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ORIGINAL ARTICLE

**Yoshiaki Tokano · Shinji Morimoto · Hirofumi Amano
Toshiaki Kawanishi · Tetsuro Yano · Masayuki Tomyo
Masahiro Sugawara · Shigeto Kobayashi · Hiroshi Tsuda
Yoshinari Takasaki · Hiroshi Hashimoto**

The relationship between initial clinical manifestation and long-term prognosis of patients with systemic lupus erythematosus

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Abstract The relationship between clinical manifestations and prognosis was examined and evaluated among systemic lupus erythematosus (SLE) patients. A total of 542 patients with SLE were selected and divided into nine groups according to their main clinical manifestation at the time of initial diagnosis. The relationship between these clinical manifestations and long-term prognosis was evaluated in respect to the survival, remission, relapse rates, the development of a new clinical manifestation, and/or damage index. Patients with neuropsychiatric SLE (NPSLE), accompanied with acute confusional state/seizure disorder, cerebral vascular disease, or pneumonitis had poor survival rates with cause of death related to their major organ involvement. Patients with nephropathy or leukopenia had lower remission rates, and an increase in relapse rates was frequently recognized in patients with pneumonitis. Body damage (damage index) was higher in patients with lupus psychosis, pneumonitis, and/or arthritis. The translation of the main manifestations after diagnosis was confirmed in 64 patients (11.8%), and often observed in patients with autoimmune hemolytic anemia and arthritis. The majority of these manifestations were nephropathy, NPSLE, thrombocytopenia, and pneumonitis, and the prognosis of patients with nephropathy and thrombocytopenia as a new main manifestation had a poor outcome. The results of long-term prognosis in SLE greatly differed with respect to the initial clinical manifestation at the time of diagnosis.

Key words Clinical manifestation · Damage index · Relapse · Survival · Systemic lupus erythematosus (SLE)

Y. Tokano · S. Morimoto (✉) · H. Amano · T. Kawanishi · T. Yano · M. Tomyo · M. Sugawara · S. Kobayashi · H. Tsuda · Y. Takasaki · H. Hashimoto
Department of Rheumatology and Internal Medicine, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
Tel. +81-3-3813-3111 (ext. 3315); Fax +81-3-5800-4893
e-mail: morimoto@med.juntendo.ac.jp

Introduction

The prognosis for systemic lupus erythematosus (SLE) has greatly improved in the last two decades.[1–11] Some studies have reported of more than 80% survival rate of 10 years for SLE.[9,11] These improvements in prognosis were related to various factors. For example, the development of therapy[12,13] revealed by the use of steroid or immune suppressive agents, the increase in the number of patients with mild disease,[2,11] having only leukopenia or skin involvement without organ involvement, are considered. Also, these improvements have altered the cause of death. For example, SLE-related cause of death has decreased, while SLE-unrelated cause of death has increased.[11,14] Thus, a number of factors are related to the change in the outcome of prognosis.

Some studies have discussed these factors related to prognosis, for example, the relation to clinical manifestations,[1,3,8,9,15–24] age,[5,25] race,[7,17] and socioeconomic status.[25–28] Concerning clinical manifestations, nephritis or central nervous involvement (so-called neuropsychiatric SLE: NPSLE) have been known to have a poor prognosis, and many studies concerning lupus nephritis have been specifically reported,[29–34] while other studies have reported on the relationship with other involvements including thrombocytopenia, hemolytic anemia, serositis, and antiphospholipid syndrome.[3,9,18–21,24] These studies revealed the relationship with the prognosis possessed by each factor involved, including patients with relapse or the translation of the main manifestation after diagnosis. However, since patients with SLE have multiple organ involvement, the therapy administered is based according to the most severe manifestation. Also, there was a difference in prognosis between new-onset cases and cases with relapse or the translation of the main manifestation. Therefore, when long-term prognosis is discussed, the major problems of importance are how the manifestation at onset or initial diagnosis is related to the prognosis or cause of death, and how many patients have had a translation of their main manifestations after diagnosis. Since previous reports did

not consider these points, we cannot simply estimate their results in heterogeneous SLE patients. Furthermore, recent prognosis of SLE has also been assessed by factors other than the survival rate, for example, the rate of remission or relapse and body damage,[35] and the importance of these factors have been pointed out.

In this study, we evaluated the long-term prognosis of SLE patients divided according to organ involvement at the time of diagnosis, and discussed their relationship with the cause of death, translation of the main manifestation after diagnosis, or relapse and body damage.

Patients and methods

Patients

Patients in this study were examined and evaluated either as an outpatient or as an inpatient at Juntendo Hospital between 1970 and 1996. The medical records at initial diagnosis of patients who fulfilled the criteria of the American College of Rheumatology (ACR)[36] were retrospectively reviewed, and patients with a follow-up period of more than 2 years and all deceased patients were included. Regarding the results, a total of 542 patients were enrolled in this study. Two hundred patients between 1970 and 1979, 277 patients between 1980 and 1989, and 65 patients between 1990 and 1996 were enrolled. For analysis, these patients were divided into nine groups according to their major clinical manifestation confirmed with the ACR criteria at the time of diagnosis, as shown in Table 1. Generally, the major clinical manifestation was defined as the most severe manifestation, and patients with antiphospholipid antibody were excluded, since this antibody has a specific influence on prognosis. Also, patients with thrombotic thorombocytopenic purpura (TTP) and hemophagocytic syndrome (HPS) were excluded, since the number of such patients is extremely limited and the clinical manifestation and prognosis is unique. Although some patients with severe organ involvement (groups I–V) also had other manifestations, the most important involvement for steroid treatment was defined as the major clinical manifestation. Patients without organ involvement (groups VII–IX) were further divided into three groups by their main clinical manifestation, according to their order of importance in selection of treatment, as shown in Table 1. The profile of the clinical manifestation in these nine groups (groups I–IX) is summarized in Table 1. Patients with NPSLE (group I) were further divided into two groups: patients with neurological disorder (24 cases) and those with the so-called lupus psychosis (10 cases). The former was further subdivided into: patients with acute confusional state/seizure disorder (so-called organic brain syndrome) (13 cases), cerebral vascular disease (CVD) (4 cases), cranial nerve disturbance (1 case), peripheral neuropathy (3 cases), and so-called lupus headache (3 cases). Patients with thrombocytopenia (group III) had less than 50000/mm^3 platelet count and received high-dose steroid treatment. Among patients with serositis

Table 1. Definition and frequency of each group

Manifestations	Group								
	I	II	III	IV	V	VI	VII	VIII	IX
(With severe organ involvement)									
NPSLE (I)	○	×	×	×	×	×	×	×	×
Thrombocytopenia (II)†	△ (14.7)††	○	×	×	×	×	×	×	×
Pneumonitis (III)	△	△	○	×	×	×	×	×	×
Serositis (IV)	△	△	△ (18.2)	○	×	×	×	×	×
AIHA (V)	△ (2.9)††	△ (12.5)	△	△	○	×	×	×	×
Nephropathy (VI)	△ (91)†††	△ (62.5)	△ (27.5)	△ (47.8)	△ (5.9)	○	×	×	×
(Without organ involvement)									
Leukopenia (VII)	△ (55.8)	△ (79.1)	△ (63.6)	△ (73.9)	△ (70.5)	△ (61.3)	○	×	×
Skin involvement (VIII)	△ (73.5)	△ (33.3)	△ (27.2)	△ (43.2)	△ (29.4)	△ (68.3)	△ (58.6)	○	×
Joint (IX)	△ (64.7)	△ (70.8)	△ (45.6)	△ (73.9)	△ (70.5)	△ (80.3)	△ (74.1)	△ (74.7)	○
No. of patients	34	22	11	23	17	259	58	91	27
% (total patients)	6.3	4.1	2.0	4.2	3.1	47.8	10.7	16.8	5.0

NPSLE, neuropsychiatric systemic lupus erythematosus; AIHA, autoimmune hemolytic anemia
○, present in all patients and main manifestation; △, present in some patients (%); ×, not present
† Patients with this manifestation with a platelet count of less than 50 000/mm^3 were required to receive high dose steroid therapy
†† Patients with NPSLE and thrombocytopenia or AIHA demonstrated acute confusional state or lupus psychosis
††† Patients with mild NPSLE (cranial nerve disturbance, peripheral neuropathy and lupus headache) had no nephropathy or mild nephropathy (intermittent proteinuria)

(group IV), 5 had pericarditis and 1 had peritonitis. Patients with only renal involvement (group VI) were divided into two groups: patients who underwent renal biopsy examination and those who did not. The former were further divided by the classification of renal pathology for lupus nephritis proposed by the World Health Organization[37]: type I, 6 cases; type II, 35 cases; type III, 12 cases; type IV, 39 cases; and type V, 14 cases. The latter were further divided into three groups: patients with intermittent proteinuria, persistent proteinuria (<3.5 g/day), or nephritic syndrome (≥3.5 g/day). Other organ involvements in groups I–V are tabulated in Table 1. The patients with a mild type of NPSLE (group I) had no renal involvement (data not shown). Although some patients with thrombocytopenia had nephropathy, not all patients underwent renal biopsy due to bleeding tendency. The pathology of patients with serositis (group IV) who underwent renal biopsy were of WHO type III (1 case) or type IV (3 cases), and that of patients with pneumonitis (group III) were of WHO type III (1 case) or type IV (2 cases). One patient in group IV had pancreatitis.

Clinical manifestations presented at any time during the follow-up period for each patient were recorded. Although these manifestations were generally defined according to the SLE classification criteria,[36] some specific examinations were also performed. For example, electroencephalography, cerebral spinal fluid, magnetic resonance imaging, and single photo emission computer tomography were performed for the diagnosis of NPSLE, and pulmonary function test, chest computer tomography, ultra cardioechography were utilized for the diagnosis of serositis or pneumonitis.

The treatment generally administered was high-dose steroid therapy (more than 1 mg/kg per day of prednisolone) for patients with severe organ involvement (NPSLE with acute confusional state/seizure disorder or cerebral vascular disease, thrombocytopenia, autoimmune hemolytic anemia [AIHA], or pneumonitis), and severe nephropathy (WHO type III or IV nephritis or nephritic syndrome), medium-dose steroid therapy (0.5–1 mg/kg per day of prednisolone) for moderate organ involvement (WHO type V nephritis, lupus psychosis, serositis), and low-dose steroid therapy (less than 0.5 mg/kg per day of prednisolone) for mild organ involvement (leukopenia, skin involvement, joint involvement). Some patients with steroid resistance, severe adverse reaction, or difficulty in tapering of steroid administration received immunosuppressive agents (azathioprine, oral or intravenous cyclophosphamide).

Definition of remission, relapse, and the development of new clinical manifestation after diagnosis

"Remission" was determined within 6 months after the diagnosis, and defined as follows. In patients with nephropathy, the criteria described in our previous report[13] were utilized. In patients with NPSLE, the improvements in patient symptoms and findings of cerebral spinal fluid or electroencephalography were used. In patients with thrombocytopenia, AIHA, and leukopenia, improvement of laboratory data was used (platelet > 100 000/mm^3, white blood cell > 4000/mm^3, Hb > 10.0 g/dl). In patients with serositis or pneumonitis, improvements seen on chest X-ray, blood oxygen level, echocardiography, or computer tomography were used. In skin or joint involvement, the improvement of symptoms was used.

"Relapse" was defined by the reproduction of the initial manifestations which once improved and the increase in the dose of steroid administered. Relapse was recorded throughout the course if this definition was fulfilled. "The translation of a main manifestation after diagnosis" was defined as the appearance of a new manifestation after more than 6 months, and other involvement that appeared within 6 months from onset was classified as an initial manifestation.

Body damage

Body damage was estimated by the damage index described in the previous report.[35] Body damage was determined by the maximum damage index throughout the course.

Serological data

CH_{50} was determined using Mayer's method. Anti-DNA antibody was determined with Farr's assay, and anti-U1 RNP and Sm antibody were determined with the double immune diffusion method. The thrombocytic antibody count was determined with the positive reactivity to platelet or the increase of platelet adhered IgG (PAIgG).

Statistical analysis

Analysis of the survival rate was determined with the life table method, and differences among groups were compared using the generalized Wilcoxon test. The differences in rate of remission, relapse, and the development of new clinical manifestations were determined with the χ^2 test. The difference in the damage index was determined with the rank-sum test.

Results

Survival rate for each manifestation

Eighty-six of 542 patients (15.9%) died, and 61 patients (11.3%) died due to SLE-related causes. Twenty-five patients (4.6%) died due to SLE-unrelated causes, and the cause of death in 11 patients (2.0%) was related to secondary complications associated with treatment (infection and atherosclerosis). Sixteen patients with NPSLE (group I), 38 patients with nephropathy (group VI), and 32 patients with other manifestations (groups II–V, VII–IX) died. The survival rates in these groups were evaluated at 2, 5, 10, 15, and 20 years.

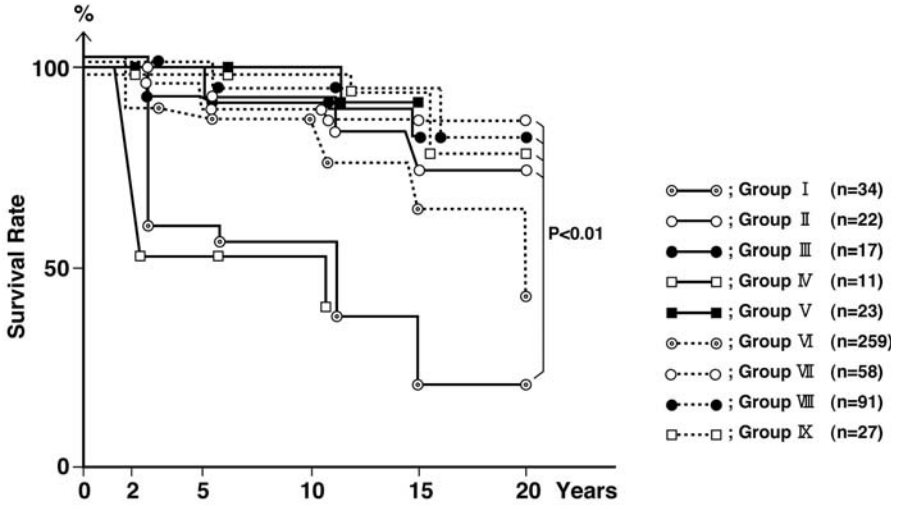

Fig. 1. Survival of patients in the nine groups described. The survival rate of patients with NPSLE (group I) and pneumonitis (group IV) was significantly lower than the other groups ($P < 0.01$).

The survival rates of each manifestation are shown in Fig. 1. Patients with NPSLE (group I) or pneumonitis (group III) had a poor prognosis, and the survival rate significantly decreased as compared with other groups (groups I, III versus groups II, IV, V, VI, VII, VIII, IX: $P < 0.01$). Patients with thrombocytopenia (group II), serositis (group IV), and AIHA (group V) generally had a good prognosis, similar to those with leukopenia (group VII), skin involvement (group VIII), or joint involvement (group IX). Among some groups, we evaluated the prognosis chronologically (1970–1979, 1980–1989, 1990–1996). However, no differences were revealed.

On the other hand, among patients with NPSLE (group I), patients with acute confusional state/seizure disorder and CVD had a poor prognosis, and the survival rates significantly decreased when compared to cranial nerve disturbance, peripheral neuropathy, or headache ($P < 0.05$: data not shown). Also, patients with psychosis had a moderately poor prognosis, although there was no significance. Although the survival rate of patients with nephropathy showed no significant difference in comparison with other groups, the survival rate of patients with WHO type III or nephritic syndrome significantly decreased when compared with other groups ($P < 0.01$: data not shown). However, when patients after 1980 were evaluated, the significance disappeared.

Cause of death for each manifestation

Next, the causes of death for each manifestation were evaluated. In patients with NPSLE, the most common cause of death in cases with acute confusional state/seizure disorder (10 cases) or CVD (2 cases) was convulsion or brain hemorrhage (11 cases) during the early stage of the disease course (less than 3 months), while that of patients with other manifestations (4 cases) was uremia (1 case) during the early stage, pneumonitis (1 case) as a development of a new manifestation, or SLE-unrelated cause of death (acute myocardial infarction [1 case], suicide [1 case]). The causes of death in patients with thrombocytopenia (group II; 4 cases) were bleeding (brain hemorrhage [1 case], gastrointestinal (GI) bleeding [1 case]), NPSLE (1 case), or pneumonitis (1 case) as the translation of the main manifestation. Among patients with pneumonitis (group III; 5 cases), the causes of death were pneumonitis (3 cases) or infections (2 cases), which mainly consisted of Carini pneumonia. Among patients with serositis (group IV; 2 cases), the causes of death were uremia (1 case) or pneumonitis (1 cases) as a translation of manifestation. Among patients with AIHA (group V; 2 cases), the causes of death were NPSLE (1 case) as a translation of a main manifestation, or infection (1 case). Among patients with nephropathy, the cause of death in 16 patients with WHO type III, type IV, persistent proteinuria, or nephritic syndrome was mainly uremia (14 cases), while only a few patients with intermittent proteinuria (1 case) and no patients with WHO type II or type V died due to uremia. The majority of the deaths caused by uremia occurred within 2 years after initial diagnosis, and were recorded in patients prior to 1980. Causes other than uremia were various. SLE-related causes were mainly identified in patients with WHO type III or type IV, or those without renal biopsy, and included pulmonary hypertension (PH), acute pneumonitis, pulmonary hemorrhage, and NPSLE. Most of these events occurred as the translation of a main manifestation. On the other hand, SLE-unrelated causes were mainly identified in WHO type I, type II, or type V, and included heart failure, infections, CVD, GI bleeding, malignancy, or suicide.

Patients without organ involvement (groups VII–IX; 19 cases) died due to various lesions associated with translation of the main manifestation (uremia [5 cases], NPSLE [1 case], PH–lung infarction [2 cases], vasculitis [1 case], intestinal perforation [2 cases]), or SLE-unrelated cause of death (infections [4 cases], heart failure [1 case], CVD [1 case], asthma [1 case]).

Remission, relapse, and body damage for each manifestation

The rates of remission within 2 years and those of relapse during 20 years of follow-up observation were evaluated for each manifestation, with the exception of patients who had

Table 2. Rate of remission, relapse, and damage index with each manifestation

Group[†]	Remission cases[a]	Relapse cases[b]	Damage index[b]
I ($n = 19$)	16 (84.2%)	2 (10.5%)	0.19 ± 0.4[e]
II ($n = 20$)	15 (75.0)	1 (5.0)	0.07 ± 0.26
III ($n = 5$)	3 (60.0)	2 (40.0)[d]	0.6 ± 0.54[e]
IV ($n = 16$)	15 (93.4)	0 (0)	0.04 ± 0.2
V ($n = 13$)	11 (84.6)	1 (7.7)	0.05 ± 0.22
VI ($n = 233$)	112 (48.1)[c]	25 (10.7)	0.11 ± 0.43
VII ($n = 44$)	21 (48.8)[c]	0 (0)	0.02 ± 0.13
VIII ($n = 51$)	33 (64.7)	0 (0)	0.08 ± 0.38
IX ($n = 22$)	16 (72.7)	3 (13.6)	0.18 ± 0.62[e]

[†] 119 patients who died within 2 years after onset were excluded, and the remaining 423 patients were included in these figures. The numbers indicate enrolled patients in each group
[a] The rate was calculated after 2 years
[b] The rate was calculated at the end point of the 20-year follow-up
[c] Significantly lower rate (VI/VII versus I/IV/V: $P < 0.01$)
[d] Significantly higher rate (III versus IV/VII/VIII: $P < 0.01$, II: $P < 0.05$)
[e] Significantly higher level (I versus IV/V/VII: $P < 0.001$; III versus II/IV/V/VII: $P < 0.001$; III versus VI/VIII: $P < 0.01$; IX versus VII: $P < 0.05$)

Table 3. Translation of a main manifestation in each group

New manifestation	Group (total number)									
	I (34)	II (22)	III (11)	IV (23)	V (17)	VI (259)	VII (58)	VIII (91)	IX (27)	Total (%)[a]
NPSLE		2			2	6	1	2	2	15 (30.6%)[d]
Thrombocytopenia				1		5			4	10 (31.3%)[d]
Pneumonitis	1	1				3				5 (31.3%)[d]
Serositis						1	1	1		3 (11.5%)
Nephropathy				4	3		6	10	3	26 (9.1%)
Others[b]						1				1
Total (%)	1 (2.9)	3 (13.6)	0 (0)	5 (21.7)	5[c] (29.4)	16 (7.3)	8 (13.7)	13 (14.3)	9 (33.3)	64 (11.8)

[a] The percentages indicate the number of new manifestations/this number + the number of this involvement at initial diagnosis
[b] Ulcerative colitis
[c] Significantly high ratio (V/IX versus I/VI: $P < 0.05$)
[d] Significantly high ratio (NPSLE, thrombocytopenia, and pneumonitis versus nephropathy: $P < 0.001$)

died within 2 years after onset. As shown in Table 2, group VI (nephropathy) and group VII (leukopenia) had significantly low rates of remission as compared to the other groups. In group VI, patients with WHO type V, intermittent proteinuria, and persistent proteinuria had low rates (data not shown). The low rate in group VII (leukopenia) was related to the fact that the leukocyte count as a parameter did not change significantly.

On the other hand, the rate of relapse was most significant in group III (pneumonitis) (Table 2). Although some patients in group VI (nephropathy) had relapse, these relapses were most frequently identified in patients with WHO type V.

Body damage was evaluated according to the damage index. As shown in Table 2, the patients in groups I (NPSLE), III (pneumonitis), and IX (arthritis) had a significantly higher damage index than the other groups. In group I, patients with psychosis had higher averages, and psychotic complications were related to these high averages. In group III, respiratory failure was related to the high average. Also, patients who received hemodialysis (HD) had higher averages in group VI. On the other hand, some patients had body damage related to adverse effects or complications (cataracts, angina, osteoporosis, avascular necrosis, osteomyelitis, premature gonadal failure, diabetes, and malignancy), and the majority of these patients were elderly and received high-dose steroid therapy. There was no relationship revealed between these adverse effects or complications and each group.

Translation of the main manifestation

The translation of the main manifestation was identified in 64 patients (11.8%), and most frequently recognized in groups IV (AIHA) and IX (arthritis), as shown in Table 3. The frequency of a new manifestation was significantly greater in NPSLE, thrombocytopenia, and pneumonitis, and the number was greatest in nephropathy (Table 3).

We also evaluated the prognosis of these patients, and the result was compared with those of patients with the same manifestation at initial diagnosis. As shown in Fig. 2A, patients with nephropathy as the translation of the main manifestation had a significantly poor prognosis ($P < 0.01$), and the majority of these patients originally belonged to

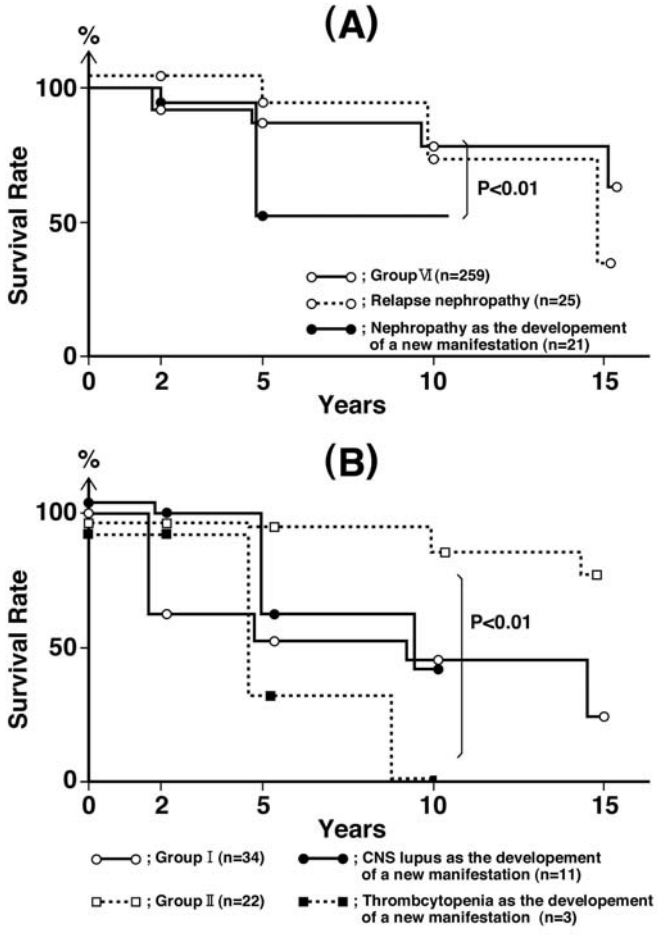

Fig. 2A,B. Survival rate of patients with translation of main manifestations. Patients followed for more than 2 years were selected in this comparison. **A** The prognosis of patients with nephropathy as the translation of a main manifestation. Twenty-five patients in group VI who had a relapse in the course were selected as relapse nephropathy for control. Patients with nephropathy as a new manifestation had a significantly worse prognosis than those with nephropathy at initial diagnosis (group VI) ($P < 0.01$). **B** The prognosis of patients with neuropsychiatric systemic lupus erythematosus (NPSLE) or thrombocytopenia as the translation of a main manifestation. Patients with thrombocytopenia as a new manifestation had a significantly worse prognosis than patients who initially had thrombocytopenia (group II) ($P < 0.01$), while in patients with NPSLE as a new manifestation, a similar prognosis to those with initial NPSLE was observed

groups VII (leukopenia), VIII (skin involvement), and IX (joint involvement). Concerning NPSLE, the difference in prognosis with translation of main manifestation was not recognized (Fig. 2B). With thrombocytopenia, patients with translation of the main manifestation had a significantly poor prognosis ($P < 0.01$) (Fig. 2B).

Factors related to translation of the main manifestation

Finally, we evaluated the factors related to the translation of main manifestation. First, we focused on the clinical data within 2 years from onset. As shown in Table 4, patients with translation of the main manifestation tended to have higher levels of anti-DNA antibodies, although there was no significance. There was also no significance in anti-U1 RNP, Sm antibody, and CH_{50} (Table 4). Although there was no significance in remission, some patients had the worst symptoms concerned with the original manifestation prior to the translation of a main manifestation.

Discussion

This single-center study is important from the standpoint that the majority of the patients received a uniform, standard form of treatment. The first characteristic of this study is the fact that the prognosis was estimated according to the clinical manifestation at the time of initial diagnosis. Previous studies enrolled patients with various disease courses or manifestations. However, we believe that the relationship between prognosis and organ involvement should be discussed as the main clinical manifestation at the time of initial diagnosis, since it is possible that some patients might have multiple organ involvement, and that the most critical manifestation among these involvements is related to the prognosis. We therefore divided these patients according to the main clinical manifestation for the investigative purpose of this study. As to the results, we were able to reveal that the prognosis and the cause of death greatly differed among these subclassification groups. For example, in patients with NPSLE, especially those with acute confusional state/seizure disorder or CVD type, had a poor prognosis and the death was caused by NPSLE-related factors. These results support the view that patients with acute confusional state/seizure disorder or CVD type require intensive therapy, as previously reported.[38] However, the prognosis of patients with recent onset of acute confusional state/seizure disorder or CVD type did not reveal any improvement, although steroid pulse therapy for these cases had been established. Thus, the management for acute confusional state/seizure disorder or CVD type of NPSLE still remain as an important issue, although some reports[22,23] neglect the relationship between the prognosis and NPSLE. Furthermore, patients with pneumonitis also had a worse prognosis, resulting in death due to this manifestation. This result suggests that the management of pneumonitis also remains as an important issue. On the other hand, patients with nephropathy did not have a relatively poor prognosis. Certainly, some patients with WHO type III or nephritic syndrome had a poor prognosis, resulting in death due to uremia. However, the majority of the deceased patients was evaluated within the last 20 years, and the deaths due to uremia have markedly decreased with the development of HD. Although previous reports have stressed nephritis as the risk factor of survival,[1,3,4] at least death due to uremia has not been a major problem in recent times. Rather, interestingly, some patients with WHO type III or type IV, or those without renal biopsy had nonrenal causative factors of death with the translation of the main manifestation, while most patients with WHO type I or type II died due to SLE-unrelated causes. This result suggests that care for other

Table 4. Clinical data of patients with or without the translation of a main manifestation

	With translation (n = 23)	Without translation (n = 60)	Significance
CH_{50} (U)			
Initial diagnosis	30.8 ± 8.5	29.3 ± 8.7	n.s.
After 2 years	27.4 ± 7.2	28.5 ± 7.1	n.s.
Anti-DNA antibody (IU/ml)			
Initial diagnosis	50.1 ± 83.6	20.5 ± 23.4	n.s.
After 2 years	47.1 ± 52.5	32.9 ± 79.6	n.s.
Anti-Sm antibody (+)	16.7%	14.6%	n.s.
Anti-U1-RNP antibody (+)	38.5%	39.0%	n.s.
Remission rate (after 2 years)	43.5%	39.3%	n.s.

severe organ involvement is required during the disease course of patients with severe nephropathy, and that SLE-unrelated cause of death is an important risk in those with mild nephropathy, even though the nephritic condition may have improved. Even if the patient suffered from renal failure and received HD, some patients may die due to nonrenal factors (infection, etc.), so specific care is required. Furthermore, concerning other manifestations the prognosis of patients with thrombocytopenia, AIHA, and serositis had a better prognosis, although some previous reports have pointed out the importance of thrombocytopenia.[18,19,22,23,35] This discrepancy may be related to the fact that patients with antiphospholipid antibody, TTP, and HPS were included in these previous studies. Indeed, our study reveals that these patients have specific results concerning the survival rate, remission, relapse, and body damage (data not shown). Therefore, we believe that patients with thrombocytopenia had a good prognosis except those with antiphospholipid antibody, TTP, and HPS. Concerning the cause of death, most patients with thrombocytopenia died due to bleeding tendency. Although patients with severe organ involvement had other involvements, the prognosis tended to be influenced by the main clinical manifestation, and this manifestation, not unexpectedly, is of major importance.

The second characteristic of this study is the fact that we also focused on remission, relapse, body damage, and the translation of the main manifestation, and related them to the prognosis. Although low rates of remission and high rates of relapse were recognized in patients with WHO type V nephropathy or pneumonitis, other manifestations were revealed to have generally excellent results, suggesting that the present therapy generally induces efficient remission. However, the problem concerning the translation of main manifestation cannot be ignored. In this study, the translation of main manifestation was recognized in 11.8% of the patients, and was frequently recognized in patients with AIHA, serositis, and leukopenia as the main manifestation at the time of initial diagnosis. Also, the prognosis of patients with translation was generally worse when compared with that of patients with the same manifestation at the time of initial diagnosis. These results suggest the importance of management for cases with translation. Although prediction for having the translation is difficult, worsening of symptoms and the change in the anti-DNA antibody level may be an important clue. Moreover, we cannot ignore the possibility that the high frequency in patients with mild involvement at initial diagnosis is related to the low dose of steroid therapy. However, we do not believe that this possibility requires intensive therapy, since most of these patients were cured by low-dose steroid therapy. On the other hand, differences were also identified concerning body damage among these groups. For example, patients with lupus psychosis or pneumonitis have a higher level of body damage. This result suggests that management of body damage and quality of life is also required for these manifestations. Since the type of damage is related to each manifestation, a variety of management protocols may be required for body damage of each manifestation. Most parameters of disease activity, for example, SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), tend to emphasize only a limited lesion, while our damage index covers various lesions. Therefore, this index was useful in this study. However, the problem is that this index contains items concerning adverse effects. Indeed, we ignored this influence, even though the result concerning the damage index did not change when we excluded this item concerning the adverse effect.

The prognoses of our SLE patients were generally favorable, and further, intravenous cyclophosphamide[39] or cyclosporine A[40] have recently contributed to the improvement of prognosis in treatment-resistant nephropathy or pneumonitis cases. Home oxygen therapy has also contributed to the improvement in quality of life in patients with pneumonitis. However, some patients with these manifestations still have poor outcomes, resistance to treatment, and poor quality of life, and treatment and management of these patients are important issues to consider in the future. Although the rate of death was not so high, the management for adverse reactions to treatment is also an important issue. In addition, it is also important that some patients had a poor prognosis due to lack of comprehension of the disease or treatment, and some previous studies pointed out the importance of socioeconomic status in the prognosis of SLE.[25–28] This problem is very difficult and may remain as a topic of concern for a long time in the future. Lastly, we would like to stress that the establishment of a concrete diagnosis of the clinical manifestation and the selection of treatment for this manifestation are important issues for the management of SLE.

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