

Prognostic Factors in Lupus Nephritis: Diagnostic and Therapeutic Delay Increases the Risk of Terminal Renal Failure

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ABSTRACT. Objective. To evaluate the prognostic significance of clinical and renal biopsy findings in an unselected cohort of patients with systemic lupus erythematosus (SLE) and nephritis.

Methods. Ninety-one patients with lupus nephritis were included in the study. Renal biopsies were classified according to the WHO criteria and examined for the presence of active and chronic histological changes. Predictors of endstage renal disease (ESRD) were identified by univariate and multivariate analyses.

Results. The median followup time was 6.1 years (0.1–30.0 yrs). In all cases, immunosuppressive treatment was initiated or intensified within one month following renal biopsy. The cumulative incidence of ESRD after 1, 5, and 10 years was 3.5%, 15%, and 17%, respectively. A variety of clinical and biopsy findings including several histological markers of chronic renal damage were identified as univariate predictors of ESRD. In multivariate regression analyses, duration of nephritis symptoms > 6 months prior to biopsy, s-creatinine > 140 $\mu\text{mol/l}$, diffuse proliferative glomerulonephritis, and tubular atrophy emerged as the strongest combination of independent risk factors (relative hazard ratios: 9.3, 5.6, 8.9, and 3.1, respectively).

Conclusion. Our results confirm the negative prognostic impact of hypercreatininemia, class IV histopathology, and tubular atrophy in lupus nephritis. Our data show that delay between onset of nephritis and renal biopsy constitutes an important risk factor of ESRD. Patients with SLE should have kidney biopsy as soon as clinical signs of nephritis are evident in order to accelerate treatment decisions and minimize risk of inflammation-induced irreversible kidney damage. (J Rheumatol 2006;33:1563–9)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS
PROGNOSIS

RENAL BIOPSY
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Nephritis is a common and serious manifestation of systemic lupus erythematosus (SLE). More than half of all patients with SLE develop nephritis during their course of illness, and in 10–25% of these the kidney disorder progresses to endstage renal disease (ESRD)^{1–3}. Several clinical and histological factors have been associated with an increased risk of renal failure in lupus nephritis. However, the prognostic value of different clinical and renal biopsy findings remains debated⁴. Hypercreatininemia is the most frequently reported clinical

predictor of progression towards ESRD^{5–14}. Other clinical factors including marked proteinuria^{6,9,15}, delay between onset of nephritis symptoms and performance of renal biopsy^{9,12,16,17}, young and old age^{5,16,18}, male gender^{8,19}, smoking²⁰, and hypertension^{2,6,7,9,10,13} have also been observed to predict adverse renal outcome, but less consistently so^{10,12–14,21,22}. The ability of histological findings to provide prognostic information in addition to clinical variables has been investigated in several studies. While some investigators found that biopsy findings add important prognostic information, others concluded that histological data do not increase the predictive strength of models based exclusively on clinical and routine laboratory variables^{6,9,12}. Frequently reported histological predictors of ESRD encompass diffuse proliferative histopathology^{8,11,21–23}, severe active glomerular and tubulointerstitial abnormalities^{5,7}, and the presence of chronic parenchymal injury^{2,5,7,13,14,18,19,23–25}.

We previously assessed the prognostic significance of clinical and histological findings in patients with lupus nephritis and s-creatinine concentrations within normal range¹¹. However, in light of the strong association between hypercreatininemia and ESRD, we decided to analyze the prognostic

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value of clinical and biopsy-derived variables in an unselected cohort of patients with SLE with glomerulonephritis. Our aim was to identify independent risk factors of chronic renal failure in lupus nephritis.

MATERIALS AND METHODS

Patients and clinical measures. Study participants were selected from a historic cohort of 513 patients with SLE²⁶. Data on patients were collected as part of a multicenter investigation describing clinical manifestations, infections, survival, and prognostic factors in Danish patients with SLE^{26,27}. In the original cohort, 59 of the patients were men and 454 patients were women. All patients met the classification criteria for SLE defined by the American College of Rheumatology (ACR)²⁸ and were seen at participating centers between 1975 and 1995. Renal biopsies were available from 128 patients. No patient had previously had a renal biopsy or been diagnosed with lupus nephritis. A complete clinical, laboratory, and biopsy data set could be retrieved for 93 Caucasian individuals with biopsy-proven lupus nephritis. Two patients presented with advanced sclerosing glomerulonephritis (World Health Organization, WHO, Class VI, see below). This morphology may represent the end stage of chronic class III, IV, or V glomerulonephritis²⁹, and it was not possible to determine from which class the sclerotic glomerular lesions of the patients had evolved. Those patients were consequently excluded from the study, leaving a total of 91 for further analyses. Fifty-five of these patients were also included in the above-mentioned study of patients with lupus nephritis and normal s-creatinine values (< 120 $\mu\text{mol/l}$ for women, < 130 $\mu\text{mol/l}$ for men)¹¹. The 37 excluded patients did not differ significantly from the included patients with regard to age at time of biopsy, female/male ratio, median s-creatinine level, or percentage progressing to ESRD (data not shown).

The following data were recorded at the time of biopsy in all cases: sex, age, date of first renal biopsy, date of onset of renal disease [defined as the date of the first observation of persistent proteinuria (> 0.5 g/day), hematuria, and/or cellular casts], serum creatinine, creatinine clearance, serum albumin, blood pressure, and level of 24-hour urinary protein excretion. Further, an analysis of the urinary sediment and a clinical disease activity score was available for all patients. Urinary sediment was considered indicative of active renal disease if analysis showed cellular or granular casts or ≥ 5 erythrocytes per high power field. Due to missing laboratory data, the disease activity score represented a modified version of the European Consensus Lupus Activity Measurement (ECLAM) using only the clinical components with unchanged scoring weights³⁰. Treatment with cyclophosphamide, azathioprine, and high-dose prednisolone was recorded. Study baseline was defined as the day on which a patient's first kidney biopsy was performed. Patients were followed until the end of 1995 or until death. No patient was lost to followup.

Histopathological analysis. All renal biopsies were examined by the same pathologist and classified according to WHO criteria for the classification of lupus nephritis³¹. Specimens were evaluated without knowledge of clinical data. Six or more glomeruli were examined in all cases. Activity and chronicity index scores were calculated using the scoring system of the US National Institutes of Health (NIH)³². According to this system, active glomerular alterations encompass cellular proliferation; fibrinoid necrosis/karyorrhexis; cellular crescents; hyaline thrombi/wire loops; and leukocyte infiltration, while mononuclear cell infiltration is regarded as an active tubulointerstitial abnormality. Chronic glomerular abnormalities include glomerular sclerosis and fibrous crescents, while chronic tubulointerstitial changes include interstitial fibrosis and tubular atrophy. Each variable is scored 0–3, weighting fibrinoid necrosis/karyorrhexis and cellular crescents by a factor 2. The tubulointerstitial index developed by Esdaile and coworkers⁹ was also calculated.

Outcome measure. The study outcome measure was ESRD, defined as the need for chronic dialysis or renal transplant. Time from kidney biopsy to development of ESRD was known in all cases.

Statistical analysis. Cumulative incidence of ESRD was calculated using life

tables and the Kaplan-Meier method. The equality of cumulative incidence curves for subgroups was tested by the log-rank test. When a trend was expected, the log-rank test for linear trend was used. Event rates were related to the total number of person-years of observation, and rate ratios of event rates were calculated in stratified analyses. Variables having a significant influence in univariate analyses were entered stepwise (p value to enter < 0.1; p value to remain < 0.05) into a multivariate regression analysis using the Cox proportional hazard model. Comparison of continuous data was performed using the Mann-Whitney rank-sum test. P values < 0.05 (2-tailed) were considered statistically significant. The correlation coefficient, r_s , between numerical variables was calculated using Spearman's rank correlation test. In correlation studies, only p values < 0.005 were considered statistically significant to reduce the risk of mass significance. All analyses were performed on a computer using the SPSS version 9.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics and renal biopsy findings. Clinical features of the 91 study participants are summarized in Table 1. As expected, most patients of the cohort were women [70/91, (77%)]. They were significantly younger than the men at the time of their SLE diagnosis (female: median age 24.1 yrs, range 10.4–61.8; male: median age 36.9 yrs, range 15.2–66.3; $p = 0.001$, Mann-Whitney test). A similar difference was detected in the non-nephritis part of the original cohort (data not shown)²⁶, confirming that SLE develops earlier in Caucasian women than in Caucasian men^{33,34}. The women were also significantly younger than the men at their first kidney biopsy (female: median age 29.2 yrs, range 10.2–63.8 yrs; male: median age 37.6 yrs, range 20.2–66.3; $p = 0.005$).

Sixteen out of 88 patients (17.5%) presented with significant hypertension, defined as a systolic blood pressure > 160 mm Hg and/or a diastolic blood pressure > 100 mm Hg. Active urinary sediment was detected in 65/91 (71%).

In all cases, immunosuppressive therapy was instituted or intensified within one month following kidney biopsy. Treatment with cyclophosphamide or azathioprine was given in 54/91 (59%) and 59/91 (65%) of the patients, respectively. Nine of the 91 patients (9%) were treated with high-dose prednisolone only. No patient received intensive immunosuppressive treatment in the period between onset of nephritis symptoms and renal biopsy.

Thirteen of 91 patients (14%) developed ESRD during 597 patient-years of followup, corresponding to an ESRD rate of 21 per 1000 patient-years. All of these patients progressed to renal dialyses. In 4 cases, renal transplant was performed. Seven ESRD patients died of complications occurring after development of chronic uremia. The cumulative incidence of ESRD after 1, 5, and 10 years was 3.5%, 15%, and 17%, respectively. Renal biopsy findings of the 91 patients are summarized in Table 2.

Correlations between variables. Several highly significant correlations were detected between clinical variables and NIH activity and chronicity index scores. These are listed in Table 3. Further, a statistically significant negative correlation was identified between s-albumin concentration and modified ECLAM score ($r_s = -0.350$, $p = 0.001$).

Table 1. Clinical data for 91 patients with lupus nephritis at the time of first renal biopsy.

	N	Median	Lower Quartile	Upper Quartile
Age, yrs	91	30	22	42
Duration of SLE, yrs	91	0.3	0	4.0
Duration of nephritis, yrs ^a	91	0.12	0.02	0.86
Duration of followup, yrs ^b	91	6.13	1.81	9.48
Serum creatinine, $\mu\text{mol/l}$	91	100	73	150
Creatinine clearance, % expected	91	81	62	100
Serum albumin, $\mu\text{mol/l}$	91	439	320	521
24-h urinary protein excretion, g	91	4.8	1.7	12.5
ECLAM score	89	4	3	4
Systolic blood pressure, mmHg	88	130	120	150
Diastolic blood pressure, mmHg	88	90	75	95

^a Duration of nephritis symptoms prior to biopsy. ^b Time from first renal biopsy to development of ESRD or end of study period. ECLAM: European Consensus Lupus Activity Measurement, modified as defined in text.

Table 2. Renal biopsy findings in 91 patients with lupus nephritis.

	WHO Class				
	I	II	III	IV	V
Number, %	0 (0)	16 (18)	10 (11)	56 (61)	9 (10)
Activity index, median (range)	—	1.5 (1–4)	4.0 (1–11)	8.0 (2–15)	1.0 (0–5)
Chronicity index, median (range)	—	1.5 (0–6)	1.5 (0–3)	2.0 (0–9)	2.0 (0–6)
Tubulointerstitial index, median (range)	—	0.5 (0–2)	1.0 (0–2)	1.0 (0–2)	1.0 (0–2)

Table 3. Clinicopathological correlations in 91 patients with lupus nephritis. To reduce risk of mass significance, only correlations with p values < 0.005 were considered statistically significant.

Variable	Patients	Activity Index		Chronicity Index	
		r_s	p	r_s	p
Duration nephritis > 1 mo ^a	51	0.052	0.71	0.278	0.04
S-creatinine	91	0.312	0.003	0.405	< 0.001
Creatinine clearance	91	-0.241	0.021	-0.303	0.003
24-h urinary protein	91	0.360	< 0.001	-0.179	0.090
S-albumin	91	-0.339	0.001	0.157	0.13
ECLAM score	89	0.083	0.44	-0.172	0.10

^a Duration of nephritis symptoms prior to biopsy > 1 mo. r_s : Spearman's rank correlation coefficient.

Predictors of ESRD: univariate analyses. The predictive value of selected histological and clinical variables is summarized in Table 4. Variables not listed include age at diagnosis; biopsy before 1990; treatment without cyclophosphamide; treatment without azathioprine; treatment with high-dose prednisolone only; hypoalbuminemia (s-albumin < 300 $\mu\text{mol/l}$); systolic blood pressure > 160 mm Hg; diastolic blood pressure > 100 mm Hg; hypertension; presence of active urinary sediment; tubulointerstitial index score; and each of the NIH activity index components. None of these variables was associated with an increased risk of ESRD in univariate analyses. In agreement with the strong predictive value of an elevated s-creatinine concentration, patients with a creatinine clearance < 60% of the expected value had a 3-times higher risk of progression to ESRD than the rest of the patients (38.5 vs 12.8 events per 1000 patient-years of observation; p = 0.02). We

did not identify associations between high activity index scores (cutoff levels tested: ≥ 5 , ≥ 7 , ≥ 10 , ≥ 11) and ESRD.

Multiple regression analysis. Risk factors identified by univariate analyses were entered into a stepwise Cox proportional hazard model. As a conservative approach, the analysis was adjusted for the effects of age at time of biopsy, gender, treatment with cyclophosphamide, and treatment with azathioprine by forced introduction of these variables in the multiple regression equation. The strongest combination of independent predictors included 2 clinical and 2 histological factors: duration of nephritis > 6 months prior to biopsy; s-creatinine > 140 $\mu\text{mol/l}$; WHO class IV histopathology; and the presence of tubular atrophy (Table 5).

DISCUSSION

Our aim was to identify predictors of ESRD in an unselected

Table 4. Predictive value of clinical and histological variables in 91 patients with lupus nephritis.

Variable	nESDR/n Total	Patient-yrs	ESRD rate/1000 Patient-yrs	Rate Ratio	p
Age at biopsy, yrs					
0-23	5/26	153	32.6	1	0.28
≥ 24	8/65	443	18.0	0.6	
Sex					
Male	1/21	117	8.5	1	0.25
Female	12/70	480	25.0	2.9	
Duration of nephritis ^a , mo					
< 6	6/61	448	13.8	1	0.01
≥ 6	7/30	148	47.1	3.4	
Disease activity ^b					
< 4	6/39	269	22.3	1.1	0.76
≥ 4	6/50	316	18.9	1	
S-creatinine, μmol/l					
< 140	6/66	450	13.3	1	0.01
≥ 140	7/25	147	47.6	3.5	
24-h urinary protein, g					
< 10.0	12/65	471	25.4	1	0.19
≥ 10.0	1/26	125	8.0	0.3	
WHO class					
IV	11/56	321	34.2	4.7	0.03
Others	2/35	275	7.2	1	
Activity index					
< 11	12/77	508	23.6	1	0.45
≥ 11	1/14	156	6.4	0.3	
Chronicity index					
≤ 3	6/70	455	13.1	1	0.01
> 3	7/21	142	49.2	3.7	
Glomerular sclerosis					
0	4/49	306	13.0	1	0.02
1	5/30	237	21.0	1.6	
2	4/12	53	75.5	5.8	
Fibrous crescents					
0	9/68	446	20.1	1	0.77
1	3/18	104	28.8	1.4	
2	1/5	46	21.7	1.1	
Interstitial fibrosis					
0	4/39	282	14.1	1	0.02
1	4/37	227	17.5	1.2	
2	4/14	86	46.5	3.3	
3	1/1	0.5	—	—	
Tubular atrophy					
0	6/56	385	15.5	1	0.008
1	3/26	166	18.0	1.1	
2	3/8	44	67.4	4.3	
3	1/1	0.5	—	—	

^a Prior to biopsy. ^b Modified ECLAM score as defined in text.

cohort of patients with SLE with nephritis. In 13 of 91 patients studied (14%), nephropathy progressed to ESRD despite immunosuppressive treatment, and the cumulative probability of maintaining renal function after 10 years was 83%. These findings are in line with renal survival data published by others^{1,2,35} and emphasize the potentially severe course of lupus nephritis. The large size of our study cohort and the long median duration of followup allowed identification of several independent risk factors of ESRD. Further, strong associations

between some studied variables were detected in clinico-pathologic correlation analyses.

Clinical risk factors for ESRD. Delay between onset of nephritis and renal biopsy emerged as a powerful independent predictor of terminal renal failure. Thus, patients having biopsy after more than 6 months of nephritis symptoms had a 9-times higher risk of developing ESRD than the other patients. This observation supports data recently published by Fiehn and coworkers, who concluded that the risk of chronic renal

Table 5. Conditional stepwise Cox regression analysis of predictors of ESRD in 91 patients with lupus nephritis. The analysis was adjusted for the effects of gender, age at time of biopsy, treatment with cyclophosphamide, and treatment with azathioprine.

Variable	Hazard Ratio	95% Confidence Interval of Hazard Ratio	p
Duration of nephritis prior to biopsy > 6 mo	9.3	1.8–47.0	0.006
S-creatinine $\geq 140 \mu\text{mol/l}$	5.6	1.3–22.7	0.016
Diffuse proliferative glomerulonephritis	8.9	1.2–62.7	0.028
Tubular atrophy*	3.1	1.3–6.9	0.007

* Relative hazard per increase of 1 point in score, range 0–3.

failure was significantly higher among patients having renal biopsy after a mean of 15 months of proteinuria than among patients biopsied after a mean duration of proteinuria of 3.9 months¹⁷. Similarly, Esdaile, *et al* found that delayed kidney biopsy increased the risk of subsequent renal failure substantially in a cohort of 87 patients with lupus nephritis, probably because early biopsy tended to accelerate treatment decisions^{9,16}. In our study, immunosuppressive treatment was intensified within one month following renal biopsy in all cases. Therefore, in agreement with previous reports, our findings show the importance of early diagnosis and prompt treatment of patients with lupus nephritis^{9,12,16,17}. A positive correlation between duration of nephritis symptoms and degree of chronic lesions was detected for patients whose renal symptoms had persisted for more than one month before a renal biopsy was performed. Although this correlation was only of borderline significance ($0.05 > p < 0.005$), it supports earlier observations¹⁶ and indicates that the extent of chronic renal alterations increases with duration of unopposed renal inflammation in lupus nephritis. Moreover, this correlation suggests a causal relationship between diagnostic delay, indicated by time to kidney biopsy, and occurrence of chronic renal lesions.

The predictive value of hypercreatininemia has been reported in a variety of studies and must be regarded as well established^{5–14}. An elevated s-creatinine at the time of renal biopsy was also identified as a strong predictor of ESRD in our analyses. We previously examined potential associations between clinicopathological variables and ESRD in patients with lupus nephritis and normal s-creatinine levels¹¹. In that study, only class IV nephritis and duration of nephritis symptoms prior to renal biopsy of more than 1 year came out as independent risk factors of ESRD in multivariate analyses. By analyzing the same variables in an unselected cohort of patients with lupus nephritis, we have identified several components of the NIH chronicity index as univariate predictors of ESRD, and the presence of tubular atrophy entered the final predictive model as a highly significant, independent risk factor. The discrepancy between these results demonstrates that hypercreatininemia in many cases reflects the presence of chronic renal lesions and, as such, indicates an increased risk of a poor renal outcome. However, in nonparametric correlation tests, we detected strong positive correlations between the

s-creatinine level and both the activity index score and the chronicity index score. These results are in line with observations by others^{18,36} and indicate that hypercreatininemia in the setting of lupus nephritis may reflect either reversible inflammatory changes within the renal parenchyma, irreversible chronic lesions, or a combination of acute and chronic alterations. Therefore, while an elevated value of s-creatinine is clearly a risk factor for ESRD, detection of hypercreatininemia *per se* does not allow the clinician to assess the extent of active and chronic renal lesions and to estimate the potential benefits of aggressive immunosuppressive and renoprotective treatment.

A positive correlation was detected between degree of proteinuria and NIH activity index score, while a negative correlation was found between serum concentration of albumin and activity score. No correlation was found between either of these variables and NIH chronicity score. As the s-albumin concentration was also inversely correlated with the ECLAM score, i.e., with general SLE activity, we conclude that 24-hour urinary protein excretion indicates the degree of renal inflammation with higher specificity than s-albumin level. These observations support the measurement of proteinuria as a clinical indicator of nephritis activity in patients with SLE.

Histological risk factors of ESRD. Two of the 4 variables entering the final Cox regression hazard model for ESRD were derived from analysis of renal biopsy specimens. Thus, histological data were shown to add important prognostic information to that provided by clinical variables. In this respect, our study extends observations by other groups^{5,7,13,18}. Among the different WHO classes of lupus nephritis, class IV nephritis is generally believed to be associated with the highest risk of progression toward terminal renal failure^{8,11,21–23}. In agreement, we identified class IV nephritis as a powerful predictor of ESRD in both univariate and multivariate regression analyses. We did not detect associations between high activity index scores and ESRD. In contrast, chronic glomerular and tubulointerstitial lesions emerged as potent risk factors of ESRD. Our data add to the growing body of evidence that chronic tubulointerstitial lesions, in particular, imply a substantial risk of a chronic renal failure^{7,19,37,38}. Thus, both tubulointerstitial components of the chronicity index, i.e., tubular atrophy and interstitial fibrosis, came out as

strong predictors of ESRD in univariate analyses. In contrast, the tubulointerstitial component of the activity index, mononuclear cell infiltration, was not a significant risk factor of ESRD. Consequently, a high score in the tubulointerstitial index developed by Esdaile, *et al*⁹ did not predict progressive kidney disease.

Our results confirm the negative prognostic impact of hypercreatinemia, class IV histopathology, and tubular atrophy in the setting of lupus nephritis. Further, our data show convincingly that delay between onset of nephritis symptoms and kidney biopsy constitutes an important, independent risk factor of terminal renal failure. From a clinical point of view, this finding underscores the need for close medical monitoring of patients with SLE and frequent urinalyses. Patients with SLE should have a renal biopsy as soon as clinical signs of nephritis are evident in order to accelerate treatment decisions and minimize risk of inflammation-induced irreversible kidney damage.

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