Determinants of Low Disease Activity and Remission in Pediatric Systemic Lupus Erythematosus Patients

Pediatrik Sistemik Lupus Eritematozus Hastalarında Düşük Hastalık Aktivitesi ve Remisyonun Belirleyicileri

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ABSTRACT

Objective: In our study, it was aimed to investigate the effects of disease symptoms at presentation in pediatric systemic lupus erythematosus (SLE) patients on low disease activity and remission success after the 2nd year of the disease.

Material and Methods: Demographic, clinical, and laboratory data of pediatric SLE patients being followed up at our center were obtained from their electronic medical records and patient files. Disease activity at 2 years after diagnosis was measured based on SLE Disease Activity Index-2000 (SLEDAI-2K) scores.

Results: In this study, 29 patients diagnosed with pediatric SLE and followed up regularly for at least 2 years were included. At 2 years following diagnosis, according to their SLE activity measurements, 14 (48.2%) patients had high disease activity status (HDAS), whereas 15 (51.7%) had low disease activity status (LDAS)-remission. There was no statistically significant difference between the initial presenting symptoms of the two groups. At 5 years following diagnosis, among 15 patients, 6 (40%) had LDAS-remission, and 9 (60%) had HDAS. The 5th-year SLEDAI-2K scores of the patients with HDAS at 2 years were significantly higher than the 5th-year scores of those with LDAS-remission at 2 years (p=0.028). It was also found that the HDAS of 8 patients who had active disease at 2 years (80%) continued at 5 years.

Conclusion: The results of our study showed that pediatric SLE presenting symptoms did not have a significant determining effect on low disease activity and remission at 2 years. On the other hand, low disease activity and remission observed at 2 years may be indicative of LDAS and remission at 5 years.

Key Words: Systemic lupus erythematosus, SLEDAI-2K, Prognosis

ÖZ

Amaç: Çalışmamızda pediatrik sistemik lupus eritematozus (SLE) hastalarında, hastalık prezentasyon bulgularının, hastalığın 2. yılındaki düşük hastalık aktivitesi ve remisyona ulaşmadaki etkilerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Merkezimizde takipli olan pediatrik SLE hastalarının elektronik tıbbi kayıtları ve hasta dosyalarından demografik, klinik ve laboratuvar verileri kaydedildi. Hastalığın 2. yılındaki aktivite ölçümü SLE Hastalığı Aktivite İndeksi-2000 (SLEDAI-2K) skoru baz alınarak hesaplandı. Prezentasyon bulguları ile düşük hastalık aktivitesi ve remisyon arasında ilişki olup olmadığı istatiksel yöntemlerle incelendi.

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Bulgular: Bu çalışmaya merkezimizde pediatrik SLE tanısı almış ve en az 2 yıl düzenli takibe gelmiş 29 hastayı dahil ettik. Tanıdan sonraki 2. yılda hastalarda SLE aktivite ölçümüne göre 14 hastada (%48.2) HDAS, 15 hastada (%51.7) LDAS-remisyon elde edilmişti. İki grup arasında başlangıçtaki prezentasyon bulguları açısından anlamlı istatiksel farklılık saptanmadı. 5. yılda 15 hastadan 6'sında (%40) LDAS-remisyon, 9'unda (%60) HDAS mevcuttu. 2. yılda HDAS'a sahip hastaların 5. yıl SLEDAI-2K skorları, 2. yılda LDAS-remisyona sahip hastaların 5. yıl SLEDAI-2K skorlarına göre anlamlı olarak yüksekti (p= 0.028). Ayrıca 2. yılda aktif olan 8 hastanın (%80) 5. yılda HDAS'ın devam ettiği gözlendi.

Sonuç: Çalışmamızda pediatrik SLE prezentasyon bulgularının hastalığın 2. yılındaki düşük hastalık aktivitesi ve remisyon üzerine belirleyici etkilerinin olmadığını gösterildi. Ayrıca 2. yılda elde edilen düşük hastalık aktivitesi ve remisyon 5. yıldaki düşük hastalık aktivitesi ve remisyonun belirleyicisi olabilir.

Anahtar Sözcükler: Sistemik lupus eritamatozus, SLEDAİ-2K, Prognoz

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystemic, and autoimmune disease that can affect many organs and systems (1). The progression and prognosis of SLE cannot be predicted. Pediatric SLE is typically more severe than adult SLE, and its 5-year mortality rate reaches 95.3% if it is untreated (2). Disease activity scores have been developed to help in the assessment of disease activity for various organs and systems. Disease activity management is one of the main determinants of prognosis. Thus, it is important to utilize activity scales that will direct the planning of the treatment (3).

The most frequently used scales for SLE are the SLE Disease Activity Index (SLEDAI), SLEDAI-2000 (SLEDAI-2K), and the British Isles Lupus Assessment Group (BILAG) Activity Index (4). SLEDAI-2K, which is the updated version of SLEDAI, which was developed first in 1985, that was introduced in 2002 is a global measure of disease activity for SLE. Low disease activity status (LDAS) and remission that are calculated with current clinical data using SLEDAI-2K have potential applications at clinics monitoring SLE patients (5).

SLEDAI-2K consists of 24 items including nine organ systems. The period assessed to identify disease activity is the previous 10 days. Scores vary between 0 and 105, and higher scores indicate higher disease activity levels (5). SLEDAI-2K can identify patients who are suitable for treatment changes or clinical studies.

In this study, it was aimed to present the demographic, clinical, and laboratory data of pediatric SLE patients who were followed up at our center in a 27-year period, as well as their prognosis. Moreover, the effects of the presenting symptoms of the disease on low disease activity and remission success at 2 years were investigated.

MATERIALS and METHODS

Design and patient selection

This study was a retrospective review of the electronic and chart medical records of 29 SLE patients who were followed regularly at a tertiary referral hospital between January 1995 and August 2022. Inclusion criteria were defined as meeting the revised American College of Rheumatology (ACR) 1982 criteria for SLE and having symptom onset before the age of 18. Patients who had missing data or were followed up for less than 2 years were excluded.

Clinical-laboratory findings and definitions

All patients were systematically evaluated: demographic characteristics, age of disease onset, disease duration, follow-up duration, symptoms, clinical characteristics, laboratory findings, treatments, and treatment outcomes were recorded.

Complete blood counts and differential counts, erythrocyte sedimentation rates (ESR), serum complement levels (C3 and C4), antinuclear antibodies (ANA), anticardiolipin (aCL) IgG/M, antibeta2glycoprotein IgG/M test results, double-stranded DNA (dsDNA) antibodies, and urine test anomalies were recorded. Complete urinalysis anomalies were determined as hematuria (>5 erythrocyte/ per high power field), proteinuria (spot urine protein/creatinine >0.2 in patients aged >2 years; spot urine protein/creatinine >0.5 in patients aged <2 years; nephrotic-level proteinuria defined as spot urine protein/creatinine >2), and pyuria (>5 leukocytes/ per high power field). ANA and anti-dsDNA values were determined using the indirect immunofluorescence method or the enzyme-linked immunosorbent assay (ELISA) method. Serum C3 and C4 values were measured by immunodiffusion or turbidimetric immunoassay.

Treatment and disease management

Induction and maintenance treatment data were collected. Previous and current treatments involving drugs such as prednisone, intravenous pulse methylprednisolone, hydroxychloroquine sulfate, methotrexate, azathioprine (AZA), cyclosporine, mycophenolate (MMF), rituximab, and cyclophosphamide (CYP) were recorded. Angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) were used for hypertension and/or proteinuria as needed. When indicated, anticoagulants were used in patients with secondary antiphospholipid syndrome.

Disease activity

For the measurement of disease activity, SLEDAI-2K scores were obtained from electronic medical records and patient files

for the time at the presentation of the disease and at 2 and 5 years after diagnosis.

SLEDAI-2K score was evaluated by considering the patients' admission and their condition in the 10 days before admission. The patients received 8 points for each parameter in the presence of episodes, psychosis, organic brain lesions, vision disorders, cranial nerve disorders, lupus headaches, cerebrovascular events, or vasculitis, they received 4 points for each parameter in the presence of arthritis, myositis, urinary casts, hematuria, proteinuria, or pyuria, they received 2 points for each parameter in the presence of rashes, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement levels, or elevated anti-dsDNA levels, and they received 1 point for each parameter in the presence of a fever, thrombocytopenia, or leukopenia (5,6).

In the measurement of SLE activity, remission was defined as an SLEDAI-2K score of 0, a prednisolone dose of 5 mg/day or lower, and using immunosuppressives at maintenance doses, LDAS was defined as an SLEDAI-2K score under 4, a prednisolone dose lower than 7.5 mg/day, and using immunosuppressives at maintenance doses, and non-optimal control-active disease (HDAS) was defined as an SLEDAI-2K score higher than 4, a prednisolone dose higher than 7.5 mg/day, and using immunosuppressives at induction doses (7).

The study was approved by the Ankara City Hospital Clinical Research Ethics Committee (Ethics ID-No: E2-22-1813). All procedures were carried out in compliance with ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis: The statistical analyses were carried out using the SPSS software version 25. The normality of the distributions of the variables was determined using visual methods (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test). Descriptive statistics are presented as mean and standard deviation values for the normally distributed variables, medians and ranges for the non-normally distributed ordinal variables, and frequencies for the categorical variables. Intergroup comparisons were made using Student's t-test for the normally distributed variables, the Mann-Whitney U test for the non-normally distributed and ordinal variables, and chi-squared or Fisher's tests for the categorical variables. Parameters with a p-value smaller than 0.025 in the univariate analyses were considered for inclusion in the model. When high correlation values were observed among these variables, they were removed from the model due to low clinical significance or high p-values. First, a univariate logistic regression analysis was conducted on the remaining variables. After the removal of the variables that were not statistically significant from the model, finally, a multivariate analysis was completed. Model fit was analyzed with the Hosmer-Lemeshow test. $p<0.050$ was accepted as statistically significant.

RESULTS

Among the 29 patients included in the study, 25 (86.2%) were female. The median age of diagnosis was 13 (3.7-17.5) years. 14 patients (48.2%) had constitutional findings. The most common organ and system involvement was renal involvement in 14 patients (48.2%). There was mucocutaneous involvement in 13 patients (44.8%), musculoskeletal involvement in 12 patients (41.3%), hematological involvement in 10 patients (34.4%), neurological involvement in 7 patients (24.1%), cardiovascular involvement in 1 patient (3.4%) and immunological involvement in 28 patients (96.5%). The clinical symptoms and system involvements of the patients at presentation are given in Table I.

Table I: Clinical findings of patients with systemic lupus erythematosus at the time of diagnosis

Gender *	
Female*	25 (86.2)
Male*	4 (13.7)
Age at diagnosis, years†	13 (9.5-14.5)
Time to diagnosis, months†	1 (0.5-2)
Constitutional findings*	14 (48.3)
Mucocutaneous involvement*	13 (44.8)
Musculoskeletal involvement*	12 (41.4)
Renal involvement*	14 (48.3)
Neurological involvement*	7 (24.1)
Hematological involvement*	10 (34.5)
Cardiovascular involvement*	1 (3.4)
Immunological involvement*	28 (96.6)
Lung involvement*	9 (31)
GIS involvement*	4 (13.8)
Eye involvement*	1 (3.4)

**n (%), †median (Q1Q3) (min-max)*

Table II: Laboratory findings at the time of diagnosis in patients with systemic lupus erythematosus

WBC† (*10^6/L)	6148 (2400-25500)
Neutrophil† (*10^6/L)	3158 (1000-15800)
Lymphocyte† (*10^6/L)	1652 (300-6900)
PLT† (*10^6/L)	250034 (6000-517000)
Hb† (g/L)	11.56 (7.6-15.4)
ESH† (mm/hr)	21.55 (2-121)
CRP†(mg/L)	14.5 (0.1-33)
C3†(g/L)	0.54 (0.18-0.91)
C4† (g/L)	0.079 (0.01-0.98)
ANA positivity*	26 (89.6)
Anti-ds DNA positivity*	22 (75.8)

n (%), †median (Q1Q3) (min-max), **WBC: White blood cell, **Hb:** Hemoglobin, **PLT:** Platelet, **ESR:** Erythrocyte sedimentation rate, **CRP:** C- Reactive protein, **C:** Complement, **ANA:** Antinuclear antibody, **Anti-dsDNA:** Anti double-stranded deoxyribonucleic acid*

Table III: Relationship of presentation findings with HDAS and LDAS-remission at 2 years in patients with systemic lupus erythematosus

	2nd year HDAS (n=14)	2nd year LDAS-Remission (n=15)	p
Gender,*			
Female	11 (78.6)	14 (93.3)	0.330
Male	3 (21.4)	1 (6.7)	
Age at diagnosis, years†	13.8 (11-14.6) (8.5-17.5)	12.4 (9.5-15) (3.7-17)	0.450
Time to diagnosis, months†	1.5 (0.7-2.3) (0-8)	1 (0-2) (0-33)	0.780
Constitutional findings*	7 (63.6)	7 (87.5)	0.340
Mucocutaneous involvement*	5 (35.7)	8 (53.3)	0.340
Musculoskeletal involvement*	4 (28.6)	8 (53.3)	0.180
Renal involvement*	9 (64.3)	5 (33.3)	0.096
Neurological involvement*	4 (28.6)	3 (20)	0.680
Hematological involvement*	5 (35.7)	5 (33.3)	1.000
Cardiovascular involvement*	1 (7.1)	0 (0)	0.480
Immunological involvement*	13 (92.9)	15 (100)	0.480
Lung involvement*	5 (35.7)	4 (26.7)	0.700
GIS involvement*	2 (14.3)	2 (13.3)	1.000
Eye involvement*	1 (7.1)	0 (0)	0.480
Complement 3†	0.47 (0.33-0.91) (0.18-1)	0.61 (0.39-0.9)	0.250
Complemant 4†	0.09 (0.05-0.11) (0.03-0.98)	0.07 (0.05-0.15) (0.01-0.3)	0.780
ANA positivity*	12 (85.7)	14 (93.3)	0.600
Anti ds DNA positivity*	10 (71.4)	12 (80)	0.680
Pulse methylprednisolone	8	10	0.710
0.5-2 mg/kg/d methylprednisolone	5	5	0.890
Cyclophosphamide	6 (42.9)	4 (26.7)	0.450
Mycophenolate Mofetil	2 (14.3)	2 (13.3)	1.000
Azathioprine	2 (14.3)	0 (0)	0.220

*****n (%), †median (Q1Q3) (min-max), **HDAS:** High disease activity score, **LDAS:** Low disease activity score

Among the patients with hematological involvement, 6 (16.7%) patients had thrombocytopenia, 7 (19.4%) had leukopenia, 6 (16.7%) had hemolytic anemia, and 7 (19.4%) had lymphopenia.

Seven patients (24.1%) had neurological involvement. 4 (11.1%) patients had epileptic seizures, 3 (8.3%) had cognitive deficits, 1 (11.1%) had mononeuritis multiplex, 1 (11.1%) had neuropathy, and 1 (11.1%) had corea. Psychiatric symptoms such as depression, anxiety disorder, and hallucinations were observed in 6 (16.7%) patients. No patients developed organic brain injury, cerebrovascular diseases, cranial nerve disorders, confusion, or pseudotumor cerebri.

Twelve (33.3%) patients had serositis. Among these 12 patients, 10 (27.7%) patients had pleurisy, and 2 (5.5%) had pericarditis. 5 (13.9%) patients had gastrointestinal system involvement (elevated liver enzymes, hepatosplenomegaly, ileocecal wall thickening, acid, and pancreatitis). One (11.1%) patient had ocular involvement (retinal hemorrhage).

Half of the patients had renal involvement. 7 (19.4%) patients had non-nephrotic proteinuria, and 4 (11.1%) had nephrotic proteinuria. Proteinuria was accompanied by hematuria in 4 (11.1%) patients, pyuria in 2 (5.6%) patients, and both hematuria and pyuria in 8 (22.2%) patients. Kidney biopsies were performed on 22 patients. 7 (19.4%) patients were class 4, 1 (2.8%) was class 1, 7 (19.4%) were class 2, 2 (5.6%) were class 3, and 2 (5.6%) were class 5. 2 (5.6%) patients had biopsy findings compatible with C3 glomerulopathy (Table I). The kidney biopsy findings of 1 (2.8%) patient were normal.

No statistically significant relationship was found between the presence of HDAS at 2 years and findings at presentation including clinical, organ involvement, and laboratory findings.

The laboratory findings of the patients at the time of their presentation are shown in Table II. Positive results were found in 33 (91.7%) patients for ANA, 26 (72.2%) patients for anti-dsDNA, and 6 (16.7%) patients for anti-Sm antibody. 10 (27.8%) patients had anticardiolipin IgG/IgM antibodies, 6 (16.7%) had lupus anticoagulants, and 2 (5.6%) had B2 glycoprotein IgG/M antibodies. The direct Coombs tests of 16 (44.4%) patients and the RF tests of 3 (8.3%) patients were positive.

All patients received hydroxychloroquine and glucocorticoids at the time of diagnosis. 18 (62.1%) patients received pulse

methylprednisolone, and 11 (37.9%) received 0.5-2 mg/kg/day glucocorticoids. Glucocorticoid treatment was reduced week by week based on the clinical status of the patients, their major organ involvement status, and disease severity. As induction treatment, the patients were given CYP [n=10, (34.4%)], MMF [n=4, (13.7%)], and AZA [n=2, (6.8%)] in the first 2 years based on their organ involvement and disease severity. At 2 years after diagnosis, all (n=29, 100%) SLE patients were using glucocorticoids. Among these patients, 12 (41.4%) patients were using low-dose glucocorticoids at <7.5 mg/day, 9 (31%) were using them at 7.5-15 mg/day, and 8 (27.6%) were using doses higher than 15 mg/day.

The median presentation SLEDAI-2K score of the participants was 15 (7-22.5). Their median SLEDAI-2K score at 2 years was 4 (0-11). According to the SLE activity measurements, 14 (48.2%) patients had HDAS, while 15 (51.7%) had LDAS-remission. We had 15 patients with regular follow-ups at 5 years after their diagnosis. Their mean SLEDAI-2K score at 5 years was 6 (2-8). At 5 years, among these 15 patients, 6 (40%) patients had LDAS-remission, and 9 (60%) had HDAS. At 5 years, LDAS-remission could be achieved in 2 of the 10 patients who had HDAS at 2 years. Moreover, at 5 years, LDAS-remission was maintained among 4 of the 5 patients who had LDAS-remission at 2 years and continued their follow-ups for 5 years. There was no statistically significant difference between the SLE activity measurements of the two groups. However, the 5th-year SLEDAI-2K scores of the patients with HDAS at 2 years were significantly higher than the 5th-year scores of those with LDAS-remission at 2 years (p=0.028). Furthermore, the HDAS status of 8 patients who had active disease at 2 years (80%) continued at 5 years. Graphic 1 shows the relationship between disease activity and SLEDAI-2K scores.

DISCUSSION

Pediatric SLE is a chronic and potentially fatal autoimmune disease that shows high variability in terms of disease presentation and progression (8). In this study, it was aimed to investigate whether symptoms at diagnosis can predict symptoms in the second year in pediatric SLE. It was shown that pediatric SLE presenting symptoms did not have a significant effect on LDAS-remission success or HDAS. On the other hand, the patients who achieved LDAS-remission at 2 years following their diagnosis had significantly lower SLEDAI-2K scores at 5 years.

In pediatric SLE cases, the goal of the clinician is to achieve LDAS-remission. Variables associated with the probability of achieving LDAS or remission in SLE, which as very high morbidity and mortality rates when untreated, guide the clinician in reaching this goal. LDAS at the time of diagnosis, lower damage index values, or the absence of lupus nephritis are indicative of lower disease severity. Older age is also predictive of LDAS (9). It was shown that patients who were younger at the onset of the disease had a higher likelihood of having active disease compared to those with an older age of onset (10). As our sample consisted of pediatric SLE patients, it may be expected that their achievement of LDAS-remission could be more difficult in comparison to patients at older ages. However nowadays, appropriate treatment approaches that can be aggressive when necessary make the goal of LDAS-remission possible.

In general, compared to adult-onset SLE patients, pediatric SLE patients are more likely to have more severe disease at the beginning with higher rates of organ involvement and a more aggressive clinical course (8). In the first year of diagnosis, 35-90% of pediatric cases may have constitutional symptoms, 20-80% may have nephritis, 20-74% may have musculoskeletal system symptoms, 60-80% may have any form of skin involvement, 15-30% may have neuropsychiatric diseases, 5-30% may have cardiovascular diseases, and 18-40% may have pulmonary diseases (11). While renal involvement was detected in 48.2% of the patients in our study, 24.1% of the patients had neurological involvement, 34.4% had hematological involvement, and 3.4% had cardiovascular involvement. Major organ involvement such as kidney and central nervous system, which are the determinants of morbidity and mortality at the onset of the disease, are high in pediatric cases. In our study, it was shown that major organ/system involvements at presentation did not have a significant effect on disease activity at 2 years. We suggest that our finding of no significant relationship between systemic involvements at presentation and LDAS-remission and HDAS outcomes was caused by the rapid and appropriate treatment of organ/system involvements by the clinician at the time of diagnosis.

Low disease activity and remission are newly emerging concepts that provide a simple method of predicting a favorable prognosis in pediatric SLE patients. High disease activity was shown to be associated with increased organ injury risk and other negative outcomes (7). Therefore, disease activity measurement is an indispensable part of current recommendations for disease management in SLE cases (12). Although there are a few recommended disease severity indices, their definitions are usually complicated (13). One of the severity indices that have been used recently involves the parameters of corticosteroid or immunosuppressant treatment requirements, as well as specific organ involvement (14). In the calculation of SLEDAI scores, the parameters are identified if symptoms are present at presentation or in the previous 10 days (6). Patients receive 8 points for each parameter in the presence of episodes, psychosis, organic brain lesions, vision disorders, cranial nerve disorders, lupus headaches, cerebrovascular events, or vasculitis, they receive 4 points for each parameter in the presence of arthritis, myositis, urinary casts, hematuria, proteinuria, or pyuria, they receive 2 points for each parameter in the presence of rashes, alopecia, mucosal

ulcers, pleurisy, pericarditis, low complement levels, or elevated anti-dsDNA levels, and they receive 1 point for each parameter in the presence of a fever, thrombocytopenia, or leukopenia. SLEDAI-2K scores vary from 0 to 105, and higher scores indicate higher disease activity levels (5,6). Among the patients included in our study, the median SLEDAI-2K score at 2 years was 4 (0-11). According to the SLE activity measurements, 14 (48.2%) patients had HDAS, while 15 (51.7%) had LDAS-remission. We had 15 patients with regular follow-ups at 5 years after their diagnosis. Their mean SLEDAI-2K score at 5 years was 6 (2-8). At 5 years, among these 15 patients, 6 (40%) patients had LDAS-remission, 9 (60%) had HDAS and LDAS-remission could be achieved in 2 of the 10 patients who had HDAS at 2 years. The 5th-year SLEDAI-2K scores of the patients with HDAS at 2 years were significantly higher than the 5th-year scores of those with LDAS-remission at 2 years. Furthermore, the HDAS status of 8 patients who had active disease at 2 years (80%) continued at 5 years. This revealed that long-term prognoses could be predictable from earlier periods of the disease, such as 2 years following diagnosis. As shown in our study, the early management of the disease allows for a good prognosis in the long term for this disease, which is difficult to manage.

The Lupus Low Disease Activity State (LLDAS) measure was developed recently by Franklyn et al. (15) LLDAS was defined as an SLEDAI-2K score of ≤4, no activity or active involvement in major organs (kidneys, central nervous system, cardiopulmonary organs, vasculitis, fever, hemolytic anemia, or gastrointestinal system), the absence of new lupus disease activity compared to a previous assessment, a global assessment value of ≤1 determined by a physician, the use of prednisone (or equivalent) at a dose of ≤7.5mg/day, and the use of immunosuppressive drugs and approved biological agents at standard maintenance doses that are tolerated well. The researchers reported a significantly lower degree of damage and significantly lower SLE damage index values among patients who showed LLDAS in at least two consecutive years compared to those who never showed LLDAS. They stated that 84% of patients with LLDAS on average met remission criteria (16). Understanding predictive factors for LLDAS-50 will allow better clinical management of SLE patients. In a recent study, it was shown that only 37.6% of 1169 SLE patients achieved LLDAS-50. In the multivariate model of the same study, African American ethnicity, hypocomplementemia, serositis, kidney involvement, arthritis, anti-RNP, anti-dsDNA, vasculitis, malar rash, discoid rash, thrombocytopenia, and immunosuppressive use were found as negative predictors of LLDAS-50. Older age at the time of diagnosis, longer disease durations, higher education levels, and higher hydroxychloroquine intake rates were positive predictors of LLDAS-50 (17,18,19). Likewise, it has been shown that LLDAS is an achievable goal in clinical practice, but the achievement of LLDAS is more difficult among patients with discoid rashes, high anti-dsDNA levels, and hypocomplementemia (19). SLEDAI scores higher than 10 have been associated with longer HDAS episodes and an increased risk of damage. Having HDAS episodes for longer than 2 years in total and experiencing 4 or more HDAS episodes may lead to an increased risk of damage (20).

The limitations of our study are that it was conducted in a single center and its retrospective design. However, its strength is that it presents the 27-year experience of a tertiary referral hospital and reflects long-term outcomes.

In conclusion, the results of our study showed that pediatric SLE presenting symptoms did not have a significant determining effect on low disease activity and remission at 2 years. We also showed that the 5th-year SLEDAI-2K scores of the patients with HDAS at 2 years were significantly higher than the 5th-year scores of those with LDAS-remission at 2 years. The majority of patients with active disease at 2 years maintained HDAS at 5 years. This suggested that the long-term prognosis of pediatric SLE patients may be associated with successful disease management in the first 2 years of the disease. Multicenter studies including larger numbers of pediatric SLE patients are needed to reveal the determinants of LDAS-remission.

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