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Association between disease activity and clinico-laboratory parameters in Systemic Lupus Erythematosus patients in Hospital Universiti Sains Malaysia: a retrospective study

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Abstract

Systemic Lupus Erythematosus (SLE) is a prototypic autoimmune disease with multi-system involvement. The clinical manifestations and laboratory parameters in SLE patients vary depending upon the disease severity. SLE affects many organs such as skin, brain, and joints, thus affecting the clinical and laboratory parameters of the patients. This study aims to determine the association between the disease activity and clinico-laboratory parameters among SLE patients at Hospital Universiti Sains Malaysia. A total of 32 medical records of SLE patients from 2010 to 2023 were retrieved. The data of clinical and laboratory parameters were obtained and analysed using SPSS 27.0. Demographic data was analysed descriptively, and the Chi square test was used to evaluate the association between SLE disease activity and the clinico-laboratory parameters. We expect the most common symptoms in SLE include arthritis, malar rash, oral ulcer, and increase anti-dsDNA particularly in active SLE. This study showed the most common symptoms were arthritis (n=14;43.8%) followed by oral ulcer (n=10;31.3%). High level of anti-nuclear antibodies (ANA) was found in 21 patients (65.6%) while 18 (56.3%) patients had elevated erythrocyte sedimentation rate (ESR). Sixteen (50.0%) patients demonstrated low serum C3 and C4 levels. Significant associations were found between the disease activity and arthritis (p=0.033), oral ulcer (p=0.002), prolonged fever (p=0.001), ANA level (p=0.009), and anti-dsDNA level (p=0.022). Arthritis was found to be the most frequent symptoms in SLE patients. High level of ANA, increased ESR and low serum complement levels correlates well with active disease. In conclusion, active SLE patients were more frequently presented with arthritis, oral ulcer, prolonged fever, and demonstrated high ANA and anti-dsDNA levels.

Keywords: *clinical parameters, disease activity, laboratory parameters, systemic lupus erythematosus*

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Introduction

Systemic Lupus Erythematosus (SLE) can be defined as a chronic autoimmune inflammatory disease with multi-system involvement and is associated with high risk of morbidity and mortality (Narváez, 2020). This disease attacks one's own tissues which leads to inflammation of the tissues in the

various organs such as skin, brain, joints, and kidney. The first classification criteria for SLE were formulated in 1971 by the American College of Rheumatology (ACR), followed by revisions in 1982 and 1997. To improve their clinical performance which reflects the new knowledge on autoantibodies, Systemic Lupus International Collaboration Clinics (SLICC) classification criteria was issued. According to SLICC, the patient must satisfy at least 4 of 17 SLICC classification criteria, including at least one clinical and one immunologic criterion (Petri *et al.,* 2012). Recently, the new 2019 EULAR/ACR classification criteria was introduced to maintain the high specificity of the ACR criteria with a sensitivity close to SLICC criteria. The new 2019 EULAR/ACR classification criteria comprise of positive ANA as an obligatory criterion, 7 clinical criteria (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and 3 immunological (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) domains, which weighted from 2 to 10 (Aringer *et al.,* 2019).

Based on the Malaysian SLE association, more than 10,000 people over the past 30 years have been diagnosed with SLE. The prevalence of this life-threatening disease affects more females than males with a ratio of 9-10:1, with the age range from 15 to 40 years old (Ramírez Sepúlveda *et al.,* 2019). The disease activity is a manifestation of clinical and laboratory features which reflects the immunologic and inflammatory manifestation of lupus at a certain point of time (Parker & Bruce, 2019). SLE disease activity is assessed using the SLE Disease Activity Index (SLEDAI) score. SLEDAI score is a global score which includes both clinical and laboratory parameters, used to measure the disease severity within the last 10 days. Patients with SLEDAI score of lower than 6 are regarded to have an inactive disease, whereas those with a score of 6 or higher are considered to have an active disease (Shamim *et al.,* 2020). SLEDAI score has been proved to be a good tool in monitoring disease activity in SLE patients since it is concise and easy to use and has demonstrated great psychometric qualities in validation (Shamim *et al.,* 2020). A high disease activity status indicates severe active disease (Koelmeyer *et al.,* 2019) and it has been found to be associated with higher relative risk of mortality (Parker & Bruce, 2019).On the other hand, a low disease activity, remission or inactive disease have been proven to be associated with reduction in disease flare, reduce risk of irreversible end organ damage and improvement in patient outcomes (Golder V & Tsang- A-Sioe., 2020).

Oral ulcers are one of the clinical manifestations in SLE patients. It is one of the listed criteria when classifying SLE patients and it is the most common oral manifestation found in SLE patients which mainly occur on the hard palate, followed by the soft palate and vermilion of the lower lip (Zakeri *et al.,* 2012). Oral manifestations may present at early stage of SLE disease. Therefore, it is crucial for the dentists to be able to detect the ulcers, especially aphthous ulcers, for early diagnosis, treatment and to prevent complications. Chronic cutaneous SLE patients may come with asymmetrically distributed, well-demarcated, red, round, or irregular-shaped, atrophic or ulcerated oral lesions. As for acute cutaneous SLE, patients have a higher prevalence of ulcers and blisters (García-Ríos *et al.,* 2022). Apart from oral ulcers, a study in Qatar had observed that SLE patients have a high prevalence of gingivitis, periodontal disease as well as cavities (Hammoudeh *et al.,* 2018). Additionally, periodontitis is also one of the main clinical manifestations in SLE which is thought to have a similar underlying pathophysiology. Elevated levels of proinflammatory cytokines, B2-glycoprotein 1-dependent anticardiolipin and tissue destruction had been found in SLE and periodontitis (Fosam, 2020).

SLE patients who underwent treatment with immunosuppressive drugs, various antimalarials and biologic agents may experience more oral lesions. For instance, methotrexate which is originally used for treatment of cancer is also used for SLE, since it can reduce joint pain and swelling by blocking folic acid production. However, this

drug is commonly associated with mouth ulcer and an increased risk of oral infection such as fungal and mycobacterium infections. Therefore, a collaboration between dentist and medical practitioners is crucial to shorten the course of the disease, to decrease the disease activity as well as to minimise the complication with the aim of improving patients' quality of life (Fosam, 2020).

The association of disease activity and clinico-laboratory parameters in our local population has not been extensively studied. The clinico-laboratory parameters are important for SLE diagnosis. Therefore, this study aimed to assess the association between SLE disease activity, clinical manifestation as well as laboratory parameters to improve the outcome, disease monitoring and SLE prognosis.

Materials and Methods

This retrospective study was carried out by accessing medical records from Record Unit, Hospital USM. Thirty-two medical records of diagnosed SLE patients between 2010 to 2023 were retrieved. The inclusion criteria include SLE patients within the age range of 18 to 60 years old who was diagnosed with the disease using the SLICC 2012 or EULAR/ACR 2019 criteria. SLE patients who have SLEDAI score of more than 6 were defined as having active disease whereas those with the score of less than 6 were considered to have inactive disease. Pregnant and lactating women, patients who had malignancy or other autoimmune or inflammatory conditions (such as rheumatoid arthritis, ankylosing spondylitis) were excluded. The study protocol was approved by the Ethics Committee of USM (USM/JEPeM/KK/23040319).

Malar rash, arthritis, alopecia, prolonged fever, photosensitivity, oral ulcers, headaches, blurred vision, alopecia, serositis, and vasculitis were among the symptoms and clinical manifestations which were obtained from medical records. Immunological investigations were comprised of antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), complement 3 (C3), and complement 4 (C4). Haematological parameters include full blood count (FBC) and erythrocyte sedimentation rate (ESR).

Data entry and analysis

Data entry was performed and analysed using SPSS Version 27.0 (IBM SPSS, Chicago, IL). Demographic data was analysed using descriptive method. Chi square test and Fisher's Exact test were used to evaluate the association between SLE disease activity, clinical features and laboratory parameters. A p value *of* <0.05 was considered statistically significant.

Results

A total of 32 SLE patients were included in this study, consisting of 16 active SLE patients and 16 SLE patients with inactive disease. Thirty (93.8%) patients were female, and 3 patients (6.3%) were male with the ratio of 15:1. The majority of patients (93.8%) were Malay, the remainder were Chinese and Siamese. The most common presenting symptoms were arthritis (43.8%), oral ulcer (31.3%), followed by malar rash, prolonged fever, and alopecia which showed the same prevalence (28.1%) (Table 1). Twenty-one (65.6%) of SLE patients had high ANA levels with the titer of 1:160 and above, while only 9 (28.1%) patients had high anti-dsDNA levels. Low serum C3 and C4 were found among SLE patients with the prevalence of 20 (62.5%) and 19 (59.4%), respectively. Elevated ESR levels were observed in 18 (56.3%) patients (Table 1).

Clinical features such as arthritis (p=0.033), oral ulcers (p=0.002), and prolonged fever (p=0.001) were significantly associated with high SLEDAI score. ANA is the only laboratory parameter that had a significant association with SLEDAI score (p=0.009), meanwhile there was no significant association between other clinical features and laboratory parameters with SLEDAI score (Table 2).

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

Variables	n (%)
Gender	
Female	30 (93.8)
Male	2 (6.3)
Race	
Malay	30 (90.6)
Chinese	2 (6.3)
Others	1 (3.1)
SLEDAI Status	
Active (≥6)	16 (50.0)
Inactive (<6)	16 (50.0)
Presenting Symptoms	
Arthritis	14 (43.8)
Malar rash	9 (28.1)
Oral ulcer	10 (31.3)
Prolonged fever	9 (28.1)
Alopecia	9 (28.1)
Blurring vision	4 (12.5)
Headache	6 (18.8)
Serositis	1 (3.1)
Vasculitis	4 (12.5)
LE non-specific lesions	2 (6.3)
LE-specific lesions	2 (6.3)
Both types of lesions	1 (3.1)
Photosensitivity	6 (18.8)
Immunological Parameters	
High level ANA	21 (65.6)
High level anti-dsDNA	9 (28.1)
Low serum C3	20 (62.5)
Low serum C4	19 (59.4)
Haematological parameters	
Elevated ESR	18 (56.3)
Anemia	14 (43.8)
Thrombocytopenia	3 (9.4)
Leucopenia	7 (21.9)

*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

Table 2. The association of SLEDAI score with demographic, clinical features, and immunological parameters of SLE patients (n=32).

Variables	SLEDAI score		*p*-value
	Active (≥6) n (%)	Inactive (<6) n (%)	
Gender			
Female	15 (46.9)	15 (46.9)	1.000
Male	1 (3.1)	1 (3.1)	
Arthritis			
Yes	10 (31.3)	4 (12.5)	0.033*
No	6 (18.8)	12 (37.5)	
Oral Ulcer			
Yes	9 (90.0)	1 (10.0)	0.002*
No	7 (31.8)	15 (68.2)	
Malar Rash			
Yes	6 (37.5)	3 (18.8)	0.238
No	10 (62.5)	13 (81.3)	
Prolonged Fever			
Yes	9 (100)	0 (0)	0.001*
No	7 (30.4)	16 (69.6)	
Alopecia			
Yes	6 (66.7)	3 (33.3)	0.433
No	10 (43.5)	13 (56.5)	
Blurring Vision			
Yes	4 (12.5)	0 (0)	0.101
No	12 (42.9)	16 (57.1)	
Headache			
Yes	5 (15.6)	1 (3.1)	0.172
No	11 (34.4)	15 (46.9)	
Serositis			
Yes	1 (3.1)	0 (0)	1.000
No	15 (46.9)	16 (50.0)	
Vasculitis			
Yes	4 (12.5)	0 (0)	0.101
No	12 (37.5)	16 (50.0)	
LE-non-specific Lesions			
Yes	2 (6.3)	0 (0)	0.484
No	14 (43.8)	16 (50.0)	
LE-specific Lesions			
Yes	2 (6.3)	0 (0)	0.484
No	14 (43.8)	16 (50.0)	
Both types of Lesions			
Yes	1 (3.1)	0 (0)	1.000
No	15 (46.9)	16 (50.0)	
Photosensitivity			
Yes	4 (12.5)	2 (6.3)	0.654
No	12 (37.5)	14 (43.8)	
ANA			
Low	2 (6.3)	9 (28.1)	0.009*
High	14 (43.8)	7 (21.9)	
Anti-dsDNA			
Low	8 (25.0)	14 (43.8)	0.054
High	8 (25.0)	2 (6.3)	

Serum C3			
Low	11 (34.4)	9 (62.5)	0.465
High	5 (15.6)	7 (21.9)	
Serum C4			
Low	9 (28.1)	10 (31.3)	0.719
High	7 (30.4)	6 (18.8)	
Elevated ESR			
Yes	10 (31.3)	8 (25.0)	0.476
No	6 (18.8)	8 (25.0)	
Anemia			
Yes	8 (25.0)	10 (31.3)	0.476
No	8 (25.0)	6 (18.8)	
Thrombocytopenia			
Yes	3 (33.3)	0 (0)	0.226
No	13 (56.5)	16 (50.0)	
Leucopenia			
Yes	5 (15.6)	2 (6.3)	0.394
No	11 (34.4)	14 (43.8)	

*Significant *p*-value <0.05, ANA (antinuclear antibody), anti-dsDNA (anti-double stranded deoxyribonucleic acid antibody), C3 (complement), C4 (complement 4), ESR (erythrocyte sedimentation rate), SLEDAI (systemic lupus erythematosus disease activity index)

Discussion

The majority of SLE patients in this study were of the Malay ethnicity, which explains the large difference in number of Malays than other ethnicities. The population bias in East Coast Peninsular Malaysia is influenced by the demographic distribution of ethnic groups, with Malays forming the majority. This explains the higher number of Malay SLE patients. This reflects the local demographic distribution rather than a true difference in disease susceptibility, leading to a skewed ratio at the sampling site (Ilias *et al.,* 2017). In this study, 30 patients were female and only 2 patients were male. The female to male ratio was 15:1 which is much higher compared to a study conducted in Qatar (9.5:1) by Hammoudeh *et al.* (2018). Females are more susceptibility to SLE due to of the effects of oestrogen and its hydroxylation and differences in gonadotropin-releasing hormone signalling (Yacoub Wasef, 2004). Oestrogen has a wide range of immunological effects, including modulating the innate and adaptive immune responses, increasing the number of immunoglobulin-secreting cells, effects on antigen presentation by dendritic cells and macrophages, as well as modulating the Th1 and Th2 responses. Although SLE commonly occurs in female at childbearing age and uncommon after menopause, in certain circumstances SLE cases had been reported in pediatric and male patients (Guéry, 2019).

A study in Kuala Lumpur, Malaysia reported that arthritis, malar rash, haematological diseases, oral ulcer, and renal disease were the most common clinical manifestations in SLE patients (Jasmin *et al.,* 2013). Our study showed similar clinical manifestations experienced by SLE patients, with the most common symptoms are arthritis, oral ulcer, and malar rash. Renal and hematological disease were not assessed in this study. Arthritis is one of the earliest clinical manifestations in SLE disease progression which influences the SLEDAI score. According to EULAR/ACR classification, arthritis is a synovitis that affects two or more joints, and it can be characterised by swelling or effusion, or by pain in two or more joints, and associated with morning stiffness for at least 30 minutes. This study shows arthritis is the most common clinical symptom in SLE patients which was present in 14 (43.8%) patients in our cohort. The result is lower compared to a previous study by Ceccarelli *et al.* (2022) which reported that 90% of the patients had arthritis.

Nevertheless, a study by Shamim *et al.* (2020) in Saudi Arabia reported a closer number to our study which is 43.5%. Our study found that there is a significant association between arthritis and disease activity (p=0.033). By contrast, there is no significant association between arthritis and disease activity in these two previous studies.

Oral ulcer was the second most common clinical presentation in our patient cohort (n=10, 31.3%). This finding is comparable with the findings of an earlier study by Hammoudeh *et al.* in 2018 with the prevalence rate of various forms of oral ulcer in SLE patients from 7.0% to 41.0%. Hammoudeh *et al.* (2018) also observed that 72.0% of SLE patients had oral ulcer and the oral manifestations in these patients can be in the form of honeycomb plaque, raised keratotic plaque, and petechiae. We found that there is a significant association between oral ulcers and disease activity (p=0.002) which is comparable to a previous study finding by Nazri *et al.* (2018) (p=0.001). There is established evidence regarding the action of circulating antigen-antibody complexes which degenerate keratinocytes of oral mucosa leading to increase in the number of oral mucosal lesions among SLE patients (García-Ríos *et al.,* 2022). Thus, it is important for dental practitioners to be able to identify oral ulcers during patients' visit as it could be an initial sign of SLE disease progression.

Other frequent clinical features observed in this study were malar rash (28.1%), alopecia (28.1%), and prolonged fever (28.1%). The prevalence of malar rash and alopecia in this study was lower than previous study by Chanprapaph *et al.* (2021), (43.2%) and (36.6%), respectively. The prevalence of prolonged fever in this study was also lower compared to a previous study (43.5%) by Shamim *et al.* (2020). There was a significant association between disease activity and prolonged fever in our study. However, there is no significant association between the two parameters in study by Shamim *et al.* (2020). The significant of presence of common symptoms in SLE such as malar rash, alopecia and prolonged fever is important for early diagnosis and treatment to prevent complications.

In our study, ANA was detected in all patients. Twenty-one patients (65.6%) had high level of ANA with the titre of 1:160 and above. Chanprapaph *et al.* (2021) reported that 69.6% of SLE patients had high ANA level which is consistent with our study. A negative ANA test cannot rule out diagnosis of SLE, since 20.0% of patients may have negative (true negative or false negative) at various stages of the disease, although typically the rate of ANA-negative lupus is much lower. The frequency of ANA negativity ranged from 5 to 23 (4.9% to 22.3%) of 103 samples for immunofluorescence assay (IFA), 12 (11.7%) and 14 (13.6%) for enzyme linked immunofluorescence assay (ELISA) and multiplex assay (Pisetsky *et al.,* 2018). Our study shows that high ANA level was associated with high disease activity (p=0.009) which is consistent with the study finding by Nazri *et al.* (2018) *(*p=0.006). The prevalence of high level of anti-dsDNA was lower in our study (28.1%) as compared to previous study (67.2%) in Thailand (Chanprapaph *et al.,* 2021) as well as study in Malaysia (78.1%) (Nazri *et al.,* 2018). A previous study by Adamichou & Bertsias in 2017 had described an increase in anti-dsDNA levels a few weeks before SLE flare with subsequent reduction during flare of the disease. Anti-dsDNA testing is crucial for accurate classification and diagnosis of SLE which might help in disease activity assessment since it correlates with disease activity particularly in patients with renal involvement (Orme *et al*., 2022).

Serum C3 and C4 were decreased in 20 (62.5%) and 19 (59.4%), respectively. These findings are consistent with previous study findings by Nazri *et al*. (2018), who reported that the prevalence of C3 and C4 levels were 22 (68.8%) and 19 (59.4%) respectively. In general, SLE patients with an active disease usually have low C3 and C4 levels. The most possible cause of decrease in complement levels is due to increase in complement consumption which suggests involvement of the classical complement pathway (Ayano & Horiuchi, 2023). However, our study found

that no significant association between the complement levels and disease activity (C3: p=0.465) and (C4: p=0.719). In contrast, a cross-sectional study conducted in Lahore reported a significant association between a high SLEDAI score and elevated anti-dsDNA titer, ESR, low haemoglobin and low complement levels (Shamim *et al*., 2020). Previous study by Al-Mughales, (2022) reported that patients with organ involvement, particularly renal problems, were found to have decreased levels of serum C3 (p=0.066) and C4 (p=0.003) levels. Eighteen patients (56.3%) had elevated ESR in this study, but the percentage is lower than previous study (78.3%) by Shamim *et al*. (2020).

Conclusion

The most common presenting symptoms in SLE patients in this study were arthritis, oral ulcer, malar rash, prolonged fever and alopecia. Arthritis, oral ulcers, and prolonged fever were found to be significantly associated with the SLE disease activity, whereas for laboratory parameters, only serum level ANA was significantly associated with SLE disease activity. One of the limitations in this study is the small sample size. Larger sample size should be considered in the future study to obtain more conclusive findings.

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