Adjusted Mean Systemic Lupus Erythematosus Disease Activity Index-2K Is a Predictor of Outcome in SLE

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ABSTRACT. ***Objective.*** To test the predictability of the adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K (AMS) for main outcomes in systemic lupus erythematosus (SLE), namely presence of damage, coronary artery disease (CAD), and avascular necrosis (AVN).

Methods. Included in this study are patients with regular followup from the University of Toronto Lupus Clinic. This was defined as a minimum of 3 visits and no absence exceeding 18 consecutive months. For each visit, AMS was evaluated. The ability of the AMS to predict each of the main outcomes was evaluated through time-dependent covariate survival analysis. Adjustments to the regression models were made to include other risk factors such as sex, age at diagnosis (AGE), SLEDAI-2K at presentation (SLEDAI), disease duration (DD), and use of corticosteroids, immunosuppressives (IM), or antimalarials (AM).

Results. Five hundred and seventy-five patients were included covering the period from 1970 to 2002. A total of 325 developed damage, 55 had CAD, and 68 had AVN. Presence of damage was not associated with sex, SLEDAI, or AM but was significantly associated with AMS, AGE, DD, and use of steroids or IM (all $p < 0.001$). CAD was not associated with SLEDAI or use of steroids or AM but with all other variables AMS ($p = 0.046$), sex ($p = 0.009$), AGE ($p < 0.0001$), DD ($p < 0.0001$), and IM ($p = 0.035$). Predictors of AVN were DD ($p = 0.032$) and IM ($p < 0.0001$) but not sex, AGE, use of steroids, AM, SLEDAI, or AMS.

Conclusion. AMS is associated with the presence of damage and CAD. It is not associated with AVN. (J Rheumatol 2005;32:824–7)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS DAMAGE
CORONARY ARTERY DISEASE ADJUSTED MEAN SLEDAI-2K AVASCULAR NECROSIS

Prospective cohort databases of patients with systemic lupus erythematosus (SLE), where patients are seen at regular intervals and standardized information is collected at each visit, are now more commonly the focus of outcomes research, with yearly, biyearly, or more regular visits. Patients may be seen at non-scheduled visits resulting in missing information[1-3].

Outcomes in SLE studies include survival, increasing damage, presence of specific organ damage such as coronary artery disease (CAD) and renal damage, among others. Many studies have analyzed the risk factors associated with each of these outcomes. Usually, the outcome is determined at a single point in time and the potential risk factors are assessed at a baseline or a fixed point. There is no universally accepted approach to summarizing risk factors over multiple visits.

The SLE Disease Activity Index (SLEDAI-2K) evaluates disease activity at the time of a patient's visit[4]. We developed the adjusted mean SLEDAI (AMS) as a way to summarize disease activity over time[5].

We have previously shown that AMS is associated with survival. Since patients with SLE have been living longer, this becomes a less common outcome measure in longitudinal cohorts. Our aim was therefore to determine the predictive power of AMS for 3 major outcomes in SLE, specifically, presence of damage, CAD, and avascular necrosis (AVN).

MATERIALS AND METHODS

Setting. Patients with SLE have been followed prospectively at the University of Toronto Lupus Clinic since 1970[6]. By October 2002, 1096 patients were registered. Clinical and laboratory information is collected according to a standard protocol at regular intervals (every 2 to 6 months) and stored on a computer database. All patients are assessed by directors of the clinic (DDG or MBU) or by a clinical fellow trained by them. Each patient undergoes a complete history and physical examination according to protocol, which includes basic demographic data, organ specific disease-related symptoms, physical findings, and laboratory evaluations. The SLEDAI-2K scores disease activity at the time of the visit. All the individual descriptors of SLEDAI-2K have been included in the standard protocol and collected over the years.

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Patient selection. To avoid analyzing patients for whom information was missing for longer periods of time, only patients followed regularly at the Lupus Clinic were included in this study. Regular followup was defined as at least 3 clinic visits and no absence from clinic exceeding 18 consecutive months.

Definition of AMS. The adjusted mean SLEDAI (AMS) is equivalent to the area under the curve of SLEDAI-2K over time divided by time interval. Mathematically, it is expressed as

$$\frac{\sum_{i=2}^{n}\left(\frac{X_i + X_{i-1}}{2}\right)ti}{\sum_{i=2}^{n} ti}$$

where X_i = SLEDAI-2K at visit i and t_i = time interval between visit i and visit i–1. In simpler terms, to evaluate AMS (1) calculate the area under the curve between each 2 visits: the length of time between 2 visits multiplied by the average of the 2 SLEDAI-2K values; (2) add up all the calculated areas; and (3) divide the result by the total length of the time period. AMS has the same units as SLEDAI-2K and is interpreted in the same way.

Outcomes and risk factors. The 3 outcomes under consideration were presence of accumulated damage, presence of first CAD, and presence of first AVN.

Accumulated damage was defined as a score ≥ 1 on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC) damage index[7]. CAD was defined as presence of myocardial infarction or angina[8]. AVN was defined by the symptom of pain appropriately localized and confirmed by imaging[9].

In addition to AMS, other important risk factors considered were sex, age at diagnosis, SLEDAI-2K at presentation, disease duration, and treatment with corticosteroids, immunosuppressives, or antimalarials ever.

Statistical analysis. Descriptive statistics were evaluated for the group as a whole and were also calculated for each of the risk factors for the presence/absence of the 3 outcomes. Tests of significance to compare the risk factors between presence/absence of each outcome were made using t tests, or chi-square tests where appropriate. For each outcome, patients were censored at the time of its first occurrence. Time-dependent covariate survival analyses were performed using the risk factors as well as AMS to determine their impact on each of the outcomes.

RESULTS

A total of 575 patients had at least 3 visits to the University of Toronto Lupus Clinic without being absent for more than 18 months between visits. Almost 2/3 of the time intervals between visits were of 3 months or less. Over 90% of all intervals between visits were within 6 months. Less than 1% of all visits included in the sample were greater than 1 year apart.

AMS was evaluated for each patient and at each visit. Table 1 shows the demographic distribution of the population assessed. The 54 men and 521 women have been followed in the clinic for an average of 23 visits for 8 years representing a mean of over 10 years of disease duration. They have been followed in the Lupus Clinic for 4594 person-years.

In this sample, 69 patients presented to their first clinic visit with pre-existing damage, 14 with CAD, and 20 with AVN. These patients were excluded from their respective outcome analyses. Therefore, there were 83 deaths in 575 patients (14.4%), 325 patients with damage out of 506 patients (64.2%), 55 CAD in 561 patients (9.8%), and 68 AVN in 555 patients (12.3%).

Table 1. Demographic distribution of patients with SLE. Values are expressed as mean ± SD (min–max) or n (%).

Sample size	575
Time interval between visits, mos	4 ± 2 (0.2–18)
Sex, female	521 (90.6%)
Number of visits	23 ± 21 (3–111)
Length of followup in clinic, yrs	8.0 ± 6.9 (0.2–31.9)
Disease duration at last clinic visit, yrs	10.6 ± 8.1 (0.3–48.9)
Age at diagnosis, yrs	32.9 ± 14.1 (5–83)
SLEDAI-2K at 1st clinic visit	10.2 ± 8.3 (0–55)
AM of SLEDAI-2K at last visit	5.85 ± 3.90 (0–23.3)
Use of steroids ever	477 (83.1%)
Use of immunosuppressives ever	278 (48.4%)
Use of antimalarials ever	397 (69.2%)
Survival status, dead	83 (14.4%)
Presence of damage	325/506 (64.2%)
Presence of CAD	55/561 (9.8%)
Presence of AVN	68/555 (12.3%)

Comparisons of risk factors between patients with and without outcome were carried out in 2 steps. First, separate univariate analyses were done for each risk factor. Second, to establish the true relationship between AMS and each outcome, time-dependent covariate survival analyses were conducted. Sex, age at diagnosis, SLEDAI-2K at presentation, disease duration, and use of medications were also included in the models.

There were 164 (90.6%) women among patients without damage and 290 (89.2%) in the group with damage (p = NS) (Table 2). The mean age at diagnosis and disease duration were similar among patients with and without damage. Patients who developed damage had a statistically higher SLEDAI-2K at presentation to clinic (mean ± SD: 11.1 ± 8.6) compared to those without damage (9.0 ± 7.8) (p = 0.006). They also had higher percentages of taking either corticosteroids or immunosuppressives but lower percentages of antimalarial use (each with p < 0.001). Using time-dependent analysis, neither sex nor SLEDAI-2K at presentation, nor antimalarial use was associated with the presence of damage. AMS had a hazard ratio (HR) of 1.04, suggesting that for each AMS unit, there was a 4% increased risk of damage. HR for age at diagnosis was 1.02 and for disease duration 1.05. Thus, the risk of damage was increased with increasing values of these risk factors. HR for corticosteroid use was 1.80 and for immunosuppressives 2.21.

Looking at the presence of CAD (Table 3), we found a lower proportion of women in the CAD group (81.8%) compared to the non-CAD group (91.9%) (p = 0.014). Patients with cardiovascular events had significantly higher mean age at diagnosis of SLE than those without CAD: 40.6 (± 13.4) and 31.7 (± 13.5), respectively, (p < 0.0001). Similarly, they also had higher SLEDAI-2K at their first clinic visit: 12.8 (± 10.4) for CAD patients compared to 9.9 (± 8.0) for non-CAD (p = 0.047). Use of medications was

Table 2. Outcome: presence of damage.

Variable	Univariate Analysis: No Damage, n = 181 (%)	Univariate Analysis: Damage, n = 325 (%)	Univariate Analysis: p	Time-Dependent Covariate Survival Analysis: Parameter Estimate ± SE	Time-Dependent Covariate Survival Analysis: Hazard Ratio (95% CI)	Time-Dependent Covariate Survival Analysis: p
Sex, female	164 (90.6)	290 (89.2)	0.62	-0.217 ± 0.185	0.81 (0.56, 1.16)	0.24
Age at diagnosis	31.7 ± 12.3	33.8 ±15.1	0.08	0.016 ± 0.004	1.02 (1.01, 1.03)	< 0.001
Disease duration in clinic	7.5 ± 6.6	7.4 ± 7.1	0.84	0.048 ± 0.011	1.05 (1.03, 1.07)	< 0.0001
SLEDAI-2K at presentation	9.0 ± 7.8	11.1 ± 8.6	0.006	-0.007 ± 0.008	0.99 (0.98, 1.01)	0.42
Steroids	131 (72.4)	280 (86.4)	< 0.001	0.587 ± 0.178	1.80 (1.27, 2.55)	0.001
Immunosuppressives	59 (32.6)	158 (48.8)	< 0.001	0.794 ± 0.124	2.21 (1.73, 2.82)	< 0.0001
Antimalarials	145 (80.1)	183 (56.5)	< 0.0001	-0.216 ± 0.008	0.81 (0.64, 1.01)	0.07
AMS	5.2 ± 3.6	7.7 ± 6.0	< 0.0001	0.036 ± 0.014	1.04 (1.01, 1.06)	0.009

CI: confidence interval; SE: standard error.

Table 3. Outcome: coronary artery disease (CAD).

Variable	Univariate Analysis: No CAD, n = 506 (%)	Univariate Analysis: CAD, n = 55 (%)	Univariate Analysis: p	Time-Dependent Covariate Survival Analysis: Parameter Estimate ± SE	Time-Dependent Covariate Survival Analysis: Hazard Ratio (95% CI)	Time-Dependent Covariate Survival Analysis: p
Sex, female	465 (91.9)	45 (81.8)	0.014	-0.949 ± 0.363	0.39 (0.19, 0.79)	0.009
Age at diagnosis	31.7 ± 13.5	40.6 ± 13.4	< 0.0001	0.065 ± 0.010	1.07 (1.05, 1.09)	< 0.0001
Disease duration in clinic	10.0 ± 7.9	11.8 ± 8.3	0.10	0.109 ± 0.024	1.12 (1.06, 1.17)	< 0.0001
SLEDAI-2K at presentation	9.9 ± 8.0	12.8 ± 10.4	0.047	0.021 ± 0.015	1.02 (0.99, 1.05)	0.17
Steroids	416 (81.8)	49 (89.1)	0.18	0.033 ± 0.477	1.03 (0.41, 2.63)	0.95
Immunosuppressives	236 (46.7)	31 (56.4)	0.17	0.658 ± 0.312	1.93 (1.05, 3.56)	0.035
Antimalarials	349 (69.1)	36 (65.5)	0.58	0.272 ± 0.293	1.31 (0.74, 2.33)	0.35
AMS	5.8 ± 4.0	6.5 ± 3.8	0.23	0.077 ± 0.039	1.08 (1.00, 1.16)	0.046

equivalent among patients with or without CAD. In the survival regression, neither SLEDAI-2K at presentation nor the use of corticosteroids or antimalarial medications was associated with the development of CAD. HR for AMS was 1.08, for female sex 0.39 (equivalent to HR for males of 2.58), for age at diagnosis 1.07, and for disease duration 1.12. The risk of CAD was greater with increases in each of the factors. The risk of developing CAD was also greater (HR = 1.93) in patients taking immunosuppressive medications.

Comparisons between patients with and without AVN did not show any differences with respect to sex (88.2% vs 91.2%; p = NS) or age at SLE diagnosis (31.3 ± 12.0 vs 33.5 ± 14.4; p = NS) (Table 4). Patients with AVN had higher SLEDAI-2K at presentation than patients without AVN, with means of 13.4 (± 9.8) and 9.8 (± 8.0), respectively, (p = 0.005). Use of immunosuppressants was higher among patients with AVN (66.2% vs 44.2%; p < 0.001) while use of antimalarials was higher in patients without AVN (52.9% in AVN vs 69.1% in non-AVN; p = 0.008). Corticosteroids were present in all 68 patients with AVN. This caused the multivariate regression model to inadequately evaluate the HR for steroid use. Lifetime cumulative steroid dose for each patient was used as a variable instead of presence of steroids in the model. AMS, sex, age at diagnosis, SLEDAI-

Table 4. Outcome: avascular necrosis (AVN).

Variable	Univariate Analysis: No AVN, n = 487 (%)	Univariate Analysis: AVN, n = 68 (%)	Univariate Analysis: p	Time-Dependent Covariate Survival Analysis: Parameter Estimate ± SE	Time-Dependent Covariate Survival Analysis: Hazard Ratio (95% CI)	Time-Dependent Covariate Survival Analysis: p
Sex, female	444 (91.2)	60 (88.2)	0.43	-0.192 ± 0.382	0.83 (0.39, 1.75)	0.62
Age at diagnosis	33.5 ± 14.4	31.3 ± 12.0	0.24	-0.017 ± 0.010	0.98 (0.96, 1.00)	0.09
Disease duration in clinic	9.9 ± 7.8	6.9 ± 6.0	< 0.001	-0.099 ± 0.046	0.91 (0.83, 0.99)	0.032
SLEDAI-2K at presentation	9.8 ± 8.0	13.4 ± 9.8	0.005	0.027 ± 0.014	1.03 (1.00, 1.06)	0.07
Steroids	392 (80.7)	68 (100)	< 0.0001			
Cumulative steroid dose				-0.003 ± 0.007	1.00 (0.98, 1.01)	0.71
Immunosuppressives	215 (44.2)	45 (66.2)	< 0.001	1.267 ± 0.307	3.55 (1.94, 6.48)	< 0.0001
Antimalarials	336 (69.1)	36 (52.9)	0.008	-0.210 ± 0.254	0.81 (0.49, 1.33)	0.41
AMS	5.9 ± 3.9	6.5 ± 3.9	0.25	-0.069 ± 0.039	0.93 (0.86, 1.01)	0.08

2K at presentation, cumulative steroid dose, and use of antimalarial drugs were not associated with the development of AVN. AVN was associated with a shorter disease duration (HR = 0.91), and use of immunosuppressive medications (HR = 3.55).

DISCUSSION

We earlier proposed a measure to summarize disease activity (measured by the SLEDAI-2K) over multiple visits[5]. The adjusted mean SLEDAI-2K (AMS) is equivalent to the area under the curve of the SLEDAI-2K by time divided by time interval. The relationship between AMS and survival was evaluated and it was found that with increased AMS, the risk for death is also increased.

Our study evaluated the relationship between AMS and the presence of other outcomes, specifically presence of overall damage, CAD, and AVN. The study group of 575 patients had very stringent followup restrictions. There was long enough disease duration and followup within the University of Toronto Lupus Clinic to have sufficient patients with the various outcomes under investigation. The patients selected did not differ from those not selected in their demographic distribution (data not shown).

As with survival, the comparison of AMS between patients with and without an outcome needs to be approached with caution. To predict the outcome, it would be inaccurate to simply compare AMS at the time of the outcome related event to the AMS at the last patient visit for the non-event group. The non-event group possibly would have had a greater number of clinic visits, which would, in turn, affect the AMS. Generally, it was found that the more visits a patient had, the greater the possibility for the AMS to be lower compared to a patient with fewer visits. In order to remove this bias, AMS could be evaluated at similar time intervals and then compared. This breakdown and ensuing series of statistical tests is not robust. It falls short in its ability to detect statistical significance since for any time period there is a small number of events. It also fails to look at all the patients in a single analysis. A more appropriate approach is the use of time-dependent covariate survival regression. In such an analysis, some or all of the independent variables, in this case AMS, change from visit to visit, in contrast to variables that remain fixed over time, such as sex or SLEDAI-2K at presentation. The survival analysis evaluates how the presence or absence of the outcome after each point in time is predicted by the independent variables at that point in time. Finally, the p values are computed to represent the entire spectrum of time under investigation.

Risk of damage increases with increases in AMS, age at diagnosis, disease duration, and use of corticosteroids and immunosuppressive medications. While the AMS incorporates the disease activity at presentation, it appears that disease activity over time is more important to the development of damage, as SLEDAI-2K at presentation was not retained in the multivariate analysis. AMS is an independent predictor along with age at diagnosis or disease duration. While there is a significant interaction between AMS and medication use, AMS, corticosteroids and immunosuppressive medications are each independent risk factors for the development of damage.

Increased AMS, age at diagnosis, disease duration, and use of immunosuppressive medications all lead to an increased risk of CAD. Men are also at greater risk than women. As with the damage, SLEDAI-2K at presentation is not a predictor of CAD. Rather, the disease activity over time is a predictor for the development of CAD. Interestingly, use of corticosteroids and antimalarials did not contribute to an increased risk for CAD in the multivariate analysis. This may be due to the correlation between AMS and medication use. In the case of the development of damage, each of these risk factors was significant. For CAD, it appears that AMS accounts for all their predictive ability.

In the development of first AVN, AMS does not play a significant role. Shorter disease duration and use of immunosuppressive medications are associated with an increased risk of AVN. This indicates that this outcome tends to occur early in the disease course and the risk of its first occurrence diminishes with time.

From our previous study and results obtained here we conclude that AMS is a risk factor for major outcomes in SLE. Only with the presence of AVN did we not see a relationship.

Thus AMS reflects disease activity over time and is an important predictor of major outcomes in patients with SLE. AMS should be included in the description of patients with SLE.

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