Frequency of Class III and IV Nephritis in Systemic Lupus Erythematosus Without Clinical Renal Involvement: An Analysis of Predictive Measures

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ABSTRACT. ***Objective.*** To determine the frequency of International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III or IV lupus nephritis in patients with systemic lupus erythematosus (SLE) without clinical renal involvement.

Methods. We investigated the renal pathology of 195 patients with SLE, including 86 patients without clinical renal involvement.

Results. Lupus nephritis other than class I was found in 58% of the patients without clinical renal involvement, and class III and IV nephritis was found in 15% of these patients. To reveal the predictive measures involved in class III or IV lupus nephritis, we explored the clinical measures in patients with SLE who did not have clinical renal involvement. Anti-dsDNA antibody titers were significantly higher ($p = 0.0266$) and C3 values were significantly lower ($p = 0.0073$) in patients with class III or IV lupus nephritis than in patients without class III or IV lupus nephritis. The sensitivity and specificity values were 77% and 73%, respectively, for cutoff levels of both 40 IU/ml for anti-dsDNA antibodies and 55 mg/dl for C3 (OR 8.8, $p = 0.0011$).

Conclusion. The frequency of nephritis, including ISN/RPS class III and IV, was unexpectedly high in SLE patients without clinical renal involvement. ISN/RPS class III or IV lupus nephritis could be hidden in patients with SLE who present both a high titer of anti-dsDNA antibody and a low concentration of C3, even when they have clinically normal urinary findings and renal function. (First Release Nov 15 2011; J Rheumatol 2012;39:79–85; doi:10.3899/jrheum.110532)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
COMPLEMENT
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Systemic lupus erythematosus (SLE) is an autoimmune disease with multiple organ manifestations, including skin lesions, arthritis, serositis, nephritis, and neuropsychiatric and hematological disorders. In the 1950s, the 5-year survival rate in patients with SLE who had World Health Organization (WHO) class IV nephritis was 17%; more recently, however, therapy with corticosteroids and immunosuppressive agents (IA) has improved the prognosis of patients with SLE. The 5-year survival rate increased to 82% in the 1990s[1]. However, WHO class IV lupus nephritis is one of the most common manifestations that contribute to endstage renal failure (ESRF). The frequency of ESRF was 40.9% in patients with WHO class IV nephritis, higher than the 2.6% frequency in those with non-class IV lupus nephritis[2]. In general, combination therapy with corticosteroids and IA, such as cyclophosphamide and mycophenolate mofetil, should be recommended in active lupus nephritis with International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III or IV. The early diagnosis and treatment of ISN/RPS class III or IV lupus nephritis is important to improve renal and overall survival in patients with SLE.

The renal manifestations of SLE range from asymptomatic urinary findings, such as microhematuria and proteinuria, to nephrotic syndrome or progressive renal impairment[3]; these manifestations are observed in 31% to 65% of patients with SLE[4]. Although renal biopsy is the "gold standard" for diagnosing and classifying lupus nephritis, it is invasive and has potential complications. Renal biopsy is not always performed on patients with SLE because some of them have normal renal findings or severe manifestations, such as thrombocytopenia, infections, or neuropsychiatric involvement. Thus, it would be beneficial if noninvasive examination could predict the development and severity of lupus nephritis when renal biopsy cannot be performed. Some markers, such as ß-1 integrin in peripheral blood T cells, urinary chemokine, and growth fac-

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tor, have been reported to predict active lupus nephritis, such as ISN/RPS class IV[5,6], although these markers are not available in clinical practice. Clinical measures such as urine sediment, proteinuria, serum complements, and anti-dsDNA antibody are considered conventional and useful predictors for the disease activity of lupus nephritis[7,8,9]. However, some patients show renal histological changes despite normal urinary findings and renal function. This condition is called silent lupus nephritis (SLN)[10,11]. Although most patients with SLN show mild lupus nephritis (i.e., ISN/RPS class II), it is believed that ISN/RPS class III or IV lupus nephritis is rare in patients with SLN[10,11]. There is a notable difference between the therapeutic strategies used for patients with SLE with or without ISN/RPS class III or IV lupus nephritis. However, the characteristics and predictive factors of ISN/RPS class III or IV lupus nephritis have not been revealed in the literature because previous studies have described only a small number of patients with SLN.

We investigated the frequency and predictive factors of ISN/RPS class III or IV lupus nephritis in SLE patients without clinical renal involvement. We analyzed the association between pathohistological renal changes and conventional clinical measures among 195 patients with SLE. We also compared patients with ISN/RPS class III or IV lupus nephritis with those with other ISN/RPS classes (I, II, or V) of lupus nephritis in patients with SLE who did not have clinical renal involvement.

MATERIALS AND METHODS

Patients. We studied 467 consecutive patients who were hospitalized at our institution between 1994 and 2005. These patients were diagnosed with SLE based on the American College of Rheumatology classification criteria[12]. Of 467 patients, 296 (63%) had a renal biopsy (276 women, 20 men). To clarify precisely the degree of pathohistological renal involvement and disease activity in SLE, renal biopsy was performed in both patients with and those without clinical renal involvement. Written informed consent was obtained from each patient. Renal biopsies could not be performed in 171 of 467 patients who did not consent to a renal biopsy or who had a poor condition for examination. The renal biopsies of 31 patients could not be confirmed based on their clinical records; these patients were excluded. We also excluded 57 patients whose renal specimens contained fewer than 10 glomeruli because they were not diagnosed accurately[13]. Other patients excluded were 1 patient with diabetic nephropathy, 1 with IgA nephropathy, 6 with antiphospholipid antibody-related microangiopathy, and 5 with interstitial nephritis. Ultimately, 195 patients were enrolled. In addition, 7 patients were counted twice because re-biopsies were performed among 195 patients. All patients were Japanese except 3, including 2 non-Japanese Asians and 1 African Canadian. The ethics committee of our institution, in accord with the Declaration of Helsinki, approved our study.

Evaluation of clinical measures. Urinary tests, including proteinuria and hematuria on a dipstick, urinary sediment and quantitative proteinuria measured by 24-h urine, serum creatinine, complement hemolytic activity (CH50), complement components (C3 and C4), and anti-dsDNA antibody, were evaluated upon admission before renal biopsy. CH50, C3, and C4 were measured by the standard method. Anti-dsDNA antibody was detected by radioimmunoassay (normal value < 6 IU/ml). The estimated glomerular filtration rate (eGFR) was calculated according to the described method using variables that included serum creatinine, age, and sex[14].

Evaluation of renal pathohistology. Renal pathohistology was classified according to the 2003 ISN/RPS classification[13]. Biopsy results obtained prior to 2003 were reviewed and reclassified according to the 2003 ISN/RPS classification. Immunohistological pathology was tested by direct immunofluorescence and/or the enzyme-labeled antibody method (streptavidin-biotin). Positive results for glomerular immune deposits were defined as (1+) or more. Cases with minor glomerular abnormalities observed by light microscopy and no evidence of immune deposits were classified as "Nil" because they could not be classified as lupus nephritis according to the 2003 ISN/RPS classification[13,15].

Definition of clinical renal involvement. Clinical renal involvement was indicated for patients when 1 or more of the following criteria were satisfied: (1) proteinuria > 400 mg per day; (2) presence of active urinary sediments (> 5 red blood cells and/or 5 white blood cells per high power field and/or cellular cast); or (3) eGFR < 67 ml/min per 1.73 m^2. We determined these cutoff levels using a receiver-operating characteristic curve to predict class III or IV among our 195 patients with SLE. Our definitions were similar to those described in other reports[10,15].

Statistical analysis. Statistical analyses was performed using the chi-square test to compare frequencies, the t test to compare mean values, and the Mann-Whitney U test to compare median values. The data were analyzed using JMP software (SAS Institute, Cary, NC, USA). P values < 0.05 indicated statistical significance.

RESULTS

Clinical features of 195 patients with SLE. The laboratory and pathohistological features of 195 patients with SLE enrolled in our study are summarized in Tables 1 and 2. The 195 patients enrolled included 109 patients with clinical renal involvement (overt subset) and 86 patients without clinical renal involvement (silent subset). Fifteen patients (8%) had no evidence of lupus nephritis as determined by light microscopy and immunofluorescence (Nil). The remaining 180 patients were classified based on the 2003 ISN/RPS classification. As shown in Table 2, the frequencies of ISN/RPS class I-V lupus nephritis were 28 (14%), 44 (23%), 36 (19%), 47 (24%), and 25 (13%), respectively. There were no patients with class VI lupus nephritis. Of the 180 patients excluded as Nil, immunohistological findings could be assessed in 169 patients. The positive frequencies of glomerular immune deposits with IgG, IgM, IgA, C3, and C1q were 131 (77.5%), 137 (81.1%), 122 (72.2%), 144 (85.2%), and 144 (85.2%), respectively.

Comparison of clinical features and ISN/RPS classification between patients with and without clinical renal involvement. As shown in Table 1, we compared the overt subset with the silent subset. The disease duration after SLE diagnosis was significantly shorter (p = 0.008) in the silent subset than in the overt subset. No significant differences were found in the frequency of treatment with and dosage of prednisolone (PSL) between the 2 subsets, although the frequency of treatment with IA was higher in the overt subset. Cyclophosphamide was administered by intravenous pulse therapy in only 2 patients of the overt subset. The remaining 3 patients were given a daily dose of cyclophosphamide orally. As expected, proteinuria was significantly increased (p < 0.0001) and serum creatinine was significantly higher (p < 0.0001) in the overt subset than in the silent subset. Although there was no significant difference between the 2 subsets in terms of anti-dsDNA antibody titer and C4, a slight difference was

Table 1. Clinical characteristics of 195 patients with SLE and comparison between patients with and without clinical renal involvement. Except for the percentages, data represent the median value and range.

Characteristics	Total, n = 195	Overt Subset, n = 109	Silent Subset, n = 86	p
Age at renal biopsy, yrs	31 (11–69)	32 (15–68)	29 (11–69)	0.10
Women, n (%)	181 (93)	100 (92)	81 (94)	0.59
Disease duration, yrs	0 (0–23)	1 (0–23)	0 (0–19)	0.008
Patients received PSL, n (%)	118 (61)	69 (63)	49 (57)	0.37
Dosage of PSL, mg/day	9 (0–80)	10 (0–80)	5 (0–60)	0.29
Patients who received IA, n (%)	20 (10)	16 (15)	4 (5)	0.03
Azathioprine, n	4	4	0	
Mizoribine, n	11	8	3	
Cyclophosphamide, n	5	4	1	
Proteinuria, mg/day	398 (0–29000)	886 (0–29000)	0 (0–350)	< 0.0001
Presence of active urinary sediments, n (%)	67 (61)	67 (61)	0 (0)	< 0.0001
Serum creatinine, mg/dl	0.7 (0.3–4.0)	0.8 (0.4–4.0)	0.6 (0.3–1.0)	< 0.0001
eGFR, ml/min/1.73 m^2	82 (12–206)	70 (12–151)	91 (68–206)	< 0.0001
Anti-dsDNA, IU/ml	41 (0–9635)	39 (0–9635)	44 (0–2180)	0.74
Anti-Sm positivity, n (%)	27 (14)	16 (15)	11 (13)	0.70
CH50, U/ml	22.6 (0–50.7)	20.9 (0–50.7)	24.5 (0–49.8)	0.049
C3, mg/dl	52 (10–150)	46 (10–150)	56 (21–129)	0.037
C4, mg/dl	11 (1–52)	11 (1–52)	11 (1–40)	0.81

P values were estimated to allow comparisons between patients with and without clinical renal involvement; SLE: systemic lupus erythematosus; overt subset: patients with clinical renal involvement; silent subset: patients without clinical renal involvement; PSL: prednisolone; IA: immunosuppressive agents; eGFR: estimated glomerular filtration rate.

Table 2. ISN/RPS classification of 195 patients with SLE and comparison between patients with and without clinical renal involvement. Data are number (%) unless otherwise indicated.

	Total, n = 195	Overt Subset, n = 109	Silent Subset, n = 86	p
ISN/RPS classification				
Nil	15 (8)	4 (4)	11 (13)	
Class I	28 (14)	3 (3)	25 (29)	
Class II	44 (23)	16 (15)	28 (33)	
Class III	36 (19)	28 (26)	8 (9)	
III, n	23	16	7	
III + V, n	13	12	1	
Class IV	47 (24)	42 (39)	5 (6)	
IV, n	34	31	3	
IV + V, n	13	11	2	
Class V	25 (13)	16 (15)	9 (10)	
Class VI	0 (0)	0 (0)	0 (0)	
Immune deposits	n = 169	n = 103	n = 66	
IgG	131 (78)	88 (85)	43 (65)	0.002
IgM	137 (81)	88 (85)	49 (74)	0.07
IgA	122 (72)	84 (82)	38 (58)	0.0007
C3	144 (85)	88 (85)	46 (70)	0.014
C1q	144 (85)	92 (89)	52 (79)	0.06

P values were estimated by the chi-square test to allow comparisons between patients with and without renal involvement. ISN/RPS: International Society of Nephrology/Renal Pathology Society; SLE: systemic lupus erythematosus; overt subset: patients with clinical renal involvement; silent subset: patients without clinical renal involvement.

found in CH50 and C3 values (p = 0.0499 and 0.0365). As shown in Table 2, nephritis other than ISN/RPS class I was found in 58% of the silent subset. ISN/RPS class III and IV lupus nephritis was found in 15% of the silent subset, although the frequency of these classes was significantly higher (p < 0.0001) in the overt subset than in the silent subset. The positive frequencies of glomerular immune deposits with IgG and IgA were higher in the overt subset than in the silent subset, although no significant difference was found in the positive frequencies of glomerular immune deposits with IgM and C1q between the 2 subsets.

In 7 patients, renal biopsy was performed twice because of the deterioration of proteinuria. Among 3 patients of the overt subset, ISN/RPS class was not transformed in 2 patients with ISN/RPS class V, although the ISN/RPS class was transformed from class II to class III in 1 patient. In contrast, among 4 patients of the silent subset, ISN/RPS class was transformed from class II to class V in 2 patients. ISN/RPS class was not transformed in the remaining 1 patient with class IV and another one with class V. Clinical renal involvement became overt in all 4 patients of the silent subset after the first renal biopsy.

Comparison of active and chronic lesions in ISN/RPS class III or IV between patients with and without clinical renal involvement. We assessed active lesions and chronic lesions in 83 patients with ISN/RPS class III or IV lupus nephritis (Table 3). Although the frequency of endocapillary proliferation and wire-loops lesion were common occurrences in both subsets, the frequency of cellular/fibrocellular crescents was significantly higher (p = 0.003) in the overt subset than in the silent subset. In addition, the rupture of glomerular basement membrane (GBM) occurred more frequently in the overt subset,

Table 3. Comparison of active and chronic lesions in ISN/RPS class III and class IV between patients with and without clinical renal involvement.

Lesion Type	Overt Subset, n = 70	Silent Subset, n = 13	p
Active lesions, n (%)			
Endocapillary proliferation	66 (94)	11 (85)	0.24
Wire loops	19 (27)	6 (46)	0.17
Cellular/fibrocellular crescents	29 (41)	0 (0)	0.003
Fibrinoid necrosis	5 (7)	1 (8)	1
Rupture of GBM	9 (13)	0 (0)	0.34
Karyorrhexis	6 (9)	2 (15)	0.60
Chronic lesions, n (%)			
Global sclerosis	30 (43)	4 (30)	0.54
Fibrous crescents/adhesions	13 (19)	1 (8)	0.44

ISN/RPS: International Society of Nephrology/Renal Pathology Society; overt subset: patients with clinical renal involvement; silent subset: patients without clinical renal involvement; GBM: glomerular basement membrane.

although there was no statistically significant difference between the 2 subsets. On the other hand, chronic lesions, such as those due to global sclerosis, were observed more frequently than expected in the silent subset as well.

Comparison of clinical features between patients with and without ISN/RPS class III or IV lupus nephritis among SLE cases with clinical renal involvement. In the 109 patients of the overt subset, the clinical features of ISN/RPS class III or IV lupus nephritis subgroup were compared with those of others (Nil, class I, II, or V; Table 4). There was no significant difference between the 2 subsets in the disease duration after SLE diagnosis. The frequency of treatment with PSL was higher in patients with ISN/RPS class III or IV lupus nephritis than in patients without ISN/RPS class III or IV lupus nephritis, although no difference was found in the frequency of treatment with IA between the 2 subsets. Renal function was significantly worse in patients with ISN/RPS class III or IV. Complement values were lower in patients with ISN/RPS class III or IV, although there was no statistically significant difference between the 2 subsets. The anti-dsDNA antibody titer was significantly higher (p = 0.0012) in patients with ISN/RPS class III or IV.

Comparison of clinical features between patients with and without ISN/RPS class III or IV lupus nephritis among SLE cases without clinical renal involvement. We analyzed the 86 patients of the silent subset in the manner described above; the results are shown in Table 5. The disease duration was significantly longer (p = 0.0184) in patients with ISN/RPS class III or IV than in those with other classes (Nil, class I, II, or V). The frequency of treatment with PSL or IA was statistically identical between the 2 subsets. Although there was no significant difference in renal function, the anti-dsDNA antibody titer was significantly higher (p = 0.0266) and the C3 value was significantly lower (p = 0.0073) in patients in ISN/RPS class III or IV than in those in other classes.

Among the silent subset, 13 patients with ISN/RPS class III or IV were followed for a median of 30 months (range 14–178 mo). Although only 2 patients in ISN/RPS class III experienced exacerbated nephritis accompanying malignancy or pregnancy, the remaining 11 patients had no exacerbation of nephritis and good prognosis with PSL therapy alone, including both induction and maintenance therapy.

Predictors for ISN/RPS class III or IV lupus nephritis in patients with or without clinical renal involvement. To predict

Table 4. Comparison of clinical characteristics between ISN/RPS class III or IV and others (Nil, class I, II, V) among patients with clinical renal involvement. Except for the percentages, data represent the median value and range.

Characteristics	Class II, IV	Nil, Class I, II, V	p
Enrolled patients, n	70	39	—
Age at renal biopsy, yrs	34 (15–64)	31 (17–68)	0.44
Women, n (%)	64 (91)	36 (92)	0.87
Disease duration, yrs	2 (0–23)	1 (0–14)	0.20
Patients who received PSL, n (%)	55 (79)	14 (36)	< 0.0001
Dosage of PSL, mg/day	10 (0–80)	10 (0–70)	0.52
Patients who received IA, n (%)	11 (16)	5 (13)	0.68
Proteinuria, mg/day	1464 (0–2900)	689 (0–7995)	0.001
Presence of active urinary sediments, n (%)	47 (67)	20 (51)	0.15
Serum creatinine, mg/dl	0.9 (0.4–4.0)	0.7 (0.5–1.3)	0.002
eGFR, ml/min/1.73 m^2	61 (12–151)	85 (35–136)	0.002
Anti-dsDNA, IU/ml	67 (0–9635)	17 (0–354)	0.001
Anti-SM positivity, n (%)	9 (13)	7 (18)	0.47
CH50, U/ml	15.8 (0–50.7)	25.3 (0–46.3)	0.091
C3, mg/dl	44 (10–136)	54 (19–150)	0.08
C4, mg/dl	9 (1–52)	13 (2–31)	0.32

P values were estimated to allow comparisons between ISN/RPS class III or IV and others. ISN/RPS: International Society of Nephrology/Renal Pathology Society; PSL: prednisolone; IA: immunosuppressive agents; eGFR: estimated glomerular filtration rate.

Table 5. Comparison of clinical features between ISN/RPS class III or IV and others (Nil, class I, II, V) among patients without clinical renal involvement. Except for percentages, data represent the median value and range.

Characteristics	Class III, IV	Nil, Class I, II, V	p
Enrolled patients, n	13	73	—
Age at renal biopsy, yrs	27 (22–56)	29 (11–69)	0.80
Women, n (%)	13 (100)	68 (93)	1
Disease duration, yrs	5 (0–9)	0 (0–19)	0.018
Patients received PSL, n (%)	9 (69)	40 (55)	0.38
Dosage of PSL, mg/day	10 (0–30)	5 (0–60)	0.35
Patients who received IA, n (%)	1 (8)	3 (4)	0.49
Proteinuria, mg/day	108 (0–300)	0 (0–350)	0.45
Serum creatinine, mg/dl	0.7 (0.5–0.8)	0.6 (0.3–1.0)	0.54
eGFR, ml/min/1.73 m^2	83 (73–133)	91 (68–206)	0.34
Anti-dsDNA, IU/ml	97 (4–2180)	35 (0–1280)	0.03
Anti-Sm positivity, n (%)	2 (15)	9 (12)	0.76
CH50, U/ml	14.5 (0–46.6)	25.5 (0–49.8)	0.02
C3, mg/dl	40 (22–99)	59 (21–129)	0.007
C4, mg/dl	10 (2–19)	13 (1–40)	0.08

P values were estimated to allow comparisons between ISN/RPS class III or IV and others. ISN/RPS: International Society of Nephrology/Renal Pathology Society; PSL: prednisolone; IA: immunosuppressive agents; eGFR: estimated glomerular filtration rate.

the development of ISN/RPS class III or IV lupus nephritis, a cutoff level for the clinical measures was estimated by calculating the receiver-operating characteristic curve. Sensitivities, specificities, positive predictive value (PPV), and negative predictive value (NPV) are shown in Table 6. In the patients of the overt subset, sensitivities and specificities were 61% and 74%, for a cutoff level of 1120 mg/day for proteinuria (OR 4.6, p = 0.0003); 56% and 80%, for a cutoff level of 63.8 ml/min/1.73 m^2 for eGFR (OR 4.9, p = 0.0004); and 47% and 87%, for a cutoff level of 75 IU/ml for the anti-dsDNA antibody (OR 6.1, p = 0.0003), respectively. PPV and NPV were about 80% and 50%, respectively, for each clinical measure within the patients of the overt subset. In contrast, in the patients of the silent subset, the sensitivities and specificities were 85% and 53%, for a cutoff level of 40 IU/ml for anti-dsDNA antibody (OR 6.3, p = 0.015); 85% and 58%, for a cutoff level of 55 mg/dl for C3 (OR 7.5, p = 0.0063); and 77% and 73%, for cutoff levels of both 40 IU/ml for anti-dsDNA antibodies and 55 mg/dl for C3 (OR 8.8, p = 0.0011). PPV and NPV were about 20%–30% and 95%, respectively, for each clinical measure among the patients of the silent subset.

DISCUSSION

We have demonstrated for the first time, to our knowledge, the frequency and predictive factors for ISN/RPS class III or IV lupus nephritis in patients with SLE without clinical renal involvement. Numerous studies have indicated that proteinuria (> 0.5 g daily) might be indispensable for active nephritis confirmed by renal biopsy. However, our data reveal that 15% of patients without clinical renal involvement showed ISN/RPS class III or IV lupus nephritis pathohistologically — a surprisingly high percentage. In the patients without clinical renal involvement, the factors predicting ISN/RPS class III or IV lupus nephritis may include long disease duration, high anti-dsDNA antibody titer, and low concentration of C3. These results suggest that the duration and intensity of immune complex-associated inflammation could contribute to the development of ISN/RPS class III or IV lupus nephritis.

It has been reported that the majority of patients with SLE had immune deposits in their kidneys, which were revealed by immunofluorescence or electron microscopy[11,16,17]. Additionally, our study showed that the disease duration was longer and the frequency of class III or IV was higher in patients with clinical renal involvement than in those without clinical renal involvement. These results indicate that disease duration is important in the development and severity of lupus nephritis. Renal disease develops within the first 3 years following the SLE diagnosis[18,19]. In our study, the renal pathohistological findings were normal in some patients, although some had elevated anti-dsDNA antibodies (up to 270 IU/ml) or decreased complement components (C3 down to 42 mg/dl). In these patients, the disease duration was short (< 1 year). These results may reflect the existence of an early phase of SLE before clinically apparent renal disease is detectable. In contrast, our study showed that the median of disease duration was 5 years in ISN/RPS class III or IV lupus nephritis without clinical renal involvement. The disease duration was signifi-

Table 6. Predictors for ISN/RPS class III or IV lupus nephritis.

Patient Group	Sensitivity, %	Specificity, %	PPV, %	NPV, %	OR (95% CI)	p
Patients of the overt subset, n = 109						
Proteinuria, ≥ 1120 mg/day	61	74	81	52	4.6 (1.9–11.0)	0.0003
eGFR, ≤ 63.8 ml/min/1.73 m^2	56	80	83	50	4.9 (2.0–12.1)	0.0004
Anti-dsDNA, ≥ 75 IU/ml	47	87	87	48	6.1 (2.2–17.3)	0.0003
Patients of the silent subset, n = 86						
Anti-dsDNA, ≥ 40 IU/ml	85	53	24	95	6.3 (1.3–30.5)	0.015
C3 ≤ 55 mg/dl	85	58	24	95	7.5 (1.5–36.1)	0.0063
Anti-dsDNA, ≥ 40 IU/ml and C3 ≤ 55 mg/dl	77	73	33	95	8.8 (2.2–35.4)	0.0011

ISN/RPS: International Society of Nephrology/Renal Pathology Society; PPV: positive predictive value; NPV: negative predictive value; eGFR: estimated glomerular filtration rate.

cantly longer (p = 0.0184) in patients with ISN/RPS class III or IV nephritis than in those without ISN/RPS class III or IV, among patients without clinical renal involvement. Chronic lesions, such as those due to global sclerosis, were observed more frequently than expected in patients without clinical renal involvement. These findings indicate that chronic inflammation can occur latently over several years, even in patients without clinical renal involvement. Renal function and urinary findings should be observed regularly in patients without clinical renal involvement, especially in those with long disease duration, such as > 5 years following SLE diagnosis. These careful observations can determine the appropriate period for performing renal biopsy and treatment and help prevent the development of ISN/RPS class III or IV lupus nephritis.

Anti-dsDNA antibody titers and complement fractions are useful in assessing SLE disease and renal activity[7,8,9]. The prognostic factors for lupus nephritis were divided into renal and nonrenal factors[19]. Renal dysfunction at presentation is associated with a poor prognosis, and a delay in starting immunosuppressive therapy significantly predicts renal failure and death from renal disease[20,21]. Nonrenal prognostic factors include male sex, hematological features such as thrombocytopenia and leukopenia, a younger age at diagnosis, persistent hypocomplementemia, increased anti-dsDNA antibody after treatment, and antiphospholipid antibody[18,19]. In particular, disease vintage, persistent hypocomplementemia, and high anti-dsDNA antibody after treatment have been found to predict renal relapse and mortality[22,23]. Additionally, the persistent elevation of anti-dsDNA antibody and low levels of complement components contributed to the development of overt lupus nephritis in patients with silent lupus nephritis for at least 24 months[15]. Although our study showed that the frequency of ISN/RPS class III or IV lupus nephritis was higher in patients with clinical renal involvement than in those without clinical renal involvement, hypocomplementemia and high anti-dsDNA antibody titers were revealed in both subsets. ISN/RPS class III or IV lupus nephritis without clinical renal involvement was associated with a decrease in C3 and an increase in anti-dsDNA antibody titer, suggesting that hypocomplementemia and high anti-dsDNA antibody titers are correlated with ISN/RPS class III or IV lupus nephritis. Clinical measures, including complement and anti-dsDNA antibody, should be monitored carefully in patients with SLE who do not have clinical renal involvement.

We also investigated the predictive factors of ISN/RPS class III or IV lupus nephritis in patients with SLE and without findings of clinical renal involvement, such as renal dysfunction, proteinuria, and active urinary sediments. First, in patients with SLE who have findings of clinical renal involvement, our study demonstrates that renal biopsy is recommended to confirm ISN/RPS class III or IV lupus nephritis in patients with proteinuria ≥ 1120 mg/day, eGFR ≤ 63.8 ml/min/1.73 m^2, or anti-dsDNA antibody > 75 IU/ml. On the other hand, our study reveals that the nephritis was found in 58% of the SLN subset. Additionally, ISN/RPS class III or IV was found in 15% of patients without clinical renal involvement. We performed further analysis to distinguish patients with ISN/RPS class III or IV lupus nephritis from those with other classes (Nil, class I, II, or V) using cutoff values for anti-dsDNA antibodies and C3. Our study shows that the PPV and NPV for ISN/RPS class III or IV lupus nephritis were about 20%–30% and 95% for each clinical measure in patients without clinical renal involvement. These results indicate that renal biopsy should not be recommended in patients with SLE without clinical renal involvement if they have anti-dsDNA antibody < 40 IU/ml and C3 > 55 mg/dl. However, it is difficult to decide whether renal biopsy should be performed in patients with SLE who do not have clinical renal involvement if they have anti-dsDNA antibody ≥ 40 IU/ml and/or C3 ≤ 55 mg/dl, because the PPV is low. Some believe that performing a renal biopsy to predict development of overt lupus nephritis (OLN) makes no sense in patients with SLE without findings of clinical renal involvement because almost all patients with SLN showed mild histological changes and a good prognosis[24]. It has been reported that endstage renal failure in patients with SLN is rare regardless of the histopathological renal lesions and that it is prudent to do a biopsy on patients with SLE in the absence of overt renal involvement, and to treat those with diffuse proliferative glomerulonephritis[25,26]. However, it remains unknown whether renal biopsy should be performed in SLE without clinical renal involvement and whether cytotoxic therapy, such as intravenous cyclophosphamide, should be used in patients with SLN, as in OLN ISN/RPS class III or IV patients with SLE. In our study, 13 ISN/RPS class III or IV patients with SLE without clinical renal involvement received PSL alone as both induction therapy and maintenance therapy. There was no recurrence during observation (median 30 mo, range 14–178 mo) in all but 2 patients. Our result is compatible with the results of previous reports. These findings indicate that the degree of progression and severity of renal dysfunction was relatively mild in ISN/RPS class III or IV SLE patients without clinical renal involvement. The reason may be that cellular/fibrocellular crescents and GBM rupture were not detected in all patients without clinical renal involvement. This finding may mean that urinary findings and renal function reflect whether these lesions that extend inflammation to extracapillary spaces coexist. IA, such as cyclophosphamide, may not need to be administered to patients without clinical renal involvement when cellular/fibrocellular crescents and GBM rupture were not revealed in kidney specimens.

There was a patient selection bias in our study because the study subjects were not consecutive. Renal biopsies were not performed in 171 of 467 patients, and an additional 101 patients were excluded for several reasons. Therefore, the frequency of lupus nephritis was not reported accurately. On the other hand, 118 patients (61%) received corticosteroids and/or immunosuppressants at renal biopsy. These treatments may

mask clinical findings indicating lupus nephritis. These potential inaccuracies represent limitations in our study.

The actual frequency of nephritis was higher than expected in patients with SLE without clinical renal involvement. ISN/RPS class III or IV lupus nephritis could be hidden in patients with SLE who present both a high titer of anti-dsDNA antibody and a low concentration of C3, even when they exhibit clinically normal urinary findings and renal function.

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