Pediatric systemic lupus erythematosus.

Retrospective analysis of clinico-laboratory parameters and their association with Systemic Lupus Erythematosus Disease Activity Index score

Siti Khadijah S.M. Nazri, *BSc,*
Kah K. Wong, *BSc, DPhil,*
Wan Zuraida W. A. Hamid, *MD, MPath.*

ABSTRACT

Objectives: To elucidate the clinico-laboratory characteristics associated with pediatric systemic lupus erythematosus (pSLE) patients with higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score in a retrospective cohort of pSLE patients.

Methods: A retrospective study involving 32 pSLE patients was conducted at Hospital Universiti Sains Malaysia, Kelantan, Malaysia between 2006 and 2017.

Results: Within the group of 32 pSLE patients, 23 were girls and 9 were boys (3:1 ratio). The most common symptom was renal disorder (n=21; 65.6%) followed by malar rash (n=9; 28.1%), oral ulcers (n=7; 21.9%), prolonged fever (n=5; 15.6%) and arthritis (n=4; 12.5%). Antinuclear antibodies (ANA) were detected in all patients and 25 patients (78.1%) were positive for anti-double stranded DNA (anti-dsDNA) antibodies. Eighteen (56.3%) patients had active SLE (SLEDAI ≥6), and these patients were significantly associated with heavy pyuria (p=0.004), a high ANA concentration (1:160; p=0.040, 1:320; p=0.006), elevated ESR (p=0.006), low C3 levels (p=0.008), oral ulcers (p=0.010), heavy hematuria (p=0.017) and heavy proteinuria (p=0.017), lupus erythematosus (LE)-nonspecific lesion manifestations (p=0.019) and malar rash (p=0.044).

Conclusion: Pediatric systemic lupus erythematosus patients with higher SLEDAI score were most significantly associated with pyuria, high ANA titers, and elevated ESR.

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Systemic lupus erythematosus (SLE) is an autoimmune disease which predominantly affects females.[1] Approximately, children signify 15% to 20% of all SLE patients. They tend to have a more severe disease than adults at the onset. Systemic lupus erythematosu is diagnosed according to the international criteria developed by the American College of Rheumatology (ACR).[2] The disease activity is evaluated according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score system.[3] The incidence of pSLE differs between 0.3 to 0.9 per 100,000 per year with an estimated prevalence between 0.3 to 8.8 per 100,000 across the world.[4] However, the prevalence and clinico-laboratory profile of pSLE among Malaysians remains unknown. Previous studies have focused on clinical manifestations and laboratory characteristics of pSLE patients, nevertheless, few studies highlight on their association with SLEDAI score particularly in Malaysia.[5,6] The aim of this study was to examine the demographic, clinical characteristics, immunological parameters, and their association with SLEDAI score in a retrospective cohort of pSLE patients admitted to the Hospital Universiti Sains Malaysia (HUSM), Kelantan Malaysia.

Methods. We retrospectively reviewed the folder of the 32 pSLE patients diagnosed between 2006 and 2017. All patients must satisfy ACR 1997 criteria and age <12 years old.[2] Patients with SLEDAI score ≥6 were defined as having active SLE disease and inactive SLE disease with SLEDAI score <6.[3] We excluded patients aged >12 years old, with hepatitis B and hepatitis C positive, chronic illnesses such as diabetes mellitus, and acute viral infections such as flu. The study protocols and written consent were approved by the Ethics Committee of USM according to the Declaration of Helsinki (USM/JEPeM/15060235). All the data were retrieved from the Unit Records of HUSM.

Symptoms and clinical presentation consisted of malar rash, arthritis, alopecia, prolonged fever, photosensitivity, oral ulcers, headaches, blurring vision, serositis, vasculitis and renal disorder. Lupus erythematosus-specific (LE-specific) lesions were characterized by the presence of malar rash, generalized lupus rash, subacute cutaneous LE and discoid rash

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presentations, whereas LE-nonspecific lesions were clarified by the presence of photosensitivity, cutaneous vasculitis, oral and nasal ulcer.

Immunological laboratory investigations comprise of antinuclear antibody (ANA) (1:40-1:320), anti-double stranded DNA (anti-dsDNA) (1:10-1:320), complement 3 (C3) (0.66-1.30 g/L), and complement 4 (C4) (0.20-0.60 g/dL). Other immunological features such as red blood cell (RBC) (male: 4.5-6.0 10^{12}/L; female: 4.0-5.5 10^{12}/L) and erythrocyte sedimentation rate (ESR) (male 0-16 mm/hour; female: 0-20 mm/hour) were included. Patients were considered to have active lupus nephritis (LN) disease if they had proteinuria (> 0.5 gm/24 hours), hematuria (>5 RBCs/high power field), and pyuria (>5 WBCs/high power field).

Histological observation was categorized according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 reclassification. There are 6 histological types of LN: 1) minimal mesangial LN, 2) mesangial LN, 3) focal LN, 4) diffuse proliferative LN, 5) membranous LN, and 6) glomerulosclerosis.[7]

All data entry and statistical analyses were performed using SPSS Statistics version 22 (IBM SPSS, Chicago, IL). The associations between the demographic features, immunological parameters, clinical features and the urine profile with the SLEDAI score were assessed using the x^2 test or Fisher's exact test. A $p<0.05$ was considered statistically significant.

Results. Age at patient diagnosis ranged from 3 months to 12 years with mean and standard deviation ages of 8.44 and 3.53 years, respectively. The study group consisted of 23 (75%) females and 9 (25%) males, for a ratio of 3:1. All patients were Malay ethnicity with the most common clinical manifestations being renal disorder (65.6%), malar rash (28.1%) and oral ulcers (21.9%) (**Table 1**). Antinuclear antibody was determined in all patients at the lowest serum dilution factor of 1:40 to test for the presence of ANA. Most of the pSLE patients were positive for ANA at the highest titer of 1:320 (n=12; 37.5%) and 1:160 (n=8; 25%), with a sequential drop in patient frequency as the dilution factor decreased to 1:80 (n=7; 21.9%) and 1:40 (n=5; 15.6%). All pSLE patients were positive for anti-dsDNA antibodies. The greatest frequency occurred at the highest serum dilution factor at 1:320 (n=11; 34.4%) followed by 1:160 (n=9; 28.2%), 1:80 (n=5; 15.6%) and 1:40 (n=4; 12.5%) (**Table 1**).

Renal biopsy was performed on 20 (62.5%) of the pSLE patients. The most frequent histological finding was diffuse proliferative glomerulonephritis (class IV) followed by minimal mesangial LN (class I), focal LN (class III), and mesangial proliferative LN (class II) (**Figure 1**).

Elevated ESR (p=0.006), oral ulcers (p=0.010) and malar rash (p=0.044) were positively associated with an active SLEDAI score. Patients with LE-nonspecific lesion manifestations were also significantly associated with SLEDAI score (p=0.019). However, no significant differences were observed between the LE-specific lesions and both types of lesions in terms of their association with SLEDAI score (**Table 2**).

For immunological parameters and urine profile, high ANA concentration (1:160; p=0.040, 1:320;

Table 1 - Demographic, clinical features and immunological parameters of pediatric systemic lupus erythematosus (pSLE) patients (n=32).

Features	n (%)
Age	
≥6	25 (78.1)
<6	7 (21.9)
Gender	
Female	23 (75.0)
Male	9 (25.0)
Race	
Malay	32 (100)
Others	0 (0.0)
Presenting symptoms	
Renal disorder	21 (65.6)
Malar-rash	9 (28.1)
Oral ulcers	7 (21.9)
Prolonged fever	5 (15.6)
Arthritis	4 (12.5)
Photosensitivity	2 (6.3)
Blurring vision	2 (6.3)
Vasculitis	2 (6.3)
Alopecia	1 (3.1)
Headache	1 (3.1)
Serositis	1 (3.1)
SLEDAI	
Active (≥6)	18 (56.3)
Inactive (<6)	14 (43.8)
Immunological parameters	
ANA	32/32 (100)
Anti-dsDNA	25/32 (78.1)
Low serum C3	22/32 (68.8)
Low serum C4	19/32 (59.4)
Elevated ESR	20/32 (62.5)
Anemia	17/32 (53.1)
Thrombocytopenia	12/32 (37.5)
Leucopenia	4/32 (12.5)
Proteinuria	12/32 (37.5)
Hematuria	12/32 (37.5)
Pyuria	8/32 (25.0)
Urinary casts	1/32 (3.1)

ANA - antinuclear antibody, Anti-dsDNA - anti-double stranded DNA, C3 - Complement 3, C4 - Complement 4, ESR - erythrocyte sedimentation rate, SLEDAI - Systemic Lupus Erythematosus Disease Activity Index

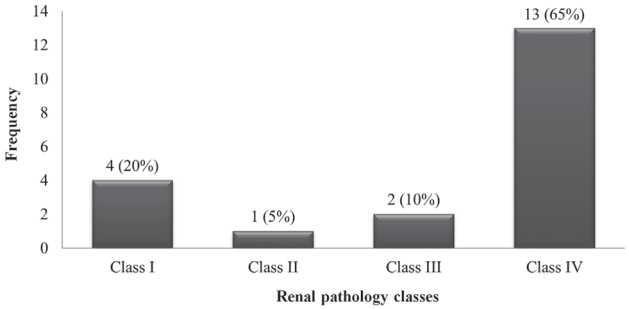

Figure 1 - Distribution of renal pathology classes (I-IV) in pSLE patients (n=32).

p=0.006), pyuria (*p*=0.004), elevated ESR (*p*=0.006), low C3 levels (*p*=0.008), heavy hematuria (*p*=0.017), and heavy proteinuria (*p*=0.017) were positively associated with SLEDAI scores (**Table 2**).

Discussion. In this retrospective study of 32 pSLE patients, approximately half of our patients were diagnosed before the age of 10. In comparison with adult SLE patients, most studies reported a lower female-to-male ratio (3-5:1) of pSLE patients,[5] which is comparable with our study and its female-to-male ratio of 3:1. The cohort of SLE patients was predominantly female. Its uncommon presentation in pre-pubertal and post-menopausal women suggests the role of endogenous sex hormones in SLE pathogenesis. All patients were of Malay ethnicity (100%) because the highest population in the Kelantan state of Malaysia is of Malay ethnic, which constitutes 95% of the whole population in the state.[5]

In our study, the most common clinical features were renal disorders, malar rash and oral ulcers, while the least common symptoms were alopecia, headaches and serositis. These observations resemble previous reports, where renal involvements and malar rash were the most common manifestations, while alopecia or serositis formed in a minority proportion of pSLE patients.[8] Renal involvement occurs regularly in juvenile SLE and tends to dominate the clinical manifestations. Our study exhibited a high percentage of renal involvement (65.6%) due to LN. Antinuclear antibody was detected in all patients in our study. The elevation of anti-dsDNA antibodies was detected in 78.1% in pSLE patients in this study, corroborating the 60–97% range reported by previous studies.[8] Complement C3 and C4 levels decreased in 68.8 % and 59.4% of our patients,

Table 2 - Association of SLEDAI score with demographic, clinical features, immunological parameters and urine profile in pSLE patients (n=32).

Variables	SLEDAI score		*P*-value
	Active n (%)	Inactive n (%)	
Age			
≥6	14 (77.8)	11 (78.6)	1.000
<6	4 (22.2)	3 (21.4)	
Gender			
Female	14 (77.8)	9 (64.3)	0.453
Male	4 (22.2)	5 (35.7)	
Arthritis			
Yes	4 (22.2)	0 (0)	0.113
No	14 (77.8)	14 (100)	
Malar rash			
Yes	8 (44.4)	1 (7.1)	0.044*
No	10 (55.6)	13 (92.9)	
Oral ulcer			
Yes	7 (38.9)	0 (0)	0.010*
No	11 (61.1)	14 (100)	
Prolonged fever			
Yes	5 (27.8)	0 (0)	0.052
No	13 (72.2)	14 (100)	
Alopecia			
Yes	1 (5.6)	0 (0)	1.000
No	17 (94.4)	14 (100)	
Photosensitivity			
Yes	1 (5.6)	1 (7.1)	1.000
No	17 (94.4)	13 (92.7)	
Blurring vision			
Yes	2 (11.1)	0 (0)	0.492
No	16 (88.9)	14 (100)	
Headache			
Yes	1 (5.6)	0 (0)	1.000
No	17 (94.4)	14 (100)	
Serositis			
Yes	1 (5.6)	0 (0)	1.000
No	17 (94.4)	14 (100)	
Vasculitis			
Yes	2 (11.1)	0 (0)	0.492
No	16 (88.9)	14 (100)	
LE-specific lesions			
Yes	7 (38.9)	3 (21.4)	0.446
No	11 (61.1)	11 (78.6)	
LE-nonspecific lesion			
Yes	9 (50.0)	1 (14.3)	0.019*
No	9 (50.0)	13 (85.7)	
Both types of lesion			
Yes	9 (50.0)	3 (21.4)	0.098
No	9 (50.0)	11 (78.6)	
ANA			
1:40	0 (0)	5 (35.7)	0.052
1:80	2 (11.1)	5 (35.4)	0.195
1:160	7 (38.9)	1 (7.1)	0.040*
1:320	9 (50.0)	3 (21.4)	0.006*
Anti-dsDNA			
1:10	1 (5.6)	0 (0)	1.000
1:20	1 (5.6)	1 (7.1)	1.000
1:40	2 (11.1)	2 (14.3)	1.000
1:80	5 (27.8)	0 (0)	0.052
1:160	5 (27.8)	4 (28.6)	1.000
1:320	4 (22.2)	7 (50.0)	0.101

Table 2 - Association of SLEDAI score with demographic, clinical features, immunological parameters and urine profile in pSLE patients (n=32). (continued)

C3			
Low	16 (88.9)	6 (42.6)	0.008*
High	1 (5.6)	5 (35.7)	0.064
Normal	1 (5.6)	3 (21.4)	0.295
C4			
Low	12 (66.7)	7 (50.0)	0.341
High	1 (5.6)	0 (0)	1.000
Normal	5 (27.8)	7 (50.0)	0.198
Anemia			
Yes	11 (61.1)	6 (42.8)	0.305
No	7 (38.9)	8 (57.1)	
Leucopenia			
Yes	3 (16.7)	1 (7.1)	0.613
No	15 (83.3)	13 (92.9)	
Thrombocytopenia			
Yes	8 (44.4)	4 (28.6)	0.358
No	10 (55.6)	10 (71.4)	
Elevated ESR			
Yes	15 (83.3)	5 (35.7)	0.006*
No	3 (16.7)	9 (64.3)	
Pyuria			
<3 wbc/hpf	10 (55.6)	14 (100)	0.004*
>3 wbc/hpf	8 (44.4)	0 (0)	
Hematuria			
<0.5 rbc/hpf	8 (44.4)	12 (85.7)	0.017*
>0.5 rbc/hpf	10 (55.6)	2 (14.)	
Proteinuria			
<1g/day	8 (44.4)	12 (85.7)	0.017*
>1g/day	10 (55.6)	2 (14.3)	
Urinary casts			
Yes	1 (5.6)	0 (0)	1.000
No	17 (94.4)	14 (100)	

*significant *p*-value <0.05, LE - lupus erythematosus, ANA - antinuclear antibody, Anti-dsDNA - anti-double stranded DNA, C3 - Complement 3, C4 - Complement 4, ESR - erythrocyte sedimentation rate, rbc/hpf - red bloods cells/high power field, wbc/hpf - white blood cells/high power field

comparable with those of previous reports.[8] Patients with anemia presented the highest frequency followed by thrombocytopenia and leucopenia, similar with observations reported by Mohamed et al[6] where pSLE patients demonstrated the highest percentage of anemia followed by thrombocytopenia and leucopenia. We observed that all patients had proteinuria and hematuria with the same frequency (37.5%), 25% had pyuria and 3.1% of patients had urinary casts, comparable with previous studies.[6,8]

Lupus nephritis was observed in 75-80% of patients in previous studies. There is a common agreement in literature that the active classes of biopsy proven LN are class III and IV, while class I, II, V, and VI are considered less active, requiring limited immunosuppressive therapy.[9] Our study demonstrated that 62.5% of pSLE had LN at the time of diagnosis, consistent with other studies in which most patients had proliferative nephritis. In this study, class IV was the most common class on the initial biopsy followed by class I, III and II. Interestingly, the majority of SLE adult patients were also class IV LN.[10] In our cohort, a high titre of ANA was significantly associated with higher disease activity, consistent with previous studies.[11] However, a high titre of anti-dsDNA showed an insignificant pattern (1:80; p=0.052) of association with a higher SLEDAI score. This could be partially explained by most patients in our cohort (n=25/32; 78.1%) were seronegative for anti-dsDNA. Our cohort of pSLE patients showed that low C3 level was significantly associated with higher SLEDAI score. Complement 3 and C4 are often low in SLE patients, particularly with active disease.[12] However, in our study, low C4 did not exhibit any association with disease activity. This suggests that C4 might be a less sensitive parameter of disease activity in pSLE patients.

It was observed that an elevated ESR value was associated with higher disease activity in our study. SLE patients with active systemic inflammation often have increased non-specific markers of inflammation such as elevated ESR.[12] For clinical presentation, we found that malar rash and oral ulcers exhibited significant associations with higher SLEDAI scores. Correspondingly, previous findings also reported that malar rash and oral ulcers were strongly associated with systemic disease activity in pSLE. In our cohort, proteinuria, hematuria and pyuria were significantly associated with higher disease activity. Prior studies suggested that proteinuria, hematuria and pyuria were associated with active renal and non-renal disease activity.[13] Hence, these 3 urinary sediments should be considered as manifestations of active pSLE.

In our study, we found that patients with LE-nonspecific lesions were significantly associated with higher SLEDAI scores (p=0.035). Previous studies also demonstrated that patients with either LE-specific or LE-nonspecific skin manifestations had significantly increased disease activity, whereas there was no association for patients with both types skin lesions.[14,15]

This study is limited by the small number of pSLE patients that may influence the impact of our findings. Therefore, validation in a larger population of pSLE patients is required. For further investigations, we also recommend that LN classes should be performed to determine whether these classes are particularly associated with the prognosis of kidney injury.

In conclusion, our retrospective analysis showed that SLE patients with higher SLEDAI score were most

significantly associated with heavy pyuria, high ANA concentration and elevated ESR, and they might be appropriate measures for pSLE disease activity. Our study also implies that mucocutaneous features might require more intensive therapy and disease monitoring.

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From the Department of Immunology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kelantan, Malaysia.

Address correspondence and reprints request to: Dr. Wan Zuraida W. A. Hamid, Department of Immunology, School of Medical Sciences, Health Campus, Hospital Universiti Sains Malaysia, Kelantan, Malaysia. E-mail: wzuraida@usm.my
ORCID ID: orcid.org/0000-0003-3039-9756

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