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Long-Term Outcome of 102 Cases of Lupus Nephritis: A Single-Center Cohort Study in Japan

Mio Kodama, Keiko Uchida*, Kazunori Karasawa, Takahito Moriyama, Kosaku Nitta

Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan
Email: *keiko.uchida@twmu.ac.jp

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Abstract

Background: The mortality rate is higher in SLE patients with lupus nephritis (LN) than in those without nephropathy. **Objectives:** The aim of this study was to identify the factors affecting the long-term renal outcome in 102 patients with LN. **Methods:** This was a retrospective cohort study. Logistic regression analysis was used in a model to determine how independent variables predicted the outcome. The survival analysis was based on the Kaplan-Meier curve with subjects censored for death. **Results:** The 15-year survival rate was 93.5%, and the renal function non-deterioration rate was 78.3%. No influence of individual types of immunosuppressant drugs used was found on the renal function deterioration rate. In this study, the results of analysis identified only daily urinary protein excretion level as having any significant effect on the risk of progression of LN to renal failure. **Conclusions:** These results suggest that remission induction therapy and maintenance therapy focused on long-term preservation of renal function need to be selected for LN patients with a high daily urinary protein value at the start of treatment and for LN patients who fail to show any reduction of the daily urinary protein excretion level to 0.5 g or less at one year after the biopsy.

Keywords

Lupus Nephritis, Outcome, Renal Function, Proteinuria, Mortality

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with diverse manifestations and the kidney is a major target organ of SLE [1] [2]. About 60% of all patients with SLE have renal disease and presence/absence of

lupus nephritis (LN) is an important prognostic factor in patients with SLE [3] [4] [5]. The mortality rate is higher in SLE patients with LN than in those without nephropathy, and about 10% of patients with LN eventually show progression to end-stage renal disease (ESRD) [6] [7]. In America and Europe, the ten years renal survival rate has improved to 80% - 90% with the implementation of current immunosuppressive regimens [8]. Although the survival prognosis of patients with SLE has improved over the past three decades, the prognosis in terms of the renal outcome has not kept pace [9] [10]. The present study was designed as a retrospective observational cohort study of patients with LN who have undergone renal biopsy, to identify the factors affecting the long-term renal outcome in patients with LN.

2. Methods

2.1. The Study Group

The study subjects were 102 SLE patients who had undergone renal biopsy and been diagnosed as having LN between 1990 and 2006 at the Department of Medicine, Kidney Center, Tokyo Women's Medical University. The study protocol was approved by the Institutional Review Board of our university, and the study was performed in accordance with the ethical principles laid out in the Declaration of Helsinki for medical research involving human subjects. Informed consent was obtained from all of the subjects.

2.2. Assessment of Laboratory Data

Data on the age, gender, laboratory test data at the time of biopsy, renal biopsy findings and the remission induction/maintenance therapy were analyzed. In cases where follow-up was possible, the relationships of the background variables to the time course of changes of the laboratory test data were analyzed using a single-factor model of Graphical Gaussian rules [11]. A Cox regression model was used to identify factors affecting the renal outcome. Deterioration of renal function was defined as elevation of the serum creatinine value to 1.5 times the level determined at the time of the biopsy and to a level higher than 1.0 mg/dL [12]. Patients whose urinary protein at the time of renal biopsy was 3.5 g/day or more were classified into the nephrotic syndrome group and patients in whom the urinary protein excretion was less than 3.5 g/day were classified into the chronic nephritic syndrome group.

2.3. Statistical Analysis

Continuous data are reported as means ± standard deviation (SD), and categorical data are reported as percentages. Differences in the baseline characteristics and biochemical parameters were assessed using Student's t-test and Mann-Whitney U test. Categorical values were compared by performing the Fisher's exact test. Logistic regression analysis was used in a model to determine how independent variables predicted the outcome. We considered some va-

riables that possess *P*-value < 0.10 in univariate logistic regression analyses as independent variables for multivariate logistic regression analyses. The survival analysis was based on the Kaplan-Meier curve with subjects censored for death. A log-rank test was used to compare the survival rates of two groups. A multivariate Cox proportional hazards model with adjustment for multivariate factors was used to evaluate mortality risk. Results were expressed as a hazard ratio (HR) with 95% confidence intervals (CIs). A p value < 0.05 was considered to be statistically significant. Multiple imputations were used to accommodate missing data and the Markov chain Monte Carlo method yielded unbiased results with accurate estimates of standard errors from the present data under the assumption that the data are multivariate normally distributed [13]. All statistical analyses were performed by using the SAS version 9.3 software program (SAS Institute Inc., Cary, NC, USA) for Windows personal computers.

3. Results

Table 1 shows the clinical data at the time of the initial renal biopsy. Analysis of the background variables revealed the following: percentage of females, 84%; mean age, 39 ± 15 years; mean follow-up period, 10 years; number of deaths during the observation period, 6 (6%). Death was attributable to infection in 4 cases (3.9%), heart failure in 1 case (1.0%), and the cause was unknown in 1 case (1.0%). The biopsy results were classified according to the World Health Organization (WHO) classification [14], as follows; class III in 13 cases (13%), class IV in 41 cases (41%) and class V in 34 cases (33%).

Laboratory tests at the time of renal biopsy yielded the following results: proteinuria, 3.63 g/day; serum albumin, 2.8 g/dL; serum creatinine, 1.18 mg/dL; serum C4 15.8 mg/dL; serum anti-ds-DNA antibody titer, 7.2 IU/mL (Table 2).

The Graphical Gaussian model prepared using the various data obtained at the time of the biopsy is shown in Figure 1. The serum C3 levels were found to show a positive correlation with the estimated glomerular filtration rate (eGFR) (positive partial correlation coefficient > 0.2) and a negative correlation with the serum total protein levels (negative partial correlation coefficient < −0.2).

Figure 2 shows a graphic representation of the cumulative death rate and the renal survival rate during the observation period. The 15-year survival rate was 93.5%, and the renal function non-deterioration rate was 78.3%.

The influence of background variables on the risk of renal function deterioration was evaluated by univariate Cox regression analysis, which identified only daily urinary protein excretion as being significantly associated with deterioration of the renal function (P = 0.033) (Table 3).

Then, the relationship between prednisolone (PSL) and individual immunosuppressants on the risk of deterioration of renal function was analyzed (Figure 3). Of all the patients, 18.8% received PSL pulse therapy (hereinafter called "pulse therapy"), 28.7% received pulse therapy + immunosuppressants, 26.7% received immunosuppressants alone, and 25.7% received oral PSL therapy alone.

Table 1. Clinical profile of the patients with lupus nephritis in this study.

		N (%)
Gender	Male	17 (16)
	Female	85 (84)
Age at biopsy (years)	<20	4 (4)
	20 - 39	52 (51)
	40 - 59	35 (35)
	>59	10 (10)
	Mean ± SD	39 ± 15
	Median	36 (16-82)
Nephropathy (first visit)	No	0 (0)
	Yes	101 (100)
	NS	45 (44)
	RPGN	2 (2)
	CGN	47 (46)
	other	7 (7)
Withdrawal	No	63 (62)
	Yes	38 (38)
	death	6 (6)
	transference	32 (31)
Follow-up years	<6	30 (30)
	6 - 10	26 (26)
	11 - 15	16 (16)
	16 - 20	26 (26)
	>20	3 (3)
	Mean ± SD	10 ± 7
	Median	9 (0 - 28)
WHO classification	I	1 (1)
	II	8 (8)
	III	13 (13)
	III + V	1 (1)
	IV	41 (41)
	IV + V	1 (1)
	V	34 (33)
	VI	1 (1)
	unknown	1 (1)

Analysis of the influence of the treatment used on the risk of renal function deterioration revealed a tendency towards higher risk of renal function deterioration during the 15-year period in the pulse therapy + immunosuppressants group and the pulse therapy alone group, although the difference was not significant. No influence of individual types of immunosuppressant drugs used was

Table 2. Laboratory data at the time of initial renal biopsy.

Biopsy	Mean ± SD	95% CI
UP (g/day)	3.63 ± 3.74	2.88 - 4.38
TP (g/dl)	5.7 ± 1.2	5.5 - 6.0
Alb (g/dl)	2.8 ± 0.8	2.6 - 3.0
Cr (mg/dl)	1.18 ± 0.91	1.00 - 1.36
eGFR (ml/min/1.73m^2)	60.4 ± 28.4	54.8 - 66.0
CH50 (U/ml)	27.1 ± 10.4	24.9 - 29.4
C3 (mg/dl)	51.6 ± 24.3	46.8 - 56.5
C4 (mg/dl)	15.8 ± 10.6	13.7 - 17.9
anti-dsDNA antibodies (IU/ml)	7.2 ± 12.3	4.5 - 9.9

UP: urinary protein, TP: total protein, Alb: albumin, Cr: creatinine, eGFR: estimated glomerular filtration rate.

Table 3. Clinicopathological factors for renal function deterioration in patients with lupus nephritis.

Variable	HR	95% CI	P-value
Age	1.004	0.967 - 1.042	0.826
UP	1.133	1.010 - 1.270	0.033
TP	0.949	0.598 - 1.504	0.823
Alb	0.804	0.420 - 1.538	0.51
Cr	1.042	0.656 - 1.655	0.862
eGFR	0.996	0.977 - 1.015	0.649
CH50	1.006	0.964 - 1.050	0.791
C3	0.991	0.969 - 1.013	0.405
C4	0.989	0.938 - 1.043	0.686
anti-dsDNA antibodies	0.987	0.958 - 1.018	0.414

found on the renal function deterioration rate.

Figure 4 shows the results of analysis of the relationships between various data obtained at the time of biopsy and the risk of deterioration of renal function. The cumulative incidence of events (death rate + renal function deterioration rate) during the observation period was higher in the group with a daily urinary protein excretion value of 3.5 g or more at the time of biopsy than in the group with a daily urinary protein excretion level of less than 3.5 g, although this difference was not statistically significant.

Figure 5 shows the time course of proteinuria and serum creatinine level in each patient. The urinary protein excretion level decreased after the start of treatment in many patients, and many patients remained free of renal function deterioration after the start of treatment.

Because the mean daily urinary protein excretion level was smaller at one year after the biopsy (0.76 g) than at the time of biopsy, the influence of the daily urinary protein excretion value at one year after the start of treatment on the risk

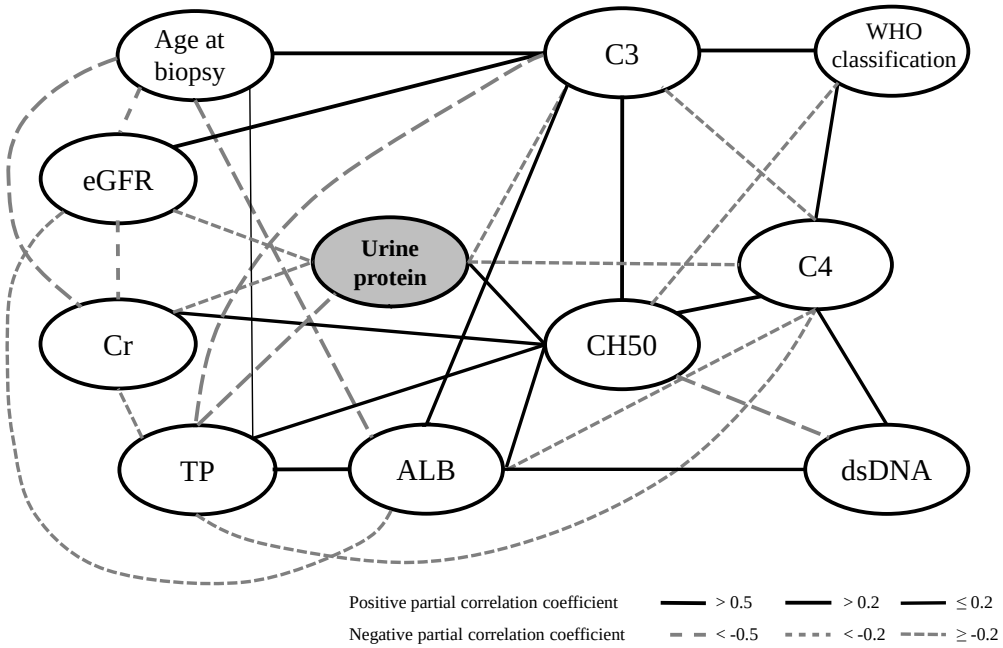


Figure 1. Correlation analysis of background factors by Graphical Gaussian model.

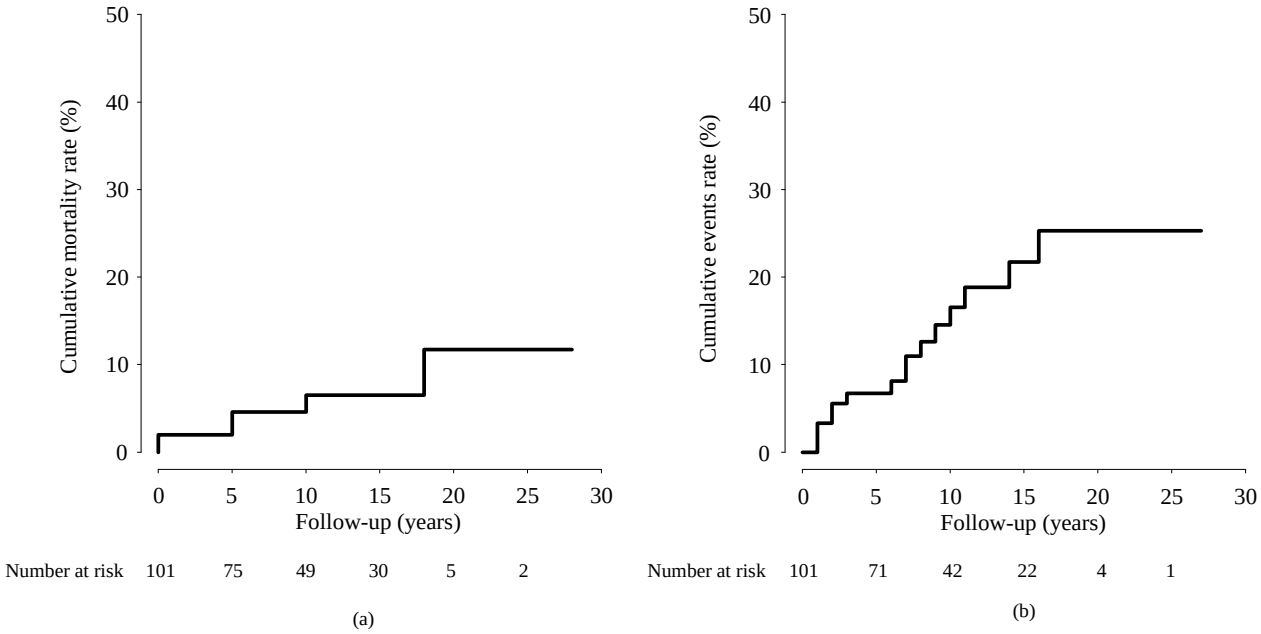
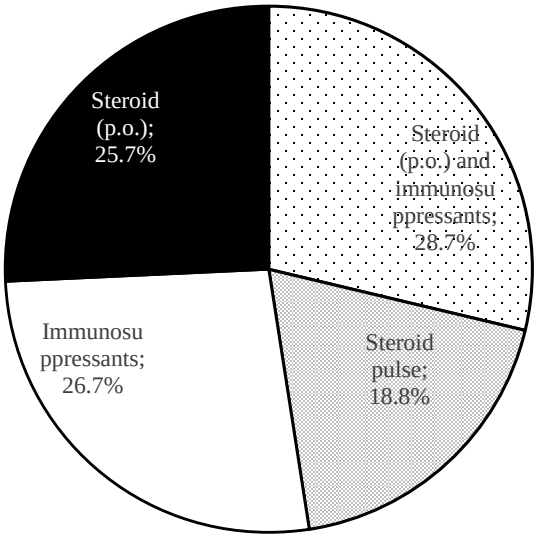


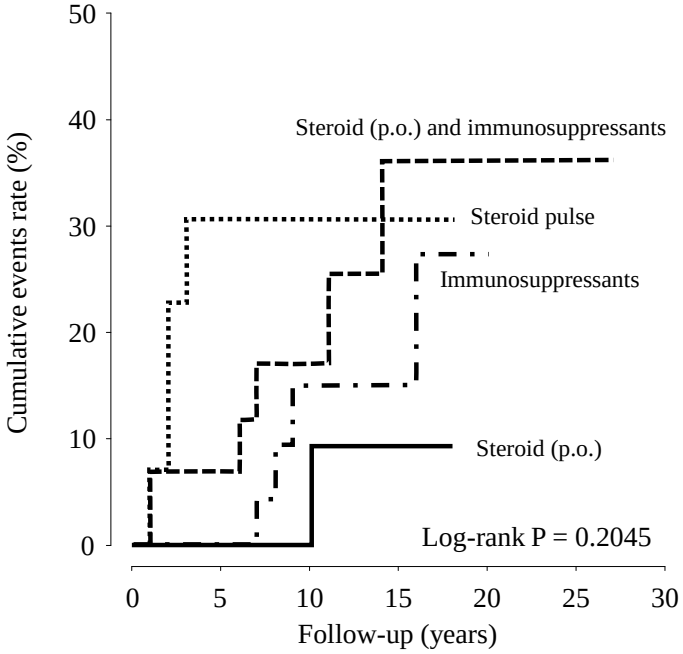
Figure 2. Cumulative death rate (a) and renal survival rate (b) of 102 patients with lupus nephritis.

of deterioration of nephropathy was analyzed (**Figure 6**). At each point of time, the death rate and the renal function deterioration rate tended to be higher in the urinary protein of 0.5 g or more group, although no statistically significant difference was observed between this group and the other group.

4. Discussion

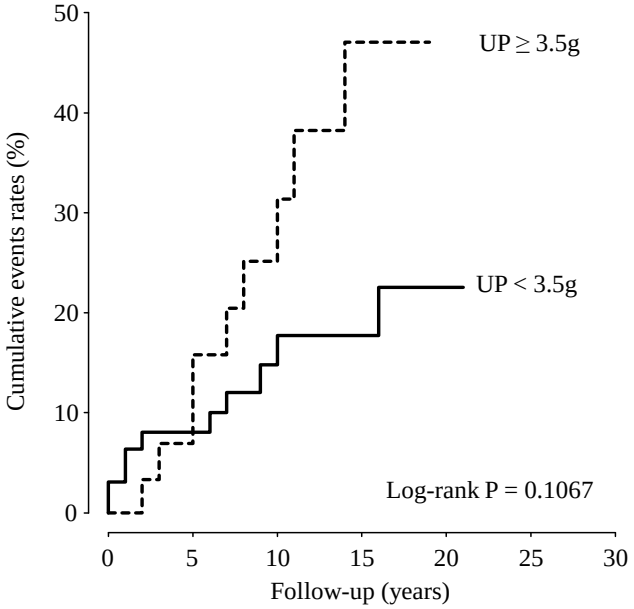
The results of this study indicate that SLE patients who underwent renal biopsy





Number of risk						
Steroid (p.o.) and immunosuppressants	29	22	13	4	2	1
Sreroid pulse	19	8	6	4	-	-
Immunosuppressants	27	24	12	7	2	-
Steroid (p.o.)	26	17	11	7	-	-

Figure 3. Comparison of therapeutic regimens associated with renal function deterioration rate.



Number at risk						
≥ 3.5g	34	21	12	4	-	-
< 3.5g	65	49	29	17	3	-

Figure 4. Comparison of cumulative death and renal function deterioration according to proteinuria ≥ 3.5 g/day or 3.5 < g/day at the time of initial renal biopsy.

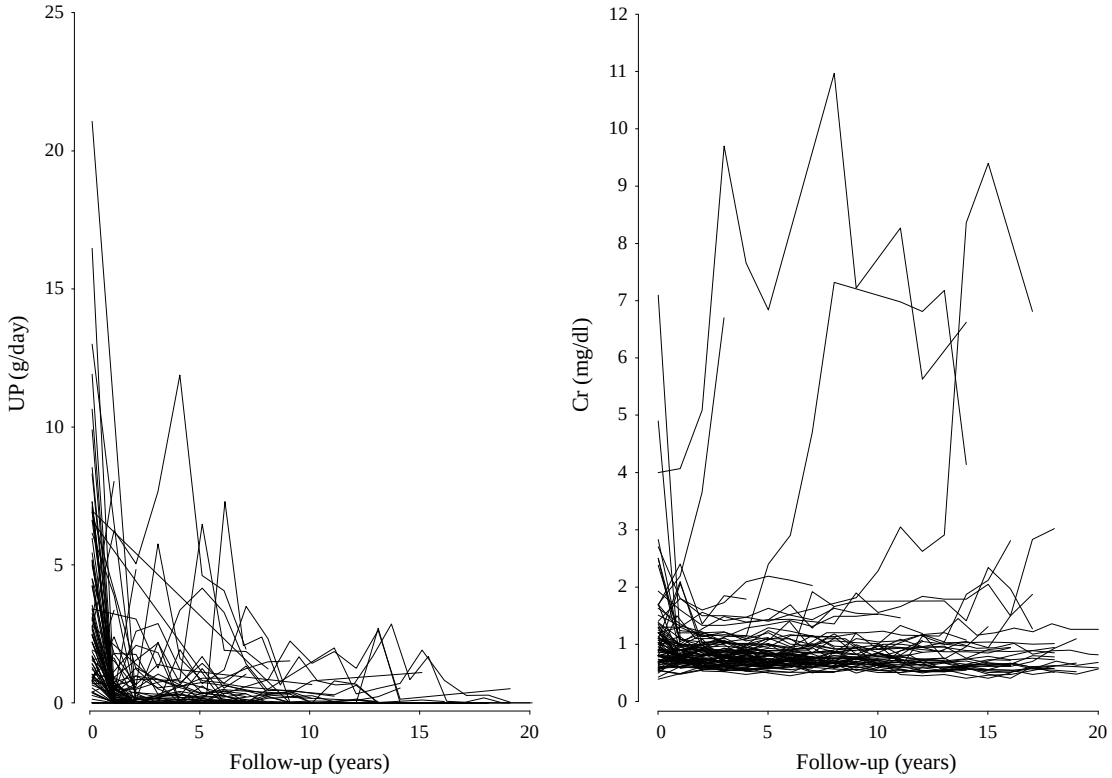
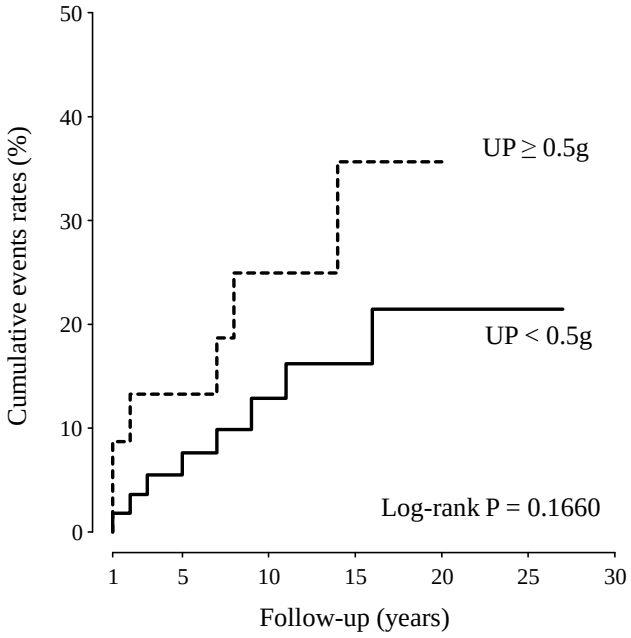


Figure 5. Time course of proteinuria (a) and serum creatinine (b) in each patient during follow-up period.



Number at risk

≥ 0.5g	23	17	8	4	1	-
< 0.5g	56	45	28	16	3	1

Figure 6. Comparison of cumulative death and renal function deterioration according to proteinuria ≥ 0.5 g/day or 0.5 < g/day after one year of induction therapy.

at our department had a high prevalence of compromised renal function and nephrotic syndrome or lupus nephritis (with urinary protein excretion levels equivalent to those in nephrotic syndrome) at the time of biopsy. According to the strategy for selection of the treatment method at our department, high-dose steroid therapy serves as the main therapy, as a rule, and if the patient proves resistant to this therapy, another method is selected from the range of steroid pulse therapy to low-dose intravenous cyclophosphamide (IVCY) therapy, occasionally accompanied by the use of other immunosuppressants in the expectation of being able to reduce the PSL dose [10]. Thus, our therapeutic strategy differs considerably from that recommended in the LN Treatment Guidelines published by the American College of Rheumatology (ACR) in 2012 [15]. According to the review published by Cameron *et al*., the 5-year survival rate was 92% in patients diagnosed as having SLE in 1990 to 1995, and 82% in patients with LN [16]. The survival data at our department were more favorable than those reported by Cameron *et al*. [16]. We additionally attempted detailed analysis of the outcome by the type of immunosuppressant used, but it was not possible for us to conduct any meaningful statistical analysis.

During the 15-year period, 22 patients with LN (21.7%) showed progression to renal failure. The present study was planned to examine the possibility of identifying, at least to some extent, factors that would be useful for predicting renal function deterioration, among the data obtained at the time of the renal biopsy. In this study, the results of analysis identified only daily urinary protein excretion level as having any significant effect on the risk of progression of LN to renal failure. The daily urinary protein excretion level determined at the time of the biopsy was correlated with the renal function level at the time of the biopsy, however, the daily urinary protein excretion value measured at the time of biopsy failed to show any significant association (beyond a tendency) with the risk of renal function deterioration after 15 years. In any event, the urinary protein excretion level was identified as a target of treatment. This finding provides statistical endorsement of our past clinical experience.

Previous studies reported poor prognostic factors. These include young age of onset of nephritis, African American ethnicity, hypertension, renal impairment at onset of LN, and poor pathologic findings on kidney biopsy [17] [18] [19] [20]. A few studies have analyzed whether the initial response to therapy predicts long-term renal outcome. Levey *et al*., found that treatment response was prognostic in a cohort of 63 patients with severe lupus nephritis [17]. Houssiau *et al*. have demonstrated that an early response to therapy at 6 months is the best predictor of good long-term renal outcome [21]. We should examine if the long-term renal outcome can be predicted by good response to therapy at 6 months.

Now, we discuss the significance of using the Graphical Gaussian model. If Cox regression analysis is employed, multivariate analysis (using multiple independent variables) is also possible. However, if there is a causal relationship be-

tween any two independent variables, multivariate analysis will not succeed. It is therefore essential to select only independent variables having no causal relationships with each other. Although correlation is not always equal to causal relationship, correlation is usually observed when there is a causal relationship. It is for this reason that we used the Graphical Gaussian model for the preliminary analysis, based on which we selected the variables to be included in the multivariate analysis, also taking into account the medical validity. This was the initial aim of the present study. Unfortunately, the univariate Cox regression analysis suggested an association only with the daily urinary protein excretion level, making it impossible for us to carry out multivariate analysis as the next step.

There are some limitations in our study. This is a retrospective study in Japanese with a small sample size. A very selective and small number of patients were given immunosuppressants. In addition, steroid dosing was not uniform in all patients. These factors could have influenced the final result.

In conclusion, among the SLE patients who underwent renal biopsy at our department between 1990 and 2009, both the prognosis in terms of the survival and that in terms of the renal outcome were comparable to or better than those reported in the literature, even though our patients did not always receive the standard recommended therapy. The daily urinary protein excretion level measured at the time of biopsy was the only factor that was identified as having any influence on the risk of renal function deterioration over the subsequent 15 years.

5. Conclusion

These results suggest that remission induction therapy and maintenance therapy focused on long-term preservation of renal function need to be selected for LN patients with a high daily urinary protein value at the start of treatment and for LN patients who fail to show any reduction of the daily urinary protein excretion level to 0.5 g or less at one year after the biopsy.

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Disclosure

The authors have no conflicts of interest to declare.

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