	Partial/Complete remission (n=44)	p-Value*
	Mean ± SD	Mean ± SD	
Hemoglobin at diagnosis (g/dl)	7.8±0.5	11.0±1.1	<0.001
Hemoglobin at 1 month of diagnosis (g/dl)	7.5±0.8	10.1±1.3	<0.001
Hemoglobin at 3 months of diagnosis (g/dl)	7.8±1.0	10.2±0.9	<0.001
Hemoglobin at 6 months of diagnosis (g/dl)	8.5±0.9	11.2±0.8	<0.001
WBC at diagnosis (k/mm^3)	3.5±0.8	6.5±0.2	0.001
WBC at 1 month of diagnosis (k/mm^3)	3.7±0.7	6.3±1.5	0.001
WBC at 3 months of diagnosis (k/mm^3)	4.7±1.0	6.7±1.3	0.004
WBC at 3 months of diagnosis (k/mm^3)	5.8±0.5	7.4±1.1	0.012
Platelets at diagnosis (k/mm3)	157.6±16.3	249.8±6.7	0.002
Platelets at 1 month of diagnosis (k/mm^3)	178.4±25.6	263.0±2.3	0.021
Platelets at 3 months of diagnosis (k/mm^3)	203.6±15.9	285.4±6.9	0.005
Platelets at 3 months of diagnosis (k/mm^3)	203.9±14.5	288.1±9.6	0.002
Creatinine at diagnosis (mg/dl)	4.42±0.57	1.69±0.08	<0.001
Creatinine at 1 month of diagnosis (mg/dl)	4.98±1.07	1.87±0.01	<0.001
Creatinine at 3 months of diagnosis (mg/dl)	5.71±1.02	1.80±0.09	<0.001
Creatinine at 6 months of diagnosis (mg/dl)	6.11±1.67	1.40±0.08	<0.001
UPCR at baseline (g/g)	5.83±1.02	3.16±0.24	<0.001
UPCR at 1 month of diagnosis (g/g)	5.56±1.97	2.63±0.33	<0.001
UPCR at 3 months of diagnosis (g/g)	5.11±1.59	1.87±0.26	<0.001
UPCR at 6 months of diagnosis (g/g)	4.35±0.93	1.03±0.06	<0.001
C3 at diagnosis (mg/dl)	26.1±2.1	48.8±8.4	<0.001
C3 at 1 month (mg/dl)	39.8±9.1	86.5±3.7	<0.001
C3 at 3 months (mg/dl)	59.0±2.1	116.7±5.4	<0.001
C3 at 6 months (mg/dl)	92.4±3.6	134.3±6.6	<0.001
C4 at diagnosis (mg/dl)	6.4±1.9	8.1±2.2	0.037
C4 at 1 month (mg/dl)	7.9±1.3	16.3±3.1	<0.001
C4 at 3 months (mg/dl)	12.5±3.9	23.4±3.6	<0.001
C4 at 6 months (mg/dl)	17.5±3.7	26.9±4.7	0.002
Serum albumin at diagnosis (g/dl)	21.4±4.9	32.5±4.6	<0.001
Serum albumin at 1 month of diagnosis (g/dl)	24.5±5.8	34.0±5.1	<0.001
Serum albumin at 3 months of diagnosis (g/dl)	26.6±5.8	36.8±4.0	<0.001
Serum albumin at 6 months of diagnosis (g/dl)	26.9±4.8	39.3±4.2	<0.001
Urinary RBCs at diagnosis (cells/HPF)	16±1.0	6.0±1.0	0.004
Urinary RBCs at 6 months of diagnosis (cells/HPF)	10.0±2.0	3.0±0.10	<0.001
eGFR at diagnosis (ml/min/1.73 m^2)	23.7±3.4	75.7±7.3	<0.001
eGFR at 6 months of diagnosis (ml/min/1.73 m^2)	13.8±2.5	83.2±2.8	<0.001

Analysis of receiver-operating characteristics curve in this study is shown in table 4.

Table (4): Receiver-operating characteristic (ROC) curve analysis for prediction of remission (partial or complete) in patients with LN

Predictor	AUC	SE	95% CI	Z	p-Value	J	Cut-off	Sens.	Spec.
SLEDAI	0.974	0.016	0.896 to 0.998	29.685	<0.0001	0.886	≤20	89	100
LNAI	0.724	0.074	0.594 to 0.832	3.016	0.0026	0.466	≤4	59	88
LNCI	0.945	0.047	0.854 to 0.987	9.436	<0.0001	0.915	≤4	98	94
Hb	0.983	0.017	0.910 to 1.000	28.075	<0.0001	0.977	>8.8	98	100
WBC	0.838	0.069	0.720 to 0.921	4.911	<0.0001	0.591	>3.4	84	75
Platelets	0.780	0.086	0.654 to 0.877	3.263	0.0011	0.602	>116	98	63
Creatinine	0.994	0.007	0.928 to 1.000	71.786	<0.0001	0.977	≤2.9	98	100
UPCR	0.889	0.053	0.782 to 0.956	7.331	<0.0001	0.784	≤4.9	91	88
eGFR	0.990	0.010	0.922 to 1.000	47.300	<0.0001	0.977	>30	98	100
C3	0.795	0.071	0.671 to 0.888	4.162	<0.0001	0.494	>19	93	56
C4	0.659	0.086	0.525 to 0.777	1.853	0.0639	0.296	>5	80	50
Serum Albumin	0.822	0.080	0.701 to 0.909	4.021	0.0001	0.636	>27	89	75
Urinary RBCs	0.771	0.074	0.645 to 0.870	3.652	0.0003	0.449	≤7	64	81

AUC = area under the ROC curve, SE = standard error, 95% CI = 95% confidence interval, Z = Z-statistic, J = J-index ([sensitivity + specificity] - 1), Sens. = sensitivity, Spec. = specificity

The multivariate analysis was carried out using two models introducing the following variables: serum creatinine level at diagnosis and urinary RBCs at diagnosis, it revealed that the serum creatinine with value≤ 2.9 mg/dL at the time of diagnosis was the only independent predictor of remission (complete or partial) at 6 months with 100% specificity and 98 % sensitivity, while the patients with a serum creatinine level >2.9 mg/dl at the time of diagnosis failed to achieve remission at 6 months [Table 5].

Table (5): Stepwise multivariable binary logistic regression analysis for prediction of partial or complete remission

Independent Variable*	B	SE	Wald χ^2 (df, 1)	p-Value	Exp(B)	95% CI for EXP(B)	
						Lower	Upper
Creatinine at diagnosis (mg/dl)	-4.935	1.444	4.077	0.043	0.007	0.000	0.865
Urinary RBCs at diagnosis (cells/HPF)	-0.334	0058	1.669	0.196	0.716	0.432	1.188
Constant	21.436	11.310					

DISCUSSION

When we compared between the remission group and the no-remission group in this study, there was a non-significant difference between both groups regarding age, sex, age at onset of SLE, age at onset of LN, duration of LN, duration of SLE , or treatment protocol. Similar to this result, there were no significant differences in clinical data of **Liu *et al.*[(9)]** patients, the proportion of immunosuppressive therapy between the remission group and non-remission group at baseline.

There was a significant difference between the remission group and the no-remission group regarding the renal histopathological class. That was not in correspondence with **Liu *et al.* [(9)]** who reported that there were no significant differences in renal pathological characteristics between the remission group and no-remission group at baseline. According to the current study, the lowest rate of remission was reported in class VI. Similar to our result, the lowest rate of remission was found in class VI in **Saleh *et al.*[(10)]** study, also **Liu *et al.* [(9)]** reported that the proportion of class V + III/IV was higher among non-responders, but no significance was achieved.

According to the current study, both SLEDAI, lupus nephritis activity index and chronicity index were significantly lower among the remission group cases when compared with the no remission group. This was in concordance with **Saleh *et al.*[(10)]** who reported that patients who achieved remission had a significantly lower total score of chronicity indices compared to those who did not achieve remission ($p<0.001$). In the current study, urinary RBCs at diagnosis were significantly higher in the no-remission group. In discordance with our study, in **So *et al.*[(11)]** study there were no significant differences among the three groups in urinary RBC numbers. The kinetics of urinary protein-to-creatinine ratio (UPCR), serum creatinine, albumin, C3 and C4 levels between the remission group and no-remission group within six months were recorded in the current study. UPCR levels in the present study were significantly lower in the remission group than in the no-remission group at 1, 3 and 6 months. The same result as what **Liu *et al.*[(9)]** reported, that the UPCR was significantly lower in the remission group than in the non-remission group at months 1, 2, 3 , and 6. Albumin levels in our study were significantly higher in the remission group than in the no-remission group at diagnosis, 1, 3, and 6 months. Similar to our result, the serum albumin was significantly higher in the remission group than in the non-remission group at months 3 and 6 in **Liu *et al.*[(9)]** study.

The serum creatinine levels in the present study were significantly lower in the remission group than in the no-remission group at diagnosis, 1, 3, and 6 months. Similarly, **Saleh *et al.*[(10)]** reported that patients who achieved remission had lower SCr at the onset of disease ($p<0.001$). That was in discordance with **Liu *et al.*[(9)]** who reported non-significant differences in serum creatinine between the remission group and no-remission group, except at month 1.

In this study, both C3 and C4 levels were higher in the remission group than in the no-remission group at months 1, 3, and 6 months. That was in concordance with **Liu *et al.*[(9)]** who reported that the C3 levels were higher in the remission group than in the no-remission group at months 1, 2 and 3.

In the current study, the kinetics of Hb, WBC and platelets counts between the remission group and no-remission group within six months were recorded. Hb, WBC and platelets count were significantly higher in the remission group than in the no-remission group at months 1, 3 and 6. Similarly, **Saleh *et al.*[(10)]** reported that patients who achieved remission had higher hemoglobin at the onset of disease.

In the current study, eGFR was significantly higher in the remission group than in the no-remission group at diagnosis and 6 months after treatment. Similarly, **Saleh *et al.*[(10)]** reported that patients who achieved remission had higher eGFR at the onset of disease. However, contrary to our result, the same study reported a non-significant difference between patients who achieved remission and patients who didn't regarding urinary RBCs.

As regarding, ROC curves using with the use of AUC values of the change percentage of SLEDAI, lupus nephritis chronicity index, Hb, WBC, creatinine, UPCR, eGFR, C3 and urinary RBCs levels were the most significant. Then, we determined the cutoff values of these parameters based on the Youden J index, the cutoff value of UPCR at month 3 was$\leq$ 4.9 g/g, having a sensitivity of 91% and a specificity of 88%. While the cutoff value of serum creatinine at month 3 was $\leq$2.9 mg/dl, having a sensitivity of 98% and a specificity of 100%. In **Liu *et al.*[(9)]** study, the area under the curve (AUC) of the change percentage of UPCR at month 3 was significant (AUC 0.778, $p = 0.002$). The cutoff value of the change percentage of UPCR at month 3 was 59%. That was in accordance with our result. According to the present study, the cutoff value of Hb at month 3 was 8.8 g/dl, having a sensitivity of 98% and a specificity of 100%. While the cutoff value of WBC at month 3 was 3.4 k/mm^3, having a sensitivity of 84% and a specificity of 75%.

the multivariate analysis was carried out using two models introducing the following variables; serum creatinine level at diagnosis and urinary RBCs at diagnosis. It revealed that the serum creatinine with value$\leq$ 2.9 mg/dL at the time of diagnosis was the only independent predictor of remission (complete or partial) at 6 months with 100% specificity and 98 % sensitivity, while the patients with a serum creatinine level >2.9 mg/dl at the time of diagnosis failed to

achieve remission at 6 months. Similar to our result, multivariate analysis carried out by **Saleh *et al.*[10]** showed that serum creatinine level was the most significant predictor of renal recovery with a value of ≤1.65 identifying the probability of renal recovery with 76% sensitivity and 71% specificity.

CONCLUSION

There was a significant difference between the remission group and the no-remission group regarding the renal histopathological class, the class VI had the lowest rate of remission.

Both activity and chronicity indices of renal biopsy and SLEDAI were lower among remission group cases when compared with no-remission group.

Urinary RBCs at diagnosis were significantly higher in the no-remission group, while eGFR was significantly higher in the remission group than in the non-remission group at diagnosis and 6 months after treatment.

Albumin levels, hemoglobin, platelet's count , WBC C3, and C4 levels were significantly higher in the remission group than in the no-remission group at diagnosis, 1, 3 , and 6 months respectively.

Serum creatinine levels, UPCR were significantly lower in the remission group than in the no-remission group at diagnosis, 1, 3 and 6 months respectively

The UPCR of≤4.9 g/g, SLEDAI of ≤20 and Hb of >8.8 g/dl at the third month were valuable for predicting remission at the sixth month in active lupus nephritis.

However, serum creatinine level ≤2.9 mg/dL at the time of diagnosis was the only independent predictor of remission at 6 months with 100% specificity and 98 % sensitivity, because of the small-size and retrospective nature of the study.

STUDY LIMITATIONS

The sample size was small and from a two center only. We used steroid-based immunosuppressive therapies combined with intravenous cyclophosphamide, mycophenolate mofetil, CSA or AZA. Although there was no difference in the proportion of immunosuppressive therapies between the remission group and no-remission group, the study rates may be different under various treatments.

RECOMMENDATIONS

More multi-centered studies are needed on larger populations and other ethnic groups to detect more predictors for remission and chronic renal failure in lupus nephritis patients.

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