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Slicc damage index score in systemic lupus erythematosus patients and its associated factors

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Abstract

The aims of this study were to determine damage index in systemic lupus erythematosus (SLE) patients based on Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) and to determine the laboratory and clinico-demographic factors affecting SDI.

This is a retrospective cohort study of 94 SLE patients attending rheumatology clinics in 2 local hospitals in Kelantan, Malaysia. The patients were divided into 2 groups based on SDI score assigned by the attending physician, 0 (without damage) or ≥1 (with damage). Newly diagnosed SLE patients with disease duration less than 6 months were excluded.

A total of 45 (47.9%) SLE patients showed damage by SDI score. Majority of the subjects had neuropsychiatric damages (21/94; 22.3%) followed by skin (12/94; 12.8%) and musculoskeletal (6/94; 6.4%) damage. SDI score was significantly associated with higher disease duration (6.2 ± 6.57 years vs 4.5 ± 3.7 years; $P = .018$), lower prednisolone dose (8.74 ± 10.89 mg vs 4.89 ± 3.81 mg; $P < .001$), hypertension ($P = .007$), and exposure to cyclophosphamide ($P = .004$). Hypertension ($P = .020$), exposure to cyclophosohamide ($P = 0.013$), and lower prednisolone dose ($P = .023$) were significantly associated with damage by multivariable analysis.

Higher SDI score was significantly associated with exposure to cyclophosphamide, suggesting that lower cyclophosphamide doses or alternative therapeutic agents are recommended.

Abbreviations: ACA = Anticardiolipin antibody, LA = Lupus anticoagulant, SDI = SLICC damage index, SLE = Systemic lupus erythematosus, SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

Keywords: anticardiolipin antibody, lupus anticoagulant, SLICC damage index, systemic lupus erythematosus, systemic lupus international collaborating clinics/American college of rheumatology

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with diverse and varied clinical manifestations and long-term outcomes. In the past few decades, there is a significant improvement in the management and survival rates, however the morbidity due to organ damage remains unresolved.[1]

Irreversible organ damage is a primary outcome in SLE. It is accrued during the course of SLE caused by both the disease itself and therapies received by patients. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) was developed in 1996[2] to assess an ongoing reflection of disease activity in SLE patients and to measure irreversible damage resulting from SLE disease activity and its treatment. All damage is scored from the time of SLE diagnosis onward regardless of whether or not the damage is attributed to lupus.

SDI contains items that represent permanent, irreversible damage in a lupus patient. Items should be present for at least 6 months with the exception that manifestations such as myocardial infarction and stroke are recorded once they occur. Damage is defined for 12 organ systems: ocular (range 0–2), neuropsychiatric (0–6), renal (0–3), pulmonary (0–5), cardiovascular (0–6), peripheral vascular (0–5), gastrointestinal (0–6), musculoskeletal (0–7), skin (0–3), endocrine (diabetes) (0–1), gonadal (0–1), and malignancies (0–2). Damage over time can only be stable or increase, theoretically to a maximum of 47 points.[3]

SDI also predicts future mortality of SLE patients. For instance, 25% of lupus patients who had damage at their first SDI assessment died within 10 years of their illness compared to only 7.3% who did not have early damage.[4] Organ damage occurs in 50% of patients within 5 years of SLE diagnosis and is associated with increased mortality. Risk factors for damage include older age at diagnosis, longer duration of SLE, African-Caribbean or Asian ethnicity, high disease activity at diagnosis, and greater overall activity during the disease course.[4]

It is vital to understand factors that relate to the development of damage in SLE patients as any interventions that can reduce damage progression are also likely to reduce future mortality.[5,6] Thus, in this study, we set out to determine the association

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between SDI with laboratory and clinico-demographic factors including disease duration, number of flare ups, age at diagnosis, ANA titer, disease co-morbidity, and treatment in a local cohort of SLE patients (n = 94).

2. Methods

2.1. Recruitment of SLE patients

We recruited SLE patients who attended specialist clinics in Hospital Universiti Sains Malaysia or Hospital Raja Perempuan Zainab II in Kelantan, Malaysia. This study has obtained approval from the Human Research Ethics Committee, Universiti Sains Malaysia and the Medical Research and Ethics Committee, Ministry of Health Malaysia.

Patients were considered eligible for the study if they were above 12 years old who fulfilled at least 4 criteria from the American College of Rheumatology Classification criteria for SLE or renal biopsy consistent with lupus nephritis (LN).[7] SDI measured cumulative and irreversible damage, irrespective of its cause, in 12 different organ systems. To be scored, each manifestation should be present for at least 6 months in accordance with the protocols adopted by Andrade et al.[8] Hence, newly diagnosed SLE patients for less than 6 months were excluded. Patients' clinico-demographic data were obtained from the unit records of each hospital and SDI score was assigned by the attending clinician according to standardized criteria.[9]

The data collected and analyzed are as follows:

(1) Demographic data: age, gender, and ethnic;
(2) Clinical data: disease duration, relapse rate, prednisolone dose, presence of hypertension, hyperlipidemia, or diabetes, administration of hydroxychloroquine (6.5 mg/kg/day), azathioprine (2.5 mg/kg/day), cyclophosphamide (7.5 mg/kg/pulse), cyclosporine (50 mg daily), prednisolone, and organs involved;
(3) Laboratory results: anticardiolipin antibody (ACA), lupus anticoagulant (LA) antibody, antinuclear antibody (ANA) titer, white cell count, hemoglobin, platelet, creatinine, and 24 hours urine protein.

2.2. Statistical analysis

All statistical analyses were performed using SPSS v22 (SPSS Inc., Chicago, IL). For univariate analysis, 2 groups of patients with or without damage by SDI score were produced. Difference between categorical variables was analyzed by Chi-squared test while independent *t* test was used for continuous numerical variables. The two-tailed Fisher's exact test was used when the expected count was less than 5. Simple logistic regression analysis was used to assess the significance of factors in predicting the outcomes. Any factor whose *P* value was less than .25 would be included in multivariable analysis with multiple logistic regressions. For all analyses, a two-tailed $P < .05$ was considered as statistically significant.

3. Results

3.1. Clinico-demographic features

A total of 94 SLE patients were included in this study. The mean age at SLE diagnosis and upon data collection was 25 and 31 years old, respectively. There were more female (92/94; 97.9%) than male patients (2/94; 2.1%). This study was conducted in Kelantan state of Malaysia where the population is predominantly of Malay population and hence majority of the patients were Malays (90/94; 95.7%) and the rest of the 4 (4/94; 4.3%) patients were of Chinese ethnicity. The mean disease duration was 5.3 years ranging from 1 to 27 years (Table 1).

Table 1

Demographic data of the SLE patients involved in this study (n = 94).

Variables	Mean (SD) or n (%)
Age (years), mean (SD)	31.01 (12.6)
Age at diagnosis (years), mean (SD)	25.68 (11.6)
Duration (years), mean (SD)	5.30 (5.3)
Relapse rate (number), mean (SD)	0.50 (0.8)
Prednisolone dose (mg), mean (SD)	6.94 (8.4)
Gender, n (%)	
Female	92 (97.9)
Male	2 (2.1)
Ethnic, n (%)	
Malay	90 (95.7)
Chinese	4 (4.3)
Hypertension, n (%)	
Yes	26 (27.7)
No	68 (72.3)
Hyperlipidemia, n (%)	
Yes	19 (20.2)
No	75 (79.8)
Hydroxychloroquine, n (%)	
Yes	90 (95.7)
No	4 (4.3)
Azathioprine, n (%)	
Yes	33 (35.1)
No	61 (64.9)
Cyclophosphamide, n (%)	
Yes	20 (21.3)
No	74 (78.7)
Cyclosporine, n (%)	
Yes	1 (1.1)
No	93 (98.9)

SLE = Systemic lupus erythematosus.

3.2. Disease damage among SLE patients

A proportion of the study population had hypertension (26/94; 27.7%) and hyperlipidemia (19/94; 20.2%) and on treatment for the condition. Other medical conditions were hypothyroid (3/94; 3.2%) and 1 patient (1.1%) for each of the following condition: hyperthyroid, left renal stone, and bronchial asthma. Of the 94 patients, 44 (46.8%) patients demonstrated 1 item of SDI with mean SDI score of 0.67. The frequency of organ damages among the study population was highest in neuropsychiatric damage (17/94; 18.1%) followed by skin damage (12/94; 12.8%), musculoskeletal (6/94; 6.4%), and diabetes (6/94; 6.4%). None of the patients had damage for peripheral vascular, gastrointestinal, premature gonadal failure, and malignancy (Table 2).

3.3. Association of SDI score with clinico-demographic features

Majority of the study population (90/94; 95.7%) were prescribed with hydroxychloroquine as well as prednisolone (60/94; 63.8%). The mean prednisolone dose taken by this study population was 6.94 mg with doses ranging from 1 mg per day on

Table 2

Organ involvement of SLE patients according to SDI score.

SDI Score				
Organ involved	**0**	**1**	**2**	**Frequency (%)**
Ocular	89 (94.7)	5 (5.3)	0	5 (5.3)
Neuropsychiatric	73 (77.7)	17 (18.1)	4 (4.3)	21 (22.3)
Renal	90 (95.7)	4 (4.3)	0	4 (4.3)
Pulmonary	90 (95.7)	4 (4.3)	0	4 (4.3)
Cardiovascular	91 (96.8)	3 (3.2)	0	3 (3.2)
Peripheral vascular	0	0	0	0
Gastrointestinal	0	0	0	0
Musculoskeletal	88 (93.6)	6 (6.4)	0	6 (6.4)
Skin	82 (87.2)	12 (12.8)	0	12 (12.8)
Diabetes	88 (93.6)	6 (6.4)	0	6 (6.4)
Premature gonadal failure	0	0	0	0
Malignancy	0	0	0	0

SDI = SLICC damage index, SLE = Systemic lupus erythematosus.

Table 3

Association of categorical variables with SDI score. $P < .05$ is emboldened.

Variables	SDI: 0	SDI: ≥1	*P* value
Gender			
Female	48	44	.497
Male	2	0	
Ethnic			
Malay	47	43	.620
Chinese	3	1	
Hypertension			
Yes	8	18	.007
No	42	26	
Hyperlipidemia			
Yes	7	12	.110
No	43	32	
Relapse Rate			
>1	13	19	.079
0	37	25	
ACL Antibody			
Positive	7	12	.110
Negative	43	32	
LA Antibody			
Positive	5	6	.584
Negative	45	38	
Hydroxychloroquine			
Yes	48	42	1.000
No	2	2	
Azathioprine			
Yes	14	19	.124
No	36	25	
Cyclophosphamide			
Yes	5	15	.004
No	45	29	
Cyclosporine			
Yes	0	1	.468
No	50	43	

ACL = Anticardiolipin antibody, LA = Lupus anticoagulant.

the last visit rheumatology clinic. Azathioprine is the most common immunosuppressive agents taken by 33 patients (35.1%) while 20 patients (21.3%) received cyclophosphamide after SLE diagnosis. One patient (1.1%) who had transverse myelitis was on cyclosporine. None of the patients had been prescribed with mycophenolate mofetil as immunosuppressive agent.

Higher SDI score was significantly associated with disease duration ($P = .018$; 6.2 ± 6.57 years vs 4.5 ± 3.7 years), total white cell count ($P = .008$; 7.55 ± 7.9 vs 6.7 ± 2.94) or creatinine levels ($P = .012$; 99.30 ± 132.37 vs 67.26 ± 16.97). Higher prednisolone dose showed highly significant relationship with lower SDI score compared with patients on lower prednisolone dose ($P < .001$; 8.74 ± 10.89 mg vs 4.89 ± 3.81 mg), and such significant relationship was also observed for patients exposed to cyclophosphamide ($P = .004$) (Table 3). There was no significant association between SDI and anticardiolipin antibodies, LA (Table 3), age of diagnosis, relapses rates, ANA titers, hemoglobin, and 24 hours urine protein (Table 4).

Two categorical (hypertension and cyclophosphomide) and 4 numerical (disease duration, white cell count, creatinine, and prednisolone dose) variables were selected for multiple logistic regression. Hypertension ($P = .020$), cyclophosphamide administration ($P = .013$), and lower prednisolone dose ($P = .023$) were significantly associated with SDI ≥1 (Table 5).

4. Discussion

Knowledge on lupus progression and damage from South East Asia is limited. To the best of our knowledge, this study is the first to report SDI in SLE patients and its associated factors from Eastern Peninsular Malaysia. Although, Malaysian population consists of 50.1% Malay ethnicity [apart from Chinese (22.6%), indigenous (11.8%), Indian (6.7%), and others (8.8%)] 95.7% of the SLE patients in our study were of the Malay ethnic origin and the rest of subjects (4.3%) of Chinese ethnicity, corroborating with the majority (1.55 of 1.67 million people; 92.5%) of Kelantan population consisting of Malay ethnic, and Kelantan is a Malaysian state where this study was conducted.

The distribution of organ damage in our cohort was neuropsychiatric damage (18.1%) followed by musculoskeletal damage (12.8%) similar with past reports.[10] However, other reports[11,12] observed the commonest system affected was musculoskeletal with the most frequent complication being avascular necrosis followed by corticosteroid-induced osteoporosis. In addition, cutaneous lesion was the most frequent system affected found in Brazilian patients with SLE.[13]

Our study reported a lower prevalence of renal damage. These were comparatively similar to the studies in West Malaysia, Korean, and South Chinese studies with 8% to 14.5% of SLE patients showing renal damage.[14] In contrast, Pakistani lupus patients demonstrated higher prevalence of renal damage (37.5%) with longer disease duration of 15 years.[15] Various factors may explain these differences such as treatment protocols or different histological renal changes that might influence the outcomes.

The most important demographic predictors of progression in damage were older age at diagnosis ($P < .05$) that is, those above 44 years old upon SLE diagnosis with rate of increase in SDI score of 0.20 per year.[16–18] Comparison between SLE patients with late onset (>49 years old at onset) vs patients with early onset showed a statistically significant difference in mean SDI scores between the two groups (2.4 ± 2.1 late onset vs 1.2 ± 0.9 early onset; $P = .001$). However in this study, there was no significant association observed between SDI with age and age at diagnosis. Majority of the patients in our cohort were less than 40 years old with mean age at diagnosis of 25.68 ± 11.58 years old.

Table 4

Association of continuous numerical variables with SDI score. $P < .05$ is emboldened.

Variables	SDI: 0	SDI: ≥1	*P* value
Age (years)	28.76 (12.094)	33.57 (12.75)	.273
Age at diagnosis (years)	24.16 (10.628)	27.41 (11.457)	.373
Disease duration (years)	4.5 (3.694)	6.20 (6.565)	.018
Relapse	0.46 (0.862)	0.55 (0.697)	.498
ANA titer	205.60 (131.803)	223.64 (125.70)	.531
White blood cell counts	6.685 (2.938)	7.857 (7.552)	.008
Hemoglobin	10.282 (2.797)	11.213 (2.082)	.173
Platelet	244.44 (121.173)	270.89 (101.322)	.274
Creatinine	67.26 (16.968)	99.30 (132.373)	.012
24 hours urine protein	360.14 (727.753)	631.16 (1100.278)	.311
Prednisolone dose (mg)	8.74 (10.889)	4.89 (3.811)	< .001

ANA = Antinuclear antibody, SDI = SLICC damage index.

Nonetheless, our finding was similar with previous study[12] which included 80 SLE patients and the authors found no association between the SDI with age and age at diagnosis.

We did not observe any significant association between the number of relapse with organ damage. This can be explained by the relatively low number of patients with relapse where only 33% of disease flares were observed in our study population. Moreover, majority of the patients in our cohort (95.7%) were on hydroxychloroquine which can prevent disease flares compared to a study by Ugarte-Gil et al[17] where 70.7% of their patients were on hydroxychloroquine and higher proportion of the patients (40%) experienced disease flares. Our results support early use of hydroxycloroquine to protect against damage, consistent with the findings of Toronto lupus cohort which showed hydroxycloroquine as protective therapeutic agent.[18]

A total of 27.7% of our study population had hypertension and they were associated with higher SDI score. Hypertension (37.4%) and depression (33.8%) were the most common comorbidity conditions with SLE. Increase in comorbid conditions is consistent with known increased mortality in SLE,[19] and hypertension increases the risk of cardiovascular events and deterioration of renal disease, contributing to organ damage in SLE patients.[20–22]

Our study showed no statistically significant association between ANA titer and SLICC damage ($P = 0.53$). In 1 study, involving 222 SLE patients, there was a significant association between ANA positivity with SDI ≥1 ($P = .007$) and the study utilized immunofluorescence microscopy for ANA test.[21]

The association of disease damage with the use of corticosteroid has been well-established.[22,23] Our study showed significant association between lower dosage of prednisolone with SDI score. Possible explanation for this observation would be that higher prednisolone dose was taken in a shorter duration. Another possibility might be due to clinical manifestations of SLE patients in our study where majority of them presented with mucocutaneous and musculoskeletal involvements by which they were prescribed maintenance low-dose prednisolone rather than immunosuppression agents. Nossent et al (1998) analyzed the association of damage with corticosteroid therapy in a cohort of 90 Afro-Carribbean patients.[24] The mean SDI scores were similar in corticosteroid users vs non-users (2.7 vs 2.04 respectively) and patients who received high doses of prednisolone did not accrue more damage than those who were not on prednisolone.[24] Higher total white blood cell count which were associated with SDI scores in our study might be explained by administration of prednisolone.

Table 5

Parameters associated with SDI according to multivariable logistic regression analysis. $P < .05$ is emboldened.

Parameters	B coefficient	Hazard ratio (95% confidence interval)	*P* value
Hypertension	1.38	3.99 (1.24–12.81)	.020
Cyclophosphamide	1.69	5.43 (1.44–20.54)	.013
Prednisolone	−0.09	0.92 (0.84–0.98)	.023
Duration	−0.30	0.74 (0.24–2.29)	.602
White blood cell counts	0.07	1.08 (0.98–1.18)	.119
Creatinine	0.01	1.01 (0.98–1.03)	.474

SDI = SLICC damage index.

In 2014, Ruiz-Arruza et al[10] demonstrated that patients with damage at 5 years received a higher mean daily prednisolone dose (10.4 vs 6 mg/day, $P < .001$) whilst patients administered with medium to high doses of prednisolone had a higher risk of accruing damage than those without prednisolone administration (adjusted odds ratio: [OR] 5.39, 95% CI: 1.59,18.27). Our studies support the potential inclusion of drug treatment as one of the items of SDI scoring.

In this study, presence of ACA ($P = .11$) and LA ($P = .58$) were not associated with risk for organ damage. Bonakdar et al[25] showed that there was a significant association between SDI accrual with positive antiphospholipid antibody. Antiphospholipid antibodies were associated with higher degree of damage at 5 years and predicted an SDI score ≥1 at 5 years. LA positivity had 0.16 rate of increase in SDI score per year ($P < .05$) and there was no strong association between damage accrual rates and history of ACL with OR (1.1; 95% CI: 1.0–1.3) ($P = .15$).[25]

In conclusion, the pattern of disease damage in our study was relatively unique from other Asian SLE cohorts with higher percentage in neuropsychiatric involvement followed by skin and mucocutaneous manifestations. We also demonstrated that lower prednisolone dose and cyclophosphamide administration were associated with increased risk of organ damage. However, there was no significant association between SDI score with number of flare ups, age at diagnosis, and ANA titer. The main limitation of our study is the relatively smaller number of patients and short follow-up period. Future multicenter retrospective studies involving larger number of cases are recommended to elucidate the treatments and clinico-demographical association with SDI scores in Asian SLE patients.

Author contributions

Conceptualization: Wan Syamimee Wan Ghazali, Nurashikin Mohammad, Kah Keng Wong.
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