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Predictors of Renal Involvement in Patients with Systemic Lupus Erythematosus

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SUMMARY From a cohort of 109 patients (105 females and 4 males) treated for systemic lupus erythematosus (SLE), 20 patients (18.3%) developed new episodes of lupus nephritis and 89 patients (81.7%) remained free of renal involvement during the follow-up period. The mean duration of follow up was 39.1 ± 54.4 months. Clinical characteristics associated with developing lupus nephritis were a high systolic blood pressure (≥ 130 mmHg), photosensitivity, cutaneous vasculitis and gastrointestinal (GI) symptoms. Laboratory abnormalities associated with the development of lupus nephritis were hemoglobin < 10 mg/dl, hematocrit < 30%, blood urea nitrogen > 12 mg/dl, serum creatinine > 1.3 mg/dl, ESR > 60, the third component of complement (C3) level < 0.45 and positive anti-dsDNA antibody. After a multivariable analysis, only high systolic blood pressure, cutaneous vasculitis, hemoglobin < 10 mg/dl and serum creatinine > 1.3 mg/dl remained as statistically significant risk factors for developing lupus nephritis.

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease that involves multiple organ systems. The clinical presentation and course of SLE varies extremely. At least 50% of patients with SLE exhibit signs of nephritis at some time during their disease.[1] Renal involvement or lupus nephritis has been identified as one of the most important factors influencing the course of SLE, but is frequently unrecognized until full-blown nephritis and/or a nephrotic syndrome with renal failure emerge. A systematic review reported that lupus nephritis adds significantly to the morbidity and mortality of SLE.[2-4] The prognosis however can usually be improved by early diagnosis and timely effective treatment.

Previous studies have suggested that lupus nephritis patients differ from those without lupus nephritis in their clinical presentation, pattern of other organ involvement, severity of disease, and prognosis[5-6], and that the nature of this disease and some of its clinical features may vary among different races. Although SLE is relatively common among Thai-Asian patients[7], the clinical predictors of developing lupus nephritis are still not known. Thus our study was designed to determine the predictive clinical and

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laboratory factors of lupus nephritis and examine renal outcomes in a cohort of SLE patients.

MATERIALS AND METHODS

The subjects of this study were patients diagnosed of SLE at Nopparat Rajathanee Hospital, Thailand from 2001 to 2005. Medical history, physical examination, clinical manifestations, laboratory findings, and outcomes were recorded on a regular follow-up schedule. Only patients who fulfilled at least four of The American College of Rheumatology (ACR) criteria for the classification of SLE[8] were included. All patients were followed up at least three monthly, or more frequently if necessary. The onset of lupus nephritis was considered when the first renal symptom or laboratory finding attributable to lupus was detected. These criteria included > 5 RBCs or any RBC casts per high-powered field in the urine; persistent proteinuria on dipstick (3+ or greater), or proteinuria > 500 mg/24 hours. End stage renal disease (ESRD) was defined by a glomerular filtration rate (GFR) of less than 15 ml/minute/1.73 m^2 or the occurrence of uremic symptoms that required dialysis. Patients were classified into two groups according to their renal involvement status: patients who developed a new onset of lupus nephritis during the follow-up (group I), and patients who remained free of renal involvement until the end of the follow-up period (group II). Patients who already had lupus nephritis at the start of the cohort were excluded from this study.

Biochemical and renal parameters including serum erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), creatinine, third component of complement (C3), total hemolytic complement (CH50), urine analysis, 24-hour proteinuria, and glomerular filtration rate (GFR) calculated by a modified Modification of Diet in Renal Disease (MDRD)[9] formula were recorded. The plasma and urine concentrations of protein, urea nitrogen and biochemical parameters were analyzed using standard techniques. Renal biopsy was considered in patients who presented with nephritis or nephrotic patterns. Renal histopathological findings were classified into six groups according to the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) 2003 Classification of Lupus Nephritis.[10] Activity indices (maximum score, 24 points) and chronicity indices (maximum score, 12 points) were determined according to histological criteria described previously.[11-12]

Statistical analysis

Continuous data were described as means and standard deviations (SD). Categorical variables were described as percentages. The means between groups were compared by Student's t-tests or rank sum tests as appropriate. The risk ratio (RR) with 95% confidence intervals (CI) was calculated. When variables appeared potentially predictive in a univariable analysis, they were evaluated using a stepwise strategy with the multivariable generalized linear model (GLM) regression appropriate for risk ratio. The changes of serum creatinine and GFR over time for each group were analyzed by the repeated measures regression technique.

RESULTS

A total of 119 patients were identified. Ten patients were excluded because of missing or incomplete follow-up. Of the remaining 109 patients, 96.3% (n = 105) were females and only 3.7% (n = 4) were male patients. The mean age at the beginning of the follow-up was 34.4 ± 11.4 years. The mean duration of follow up was 39.1 ± 54.4 months. All subjects were Thai-Asian patients. There were no differences in gender distribution or duration of disease between the renal involvement and no renal involvement groups (Table 1).

Sixty patients, who already had lupus nephritis at the beginning of the follow-up, were excluded. Twenty patients (18.3%) developed clinical lupus nephritis during follow-up (group I) and 89 patients (81.7%) remained free of renal symptoms until the end (group II). The most common initial features of SLE were cutaneous lesions (83.5%), arthritis or arthralgia (74.3%), and hematological involvement (52.3%). Less common manifestations were cardiovascular, ophthalmologic and gastrointestinal (Table 2).

There were no significant differences in the presenting features between the two groups of SLE patients except for a higher systolic blood pressure (group I: 125.9 ± 15.8, group II: 114.8 ± 17.2, $p <$

0.010), a higher proportion of photosensitivity (group I: 60.0%, group II: 33.7%, $p < 0.041$), cutaneous vasculitis (group I: 55.0%, group II: 21.3%, $p < 0.005$), and edema (group I: 75.0%, group II: 31.5% , $p < 0.001$). The laboratory profiles of group I compared to group II showed significantly lower hemoglobin, hematocrit and complement C3, but significantly higher BUN, creatinine, ESR, and a larger proportion of sera positive for anti-dsDNA antibody (Table 3). Almost all patients (95.4%) were antinuclear antibody (ANA) positive with varying patterns such as speckle, nucleolar, homogeneous, and peripheral (52.3%, 19.3%, 12.8% and 1.8% respectively), with no difference in the distribution of these among the two groups.

The risk ratios and 95% CIs were as follows: high systolic blood pressure (≥ 130 mmHg) (RR = 2.79, 95% CI = 1.31 to 5.96), photosensitivity (RR = 2.39, 95% CI = 1.07 to 5.36), cutaneous vasculitis (RR = 3.22, 95% CI = 1.48 to 6.98), gastrointestinal (GI) system (RR = 3.03, 95% CI = 1.22 to 7.53); hemoglobin < 10 mg/dl (RR = 3.08, 95% CI = 1.53 to 6.19), hematocrit < 30% (RR = 4.45, 95% CI = 1.76 to 11.26), blood urea nitrogen > 12 mg/dl (RR = 1.89, 95% CI = 1.27 to 2.80), serum creatinine > 1.3 mg/dl (RR = 4.45, 95% CI = 1.42 to 13.92), ESR > 60 (RR = 2.30, 95% CI = 1.60 to 3.29), C3 levels < 0.45 (RR = 8.90, 95% CI = 2.43 to 32.60) and positive anti-dsDNA antibodies (RR = 2.95, 95% CI = 1.18-7.38) (Table 4). After a multivariable analysis, only four of these remained statistically significant: high systolic blood pressure (≥ 130 mmHg) (RR = 2.454, 95% CI = 1.30 to 4.64), cutaneous vasculitis (RR = 2.56, 95% CI = 1.37 to 4.80), hemoglobin < 10 mg/dl (RR = 2.25, 95% CI = 1.20 to 4.25) and serum creatinine > 1.3 mg/dl (RR = 2.32, 95% CI = 1.20 to 4.81).

The most common manifestations of renal involvement in SLE patients were edema (75.0%). Urine sediment corresponding to a nephritis picture (defined as > 5 RBCs or any RBC casts per high-powered field in urine) and hypertension (blood pressure > 140/90 mmHg) were reported in 60.0% and 42.5% of the cases. The mean value of proteinuria was 2,152.3 ± 1,620.2 mg/day. Thirteen patients underwent renal biopsy. The most common renal

Table 1 General characteristics of SLE patients with renal involvement (n = 20) and without renal involvement (n = 89)

Characteristics	With renal involvement **N** (%)	Without renal involvement **N** (%)	*p*-value
Age (years)*	30.0 (12.1)	35.3 (11.2)	0.057
Gender			
Male	1 (5.0)	3 (3.4)	0.561
Female	19 (95.0)	86 (96.6)	
Monthly income (Baht)*	6,833 (763)	4,714 (2,571)	0.174
Education			
Non-university	11 (73.3)	59 (85.4)	0.306
University graduate	3 (20.0)	5 (7.3)	
Post-graduate	1 (6.7)	5 (7.3)	
Duration of follow up (months)*	30.4 (40.3)	41.1 (57.1)	0.433
Job			
Government officials	1 (5.3)	7 (8.9)	0.839
Employees	9 (47.4)	30 (38.0)	
Unemployed	7 (36.8)	28 (35.4)	
Students	2 (10.5)	14 (17.7)	
Sun exposure			
Under sun	11 (68.7)	45 (90.0)	0.054
In shadow	5 (31.3)	5 (10.0)	

*mean (SD)

histopathology was class IV (61.5%). Crescentric change and hyaline thrombi were found 2.9% and 14.7% of biopsies, respectively. Most renal tissues (61.5%) did not exhibit tubulointerstitial fibrosis, and the mean activity and chronic indices according to histological criteria described previously[11-12] were 6.1/24 and 1.8/12, respectively.

The baseline mean serum creatinine among the two groups was different: group I, 1.19 ± 0.87 mg/dl, and group II, 0.85 ± 0.22 mg/dl (p = 0.029), but the mean GFRs were similar. During the follow-up, renal functions were significantly more impaired in group I, compared to group II (Table 5). Serum creatinine in group I rose from 1.19 ± 0.87 to 3.22 ± 3.67 mg/dl (Fig. 1). The GFR in group I declined from 75.4 ± 31.7 to 49.8 ± 38.4 ml/minute/1.73 m^2 (Fig. 2). On average, the GFR in group I dropped by 8.2% per year ($p < 0.001$). Patients in group II showed less progressive renal impairment over time as their GFR dropped by 5.7% per year ($p < 0.001$).

The total number of patients who progressed to end stage renal disease was small, 2 out of 20 (10.0%) patients in group I, and none out of 89 patients in group II. One patient died from active SLE, with a follow-up of 21 days after SLE diagnosis. The mortality rate was 0.9%.

DISCUSSION

We found a significant relationship between the initial clinical features of high systolic blood pressure, photosensitivity, cutaneous vasculitis, and GI symptoms and a subsequent onset of renal involvement in SLE. Patients with initial laboratory findings of a low hemoglobin, hematocrit and complement C3 as well as a high BUN, creatinine and ESR and positive anti-dsDNA antibodies were more likely to develop lupus nephritis than those without such initial laboratory abnormalities, similar to a previous study.[6] When a multivariate analysis was performed, only high systolic blood pressure, cuta-

Table 2 Baseline clinical characteristics of SLE patients with renal involvement (n = 20) and without renal involvement (n = 89)

Characteristics	With renal involvement N (%)	Without renal involvement N (%)	*p*-value
Systolic BP (mmHg)*	125.9 (15.8)	114.8 (17.2)	0.010
Diastolic BP (mmHg)*	78.4 (13.2)	73.8 (12.3)	0.144
Fever	10 (50.0)	30 (33.7)	0.203
Cutaneous SLE	17 (85.0)	74 (83.2)	1.000
Malar rash	13 (65.0)	55 (61.8)	1.000
Discoid LE	5 (25.0	26 (29.2)	0.790
Oral ulcer	9 (45.0)	36 (40.5)	0.803
Hair loss	6 (30.0)	42 (47.2)	0.215
Photosensitivity	12 (60.0)	30 (33.7)	0.041
Vasculitis lesion	11 (55.0)	19 (21.3)	0.005
Raynaud's phenomenon	5 (20.0)	21 (23.6)	1.000
Musculoskeletal system	13 (65.0)	68 (76.4)	0.395
Neurological system	5 (25.0)	13 (14.6)	0.316
Respiratory system	2 (10.0)	12 (13.5)	1.000
Cardiovascular system	0 (0)	2 (2.2)	1.000
Gastrointestinal system	3 (15.0)	3 (3.4)	0.074
Edema	15 (75.0)	28 (31.5)	0.001
Hematological system	11 (55.0)	46 (51.7)	0.810
Lymphadenopathy	2 (10.0)	3 (3.4)	0.227
Splenomegaly	0 (0)	0 (0)	-
Ophthalmologic system	0 (0)	3 (3.4)	1.000

*mean (SD)

neous vasculitis, low hemoglobin and high serum creatinine were shown to be independent predictors of lupus nephritis. Antibodies to DNA seem to have an important role in disease expression. Some experimental studies demonstrated a more direct link between anti-dsDNA and nephritis.[13-14] Another study indicated that anti-dsDNA may induce glomerular immune deposits and nephritis in mice.[15] We also found that the presence of anti-dsDNA was a factor associated with the presence of nephritis, but in a multivariable analysis it did not reach a significant level, probably because the number of patients tested was too small (19 cases).

This is the first cohort study to demonstrate a significant contribution of photosensitivity, cutaneous vasculitis, and GI symptoms to renal involvement in SLE. These findings are in discordance with previous studies which indicated that patients with lupus nephritis were more likely to have alopecia and oral ulceration than those without, but were less likely to have arthritis, facial rash, and Raynaud's phenomenon.[5] Several studies suggested that there were no non-renal clinical manifestations of SLE that could reasonably predict the likelihood of developing lupus nephritis.[16-17] The reason for this apparent discordance remains unclear. It has been speculated that a variation in genetic predisposition, responses to different triggering mechanisms and different individual environments or cultural effects may be involved. Some centers reported that male patients and patients with an early onset of lupus are more likely to have renal involvement[18], but we did not find any differences in gender and age between lupus nephritis and non lupus nephritis patients.

Although clinical nephritis can occur at any time in the course of SLE, it usually occurs in the first few years of the disease and rarely develops after 5 years of illness.[19] The mean follow-up time of our cohort was nearly 4 years, and which made it possible to detect almost all patients who would have had subsequent onsets of renal involvement. The prevalence of lupus nephritis in our study was 47.3% which includes the existing cases (60 patients) as well as the new cases whose onset was during fol-

Table 3 Laboratory findings of SLE patients with renal involvement (n = 20) and without renal involvement (n = 89)

Characteristics	With renal involvement mean (SD)	Without renal involvement mean (SD)	*p*-value
Hemoglobin (g/dl)	10.5 (2.1)	11.6 (1.7)	0.013
Hematocrit (%)	32.3 (5.8)	36.1 (4.5)	0.002
WBC (per mm^3)	5,817 (2,059)	6,487 (2,846)	0.323
Lymphocyte count (per mm^3)	1,561 (774)	1,951 (1,031)	0.114
Platelet count (100,000/mm^3)	2.3 (0.9)	2.4 (0.8)	0.569
Positive Coomb's test*	9 (45.0)	23 (25.8)	0.079
BUN (mg/dl)	23.2 (21.4)	12.2 (5.4)	< 0.001
Serum creatinine (mg/dl)	1.19 (0.87)	0.85 (0.22)	0.029
GFR (ml/min/1.73m^2)	75.4 (31.7)	86.7 (22.9)	0.079
Positive anti-DNA antibody*	7 (87.5)	5 (45.5)	0.147
ESR (mm/hour)	84.1 (28.1)	57.3 (26.2)	< 0.001
C3 (d/L)	0.51 (0.47)	0.91 (0.39)	0.018
CH50 (%)	18.0 (0)	44.6 (33.8)	0.351
ANA pattern*			
Negative	1 (5.9)	4 (4.9)	0.265
Speckle	7 (41.2)	50 (61.0)	
Nucleolar	4 (23.5)	17 (20.7)	
Homogeneous	5 (29.4)	9 (11.0)	
Perinuclear	0 (0)	2 (2.4)	

* N (%)

low-up (12 patients). The incidence of new onset lupus nephritis was 18.3%. Similar findings were published on the Singaporean[20] and Chinese populations.[21] The most frequent sequence of presentation in our population was initial cutaneous lesions followed by arthritis or arthralgias and hematological

Table 4 Risk ratio (RR) and 95% confidence interval (CI) of RR of clinical findings associated with a new incidence of lupus nephritis

Characteristics	Risk ratio (RR)	95% CI of RR	*p*-value
Systolic BP > 130 mmHg	2.79	1.31-5.96	0.009
Systolic/diastolic BP > 130/85 mmHg	2.41	1.11-5.22	0.025
Photosensitivity	2.39	1.07-5.36	0.029
Cutaneous vasculitis	3.22	1.48-6.98	0.002
GI manifestation	3.03	1.22-7.53	0.039
Hemoglobin < 10 g/dl	3.08	1.53-6.19	0.002
Hematocrit < 30%	4.45	1.76-11.26	0.001
BUN > 12 mg/dl	1.89	1.27-2.80	0.007
Creatinine > 1.3 mg/dl	4.45	1.42-13.92	0.007
ESR > 60 mm/hour	2.30	1.60-3.29	< 0.001
C3 < 0.5 d/l	8.90	2.43-32.60	< 0.001
Positive anti-DNA antibodies	2.95	1.18-7.38	0.019

Table 5 Follow-up serum creatinine and glomerular filtration rate (GFR) of SLE patients with renal involvement (n = 20) and without renal involvement (n = 89)

Characteristics	With renal involvement mean (SD)	Without renal involvement mean (SD)	*p*-value
Serum creatinine (mg/dl)			
Baseline	1.19 (0.87)	0.85 (0.22)	0.029
Month 6	1.23 (0.50)	0.91 (0.20)	0.092
Month 12	1.36 (0.59)	0.94 (0.17)	0.021
Month 36	1.67 (1.08)	0.93 (0.17)	0.017
Month 60	3.22 (3.67)	0.85 (0.16)	0.031
GFR (ml/minute/1.73 m^2)			
Baseline	75.4 (31.7)	86.7 (22.9)	0.098
Month 6	67.5 (30.7)	79.0 (18.4)	0.135
Month 12	58.1 (23.8)	75.9 (15.6)	0.017
Month 36	53.0 (28.4)	75.2 (18.9)	0.016
Month 60	49.8 (38.4)	78.4 (19.8)	0.044
ESRD (n, %)	2 (10.0)	0 (0)	0.016
Death (n, %)	0 (0)	1 (1.1)	0.158

manifestations. These findings were similar to other studies.[22-23] Cardiovascular, ophthalmologic and gastrointestinal manifestations were less prevalent in our series.

The criteria for the diagnosis of lupus nephritis by the ACR have helped physician recognize and diagnose this disease, but these criteria occasionally lack the sensitivity for diagnosing early or mild cases of lupus nephritis. At the beginning of the study, our patients with new episodes of lupus nephritis exhibited several clinical symptoms such as high blood pressure, high ESR, low C3, and renal insufficiency which actually represented lupus nephritis, but were not components of renal disorder according to the ACR criteria.

Another criticism of the ACR criteria is based on considerable evidence that the natural history of lupus nephritis differs among various racial, ethnic and socioeconomic groups. This 5-year study on the renal functions of SLE patients documented that SLE patients with lupus nephritis had worse renal functions than patients without lupus nephritis. Several clinical studies have supported these findings. In our study, the incidence of progression to ESRD was low (10% of patients with lupus nephritis) similar to another study which reported that not more than 10-15% of patients with lupus developed ESRD.[24] Our low mortality rate might have been due to the fact that our study was conducted in a general care hospital, which may differ from other studies done in tertiary care hospitals.[25-26] Some SLE patients with severe disease were not referred to our hospital. On the other hand, as there is a center for SLE in our hospital, greater awareness, a more accurate diagnosis of SLE disease, better supportive care and more appropriate treatment might have also contributed to the lower mortality rate.

Our study did not pursue some serological and genetic analyses such as anti-RNP antibodies and anti-Sm antibodies, which were previously reported to be associated with developing nephritis in Afro-Caribbeans.[27] More recently a strong genetic association between a polymorphic allele of the Fc gamma receptor IIA and lupus nephritis was reported.[28] We did not perform renal biopsies on all SLE patients as this was not the purpose of our study. Although the majority of patients had class IV nephritis, at least 30 % had other benign types of renal disease. It should be kept in mind that the predictive factors for lupus nephritis in our study may be generalized as predictive factors for all renal developments.

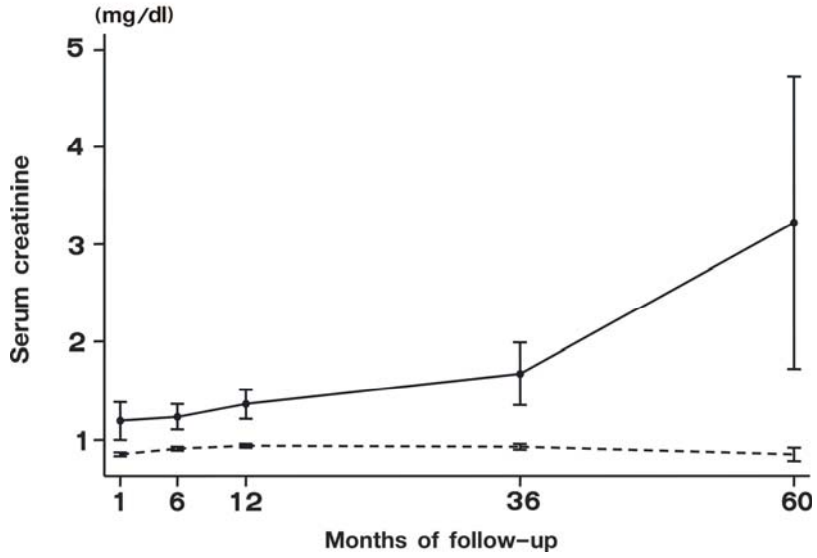

Fig. 1 Mean (connected) and standard error (vertical lines) of serum creatinine in SLE patients with new lupus nephritis (n = 20, solid line) and those without (n = 89, dotted line) at baseline (month 1), month 6, 12, 36 and 60.

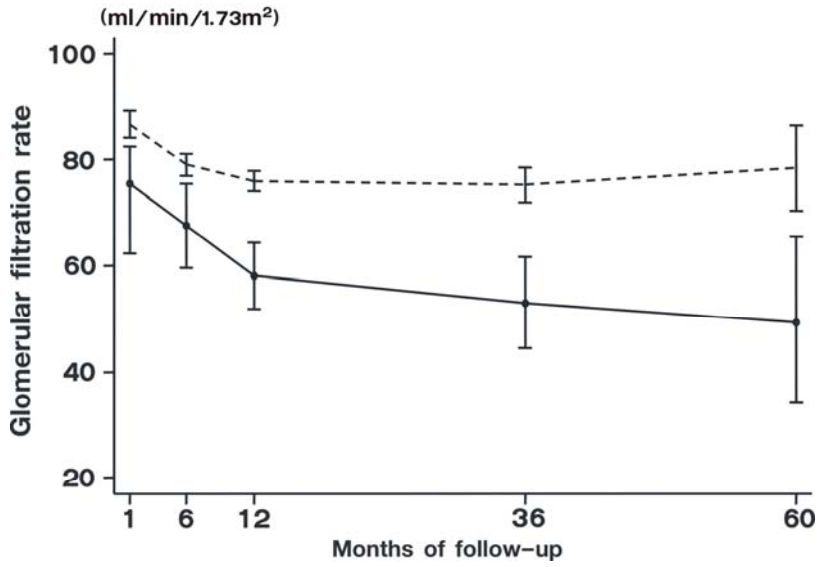

Fig. 2 Mean (connected) and standard error (vertical lines) of glomerular filtration rate in SLE patients with new lupus nephritis (n = 20, solid line) and those without (n = 89, dotted line) at baseline (month 1), month 6, 12, 36 and 60.

In conclusion, although the reasons why some patients with lupus develop clinical nephritis remain elusive, those who developed nephritis were likely to have a high systolic blood pressure, cutaneous vasculitis, anemia or azotemia. Greater awareness of these clinical features should help to improve the prognosis of SLE patients.

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REFERENCES

1. Ruiz-Irastorza G, Khamashta MA, Castellino G, Hughes GR. Systemic lupus erythematosus. Lancet 2001; 357: 1027-32.
2. Donadio JV Jr, Hart GM, Bergstralh EJ, Holley KE. Prognostic determinants in lupus nephritis: a long-term clinicopathologic study. Lupus 1995; 4: 109-15.
3. Ward MM, Pyun E, Studenski S. Mortality risks associated with specific clinical manifestations of systemic lupus erythematosus. Arch Intern Med 1996; 156: 1337-44.
4. Vu TV, Escalante A. A comparison of the quality of life of patients with systemic lupus erythematosus with and without end stage renal disease. J Rheumatol 1999; 26: 2595-601.
5. Wallace DH, Hahn BH. Dubois' lupus erythematosus, 4th edition. Baltimore: Lea & Febiger; 1993.
6. Petri M. Hopkins Lupus Cohort. 1999 update. Rheum Dis Clin North Am 2000; 26: 199-213.
7. Lee SS, Li CS, Li PC. Clinical profile of Chinese patients with systemic lupus erythematosus. Lupus 1993; 2: 105-9.
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999; 130: 461-70.
10. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, *et al*. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004; 15: 241-50.
11. Schwartz MM, Lan SP, Bernstein J, Hill GS, Holley K, Lewis EJ. Role of pathology indices in the management of severe lupus glomerulonephritis. Lupus Nephritis Collaborative Study Group. Kidney Int 1992; 42: 743-8.
12. Boumpas DT, Balow JE. Outcome criteria for lupus nephritis trials: a critical overview. Lupus 1998; 7: 622-9.
13. Dang H, Harbeck RJ. The *in vivo* and *in vitro* glomerular deposition of isolated anti-double-stranded-DNA antibodies in NZB/W mice. Clin Immunol Immunopathol 1984; 30: 265–78.
14. Koffler D, Schur PH, Kunkel HG. Immunological studies concerning the nephritis of systemic lupus erythematosus. J Exp Med 1967; 126: 607–23.
15. Vargas MT, Gustilo K, D'Andrea DM, Kalluri R, Foster MH, Madaio MP. Structural features of nephritogenic lupus autoantibodies. Methods 1997; 11: 62–9.

16. Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. Kidney Int 1994; 45: 544-50.
17. Wallace DJ, Podell TE, Weiner JM, Cox MB, Klinenberg JR, Forouzesh S, *et al.* Lupus nephritis. Experience with 230 patients in a private practice from 1950 to 1980. Am J Med 1982; 72: 209-20.
18. Petri M. Epidemiology of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2002; 16: 847-58.
19. Nossent HC, Henzen-Logmans SC, Vroom TM, Berden JH, Swaak TJ. Contribution of renal biopsy data in predicting outcome in lupus nephritis. Analysis of 116 patients. Arthritis Rheum 1990; 33: 970-7.
20. Edwards CJ. Lupus in Singapore. Lupus 2001; 10: 889-91.
21. Mok CC, Lau CS. Lupus in Hong Kong Chinese. Lupus 2003; 12: 717-22.
22. Huong DL, Papo T, Beaufils H, Wechsler B, Bletry O, Baumelou A, *et al.* Renal involvement in systemic lupus erythematosus. A study of 180 patients from a single center. Medicine (Baltimore) 1999; 78: 148-66.
23. Martins L, Rocha G, Rodrigues A, Santos J, Vasconcelos C, Correia J, *et al.* Lupus nephritis: a retrospective review of 78 cases from a single center. Clin Nephrol 2002; 57: 114-9.
24. Bono L, Cameron JS, Hicks JA. The very long-term prognosis and complications of lupus nephritis and its treatment. QJM 1999; 92: 211-8.
25. Kasitanon N, Louthrenoo W, Sukitawut W, Vichainun R. Causes of death and prognostic factors in Thai patients with systemic lupus erythematosus. Asian Pac J Allergy Immunol 2002; 20: 85-91.
26. Shayakul C, Ong-aj-yooth L, Chirawong P, Nimmannit S, Parichatikanond P, Laohapand T, *et al.* Lupus nephritis in Thailand: clinicopathologic finding and outcome in 569 patients. Am J Kidney Dis 1995; 26: 300-7.
27. Alba P, Bento L, Cuadrado MJ, Karim Y, Tungekar MF, Abbs I, *et al.* Anti-dsDNA, anti-Sm antibodies, and the lupus anticoagulant: significant factors associated with lupus nephritis. Ann Rheum Dis 2003; 62: 556-60.
28. Salmon JE, Millard S, Schachter LA, Arnett FC, Ginzler EM, Gourley MF, *et al.* Fc gamma RIIA alleles are heritable risk factors for lupus nephritis in African Americans. J Clin Invest 1996; 97: 1348-54.