OPEN

Thrombocytopenia in Systemic Lupus Erythematosus

Clinical Manifestations, Treatment, and Prognosis in 230 Patients

Jin-Hee Jung, MD, Moon-Seung Soh, MD, Young-Hwan Ahn, MD, Yoo-Jin Um, MD, Ju-Yang Jung, MD, Chang-Hee Suh, MD, PhD, and Hyoun-Ah Kim, MD, PhD

Abstract: The aim of the study was to examine the clinical characteristics and prognosis according to severity of thrombocytopenia and response to treatment for thrombocytopenia in patients with systemic lupus erythematosus (SLE).

We retrospectively evaluated 230 SLE patients with thrombocytopenia, and reviewed their clinical data and laboratory findings. Thrombocytopenia was defined as platelet counts under $100,000/mm^3$, and patients were divided into 3 thrombocytopenia groups according to severity: mild (platelet counts $>50,000/mm^3$), moderate ($>20,000/mm^3$, $\leq50,000/mm^3$), and severe ($\leq20,000/mm^3$). Clinical characteristics, treatments, and prognoses were compared among the groups. Furthermore, complete remission of thrombocytopenia was defined as platelet counts $>100,000/mm^3$ after treatment.

There was no significant difference in clinical or laboratory findings among the groups according to severity of thrombocytopenia. However, hemorrhagic complications were more frequent in severe thrombocytopenia ($P < 0.001$) and mortality was also higher ($P = 0.001$). Complete remission was achieved in 85.2% of patients. The clinical characteristics and modality of treatment did not differ between the patients with and without complete remission. Mortality in patients with complete remission (1.5%) was significantly lower than in those without complete remission (29.4%, $P < 0.001$). Survival was significantly higher in patients with complete remission from thrombocytopenia (odds ratio = 0.049, 95% confidence interval: 0.013–0.191, $P < 0.001$).

The severity of thrombocytopenia in SLE patients can be a useful independent prognostic factor to predict survival. Moreover, complete remission of thrombocytopenia after treatment is an important prognostic factor. The severity of thrombocytopenia and response to treatment should be closely monitored to predict prognosis in SLE patients.

(*Medicine* 95(6):e2818)

Abbreviations: ACR = American College of Rheumatology, ANA = antinuclear antibodies, anti-dsDNA = anti-double-stranded DNA, C3 = complement 3, C4 = complement 4, CI = confidence interval, SLE = Systemic lupus erythematosus, SLEDAI = systemic lupus erythematosus disease activity index.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting diverse organs of the body and causing chronic inflammation. It shows a broad spectrum of clinical manifestations and is associated with several autoantibodies.[1] Hematologic abnormalities, including thrombocytopenia and leucopenia, are common clinical manifestations of SLE. Thrombocytopenia is known as one of the hematological criteria of SLE, according to the American College of Rheumatology (ACR) classification criteria.[2] Its prevalence has been estimated to range from 10% to 40%, but severe thrombocytopenia is relatively uncommon.[3,4]

There have been several studies about the association between thrombocytopenia and prognosis in SLE patients.[4–9] In previous studies, thrombocytopenia has been shown to be associated with other severe clinical manifestations of SLE, such as neuropsychiatric symptoms, kidney involvement, and hemolytic anemia.[5,8–10] It is also known to have an association with the prognosis of SLE, including death.[5,8,9,11–13] However, the characteristics and prognosis according to severity of thrombocytopenia have been examined in few studies. Moreover, the prognosis according to remission of thrombocytopenia is unknown.

Therefore, in this study, we retrospectively reviewed patients with SLE who developed thrombocytopenia, and analyzed differences in clinical and laboratory findings and prognosis according to severity of thrombocytopenia. Furthermore, we investigated the treatment of thrombocytopenia, and whether remission of thrombocytopenia was associated with other clinical manifestations and prognosis.

METHODS

Subjects

We retrospectively reviewed 267 SLE patients with thrombocytopenia who attended the Department of Rheumatology of Ajou University Hospital from July 1997 to May 2015. All patients met 4 or more of the ACR criteria for the diagnosis of SLE, and all patients had antinuclear antibodies (ANA).[2] Thrombocytopenia secondary to lupus was defined according to the ACR criteria as a platelet count of $<100,000/mm^3$. Thirty-seven patients were excluded with other causes related to thrombocytpenia, such as drug-induced thrombocytpenia, sepsis, chemotherapy for combined malignancy, hematological disease (diagnosed by bone marrow biopsy), and liver cirrhosis. As a result, 230 patients were enrolled.

We divided patients according to severity of thrombocytopenia into 3 groups (mild, moderate, and severe), and compared baseline demographic, clinical, and laboratory findings. Mild thrombocytopenia was defined as platelet counts of $>50,000/mm^3$, whereas platelet counts between $20,000/mm^3$ and $50,000/mm^3$ were classified as moderate thrombocytopenia, and severe thrombocytopenia was defined as platelet counts of $\leq20,000/mm^3$.

Patients were excluded if their medical records were incomplete or insufficient for diagnosis of SLE at the time of diagnosis and throughout the follow-up period. This study was approved by the Institutional Review Board of our hospital (AJIRB-MED-OBS-15-233).

Variables

We ascertained the age at the time the lowest thrombocytopenia appeared, gender, and smoking history of the patients. We reviewed laboratory findings and clinical manifestations at the time that the platelet count was lowest and throughout the follow-up period. Laboratory results including complete blood counts, C-reactive protein, erythrocyte sedimentation rate, complement (C3 and C4), and autoantibodies were recorded. Autoantibodies included ANA, anti-double-stranded DNA (anti-dsDNA) antibody, anti-Sm, anti-RNP, anti-Ro, anti-La, IgG and IgM anticardiolipin antibody, and lupus anticoagulant. We also investigated clinical manifestations, such as mucocutaneous, musculoskeletal, pulmonary, cardiac, renal, neurological, and hematological manifestations described by the ACR. Disease activity at the time of thrombocytopenia was assessed using the SLE Disease Activity Index (SLEDAI).[14]

We also reviewed medications used for managing thrombocytopenia. The use of glucocorticoids, hydroxychloroquine, cyclophosphamide, azathioprine, tacrolimus, danazol, intravenous immunoglobulin, and rituximab was recorded. In addition, the initial dose of glucocorticoids (prednisone equivalent) for controlling thrombocytopenia was calculated.

We investigated numbers of hospitalization and chief complaints at that time of the patients throughout the follow-up period. A relapse of thrombocytopenia was defined as a reduction of the platelet count $<100,000/mm^3$ after complete remission (at least 2 consecutive increases of platelet counts $>100,000/mm^3$). We counted number of hospitalizations due to hemorrhagic manifestations, infectious complications, or flares of SLE, defined as an increase of the SLEDAI score of >4 in comparison with the previous SLEDAI score. Follow-up period was defined as the duration from the time of the most severe thrombocytopenia to May 2015 or to the time of follow-up loss, including deaths.

Statistical Analysis

All data are expressed as means ± standard deviation, and a *P* value of <0.05 was considered to indicate statistical significance. Clinical features and laboratory findings were compared among the groups (mild, moderate, and severe thrombocytopenia) using one-way ANOVA for continuous variables and Pearson χ^2 test for categorical variables. The characteristics of patients with and without complete remission were compared with independent *t* tests for continuous variables and Pearson χ^2 for categorical variables. In addition, the variables that had effects on mortality were analyzed by logistic regression analysis. The association between mortality and complete remission of thrombocytopenia was examined with a Cox proportional hazard model. The Kaplan-Meier method was used to prepare survival curves. The SPSS for Windows software (ver. 12.0; SPSS Inc, Chicago, IL) was used for statistical analyses.

RESULTS

Clinical Findings in SLE Patients With Thrombocytopenia

Table 1 shows the clinical characteristics and laboratory findings according to severity of thrombocytopenia in 230 SLE patients with thrombocytopenia. Of the 230 patients, 126 (54.8%), 57 (24.8%), and 47 (20.4%) had mild (platelet count $>50,000/mm^3$), moderate (platelet count $>20,000/mm^3$, $\leq50,000/mm^3$), and severe thrombocytopenia (platelet count $\leq20,000/mm^3$), respectively. The mean age of the 230 SLE patients with thrombocytopenia was 41.8 ± 15.3 years and 84.3% were women. The mean duration of follow-up was 65.8 ± 48.2 months. Thrombocytopenia developed a mean duration of 23.7 ± 58.1 months after SLE diagnosis. There were no significant differences in mean age or gender distribution among the groups. Clinical features also showed no difference among groups except hemolytic anemia. Hemolytic anemia was more common in patients with moderate (28.1%) and severe thrombocytopenia (27.7%) than in those with mild thrombocytopenia (11.1%, $P = 0.005$). Disease activity did not differ among the groups.

White blood cell count and hemoglobin levels were significantly different among the groups. Hypocomplementemia 4 were most common in the moderate thrombocytopenia group ($P = 0.031$), and the mean titer of anti-dsDNA was highest in that group ($P = 0.001$).

There was no difference in the use of glucocorticoids or hydroxychloroquine among the groups (Table 2). However, the dose of glucocorticoids used for the initial treatment of thrombocytopenia was higher in the severe thrombocytopenia group (478.4 ± 585.3 mg/d of prednisolone equivalent) versus the mild and moderate thrombocytopenia groups ($P = 0.001$). The use of danazol, azathioprine, cyclophosphamide, intravenous immunoglobulin, and rituximab was more common in severe thrombocytopenia ($P < 0.001$, 0.033, <0.001, <0.001, and 0.02, respectively). Three patients had splenectomies for the treatment of thrombocytopenia; all of them had severe thrombocytopenia.

In patients with severe thrombocytopenia, the rate of complete remission was lower (31 patients, 66%) than in those with mild (116 patients, 92.1%) or moderate thrombocytopenia (49 patients, 86%, $P < 0.001$). Total numbers of hospitalizations were not different among the groups. However, relapse was more frequent in patients with severe thrombocytopenia (3.23 ± 3.14) than in patients with mild (1.61 ± 1.63) or moderate (1.81 ± 1.58, $P < 0.001$) thrombocytopenia. Hospitalizations due to hemorrhagic manifestations were more frequent in the severe thrombocytopenia group (0.36 ± 0.67, $P < 0.001$). Mortality was significantly elevated according to the severity of thrombocytopenia (14.9% vs 8.8% vs 0.8%, $P = 0.001$; Table 2).

Comparison Between Patients With and Without Complete Remission

We divided the patients into 2 groups according to achieving for complete remission of thrombocytopenia after treatment. In total, 196 (85.2%) patients achieved complete remission, defined as a platelet count $>100,000/mm^3$ in 2 consecutive tests after treatment. The mean age differed significantly; 40.1 ± 14.5 years in patients with complete remission and 51.1 ± 16.7 years in those without complete remission ($P < 0.001$). Other clinical features of SLE showed no difference between the 2 groups. The mean SLEDAI score was 8.7 ± 5.7 in patients with complete remission compared with 6.7 ± 6.3 in those without complete remission; this difference was not significant. Anti-dsDNA antibody was higher in the complete remission group ($P < 0.001$; Table 3).

There was no difference in treatment between the 2 groups except use of danazol. The use of danazol was more frequent in

TABLE 1. Basal Characteristics and Laboratory Findings of 230 Patients Classified by Severity of Thrombocytopenia

	All (n = 230)	≤20 ($\times 10^3$/mm^3) (n = 47)	>20 ($\times 10^3$/mm^3), ≤50 ($\times 10^3$/mm^3) (n = 57)	>50 ($\times 10^3$/mm^3) (n = 126)	P
Age, y	41.8 ± 15.3	45 ± 16.1	41.3 ± 14.6	40.8 ± 15.3	0.265
Woman (%)	194 (84.3)	38 (80.9)	49 (86)	107 (84.9)	0.596
Smoking (%)	34 (14.8)	10 (21.3)	9 (15.8)	15 (11.9)	0.294
Clinical manifestations					
Malar rash (%)	35 (15.2)	5 (10.6)	12 (21.1)	18 (14.3)	0.308
Skin rash (%)	35 (15.2)	7 (14.9)	7 (12.3)	21 (16.7)	0.745
Alopecia (%)	29 (12.6)	3 (6.4)	11 (19.3)	15 (11.9)	0.134
Photosensitivity (%)	26 (11.3)	6 (12.8)	6 (10.5)	14 (11.1)	0.933
Oral ulcer (%)	38 (16.5)	8 (17)	9 (15.8)	21 (16.7)	0.984
Arthritis (%)	75 (32.6)	11 (23.4)	24 (42.1)	40 (31.7)	0.123
Serositis (%)	33 (14.3)	7 (14.9)	10 (17.5)	16 (12.7)	0.682
Renal involvement (%)	91 (39.6)	17 (36.2)	26 (45.6)	48 (38.1)	0.545
CNS involvement (%)	14 (6.1)	5 (10.6)	3 (5.3)	6 (4.8)	0.34
Hematologic abnormality (%)					
Leukopenia	81 (35.2)	13 (27.7)	18 (31.6)	50 (39.7)	0.271
Hemolytic anemia	43 (18.7)	13 (27.7)	16 (28.1)	14 (11.1)	0.005
Fever (%)	85 (37)	11 (23.4)	25 (43.9)	49 (38.9)	0.079
SLEDAI	8.4 ± 5.8	7.2 ± 6	9 ± 5.8	8.6 ± 5.8	0.255
Follow-up duration, mo	65.8 ± 48.2	71.6 ± 51.5	68 ± 48.8	62.9 ± 46.7	0.532
Thrombocytopenia development from SLE diagnosis, mo	23.7 ± 58.1	10.6 ± 50.5	29.1 ± 54.1	26.2 ± 61.9	0.21
Laboratory findings					
WBC ($\times 10^3$/mm^3)	5.1 ± 3.8	6.6 ± 4.9	5.3 ± 4.3	4.3 ± 2.7	0.001
Hemoglobin, g/dL	10.3 ± 2.3	10 ± 2.4	9.4 ± 2.8	10.7 ± 2.1	0.016
ESR, mm/h	29.6 ± 26.6	30.7 ± 30.9	29.7 ± 28.2	29 ± 23.7	0.889
CRP, mg/dL	2.56 ± 5.49	3.25 ± 6.54	3.81 ± 7.64	1.83 ± 3.86	0.054
Complement 3, mg/dL	71.5 ± 37.1	79.3 ± 39	54 ± 36.5	72.1 ± 34.8	0.056
Complement 4, mg/dL	15.5 ± 11	16.7 ± 11.8	10.2 ± 8.8	16.3 ± 10.7	0.031
Autoantibodies					
Anti-dsDNA antibody, IU/mL	28. 5 ± 36.1	13.8 ± 20.3	40.6 ± 42.5	28.6 ± 35.7	0.001
Anti-RNP (%)	36/179 (20.1)	2/31 (6.5)	11/44 (25)	23/104 (22.1)	0.105
Anti-Sm (%)	16/179 (8.9)	2/31 (6.5)	4/44 (9.1)	10/104 (9.6)	0.863
Anti-Ro (%)	71/183 (38.8)	15/36 (41.7)	10/41 (24.4)	46/106 (43.4)	0.098
Anti-La (%)	18/183 (9.8)	4/36 (11.1)	3/41 (7.8)	11/106 (10.4)	0.821
Anti-cardiolipin IgM (%)	110/224 (49)	26/47 (55.3)	29/56 (51.8)	55/121 (45.5)	0.465
Anti-cardiolipin IgG (%)	72/224 (32.1)	11/47 (23.4)	23/56 (41.1)	38/121 (31.4)	0.155
Lupus anticoagulant (%)	66/218 (30.3)	16/45 (35.6)	18/54 (33.3)	32/119 (26.9)	0.477

anti-dsDNA antibody = anti-double stranded DNA antibody, CNS = central nervous system, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, SLEDAI = systemic lupus erythematosus disease activity index, WBC = white blood cell.

The *P* values show differences among the 3 groups by using one-way ANOVA and Pearson χ^2 test.

the group without complete remission (11.8%, *P* = 0.004; Table 4). The frequency of hospitalization was similar between the 2 groups. Mortality in patients with complete remission (1.5%) was significantly lower than in those without complete remission (29.4%, *P* < 0.001).

Variables Affecting Mortality in SLE Patients With Thrombocytopenia

We analyzed the variables affecting the mortality (Table 5). Disease activity, presenting as SLEDAI score, was significantly related to mortality (odds ratio [OR] = 1.111, 95% confidence interval [CI]: 1.015–1.216, *P* = 0.022). Mortality was significantly lower in the group with complete remission (OR = 0.049, 95% CI: 0.013–0.191, *P* < 0.001; Figure 1). Furthermore, we compared mortality according to the treatment

of thrombocytopenia. We divided patients according to 5 treatment steps: patients used only hydroxychloroquine for step 1, with glucocorticoids regardless of the use of hydroxychloroquine for step 2; patients were treated with glucocorticoids and cyclophosphamide regardless of the use of hydroxychloroquine in step 3, and were treated with glucocorticoids and intravenous immunoglobulin in step 4; finally, patients underwent a splenectomy or used rituximab in step 5. Among these treatment groups, there was no significant difference in mortality rate. This means the complete remission from thrombocytopenia was an independent predictor of survival.

The causes of death were variable. Infection, including pneumonia and other sepsis, was most common (7 patients, 53.8%). Hemorrhagic manifestations, like intracranial hemorrhage and hemoptysis, were also causes of death in 2 patients. Two patients died due to renal failure and pulmonary edema

TABLE 2. Treatment and Prognosis of 230 Patients Classified by Severity of Thrombocytopenia

	All (n = 230)	≤20 (×10³/mm³) (n = 47)	>20 (×10³/mm³), ≤50 (×10³/mm³) (n = 57)	>50 (×10³/mm³) (n = 126)	*P*
Glucocorticoid (%)	208 (90.4)	45 (95.7)	54 (94.7)	109 (86.5)	0.082
Initial dose of glucocorticoid (mg, prednisolone equivalent)	258.2 ± 479.5	478.4 ± 585.3	284.6 ± 487.2	41.8 ± 83	0.001
Hydroxychloroquine (%)	184 (80)	33 (70.2)	48 (84.2)	103 (81.7)	0.158
Danazol (%)	8 (3.5)	7 (14.9)	1 (1.8)	0 (0)	<0.001
Azathioprine (%)	19 (8.3)	8 (17)	5 (8.8)	6 (4.8)	0.033
Tacrolimus (%)	7 (3)	1 (2.1)	1 (1.8)	5 (4)	0.664
Cyclophosphamide (%)	45 (19.6)	10 (21.3)	22 (38.6)	13 (10.3)	<0.001
IVIG (%)	43 (18.7)	28 (59.6)	12 (21.1)	3 (2.4)	<0.001
Rituximab (%)	2 (0.9)	2 (4.3)	0 (0)	0 (0)	0.02
Splenectomy (%)	3 (1.3)	3 (6.4)	0 (0)	0 (0)	0.03
Complete remission (%)	196 (85.2)	31 (66)	49 (86)	116 (92.1)	<0.001
Duration to complete remission, d	88.4 ± 262.3	118.5 ± 308.2	178.9 ± 434.6	41.8 ± 83	0.006
Frequency of flare	1.72 ± 2.3	1.26 ± 1.57	1.88 ± 2.16	1.82 ± 2.58	0.304
Frequency of relapse	0.35 ± 0.78	3.23 ± 3.14	1.81 ± 1.58	1.61 ± 1.63	<0.001
Number of hospitalizations	3.47 ± 3.72	3.57 ± 4.49	3.54 ± 3.55	3.39 ± 3.51	0.943
Chief complaint at hospitalization					
Hemorrhagic manifestations	0.14 ± 0.44	0.36 ± 0.67	0.12 ± 0.47	0.06 ± 0.25	<0.001
Infection	0.61 ± 1.38	0.6 ± 1.44	0.84 ± 1.53	0.52 ± 1.29	0.336
Thrombosis	0.07 ± 0.30	0.13 ± 0.45	0.04 ± 0.19	0.06 ± 0.28	0.283
Death (%)	13 (5.6)	7 (14.9)	5 (8.8)	1 (0.8)	0.001

IVIG = intravenous immunoglobulin.
The *P* values show differences among the 3 groups by using one-way ANOVA or Pearson χ^2 test.

caused by disease flare with lupus nephritis. In addition, 2 patients expired because of their malignancies (ovarian cancer and anal cancer).

DISCUSSION

This is the first reported study to analyze differences in clinical manifestations, treatment, and prognosis according to severity of thrombocytopenia in SLE patients. Furthermore, we evaluated the clinical characteristics of patients who were recovered to platelet counts >100,000/mm³, and assessed a possible relationship between complete remission from thrombocytopenia and prognosis.

Thrombocytopenia is a common clinical manifestation in SLE, and several investigators have reported close associations between thrombocytopenia and serious clinical manifestations.[4,13] In some studies, patients who were thrombocytopenic more frequently exhibited neurological manifestations, kidney disorders, and hematological abnormalities.[5,6,8–10,15,16] Low complement levels and elevated anti-dsDNA antibody have also been observed among patients with thrombocytopenia.[5,15] Furthermore, most previous studies showed that disease activity also correlated with thrombocytopenia.[5] In this study, we evaluated whether several clinical manifestations, and disease activity, of SLE showed correlations with the severity of thrombocytopenia, although we did not compare the SLE patients who were thrombocytopenic to those who were not. Our data showed that the severity of thrombocytopenia was not related to other clinical manifestations, including neurological symptoms, kidney involvement, and disease activity. However, hemolytic anemia was more frequent in patients with platelet counts <50,000/mm³ than those with mild thrombocytopenia. In addition, the patients with moderate thrombocytopenia

(platelet count >20,000/mm³, ≤50,000/mm³) had higher anti-dsDNA antibody levels and lower complement levels, and it maybe reflecting a direct effect of SLE disease activity than the patients with mild or severe thrombocytopenia.

Because of the pathogenesis of thrombocytopenia in SLE, which is immune system-mediated, glucocorticoids are used as the first-line treatment.[17] For patients who fail to respond to glucocorticoids or those who require continuous moderate doses of glucocorticoids to treat the thrombocytopenia, second-line therapeutic agents, including azathioprine, cyclophosphamide, danazol, and intravenous gamma globulin, have been used to treat thrombocytopenia in SLE.[17–19] There are many case reports indicating that hydroxychloroquine, intermittent cyclophosphamide, danazol, intravenous immunoglobulin, and anti-CD20 antibody (rituximab) had positive effect in treating thrombocytopenia.[18–25] In this study, second-line therapeutic agents, such as danazol, azathioprine, cyclophosphamide, and intravenous immunoglobulin, were used mainly in patients with severe thrombocytopenia. A recent study reported that 88% of patients responded to treatment, and that a complete response (platelet counts >150,000/mm³) was observed in 61%.[26] Although their definition of complete remission was different, in our study we showed that 85.2% of patients experienced complete remission, with platelet counts >100,000/mm³ after treatment. We analyzed the characteristics of the patients with complete remission, and they tended to be younger than those without complete remission and had less severe thrombocytopenia.

Factors associated with prognosis of SLE are known to include man gender, age at first diagnosis of SLE, and renal, heart, and central nervous system involvement at disease onset.[7] In previous studies, the mortality of thrombocytopenic patients with SLE was significantly high.[5,6,13,15] The mortality of

TABLE 3. Basal Characteristics and Laboratory Findings According to Complete Remission of Thrombocytopenia

	Complete Remission (n = 196)	Without Complete Remission (n = 34)	*P*
Age, y	40.1 ± 14.5	51.1 ± 16.7	<0.001
Woman (%)	167 (85.2)	27 (79.4)	0.391
Smoking (%)	26 (13.3)	8 (23.5)	0.12
Clinical manifestations			
Malar rash (%)	31 (15.8)	4 (11.8)	0.544
Skin rash (%)	29 (14.8)	6 (17.6)	0.669
Alopecia (%)	25 (12.8)	4 (11.8)	0.872
Photosensitivity (%)	20 (10.2)	6 (17.6)	0.206
Oral ulcer (%)	31 (15.8)	7 (20.6)	0.489
Arthritis (%)	66 (33.7)	9 (26.5)	0.408
Serositis (%)	4 (11.8)	29 (14.8)	0.794
Renal involvement (%)	78 (39.8)	13 (38.2)	0.864
CNS involvement (%)	12 (6.1)	2 (5.9)	0.957
Hematologic abnormality (%)			
Leukopenia	71 (36.2)	10 (29.4)	0.443
Hemolytic anemia	36 (18.4)	7 (20.6)	0.759
Severe thrombocytopenia <20,000/mm^3 (%)	31 (15.8)	16 (47.1)	<0.001
Fever (%)	76 (38.8)	9 (26.5)	0.17
SLEDAI	8.7 ± 5.7	6.7 ± 6.3	0.069
Follow-up duration, mo	69.3 ± 46.9	46 ± 51.1	0.008
Thrombocytopenia development from SLE diagnosis, mo	24.9 ± 57.3	16.9 ± 62.4	0.459
Laboratory findings			
WBC (×10^3/mm^3)	4.9 ± 3.6	6.3 ± 5.1	0.056
Hemoglobin, g/dL	10.4 ± 2.3	9.9 ± 2.6	0.319
Platelet (×10^3/mm^3)	55.6 ± 29.2	34.6 ± 29.9	<0.001
ESR, mm/h	30.5 ± 26.8	24.8 ± 25.7	0.253
CRP, mg/dL	2.18 ± 4.85	4.73 ± 8.04	0.082
Complement 3, g/dL	71.4 ± 37.2	71.9 ± 36.6	0.942
Complement 4, mg/dL	15.4 ± 10.8	16.4 ± 11.9	0.625
Autoantibodies			
Anti-ds DNA antibody, IU/mL	31.3 ± 37.3	12.5 ± 22.1	<0.001
Anti-RNP (%)	34/156 (21.8)	2/23 (8.7)	0.143
Anti-Sm (%)	13/156 (8.3)	3/23 (13)	0.46
Anti-Ro (%)	62/157 (39.5)	9/26 (34.6)	0.637
Anti-La (%)	15/157 (9.6)	3/26 (11.5)	0.753
Anti-cardiolipin IgM (%)	93/193 (48.2)	17/31 (54.8)	0.492
Anti-cardiolipin IgG (%)	64/193 (33.2)	8/31 (25.8)	0.416
Lupus anticoagulant (%)	57/188 (30.3)	9/30 (30)	0.972

anti-dsDNA antibody = anti-double stranded DNA antibody, CNS = central nervous system, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, SLEDAI = systemic lupus erythematosus disease activity index, WBC = white blood cell.

The *P* values show differences between the 2 groups using independent *t* or Pearson χ^2 test.

thrombocytopenic patients was 24%, which was a significantly higher rate compared with those who were not thrombocytopenic (hazard ratio [HR] = 2.855, *P* < 0.001).[5] A recent study reported a mortality rate in thrombocytopenic patients of 17.1%, which was significantly different to nonthrombocytopenic patients (HR = 1.79, *P* = 0.045).[6] In our study, the mortality of thrombocytopenic patients was 5.6%, lower than in previous studies. Furthermore, we found that the severity of thrombocytopenia affected the mortality rate. In patients with severe thrombocytopenia, a significantly higher mortality was seen at 14.9%, compared with patients with moderate and mild thrombocytopenia (8.8% and 0.8%, respectively). In previous studies, other clinical outcomes, such as disease flare, infectious complications, and major hemorrhagic events, have also been associated with thrombocytopenia.[6] In this study, in a comparison

according to severity of thrombocytopenia, rates of hospitalization for hemorrhagic complications and relapse of thrombocytopenia were higher in severe thrombocytopenic patients. However, hospitalizations for other causes, including disease flare and infection, did not differ among the groups. Our data demonstrated that the severity of thrombocytopenia also affected the survival of SLE patients regardless of other severe clinical manifestations, abnormal laboratory findings, and disease activity. Interestingly, we found that thrombocytopenia recovering completely was important with regard to survival. Although the characteristics and treatment did not differ between the patients with and without complete remission, mortality was significantly higher in the patients without complete remission. The patients with complete remission were younger; however, age was not associated with survival

TABLE 4. Treatment and Prognosis According to Complete Remission of Thrombocytopenia

	Complete Remission (n = 196)	Without Complete Remission (n = 34)	*P*
Glucocorticoid (%)	179 (91.3)	28 (82.4)	0.107
Initial dose of glucocorticoid (mg, prednisolone equivalent)	275.1 ± 490.3	160 ± 404.1	0.147
Hydroxychloroquine (%)	157 (80.1)	27 (79.4)	0.926
Danazol (%)	4 (2)	4 (11.8)	0.004
Azathioprine (%)	14 (7.1)	5 (14.7)	0.139
Tacrolimus (%)	7 (3.6)	0 (0)	0.263
Cyclophosphamide (%)	40 (20.4)	5 (14.7)	0.439
IVIG (%)	35 (17.9)	8 (23.5)	0.434
Rituximab (%)	1 (0.5)	1 (2.9)	0.159
Splenectomy (%)	2 (1)	1 (2.9)	0.362
Death (%)	3 (1.5)	10 (29.4)	<0.001
Frequency of flare	1.83 ± 2.38	1.09 ± 1.73	0.085
Number of hospitalizations	3.51 ± 3.79	3.24 ± 3.36	0.697
Chief complaint at hospitalization			
Hemorrhagic manifestations	0.13 ± 0.43	0.21 ± 0.48	0.335
Infection	0.54 ± 1.21	1.03 ± 2.11	0.057
Thrombosis	0.08 ± 0.326	0 ± 0	0.146

IVIG = intravenous immunoglobulin.
The *P* values show differences between the 2 groups using independent *t* or Pearson χ^2 test.

in a logistic regression analysis. We found additional prognostic factors for SLE: severity of thrombocytopenia and complete remission of thrombocytopenia.

Our study had several limitations. First, it was based on retrospectively collected data; thus, some data were not available in a few patients. For example, severe thrombocytopenia is sometimes related with a combination of factors, such as antiphospholipid antibodies or infections. However, given the nature of the current retrospective study, we could not rule out those things in severe cases. Furthermore, selection bias may exist because all patients were from a single center. Second, we did not compare the data for thrombocytopenia with controls having no thrombocytopenic event. However, in previous studies, there were many results where the patients with thrombocytopenia had differences

TABLE 5. Variables Independently Associated With Mortality in Patients With Systemic Erythematosus Lupus and Thrombocytopenia

Variables	Odds Ratio (95% CI)	*P*
Female gender	1.745 (0.483–6.298)	0.395
Age	1.034 (0.998–1.073)	0.067
SLEDAI	1.111 (1.015–1.216)	0.022
Complete remission	0.049 (0.013–0.191)	<0.001
Treatment[*]	1.059 (0.613–1.829)	0.838

CI = confidence interval, SLEDAI = systemic lupus erythematosus disease activity index.

[*] We divided the patients according to 5 steps of treatment: patients used only hydroxychloroquine for step 1, with glucocorticoids regardless of the use of hydroxychloroquine for step 2; patients were treated with glucocorticoids and cyclophosphamide regardless of the use of hydroxychloroquine in step 3, and were treated with glucocorticoids and intravenous immunoglobulin in step 4; finally, patients underwent a splenectomy or used rituximab in step 5.

in clinical findings and prognosis in comparison with control groups. Thus, we focused on the clinical characteristics and laboratory findings of thrombocytopenic patients according to degree of thrombocytopenia severity.
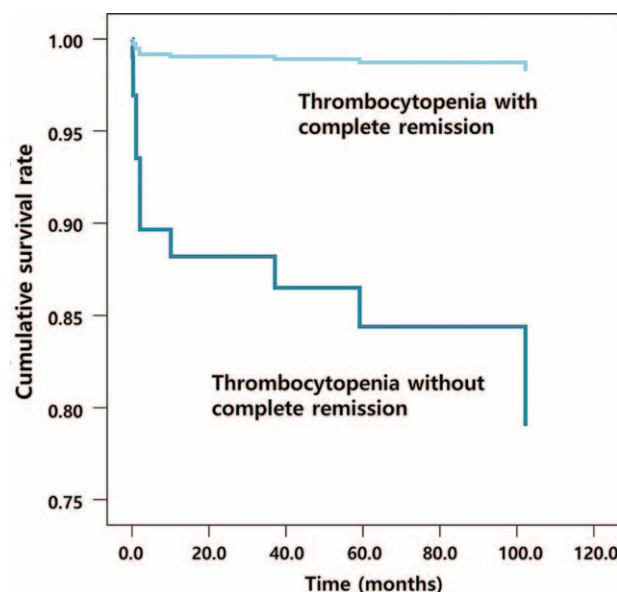
In conclusion, the severity of thrombocytopenia in SLE patients can be a useful independent prognostic factor to predict survival. Moreover, response to treatment of thrombocytopenia

FIGURE 1. Overall survival rate in patients with systemic lupus erythematosus and thrombocytopenia according to complete remission. Mortality in patients with complete remission was significantly lower than in patients without complete remission (OR = 0.049, 95% CI = 0.013–0.191, *P* < 0.001).

is also important because failure to achieve complete remission of thrombocytopenia has a close association with mortality. The severity of thrombocytopenia and the response to treatment should be closely monitored to predict the prognosis in SLE patients.

REFERENCES

1. Kotzin BL. Systemic lupus erythematosus. *Cell.* 1996;85:303–306.

2. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25:1271–1277.

3. Fayyaz A, Igoe A, Kurien BT, et al. Haematological manifestations of lupus. *Lupus Sci Med.* 2015;2:e000078.

4. Keeling DM, Isenberg DA. Haematological manifestations of systemic lupus erythematosus. *Blood Rev.* 1993;7:199–207.

5. Fernandez M, Alarcon GS, Apte M, et al. Systemic lupus erythematosus in a multiethnic US cohort: XLIII. The significance of thrombocytopenia as a prognostic factor. *Arthritis Rheum.* 2007;56:614–621.

6. Jallouli M, Frigui M, Marzouk S, et al. Clinical implications and prognostic significance of thrombocytopenia in Tunisian patients with systemic lupus erythematosus. *Lupus.* 2012;21:682–687.

7. Manger K, Manger B, Repp R, et al. Definition of risk factors for death, end stage renal disease, and thromboembolic events in a monocentric cohort of 338 patients with systemic lupus erythematosus. *Ann Rheum Dis.* 2002;61:1065–1070.

8. Miller MH, Urowitz MB, Gladman DD. The significance of thrombocytopenia in systemic lupus erythematosus. *Arthritis Rheum.* 1983;26:1181–1186.

9. Zhao H, Li S, Yang R. Thrombocytopenia in patients with systemic lupus erythematosus: significant in the clinical implication and prognosis. *Platelets.* 2010;21:380–385.

10. Feinglass EJ, Arnett FC, Dorsch CA, et al. Neuropsychiatric manifestations of systemic lupus erythematosus: diagnosis, clinical spectrum, and relationship to other features of the disease. *Medicine (Baltimore).* 1976;55:323–339.

11. Ward MM, Pyun E, Studenski S. Mortality risks associated with specific clinical manifestations of systemic lupus erythematosus. *Arch Intern Med.* 1996;156:1337–1344.

12. Ward MM, Pajevic S, Dreyfuss J, et al. Short-term prediction of mortality in patients with systemic lupus erythematosus: classification of outcomes using random forests. *Arthritis Rheum.* 2006;55:74–80.

13. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 5-year period. A multicenter prospective study of 1,000 patients. European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore).* 1999;78:167–175.

14. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum.* 1992;35:630–640.

15. Reveille JD, Bartolucci A, Alarcon GS. Prognosis in systemic lupus erythematosus. Negative impact of increasing age at onset, black race, and thrombocytopenia, as well as causes of death. *Arthritis Rheum.* 1990;33:37–48.

16. Sultan SM, Begum S, Isenberg DA. Prevalence, patterns of disease and outcome in patients with systemic lupus erythematosus who develop severe haematological problems. *Rheumatology (Oxford).* 2003;42:230–234.

17. Hepburn AL, Narat S, Mason JC. The management of peripheral blood cytopenias in systemic lupus erythematosus. *Rheumatology (Oxford).* 2010;49:2243–2254.

18. Blasco LM. Hydroxychloroquine alone for severe immune thrombocytopenic purpura associated with systemic lupus erythematosus. *Lupus.* 2013;22:752–753.

19. Boumpas DT, Barez S, Klippel JH, et al. Intermittent cyclophosphamide for the treatment of autoimmune thrombocytopenia in systemic lupus erythematosus. *Ann Intern Med.* 1990;112:674–677.

20. Roach BA, Hutchinson GJ. Treatment of refractory, systemic lupus erythematosus-associated thrombocytopenia with intermittent low-dose intravenous cyclophosphamide. *Arthritis Rheum.* 1993;36:682–684.

21. Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, et al. Successful therapy with danazol in refractory autoimmune thrombocytopenia associated with rheumatic diseases. *Br J Rheumatol.* 1997;36:1095–1099.

22. Maier WP, Gordon DS, Howard RF, et al. Intravenous immunoglobulin therapy in systemic lupus erythematosus-associated thrombocytopenia. *Arthritis Rheum.* 1990;33:1233–1239.

23. ter Borg EJ, Kallenberg CG. Treatment of severe thrombocytopenia in systemic lupus erythematosus with intravenous gammaglobulin. *Ann Rheum Dis.* 1992;51:1149–1151.

24. Lee JW, Kim HA, Sung JM, et al. Successful treatment of refractory immune thrombocytopenia with anti-CD20 antibody in a patient with systemic lupus erythematosus. *Lupus.* 2010;19:227–228.

25. Chen H, Zheng W, Su J, et al. Low-dose rituximab therapy for refractory thrombocytopenia in patients with systemic lupus erythematosus—a prospective pilot study. *Rheumatology (Oxford).* 2011;50:1640–1644.

26. Arnal C, Piette JC, Leone J, et al. Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. *J Rheumatol.* 2002;29:75–83.