

*Original Article***Evaluation of damage index and its association with risk factors in patients with systemic lupus erythematosus**

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Abstract

BACKGROUND: This study aimed to determine the value of damage index in patients with systemic lupus erythematosus (SLE) and the association between damage index and disease severity, flare up numbers, disease duration, and anti-phospholipid antibodies.

METHODS: Eighty patients with systemic lupus erythematosus were included. The damage was measured using the SLICC (Systemic Lupus International Collaborating Clinics)/ACR damage index (SDI). The disease flare was defined by the increase in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). The disease severity surrogates were the presence of class III/IV glomerulonephritis, the presence of severe central nervous system (CNS) involvement, and cyclophosphamide administration. Analysis was performed by independent Student-t and chi-square tests via SPSS₁₆ software.

RESULTS: There were significant association between the damage accrual and the disease severity, flare-up, and anti-phospholipid antibodies ($p = 0.001$, $p = 0.004$, and $p = 0.05$, respectively).

CONCLUSIONS: The disease severity, frequency of flares, and positive antiphospholipid antibodies are associated with damage accrual in patients with systemic lupus erythematosus.

KEYWORDS: Systemic Lupus Erythematosus, Damage Index, Antiphospholipid Antibody.

JRMS 2011; 16(Special Issue): 427-432

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease associated with significant morbidity and mortality. Ongoing increases in the life expectancy over the last decades have transformed SLE into a chronic disease that affects individuals with life threatening irreversible end organ damage and debilitating clinical feature.¹ Chambers et al evaluated damage accrual and mortality in British patients with SLE under long-term follow-up for more than 10 years and showed that increase in damage score was associated with a higher risk of death overall.² Another study on 105 patients with SLE in Brazil determined that damage accrual during follow-up was the strongest predictor of death.³

Several studies have evaluated the damage index and its association with some proposed risk factors; they reported conflicting results based on the type of geographic aspects of studied population. For example a study conducted in 221 patients with SLE showed age, presence of antiphospholipid antibodies, steroid use, and hypertension as predictors of damage progression.⁴ Another study conducted by La Gonzalez et al showed age, gender, ethnicity and menopause as significant predictors of damage accrual.⁵

We tried to apply the most important risk factors in one study in our population and ethnicity. This study was performed to determine the association of damage index and severe

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disease, flare-up, duration, age of onset, gender, and antiphospholipid antibodies among patients with SLE in Isfahan, Iran.

Methods

This analytic cross-sectional study was performed on 80 patients with SLE. The patients were enrolled by simple sampling method from Outpatient Clinic of Alzahra Hospital in Isfahan, Iran. They all met American College of Rheumatology (ACR) criteria for SLE.⁶ The patients were excluded if their disease duration was less than 6 months. Information such as age, sex, disease duration, time of disease onset, antibody markers, and organ involvement were obtained by reviewing the clinic files of all patients and through face-to-face interviews by a rheumatologist.

Systemic Lupus International Collaborative Clinics/ACR Damage Index (SLICC/ACR-DI), which Gladman et al determined it as a valid measure in SLE was used to document each patient.⁷⁻¹⁵ A flare of SLE was defined as an increase of more than 3 points compared to previous assessments in the SLEDAI-2K.¹⁶ SLE disease activity index was defined as the reversible manifestation of the underlying inflammatory process¹⁷ which evaluated the disease activity at the time of a patient's visit.¹⁸ The severity index does not look at the effects of treatment, but rather scores the effects of active disease over time and is a record of these events (not necessarily irreversible) over the course of a patient's illness.¹⁹

Surrogates for severe disease were as: 1. The presence of class III/IV glomerulonephritis (GN); 2. The presence of severe central nervous system (CNS) involvement (psychosis, seizure,

altered conscious state); and 3. Intravenous Cyclophosphamide pulse administration.²⁰ Antiphospholipid antibodies (aPL) were lupus anticoagulant (LA), anticardiolipin IgG or IgM isotype antibodies (aCL), and anti-Beta2 glycoprotein I antibodies (anti-B2GPI) present in medium or high titer on two or more occasions, 12 weeks or more apart.²¹ The time of disease onset was defined as the time at which patients met 4 components of the ACR criteria for SLE. The disease duration was defined as the interval between time of diagnosis and the time 0.²²

Data were expressed as mean \pm SD and percentiles. We performed bivariate analyses by chi-square for qualitative variables and independent sample t-test for quantitative variables. The significant level was set on 0.05 in all statistical analyzes. Data analyzes were performed with SPSS software (version 16, Chicago, IL).

Results

The demographic and clinical characteristics of subjects with and without damage are presented in Table 1 and 2. Of the patients, 67 (83.8%) were women and 13 (16.3%) were men. The mean age of the patients was 28.8 years (SD = 9.36, range: 16-60). 55% of the patients were in the 20-35 years age group. The mean age at disease onset was 23.8 years (SD = 8.84, range: 8-53). The mean disease duration was 60.6 months (SD = 3.35, range: 6-180 months). Approximately 38% of our patients had at least one item of damage index. The mean SDI was 0.59 (SD = 1.002, range: 0-5). The mean flare-up numbers was 2.7 (SD = 5.7, range: 0-10).

The frequency of organ damages among our patients were skin damage (31.8%), neuropsychiatric damage (27%), cardiovascular (14%),

Table 1. Demographic and clinical quantitative characteristic of 80 SLE patients with and without damage

Variable	Damage index (Mean \pm SD)		P value
	Positive (No = 30)	Negative (No = 50)	
Age (year)	30.23 \pm 12.3	28.02 \pm 7.06	0.3
Duration	5.97 \pm 4.24	4.49 \pm 2.59	0.056
Age at disease onset	11.4 \pm 24.3	7 \pm 23.5	0.7
Flare up numbers	9 \pm 4.23	1.28 \pm 1.8	0.004

Data expressed as mean \pm SD p-value: obtained from independent sample t-test.

Table 2. Demographic and clinical qualitative characteristic of 80 SLE patients with and without damage

Variable	Damage index		P value	OR	95% Confidence Interval	
	Positive (n = 30)	Negative (n = 50)			Lower	Upper
Sex	Male	6	0.48	1.5	0.46	5.1
	Female	24				
APA	Positive	12	0.046	2.67	0.97	7.3
	Negative	18				
Severity	Positive	16	0.001	5.2	1.9	14.4
	Negative	14				

P value: obtained from chi-Square test. Significant level: $p < 0.05$.

*Antiphospholipid antibody

Table 3. Frequency of damage index in 80 SLE patients

System damage	No.	%
Ocular	3	7
Neuropsychiatric	12	27
Renal	1	2
Pulmonary	3	7
Cardiovascular	6	14
Peripheral vascular	2	4.5
Gastrointestinal	0	0
Skin	14	31.8
Musculoskeletal	2	14
Premature gonadal failure	1	2
Diabetes mellitus	0	0
Malignancy	0	0

ocular (7%), pulmonary (7%), musculoskeletal (4.5%), peripheral vascular (4.5%), renal (2%), and gonadal failure (2%). The results are shown in Table 3.

Among the patients, 25 (31.3%) had severe disease, and 22 (27.5%) were antiphospholipid antibody positive. There was a significant association between SDI and severe disease ($p = 0.001$) and there was a significant association between the damage accrual and numbers of flares ($p = 0.004$). No statistically significant association was observed between the damage index, the gender, the disease duration, the age, and the age at disease onset.

Discussion

In our study, damage was detected in 38% of the patients that was in agreement with results of the previous studies.^{23,24} The range of the damage score in our patients was 0-5, similar to

the findings of research conducted by Hanly et al.²⁵ While the overall accrual of damage is gradual, the specific systems demonstrate varying patterns of damage accrual between ethnic groups, and damage in different organ systems in SLE does not follow a common pattern.²⁶⁻²⁹ For example, some investigators have reported kidney and musculoskeletal system as the most involved organs^{30,31} and some of them reported neuropsychiatric damage as the most frequent.^{32,33} However, similarly to other studies, skin was the most frequent damaged organ in our patients.^{34,35}

While several studies have investigated the relationship between disease activity and damage index, there are few studies evaluating the association between disease flare-up and severity with damage index. While the disease severity and flare are terms that reflect the cumulative disease activity over time, as ex-

pected, our study showed significant association between damage and frequency of disease flares that was similar to the results of Bandeira et al study which showed that patients who accrued new damage had a significantly greater frequency of disease flares in the 0-3 year follow-up period,¹⁶ and also the study of Nosent who found a significant association between damage and disease exacerbations.³⁴

Previous studies revealed divergent results on the association between damage and gender, age, age at disease onset, and sex, some conducted by Marx et al,³⁷ Sayarlioglu et al,³⁸ and Yee et al³⁹ which showed no significant association between damage and age, damage and age at disease onset, and damage and sex respectively, although the latter found significant association between the damage with age.

The search for a relationship between damage and disease duration in patients with SLE has yielded diverging results. Although several studies have found significant association between damage and disease duration ($p < 0.001$),^{16,33,40-42} we found no significant association between them ($p = 0.056$), which was like some other studies.^{37,43} This could be explained by the fact that in our study, only five out of eighty patients had the disease duration more than 10 years and the mean disease duration of our patients was low (5 years), on the other hand as Bridget et al reported that it is important to include only patients with short duration disease in assessing damage trials, as it is hard to evaluate differences in damage ac-

crual if patients had varying periods of disease activity and therapy before the clinical trial.⁴⁴

A few studies have evaluated correlation between damage and antibodies, and some of them reported that although auto antibodies are useful in diagnosis and predicting disease activity in SLE, they do not appear to be predictive of damage ($p < 0.001$).^{40,45} Our study found good association between damage index and antiphospholipid antibodies ($p = 0.046$) that comply with the finding of other researches ($p < 0.001$).⁴⁶⁻⁴⁸ Also, one study reported that aPL can predict early damage in patients with SLE ($p = 0.03$).⁴⁹

Although the results of this research is encouraging and promising, additional researches are needed and there are limitations as the absence of a comparison group, and its cross-sectional design. Nevertheless, it could be concluded that damage index in Iranian patients is relatively high and disease severity, flares, and antiphospholipid antibodies are associated with it. To reduce the occurrence of chronic damage, more attention should be given to the individual clinical and therapeutic decisions in SLE patients.⁵⁰ So, prompt treatment of disease flares, more attention to antiphospholipid antibody positive patients and prevention of severity is mandatory for reducing damage accrual.

Acknowledgment

We would like to thank the Office of Vice Chancellor for Research of Isfahan University of Medical Sciences for financial supports.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

ZSB has planned the study, collected the data, and finalized the manuscript. NM did the laboratory procedures and statistical analysis and prepared the first version of manuscript. MK supervised the project and help in the laboratory analysis. All authors read and approved the final manuscript.

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