

LUPUS NEPHRITIS- A STUDY ON CLINICAL & HISTOMORPHOLOGICAL VARIABLES IN RELATION TO PROGNOSIS, IN NORTH KERALA

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ABSTRACT

BACKGROUND

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multiple organ systems either simultaneously or sequentially with relapsing and remitting course.¹ Renal disease affects 38% of patients with SLE, with a range of 12–69% and it adds significantly to the morbidity and mortality of SLE patients.² Although the availability of dialysis, transplantation and immunosuppressive therapy have improved patient survival, approximately 20% of SLE patients still die from disease or associated complications.³

In this study, we evaluated the clinical and pathological changes in lupus nephritis and tried to evolve simple criteria to predict cases that have poor outcome.

The objectives of the study were - 1. To evaluate and compare the clinical outcome of lupus nephritis patients having different clinical and histological parameters. 2. To construct a scoring system for predicting cases with bad outcome.

MATERIALS AND METHODS

Lupus nephritis patients diagnosed by renal biopsy in a 4½ year period were reassessed. They were grouped into Poor outcome group (Death due to disease or serum creatinine of ≥ 2 mg/dl) and Good outcome group (all others). Activity and chronicity indices and other glomerular, tubular and vascular variables in the renal biopsy were semi quantitatively graded. These variables and the initial clinical parameters were compared in the two groups. A predictive scoring system was constructed with the significantly different parameters. The data was analysed with the help of computer software SPSS.

RESULTS

40 cases with adequate follow up were available with minimum 2 years and maximum 12 years follow up. 12 cases belonged to the poor outcome and 28 cases to the good outcome groups. The variables that significantly differed in the two outcome groups were added up for a predictive score namely serum creatinine, tubular atrophy, tubular dilatation, interstitial fibrosis and histological class IV. Predictive scores ≥ 5 had sensitivity and specificity of 0.75 for predicting cases with adverse outcome.

CONCLUSION

Initial serum creatinine and selected graded parameters on renal biopsy can predict eventual outcome of Lupus nephritis with fairly high sensitivity and specificity.

KEYWORDS

Lupus nephritis; Biopsy; Creatinine; Retrospective study.

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BACKGROUND

Nephritis is one of the most serious manifestations of systemic lupus nephritis (SLE), the prototype of autoimmune disease and it adds significantly to the morbidity and mortality of SLE patients. Only 25-50% of patients have early abnormalities but up to 60% of adults and 80% of children develop renal abnormalities later during the course of the illness.⁴ The clinical spectrum of lupus nephritis is wide

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and renal biopsy is indicated in all SLE patients having abnormalities of the urine sediment or renal function.⁵ The pathologic findings of lupus nephritis are extremely diverse and may occur in any or all four renal compartments, glomeruli, tubules, interstitium and blood vessels.⁶

Some authors have proposed that histological indices derived from semi quantitative analysis of activity and chronicity in renal biopsies of patients with lupus nephritis have a prognostic value and can be a therapeutic guide.^{7,8} Hence this study was undertaken to predict cases of lupus nephritis that have poor outcome.

Aims and Objectives

1. To evaluate the clinical outcome of adult patients diagnosed to have Lupus nephritis by renal biopsy in the Department of Pathology, Govt. Medical College Kozhikode.



- To compare the clinical outcome of patients having different clinical and histological parameters at the time of initial renal biopsy.
- To construct a scoring system capable of predicting cases with bad outcome.

Setting and Design

This was a Retrospective cohort study involving all SLE patients who underwent renal biopsy during a period of 4½ years from Government Medical College hospital, Kozhikode.

MATERIALS AND METHODS

Initial Clinical Evaluation

The medical records were reviewed and the following information at the time of the renal biopsy was recorded such as age, sex, presence or absence of hypertension (defined as blood pressure >140/90 mm Hg or the use of antihypertensive agents), 24-hour urine protein excretion, urine microscopy and serum creatinine.

Histopathological Examination

All cases were classified according to International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification (2003) of lupus nephritis.⁹ Activity index and chronicity index were computed as shown by Austin et al.⁸ See Table 1.

Index of activity (0,1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24)	
Endocapillary hypercellularity	(0-3 +)
Leukocyte infiltration	(0-3 +)
Subendothelial hyaline deposits	(0-3 +)
Fibrinoid necrosis/karyorrhexis	(0-3 +) × 2
Cellular crescents	(0-3 +) × 2
Interstitial inflammation	(0-3 +)
Index of chronicity (0,1,2,3,4,5,6,7,8,9,10,11,12)	
Glomerular sclerosis	(0-3 +)
Fibrous crescents	(0-3 +)
Tubular atrophy	(0-3 +)
Interstitial fibrosis	(0-3 +)

Table 1. Activity and Chronicity Indices

Semi quantitative histologic scoring was performed by assigning points (0 to 3) for a number of glomerular, interstitial, and vascular features of the renal biopsy other than those included as components of the activity and chronicity indices.¹⁰ The components used for scoring: In Glomeruli - Mesangial matrix increase & Capillary narrowing or disruption; In Tubulointerstitial compartment - Presence of RBC casts or proteinaceous casts, Interstitial oedema, Tubular dilatation & Vacuolization; in Vessels- Reduction in vascular caliber because of sclerosis, Intimal thickening & Medial hypertrophy.

Histological grading was done by an observer (Principal investigator) blind to the clinical status of the patient. Immunofluorescence for IgG, IgM, IgA and C3 were done in 18 cases. The data was collected from the case sheets and the records of Department of Nephrology.

Follow up

The addresses and phone numbers of patients were obtained from the Hospital Records library and Nephrology case records. Patients were enquired about the present clinical status and evaluated further.

Final Clinical Evaluation of Patients

The patients were seen in the nephrology Out-Patient clinic. Freshly voided midstream urine sample and 4 ml of blood were collected. Urine protein estimation was done on a filtered sample by the heat and acetic acid test and graded from 0 to 4+. Urine microscopy was done by centrifuging at 1000 rpm for 10 minutes. Low and high power examination was done. Complete Blood Count was done using the Sysmex KX21 automated blood cell counter. The separated serum samples were used to estimate serum creatinine.

Data Analysis

For the analysis, patients were divided into two groups:

- Poor prognosis group: Death due to disease or those with serum creatinine of 2 mg/dl or more at a minimum of 2 years follow up.
- Good prognosis group: All other patients.

The groups were compared for-

- Initial clinical parameters.
- Activity and Chronicity indices and their individual components.
- Other graded morphological variables in the renal biopsy.
- The clinical and histological variables that were significantly different between the two outcomes groups were used to construct a predictive score (see results section).

The optimum cut-off value to predict the cases with adverse outcome was determined by ascertaining the best sensitivity, specificity and predictive values. The predictive score was calculated by adding up initial serum creatinine (rounded up to the nearest integer), grades of tubular atrophy, interstitial fibrosis and tubular dilatation along with the histological class in which Class IV was scored as +1, class V as 0 and the rest as -1.

Inclusion Criteria

Patients with Systemic Lupus Erythematosus admitted to the Nephrology Department, Medical College, Kozhikode and whose renal biopsy was diagnosed at the Department of Pathology, Govt. Medical College Kozhikode during a 4½ year period.

Exclusion Criteria

- Cases for which follow up data could not be obtained.
- Cases for which the renal biopsy was not adequate.

Ethics

This study has been approved by Institutional Ethics Committee of Government Medical College, Kozhikode.

Statistical Analysis

Data was analysed with the help of computer software SPSS. Qualitative variables were presented as frequencies and percentages. Association of prognostic factors was tested using chi-square test. A p value of ≤ 0.05 was considered as statistically significant. Association between socio

demographic, clinical and histologic parameters with poor outcome was estimated in terms of Odds Ratio and its 95% Confidence intervals. Final serum creatinine value was correlated with clinical, histological features, activity and chronicity indices

RESULTS

Patient data- There were 40 cases for which adequate follow up was available. The female: male ratio was 7:1 (35 females and 5 males) and the mean age 27 years (Figure 1). The minimum follow-up period was 2 years and the maximum 12 years. There were 6 deaths due to disease among the 40 patients followed up (15%). In addition, 6 patients (15%) had creatinine levels of 2 mg/dl or more at follow-up. Figure 2 shows the different clinical features at time of biopsy.

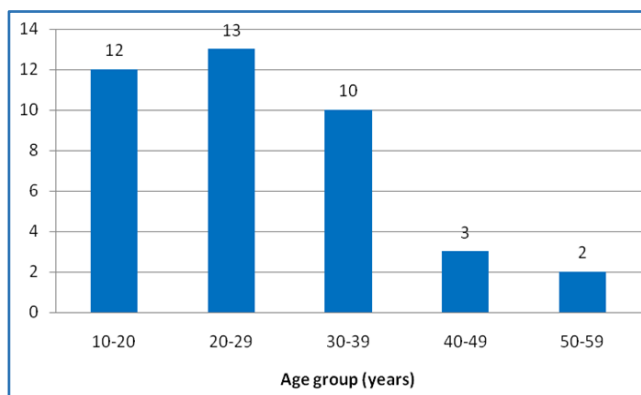


Figure 1. Age at Clinical Presentation

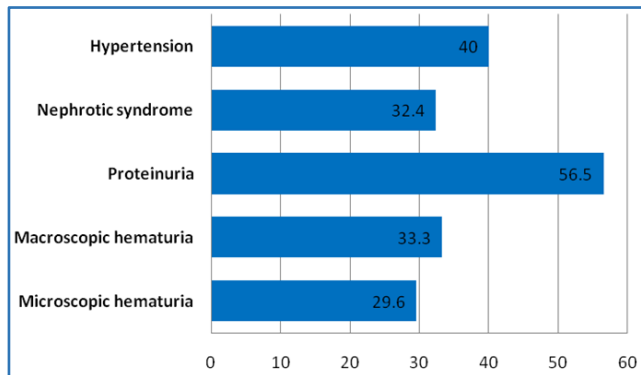


Figure 2. Clinical Features at the Time of Biopsy (%)

Among the clinical features only the level of serum creatinine was found to affect prognosis as the p value was <0.05 and statistically significant. (Table 2)

Parameter	Odds Ratio	95% CI	p
Age ≥ 30 years	0.44	0.09 – 2.0	0.24
Presence of Hypertension	1.2	0.18 – 7.8	0.61
Nephrotic syndrome	1.3	0.32 – 5.5	0.48
Heavy haematuria (≥ 30 cells/hpf)	4.0	0.58 – 27.4	0.16
S Creatinine >2 mg/dl	11.7	2.2 – 61.3	0.003

Table 2. Risk Estimates of Initial Clinical Predictors for Poor Outcome (χ2 test)

The histological class that was found to be significantly different in the two outcome groups was class IV (p=0.032). (Table 3)

Class	% Cases with Poor Outcome	Odds Ratio	95% CI	p
I	0.0	0.00	0.0-8.19	0.484
II	14.3	0.33	0.04- 3.12	0.306
III	0.0	0.00	0.0- 1.83	0.149
IV	43.5	5.80	1.10- 31.27	0.032
V	33.3	1.18	0.10- 14.42	0.668

Table 3. Risk Estimates of Histological Class for Poor Outcome (χ2 test)

The variables that were found to significantly differ in the two outcome groups were serum creatinine (p=0.002), tubular atrophy (p=0.013), tubular dilatation (p=0.032), interstitial fibrosis (p=0.004) and histological class IV (p=0.032). (Table 4, 5, 6)

Parameter	Correlation Co-efficient	p
Cellular proliferation	0.03	0.27
Leukocyte exudation	0.03	0.30
Karyorrhexis and Fibrinoid necrosis	0.00	0.88
Cellular crescents	0.04	0.21
Wireloops and hyaline thrombi	0.05	0.15
Interstitial infiltrate	0.01	0.64
Activity Index	0.07	0.10
Glomerular sclerosis	0.01	0.65
Fibrous crescents	0.01	0.61
Interstitial fibrosis	0.20	0.004
Tubular atrophy	0.15	0.013
Chronicity Index	0.13	0.024

Table 4. Relationship of Activity and Chronicity Indices and Their Components to Serum Creatinine

Parameter	Correlation Co-efficient	p
Age	0.00	0.927
Duration of illness	0.03	0.297
Duration before biopsy	0.02	0.369
Serum creatinine at time of biopsy	0.23	0.002
Mesangial matrix	0.05	0.171
Glomerular capillary narrowing	0.05	0.148
RBC / Protein casts	0.01	0.655
Interstitial oedema	0.02	0.394
Tubular dilatation	0.12	0.032
Tubular vacuolization	0.01	0.604
Vascular intimal fibrosis	0.08	0.075
Medial hypertrophy	0.08	0.082

Table 5. Relationship of Clinical and Other Histological Parameters to Serum Creatinine

Variable	Co-efficient	SE	F-test	P-Value
Histological class IV	0.136	0.136	1.0106	0.32230
Interstitial fibrosis	0.172	0.132	1.7034	0.20115
Serum creatinine	0.089	0.041	4.8313	0.03530
Tubular dilatation	0.002	0.113	0.0003	0.98542
Tubular atrophy	0.013	0.146	0.0081	0.92875
Constant	-0.078	0.146	0.2868	0.59598
Correlation Coefficient: R ² = 0.38				
Table 6. Multiple Linear Regression of the Significant Parameters				

Distribution of predictive scores in the two outcome groups are shown in figure 3. Predictive scores ≥ 5 had a sensitivity of 0.75 and a specificity of 0.75 for predicting cases with adverse outcome. (Table 7)

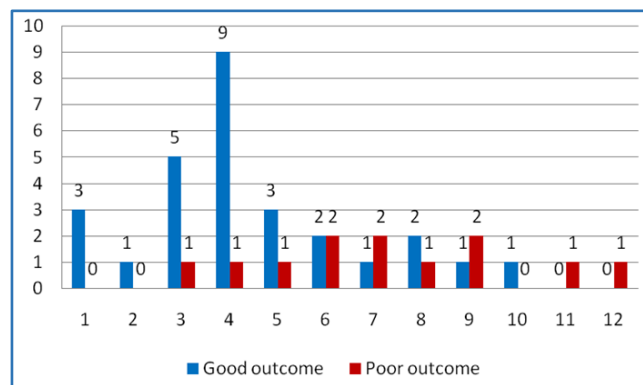


Figure 3. Distribution of Predictive Scores in the Two Outcome Groups

Parameter	Cut-off		
	≥ 4	≥ 5	≥ 6
Sensitivity	0.83	0.75	0.58
Specificity	0.64	0.75	0.82
Positive Predictive Value	0.50	0.56	0.58
Negative Predictive Value	0.90	0.88	0.82
Table 7. Diagnostic Efficacy Parameters for Prediction of Poor Prognosis with Different Cut off Predictive Scores			

Figures 4 to 12 show various histological changes in representative sections.

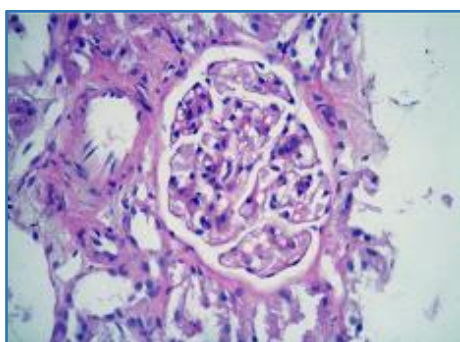


Figure 4. Lupus Nephritis Class I (Minimal Mesangial Lupus Nephritis) H&E x 100

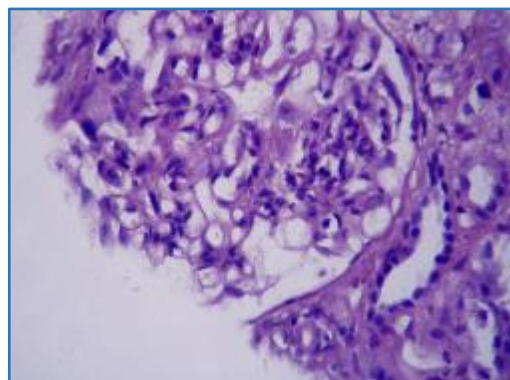


Figure 5. Lupus Nephritis Class II (Mesangial Proliferative Lupus Nephritis) H&E x 400

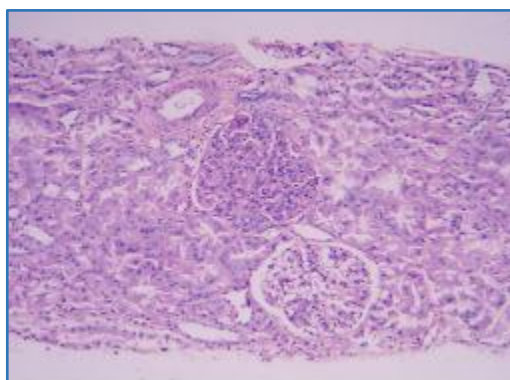


Figure 6. Lupus Nephritis Class III (Focal Lupus Nephritis). Note One Proliferated and One Normal Glomerulus. H&E x 100

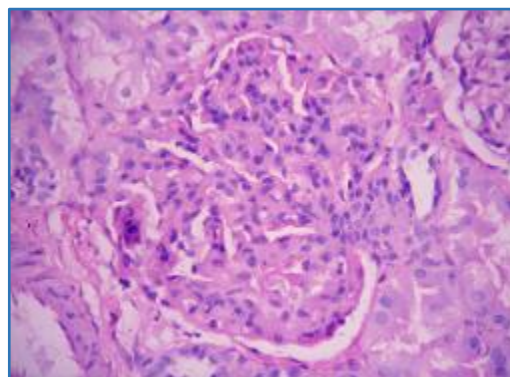


Figure 7. Lupus Nephritis Class IV (Diffuse Lupus Nephritis) H&E x 400

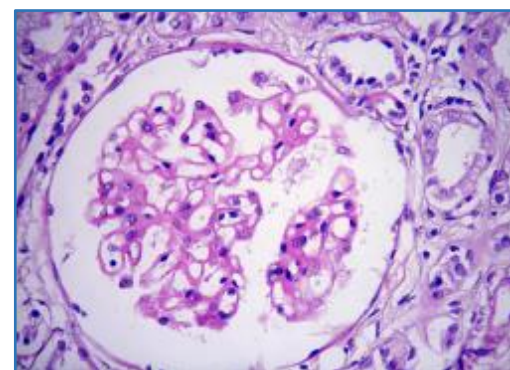


Figure 8. Lupus Nephritis Class V (Membranous Lupus Nephritis) H&E x 400

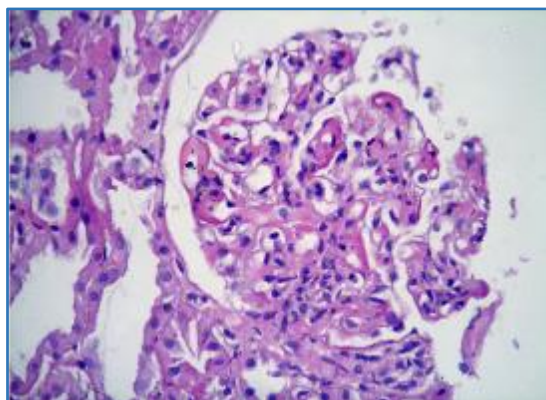


Figure 9. Proliferated Glomerulus with Wire-Loop Lesions. H&E x 400

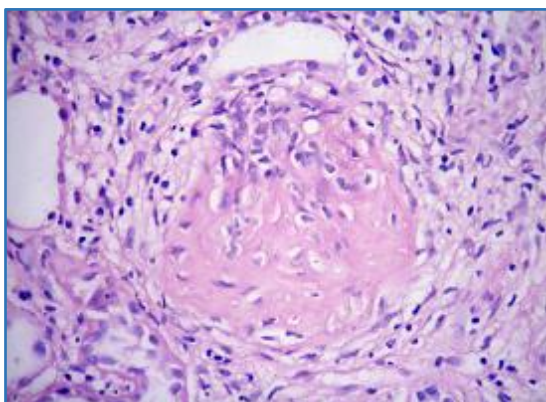


Figure 10. Sclerosed Glomerulus. H&E x 400

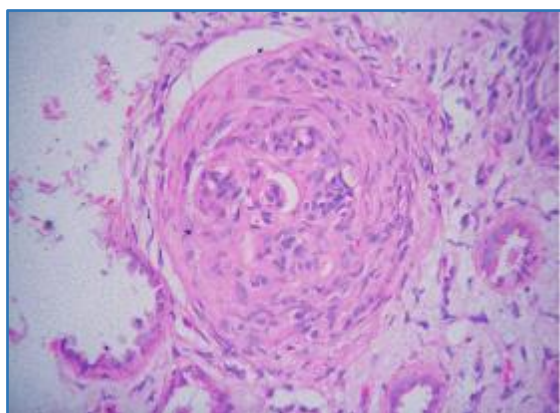


Figure 11. Fibro-Cellular Crescent. H&E x 400

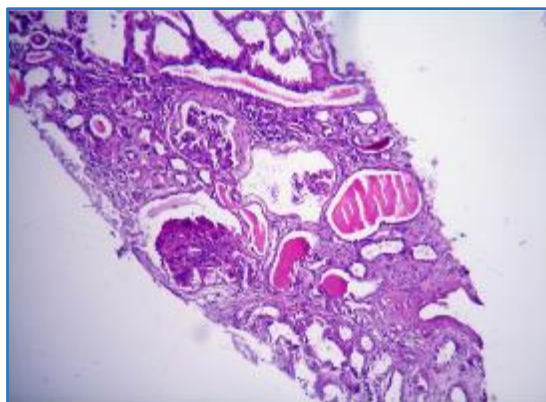


Figure 12. Tubular Dilatation and Casts in an Area of Tubular Atrophy. H&E x 100

DISCUSSION

Systemic lupus erythematosus (SLE) is known to be much more prevalent in females than in males.¹¹ The ratio was 7:1 in our study. The most constant feature, which was found in nearly all patients with clinical lupus nephritis, was proteinuria. According to Vozmediano et al an increase in proteinuria of 1 g/day increases the likelihood of worse renal function cases by 15% at the time of renal biopsy. However, in the same study initial elevation of serum creatinine concentration did not influence the prognosis.¹² Initial heavy proteinuria or even nephrotic syndrome did not have bearing on ultimate prognosis in our series. The levels of serum creatinine on the other hand were found to affect prognosis. None with an initial creatinine value ≤ 2.5 mg /dl had an adverse outcome in this study.

Male gender, age greater than 31 years, hypertension, azotaemia, anaemia, hypertension, and haematocrit have variously been implicated in worse prognosis in some studies.¹²⁻¹⁶ In the present study none of these were statistically significant.

Activity index and Chronicity index and their individual components – either some or all – have been found to be predictors of renal failure by many workers.^{12,17-19} Of these the Chronicity index and its components have been more consistently found to correlate with long term prognosis.²⁰ In our study Chronicity indices and two of its components - tubular dilatation and interstitial fibrosis were found to be significant.

Semi quantitative grading of various changes in renal biopsies in different diseases has been in use for study of many glomerular diseases.²¹⁻²³ We have used a similar grading system modified to suit diffuse endocapillary proliferative glomerulonephritis. We have further tried to predict those cases with adverse outcome by combining the clinical and histological parameters which differed significantly between the groups with good and poor outcomes.

Crescents have been found to be positively correlated with adverse outcome in some studies.^{24,25} But it was not found significant in this study. As in other studies the Lupus class associated with worse prognosis was Class IV.²⁶ The degree of glomerular tuft hyper cellularity, the amount of neutrophil infiltration of glomeruli, glomerular necrosis, adhesions and glomerular capillary thromboses have all been attributed to worse outcome in different studies.^{18,27} None of these were significant in our study. The histological variables that were found to be significantly different in the two outcome groups in our study were serum creatinine, tubular atrophy, tubular dilatation, interstitial fibrosis and histological class IV.

In a study by Christine Hsieh severe interstitial inflammatory cell infiltration in renal biopsies of patients with diffuse proliferative glomerulonephritis were associated with poor outcome.²⁸ But this was not statistically significant in this study probably because of the small number of cases. Vascular changes such as arteriolar sclerosis and arterial sclerosis have also been suggested to be a harbinger of poor

prognosis by Huang J et al.²⁹ These too have not been found to be significant in our series.

We could obtain follow-up data in only about 60% of our patients. This could be a serious flaw in studies that try to determine the absolute prognosis that is the proportion of patients eventually dying or developing renal failure. But as our study only aims at relative prognosis by group comparisons this would not be problematical.

The novelty of the current study is in the formulation of a predictive scoring system incorporating selected clinical and histological parameters with sensitivity of 0.75 and a specificity of 0.75 for predicting cases with adverse outcome.

CONCLUSION

Initial serum creatinine and selected graded parameters on renal biopsy namely tubular atrophy, tubular dilatation, interstitial fibrosis and histological class IV can predict eventual outcome of lupus nephritis with fairly high sensitivity and specificity.

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