Original Article

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Pathology Section

Clinicopathological Assessment of Modified Activity and Chronicity Indices in Lupus Nephritis at a Teaching Hospital in Mysore, India

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ABSTRACT

Introduction: In 20-49% of patients with Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN) is a major complication and, therefore, an important prognostic determinant of SLE. The Activity and Chronicity Indices (AI and CI), used as adjuncts to the histological classification of LN, assist in identifying patients who will benefit from immuno-suppressive therapy.

Aim: To investigate the correlation of AI and CI in patients with biopsy-proven LN with clinical and laboratory findings.

Materials and Methods: A cross-sectional study was conducted as the Departments of Pathology and Nephrology, JSS Medical College and Hospital Mysore, India from January 2023 to March 2023, by retrieving the data of 56 patients with biopsy proven LN. AI and CI were assessed and classified. Data from multiple groups were compared using Pearson's chi-square test, and between two groups using independent samples t-test with Statistical Package for Social Sciences (SPSS) version 21.0. Pearson's correlation coefficient (r-value) was calculated using Microsoft excel 2021.

Results: Renal biopsies from 56 cases with biopsy-proven LN were studied, with a mean age of 28±10.30 years and a M:F ratio of 1:10.2. Of the 56 biopsies studied, active lesions were seen in 47 (83.9%) and chronic lesions in 21 (37.5%). AI showed statistical significance with hypertension (p=0.049) and haematuria (p=0.005), with proteinuria (p=0.001, r=0.72), serum creatinine (p=0.037, r=0.62), and blood urea nitrogen (p=0.003, r=0.55) showing a statistically significant positive correlation. CI showed a statistically significant positive correlation with proteinuria (p=0.028, r=0.039) and serum creatinine (p=0.010, r=0.58). Both AI and CI showed statistical significance with the degree of renal insufficiency, with CI (p=0.008) displaying a stronger statistical significance than AI (p=0.012).

Conclusion: In conclusion, the management and prognosis of patients with suspected LN are greatly facilitated through information obtained from renal biopsy, especially AI and CI, which are useful guides to treatment. It is important to study renal biopsy for the constellation of features in LN for better patient management.

Keywords: Activity index, Renal biopsy, Systemic lupus erythematosus

INTRODUCTION

The most common manifestation of SLE is LN, which is a major cause of morbidity. It occurs in about 20-49% of patients in the course of their disease [1]. The clinical presentation can be diverse, varying from subclinical disease to an aggressive form that rapidly progresses to End-Stage Renal Disease (ESRD) within 15 years in about 10-30% of the patients [1,2]. LN can involve any renal compartment. Therefore, renal biopsies in patients with SLE provide a direct assessment of renal involvement and establish the site of injury [2,3]. It is critical in determining the class of LN, the extent of histopathological chronicity and activity, and the long-term prognosis of the disease [3,4]. The nature and severity of the clinical features of LN and the underlying histological severity do not always correlate. However, poor renal survival has been associated with certain histological and clinical parameters [2]. Renal biopsy, therefore, serves as a guide for therapy [5].

Pirani CL et al., were the first to introduce the concept of active and chronic lesions, which was further modified by Morel ML et al., [6,7]. The widely used National Institute of Health (NIH)-AI and CI were based on the paper by Austin III HA and have been used to report the activity and chronicity in a semi-quantitative way [8]. Recently, a modified NIH activity and chronicity scoring system has been proposed by Bajema IM et al., which does not restrict AI and CI to classes III and IV as done previously [5]. Also, it has been recommended that in AI, the category of "fibrinoid necrosis/karyorrhexis" be changed to include only fibrinoid necrosis, which is the significant finding. Since "leucocyte infiltrate" refers to the presence of neutrophils only, and it has now been recommended that karyorrhexis, which represents apoptotic neutrophils, be included in this category, the name and description of this category have been changed to "neutrophil and karyorrhexis". Further, crescents have been defined as cellular crescents (>75% cells and fibrin, and <25% fibrous matrix), fibrous crescents (>75% fibrous matrix, and <25% cells and fibrin), and fibrocellular crescents (25-75% cells and fibrin, and the remainder fibrous matrix). As previously, it wasn't clear when fibrocellular crescents were to be included in the "cellular crescents" category of AI, it has been recommended that crescents meeting the description of fibrocellular crescents be included in the category of "cellular/fibrocellular crescents". Also, the term endocapillary proliferation in the AI has been replaced by "endocapillary hypercellularity".

The original description referred to only the presence of monocytes with respect to inflammatory cells in this category. Further studies are needed in this reference, and it has been recommended that neutrophils be scored as a separate entity for now [5]. Activity scores predict decreased survival and the responsiveness to immuno-suppressive therapy, while chronicity scores reflect glomerular sclerosis, an indicator of diminishing renal function. The activity and chronicity scores thus assist in identifying patients who will benefit from immunosuppressive therapy or might require renal replacement therapy [9].

These scores are used as an adjunct to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of LN by many practicing pathologists, although the reproducibility and the predictability of these indices have been questioned by some [9]. Many clinicopathological studies of classes of LN have been done in the past [9,10]. Our previous study found that classes of LN showed statistical significance with proteinuria and haematuria, and no statistical significance was seen between classes of LN and anaemia, serum creatinine, or blood urea nitrogen [10]. However, very few studies have been done for AI and CI [11,12]. It is therefore appropriate to document the association of AI and CI with clinical and laboratory findings in SLE patients using the revised "2018 recommendations for the ISN/RPS classification of LN" [5]. The objective of this study was to correlate AI and CI on renal biopsies with clinical and laboratory findings in patients with LN.

MATERIALS AND METHODS

A cross-sectional study was conducted as the Departments of Pathology and Nephrology, JSS Medical College and Hospital Mysore, India from January 2023 to March 2023. Ethical clearance from the Institutional Ethical Committee was obtained vide JSSMC/IEC/0372023/19 NCT/2023-24.

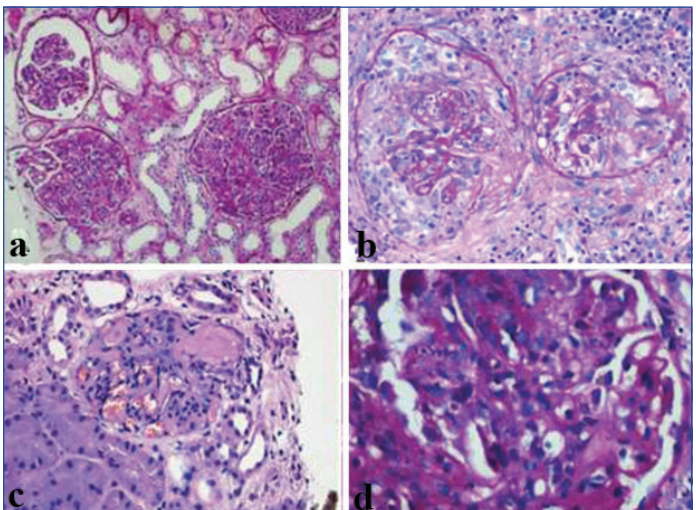
Inclusion criteria: Patients with biopsy-proven LN were included in the study.

Exclusion criteria: The core biopsies having fewer than six glomeruli on light microscopic examination were excluded.

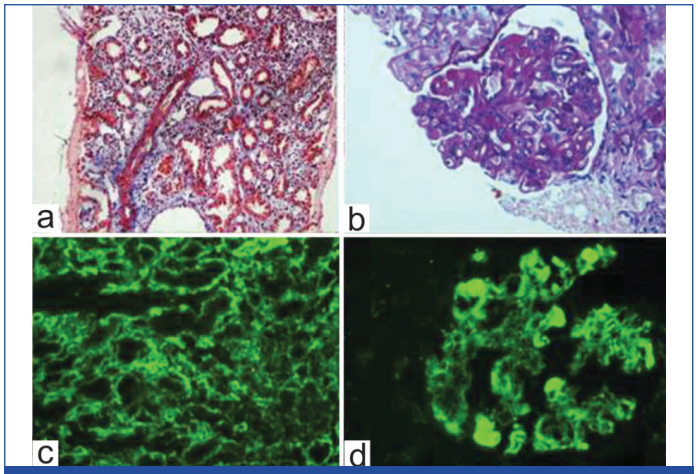
Procedure

Two cores of renal tissue were obtained from each of the fifty-six SLE patients undergoing renal biopsy, which were studied by Light Microscopy (LM) and Immunofluorescence (IF) studies. Tissues for LM were collected in 10% formalin and were studied using Haematoxylin and Eosin (H&E), Periodic Acid Schiff (PAS), Masson's trichrome (MTS), and Jones Methanamine Silver(JMS) stains. Tissues for IF were collected in Phosphate-Buffered Saline (PBS), stained with Fluorescein Isothiocyanate (FITC) labelled anti-human antibodies of IgG, IgA, IgM, C3, C1q, kappa, and lambda light chains (DACO), and studied under an immunofluorescent microscope-Olympus BX 41.

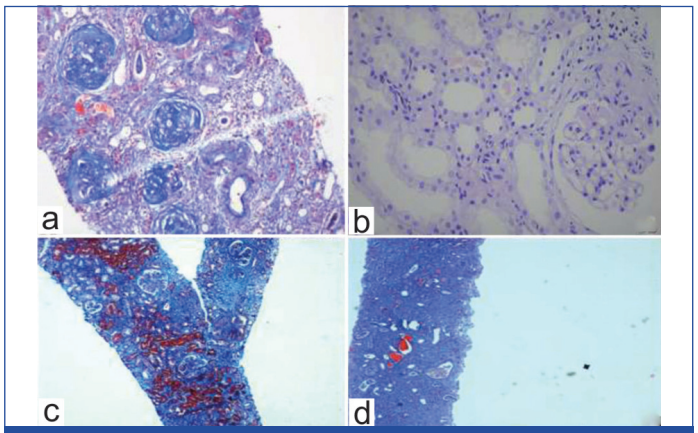
The biopsies were divided into classes I to VI according to the "2018 recommendations for the ISN/RPS classification of LN" [5], and AI and CI were assessed according to "Revision of classification of LN" by Bajema IM et al., [Table/Fig-1-3] [5]. For the purpose of this study, AI was divided into four groups: 1) AI of 0-5; 2) AI of 6-10; 3) AI of 11-15; and 4) AI of ≥16. Similarly, CI was divided into three groups: 1) CI of 0-3; 2) CI of 4-8; 3) CI of 9-12 [13].



[Table/Fig-1]: (a) Endocapillary hypercellularity (PAS, X100); (b) Circumferential cellular crescent (PAS, X200); (c) Fibrinoid necrosis (H&E, X100); (d) Karyorrhectic debris (PAS, X400).



[Table/Fig-2]: (a) Interstitial inflammation (MTS, X100); (b) Wireloop lesions and hyaline thrombi (PAS, X200); (c) Tubulo-interstitial deposits (C1q, X400); (d) Subendothelial deposits and hyaline thrombi (IgG, X200).



[Table/Fig-3]: (a) Glomerular sclerosis (MTS, X100); (b) Partial Fibrous crescent (H&E, X100); (c) Moderate interstitial fibrosis and tubular atrophy (MTS, X40); (d) Severe interstitial fibrosis and tubular atrophy (MTS, X40).

STATISTICAL ANALYSIS

The statistical analyses were performed using the SPSS version 21.0. All continuous variables were expressed as mean±SD, and categorical variables were presented as percentages. Comparison of data from multiple groups was made by Pearson's chi-square test and between two groups by independent samples t-test. The p-values of less than 0.05 were considered statistically significant. Pearson's correlation coefficient (r-value) was also calculated.

RESULTS

A total of 56 patients with biopsy-proven LN were studied, with ages ranging from nine years to 55 years with a mean of 28.05±10.30 years. The maximum number of cases, 28 (50%) of the 56 patients, were found to be in the range of 21-30 years. Fifty-one out of 56 patients (91.1%) were females and five patients (8.9%) were males, with a male-to-female ratio of 1:10.2.

The most common clinical features were hypertension in 23 (52.3%) patients, followed by oedema in 26 (46.4%) patients. Skin lesions, malar rash, oral ulcers, joint pains suggestive of arthritis, and pregnancy-related complications in the form of a history of recurrent pregnancy loss and Anti-Phospholipid Antibody (APLA) syndrome were also seen. A neurological disorder in the form of optic neuritis was noted in one patient. Hypertension showed statistical significance with AI (p=0.049) and no statistical significance with CI (p=0.10). Haematuria showed a strong statistical significance with AI (p=0.005) but not with CI (p=0.635).

Proteinuria (p=0.001, r=0.72), serum creatinine (p=0.037, r=0.62), and Blood Urea Nitrogen (BUN) (p=0.003, r=0.55) showed a significant statistical correlation with AI, while haemoglobin levels (p=0.719, r=-0.07) did not show any statistically significant correlation with AI [Table/Fig-4].

Laboratory/Clinical parameters	Mean±SD				p-value	R-value
	Group-1 AI (0-5)	Group-2 AI (6-10)	Group-3 AI (11-15)	Group-4 AI (>15)		
Haemoglobin (g/dL)	9.63±1.705	8.65±1.150	9.08±1.644	10±1.57	0.719	-0.07
Serum creatinine (mg/dL)	1.21±0.978	1.66±1.067	3.34±2.120	3.9±1.25	**0.037**	0.62
Blood urea nitrogen (md/dL)	38.38±28.043	64.24±42.388	77.80±42.605	88±35.6	**0.003**	0.55
24 hours urine protein (gm/24 hours)	1.15±0.795	2.51±1.597	2.78±0.934	3.85±1.587	**0.001**	0.72
Haematuria, n (%)	7 (15.56)	7 (15.56)	6 (13.33)	1 (2.22)	**0.005**	-
Hypertension, n (%)	8 (18.18)	11 (25)	3 (6.8)	1 (2.27)	**0.049**	-

[Table/Fig-4]: Laboratory values and clinical parameters in the modified NIH Lupus Nephritis (LN) activity index (AI) scoring system.

Proteinuria (p=0.028, r=0.39) and serum creatinine (p=0.010, r=0.58) also showed a significant statistical correlation with CI. BUN (p=0.143, r=0.024) and haemoglobin (p=0.372, r=-0.15) did not show any statistically significant correlation with CI in this study [Table/Fig-5].

Laboratory/ Clinical parameters	Mean±SD			p-value	R-value
	Group 1 CI (0-3)	Group 2 CI (4-8)	Group 3 CI (9-12)		
Haemoglobin (g/dL)	9.47±1.636	8.73±0.811	7.3±0.05	0.372	-0.15
Serum creatinine (mg/dL)	1.37±1.054	2.70±1.619	5.3±2.54	**0.010**	0.58
Blood urea nitrogen (md/dL)	51.92±38.576	52.08±45.569	123±72.3	0.143	0.24
24 hours urine protein (gm/24 hours)	1.72±1.314	1.88±1.825	2.97±1.62	**0.028**	0.39
Haematuria (n=45), n (%)	18 (40)	3 (6.67)	Nil	0.635	-
Hypertension (n=44), n (%)	17 (38.64)	6 (13.64)	Nil	0.10	-

[Table/Fig-5]: Renal function values in the NIH Lupus Nephritis (LN) chronicity index (CI) scoring system.

Renal function was categorised by the level of serum creatinine (mg/dL) as follows: normal to mild renal insufficiency (<1.5), moderate renal insufficiency (1.5-3.0), and advanced renal insufficiency (≥3.0). Both AI (p=0.012) and CI (p=0.008) showed statistical significance with the degree of renal insufficiency, with CI showing a stronger statistical significance than AI [Table/Fig-4,5].

The distribution of mean AI and CI according to the classes of LN is shown in [Table/Fig-6]. Of the 56 biopsies studied, active lesions were seen in 47 (83.9%) of the biopsies. The mean AI in this study was 5.48±4.138. Chronic lesions were seen in 21 (37.5%) of the biopsies studied with a mean of 1.52±2.374. The distribution of the various active and chronic lesions seen in this study is listed in [Table/Fig-7]. Regardless of the presence of tubular atrophy and interstitial fibrosis, Tubulo-interstitial Inflammation (TII) was seen in 36 (64.3%) of the biopsies. Statistical significance was seen between serum creatinine and the presence of tubular atrophy and interstitial fibrosis (p=0.025) as well as TII (p=0.002). Proteinuria also showed statistical significance with TII (p=0.003) but not with tubular atrophy (p=0.078) and interstitial fibrosis (p=0.078).

Clinical and Pathological parameters	Mean±SD					Mean values
	Class-II	Class-III	Class-IV	Class-V	Class-VI	
Mean AI	0	3.00±1.080	8.13±3.442	2.29±2.984	0	5.48±4.138
Mean CI	0.50±1.000	0.46±0.967	1.26±1.932	4.14±3.132	9±4.6	1.52±2.374

[Table/Fig-6]: The distribution of mean AI and CI according to the classes of LN.

Lesions	n (%)
Active lesions	
Endocapillary hypercellularity	47 (83.9)
Neutrophils/Karyorrhexis	39 (69.6)
Hyaline deposits	24 (42.9)
Fibrinoid necrosis	2 (3.6)
Cellular/Fibrocellular crescents	14 (25)
Interstitial inflammation	30 (53)
Chronic lesions	
Glomerular sclerosis	23 (41.1)
Fibrous crescents	6 (10.7)
Tubular atrophy	15 (26.8)
Interstitial fibrosis	15 (26.8)

[Table/Fig-7]: Distribution of active and chronic lesions.

DISCUSSION

Renal involvement is common in SLE and often determines the course of the disease. Most of these patients present with Class-IV of the revised ISN/RPS classification of LN. Up to 40% of the patients with diffuse proliferative glomerulonephritis die or lose their renal function within five years after diagnosis [14].

In the past, patients often presented with renal failure, massive proteinuria, and histological signs of chronicity. More has been learned in the recent years about the disease, its risk factors such as hypertension, nephrotic syndrome, and APLA syndrome, as well as its severity and characteristic clinical signs. With a better understanding and the prompt decision to investigate, there has been a reduction in the interval between the first detection of proteinuria and kidney biopsy. This has led to a significant decrease in proteinuria, renal failure, and histological signs of chronicity at the time of diagnosis. Over the past decade, advances in the diagnosis and management of LN have considerably improved prognosis and survival in patients with SLE [14,15].

The most common clinical complication encountered in this study was hypertension, which showed a significant statistical correlation with AI and no correlation with CI. It has been seen that in proliferative LN, haemodynamic changes in the kidney, such as an increase in renal vascular resistance which leads to a decrease in renal blood flow, are aggravated by the loss of nephrons and progressive glomerular damage. Inflammatory cytokines contribute to the insult and exacerbate the increase in renal vascular resistance and reduced Glomerular Filtration Rate (GFR). These changes can worsen existing hypertension or cause new-onset hypertension, further exacerbating haemodynamic changes in the kidney [16]. In this study, the majority of Class-IV patients had hypertension, which is consistent with previous studies [2,17]. These findings emphasise the need to effectively treat this risk factor.

Studies have shown that proteinuria is one of the dominant signs of LN and is considered a characteristic feature in patients with LN [17,18]. In this study, there was a statistically significant correlation of proteinuria with CI (p=0.028, r=0.39), which showed a stronger statistical correlation with AI (p=0.001, r=0.72). This is explained

by the deposition of immune complexes and endocapillary hypercellularity, which are part of the AI, and are implicated in causing a disruption to the filtration barrier [19].

However, in some patients with LN, proteinuria develops in the absence of immune complex depositions. It appears that extensive podocyte effacement as a result of podocyte injury causes the development of proteinuria and nephrotic syndrome in these patients [19]. These findings support the hypothesis that the severity of lesions in LN does not always correlate with the degree of proteinuria [20], which was reflected in the present study as proteinuria showed a weak statistical correlation with classes of LN.

Proteinuria showed statistical significance with TII (p=0.003), which is one of the parameters of AI scoring, but proteinuria did not show any statistical significance with tubular atrophy (p=0.078) and interstitial fibrosis (p=0.078), which are parameters of CI scoring. The strong statistical significance of proteinuria with TII is consistent with previous studies [21,22], which have suggested that TII may be largely secondary to damage caused to the tubules and the interstitium by glomerular proteinuria rather than deposition of immune complexes alone [21,22].

Haematuria showed statistical significance with AI (p=0.005) but not with CI (p=0.635) in this study. Haematuria in LN occurs due to damage to the Glomerular Basement Membrane (GBM) and is associated with high AI. In this study, haematuria was seen predominantly in patients with Class-III and Class-IV LN, which is in accordance with previous studies that have found it to be most commonly present in patients having proliferative LN [23-25].

It has been observed that elevated serum creatinine levels at the time of renal biopsy are indicative of a poor clinical outcome and are associated with the rapid development of renal failure [9,14]. Previous studies have shown that serum creatinine has a significant positive correlation with high AI and CI [20,26], which is supported by the present study.

As previously discussed, cytokine and chemokine production resulting from the inflammatory process in LN leads to the chemotaxis of leucocytes to the glomeruli. This causes further injury and loss of nephrons, atrophy, and reduction of GFR, thereby exacerbating hypertension and worsening renal outcomes [16,27,28]. This explains the strong statistical significance of the degree of renal insufficiency with AI (p=0.012) and CI (p=0.008) in this study, which is consistent with previous studies [8,13,29,30].

It has been noted that regardless of the presence of tubular atrophy or fibrosis, TII is associated with worsening renal function at biopsy and with renal survival, and therefore, the severity of interstitial nephritis is an independent prognostic indicator [31]. In the present study, serum creatinine, which reflects the degree of renal insufficiency, showed statistical significance with tubular atrophy and interstitial fibrosis (p=0.032) as well as TII p<0.0001.

Because of the above, it has been indicated that the lack of cut-off values in the ISN/RPS classification for reporting of severity of tubulo-interstitial lesions is a drawback that needs to be addressed. In the present NIH classification, interstitial inflammation is a part of AI, and interstitial fibrosis and tubular atrophy are separate entities in CI. Studies are being done to determine whether interstitial fibrosis and tubular atrophy should be combined into a single parameter instead of being considered separately. Also, it must be determined whether distinguishing between interstitial inflammations in areas with or without interstitial fibrosis has any clinical value [5].

The mean CI of Class-IV with segmental lesions (2.00±3.464) was found to be higher than that of Class-IV with global lesions (1.18±1.786) in the present study, whereas the mean AI of Class-IV with global lesions (8.50±3.372) was higher than that of Class-IV with segmental lesions (4.67±2.082). This can be explained by the presence of somewhat more sclerotic glomeruli among the cases with segmental proliferation in this study. CI showed marginal statistical significance (p=0.048), whereas AI showed no statistical significance. This is consistent with previous studies [32].

Bajema IM et al., suggest the elimination of the S and G subdivisions of Class-IV due to the lack of reproducibility and poor corroboration of clinical significance, which is consistent with the present study [5].

LN has a highly variable course and outcome which has evoked the need for further investigation of prognostic features that would help identify those at high-risk of renal failure [8]. Some studies have shown that AI and modified AI are significant predictors of outcomes, especially at the second biopsy [12,13,33], while others have not [34]. It has been observed that AI contributes significantly to the information provided by serum creatinine [30,35,36], and classes of LN [5]. A high AI is often associated with the presence of severely active lesions such as crescents and fibrinoid necrosis, with a tendency for such fulminant lesions to undergo sclerosis with permanent loss of functional renal tissue, which is irreversible. Therefore, patients with higher AI are at a significantly increased risk of ESRD [8], which is consistent with this study, demonstrating a statistically significant correlation (p=0.012) between AI and renal insufficiency. Less severe active lesions, associated with a lower AI, are potentially reversible and are weaker predictors of long-term renal outcomes [8].

In this study, CI (p=0.008) showed a stronger statistical significance with renal insufficiency than AI, which supports many studies that have found CI to be a better indicator of prognosis than AI, especially on repeat biopsies [8,29,30]. The CI is an indicator of chronic renal damage that is thought to be irreversible and therapeutically unresponsive. Hence, in distinguishing between chronic parenchymal damage and glomerular "activity", the CI has focused attention on untreatable abnormalities, which explains the reason for poorer prognosis in patients with higher CI [29].

Limitation(s)

The study was a cross-sectional study and is thus limited by the unavailability of follow-up data.

CONCLUSION(S)

A high AI and/or CI on renal biopsy, the presence of tubulo-interstitial lesions, and vascular lesions have been linked to poor outcomes. Hence, the modified NIH activity and chronicity scoring system adds valuable information to the 2018 changes in the ISN/RPS classification of LN, especially in directing treatment and prognosis. The presence of active lesions, reflected by the AI, would suggest that the disease is more likely to respond to immuno-suppressive therapy, whereas a high CI indicates that the nephritis is less likely to respond to immuno-suppression and is an indicator for renal replacement in the form of dialysis or transplant. Several large studies have been reported from all around the world, although studies involving the Indian population are sparse. Further large cohort long-term studies with a focus on therapeutic outcome and prognosis will be a step forward in providing valuable prognostic data through consistent histopathological lesions and their association with clinical and therapeutic parameters.

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