ORIGINAL ARTICLE

Evaluating Activity and Chronicity Indices in Lupus Nephritis Using the Recent NIH-Modified Activity Index Scores: A Comprehensive Correlation Analysis with Renal Function

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ABSTRACT

Objective: To study the correlation between activity and chronicity indices in renal biopsies and renal functions among lupus nephritis patients.

Study Design: Prospective cross-sectional study**.**

Place and Duration of Study: This study was carried out from October 2021 to 2022 at Department of Histopathology, Shifa International Hospital Islamabad.

Materials and Methods: Clinical data, including history, age, serum creatinine, serum and urine albumin levels, ANA and Anti Ds DNA status, were obtained from the hospital's medical electronic records. Renal biopsies for light microscopy were assessed and scored for activity index and chronicity index using the recent (2018) NIH-modified activity and chronicity index scores (Table I). Immunofluorescence slides were viewed for full house deposits of IgG, IgA, IgM, C3 and C1q as seen in lupus nephritis. Data was incorporated into data management software, and statistical analysis was conducted using IBM SPSS version 23.0.

Results: Among the 91 renal biopsies, 12 (13.2%) were male patients and 79 (86.8%) were female patients. The mean activity index score was 6.42±3.9 (ranging from 0 to 16 out of 24), while the mean chronicity score was 2.25±2.0 (ranging from 0 to 8 out of 12). Comparisons of activity and chronicity index scores with lupus classes revealed a significant association. Mean activity scores for lupus Class 1 to 5 were 2.07±1.6, 3.40±2.3, 8.21±3.3, 3.00±2.3, and 5.00±0.5 respectively, similarly mean chronicity scores for lupus grade 1 to 5 were 0.50±0.5, 0.80±0.8, 2.75±1.9, 3.00±2.7, and 7.00±0.5 respectively. These scores were compared with lupus classes, revealing significantly higher mean activity and chronicity index scores for higher lupus classes. A positive correlation between index scores and elevated creatinine levels ($p<0.001$) was observed.

Conclusion: The study concludes that NIH-modified activity index and chronicity index scores are positively associated with lupus classes and clinical parameters, including serum creatinine, albumin, and urine protein.

Key Words: *Activity Index, Chronicity Index, Lupus Nephritis, Serum Creatinine.*

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic, chronic autoimmune illness that affects almost every organ in the body.Renal involvement, which occurs in more than 50% of patients within the first year of diagnosis, is associated with higher morbidity and mortality.[1]After diabetes mellitus, lupus nephritis (LN) is the second most prevalent cause of renal impairment overall2.Its etiology is complex and includes environmental variables, complement activation, autoantibodies, and genetic factors.[2] Advances in therapeutic approaches have improved the prognosis and outcomes of lupus nephritis over the last decade. Renal biopsy remains the gold standard for diagnosis and managementz.[3]

When examined under a light microscope, lupus nephritis can have morphological characteristics that range from normal findings to severe symptoms including glomerulosclerosis, crescents, and endocapillary hypercellularity. Immunofluorescence often shows sub-endothelial deposits in addition to granular full-house deposits in the tubular basement membrane and mesangio-capillary pattern.[4]

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More over 10% of patients develop endstage renal disease within 15 years, demonstrating the substantial impact of LN on morbidity and mortality.[5] The International Society of Nephrology and Renal Pathology Society (ISN/RPS) classified LN into six classes in 2003, which were updated in 2008 to include Class I: Minimal Mesangial Lupus Nephritis, Class II: Mesangial Proliferative Lupus Nephritis, Class III: Focal Lupus Nephritis, Class IV: Diffuse Lupus Nephritis, Class V: Membranous Lupus Nephritis, Class VI: Advanced Sclerosing Lupus Nephritis.[6,7,8]

Recent studies have underscored the importance of assessing activity and chronicity indices in renal biopsies of LN patients.[9,10] This may be due to limited data in several studies, producing false negative correlations. International renal societies have advocated for incorporating these indices into LN workup to enhance the prognostic value of renal biopsy.[11]

This study aimed to correlate renal functions with activity and chronicity indices in renal biopsies of lupus nephritis patients and establish a model of histological features associated with long-term kidney function impairment in the Pakistani population.

Materials and Methods

The study included 91 adequate renal biopsies from diagnosed/ suspected systemic lupus erythematosis patients (ANA/ Anti Ds DNA positive/ clinical picture) that were prospectively analyzed between October 2021 and 2022 at Shifa International hospital after approval by the Institutional Review Board (IRB). Clinical data, including history, age, serum creatinine, serum and urine albumin levels, ANA, and Ds DNA levels, were accessed from hospital's electronic records. Only cases with adequate renal biopsies, with separate cores for light microscopy (LM) and immunofluorescence (IF), were included. Biopsies lacking glomeruli or consisting entirely of globally sclerosed glomeruli were excluded. Hematoxylin and eosin staining was performed on all renal biopsies, cut at 6 microns, with additional special stains (PAS, Jones silver, Trichrome). Direct immunofluorescence testing was applied separately to cores submitted in normal saline, using IgG, IgA, IgM, C3, and C1q immunofluorescence antibodies. Clinical details of each case were recorded on a specifically designed questionnaire, including history, age, serum creatinine, serum and urine albumin levels, ANA, and Ds DNA levels. Renal biopsies were evaluated and calculated for activity and chronicity indices using standard chart(Table I) biopsies were also assessed for ISN/RPN lupus classes histologically and confirmed through special stains. Data were incorporated into data management software, and statistical analysis was conducted using IBM SPSS version 23.0.

Descriptive statistics, including frequency and percentage for categorical variables, and mean values with standard deviations for continuous variables, were reported. Gender and comorbid conditions such as hypertension, diabetes mellitus, Anti Ds antibodies, and ANA antibodies were qualitative variables, while activity index score, chronicity index score, serum creatinine, serum protein, and urinary protein levels were quantitative variables.

Spearman correlation tests were used to to measure the monotonic association between activity and chronicity scores with lupus classes, with results reported as correlation coefficients and significance values. Additionally, one-way ANOVA tests were used to compare means of activity and chronicity scores with mean values of serum creatinine, albumin, and urinary protein. A significance level of $p \leq 0.05$ was considered statistically significant.

Results

A total of 91 renal biopsies of either known SLE or suspected cases were included out of all the renal biopsies between the time frame in the study, including 12 (13.2%) males and 79 (86.8%) females. The majority of participants, 38 (41.8%), fell within the 21-30 years age group, while 21 (23.1%) patients belonged to the 11-20 years age group. Among the participants, 54 (59.3%) had elevated creatinine values, 41 (45.0%) had low serum albumin levels, 58 (63.7%) exhibited high urinary protein levels, 32 (35.2%) had decreased serum C3 and C4 complement levels, and 59 (64.8%) tested positive for anti-dsDNA antibodies.

Lupus class distribution among the study participants is illustrated in Figure 1, with 14 (15.4%) classified as lupus class 1 (mesangial expansion), 10 (11.0%) as lupus class 2 (Mesangioproliferative), 61 (67.0%) as lupus class 3 (focal lupus nephritis), 5 (5.5%) as lupus class 4 (diffuse lupus nephritis), and 1

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(1.1%) as lupus class 5 (membranouslupus nephritis) Direct immunofluorescence showed predominantly full-house deposits as seen in lupus nephritis.

Activity and chronicity index scores were calculated for each participant. The mean activity index score was 6.42±3.9 (ranging from 0 to 16 out of 24), while the mean chronicity score was 2.25±2.0 (ranging from 0 to 8 out of 12). Comparisons of activity and chronicity index scores with lupus classes revealed a significant association, as depicted in Figure 3. Mean activity scores for lupus class 1 to 5 were 2.07±1.6, 3.40±2.3, 8.21±3.3, 3.00±2.3, and 5.00±0.5 respectively, similarly mean chronicity scores for lupus class 1 to 5 were 0.50±0.5, 0.80±0.8, 2.75±1.9, 3.00±2.7, and 7.00±0.5 respectively.

Exploration of the correlation between lupus classes and activity index score yielded a significant positive correlation (r=0.446, p<0.001), as did the correlation between lupus class and chronicity index score (r=0.495, p<0.001).

Furthermore, the association of activity and chronicity index scores with clinical and laboratory parameters was assessed (Table 3). Significant associations were found between creatinine levels and both activity index (p=0.008) and chronicity index (p=0.001), with higher scores observed in patients with elevated serum creatinine levels. While higher scores were noted for patients with lower serum albumin, raised urinary protein, positive anti-dsDNA test results, and low C3 and C4 complement levels compared to those with normal results.

Table I: Modified NIH Indices (2018) Activity and Chronicity Index Score

MODIFIED NIH ACTIVITY INDEX	SCORE
Endocapillary hypercellularity	0 - 3
Neutrophils and/ or karyorrhexis	0 - 3
Fibrinoid necrosis	(0 – 3) x 2
Hyaline deposits	0 - 3
Cellular and / or fibro -cellular crescents	(0 – 3) x 2
Interstitial inflammation	0 - 3
Total	0 - 24
MODIFIED NIH CHRONICITY INDEX	**Score**
Global sclerosis	0 - 3
Fibrous crescents	0 - 3
Tubular atrophy	0 - 3
Interstitial fibrosis	0 - 3
Total	0 - 12

Table II: Association of mean activity and chronicity score with clinical/laboratory parameters

	Activity score (mean)	P value	Chronicity score (mean)	P value
Creatinine				
• < 1	• 4.3	0.008	0.86	0.001
• 1.1-2.0	• 7.5		2.1	
• 2.1-3.0	• 7.7		2.5	
• >3	• 7.9		3.3	
Serum albumin				
• <1.5	• 3.2	0.349	0.8	0.477
• 1.6-2.5	• 7.2		2.3	
• 2.6-3.5	• 6.0		1.9	
• >3.5	• 6.0		1.0	
Urine protein				
• <3 gm	• 4.7	0.071	1.5	0.291
• >3 gm	• 7.2		2.2	
Serum C3 and C4				
• Low	• 7.2	0.155	2.6	0.590
• Normal	• 5.6		2.2	

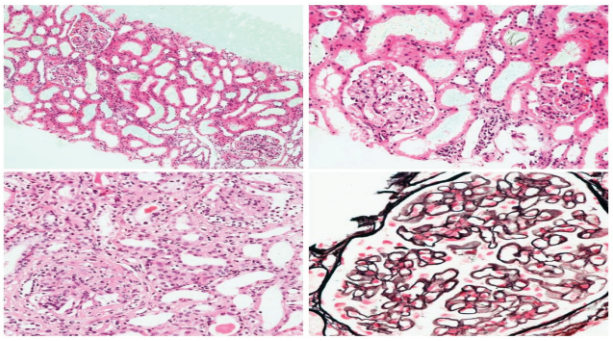

Figure 1: [Left upper: Class II(Mesangial hypercellularity), Right upper: Class III(Endocapillary proliferation less than 50%) Left lower: Class IV(Endocapillary proliferation more than 50%) Right lower: Class V(Membranous GN)

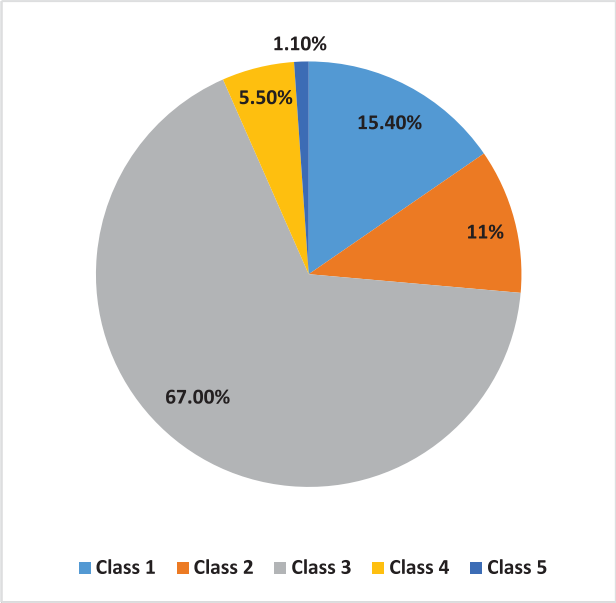

Figure 2: Distribution of Study Participants as per Lupus Nephritis Class

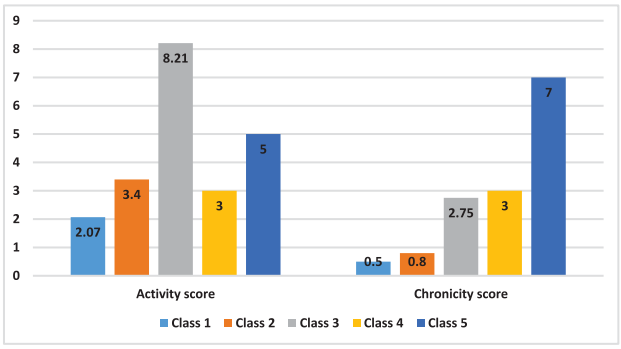

Figure 3: Mean Activity and Chronicity Score as per Lupus Grade among Study Participants (n=91)

Discussion

Renal biopsy is the most accurate way to diagnose lupus nephritis and assess the chronicity and activity of the condition to predict how renal function would deteriorate over time.

In our cohort, a substantial proportion of participants fell within the 21-30 years age group, followed by the 11-20 years age group. This age distribution reflects the peak onset period for lupus nephritis, which typically occurs during young adulthood. However, participants across a wide age range were included in the study, indicating the relevance of lupus nephritis across different age groups. 79 (86.8%) female patients and 12 (13.2%) males in our study reflects the female predominance of the disease process.

The distribution of creatinine levels provides insights into renal function among the participants. A considerable number of participants had creatinine levels above 1 mg/dL, indicating impaired renal function, while a notable portion had creatinine levels within the 1.1-2.0 mg/dL range. This underscores the significance of monitoring renal function in lupus nephritis patients, as elevated creatinine levels can indicate renal damage and disease progression. Serum albumin levels were also assessed, with a substantial proportion of participants having albumin levels less than 1.5 g/dL, with significant proteinuria (>3 grams) reflecting protein loss in the urine.

Assessment of serum C3 and C4 levels revealed that a considerable proportion of participants had low levels of complement components, which is commonly observed in active SLE and lupus nephritis. The presence of low complement levels suggests ongoing immune dysregulation and complement consumption. Anti-dsDNA levels were positive in 59 (64.8%) patients, and 19 (20.9%) patients were diagnosed to have SLE after diagnosis of lupus nephritis on renal biopsy.

The activity index in renal biopsy evaluates the severity of active inflammation and injury, while the chronicity index assesses the extent of irreversible structural changes and scarring within renal tissues. The majority of participants exhibited varying degrees of activity index ranging from endocapillary proliferation, glomerular neutrophilic infiltration, and cellular crescents, reflecting ongoing immune-mediated injury. Fibrinoid necrosis/karyorrhexis, although less commonly observed, is a hallmark feature of significant vascular injury and thrombotic microangiopathy. The majority of participants in this study did not exhibit significant fibrinoid necrosis/karyorrhexis, indicating a lower prevalence of severe vascular lesions in the cohort. The presence of hyaline deposits reflects previous episodes of glomerular injury and repair. Similarly, the majority of participants displayed varying degrees of chronicity index ranging from global sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis, reflecting poor long-term outcomes.

Table II presents the association of mean activity and chronicity scores with various clinical and laboratory parameters in the study cohort, shedding light on the relationship between histopathological features and disease severity.

Higher mean activity and chronicity scores were significantly associated with elevated creatinine levels (>1 mg/dL), with larger number associated with activity. A retrospective study by Prasan wong et al. examined 38 patients and noted significant correlations between serum creatinine. They concluded that the modified National Institutes of Health (NIH) scoring system showed stronger associations with clinical and outcome indicators compared to traditional scores.[12]

In another retrospective cohort study conducted by Nakagawa et al. involving Japanese population with biopsy-proven LN, 66 subjects with a mean age of 31 years were included. They observed that a higher chronicity index correlated with an increased cumulative incidence of primary outcomes ($p<0.001$).[13]

Another study by Moroni et al. followed 203 lupus

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nephritis (LN) patients for 14 years. They reported significant correlations between components of the activity, chronicity index and clinical-laboratory indicators like serum creatinine levels.[6]

In a study involving 301 patients with biopsy-proven lupus nephritis (LN), it was reported that the presence of globally sclerotic glomeruli predicted kidney survival in univariate analysis but not in multivariate analysis.[15] Instead, in a cohort of 105 patients followed for 9.9 years, factors such as fibrinoid necrosis, fibrous crescents, interstitial fibrosis/tubular atrophy, deranged renal function, and non-White race were predictive of end-stage kidney disease (ESKD).[16]

Furthermore, in another similar study, the revised ISN/RPS classification was utilized to assess the outcome of 101 Chinese patients with LN over approximately 10 years, elevated chronicity index emerged as independent risk factors for a composite renal outcome, which includes a reduction in estimated glomerular filtration rate (eGFR) of 30% or more, ESKD, and mortality.[17]

Although there are variations in findings, all the studies affirm the effectiveness of NIH-modified activity index and chronicity index scores in forecasting prognosis and the likelihood of future complications in lupus nephritis patients.

Conclusion

This study supports that the NIH-modified activity index and chronicity index scores demonstrate positive associations with key clinical parameters such as serum creatinine, albumin, and urine protein. This scoring system holds promise for predicting the prognosis and assessing the risk of future complications among patients with lupus nephritis.

Limitation

Lower serum albumin raised urinary protein, positive anti-dsDNA test results, and low C3 and C4 complement levels compared to those with normal results were seen with higher activity chronicity indices but results were not statistically significant. This is because we do not find all the laboratory parameters with each biopsy as we receive bulk of biopsies from outside Shifa international hospital.

Conflict of Interest: None

Funding Disclosure: None

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.