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

MIKKEL FAURSCHOU, HENRIK STARKLINT, POUL HALBERG, and SØREN JACOBSEN

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 µmol/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
GLOMERULONEPHRITIS

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)\(^\text{1-3}\). 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 debated\(^\text{4}\). Hypercreatininemia is the most frequently reported clinical predictor of progression towards ESRD\(^\text{5-14}\). Other clinical factors including marked proteinuria\(^\text{6,9,15}\), delay between onset of nephritis symptoms and performance of renal biopsy\(^\text{9,12,16,17}\), young and old age\(^\text{5,16,18}\), male gender\(^\text{8,19}\), smoking\(^\text{20}\), and hypertension\(^\text{2,6,7,9,10,13}\) have also been observed to predict adverse renal outcome, but less consistently so\(^\text{10,12-14,21,22}\). 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\(^\text{6,9,12}\). Frequently reported histological predictors of ESRD encompass diffuse proliferative histopathology\(^\text{8,11,21-23}\), severe active glomerular and tubulointerstitial abnormalities\(^\text{5,7}\), and the presence of chronic parenchymal injury\(^\text{2,5,7,13,14,18,19,23-25}\).

We previously assessed the prognostic significance of clinical and histological findings in patients with lupus nephritis and s-creatinine concentrations within normal range\(^\text{11}\). However, in light of the strong association between hypercreatininemia and ESRD, we decided to analyze the prognostic...
value of clinical and biopsy-derived variables in an unselec-
ted 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 his-
toric cohort of 513 patients with SLE. Data on patients were collected as
part of a multicenter investigation describing clinical manifestations, infec-
tions, survival, and prognostic factors in Danish patients with SLE. 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) and were seen at participating centers
between 1975 and 1995. Renal biopsies were available from 126 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 rep-
resent the end stage of chronic class III, IV, or V glomerulonephritis, and
it was not possible to determine from which class the sclerotic glomerular
lesions of the patients had evolved. Those patients were consequently exclud-
ed 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 µmol/l for women, <
130 µmol/l for men). 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 ery-
throcytes 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 weights (1). Treatment with cyclophosphamide, aza-
thioprine, 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 nephritis. Specimens were evaluated without knowledge of clinical
data. Six or more glomeruli were examined in all cases. Activity and chronic-
ity index scores were calculated using the scoring system of the US National
Institutes of Health (NIH). According to this system, active glomerular
alterations encompass cellular proliferation; fibroinoid 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 inter-
stitial fibrosis and tubular atrophy. Each variable is scored 0–3, weighting fib-
roinoid necrosis/karyorrhexis and cellular crescents by a factor 2. The tubu-
lointerstitial index developed by Esdaille and coworkers 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 con-
sidered statistically significant. The correlation coefficient, r, between
numerical variables was calculated using Spearman’s rank correlation test.
In correlation studies, only p values < 0.005 were considered statistically signif-
ificant 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-nephritic part of the original cohort (data not shown),
confirming that SLE develops earlier in Caucasian women than in Caucasian men.

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 pred-

nisolone only. No patient received intensive immunosuppres-
sive treatment in the period between onset of nephritis symp-
toms 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 sum-
marized 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 = -0.350, p = 0.001).
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 µmol/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 µmol/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
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 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 clinicopathologic 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 4. Predictive value of clinical and histological variables in 91 patients with lupus nephritis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>nESDR/n Total</th>
<th>Patient-yrs</th>
<th>ESRD rate/1000 Patient-yrs</th>
<th>Rate Ratio</th>
<th>p</th>
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<td>Age at biopsy, yrs</td>
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<td></td>
<td></td>
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<td>0–23</td>
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<td>153</td>
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<td>≥ 24</td>
<td>8/65</td>
<td>443</td>
<td>18.0</td>
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<tr>
<td>Sex</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
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<td>117</td>
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<td>0.25</td>
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<tr>
<td>Female</td>
<td>12/70</td>
<td>480</td>
<td>25.0</td>
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<td>Duration of nephritis&lt;sub&gt;a&lt;/sub&gt;, mo</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>6/61</td>
<td>448</td>
<td>13.8</td>
<td>1</td>
<td>0.01</td>
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<tr>
<td>≥ 6</td>
<td>7/30</td>
<td>148</td>
<td>47.1</td>
<td>3.4</td>
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<td>Disease activity&lt;sub&gt;b&lt;/sub&gt;</td>
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<td>&lt; 4</td>
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<td>1.1</td>
<td>0.76</td>
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<td>316</td>
<td>18.9</td>
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<td>450</td>
<td>13.3</td>
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<td>≥ 140</td>
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<td>147</td>
<td>47.6</td>
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<td>24-h urinary protein, g</td>
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<td>&lt; 10.0</td>
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<td>471</td>
<td>25.4</td>
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<td>0.19</td>
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<td>≥ 10.0</td>
<td>1/26</td>
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<td>321</td>
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<td>Others</td>
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<td>7.2</td>
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<td>Activity index</td>
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<td>&lt; 11</td>
<td>12/77</td>
<td>508</td>
<td>23.6</td>
<td>1</td>
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<tr>
<td>≥ 11</td>
<td>1/14</td>
<td>156</td>
<td>6.4</td>
<td>0.3</td>
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<td>Chronicity index</td>
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<tr>
<td>≤ 3</td>
<td>6/70</td>
<td>455</td>
<td>13.1</td>
<td>1</td>
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<tr>
<td>&gt; 3</td>
<td>7/21</td>
<td>142</td>
<td>49.2</td>
<td>3.7</td>
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<td>Glomerular sclerosis</td>
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<td>21.0</td>
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<td>2</td>
<td>4/12</td>
<td>53</td>
<td>75.5</td>
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<td>Fibrous crescents</td>
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<tr>
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<td>104</td>
<td>28.8</td>
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<tr>
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<td>1/5</td>
<td>46</td>
<td>21.7</td>
<td>1.1</td>
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<td>Interstitial fibrosis</td>
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<td>227</td>
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<tr>
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<td>4/14</td>
<td>86</td>
<td>46.5</td>
<td>3.3</td>
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<tr>
<td>3</td>
<td>1/1</td>
<td>0.5</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6/56</td>
<td>385</td>
<td>15.5</td>
<td>1</td>
<td>0.008</td>
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<tr>
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<td>3/26</td>
<td>166</td>
<td>18.0</td>
<td>1.1</td>
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<tr>
<td>2</td>
<td>3/8</td>
<td>44</td>
<td>67.4</td>
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<td></td>
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<tr>
<td>3</td>
<td>1/1</td>
<td>0.5</td>
<td>—</td>
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<sup>a</sup> Prior to biopsy. <sup>b</sup> Modified ECLAM score as defined in text.
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 months. 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. 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. 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 observations 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. 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 levels. 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 univariable 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 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. 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. 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. Thus, both tubulointerstitial components of the chronicity index, i.e., tubular atrophy and interstitial fibrosis, came out as

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval of Hazard Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of nephritis prior to biopsy &gt; 6 mo</td>
<td>9.3</td>
<td>1.8–47.0</td>
<td>0.006</td>
</tr>
<tr>
<td>S-creatinine ≥ 140 μmol/l</td>
<td>5.6</td>
<td>1.3–22.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Diffuse proliferative glomerulonephritis</td>
<td>8.9</td>
<td>1.2–62.7</td>
<td>0.028</td>
</tr>
<tr>
<td>Tubular atrophy*</td>
<td>3.1</td>
<td>1.3–6.9</td>
<td>0.007</td>
</tr>
</tbody>
</table>

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

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**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.
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 did not predict progressive kidney disease.

Our results confirm the negative prognostic impact of hypercreatininemia, 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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