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Analysis of clinical risk factors in relapsed patients with class IV lupus nephritis

JING WANG[1], YUAN-YUAN QI[1], XUE-PING CHEN[1], LI MA[1], LI-LI ZHANG[1], YU ZHAO[1] and MEI WANG[2]

[1]Department of Nephropathy, Lanzhou University Second Hospital;
[2]Department of Obstetrics and Gynecology, Gansu Province People's Hospital, Lanzhou, Gansu 730000, P.R. China

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Abstract. The present study aimed to investigate risk factors for renal recurrence in patients with type IV lupus nephritis (LN). Univariate and multivariate analyses were conducted to using the Cox proportional hazard model and the Kaplan-Meier method. A total 244 patients were diagnosed with type IV LN; 100 (28.49%) relapsed and 144 (41.03%) recovered successfully. Kaplan-Meier method analysis indicated that patients with type IV LN affecting the digestive tract had high renal recurrence rates. Patients with hyperglobulinemia, positive anti-ribonucleoprotein and anti-Sjögren's syndrome type B (anti-SSB) antibodies, thrombus in the loop or non-inflammatory necrotizing vasculopathy also had a high recurrence rate. Furthermore, patients achieving partial remission had an increased recurrence rate compared with patients achieving complete remission. Patients undergoing maintenance treatment with glucocorticoids alone had a higher recurrence rate compared with patients who used alternative treatment schemes. Univariate and multivariate regression analyses by the Cox proportional hazard model determined that the effect of systemic lupus erythematosus in the gastrointestinal tract, increased serum globulin levels and positive anti-SSB antibody at onset were risk factors for the recurrence of LN type IV. The present study demonstrated that clinical risk factors of renal recurrence in patients with LN type IV include LN in the gastrointestinal tract, increased serum globulin levels, positive anti-SSB antibodies at onset and the use of glucocorticoid-only maintenance treatment.

Introduction

Systemic lupus erythematosus (SLE) is associated with a broad spectrum of clinical and immunologic manifestations (1), of which lupus nephritis (LN) is the most common cause of morbidity and mortality. LN affects ~40% of patients with SLE and requires prompt treatment with immunosuppressants (2). Although induction treatment with glucocorticoids combined with mycophenolate mofetil (MMF) or cyclophosphamide (CTX) may cause partial remission (PR) or complete remission (CR) in patients (3), renal recurrence during maintenance treatment, including glucocorticoids combined with MMF, *Tripterygium wilfordii*, leflunomide, tacrolimus or azathioprine, remains very common and is observed in up to 30% of patients with LN (4). Renal recurrence causes an increase in urinary protein and serum creatinine levels, the development of active urinary sediments or a decrease in the glomerular filtration rate, as well as other complications (5). A large proportion of patients with LN that experience renal recurrence may achieve remission again following prompt treatment; thus, the early identification and prevention of renal recurrence is essential (6). To the best of our knowledge, a reliable and useful clinical predictor or marker of renal recurrence has not yet been identified (7). Therefore, the aim of the present study was to analyze the baseline clinical data of patients with LN type IV to identify any clinical indices that may be used to predict renal recurrence.

Patients and methods

Patients. A total of 244 patients were enrolled in the present study between May 1998 and May 2013, providing they met the following conditions: Diagnosis of SLE and further diagnosis of LN type IV by renal biopsy in the Second Hospital Affiliated to Lanzhou University (Gansu, China), with complete clinical, pathological and laboratory test records and the achievement of clinical remission following induction therapy. Patients with or without renal recurrence were included in the current study. Baseline clinical features, laboratory indexes, pathological results and treatment situations were compared between patients with LN type IV with or without renal recurrence.

Pathological classification of renal biopsy. LN glomerular pathological classification was based on the International Society of Nephrology/Renal Pathology Society 2003 classification system (8). LN type IV was diagnosed when the affected glomerular area was >50%. LN Type IV with diffuse lesions was identified by observation under a light

Correspondence to: Professor Jing Wang, Department of Nephropathy, Lanzhou University Second Hospital, 82 Linxia Road, Chengguan, Lanzhou, Gansu 730000, P.R. China
E-mail: jingwang_doc16@163.com

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microscope revealing fuchsinophilic protein deposition or rete pegs occurring on the lateral side of the glomerular basement membrane; immunofluorescence revealing fine granular deposits of immunoglobulin and complement along the glomerular basement membrane or electron microscopy revealing that electron dense or rete pegs forming on the lateral side of the basement membrane, and was classified as LN type IV + V. Scoring of the renal active index and chronic index was based on a method outlined in a previous study (9). Atherosclerosis was confirmed when arterial intima fibrous thickening and hyaline degeneration were observed under a light microscope; necrosis, thrombosis and inflammatory cell infiltration were not observed and there was no immunoglobulin (Ig) deposition observed via immunofluorescence. Non-inflammatory necrotic vasculopathy (NNV) was confirmed when vascular wall necrosis was observed using a light microscope, no inflammatory cell infiltration was observed on the vessel wall or in the surrounding area, and immunoglobulin and complement and fibrin-related antigen were observed on the vascular walls, as well as in the lumen via immunofluorescence. Immune complex deposition was determined when morphology was normal under light microscopy, there was no thrombus and necrosis and the vascular lumen had no stenosis, and vascular wall immune deposits were found to contain IgG, IgA, IgM and/or complement components via immunofluorescence. Vasculopathy-free was classified when the morphology of interstitial blood vessels was normal and no IgG, IgA, IgM and complement deposition were found on the blood vessel wall via immunofluorescence (10).

Clinical data. The following clinical and laboratory indicators were collected: Sex, age, SLE course, LN course, laboratory results and immunological indexes.

Treatments. All patients underwent immunosuppressant therapy, including prednisone (0.5-0.6 mg/kg for 4 weeks then tapered to a maintenance dose; Hubei Pharmaceutical Co., Ltd., Wuhan, China) combined with IV CTX (500-1,000 mg/m^2 body surface area monthly; Purdue Pharma, Stamford, CT, USA), MMF (1,500-2,000 mg daily. Roche Diagnostics, Basel, Switzerland) tacrolimus (FK; 0.05-0.1 mg/kg daily. Fujisawa Ireland Ltd., Kerry, Ireland). Maintenance treatment included the combination treatment of prednisone (5 mg, daily), *Tripterygium wilfordii* polyglycoside (60 mg daily; Jiangsu Taizhou Pharmaceutical Co., Ltd., Nanjing, China), leflunomide (20 mg daily; Suzhou Xinkai Pharmaceutical Co., Ltd., Suzhou, China), MMF (500-1,000 mg daily), FK (0.05 mg/kg daily) or azathioprine (50-10 mg daily).

Renal recurrence. Renal recurrence refers to the phenomenon when patients with LN that have achieved complete remission (CR) or partial remission (PR) for >3 months experience a rapid increase in serum creatinine levels or albuminuria (11). Renal recurrence includes nephritis recurrence and nephrotic recurrence. In the current study, nephritis recurrence was classified as an increase of ≥25% in serum creatinine levels with or without an increase in urinary protein. Nephrotic recurrence was classified when urinary protein increased ≥1 g following CR or when urinary protein increased by >2 times that of the previous level following PR (11). Patients were divided into 2 groups depending on whether they experienced renal recurrence or not. There were 100 patients with renal recurrence (83 females and 17 males; mean age, 30.86 years) and 144 patients without renal recurrence (125 female and 19 males; mean age, 29.74 years).

Curative effects. CR was achieved when urinary protein levels were ≤0.4 g/D and levels of serum albumin and serum creatinine were ≥35 g/l and ≤120 mmol/l, respectively. PR referred to a ≥50% decrease in levels of urinary protein and serum creatinine compared with base values and plasma albumin ≥30 g/l. Clinical remission referred to patients that achieved CR or PR. No remission referred to no improvement in urine test results or renal functions (an increase or decrease in serum creatinine that was <50% of the base value) (12).

Follow-up. Patients were followed-up once every 2-3 months. A follow-up with a ≥6 month duration was defined as a follow-up. A follow-up with a duration of <6 months was defined as withdrawal from the study.

Statistical analysis. All data were analyzed using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). Normally distributed measurement data were expressed as the mean ± standard deviation and non-normally distributed measurement data were expressed as the median (lower quartile-upper quartile). Count data were compared using the χ^2 test and measurement data were compared using Student's t test. The recurrence survival curve was estimated using the Kaplan Meier-method and survival curves between groups were compared using the Log-Rank test. Risk factors for recurrence were analyzed using univariate and multivariate analyses with the Cox proportional hazard model. P<0.05 was determined to indicate a statistically significant difference.

Results

Renal recurrence in patients with LN type IV. A total of 351 patients with LN type IV with complete clinical information and follow-ups were included in the current study. Among these patients, 100 patients (28.49%) relapsed and 144 patients (41.03%) did not relapse. The remaining patients either only received initial treatment (53; 15.10%) or did not respond to follow up (54; 15.38%).

The average follow-up duration of patients who relapsed was 49.50 months (range, 13-207 months). The average age of patients who relapsed was 30.86±9.74 years (range, 12-54 years). Among these patients, 83 (83%) were female and 17 (17%) were male. Mean SLE course was 19.50 months (range, 4.25-60 months), mean LN course was 9 months (range, 2-24 months) and average recurrence time was 31.15±26.74 months. The average follow-up duration of non-relapsed patients was 33 months (range, 13-220 months) and the average age of these patients was 29.74±9.68 years (range, 4-53 years). Among these patients, 125 (86.81%) were female and 19 (13.19%) were male. Mean SLE course was 23.50 months (range, 4-60 months) and the mean LN course was 7.50 months (range, 1-36 months). Differences in age, sex, SLE and LN courses between the two groups

Table I. Comparison of baseline clinical data between the two groups.

Factors	Groups		P-value
	Group with renal recurrence (n=100)	Group without renal recurrence (n=144)	
General information			
Sex, male/female (%)	17 (17)/83 (83)	19 (13.19)/125 (86.81)	0.41
Onset age (years old)	27.45±9.178	25.98±9.911	0.241
Age (years old)	30.86±9.744	29.74±9.678	0.377
Course of SLE (months)	19.5 (4.25-60)	23.50 (4-60)	0.772
Course of LN (months)	9.00 (2-24)	7.50 (1-36)	0.763
Manifestation of kidney and others			
Facial erythema (%)	51/99 (51.52)	70/144 (48.61)	0.656
Discoid erythema (%)	6/100 (6)	7/144 (4.86)	0.697
Fever (%)	51/100 (51)	58/144 (40.28)	0.098
Arthralgia (%)	72/100 (72)	69/144 (47.92)	0.001
Alopecia (%)	27/100 (27)	24/144 (16.67)	0.051
Spleen (%)	11/100 (11)	7/144 (4.86)	0.071
Intestine (%)	3/100 (3)	0/144 (0)	0.068
Hypertension (%)	44/100 (44)	69/143 (48.25)	0.513
Malignant hypertension (%)	7/100 (7)	9/143 (6.29)	0.827
Gross hematuria (%)	26/100 (26)	27/143 (18.88)	0.186
Massive proteinuria (%)	40/100 (40)	77/144 (53.47)	0.038[a]
Hypoproteinemia (%)	74/100 (74)	94/141 (66.67)	0.222
Abnormal renal function (%)	21/100 (21)	31/141 (21.99)	0.855
Laboratory examination			
Hb (g/dl)	9.01±2.14	9.56±2.19	0.053
PLT (/mm^3)	11.60 (8-16.6)	12.10 (8.7-17.6)	0.331
ALB (g/l)	25.59±6.83	26.60±7.47	0.284
GLO (g/l)	24.6 (13.4-54.8)	22.50 (10-45.1)	0.022[a]
CREA (mg/dl)	1 (0.42-8.12)	0.91 (0.26-4.90)	0.309
BUN (mg/dl)	14.94 (2.4-74)	14.28 (2.5-96.)	0.729
UA (μmol/l)	422 (350.25-521.50)	400.5 (333.75-504.50)	0.402
UPR (g/24 h)	3.09 (1.64-5.49)	3.64 (2.17-5.34)	0.207
Urine NAG	39.2 (28.85-58.68)	44.00 (24.40-65.10)	0.422
Urine C3	2 (0~43)	2.09 (0~32)	0.015[a]
Urine α_2m (μg/l)	2 (0~32)	3.44 (0~200)	0.004[a]
Autoantibody (%)			
RNP	37/97 (38.14)	25/133 (18.80)	0.001[a]
SSA	22/70 (31.43)	35/109 (32.11)	0.924
SSB	12/70 (17.14)	11/109 (10.09)	0.169
RF	3/59 (5.08)	10/114 (8.77)	0.570
ANCA	3/71 (4.23)	3/106 (2.83)	0.937
ANA	93/100 (93)	130/143 (90.91)	0.559

Data are presented as the median (lower-quartile-upper quartile). [a]P<0.05. SLE, systemic lupus erythematous; LN, lupus nephritis; Hb, hemoglobin; PLT, platelet count; ALB, albumin; GLO, globulin; CREA, creatinine; BUN, blood urea nitrogen; UA, uric acid; UPR, urine protein quantitation in 24 h; NAG, N-acetyl-β-D-glucosidase; α_2m, macroglobulin; C3, complement protein 3; RNP, ribonucleoprotein; SSA, Sjögren's syndrome type A; SSB, Sjögren's syndrome type B; RF, rheumatoid factor; ANCA, anti-neutrophil cytoplasmic antibody; ANA, anti-nuclear antibody.

were not significant (Table I). In the recurrence group the average recurrence time was 31.15±26.74 months. A total of 66 (66%) patients had nephrotic recurrence, 31 (31%) patients had nephritis recurrence, and average recurrence times were

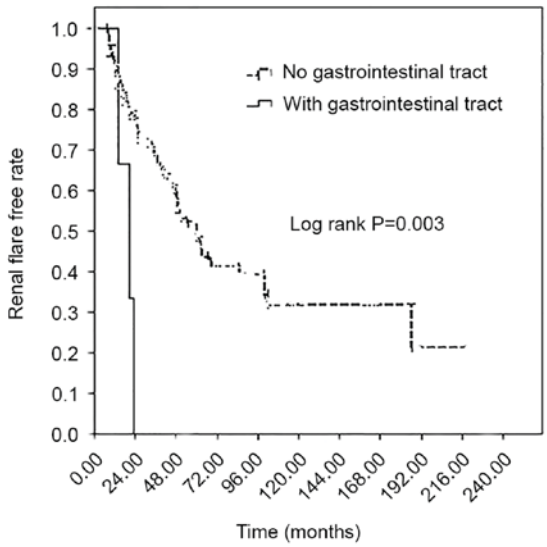

Figure 1. Kaplan-Meier method analysis for the effect of gastrointestinal tract syndrome on renal recurrence rate of patients with lupus nephritis.

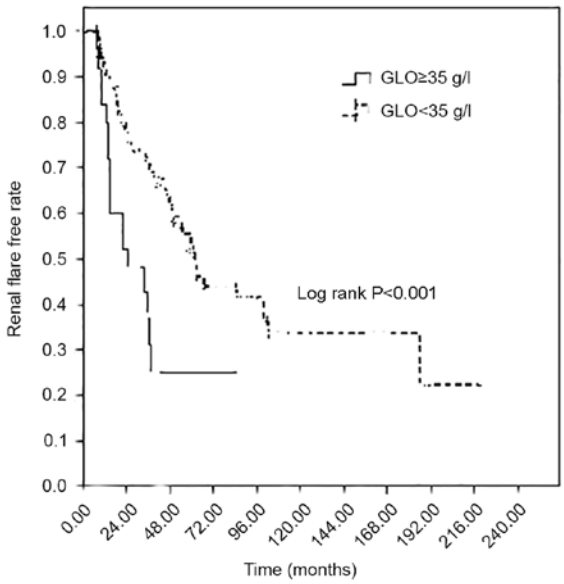

Figure 2. Kaplan-Meier method analysis for the effect of hyperglobulinemia on renal recurrence rate of patients with lupus nephritis. GLO, globulin.

26.67±20.17 and 38.22±35.46 months, respectively (P>0.05). A total of 3 (3%) patients exhibited extra-renal recurrence and average renal recurrence time was 56.67±30.14 months. Recurrence rates at months 12, 24, 36 and 60 were 8, 23, 31 and 48%, respectively. In the recurrence group, 31 patients (31%) had increased levels of creatinine, 9 (9%) developed end-stage renal failure (ESRF) and 5 (5%) succumbed. The survival rates of patients in the relapse group in years 1, 5 and 10 were 97, 92 and 70.9%, respectively; whereas the survival rates of patients that did not experience renal recurrence were 99, 95.2 and 80.4% in years 1, 5 and 10, respectively. The incidence of increased levels of creatinine, ESRF and mortality rates were significantly higher in patients with recurrence than in patients without recurrence.

Effects of renal and extra-renal manifestations at onset of renal recurrence. Patients with LN type IV with recurrence had significantly higher incidences of arthralgia compared with patients without recurrence and the incidence of proteinuria was significantly decreased in patients with LN type IV with recurrence compared with patients with LN type IV without recurrence (P<0.05; Table I). However, analysis by the Kaplan-Meier method indicated that arthralgia, alopecia and proteinuria had no influence on the recurrence rate (data not shown). Patients with LN type IV that affected the digestive tract also had higher renal recurrence rates (P=0.003; Fig. 1).

Effect of different laboratory tests at the onset on renal recurrence. Patients with LN type IV that experienced recurrence had significantly increased globulin levels compared with patients without recurrence; furthermore, levels of urinary C3 and macroglobulin were significantly decreased in relapsed patients compared with non-relapsed patients (all P<0.05, Table I). Further analysis by the Kaplan-Meier method demonstrated that the renal recurrence rate was higher in patients with high globulin levels (P<0.01; Fig. 2) however, levels of urinary C3 and α2m had no effect on recurrence rates (data not shown).

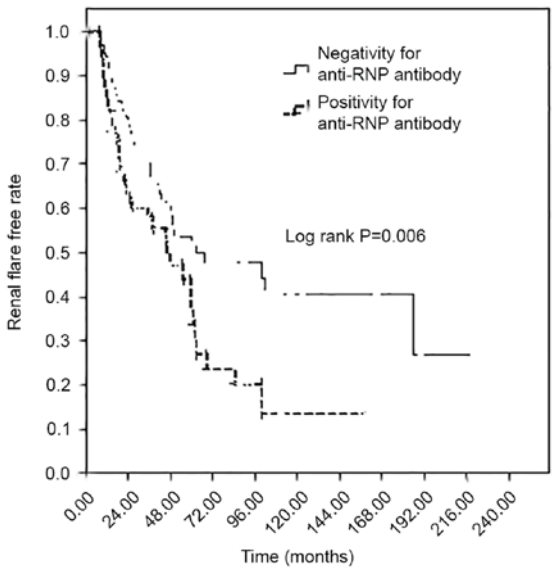

Figure 3. Kaplan-Meier method analysis for the effect of anti-RNP antibody on renal recurrence rate of patients with lupus nephritis. RNP, ribonecleoprotein.

Effect of different serum auto-antibody profiles at the onset on renal recurrence. Patients with LN type IV with recurrence had a significantly increased level of positive ribonucleoprotein (RNP) antibody compared with patients without recurrence (P=0.001; Table I). Further analysis by the Kaplan-Meier method demonstrated that patients with positive anti-RNP and anti-SSB antibodies had significantly increased recurrence rates (P=0.006; Fig. 3).

Effects of different renal histopathology at the onset on renal recurrence. Loop thrombus and NNV were significantly increased in patients with LN type IV with recurrence compared with patients without recurrence (both P<0.05; Table II). Further analysis by the Kaplan-Meier method

Table II. Pathological characteristics of renal tissue of patients with lupus nephritis type IV.

Factors	Groups		P-values
	Group with renal recurrence (n=100)	Group without renal recurrence (n=144)	
AI, %	8 (6-11)	8 (5-10)	0.436
CI, %	1 (0-3)	1 (0-2)	0.151
Ratio of global sclerosis, %	0 (0-7.1)	0 (0-7.56)	0.366
Ratio of segmental sclerosis, %	0 (0)	0 (0)	0.254
Loop necrosis (%)	41/100 (41)	58/141 (41.13)	0.983
Wire-loops (%)	29/100 (29)	37/140 (26.43)	0.660
Loop thrombus (%)	31/100 (31)	28/141 (19.86)	0.047[a]
Vasculopathy (%)	62/100 (62)	88/144 (61.11)	0.888
AS (%)	37/100 (37)	67/144 (46.53)	0.139
IM (%)	15/100 (15)	17/144 (11.81)	0.467
NNV (%)	10/100 (10)	4/144 (2.78)	0.017[a]

Data are presented as the median (lower quartile-upper quartile). [a]P<0.05. AI, active index; CI, chronic index; AS, atherosclerosis; IM, immune complex deposition; NNV, non-inflammatory necrotic vasculopathy.

Table III. Comparison of induction and maintenance treatment.

Factors	Group with renal recurrence (n=100)	Group without renal recurrence (n=144)	P-value
Induction treatment			
P+CTX (%)	44/100 (44.0)	60/144 (41.6)	0.845
P+MMF (%)	25/100 (25.0)	27/144 (18.4)	0.284
P (%)	24/100 (24.0)	39/144 (27.0)	0.679
P+FK (%)	5/100 (5.0)	13/144 (9.0)	0.385
MMF+FK (%)	2/100 (2)	5/144 (3.0)	0.405
Maintenance treatment			
P+TW (%)	63/82 (76.83)	83/114 (72.81)	0.524
P (%)	7/82 (8.54)	7/114 (6.14)	0.521
P+MMF (%)	5/82 (6.09)	7/114 (6.14)	0.990
P+LFMT (%)	3/82 (3.66)	8/114 (7.02)	0.488
P+AZA (%)	2/82 (2.44)	4/114 (3.51)	0.992
P+CSA (%)	1/82 (1.22)	1/114 (0.87)	0.896
P+FK (%)	1/82 (1.22)	4/114 (3.51)	0.587

P, prednisone; CTX, cyclophosphamide; MMF, mycophenolate mofetil; FK, tacrolimus; TW, *Tripterygium wilfordii* polyglycoside; LFMT, leflunomide; AZA, azathioprine; CSA, cyclosporin.

revealed that patients with thrombus in the loop or NNV had a significantly higher recurrence rate (P<0.05; data not shown).

Effect of different treatment schemes and curative efficacies on renal recurrence. The number of patients receiving each type of treatment in each group is displayed in Table III. The difference between the group with recurrence and the group without recurrence during the induction treatment and maintenance treatment periods was not significant, Analysis by the Kaplan-Meier method revealed that the difference in recurrence rate between patients receiving different induction period treatment schemes was not significant and patients who used glucocorticoids alone for maintenance treatment had a higher recurrence rate compared with patients who used other treatment schemes. However, the difference in the recurrence rate between patients using glucocorticoids combined with different immunosuppressants for maintenance treatment was not significant (P>0.05; data not shown).

Curative efficacies on renal recurrence. A total of 18 patients achieved CR in the group with renal recurrence, with an

Table IV. Rates and time of remission.

Factors	Group with renal recurrence (n=100)	Group without renal recurrence (n=144)	P-values
PR rate (%)	82 (82)	77 (51.39)	0.023[a]
CR rate (%)	18 (18)	67 (46.53)	0.001[a]
PR time	6 (4-8.75)	5 (2.5-7)	0.002[a]
CR time	7 (4-10.25)	10 (6-12)	0.318

All data are presented as n (%) or the median (range). [a]P<0.05. PR, partial remission; CR, complete remission.

average CR time of 7 months (range, 4-10.25 months) and 82 patients achieved PR with an average PR time of 6 months (range, 4-8.75 months). A total of 67 patients achieved CR in the group without renal recurrence with an average CR time of 10 months (range, 6-12 months) and 77 patients achieved PR, with an average PR time of 5 months (range, 2.5-7 months). PR durations were significantly longer in patients experiencing recurrence (P<0.01; Table IV). Analysis using the Kaplan-Meier method indicated that patients achieving PR had a higher recurrence rate than patients achieving CR (P=0.01; data not shown).

Cox regression analysis of risk factors for renal recurrence in patients with LN type IV. Univariate and multivariate Cox's regression analysis indicated that SLE affecting the gastrointestinal tract, increased levels of serum globulin and positive serum anti-SSB antibody from the onset were risk factors for renal recurrence in patients with LN type IV (Table V).

Discussion

The present study demonstrated that patients with LN type IV had a renal recurrence rate of ≤28.5% and the average recurrence time was 30 months. Following the induction period, 244 patients achieved remission; however 100 patients experienced renal recurrence during maintenance treatment, which is consistent with the results of a previous study (12). The current study also demonstrated that patients with LN type IV who achieved PR rather than CR were more likely to experience relapse, which was also demonstrated in a study by Illei *et al* (13).

It has previously been demonstrated that male patients with SLE and early renal damage and/or hypertension who received incorrect treatment with cytotoxic drugs and underwent a shorter induction treatment course were prone to renal recurrence during the disease course (14). Additionally, African Americans with LN type IV have a high risk of recurrence ≤1 year following remission (15). However, to the best of our knowledge, it remains unknown whether certain ethnicities are more likely to experience renal recurrence.

Age at onset may also affect renal recurrence. A study conducted in South Korea demonstrated that patients with LN type IV aged <28 years old were more likely to experience renal recurrence (16). However, the results of the present study did not identify an association between age and renal recurrence in patients with LN type IV. Furthermore, baseline clinical manifestations and associated laboratory indicators in patients with or without renal recurrence were compared and it was demonstrated that hypertension, renal impairment, hemuresis, extra renal damage to the blood system and skin damage at onset had no effect on the incidence of renal recurrence. However, patients with LN type IV that affected the gastrointestinal tract had higher renal recurrence rates during the course of the disease. Varying degrees of anorexia, nausea, vomiting and other gastrointestinal symptoms are present in ~50% of patients with SLE. In addition to the direct effects of SLE, the aforementioned manifestations are often associated with the toxic side effects of drugs (17). The results of the present study differ to those of previous studies (17), as no differences in renal recurrence were observed between patients with or without gastrointestinal syndrome. Therefore, it remains controversial whether gastrointestinal symptoms indicate the presence of renal recurrence in the course of LN type IV for patients at onset or in stable conditions following remission and further studies are required to determine this. The present study demonstrated that differences in laboratory indices, including proteinuria, serum creatinine and plasma albumin did not influence the likelihood of renal recurrence. However, patients with LN type IV experiencing recurrence had higher globulin levels compared with patients without recurrence and patients with high globulin levels had increased renal recurrence rates. Therefore, increased levels of serum globulin may be a risk factor for renal recurrence in patients with LN type IV. Furthermore, the present study demonstrated that patients with LN type IV with NNV or thrombus in the loop were prone to experiencing renal recurrence. Thus, increased clinical attention should be given to patients with this form of the disease.

The presence of positive anti-nucleosome antibody or a significant increase in levels of anti-double stranded-DNA (anti-ds-DNA) antibody may be used to predict recurrence (18). It has been demonstrated that anti-ds-DNA antibody titer significantly increases 8-10 weeks prior to recurrence (18). Normal serum complement levels and low anti-ds-DNA antibody titer in patients with SLE at onset indicates a reduction in the risk of recurrence (19). Coremans *et al* (20) identified that a titer of anti-C1q antibody may predict the recurrence of LN and that this value may be superior to anti-ds-DNA antibody. However, the results of the present study did not identify any effect of the differences in the aforementioned antibody levels on renal recurrence in patients with LN type IV. This may be explained by the number and ethnicity of the patients in the current study, as well as the method of antibody detection. The current study demonstrated that patients with LN type IV and recurrence had higher levels of positive RNP antibody compared with patients without recurrence and patients with positive anti-RNP and anti-SSB antibodies experienced increased recurrence rates. The anti-RNP antibody is associated with Raynaud's phenomenon and pulmonary arterial hypertension, which are risk factors for mixed connective tissue disease (MCTD) and may also indicate vasculopathy (21). Furthermore, anti-RNP antibodies serve a role in inherent and adaptive immune responses and indicate

Table V. Cox regression analysis of risk factors for renal recurrence in patients with lupus nephritis type IV.

	Univariate analysis		Multivariate analysis	
Factors	RR (95% CI)	P-values	RR (95% CI)	P-values
Arthralgia	0.519 (0.335-0.804)	0.003[a]	0.689 (0.232-1.253)	0.198
Globulin	1.049 (1.021-1.077)	0.001[a]	1.038 (1.004-1.073)	0.028[a]
Anti-SSB antibody	0.353 (0.186-0.671)	0.001[a]	0.386 (0.191-0.778)	0.008[a]
Gastrointestinal tract	0.202 (0.063-0.648)	0.007[a]	0.192 (0.058-0.640)	0.007[a]

[a]P<0.05. RR, renal recurrence; CI, confidence intervals.

the possible pathogenesis of MCTD (21). Anti-RNP antibodies are also associated with kidney damage (22) however their role in LN type IV and whether they are able to predict renal recurrence remains unknown. Anti-SSA antibodies are closely associated with anti-SSB antibodies, which are associated with blood system disorders, proteinuria, rash and pericarditis in SLE (23). Further studies are required to determine whether the occurrence of anti-SSB antibodies at the onset of the disease in patients with LN type IV influences the outcome of renal recurrence.

The effect of the combination treatment of glucocorticoids with routine immunodepressants on the recurrence of LN remains controversial. It has been identified that patients undergoing combination treatment of glucocorticoids with acetazolamide have a higher recurrence rate compared with patients receiving glucocorticoids combined with CTX as an induction therapy (24). Chan *et al* (25) demonstrated that the recurrence rates in patients with proliferative LN did not differ significantly between patients using glucocorticoids with MMF for induction and maintenance treatment, and those using glucocorticoids and CTX for induction treatment and AZA for maintenance treatment over a 5-year follow-up period. Dooley *et al* (26) demonstrated that, after 6 months induction therapy with combination treatment of glucocorticoids and MMF or CTX, patients who used glucocorticoids with MMF for maintenance treatment had a significantly lower recurrence rate compared with patients who used glucocorticoids with AZA. Yap *et al* (27) demonstrated that following MMF induction treatment, patients receiving AZA for maintenance treatment had an increased renal recurrence rate. In addition, a recent study based on Chinese populations with LN indicated that if AZA replaced MMF during the first 24 months of induction treatment, the risk of renal recurrence increased (28).

The use of antimalarial drugs may also reduce recurrence rates, including the renal recurrence rate (29). Subsequently, the American College of Rheumatology and European League Against Rheumatism guidelines recommend that unless there are contraindications, all patients with LN should be treated with antimalarial drugs (30). However, it remains unclear whether the use of hydroxychloroquine in the Asian population reduces recurrence and only a small number of related studies have been conducted (30). To determine whether prolonged maintenance treatment reduces renal recurrence rate, one study demonstrated that the use of CTX for maintenance treatment extended to 30 months may lower the renal recurrence rate (31). Patients with LN undergoing treatment MMF for <24 months were more prone to renal recurrence compared with patients with LN who received MMF for induction therapy and continued to use MMF for a longer duration (31). However, a longer period of maintenance treatment may result in an increased risk of side effects caused by the accumulation of drugs (32). The present study demonstrated that among routine induction treatment schemes using glucocorticoids with various immunosuppressants, the difference in renal recurrence was not significant. However, the renal recurrence rate in patients who used glucocorticoids alone for maintenance treatment was higher than in patients who used glucocorticoids with immunosuppressants. At present, it remains controversial whether the use of glucocorticoids combined with immunosuppressant therapy decreases the risk of renal recurrence. Thus, routine immunosuppressant therapy has limited effects in reducing renal recurrence. Individual target therapies for the pathogenesis of LN, such as treatment with rituximab, may reduce renal recurrence rates in the future (33).

There were certain limitations of the current study. The participants consisted solely of patients with LN type IV and the clinical predictors analyzed included baseline clinical, pathological and laboratory results and treatment situations only. The association between changes in the aforementioned indicators during follow-up and the time of renal recurrence was not included in this analysis. Furthermore, these data came only from a single-center analysis and thus require further validation.

In conclusion, the current study comprehensively evaluated a series of clinical indicators of LN type IV, including clinical manifestations and laboratory indices, histopathological changes and the combination treatment of glucocorticoids with immunosuppressants. It was demonstrated that the number of clinical indicators that may be used to predict renal recurrence in patients with LN remains limited. Therefore, further investigations into novel biomarkers for the early prediction of LN renal recurrence are required.

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