Summarizing Disease Features Over Time: II. Variability Measures of SLEDAI-2K

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ABSTRACT. ***Objective.*** To determine if the variability of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), along with the Adjusted Mean SLEDAI-2K (AMS), can better predict major outcomes in SLE than the AMS alone.

Methods. Patients were followed in the Lupus Clinic at 2–6 month intervals. Clinical and laboratory information necessary to compute the SLEDAI-2K and Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index was collected prospectively and entered onto a computerized database. Patients followed for a minimum of 3 visits, and without absence for a period > 18 consecutive months, were included in the study. Six different approaches to measure variability of SLEDAI-2K were evaluated for each visit, along with AMS. Approaches were the standard deviation, the slope, average rate of change by visit, the range, the coefficient of variation, and the Percentage of the visits with a change in SLEDAI-2K ≥ 3. The SLE outcomes under study were death, presence of damage, coronary artery disease (CAD), and osteonecrosis (ON). The predictability of each outcome was evaluated through time-dependent covariate survival analyses. Regression models included other known major risk factors such as sex, age at diagnosis, SLEDAI-2K at presentation, and disease duration.

Results. Five hundred seventy-five patients seen from 1970 to 2002 were included. The average time between visits was 4.0 ± 2.2 months. Eighty-five patients died, 325 developed damage, 55 had CAD, and 68 had ON. None of the 6 variability measures added more statistical significance in the prediction of any of the 4 outcomes. For the prediction of survival, AMS [hazard ratio (HR) = 1.16, $p < 0.0001$] and age at diagnosis (HR 1.05, $p < 0.0001$) were the only significant risk factors. For presence of damage, AMS (HR 1.06, $p < 0.0001$), age at diagnosis (HR 1.02, $p = 0.0004$), and disease duration (HR 1.05, $p < 0.0001$) were predictors. CAD was predicted by AMS (HR 1.12, $p = 0.0003$), male sex (HR 2.31, $p = 0.02$), age at diagnosis (HR 1.06, $p < 0.0001$), and disease duration (HR 1.10, $p < 0.0001$). For ON, SLEDAI-2K at presentation (HR 1.04, $p = 0.003$) and disease duration (HR 0.92, $p = 0.05$) were significant risk factors.

Conclusion. Multivariate analysis revealed that AMS, independent of variability of the SLEDAI-2K, is an important predictor of major outcomes in SLE. (First Release Dec 15 2006; J Rheumatol 2007;34:336–40)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY
SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000
ADJUSTED MEAN SLEDAI-2K OUTCOME ASSESSMENT

The assessment of disease activity over time in patients with systemic lupus erythematosus (SLE) has been difficult. While valid disease activity measures such as the SLE Disease Activity Index (SLEDAI) and its modification, SLEDAI 2000 (SLEDAI-2K), function very well to describe disease activity at an individual visit, it is inappropriate to use means of the visits particularly because of different observation times[1,2]. We have previously proposed the Adjusted Mean SLEDAI (AMS) as a way to summarize SLEDAI-2K over multiple visits[3]. Subsequently, we and others have shown that AMS is associated with major outcomes in SLE, namely survival[3,4], presence of damage[4,5], and development of coronary artery disease (CAD)[6].

Another important aspect of SLEDAI-2K over time not yet considered is that of fluctuation from visit to visit. Some patients have consistently high or constantly low values of SLEDAI-2K, while others tend to have multiple highs and lows. As noted by Barr, *et al*[7], many different patterns can be seen when looking at plots of SLEDAI-2K through time.

Just as any variable is minimally described by its mean and standard deviation, we sought to find a measure of variability to describe SLEDAI-2K over time as a possible adjunct to the AMS.

Therefore, our aims are 2-fold: (1) to define variability of

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SLEDAI-2K over time and quantify it, and (2) to test if the variability of SLEDAI-2K over time adds to the AMS in the prediction of major SLE outcomes.

MATERIALS AND METHODS

Patient population. The University of Toronto Lupus Clinic database was used[3]. Patients attending the University of Toronto Lupus Clinic at "regular" intervals, for a minimum of 3 visits and never away from the clinic for a period exceeding 18 consecutive months, were included. We followed patients at 2–6 month intervals according to a standard protocol, which included clinical and laboratory evaluations. Information to calculate the SLEDAI-2K score was collected at each visit. All information was entered onto an Oracle database.

Evaluation of disease activity. SLEDAI-2K was used as the measure of disease activity[2]. SLEDAI-2K has been validated against SLEDAI and has been shown to be reliable at different levels of disease activity[2,8,9]. The AMS is equivalent to the area under the curve of SLEDAI-2K over time. The following notations are used here: X_i is the SLEDAI-2K value at Visit i, $\bar{X}$ the average SLEDAI-2K values in a given time interval, t_i is the length of time between visits i and i–1, $\bar{t}$ is the mean time, and n is the number of visits in the interval.

AMS is defined as:

$$\text{AMS} = \frac{\sum_{i=2}^{n}\left(\frac{Xi + Xi-1}{2}\right)ti}{\sum_{i=2}^{n} ti}$$

Definition of variability measures: 6 different approaches. The variability of SLEDAI-2K over time was evaluated through multiple approaches. They are (1) the standard deviation (SD), (2) the slope, (3) the rate of change by visit, (4) the range, (5) the coefficient of variation, and (6) the percentages of visits with a change of score ≥ 3 in SLEDAI-2K.

(1) The standard deviation. This is the standard deviation of the SLEDAI-2K measurements in the time interval under consideration. It is centered on the average SLEDAI-2K values and disregards the length of time between visits.

$$\text{SD} = \frac{\sum_{i=1}^{n}(Xi - \bar{X})^2}{n-1}$$

(2) The slope. In a plot where SLEDAI-2K is on the y-axis and time is on the x-axis, the slope gives an idea of the general pattern of change over time. If the slope is high and positive, the patient's disease activity is rapidly worsening. If it is negative, the disease activity is improving. If it is close to 0, the patient's disease activity remains relatively unchanged.

A linear regression model is run for each patient using SLEDAI-2K as the dependent variable and time as the independent variable. The value of the slope obtained is used.

$$\text{Slope} = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(t_i - \bar{t})}{\sum_{i=1}^{n}(X_i - \bar{X})^2}$$

(3) The rate of change by visit (Changev). This approach looks at the sum of the absolute change in SLEDAI-2K between each set of 2 visits and averages that sum by the number of intervals between visits.

$$\text{Changev} = \frac{\sum_{i=1}^{n-1}\left|(X_{i+1} - X_i)\right|}{n-1}$$

(4) The range. This is the usual definition of range, namely, the maximum value of SLEDAI-2K minus the minimum value of SLEDAI-2K for each patient.

$$\text{Range} = \text{Max}X_i - \text{Min}X_i$$

(5) The coefficient of variation (Cvams). This is defined as the standard deviation divided by the mean.

$$\text{Cvams} = \frac{SD}{\bar{X}}$$

(6) The percentage of visits with change in SLEDAI-2K ≥ 3. This is defined as the percentage of visits where the change in SLEDAI-2K is greater than or equal to 3 — either a worsening or an improvement.

$$\text{Percent} = \frac{\sum_{i=1}^{n-1}(\left|X_{i+1} - X_i\right| \geq 3)}{n-1}100\%$$

Definition of outcome measures. The 4 outcomes under consideration were survival, presence of accumulated damage, the presence of coronary artery disease, and the presence of osteonecrosis (ON). Accumulated damage is defined as a score ≥ 1 on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)[10,11]. CAD is defined as presence of myocardial infarction, angina, or sudden unexplained death[6]. ON is defined by the symptoms of pain in the affected joint and confirmed by imaging[6].

In addition to AMS, other important risk factors included were sex, age at diagnosis, SLEDAI-2K at presentation, and disease duration.

Statistical analysis. Descriptive statistics of all 6 variability measures were evaluated. The effect of variability measures on survival was evaluated in 3 steps: (1) t tests were used to determine the difference in magnitude of each of the variability measures at the last visit in patients who died compared to patients who survived. (2) Time-dependent covariate analysis was used to measure if the variability measures were associated with death. Regressions were run separately for each variability measure. And (3), time-dependent covariate analyses were run using each of the variability measures along with known risk factors for survival. Again, separate regression models were run for each of the variability measures. These steps were repeated for each of the outcomes measures, namely, presence of CAD, presence of damage, and presence of ON. The risk factors used in the step (3) regressions were, for survival: AMS and age at diagnosis of SLE; for ON: SLEDAI-2K at presentation and disease duration; for CAD: AMS, sex, age at diagnosis of SLE, and disease duration; and for damage: AMS, age at diagnosis of SLE, and disease duration.

RESULTS

A total of 575 patients had at least 3 visits to the Lupus Clinic without being absent for more then 18 months between visits. Almost two-thirds of the time intervals between visits were of 3 months or less. Over 90% of all intervals between visits were within 6 months. Less then 1% of all visits included in the sample were ≥ 1 year apart.

AMS and each of the 6 variability measures were evaluated for each patient at each visit. The description of this population has been published[3,6]. Briefly, it comprised 521 women and 54 men. The mean age at SLE diagnosis was 32.9 years and they were followed in clinic for an average of 8.0 years. Their mean SLEDAI-2K at presentation to the clinic was 10.2. Their AMS at last visit is 5.85. In this sample, 69 patients presented to their first clinic visit with preexisting damage, 14 with cardiovascular disease, and 20 with ON. These patients were excluded from their respective outcome analysis. There were therefore 85 deaths in 575 patients (14.4%), 325 patients with damage out of 506 (64.2%), 55 CAD in 561 patients (9.8%), and 68 ON in 555 patients (12.3%).

Figure 1 represents 2 real patients with very similar AMS but quite different variability. Patient 1 had AMS of 9.7 and a disease activity fluctuating between 4 and 16 at all times. Patient 2 had AMS of 10.0, but showed much more variability, with very high SLEDAI-2K in the early years with progressive improvement to SLEDAI-2K of 0. When each variability measure was applied to these 2 patients, differences in "magnitude" were seen consistent with what we observed. SD, Changev, Range, and Cvams were greater in Patient 2 than Patient 1. The Slope was close to 0 for Patient 1 and negative in Patient 2. Percent was greater in Patient 1 than Patient 2, indicating that Patient 1 had more ups and downs and Patient 2 had fewer visit intervals with changes.

Table 1 gives the descriptive statistics of the variability measures at the last clinic visit. Also included are the correlation coefficients of the measures with AMS. The correlations with AMS are somewhat strong but not close to unity, which encourages us to believe that indeed, the variability measures are recording a different facet of SLEDAI-2K over time.

Table 2 gives the comparison of each variability measure at last available visit for patients with and without outcomes present. For survival, all 6 have statistically significant p values. For presence of ON, SD and Changev are the only 2 measures with $p < 0.05$. For CAD, SD, Changev, Range, and Percent are all significant. Finally, for damage, all except Range are statistically significant.

Table 3 shows the results from the time-dependent covariate survival analysis for the prediction of each major SLE outcome. For each regression, a variability measure was used to model one of the outcomes, and hazard ratio (HR) and p values are presented. All variability measures are associated with survival with the exception of Slope. Variability does not seem to be associated with presence of ON, as none of the measures was statistically significant. Variability as measured by SD, Changev, Range, and Percent was associated with presence of CAD. SD, Changev, and Range were associated with presence of damage.

Finally, time-dependent-covariate models were run including known risk factors along with each variability measure to evaluate if the inclusion of the variability measure would add to the explanation of outcomes. Included in the models are the following risk factors.

For survival

AMS: HR = 1.16 (1.11, 1.21), $p < 0.0001$

Age at SLE diagnosis: HR = 1.05 (1.04, 1.07), $p < 0.0001$

Table 1. 6 variability measures at last clinic visit.

	Min, Max	Mean ± SD	Median	Correlation Coefficient with AMS
SD	0, 15.3	4.1 ± 2.2	3.7	0.56
Slope	–6.7, 1.5	–0.12 ± 0.52	–0.02	–0.24
Changev	0, 12.6	3.2 ± 1.8	3.0	0.70
Range	0, 55	14.0 ± 8.5	12.0	0.37
Cvams	0, 8.2	0.9 ± 0.6	0.8	–0.48
Percent	0, 100	41.6 ± 20.9	41.8	0.59

AMS: Adjusted Mean SLEDAI-2K.

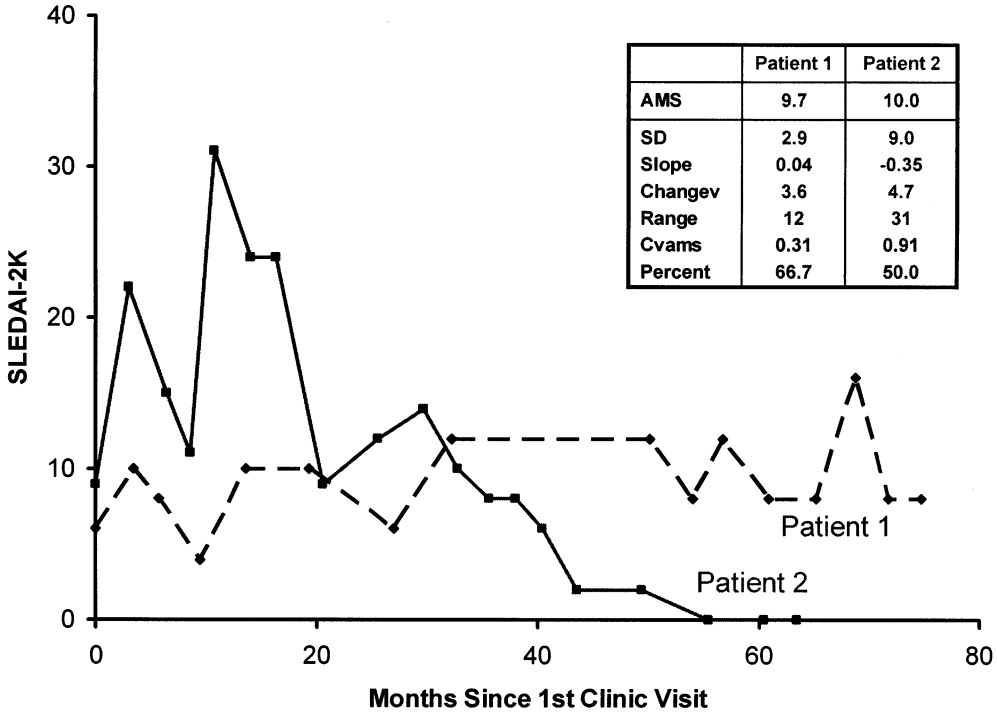

Figure 1. Two patients with the same AMS but different variation.

Table 2. t tests for outcomes at last clinic visit.

Survival	Alive (n = 490)	Dead (n = 85)	p
SD	3.93 ± 2.03	5.01 ± 2.75	0.0008
Slope	–0.10 ± 0.36	–0.25 ± 1.04	0.22
Changev	3.10 ± 1.63	4.10 ± 2.22	0.0001
Range	13.5 ± 7.8	17.2 ± 11.2	0.004
Cvams	0.95 ± 0.66	0.76 ± 0.36	0.0002
Percent	40.2 ± 20.7	49.4 ± 20.2	0.0002
Damage	**No (n = 181)**	**Yes (n = 325)**	**p**
SD	3.65 ± 2.16	4.38 ± 2.93	0.002
Slope	–0.11 ± 0.26	–0.40 ± 2.19	0.02
Changev	2.96 ± 1.74	3.99 ± 2.96	< 0.0001
Range	11.6 ± 7.5	12.5 ± 8.7	0.22
Cvams	0.96 ± 0.79	0.81 ± 0.57	0.03
Percent	39.5 ± 21.2	47.1 ± 29.6	0.001
CAD	**No (n = 506)**	**Yes (n = 55)**	**p**
SD	4.01 ± 2.21	4.91 ± 2.05	0.004
Slope	–0.12 ± 0.47	–0.07 ± 0.37	0.32
Changev	3.20 ± 1.78	3.97 ± 1.81	0.003
Range	13.5 ± 8.3	17.2 ± 9.3	0.002
Cvams	0.93 ± 0.67	0.88 ± 0.36	0.42
Percent	41.0 ± 21.3	49.7 ± 17.9	0.001
ON	**No (n = 487)**	**Yes (n = 68)**	**p**
SD	4.02 ± 2.18	4.66 ± 2.50	0.03
Slope	–0.13 ± 0.55	–0.23 ± 0.94	0.40
Changev	3.24 ± 1.81	3.82 ± 2.03	0.015
Range	13.4 ± 8.1	15.3 ± 9.6	0.13
Cvams	0.90 ± 0.62	1.02 ± 0.98	0.30
Percent	41.6 ± 21.5	45.6 ± 23.1	0.16

CAD: coronary artery disease, ON: osteonecrosis.

Table 3. Time-dependent covariate analysis—one variable at a time entered into the regression model.

	Survival		ON		CAD		Damage	
	HR	p	HR	p	HR	p	HR	p
SD	1.11	0.0016	1.07	0.11	1.13	0.008	1.05	0.011
Slope	0.91	0.36	0.94	0.70	1.09	0.77	0.90	0.065
Changev	1.08	0.015	1.06	0.16	1.13	0.010	1.04	0.018
Range	1.04	0.0004	1.02	0.08	1.03	0.043	1.02	0.011
Cvams	0.47	0.012	1.03	0.87	0.70	0.23	0.83	0.15
Percent	1.01	0.020	1.00	0.40	1.02	0.021	1.00	0.69

ON: osteonecrosis, CAD: coronary artery disease, HR: hazard ratio.

For ON

SLEDAI-2K at presentation: HR = 1.04 (1.01, 1.06), p = 0.003

Disease duration: HR = 0.92 (0.85, 1.00), p = 0.048

For CAD

AMS: HR = 1.12 (1.05, 1.19), p = 0.0003

Sex (male): HR = 2.31 (1.15, 4.66), p = 0.019

Age at SLE diagnosis: HR = 1.06 (1.04, 1.08), p < 0.0001

Disease duration: HR = 1.10 (1.05, 1.15), p < 0.0001

For damage

AMS: HR = 1.06 (1.04, 1.08), p < 0.0001

Age at SLE diagnosis: HR = 1.02 (1.01, 1.02), p = 0.0004

Disease duration: HR = 1.05 (1.03, 1.07), p < 0.0001

Table 4 shows the HR and p values for each variability measure as it was added to a model already containing the above risk factors. None of the variability measures were now significantly associated with any of the outcome measures.

Table 4. Hazard ratios for adding the variability measures (one variable at a time) to models including known risk factors.

	Survival*		ON**		CAD†		Damage‡	
	HR	p	HR	p	HR	p	HR	p
SD	1.01	0.75	0.91	0.19	1.09	0.12	1.00	0.99
Slope	1.02	0.76	1.21	0.29	1.15	0.55	0.99	0.78
Changev	0.99	0.70	0.98	0.73	1.08	0.19	0.99	0.68
Range	1.02	0.14	0.97	0.16	1.03	0.11	1.01	0.46
Cvams	0.69	0.21	0.92	0.68	0.78	0.37	1.06	0.65
Percent	1.01	0.31	1.00	0.96	1.02	0.05	1.00	0.07

* Model including AMS and age at SLE diagnosis. ** Model including SLEDAI-2K at presentation and disease duration. † Model including AMS, sex, age at SLE diagnosis, and disease duration. ‡ Model including AMS, age at SLE diagnosis, and disease duration. ON: osteonecrosis, CAD: coronary artery disease.

DISCUSSION

The lifetime experience of SLE is characterized by changes in disease activity. Flares in disease activity occur in 40–60% of SLE patients per year[12,13]. We have previously reported on the derivation of the AMS, a measure of average SLEDAI-2K over time, and have shown this measure to be associated with 3 major SLE outcomes: survival, damage, and CAD[3].

In evaluating AMS, it was clear that the average does not reflect the variability in disease activity. Are patients with less variation (fewer peaks and valleys) less at risk for major outcomes than patients with multiple extremes? We aimed to determine if variability plays a role in the development of major SLE outcomes beyond the already known risk factors.

First, we determined different approaches to measuring variability. Six measures were evaluated. Univariate analyses (t tests), as well as regression models where each variability measure was included alone, showed that a number of variability measures were associated with each of the outcomes.

On multivariate survival analysis where known risk factors were included in the models, none of the variability measures was associated with a major outcome.

Although theoretically, variability is important in the evaluation of disease activity over time, the proposed measures of variability included in our study do not contribute additional information to that derived from AMS and other known risk factors in the prediction of major SLE outcomes in patients with regular followup.

REFERENCES

1. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, and The Committee on Prognosis Studies in SLE. The development and validation of the SLE Disease Activity Index (SLEDAI). Arthritis Rheum 1992;35:630-40.
2. Gladman DD, Ibañez D, Urowitz MB. SLE Disease Activity Index 2000. J Rheumatol 2002;29:288-91.
3. Ibanez D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol 2003;30:1977-82.
4. Nossent JC. Course and prognostic value of Systemic Lupus Erythematosus Disease Activity Index in black Caribbean patients. Semin Arthritis Rheum 1993;23:16-21.
5. Nossent JC. SLICC/ACR Damage Index in Afro-Caribbean patients with systemic lupus erythematosus: Changes in and relationship to disease activity, corticosteroid therapy and prognosis. J Rheumatol 1998;25:654-9.
6. Ibanez D, Gladman DD, Urowitz MB. Adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K is a predictor of outcome in SLE. J Rheumatol 2005;32:824-7.
7. Barr SG, Zonana-Nacach A, Magder LS, Petri M. Patterns of disease activity in systemic lupus erythematosus. Arthritis Rheum 1999;42:2682-8.
8. Gladman DD, Goldsmith CH, Urowitz MB, et al. Cross-cultural validation of three disease activity indices in systemic lupus erythematosus (SLE). J Rheumatol 1992;19:608-11.
9. Gladman DD, Goldsmith CH, Urowitz MB, et al. Sensitivity to change of 3 systemic lupus erythematosus disease activity indices: international validation. J Rheumatol 1994;21:1468-71.
10. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the SLICC/ACR damage index for SLE. Arthritis Rheum 1996;39:363-9.
11. Gladman D, Urowitz MB, Goldsmith C, et al. The reliability of the SLICC/ACR damage index for SLE. Arthritis Rheum 1997;40:809-13.
12. Urowitz MB, Gladman DD, Farewell VT, Stewart J, McDonald J. Lupus and pregnancy studies. Arthritis Rheum 1993;36:1392-7.
13. Petri M, Genovese M, Engle E, Hochberg M. Definition, incidence, and clinical description of flare in systemic lupus erythematosus. A prospective cohort study. Arthritis Rheum 1991;34:937-44.