Relation between histopathological findings and the treatment response in lupus nephritis patients at Sohag Governorate

Emad Ahmed Mohamed, lofty Hamed Abo-Dahab,
Ahmed Mahmoud Helmy, Ahmed Nagah Noureldeen

*Department, Faculty of Medicine, Sohag University, Egypt

Abstract

Background:- lupus nephritis occurs in up to 60-70 % of patients with SLE and also constitutes one of the major organ manifestations that considerably alters the course and prognosis of SLE. LN is considered a major cause that leads to renal failure, which has a major impact on the short and long-term outcomes of patients with SLE. Regimens containing immunosuppressive drugs are the main treatment for active LN and early treatment response can predict long-term prognosis, So we aim to find reliable predictors of early treatment response in patients with SLE. Finding more comprehensive parameters to develop a better treatment regimen may help decrease longer-term morbidity and mortality.

Aim of the study: to examine the predictive factors of renal remission in lupus nephritis patients with lupus nephritis.

Results: In our study, after diagnosis by six months, about 61% of patients achieved remission. We found that the Chronicity index and Presence of interstitial fibrosis, are reliable factors for predicting the treatment response either the responder or not at the end of the sixth month of treatment.

On multivariate analysis, the Chronicity index was considered an independent predictor of disease remission after 6 months

Conclusion: Chronicity index ≤ 3 was considered of significant value for detecting treatment response at the sixth.

Keywords: lupus nephritis**.** Treatment response, histopathological examination, chronicity index.
DOI: 10.21608/SMJ.2023.210481.1389

Introduction

SLE is an autoimmune disease in which many organs of the body get affected secondary to immune deposits. Lupus nephritis (LN) is considered one of the main manifestations of SLE and may lead to end-stage renal disease, that have a major effect on the mortality and morbidity of SLE patients.[1] Immunosuppressive treatment is the major therapy for active LN. induction therapy is given for six months then treatment responses are evaluated. In patients with no response to immunosuppressive t-herapy, deterioration of renal function can occur [2].

Nephrotic syndrome is the most frequent clinical manifestation of LN. The ten-year renal survival rate is approximately 80–90% with the introduction of the current treatment strategies.[3]

Clinical studies in LN usually use complete remission (CR) as the primary endpoint. By studying the following factors as estimated glomerular filtration

rate (eGFR), serum albumin (Alb), and proteinuria. [4].

Renal biopsy is mandatory in the diagnosis and staging of lupus nephritis and for the exclusion of other etiologies. Acc-ording to the biopsy there are six classes of LN were described. The biopsy findings determine the treatment regimen for lupus nephritis. [5]

A good treatment response is supposed to predict prognosis, it is beneficial to develop a better treatment protocol and adjust it to reach a better result. [6]

Materials and Methods
Study population
This study is a single-center, prospective cohort study clinical-based study. Was done at Sohag University Hospital over two years duration during the period from October 2020 to September 2022 and included 76 participants

Patients:
76 Patients attended the outpatient nephrology clinic of Sohag University Hospital during the duration of this study and were diagnosed with SLE (65 females and 11 males), All patients were diagnosed after fulfilling the diagnostic criteria for SLE. [7]

Methods
In our study all patients were subjected to history taking and comprehensive clinical examination then we assessed The global disease activity by SLE disease activity index (SLEDAI) then Laboratory investigations, including CBC, S Creatinine, and Estimated glomerular filtration rate (eGFR), uPCR and Serum Albumin

Pathologic characteristics include:
1. Stage of LN
2. Glomerular sclerosis percentage,
3. Presence of Crescent
4. Presence of Capillary necrosis,
5. Presence of Mesangial proliferation,
6. Presence of Interstitial inflammation
7. activity index
8. chronicity index

According to the treatment response after 6 months, The patients were divided into two groups:
- **Group A**: LN in patients who achieved complete or partial renal remission
- **Group B**: LN patients in which renal remission was not achieved

Statistical analysis
Pearson's correlation analysis was used to find the correlation between two quantitative variables.

Proportional logistic regression models were constructed to identify the predicttors of treatment response among the 3 groups in multivariate models

For all these tests, the level of signifycance (P-value) was calculated and if the P-value was less than 0.05, the result was considered significant.

Receiver operating characteristic curves (ROC curves) were applied to find the best cut-off values, sensitivity, specificity, and diagnostic accuracy of various variables for the prediction of treatment response. The validity of the model was measured by the area under the curve (AUC).

Results
This Study included a total of 76 participants diagnosed with SLE with active lupus nephritis. After establishing the diagnosis and starting treatment, follow-up of these cases was done over a per-iod of 6 months.

In the present study, 22 cases (28.9%) of cases didn't have remission, 19 cases (25%) achieved partial remission (31.7 %) and 35 cases (46.1%) achieved complete remission

In our study, we found that the percentage of female patients is 65 patients (85.5 %) and the ratio is (8.6 female: 1 male). The age of the patients in the study ranged from 18 to 47 years.

In the present study the staging of the cases was done by renal biopsies and

our results were found to be as the following: None of the patients had (class I or class VI), while class II in 8 patients (10.5%), class III in 18 patients (23.7%), class IV in 40 patients (52.6%) and class V in 10 patients (13.2%). (Figure 1)

There was no significant statistical difference as regards the histopathological class of LN patients between both groups.

- (In Table 1) Also there was no statistical difference between the two groups as regard Activity index, presence of crescents, Capillary necrosis, Mesangial proliferation or presence of TMA.

On the other side, in this study we found that the chronicity index were obviously lower in group I that have good treatment response, and higher in patients who do not achieve remission. (p-value 0.001). Also, the percentage of glomerular sclerosis, the severity of interstitial fibrosis, and the degree of tubular atrophy were higher in the no-remission group rather than in patients with remission with (p-value 0.01) for glomerular sclerosis, (p-value 0.002) for the interstitial fibrosis and (p-value 0.004) for the presence of tubular atrophy. (Figure 2)
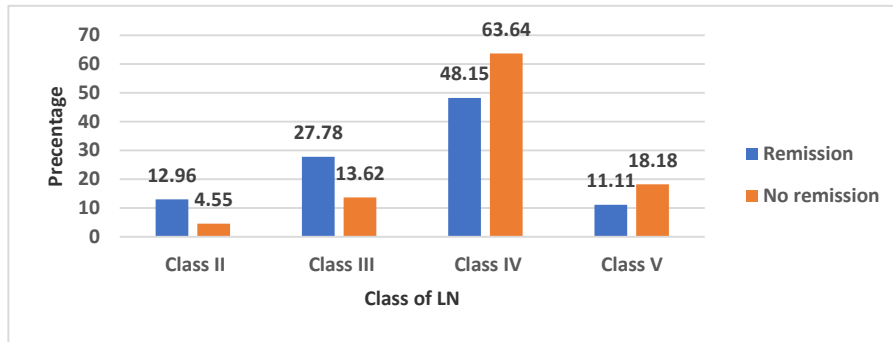
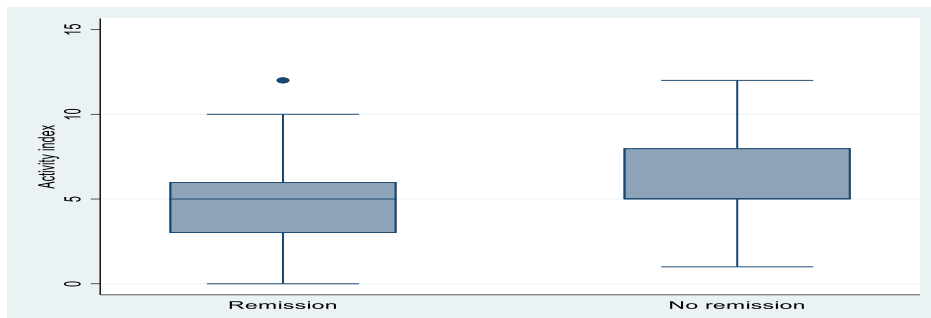**(Figure 1):- Class of LN of the studied population**
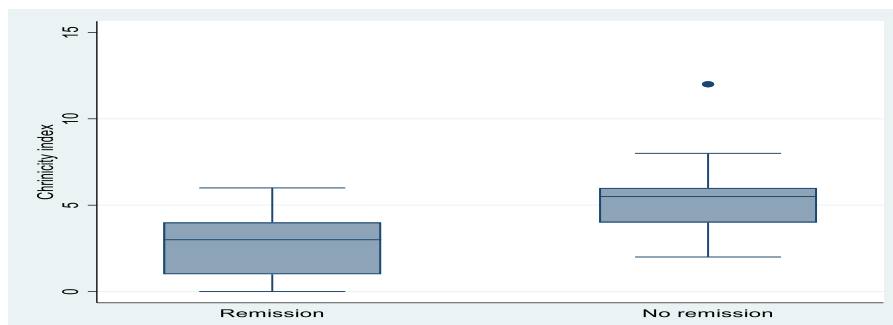

Figure (2-A): Activity index of the studied population

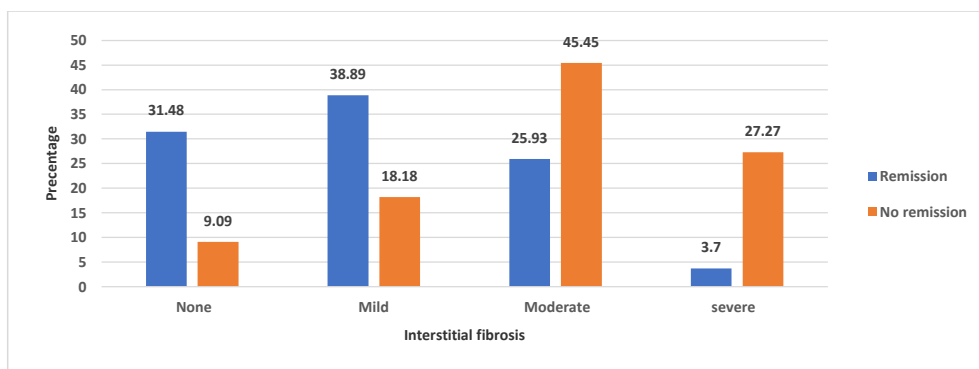
Figure (2-B): Chronicity index of the studied population

Figure (2-C): Interstitial fibrosis of the studied population

Table (1): Renal histopathological Characteristics of the studied population:

Variable	Remission N=54	No remission N=22	P value
Class of LN			
Class II	7 (12.96%)	1 (4.55%)	
Class III	15 (27.78%)	3 (13.62%)	0.30
Class IV	26 (48.15%)	14 (63.64%)	
Class V	6 (11.11%)	4 (18.18%)	
Activity index			
Mean ± SD	4.98±2.55	5.81±2.59	0.20
Median (range)	5 (0:12)	5 (1:12)	
Chronicity index			
Mean ± SD	2.74±1.99	5.36±2.03	<0.0001
Median (range)	3 (0:6)	5.5 (2:12)	
Glomerular sclerosis			
Absent	30 (55.56%)	15 (68.18%)	0.01
Present	24 (44.44%)	7 (31.82%)	
Presence of crescents			
No/Mild	29 (53.70%)	10 (45.45%)	0.51
Moderate/severe	25 (46.30%)	12 (54.55%)	
Capillary necrosis			
Absent	45 (83.33%)	18 (81.82%)	0.87
Present	9 (16.67%)	4 (18.18%)	
Mesangial proliferation			
Absent	33 (61.11%)	13 (59.09%)	0.87
Present	21 (38.89%)	9 (40.91%)	
Interstitial fibrosis			
Absent	17 (31.48%)	2 (9.09%)	0.002
Mild	21 (38.89%)	4 (18.18%)	
Moderate	14 (25.93%)	10 (45.45%)	
severe	2 (3.70%)	6 (27.27%)	
Tubular atrophy			
No/Mild	39 (72.22%)	8 (36.36%)	0.004
Moderate/severe	15 (27.78%)	14 (63.64%)	
Presence of TMA			
Absent	50 (92.59%)	19 (86.36%)	0.39
Present	4 (7.41%)	3 (13.64%)	

Discussion

During the clinical evaluation of LN, it is mandatory to perform a histaopatholo-gical analysis through a renal biopsy specimen to determine the LN class and exclude other associated conditions. Among 76 renal biopsies evaluated, we found that class IV has the highest percentage among our patients (51%). This finding was found to be in concordance with the results of other studies as the following: from Taiwan (62%) [8], Morocco (62.5%) [9]. , Tuni-sia (10), South Africa (11) the USA (32%) [12]. However, on the cont-

rary, there is a study of reported that class III was the most frequent class and was done in Egypt (35.07%) [13]

We found that there was no significant difference between patients who achieve remission and those who not achieve remission regarding the class of renal histopathology . These results w-as inmatching with (Liu et al. 2019)[14] who had a conclusion that there were no significant differences as regards the class of lupus nephritis between the two groups at the time of diagnosis. In contrast (Mahmud, et al. 2018) [15] and (Saleh et al.2020) .[13] who reported that class VI has the worst prognosis.

The histopathological analysis provides information about the LN class and about the severity and extent of kidney histological damage, and the presence of specific lesions as the presence of cresc-ents, Capillary necrosis, Mesangial pr-oliferation or presence of TMA Bro-derA, et al,. 2018).[16]

In this study, we found that there was a significant difference between the two groups as regards the chronicity index (p-value 0.001). Also, the percentage of Glomerular sclerosis, the severity of Interstitial fibrosis, and the degree of Tubular atrophy were lower in 1st group. These findings are understanddable as the previous lesions and high CI are histological evidence of advanced renal disease and a sign of irreversible histological damage indicating resistance to treatment and poor outcome. The latter observation is consistent with the finding of (Contreras G et al,. 2005),[12] (Ismail MI, et al,. 2016) (17) and (Austin, et al,. 2009). [18]

On the contrary (Contreras G et al,. 2005) (12) found that the activity index score was significantly lower in the remission group, in our study there was no significant statistical difference between the remission and No remission groups as regards the Activity index. The latter finding supports the

observation by (Malvar, et al,. 2017). [19] that active and chronic histological lesions may not follow a parallel course.

Also, we found the other histopathological findings in renal biopsy such as Capillary necrosis, Mesangial proliferation, and the Presence of TMA , have no statistical difference between the two groups.

The variation of results may be due to differences in sample size, age of patients, or different ethnic groups.

Conclusion
It is important to identify early predictive factors for treatment response in a patient with lupus nephritis to allow early treatment adjustment to get a better outcome for these patients.

Ethical approval

References
1. Ward MM. Access to care and the incidence of end-stage renal disease due to systemic lupus erythematosus. J Rheumatol. 2010;37:1158–63.

2. Costenbader KH, Desai A, Alarco´ n GS, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. Arthritis Rheum 2011; 63: 1681–1688.

3. Faurschou M, et al. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. Arthritis Care Res. 2010;62:873–80

4. Furie R, et al. Efficacy and safety of abatacept in lupus nephritis: A twelve-month, randomized, double blind study. Arthritis Rheumatol 2014; 66: 379–389.

5. Dall'Era M, et al. Predictors of long term renal outcome in lupus nephritis trials: Lessons learned from the Euro-Lupus

Nephritis cohort. Arthritis Rheumatol 2015; 67: 1305–1313.

6. Liu Z, et al. Multi target therapy for induction treatment of lupus nephritis: A randomized trial. Ann Intern Med2015; 162: 18–26.

7. Parodis, I., Tamirou, F., & Houssiau, F. A. (2020). Prediction of prognosis and renal outcome in lupus nephritis. *Lupus Science & Medicine*, *7*(1), e000389

8. Hsu C, Chiu W, Yang T. (2011). Age-and gender-related long-term renal outcome in patients with lupus nephritis. Lupus; 20: 1135–1141.

9. Haddiya I, Hamzaoui H, Tachfouti N. (2013). Features and outcomes of lupus nephritis in Morocco: analysis of 114 patients. Int J Nephrol Renovasc Dis; 6: 249

10. Beji S, Kaaroud H, Moussa FB. (2005) Nephropathie lupique: a` propos de 211 cas. Rev Med Interne 2; 26: 8–12

11. Ayodele OE, Okpechi IG, Swanepoel CR. (2010) Predictors of poor renal outcome in patients with biopsy-proven lupus nephritis. Nephrology (Carlton) ; 15: 482–490.

12. Contreras G, Pardo V, Cely C. (2005). Factors associated with poor outcomes in patients with lupus nephritis. Lupus 2005; 14: 890–895

13. Saleh M, Eltoraby E, Tharwat S. (2020): Clinical and histopathological features and short-term outcomes of lupus nephritis: a prospective study of 100 Egyptian patients. Lupus, 29(8):993-1001.

14. Liu G, Wang H, Le J. (2019): Early-stage predictors for treatment responses in patients with active lupus nephritis. Lupus, 28(3):283-9.

15. Mahmoud G, Shahin A, Zayed H, Moghazy A, Eissa B. (2018). Clinical and immunological pattern and outcome of Egyptian systemic lupus erythematosus patients: a single center experience. Lupus; 27: 1562–1569.

16. Broder A, Mowrey WB, Khan HN, (2018). Tubulointerstitial damage predicts end stage renal disease in lupus nephritis with preserved to moderately impaired renal function: a retrospective cohort study. Semin Arthritis Rheum;47:545–51.

17. Ismail MI, Lakouz K, Abdelbary E. (2016). Clinicopathological correlations of renal pathology: a single center experience. Saudi J Kidney Dis Transplant; 27: 557–562.

18. Austin HA, Balow JE. (2009) Natural history and treatment of lupus nephritis. Semin Nephrol ; 19: 2–11.

19. Malvar A, Pirruccio P, Alberton V. (2017). Histologic versus clinical remission in proliferative lupus nephritis. Nephrol Dial Transplant;32:1338–44.