Clinical Usefulness of a Prognostic Score in Histological Analysis of Renal Biopsy in Patients with Lupus Nephritis

SHOICHIRO KOJO, KEN-EI SADA, MIZUHO KOBAYASHI, MIE MARUYAMA, YOHEI MAESHIMA, HITOSHI SUGIYAMA, and HIROFUMI MAKINO

ABSTRACT. *Objective.* To evaluate active and chronic lesions in association with renal outcome according to the International Society of Nephrology/Renal Pathology Society classification in patients with lupus nephritis.

Methods. A retrospective analysis of 99 biopsy-proven subjects with lupus nephritis from 1990 to 2006 was performed in our center using the new classification. Each histological lesion was evaluated by multivariate survival analysis as predictive factor for renal insufficiency in patients with lupus nephritis, and independent predictors were graded to develop the prognostic score based on the regression coefficient. A receiver operating-characteristic curve based on the prognostic score was plotted to determine the most appropriate cutoff point.

Results. In class IV, the IV-G group tended to exhibit a worse renal outcome compared with the IV-S group, but the difference was not significant (log-rank test, p = 0.4330). Independent histological predictors of poor renal outcome were extracapillary proliferation, glomerular sclerosis, and fibrous crescents analyzed by Cox proportional hazards model, while predictors of favorable renal outcome were hyaline thrombi and fibrous adhesions. By the prognostic score, renal outcome was significantly worse in the group with the higher score (≥ 0.25) than in the group with the lower score (< 0.25) in class IV patients (log-rank test, p < 0.001).

Conclusion. These results demonstrate the advantage of our prognostic score compared to subclasses in predicting the renal outcome of class IV patients [University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN 000001943]. (First Release Aug 1 2009; J Rheumatol 2009;36:2218–23; doi:10.3899/jrheum.080793)

Key Indexing Terms:
LUPUS NEPHRITIS   PROGNOSIS SCORING SYSTEM   RENAL OUTCOME
INTERNATIONAL SOCIETY OF NEPHROLOGY/RENAL PATHOLOGY SOCIETY CLASSIFICATION

In 2002, an international group of pathologists, nephrologists, and rheumatologists convened to formulate a new classification of lupus nephritis (LN). In order to accommodate the clinicopathologic and pathogenetic insights that have accumulated since the 1982 and 1995 modifications of the original 1974 World Health Organization classification and to eliminate inconsistencies and ambiguities in regard to the previous classification, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification was proposed[1].

From the Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

S. Kojo, MD; K. Sada, MD, PhD; M. Kobayashi, MD, PhD; M. Maruyama, MD; Y. Maeshima, MD, PhD, Senior Assistant Professor; H. Sugiyama, MD, PhD, Professor; H. Makino, MD, PhD, Professor.

Address correspondence to Dr. S. Kojo, Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama City, Okayama, 700-8558, Japan.

According to the new classification, active lesions are defined as endocapillary proliferation, karyorrhexis, fibrinoid necrosis, rupture of glomerular basement membrane, cellular or fibrocellular crescents, wire-loop lesions, and hyaline thrombi, while chronic lesions are defined as glomerular sclerosis, fibrous adhesions and fibrous crescents[1]. In assessing the extent of the lesions, glomeruli with both active and sclerotic lesions are evaluated. In the new classification, the most important changes have come in class IV, defined as diffuse LN involving 50% or more of all glomeruli. This class is subdivided into diffuse segmental LN (class IV-S) when > 50% of the involved glomeruli exhibit segmental lesions, and diffuse global LN (class IV-G) when > 50% of the involved glomeruli exhibit global lesions.

This new classification has achieved one of its aims in improving interobserver reproducibility by clarification of definition[2]. In regard to renal outcome, Yokoyama, *et al* report that class IV in the new classification serves as a significant risk factor for renal outcome, but not category IV in the older classification[3]. Although several studies have

shown clinical and morphological differences between IV-S and IV-G, they have failed to show differences in renal outcome[3-5]. And Schwartz, *et al* report that important pathogenetic and prognostic implications of the segmental glomerular lesion are not reflected in the new classification[6].

We performed a semiquantitative analysis of active and chronic lesions defined by the new classification in patients with LN and evaluated the association between the new classification and renal outcome. We also attempted to define a novel prognostic score based on the regression coefficient in class IV patients.

MATERIALS AND METHODS

Patients. Of 102 patients with biopsy-proven LN in our hospital (a referral center) from 1990 to 2006, 99 patients except for the cases of death were reclassified according to the new classification with no information on the renal outcome. Three deaths were excluded to clarify the relationship between histological findings and renal prognosis, since they died of chronic myeloid leukemia, interstitial pneumonitis, and sudden death of unknown origin, but not due to LN, and their renal function had been affected by various clinical conditions (e.g., concomitant use of antibiotics or circulatory failure).

Stored slides of eligible patients were reviewed by several nephrologists in our department for reevaluation based on the new classification. After reevaluation, we reviewed the correlation between histological features and renal outcome retrospectively. Clinical data at the time of renal biopsy were collected from medical records and electronic databases. The primary endpoint was defined as 1.5 times the elevation of the serum creatinine level from baseline (excluding cases of reversible azotemia) or the initiation of dialysis therapy. The following clinical features at the time of renal biopsy were recorded: age, sex, blood pressure (BP), serum creatinine, creatinine clearance, glomerular filtration rate (GFR), 24-hour urinary protein excretion, hemoglobin, platelets, and anti-dsDNA antibodies. Serum creatinine was measured by the enzymatic method, not by the Jaffe method. Creatinine clearance was calculated by the following formula: creatinine clearance = (urinary creatinine/serum creatinine) × urinary volume/body surface area/ 1.73. Estimated GFR was determined using the MDRD Study equation modified for Japanese: $eGFR = 175 \times Cr^{-1.154} \times age^{-0.203} \times 0.741$ (if women, $\times 0.742$)[7].

This trial is registered with the University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN 000001943.

Renal biopsy. Following the ISN/RPS definition, each histological lesion was analyzed for predictive value. For quantitative analysis, each histological lesion was recorded as follows: (1) histological findings involving less than half of the glomerular tuft, graded 0.5 point; (2) histological findings involving no less than half of the glomerular tuft, graded 1.0 point. Histological scores were calculated for each lesion separately, and we defined the sum of points divided by the total number of glomeruli as the histological score of each lesion (see below).

Histological score = (0.5 × number of glomeruli with segmental lesion + 1 × number of glomeruli with global lesion)/total number of glomeruli

To develop a prognostic score based on independent predictors of renal prognosis in the multivariate model, an integer score derived from the beta-coefficient in each independent predictor was graded. The integer scores were assigned by dividing each beta-coefficient by the absolute value of the smallest beta-coefficient in the multivariate model. The score for each lesion was summed to attain the prognostic score for each patient. A receiver-operating characteristic (ROC) curve was plotted from datasets of prognostic score and renal outcome, and a cutoff point was defined so that the sum of the sensitivity and the specificity was the highest.

Statistical analysis. All statistical analyses in this study were performed using the Statistical Package of JMP for Windows software, version 6.0.3 (SAS Institute, Cary, NC, USA). All results were expressed as mean ± standard deviation (SD). Multiple comparisons of the histological scores between groups were performed by Tukey-Kramer test. Multivariate survival analyses were used to identify variables that predict renal outcome. The cumulative renal survival curves were derived and plotted by the Kaplan-Meier method. Analysis of the survival curves obtained for different subgroups of patients was assessed by log-rank test. Cox proportional hazards model for estimating the hazard ratio and 95% confidence interval were used to identify the predictive factors for renal insufficiency. Proportionality in the proportional hazards model was assessed by Weibull distribution. ROC analysis was used to define cutoff points for predicting poor renal prognosis. The most appropriate cutoff point was determined by finding the highest point on the vertical axis and the furthest to the left on the horizontal axis (upper left corner). The accuracy of prognostic score was measured by the area under the ROC curve. P values < 0.05 were considered significant for all statistical analyses.

University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN 000001943.

RESULTS

Patient characteristics at study entry. The baseline clinical characteristics of patients are presented in Table 1. Patients recruited for study had a mean age of 37.0 ± 13.3 years (range 14–72), 85 women and 14 men, and the mean observation period was 65.2 months. All patients received prednisone as initial treatment, mean dosage 37.2 ± 16.3 mg/day. Immunosuppressive reagents were used in 45 (48.2%) patients.

Evaluation according to ISN/RPS classification. The prevalence of classes according to the new ISN/RPS classification was as follows: class I, 3 (3%), class II, 13 (13%), class III, 9 (9%), class IV-S, 20 (20%), class IV-G, 45 (46%), class V, 8 (8%), and class VI, 1 (1%). One-ninth (11.1%) of class III,

Table 1. Baseline clinical characteristics of 99 patients with biopsy-proven lupus nephritis.

Characteristic	
Age at renal biopsy, yrs	37.0 ± 13.3
Female (%)	85 (85.9)
Blood pressure, mmHg	
Systolic	127.5 ± 22.0
Diastolic	75.9 ± 13.6
Serum creatinine, mg/dl	0.89 ± 0.61
Creatinine clearance, ml/min	75.2 ± 37.8
Estimated GFR, ml/min/1.73 m²	72.2 ± 29.3
Proteinuria, g/day	2.71 ± 3.10
Anti-dsDNA, IU/ml	141.8 ± 268.5
Dose of prednisone pulse (%)	37.2 ± 16.3
Methylprednisolone pulse (%)	40 (48.2)
Immunosuppressive drug (%)	45 (51.1)
Cyclophosphamide (%)	25 (30.1)
Cyclosporine (%)	12 (14.5)
Tacrolimus (%)	5 (6.2)
Azathioprine (%)	1 (1.2)
Mizoribine (%)	9 (10.8)

GFR: glomerular filtration rate. Values are expressed as mean ± SD, or no. (%).

1/20 (5.0%) of class IV-S, 9/45 (20.0%) of class IV-G, 2/8 (25.0%) of class V, and 1/1 (100%) of class VI patients reached the renal endpoint. The mean followup period was 66 months (range 8–161). One of 45 (2.2%) of class IV-G, 1/8 (12.5%) of class V, and 1/1 (100%) of class VI required chronic dialysis therapies and their followup periods were 25, 44, and 125 months, respectively. Since class IV patients exhibit severe lupus nephritis and undergo poor renal outcome[3], we compared renal outcome between class IV-S and class IV-G. Class IV-G group tended to exhibit a worse renal outcome than class IV-S group, but the difference was not significant (log-rank test, p = 0.4330; Figure 1).

Evaluation according to histological score. The mean histological scores among classes III, IV-S, and IV-G are shown in Table 2. Endocapillary proliferation score (class III, 0.09 ± 0.10; class IV-S, 0.28 ± 0.15; class IV-G, 0.46 ± 0.36) was significantly higher in class IV-G than in class III (p = 0.0021), and wire-loop lesions were more notable in class IV-G than classes III and IV-S (p = 0.0054 compared to class III or IV-S). The histological scores for karyorrhexis, necrosis, rupture of glomerular basement membranes, extracapillary proliferation, hyaline thrombi, glomerular sclerosis, fibrous adhesions, and fibrous crescents were similar among class III, IV-S, and IV-G.

Using a Cox proportional hazards model for estimating the hazard ratio (HR) and 95% confidence interval of renal insufficiency adjusted for age and sex with all histological scores, in all patients, extracapillary proliferation (HR 2.70, 95% CI 1.02–6.67, p = 0.0469), glomerular sclerosis (HR 1.69, 95% CI 1.34–2.21, p < 0.0001), and fibrous crescents (HR 9.98, 95% CI 1.12–79.4, p = 0.0400) were identified as predictors of a poor prognosis. Hyaline thrombi (HR 0.26, 95% CI 0.02–0.81, p = 0.0169) and fibrous adhesions (HR 0.12, 95% CI 0.01–0.70, p = 0.0139) emerged as predictors of a favorable prognosis (Table 3). As a strong correlation (r = 0.823) was observed between necrosis and extracapillary proliferation, only extracapillary proliferation was included in this analysis.

Evaluation based on prognostic score. The following variables were included as independent predictors of renal prognosis in the multivariate model with a p value < 0.05: extracapillary proliferation, hyaline thrombi, glomerular sclerosis, fibrous adhesions, and fibrous crescents. A formula for prognostic score based on these predictors was defined as:

Prognostic score = (2 × extracapillary proliferation score + glomerular sclerosis score + 4 × fibrous crescents score) – (2 × hyaline thrombi score + 4 × fibrous adhesions score)

Prognostic score for each patient ranged from –1.35 to 1.15. In the model performance indices, the area under the ROC curve was 0.794 and the positivity cutoff point was defined as 0.25 (Table 4). It was generally considered that the area of 0.794 represents a fair test. Given that the positivity criterion for prognostic score was > 0.25, the prognostic score had a sensitivity of 71.4% and a specificity of 85.9%. In class IV patients, renal outcome in the group with higher prognostic score (≥ 0.25) was significantly worse than in the group with the lower prognostic score (< 0.25) (log-rank test, p < 0.0001; Figure 2). In regard to the proportionality, 2 curves given by the "score ≥ 0.25" group and the "score < 0.25" group were parallel by Weibull distribution.

DISCUSSION

We assessed the semiquantitative distributions of active and chronic lesions based on a new classification in patients with lupus nephritis, and evaluated the association between the new classification and renal outcome. The main findings were: (1) each active or chronic lesion showed a different distribution using the new classification; (2) extracapillary proliferation, glomerular sclerosis, and fibrous crescents were considered significant risk factors for poor renal outcome, while hyaline thrombi and fibrous adhesions were considered significant risk factors for favorable renal outcome; and (3) the prognostic score on the regression coefficient-based scoring system revealed distinct differences in renal outcome among patients within class IV.

We found that endocapillary proliferation and wire-loop lesions were more frequent in the IV-G group than in the other groups, while necrosis and extracapillary proliferation were observed to be similar in both the IV-G and IV-S groups. One study reports that endocapillary proliferation and wire-loops were more frequent in the IV-G group than in the IV-S group, but necrosis was less frequent in the IV-G group than in the IV-S group[5]. As for necrosis and extracapillary proliferation, the differences between that report and our observations may be attributable to the different methods utilized in evaluating each lesion. The Hill report[5] grad-
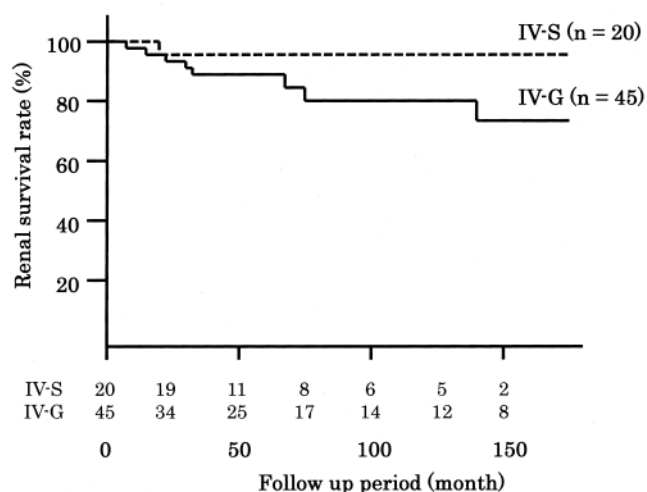

Figure 1. Cumulative renal survival curves for IV-S and IV-G groups were derived by Kaplan-Meier method. Class IV-G group tended to exhibit a worse renal outcome than class IV-S, but the difference was not significant (log-rank test, p = 0.4330).

Table 2. Glomerular scores for classes III, IV-S, and IV-G. Histological findings that involved less than half the glomerular tuft graded 0.5 points; histological findings that involved not less than half the glomerular tuft graded 1.0 points. We defined the sum of points divided by the total number of glomeruli as histological score of each lesion (see equation in the text).

	All	III	IV-S	IV-G	p
Endocapillary proliferation	0.27 ± 0.32	0.09 ± 0.10	0.28 ± 0.15	0.46 ± 0.36	0.0021*
Karyorrhexis	0.07 ± 0.12	0.02 ± 0.05	0.06 ± 0.09	0.11 ± 0.16	0.12
Necrosis	0.08 ± 0.13	0.05 ± 0.06	0.09 ± 0.10	0.11 ± 0.17	0.48
Extracapillary proliferation	0.03 ± 0.08	0.01 ± 0.02	0.04 ± 0.05	0.05 ± 0.11	0.39
Wire-loops	0.14 ± 0.29	0.00 ± 0.00	0.06 ± 0.14	0.29 ± 0.38	0.0054**
Hyaline thrombi	0.02 ± 0.05	0.00 ± 0.00	0.01 ± 0.04	0.03 ± 0.07	0.35
Glomerular sclerosis	0.12 ± 0.19	0.13 ± 0.16	0.06 ± 0.12	0.17 ± 0.21	0.12
Fibrous adhesions	0.03 ± 0.07	0.01 ± 0.02	0.05 ± 0.11	0.03 ± 0.06	0.30
Fibrous crescents	0.01 ± 0.03	0.00 ± 0.00	0.01 ± 0.03	0.10 ± 0.03	0.65

Values are expressed as mean ± SD. * p < 0.05, III versus IV-G; ** p < 0.05, III versus IV-S; p < 0.05, III versus IV-G.

Table 3. Cox proportional hazards models to estimate hazard ratios (95% confidence interval) were used to identify predictive factor of renal insufficiency. An integer score derived from the beta-coefficient in each independent factor was assigned.

	ß-coefficient	Hazard Ratio (95% CI)	p	Integer Score
Age	–0.02	0.98 (0.94–1.03)	0.44	—
Sex	–0.22	0.80 (0.36–2.30)	0.64	—
Endocapillary proliferation	–0.30	0.74 (0.46–1.04)	0.09	0
Karyorrhexis	0.70	2.01 (0.86–4.39)	0.10	0
Extracapillary proliferation	0.99	2.70 (1.02–6.67)	0.0469	2.0
Wire-loops	0.10	1.10 (0.86–1.35)	0.40	0
Hyaline thrombi	–1.35	0.26 (0.02–0.81)	0.0169	–2.0
Glomerular sclerosis	0.52	1.69 (1.34–2.21)	< 0.0001	1.0
Fibrous adhesions	–2.11	0.12 (0.01–0.70)	0.0139	–4.0
Fibrous crescents	2.30	9.98 (1.12–79.4)	0.0400	4.0

Table 4. ROC curve for prognosis score. ROC analysis was used to define cutoff points for predicting poor renal prognosis. The ROC curve was plotted for finding the highest point on the vertical axis and the furthest to the left on the horizontal axis (upper left corner) to determine the most appropriate cutoff value (not shown). Accuracy was measured by the area under the ROC curve; area of 0.794 generally considered to represent a fair test.

Index	Estimates
Sensitivity*	0.714
Specificity*	0.859
Likelihood ratio*	
Positive test result*	5.05
Negative test result*	3.01
Area under the ROC curve	0.794

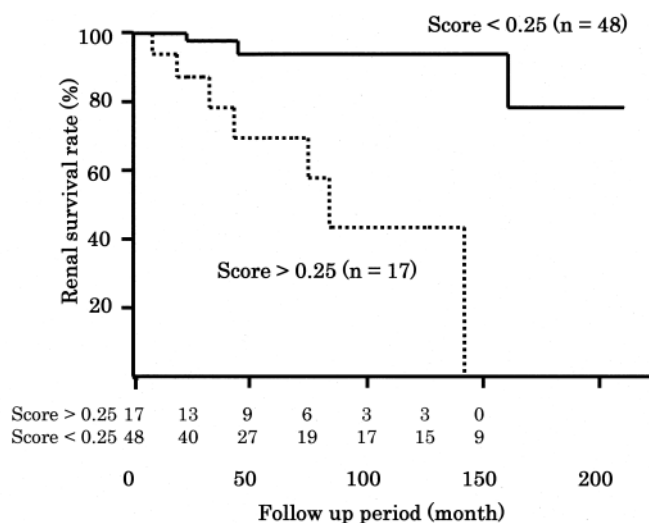* Given the positivity criteria for the total prognostic score 0.25.

Figure 2. Cumulative renal survival curves for prognostic scores were derived by Kaplan-Meier method. Different outcomes of patients with class IV lupus nephritis by prognostic score. In class IV patients, renal outcome in the group with the higher prognostic score (> 0.25) was significantly worse than that in the group with the lower prognostic score (< 0.25) (log-rank test, p < 0.0001).

ed each lesion according to the proportion of affected glomeruli within "viable" glomeruli. In our study, we observed and scored all affected glomeruli including sclerotic glomeruli. Considering the complex pathogenic mechanisms involved in class IV, it may be difficult to distinguish IV-S and IV-G only by responsiveness to treatment.

The proportions of extracapillary proliferation, hyaline thrombi, glomerular sclerosis, fibrous adhesions, and fibrous crescents were selected as independent factors for renal outcome in our study. In regard to reports for predic-

tors of a poor prognosis, Austin, *et al* also report that the combination of cellular crescents and interstitial fibrosis is a
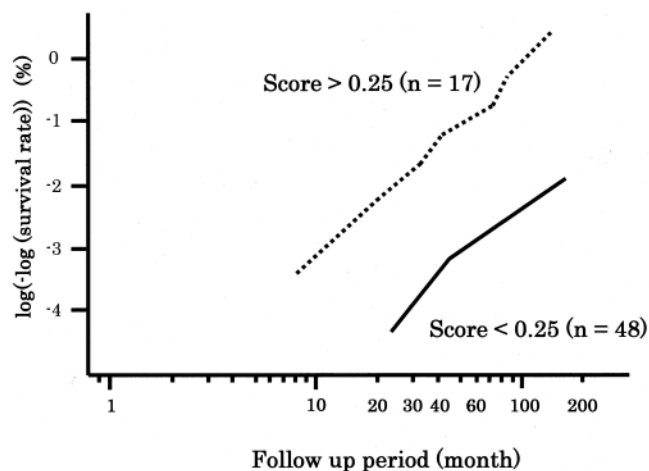
Figure 3. Cumulative curves were plotted by Weibull distributions to assess proportionality in the proportional hazards model for histological features.

risk factor for developing renal insufficiency[8]; and moreover, the presence of glomerular sclerosis is a poor prognostic factor by univariate analysis. We did not include the interstitial alterations to our multivariate analysis due to lack of any definition in the ISN/RPS classification. However, we found that the glomerular sclerosis score correlated with interstitial alterations based on Austin's previous definition (data not shown). Therefore, we weighted glomerular sclerosis highly in our score, since it may reflect the interstitial change. Najafi, *et al* report that segmental necrotic lesions observed in more than 50% of glomeruli were associated with poor renal outcome[9]. Similarly, the quantity of extracapillary proliferations was selected as an independent risk factor for renal outcome in our study. Surprisingly, hyaline thrombi and fibrous adhesions were beneficial factors for renal outcome in our study. Hyaline thrombi are often observed with massive wire-loop lesions in class IV, which are generally responsive to the standard treatments. This might explain why hyaline thrombi were a beneficial factor in our results. Fibrous adhesions are often accompanied by segmental sclerosis. We simply evaluated quantities of glomerular sclerosis and did not classify sclerotic lesions into global or segmental involvement. Our findings may indicate that segmental sclerosis is associated with a better renal outcome than global sclerosis.

Since the 1970s, renal pathologists and nephrologists have been attempting to predict renal outcome based on renal biopsy findings in patients with lupus nephritis. Austin, *et al* presented the concept of the activity index (AI) and the chronicity index (CI), and they have been widely accepted[10]. They report that while the AI tends to decrease after treatments, the CI tends to increase. Other studies report the AI showed little predictive power for renal outcome[11,12]. Therefore, Austin, *et al* state that the CI is a predictive factor for renal outcome[13]. Although some reports

support such correlation between CI and renal outcome[14,15], others failed to find a correlation and point out that there is no clear cutoff point separating renal outcomes[13,16]. Moreover, Schwartz, *et al* point out that these indices are too subjective to be used in selecting therapies or predicting the renal outcome[17]. Although the AI was defined as the sum of the individual scores of the following measures representative for active lupus nephritis [glomerular proliferation, leukocyte exudation, karyorrhexis/fibrinoid necrosis (× 2), cellular crescents (× 2), hyaline deposits, and interstitial inflammation], these weightings were not based on statistical analysis. Although the CI consisted of the sum of the individual scores of the following measures representative for chronic irreversible lupus nephritis (glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis), it was not revealed whether the simple sum of each score was relevant to renal outcome. Although Yokoyama, *et al* reported that class IV is a significant risk factor for renal outcome[3], other studies fail to show a different outcome in class IV subclasses[5,6]. We assigned more or less importance to lesions, and selected as prognostic factors based on multivariate analysis and established our renal prognostic score. Although there were no statistically significant differences in renal outcomes among class IV subclasses, our prognostic score revealed significant differences regarding renal outcome in class IV patients. It may be important to emphasize lesions related with renal outcomes quantitatively rather than absolutely dividing them into "segmental" or "global" lesions.

Several limitations of this study should be noted. Only 14 patients reached the primary endpoint, so we evaluated the validity of our prognostic score insufficiently. We should evaluate the validity of our prognostic score in the other subset of patients in the future to fully validate our prognostic formula. Since this was a retrospective single-center study, we did not evaluate the therapeutic response to each lesion sufficiently. A larger multicenter prospective study would reveal the therapeutic response to each lesion and might lead to calculation of a more precise prognostic score.

Although some active lesions showed different distributions, among class III, IV-S, and IV-G, the others were similar. Our prognostic score on the regression coefficient-based scoring system might be useful in predicting renal outcome in patients with class IV lupus nephritis. It may be helpful to compare the baseline assessment of patients with lupus nephritis among several clinical studies.

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