ORIGINAL

Observations on the occurrence of exacerbations in clinical course of systemic lupus erythematosus

Reiko Tomioka[1], Kenji Tani[2], Keiko Sato[1], Chiyuki Suzuka[1], Yuko Toyoda[1], Jun Kishi[1], and Saburo Sone[1]

[1]*Department of Internal Medicine and Molecular Therapeutics, and* [2]*Department of Community and Primary Care Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan*

Abstract : Systemic lupus erythematosus (SLE) is a chronic disease that is characterized by an undulating course of exacerbations and remissions, and a major determinant of long-term prognosis is organ damage consequent to tissue injury that accompanies disease activity and toxicity of therapy. In this study, we evaluated which patients with SLE will develop an exacerbation and whether factors can be identified to predict the development of an exacerbation. Fifty-seven SLE patients (52 females) were included in this study. The exacerbation of SLE was found in 15 patients (26.3%). A relatively increased incidence of an exacerbation was found in younger SLE patients. An increased percentage of patients who had lupus nephritis at the time of diagnosis of SLE was found in patients with a subsequent exacerbation when compared with that in those without it. Increased incidence of an exacerbation was observed in patients who had decreased number of WBC and platelets, decreased level of C3 and CH50, and the presence positivity of anti-Sm antibodies at the time of the diagnosis. This study suggests that age, renal involvement, and the presence of decreased number of WBC and platelets, decreased level of complements anti-Sm antibodies are predictors of exacerbation. J. Med. Invest. 55 : 112-119, February, 2008

Keywords **:** *systemic lupus erythematosus, exacerbation, lupus nephritis, anti-Sm antibodies*

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a wide variety of autoantibodies which may affect the skin, joints, lungs, heart, serous membranes, nervous system and other organs (1). SLE predominantly affects women : the female : male ratio is about 9 : 1, and more than 80% of the cases occur in women during their child-bearing years (2). SLE is a chronic disease that is characterized by an undulating course of exacerbations and remissions, and a major determinant of long-term prognosis is organ damage consequent to tissue injury that accompanies disease activity and toxicity of therapy (3, 4). In the past 40 years, prognosis for patients with SLE has improved, with 10-year survival now approximately 90% (5). The improved prognosis may be due an earlier disease diagnosis, and due in part to the availability of multiple serological tests for SLE, use of corticosteroids and other immunosuppressive agents and availability of renal dialysis and transplantation. Although SLE patients are now possible to obtain long periods of remission in the disease course, some patients with SLE still carry a heavy burden of morbidity due to organ damage, and repeat exacerbations

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Address correspondence and reprint requests to Saburo Sone, M.D., Department of Internal Medicine and Molecular Therapeutics, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-2134.

during the disease course (6). Therefore, it is important to clarify features at onset to distinguish patients who developed a subsequent exacerbation from those who did not. Studies of variables which affect exacerbations in SLE have identified various factors including clinical and laboratory features (6, 7). However, the contribution of the initial clinical and laboratory features to the course of SLE has not yet been clarified. The aim of this study was to evaluate which patients with SLE will develop an exacerbation and whether factors can be identified to predict the development of an exacerbation.

PATIENTS AND METHODS

Patients

Patients with SLE diagnosed at Tokushima University Hospital between December 1989 and November 2005 were included in this study. SLE was diagnosed according to the criteria of American College of Rheumatology for SLE (8). Table 1 shows the baseline patient characteristics. Patients with SLE consisted of 52 females and 5 males aged 40.2± 17.2 y.o. on average (male ; 50.6±9.7 y.o., female ; 39.2±17.5 y.o.). Figure 1 shows age of patients at the time of diagnosis of SLE, showing that the most patients were diagnosed in twenties, and 64.9% of patients were diagnosed when they were between 20 and 49 y.o.. As shown in Table 1, association of other collagen vascular diseases was seen in 10 patients with SLE : 5 rheumatoid arthritis, 3 Sjogren's syndrome, a mixed connective tissue disease, and a polymyositis. The complication of pleuritis and pericarditis was found in 22 patients (38.6%) and 11 patients (19.3%), respectively. The complication of lupus nephritis, pulmonary involvements and neuropathy was found in 21 patients (36.8%), 12 patients (21.1%) and 7 patients (12.3%), respectively.

SLE disease activity index (SLE-DAI) was calculated as a measure of systemic activity of the disease at the time of the diagnosis (9). At each monthly visit, levels of C3, C4, CH50 and anti-dsDNA antibodies, complete blood cell counts, analyses of hepatic and renal function, and urinalysis were examined. An exacerbation was defined as one or more of the following 3 features : 1) a >3-point change in the SLE-DAI score, 2) a clinical exacerabation with or without serologic activity. A serologic exacerbation was defined as an elevation of anti-dsDNA antibody levels by 25% (to the abnormal range) or a decrease of C3 and CH50 by 25%, 3) an increase in the dosage of corticosteroid or an addition of immunosuppressive agent was considered in tapering of corticosteroid dosage. Diabetes mellitus and aseptic necrosis of the femoral head were complicated in 10 patients (17.5%) and 6 patients (10.5%), respectively, with SLE patients after the treatment with corticosteroid (data not shown).

Table 1 Patient characteristics at the time of diagnosis of SLE

Number of patients	57
Sex (M / F)	5 / 52
Average age (y.o.)	40.2±17.2
Other collagen vascular diseases (+)	RA : 5, SjS : 3, MCTD : 1, PM : 1
Prednisolone (+)	55 (96.5)
Average in the starting dose	45.4 ± 11.0 mg/day
mPSL pulse therapy (+)	27 (47.4)
Immunosuppressive agent (+)	2 (3.5)
Pleuritis (+)	22 (38.6)
Pericarditis (+)	11 (19.3)
Lupus nephritis(+)	21 (36.8)
Pulmonary involvements (+)	12 (21.1)
Neuropathy (+)	7 (12.3)

Parentheses show perecentages, Values express as mean ± SD.
RA ; rheumatoid arthritis, SjS ; sjogren's syndrome, MCTD ; mixed connective tissue disease, PM ; polymyositis, mPSL ; methylprednisolone.

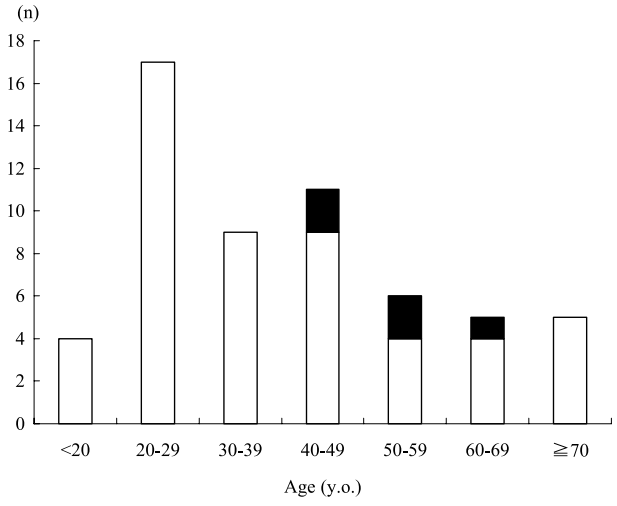

Figure 1. Age at the time of diagnosis. Closed columns show male, and open columns show female.

Statistical analysis

All results are expressed as mean±SD. Statistical analyses were performed using Statview software. The results were regarded as significant when p value was <0.05.

RESULTS

Treatment

Fifty five patients (96.5%) with SLE received the therapy with corticosteroids using oral prednisolne as the initial treatment (Table 1). Figure 2 shows the starting dose of prednisolone : none (2 patients, 3.5%), <20 mg/day (none), 20-29 mg/day (3 patients, 5.3%), 30-39 mg/day (7 patients, 12.3%), 40-49 mg/day (17 patients, 29.8%), 50-59 mg/day (17 patients, 29.8%), ≧60 mg/day (11 patients, 19.3%). All of patients treated with corticosteroid received over or equal to dose of 20 mg/day of prednisolone, and the mean starting dose of prednisolone is 45.4± 11.0 mg/day. The treatment with methylprednisolone (mPSL) pulse therapy was carried out for 27 patients (47.4%) as the initial treatment (Table 1). Immunosuppressive agent was carried out for 2 patients (3.5%) as the initial treatment. Cyclophosphamide was used in these two patients as the immunosuppressive agent.

Exacerbations

The exacerbation of SLE was found in 15 patients (26.3%), 14 females and a male during the disease course (Table 2 and Figure 3). The total number of exacerbations observed in the 15 patients was 29 times. One exacerbation was observed in 9 patients, 2 exacerbations were in 3 patients, 3 exacerbations in a patient, and 4 exacerbations in 3 patients. While the mean disease duration of SLE patients with an exacerbation was 12.3±4.8 years (3.8-17.5 years), the time interval between the diagnosis of SLE and the occurrence of the first exacerbation was 4.8±4.7 years on average (0.1-12.7 years) ; <1 year in 4 patients, 1-2.9 years in 4 patients, 3-4.9 years in a patient, 5-6.9 years in a patient, 7-8.9 years in 2 patients, and 11-12.9 years in 3 patients. The time interval between the diagnosis of SLE and the occurrence of an exacerbation in all exacerbations was <1 year in 4 patients, 1-2.9 years in 4 patients, 3-4.9 years in 5 patients, 5-6.9 years in 3 patients, 7-8.9 years in 7 patients, 9-10.9 years in a patient, and 11-12.9 years in 5 patients. The average dose of prednisolone used to maintain before the first exacerbation was 12.2±12.3 mg/day, and the dose was increased in all patients to 45.8±14.7 mg/day (Table 3). For the first exacerbation, 9 patients

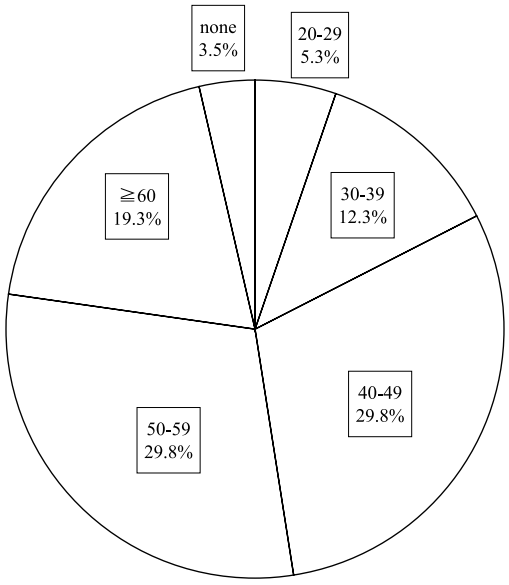

Figure 2. The dose of prednisolone (mg/day) at the initial therapy.

Table 2 The duration from the time of diagnosis of SLE to an exacerbation

Duration (months)	No. of the first exacerbation	No. of all exacerbations
<12	4	4
12 - 35	4	4
36 - 59	1	5
60 - 83	1	3
84 - 107	2	7
108 - 131	0	1
132 - 156	3	5
Total	15	29

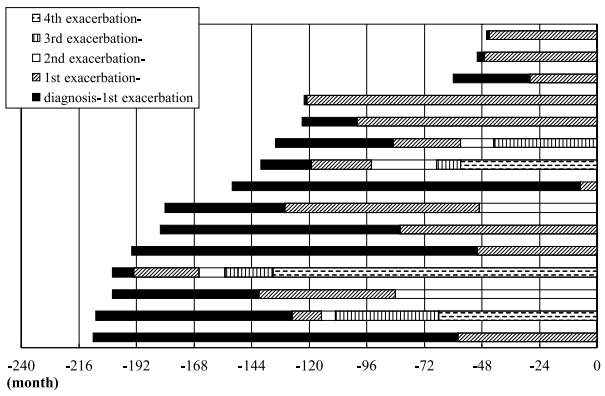

Figure 3. Time course of exacerbations in 15 patients with SLE who had at least one exacerbation.

Table 3 The treatment for the first exacerbation

No.	The dose of prednisolone used to maintain before the first exacerbation (mg/day)	Treatment		
		Prednisolone (mg/day)	mPSL pulse therapy	Immunosuppressive agent
1	12.5	40	+	-
2	35	60	+	-
3	10	50	+	mizoribin
4	2.5	60	+	-
5	7.5	50	+	-
6	0	20	-	-
7	5	40	-	-
8	5	50	-	-
9	17.5	45	-	-
10	15	50	+	-
11	0	60	+	-
12	40	60	+	-
13	22.5	60	+	-
14	10	22.5	-	-
15	0	20	-	-

The average dose of prednisolone used to maintain before the first exacerbation was 12.2± 12.3 mg/day. The dose of prednisolone was increased to 45.8± 14.7 mg/day for the treatment.

(60.0%) were treated with mPSL pulse therapy, and one patient (0.7%) was with immunosuppressive agent, mizoribin.

Comparison of clinical data between patients with and without an exacerbation

Figure 4 shows the comparison of age at the time of diagnosis of SLE between patients with and without a subsequent exacerbation. The mean age of patients with an exacerbation (33.1± 10.2 y.o.) was younger than those without it (42.7± 18.5 y.o.) though there was no significant difference. The percentage of patients with an exacerbation was 34.1% of patients younger than 50 y.o., and 6.3% of patients over or equal to 50 y.o..

Contribution of the initial factors to an exacerbation

Clinical findings at the time of diagnosis of SLE were shown in Table 4 comparing between patients with and without a subsequent exacerbation. The percentage of patients who had lupus nephritis at the time of the diagnosis was higher in patients with an exacerbation (60.0%) than that in those without it (19.0%). There was no difference in skin involvements, arthritis, central nerve system (CNS) lupus, pericarditis and pleuritis between patients with and without a subsequent exacerbation. Table 5 shows

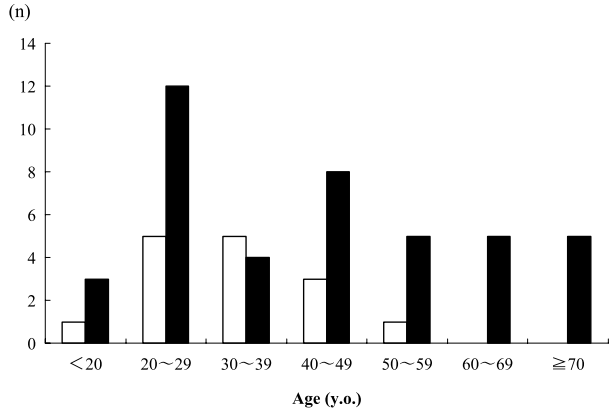

Figure 4. Age at the time of diagnosis of SLE. Open columns show patients with a subsequent exacerbation, and closed columns show those without a subsqeunt exacerbation.

Table 4 Clinical findings at the time of diagnosis of SLE

	Patients with exacerbation (n=15)	Patients without exacerbation (n=42)
Skin involvements	10 (66.7)	28 (66.7)
Arthritis	12 (80.0)	31 (73.8)
CNS lupus	0 (0.0)	3 (7.1)
Lupus nephritis	9 (60.0)	8 (19.0)
Pericarditis	4 (26.7)	6 (14.3)
Pleuritis	6 (40.0)	14 (33.3)

Parentheses show perecentages, CNS ; central nerve system

Table 5 Laboratory data at the time of diagnosis of SLE

	Patients with exacerbation	Patients without exacerbation
Leukopenia	6 / 6 (100)	20 / 40 (50.0)
Thrombocytopenia	3 / 5 (60.0)	8 / 39 (20.5)
Elevated ESR	4 / 4 (100)	28 / 34 (82.4)
Anti-dsDNA antibodies	6 / 11 (54.5)	30 / 39 (76.9)
Anti-Sm antibodies	3 / 4 (75.0)	4 / 35 (11.4)
Decreased C3	10 / 11 (90.9)	24 / 36 (66.7)
Decreased C4	7 / 11 (63.6)	23 / 36 (63.9)
Decreased CH50	11 / 11 (100)	27 / 37 (73.0)
Positive immune complexes	3 / 5 (60.0)	16 / 27 (59.3)
Positive anti-SS-A antibodies	1 / 4 (25.0)	14 / 32 (43.8)
Positive anti-SS-B antibodies	1 / 4 (25.0)	4 / 31 (12.9)

Parentheses show percentages, ESR ; erythrocyte sedimentation rates

the comparison of data in hematological and immunological tests at the time of the diagnosis between patients with and without a subsequent exacerbation. The percentages of patients who had decreased number of WBC and platelets, decreased level of C3 and CH50, and the presence of anti-Sm antibodies at the time of the diagnosis were higher in patients with a subsequent exacerbation than in those without it. Decreased level of C3 was found more frequently in patients with positive anti-Sm antibodies than in those with negative anti-Sm antibodies (83.3% and 55.2%, respectively). The percentage of patients who had positive anti-dsDNA antibody at the time of the diagnosis was not higher in patients with a subsequent exacerbation than in those without it.

The difference in treatment

The dose of prednisolone at the initial treatment was compared between patients with and without an exacerbation (Figure 5). All patients were treated with more than or equal to 20 mg of prednisolone except 2 cases treated without prednisolone. The mean dose of prednisolone was not significantly different between patients with and without an exacerbation (46.3±11.1 mg/day and 43.3±11.0 mg/day, respectively). There was no difference in percentages of patients with an exacerbation between patients treated with and without mPSL pulse therapy (22.2% and 30.0%, respectively) (Figure 6).

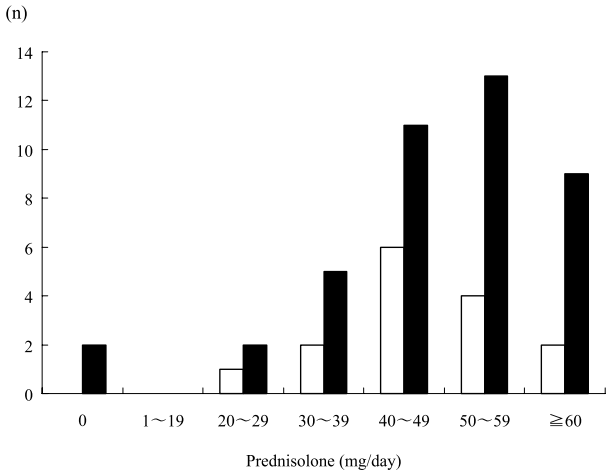

Figure 5. The dose of prednisolone at the initial therapy. Open columns show patients with a subsequent exacerbation, and closed columns show those without a subsequent exacerbation.

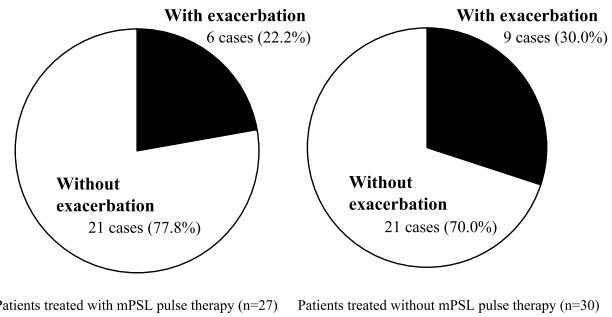

Figure 6. The difference in occurrence of exacerbations between patients with and without the therapy with methylprednisolone (mPSL) pulse at the time of diagnosis of SLE.

Prognosis

Three patients died during the course. Their mean age was 69.0± 7.5 y.o.. Two patients died at 2 months after the diagnosis during the initial treatment due to disseminated intravascular coagulation and CNS lupus. A patient died at 32 months after the diagnosis due to hepatic carcinoma.

DISCUSSION

The clinical course of SLE is characterized by periods of exacerbations and remissions. In this study, we examined how many times an exacerbation took place in the course of SLE and determined whether any factors distinguished those patients who developed a subsequent exacerbation from those who did not. Fifteen patients (26.3%) had exacerbations during the disease course. The total number of exacerbations in the 15 patients was 29 times. While the mean disease duration of the follow up is 12.3± 4.8 years, the mean duration between the diagnosis of SLE and the first exacerbation is 4.8± 4.7 years. Swaak, *et al.* reported that exacerbations were observed in 62 (56.4%) of 110 patients with SLE (10). Bujan, *et al.* (11) demonstrated that, during 9.5 years as the mean duration of the follow up, SLE patients had a mean of 4.6 flares per patient, 18.9% had no flare, and major flares were 54.7% among the total number of flares. The difference in the percentage of exacerbations between our study and the previous reports may be explained by that in the severity of patients and the definition of an exacerbation. For example, in the previous reports an exacerbation was simply defined as any clinical event attributable to the disease activity. On the other hand, in our study, an exacerbation was defined using 3 features of clinical and serological findings, indicating that an exacerbation detected by our definition was relatively severer than that in previous reports and needed any modifications of therapy such as an increase of the dose of prednisolone.

The most commonly used corticosteroid in the treatment of patients with SLE is oral prednisolone. Prednisolone at doses up to 20 mg/day is used frequently to treat symptoms of mild to moderate SLE, and higher doses of 1 to 1.5 mg/kg body weight prednisolone improves survival of patients with severe SLE (12). In this study, oral prednisolone was used in the initial therapy for 96.5% of patients with SLE, and the starting dose of prednisolone was more or equal to 20 mg/day in all patients. In the initial therapy, the treatment with mPSL pulse therapy was performed in 47.4% of patients with SLE just before the treatment with oral prednisolone. The therapy with mPSL pulse has commonly used in the treatment of severe manifestations including lupus nephritis (13, 14). Isenberg, *et al.* reported that mPSL pulse therapy on patients with active SLE was effective and safe (15). However, other studies demonstrated that mPSL pulse therapy produces greater immunosuppression and risk of osteoporotic fractures than oral prednisolone (16-18). On the other hand, two patients received cyclophosphamide as the initial therapy. Recent studies have shown that both patients and renal survivals are significantly better in patients receiving cyclophosphamide in addition to oral prednisolone than those given oral prednisolone alone (19-21). In this study, addition of immunosuppressive agent to prednisolone was performed in 3.5% of SLE patients mainly for the treatment of lupus nephritis.

This study showed that there was an indication that mean age at the time of diagnosis of SLE was younger in SLE patients with a subsequent exacerbation than in those without it. This is consistent with data by Swaak, *et al*. (10) that younger patients were more prone to develop an exacerbation. They also showed that a relatively increased exacerbation incidence was found in male patients compared with female patients. However, our study could not show the difference in the incidence of an exacerbation between male and female because there were a few numbers of male patients.

Patients who had lupus nephritis at the time of the diagnosis showed a subsequent exacerbation more frequently than those who did not. It has been shown that at least 50% of patients with SLE exhibit signs of nephritis during the disease course, and nephritis with impaired renal function may be a major cause of morbidity (22). Our data suggest that the presence of lupus nephritis at the time of the diagnosis may increase the risk of a subsequent exacerbation. This study also showed that, in 13 patients with lupus nephritis who received mPSL pulse therapy at the first treatment, a subsequent exacerbation was found in 5 patients but not in 8 patients. On the other hand, all patients (4 patients) with lupus nephritis who did not receive mPSL pulse therapy at the first treatment showed a subsequent exacerbation. These data suggest that mPSL pulse therapy at the first treatment is effective to decrease the risk of a subsequent exacerbation in SLE pa-

tients with lupus nephritis. In this study, there was no difference in the presence of skin involvements, arthritis, CNS lupus, pericarditis and pleuritis at the time of the diagnosis between patients with and without a subsequent exacerbation. In laboratory tests, percentages of patients who had decreased number of WBC and platelets, decreased levels of C3 and CH50, and the presence of anti-Sm antibodies at the time of the diagnosis were higher in patients with a subsequent exacerbation than in those without it. Anti-Sm antibodies were prone to be positive in SLE patients with decreased level of complements. A previous report has also shown that, at the time of diagnosis, patients who developed a subsequent exacerbation had the positive anti-Sm antibodies more frequently than those who did not (10). Anti-Sm antibodies have been identified in the sera of about one-third of SLE patients (23), and have been shown to have the ability to activate complements (24). Thus, anti-Sm antibodies may be a useful marker in the activation of complements and a subsequent exacerbation in SLE patients.

This study showed that there was no difference in the initial dose of prednisolone between patients with and without a subsequent exacerbation. The initial dose of prednisolone was decided by the disease activity of SLE at the time of the diagnosis. Similarly, the treatment with mPSL pulse therapy was performed to SLE patients with severe organ involvements and high disease activity. Therefore, it may be difficult to compare the clinical course between patients who were treated with high dose of prednisolone and mPSL pulse therapy and those who were not because the disease activity at the time of diagnosis was different between these two groups.

In summary, we have shown clinical series of SLE patients with an exacerbation in our clinical department. The data indicate that a relatively increased exacerbation incidence was found in younger SLE patients. Clinical and laboratory factors at onset to influence a subsequent exacerbation are the presence of lupus nephritis, decreased number of WBC and platelets, decreased level of complements and the presence of anti-Sm antibodies. This study suggests that SLE patients who are positive in these parameters at onset require careful monitoring in the disease course.

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