



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<sup>3</sup>. 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<sup>2</sup>. SLEDAI-2K has been validated against SLEDAI and has been shown to be reliable at different levels of disease activity<sup>2,8,9</sup>. 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:

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

**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  $\geq 3$  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.

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

(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.

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

(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.

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

(6) The percentage of visits with change in SLEDAI-2K  $\geq 3$ . 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.

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

**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  $\geq 1$  on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)<sup>10,11</sup>. CAD is defined as presence of myocardial infarction, angina, or sudden unexplained death<sup>6</sup>. ON is defined by the symptoms of pain in the affected joint and confirmed by imaging<sup>6</sup>.

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 than 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 than 1% of all visits included in the sample were  $\geq 1$  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<sup>3,6</sup>. 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

Table 1. 6 variability measures at last clinic visit.

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

AMS: Adjusted Mean SLEDAI-2K.

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),  $p < 0.0001$

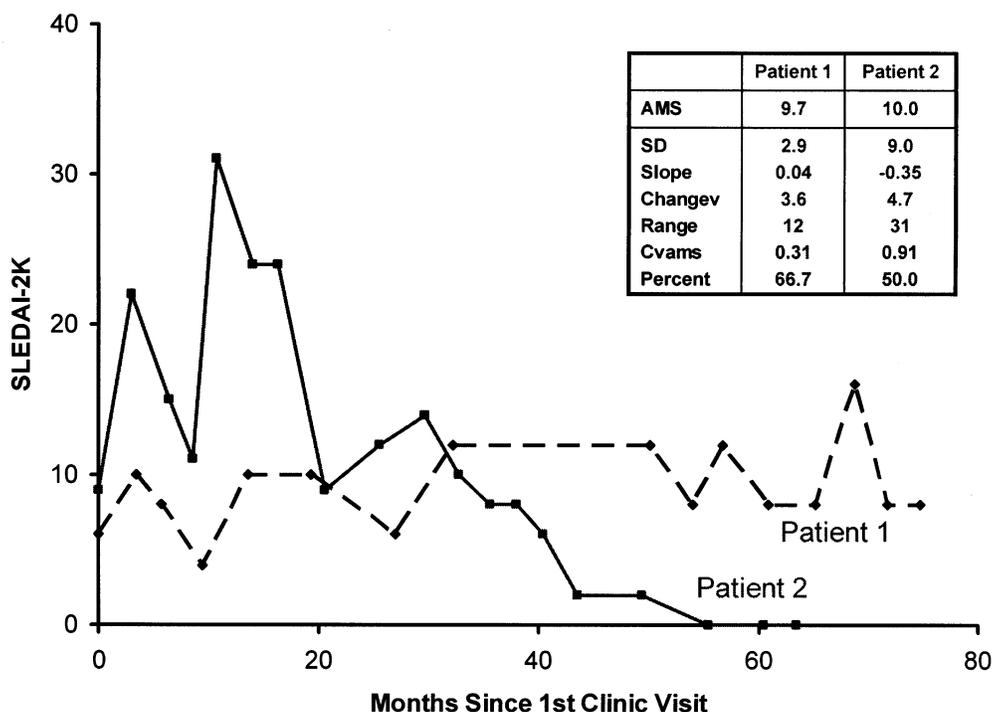


Figure 1. Two patients with the same AMS but different variation.

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<sup>12,13</sup>. 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<sup>3</sup>.

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.

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