Predictors of end-stage renal disease and recurrence of lupus activity after initiation of dialysis in patients with lupus nephritis

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Abstract

Objectives

The present paper aims at identifying the predictors of end-stage renal disease (ESRD) and at determining the long-term outcome of ESRD patients according to renal replacement modality in Korean patients with lupus nephritis (LN).

Methods

Between 1985 and 2010, 321 Korean patients with LN were enrolled in this study. We analysed the clinical and laboratory indices, the treatment responses and the biopsy findings. The events of interest were estimated by the Kaplan-Meier method and the risk factors were assessed by univariate and multivariate Cox proportional hazards regression analyses.

Results

The median follow-up time after the diagnosis of LN was 84 months. During follow-up, twenty-nine patients evolved to ESRD. Renal survival rate at 5 and 10 years after LN onset was 95.9% and 91.1%, respectively. Deteriorated renal function (estimated glomerular filtration rate <60 ml/min/1.73m^2) at LN onset (hazard ratio: 9.223) was found to be an independent risk factor for the development of ESRD. Recurrence of lupus nephritis in renal allograft and flare-ups of lupus activity were not observed among the patients undergoing kidney transplantation (KT) (n=11). In contrast, those with maintenance dialysis (n=18) developed 13 episodes of lupus flare in 10 patients and 5 died of either infection (n=2) or lupus flare (n=3).

Conclusion

The impaired renal function at baseline is an independent predictor of ESRD in Korean patients with LN. The benefits of KT on the control of lupus activity and survival should be emphasised.

Key words

lupus nephritis, end-stage renal disease, predictors, prognosis, kidney transplantation

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Introduction

Lupus nephritis (LN) accounts for most of the morbidity and mortality of patients with systemic lupus erythematosus (SLE). Despite advances in the management strategies, 5 to 22% of LN patients eventually progress to end-stage renal disease (ESRD), requiring either dialysis or transplantation (1-3). Renal failure remains an independent risk factor for death in patients with LN.

A number of demographic, histopathological, serological and racial factors have been discovered to be associated with the outcome of LN (4, 5). Many multivariate or adjusted analyses have revealed more than twenty risk factors associated with progressive renal failure. These risk factors are male gender, age less than 24 years, crescents in more than 50% of the glomeruli, high chronicity index, treatment with steroids alone, initial high serum creatinine level, relapse, hypertension, anaemia and serum antiphospholipid antibodies (5-7). However, due to differences in the definition of outcome measures, the composition of the cohort studied, the duration of follow-up and the number of patients enrolled, the predictive factors associated with poor renal outcome have varied with different studies. In addition, it has been recently shown that ethnicity may affect the treatment response and clinical course of LN (8, 9). Therefore, it is difficult to extrapolate the previously known risk factors for progressive renal failure to Korean patients with LN.

Interestingly, the SLE disease activity has been reported to decline in patients who progress to ESRD, but the disease activity is not abolished in many studies (3, 10). Nossent *et al*. reported that the survival of renal graft in SLE was good. They also identified that the disease activity after kidney transplantation (KT) is low and the recurrence of LN is rare (11). In their report, the use of immunosuppressive agents was decreased after transplantation. Nevertheless, the "burnout" phenomenon of lupus activity in patients with ESRD has made many rheumatologists anticipate that lupus activity in patients undergoing maintenance dialysis tends to be low enough to avoid life-threatening SLE flare-ups. The recurrence of LN after KT is an issue of great concern (12) and could be an obstacle to undergo KT in SLE patients with ESRD.

There has been no investigation to clarify the risk factors of developing ESRD or the long-term prognosis in Korean patients with LN. Therefore, we conducted an observational cohort study of 321 Korean patients with LN. We examined the cumulative incidence of ESRD in the patients with LN and we also investigated their clinical, laboratory and histopathological characteristics and mortality. Finally, we identified the risk factors for the development of ESRD and suggested the relationship between mortality or disease flare-ups and the treatment options of renal replacement in the patients with LN-induced ESRD.

Patients and methods

Subjects

Between January 1985 and January 2011, 451 patients with lupus nephritis were identified from the lupus cohort at Seoul St. Mary's Hospital. All the patients met the classification criteria for SLE, as defined by the American College of Rheumatology (ACR) criteria (13). Subjects were excluded if they had less than 6 months of follow-up after the diagnosis of LN, they had diabetes as a comorbid condition or they lacked clinical data. The patients who underwent quantitative examination for proteinuria at the onset of LN and whose results met the ACR renal disorder criterion (14) were recruited for this study. Finally, 321 patients were enrolled. The study received approval from the Institutional Review Board of Seoul St. Mary's Hospital (KC11RISI0090).

Definition

The response criteria were defined according to the ACR 2006 clinical trial criteria (15). Complete remission (CR) was defined as (1) a normal glomerular filtration rate (GFR) ≥90mls/min/1.73m2 or >25% increase from baseline, (2) a urine protein-to-creatinine ratio <0.2 or a dipstick test of 0 to trace, (3) less than five red blood cells /high power field (HPF) and (4) no cellular casts in the urine. Partial remission (PR) was defined as meet-

ing the ACR 2006 clinical trial criteria for remission with the exception of a urine protein-to-creatinine ratio between 0.2 and 2. If the patients met at least two parameters, but they were missing information on the other criteria, then they were labelled as partial responders. Patients were defined as non-responders if they failed to meet any of the criteria for remission. Nephrotic proteinuria was defined as proteinuria >3.5g/24hr or a uninary protein:urinary creatinine ratio of >3.0. Hypertension (HTN) was defined as a supine systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) ≥90mmHg. Initial-onset LN (I-LN) was defined as LN diagnosed at the time of SLE onset. In contrast, delayed-onset LN (D-LN) was defined as newly developed LN after the onset of SLE.

Collection of the clinical, laboratory and histological data

The demographic data, clinical data (the treatment regimens, the body mass index [BMI] and blood pressure), the autoantibody profiles measured at the onset time of LN (anti-double stranded DNA [anti-dsDNA], anti-nuclear, anti-ribonucleoprotein [RNP], anti-Ro/La, anti-cardiolipin antibodies and lupus anticoagulants [LAC]), the biochemical parameters (haemoglobin [Hb], the presence or absence of thrombocytopenia (defined as less than 100,000/mm^3), the serum creatinine, serum albumin and serum complement (C3, C4) levels, the level of 24-hr urinary protein excretion, the absence or presence of haematuria (>5 erythrocytes/HPF) and the estimated GFR (eGFR) at baseline and 6 and 12 months after the diagnosis of LN were obtained from the medical records review. The GFR was calculated by the Modification of Diet in Renal Disease study equation: eGFR (ml/minute/1.73m^2) = 1.86 x [serum creatinine (mg/dl)]$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x(1.21 if African American).

The histological pattern of disease was established using the 1982 modified World Health Organisation (WHO) classification, and the activity and chronicity index (AI and CI) scores were calculated using the scoring systems of the US National Institutes of Health (NIH) (16). Other pathological findings were also reviewed at the same time. The renal biopsies have been interpreted simultaneously by two different pathologists.

Table I. Clinical characteristics and renal parameters at the presentation of lupus nephritis according to the renal survival.

	Renal survival		*p*-value
	Non-ESRD (n=292)	ESRD (n=29)	
Gender (female)	268/292 (91.8)	27/29 (93.1)	0.803
Age at onset of SLE, years	26.8 ± 10.5	25.1 ± 8.6	0.542
Age at onset of LN, years	28.6 ± 10.5	28.0 ± 7.3	0.946
Disease duration at the time of LN onset, months	22.1 ± 40.3	29.2 ± 35.6	0.083
Disease duration at the time of LN onset, months (restricted to patients with D-LN)	52.9 ± 47.5	46.4 ± 34.9	0.859
BMI	22.1 ± 3.4	22.1 ± 1.9	0.806
Newly developed HTN in previously normotensive patients	33/186 (17.7)	2/12 (16.7)	0.925
SBP, mmHg	120.5 ± 17.4	129.2 ± 25.4	0.176
DBP, mmHg	76.7 ± 11.7	83.3 ± 18.3	0.031
Hb, g/dl	10.6 ± 2.2	9.4 ± 1.5	0.022
Hb ≤11 g/dl	133/221 (60.2)	15/16 (93.8)	0.007
Platelet <100,000/μl	26/220 (11.8)	1/16 (6.3)	0.499
ANA positivity	257/271 (94.8)	20/24 (83.3)	0.024
Anti-RNP antibody positivity	68/135 (50.4)	0/10 (0.0)	0.002
Anti-Ro antibody positivity	99/169 (58.6)	2/13 (15.4)	0.003
Anti-La antibody positivity	30/140 (21.4)	1/10 (10.0)	0.389
Increased anti-dsDNA antibody	156/188 (83.0)	11/14 (78.6)	0.674
C3, mg/dl	44.5 ± 24.4	47.8 ± 25.6	0.608
C4, mg/dl	10.7 ± 7.3	11.7 ± 5.0	0.157
I-LN	168/290 (57.9)	10/27 (37.0)	0.036
Cr, mg/dl	0.92 ± 0.42	1.72 ± 2.13	0.002
eGFR at LN, ml/min/1.73m^2	86.9 ± 29.7	61.6 ± 30.8	0.004
eGFR at LN <60 ml/min/1.73m^2	42/224 (18.8)	9/15 (60.0)	<0.001
Proteinuria, g/24hours	5.32 ± 5.92	6.11 ± 6.86	0.990
Nephritic proteinuria	115/217 (53.0)	7/14 (50.0)	0.828
Haematuria	160/222 (72.1)	13/16 (81.3)	0.426
Serum albumin, g/dl	2.83 ± 0.68	2.68 ± 0.62	0.436

Values are given as mean ± SD for the continuous variables, and n (%) for the categorical variables. SLE: systemic lupus erythematosus; LN: lupus nephritis; D-LN: delayed-onset LN; BMI: body mass index; HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: haemoglobin; ANA: anti-nuclear antibody; anti-RNP antibody: anti-ribonucleoprotein antibody; dsDNA: double-stranded DNA; I-LN: Intitial-onset LN; Cr: creatinine; eGFR: estimated glomerular filtration rate.

Treatment regimen

This was a retrospective, observational study and consequently the therapeutic regimens were not standardised.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software package standard version 16.0 (SPSS Inc., Chicago, IL). When comparing the two groups, the Mann-Whitney U-test was used for the continuous variables and the chi-square test was employed for the categorical variables. Cox's proportional hazards model for estimating the hazard ratio (HR) and the 95% confidence interval (CI) was used to identify the predictive factors for the development of ESRD. The cumulative incidence of events of interest over time was determined using life-table analysis and the Kaplan-Meier plot. The events of interest were compared using the log-rank test. The *p*-values less than 0.05 (two-tailed) were considered as statistically significant.

Results

Baseline demographic, clinical and laboratory profiles

Among our 321 patients with LN, we identified twenty-nine patients who developed ESRD during the follow-up period. The median duration of follow-up was 84 months. There was no difference in the baseline demographic characteristics, which included gender and age at the onset of LN and SLE, between

the patients who developed ESRD and those who did not (Table I). All the study subjects were Korean. The disease duration at the time of LN onset was not different. The BMI, newly developed HTN, the presence of thrombocytopenia, positivity for anti-La and anti-dsDNA antibodies, the C3 and C4 levels, the presence of haematuria and the serum albumin level at LN onset were not associated with the development of ESRD. The proportion of patients with Hb level ≤11 g/dl at baseline was greater for the patients with ESRD. Our data showed the anti-Ro and anti-RNP antibody positivity were correlated with better prognosis for renal survival. The proportions of the patients with LAC or anti-cardiolipin antibody positivity were not different between the groups (data not shown). Interestingly, the rate of I-LN was significantly higher in the non-ESRD group, as compared with that of the ESRD group. The renal function at the time of LN onset represented by the serum creatinine and eGFR was significantly decreased in the patients with ESRD. The level of 24-hr proteinuria and the rate of nephrotic proteinuria were not different between the groups.

Renal biopsy findings

The characteristics of the renal histopathology in the two groups are summarised in Table II. Two hundred and two patients (69.2%) from the non-ESRD group underwent renal biopsy and 20 patients (69.0%) from the ESRD group underwent renal biopsy. Proliferative lupus glomerulonephritis (WHO class III and class IV) comprised a higher proportion in the ESRD group (85%), compared to that of non-ESRD (73.3%). We identified that a high AI (12 or higher), a high CI (4 or higher), presence of glomerular sclerosis, fibrous crescent formation and the presence of chronic tubulointerstitial changes were associated with the development of ESRD.

Treatment strategies and the clinical profiles following induction therapy

Sixty-seven percent of the patients with renal survival were treated with cytotoxic agents, including cyclophosphamide (CYC) and mycophenolate mofetil (MMF), as primary induction therapy.

Table II. Comparison of the initial renal biopsy findings according to renal survival in the patients with lupus nephritis.

	Renal survival		*p*-value
	Non-ESRD	ESRD	
WHO classification			0.027
II	13/202 (6.4)	–	
III	16/202 (7.9)	–	
III+IV	1/202 (0.5)	–	
III+V	8/202 (4.0)	2/20 (10.0)	
IV	115/202 (56.9)	13/20 (65.0)	
IV+V	8/202 (4.0)	2/20 (10.0)	
V	37/202 (18.3)	2/20 (10.0)	
V+II	4/202 (2.0)	–	
VI	–	1/20 (5.0)	
Activity index score	5.9 ± 3.7	8.0 ± 3.8	0.069
Activity index score ≥12	10/137 (7.3)	3/11 (27.3)	0.024
Chronicity index score	2.3 ± 2.0	5.8 ± 2.1	<0.001
Chronicity index score ≥4	36/136 (26.5)	9/11 (81.8)	<0.001
Present glomerular sclerosis	70/127 (55.1)	11/12 (91.7)	0.014
Present crescent formation	41/124 (33.1)	10/12 (83.3)	0.001
Cellular crescent	31/122 (25.4)	6/12 (50.0)	0.069
Fibrocellular crescent	20/122 (16.4)	4/12 (33.3)	0.144
Fibrous crescent	5/124 (4.0)	4/12 (33.3)	<0.001
Present tubular atrophy	88/133 (66.2)	12/12 (100.0)	0.015
Present interstitial fibrosis	83/133 (62.4)	12/12 (100.0)	0.009

Values are given as mean ± SD for continuous variables, and n (%) for the categorical variables. ESRD: end-stage renal disease; WHO: World Health Organization.

Table III. The difference in clinical parameters that represent a treatment response according to the final renal survival.

	Renal survival		*p*-value
	Non-ESRD (n=292)	ESRD (n=29)	
Serum Cr at 6 months, mg/dl	0.83 ± 0.32	3.03 ± 2.89	<0.001
eGFR at 6 months, ml/min/1.73m^2	92.5 ± 27.1	46.0 ± 36.9	<0.001
Δ eGFR at 6 months, ml/min/1.73m^2	8.3 ± 29.7	-14.4 ± 34.4	0.045
Proteinuria at 6 months, g/24hr	1.61 ± 2.14	2.59 ± 1.21	0.005
Serum albumin at 6 months, g/dl	3.57 ± 0.54	3.25 ± 0.44	0.020
C3 at 6 months, mg/dl	72.4 ± 27.9	56.6 ± 27.9	0.055
C4 at 6 months, mg/dl	17.2 ± 9.3	18.9 ± 10.6	0.500
Hb at 6 months, g/dl	11.6 ± 1.6	10.2 ± 1.9	0.010
Δ Hb at 6 months, g/dl	1.12 ± 2.15	0.21 ± 2.58	0.166
Serum Cr at 12 months, mg/dl	0.86 ± 0.49	2.66 ± 2.44	<0.001
eGFR at 12 months, ml/min/1.73m^2	91.4 ± 29.0	44.3 ± 31.7	<0.001
Δ eGFR at 12 months, ml/min/1.73m^2	5.5 ± 32.0	-16.5 ± 19.2	0.007
Proteinuria at 12 months, g/24hr	3.63 ± 6.31	2.53 ± 1.66	0.469

Values are given as mean ± SD. ESRD: end-stage renal disease; Cr: creatinine; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; Δ eGFR at a given time: defined as the eGFR at a given time – the eGFR at the onset of LN.

The majority of the patients (92%) who progressed to ESRD were also treated with these agents as induction therapy. As regards maintenance therapy, both groups showed similar rates of treatment with CYC, MMF or azathioprine (38.9% *vs*. 36.8%, 15.3% *vs*. 10.5% and 17.2% *vs*. 21.1% in the non-ESRD and the ESRD patients, respectively). Briefly, it could be concluded that the patients who finally progressed to ESRD were administered no less cytotoxic agents than those with renal survival. According to the previously defined remission criteria, we classified the cohort patients into 4 groups according to the treatment response at 6 and 12 months following induction therapy. Forty-four percent of the patients with renal survival had achieved

CR or PR at 6 months after induction therapy, whereas only 4% of the patients who developed ESRD achieved the remission criteria at that time. The 12 months evaluation showed similar results (49.8% and 5.0% in non-ESRD and ESRD patients, respectively).

Table III shows the different clinical profiles presented at 6 and 12 months after induction therapy. The average GFR normally declines 0.96 ml/min/year or about 10 ml/min/decade (17). While the eGFR of the non-ESRD group tended to increase following induction therapy, the patients who went on to ESRD showed worsening renal function during the same period. This result suggests that a relatively rapid decline of the eGFR within 12 months after induction therapy could predict a poor renal outcome in the patients with LN.

Patient survival and causes of death

In this study, we found 25 mortality cases during the follow-up period. Twenty cases among them had developed in non-ESRD group. And remaining five cases occurred in the patients who progressed into ESRD. The 5 and 10-year cumulative patient survival rates are 95.3% and 80.2% respectively. Twelve patients died of disease flares (haematologic manifestation [n=5], diffuse alveolar haemorrhage [n=4], neuropsychiatric manifestation [n=3]). The other causes of death are infection (n=9), bleeding (n=3), and heart failure (n=1).

Predictors of developing ESRD in the patients with LN

For our LN cohort, ESRD occurred in 4.1% and 8.9% of all the patients within 5 years and 10 years after the diagnosis of LN, respectively. The mean time interval between LN onset and the evolution to ESRD was 95.4 months. Univariate and multivariate Cox regression analyses were performed to assess the effects of variables on the development of ESRD, in which the potential confounders were included (Table IV). On univariate analysis, various factors seem to be risk factors for the development of ESRD. They included the D-LN, low Hb level at LN onset, impaired renal function (eGFR <60 ml/min/1.73 m^2) at baseline, high histological indices (AI and CI), the presence of glomerular sclerosis, the presence of fibrous crescent and the absence of anti-Ro antibody. The variables of $p<0.20$ in the univariate analysis were included in the multivariate model. Only one variable was selected among those involved in multicollinearity. To assess multicollinearity, we used the variance inflation factor, values of which greater than five were considered to show multicollinearity. On multivariate analysis, only deteriorated renal function at the time of LN onset remained significantly associated with the development of ESRD. Figure 1 shows the cumulative incidence of developing ESRD in the patients with LN, according to baseline renal function. The patients with relatively preserved renal function (eGFR at LN onset ≥60 ml/min/1.73m^2) showed a

Table IV. Cox proportional hazards regression analyses for the predictors of developing ESRD in patients with LN. Conditional stepwise analysis with adjustment for the effect of age and gender.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
D-LN	3.581 (1.578–8.126)	0.002		
Absent anti-Ro antibody	5.297 (1.159–24.201)	0.031		
Absent anti-RNP antibody	55.641 (0.253–12254.254)	0.144		
Hb at LN ≤ 11g/dl	7.686 (1.014–58.277)	0.048		
Serum Cr[a] at LN	2.548 (1.492–4.350)	0.001		
eGFR at LN < 60 ml/min/1.73m^2	6.083 (2.160–17.128)	0.001	9.223 (1.633–52.100)	0.012
eGFR at LN[b]	0.748 (0.621–0.901)	0.002		
AI ≥ 12	3.985 (1.047–15.167)	0.043		
CI ≥ 4	12.311 (2.633–57.549)	0.001		
Glomerular sclerosis	10.456 (1.336–81.858)	0.025		
Fibrous crescent	7.462 (2.244–24.810)	0.001		
Tubular atrophy	42.794 (0.311–5895.884)	0.135		
Interstitial fibrosis	45.051 (0.350–5806.013)	0.125		

a: change in Cr by 1mg/dl; b: change in eGFR by 10 ml/min/1.73m2; HR: hazard ratio; 95% CI: 95% confidence interval; D-LN: delayed-onset lupus nephritis; Hb: haemoglobin; Cr: creatinine; eGFR: estimated glomerular filtration rate; AI: activity index; CI: chronicity index.

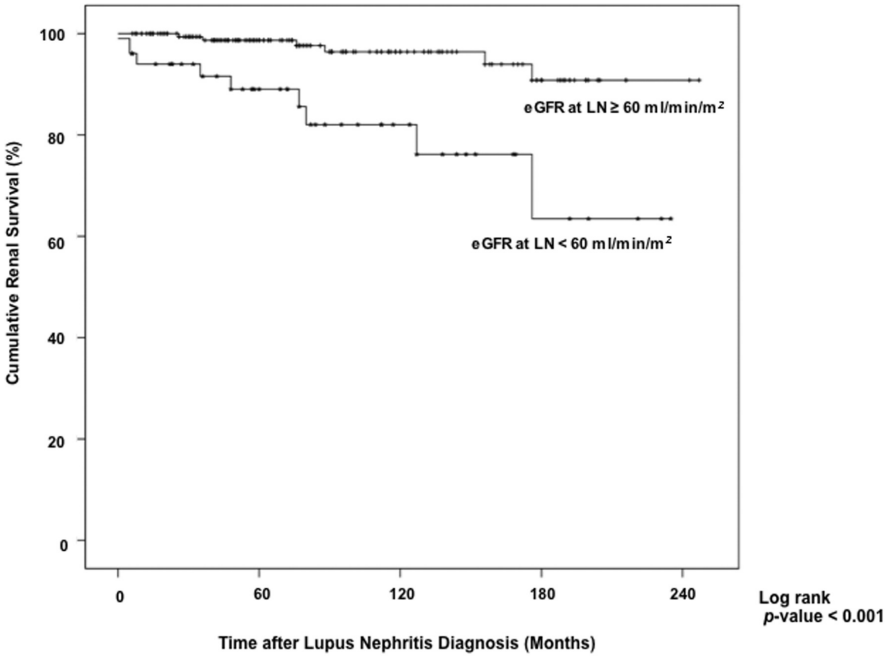

Fig. 1. Kaplan-Meier curve compared cumulative renal survival in patients with LN according to the initial renal function. Patients who showed preserved renal function at the time of LN onset showed higher renal survival rate than those with impaired renal function.

low incidence of ESRD (4%) within 10 years after LN. In contrast, a larger portion of the patients (24%) who showed deteriorated renal function (eGFR <60 ml/min/1.73m^2) at LN onset progressed to ESRD within the same period.

The effects of renal replacement modality on lupus flare-ups and mortality in the patients with ESRD due to LN

Among the 29 patients with ESRD, the majority (n=27) were female. The mean age at the initiation of dialysis was 35 years. The median interval between LN onset and the initiation of maintenance dialysis was 83 months (range 0 to 228 months). On reviewing the types of renal replacement modality, 18 patients have steadily maintained dialysis after ESRD onset and 11 have undergone KT (10 recipients of living donor transplantation and 1 recipient of deceased donor transplantation). The median duration of dialysis before transplantation was 10 months. In the patients who progressed into ESRD, all the mortalities occurred from the group that was on maintenance dialysis. Out of five deceased cases in ESRD group, three patients died as a result of disease flare-ups and the remaining two patients died of infection. In contrast, all 11 patients who underwent KT survived during the follow-up period (median follow-up periods after KT and ESRD diagnosis were 47 and 53 months, respectively). For the allograft survival, two recipients developed allograft loss due to chronic allograft rejection, which were confirmed by renal biopsies. None of the patients who had undergone KT developed renal flare-up, non-renal flare-up or death during the follow-up period. Immunosuppressants administered to those patients were composed of a calcineurin inhibitor (cyclosporine or tacrolimus) and prednisolone (dose ranging from 2.5 mg to 10 mg), with or without mycophenolate mofetil. On the other hand, 10 out of 18 patients undergoing maintenance dialysis developed thirteen episodes of disease flare-up that required hospitalisation after ESRD diagnosis during a median follow-up period of 29 months. As shown in Table V, all the patients had received prednisolone for the maintenance therapy before the diagnosis of SLE flare-ups. The majority of flare-ups required high-dose glucocorticoid therapy and two cases required plasmapheresis. Among the flares, three events led to death, despite of the immediately administered immunosuppressive therapy. Seven out of 13 flare-up episodes occurred within six months after the diagnosis of ESRD. Among the patients with ESRD, the Kaplan-Meier curves showed a statistically significant lower risk of death and disease flare-up for the patients with KT, compared to patients on maintenance dialysis (Fig. 2).

Table V. Summary of clinical characteristics of 13 SLE flare events in 10 patients with ESRD.

Patient number	Flare case number	Age/sex	Administered medication before flare	Interval from ESRD diagnosis to flare (months)	Flare event	Treatment	Prognosis
1	1	47/F	PD 7.5mg	4	thrombocytopenia, arthritis	High dose steroid	I
1	2	47/F	PD 2.5mg	5	TTP	Plasmapheresis	I
2	3	52/F	PD 7.5mg	0.5	pancytopenia	High dose steroid	I
2	4	53/F	PD 10mg	14	LMV	High dose steroid	I
3	5	27/F	PD 62.5mg	1	CNS vasculitis	High dose steroid	I
3	6	28/F	PD 30mg + Cs 200mg	11	arthritis	High dose steroid	I
4	7	32/F	PD10mg	5	alveolar haemorrhage	High dose steroid	I
5	8	35/F	PD 30mg + mizoribine	4	CNS vasculitis	High dose steroid	E
6	9	32/F	PD 30mg + HCQ	29	CNS vasculitis	High dose steroid	I
7	10	33/F	PD 7.5mg	78	HPS	Steroid + Plasmapheresis	E
8	11	50/F	PD 20mg	2	thrombocytopenia	High dose steroid	E
9	12	42/F	PD 10mg	40	CNS vasculitis	High dose steroid	I
10	13	38/F	PD10mg + AZP	86	LMV	High dose steroid	I

ESRD: end-stage renal disease; F: female; PD: prednisolone; I: improved; E: expired; Cs: cyclosporine; HCQ: hydroxychloroquine; AZP: azathioprine; TTP: thrombotic thrombocytopenic purpura; LMV: lupus mesenteric vasculitis; CNS: central nervous system; HPS: haemophagocytic syndrome.

Discussion

This is the first study that identified the time-dependent predictive factors for the development of ESRD and the long-term prognosis in Korean patients with LN-induced ESRD. Although the survival and renal outcome of LN patients have been investigated in both short- and medium-term follow-up studies, our study was based on long-term cohort data.

The 5-year incidence of ESRD in our cohort was lower than that from the UK, in which ESRD occurred at a rate ranging from 6.9 to 8.1% during the past three decades (18). Ten year renal survival rate of our study is good in comparison to other series. In other previous reports, that was revealed to be about between 80 and 85% (19-22). Even when restricting the analysis to the patients who failed to achieve remission at 6 months after induction

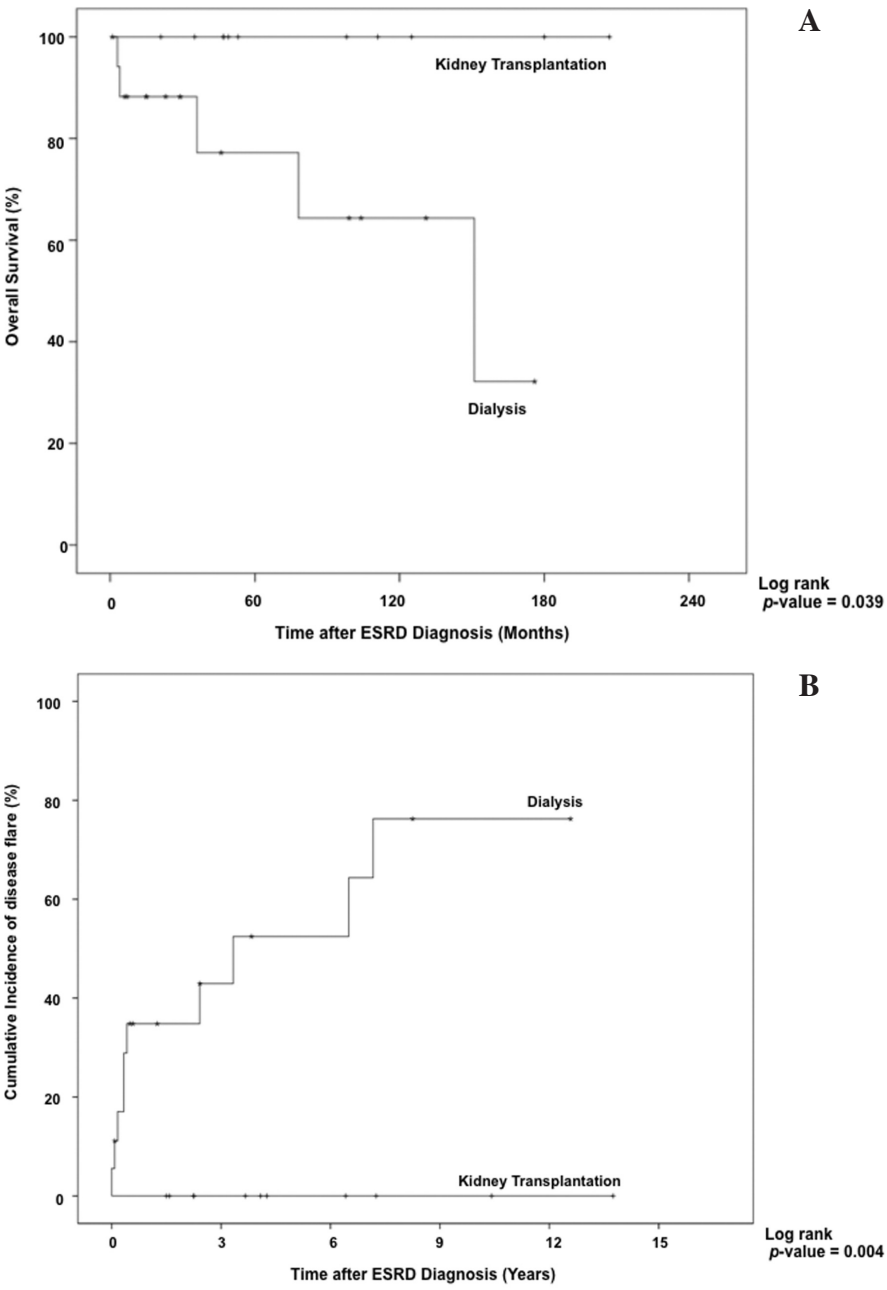

Fig. 2. Kaplan-Meier curves compared cumulative survival (**A**) and the incidence of SLE flare-up (**B**) in patients with ESRD, according to the renal replacement modalities. Patients who had sustained dialysis after ESRD onset showed poor survival and more frequent episodes of disease flare-up than those who underwent KT.

therapy, several factors remained as significantly poor prognostic factors for renal survival in the univariate analysis (the HRs for eGFR at LN <60 ml/min/1.73m^2 , D-LN, CI ≥4 and present fibrous crescent were 4.32, 3.38, 10.53 and 16.25, respectively). On multivariate analysis, impaired renal function at LN onset (HR=5.34) and present fibrous crescent (HR=6.04) were finally the only independent risk factors for the progression to ESRD. That suggested that other factors besides achieving remission could affect renal survival.

Although some studies showed disappointing results, the therapeutic options for the treatment of LN have increased, such as MMF, anti-CD20 and other B-cell directed therapies. Since achieving remission is basically an important issue for preventing renal dysfunction in patients with LN, those agents have been thought to have beneficial effects on the preservation of renal function. However, it is not yet known whether these treatments will reduce the development of ESRD.

Ward MM reported that the incidence of ESRD secondary to LN in the US rose from 1.13 in 1982 to 3.20 cases per million in 1995 (23), and this had not decreased between 1996 and 2004 (24). The same is true of the data from the UK (18). When combined with these discouraging reports, our study also showed that it might be difficult to prevent the development of ESRD in the patients with LN, because the baseline renal function (the only significant risk factor for the progression to ESRD in our study) is an unpredictable and uncorrectable factor. Without the development of novel drugs, preventing the occurrence of ESRD due to LN is still a difficult and complicated task.

Considering survival, the cumulative 5-year survival of the patients with LN has increased from below 50% in the 1960s to more than 80% in the 1990s (25). However, recent reports from both the US and the UK showed a constant mortality rate from mid 1990s to mid 2000s (18, 26). That implicated we are now facing the limitations of the currently used treatment strategies to achieve survival benefit for LN patients.

A recent article by Rietveld and Berden (27) reviewed the results of the various forms of renal replacement therapy in LN patients. Although the clinical and serological disease activity tended to decrease during the dialysis in lupus patients, there are some reports on ongoing extrarenal disease activity in the first year after the initiation of dialysis (28, 29).

In 1975 the American Colleges of Surgeons/NIH Transplant Registry reported that the allograft and recipient survival rates of LN patients were comparable with those of the non-SLE KT recipients (30). Recently, a large follow-up study that used the data from both the United States Renal Data System and United Network of Organ Sharing registry has compared 2886 SLE recipients with 89958 non-SLE recipients (31). Among the living allograft recipients, there was no difference in allograft and recipient survival, as compared with those of the non-SLE recipients. A study by Nossent

et al. (11) revealed that the maximal non-renal Systemic Lupus Erythematosus Disease Activity Index decreased after transplantation compared to during dialysis and before dialysis. However, the clinical outcome of KT in SLE patients remains a topic of controversy, due to concerns about disease recurrence and allograft rejection.

The present study showed the excellent survival, no recurrence of LN, as well as stable disease activity in the patients undergoing KT. On the other hand, those under dialysis underwent disease flares, even though all of the patients had taken low to medium dose of glucocorticoids (32). It might be a hasty conclusion that KT is superior than dialysis in survival and stabilisation of disease activity, owing to a limited number of patients with ESRD. Unfortunately, we cannot ascertain whether or not there is a difference in medical condition or disease activity at the time to start dialysis between the groups. Those factors might contribute to better survival and lessen the disease flare-ups in KT recipients. Additionally, immunosuppressants to avoid graft rejection could stabilise the disease activity. Nevertheless, KT as a renal replacement modality should be more stressed in the LN patients who progress to ESRD, when judging on the previous reports and our present study.

Like our study, Chien *et al*. (33) previously reported that a lower anti-Ro antibody titer was correlated with the occurrence of proteinuria in Taiwanese patients with SLE. Although the significance of anti-RNP antibody in the pathogenesis of LN remains uncertain, our results show that anti-RNP antibody positivity is correlated with a renal survival. Likewise, several studies elucidated anti-RNP antibodies exert opposite effects on the severity of LN (34, 35).

The onset time of LN was revealed to be a predictor for the development of ESRD in univariate Cox regression model. Because, it is notorious that the prompt therapy with immunosuppressive agents in LN has a beneficial effect on long-term renal function (36), it is also speculated that the patients with D-LN had received treatment later than those with I-LN.

In conclusion, deteriorated renal function at LN onset predicts the development of ESRD in Korean patients with LN. Among the patients who progressed to ESRD due to LN, those who underwent KT showed excellent clinical course without any evidence of renal flare-up, non-renal flare-up or death during the follow-up period. In contrast, the patients under maintenance dialysis showed a significantly greater frequency of disease flares-ups and death.

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