Summarizing Disease Features Over Time: I. Adjusted Mean SLEDAI Derivation and Application to an Index of Disease Activity in Lupus

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ABSTRACT. ***Objective***. To develop a measurement of lupus disease activity over time.

Methods. We studied patients from the University of Toronto Lupus Clinic with "regular" followup, defined as having been in the clinic for at least 3 visits and never having been away from the clinic for a period exceeding 18 consecutive months. For each visit, disease activity was evaluated with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). The common approach to summarize over multiple visits by calculating a mean ignores the presence of varying time intervals between visits. We used the adjusted mean SLEDAI-2K (AMS), determined by the calculation of the area under the curve of SLEDAI-2K over time by adding the area of each of the blocks of visit interval and then dividing by the length of time for the whole period. The resulting AMS has the same units as the original SLEDAI-2K. A time-dependent covariate survival analysis was done to test which of AMS, SLEDAI-2K at presentation, sex, and age at diagnosis is the best predictor of mortality.

Results. A total of 575 patients with regular followup were included. Only AMS and age at diagnosis were significant predictors. Odds ratio (OR) and 95% confidence intervals (CI) for AMS: OR 1.15 (CI 1.09, 1.20), p = 0.0001; age at diagnosis: OR 1.05 (CI 1.03, 1.06), p = 0.0001.

Conclusion. AMS represents an average disease activity measure over time and is strongly associated with mortality. (J Rheumatol 2003;30:1977–82)

Key Indexing Terms:
LUPUS DISEASE ACTIVITY OVER TIME MORTALITY

Prospective cohort database information on patients with chronic conditions is now more frequently being gathered. Patients are seen at regular intervals, and standardized information is collected at each visit, with important new data being obtained on predisposing factors for mortality or other serious events, disease patterns, trends, and efficacy and side effects of medications, to name a few.

In systemic lupus erythematosus (SLE), a variety of indices are available to measure dimensions such as disease activity and quality of life. These indices are usually compiled and evaluated on a visit-to-visit basis, thus reflecting their respective domain for a single point in time. There is no universally accepted approach to summarizing indices over multiple visits covering months, years, or possibly decades of followup. Barr, *et al*[1] have suggested a subjective disease activity classification (relapsing-remitting, chronic active, or long quiescent) of SLE patients based on interpreting the plot of disease activity over time. We had originally suggested measuring area under the curve of SLE Disease Activity Index for calculating disease activity over time[2]. Nossent, *et al*[3] have also used this approach.

The aims of our study were (1) to derive a measure that reflects the average over time (adjusted mean, AM) from visit to visit in a given factor and time interval, (2) to use SLEDAI 2000 (SLEDAI-2K) (a disease activity index for SLE patients) as an example of the proposed measure, and (3) to test the ability of AM of SLEDAI-2K (AMS) to predict mortality in a cohort of patients with SLE.

MATERIALS AND METHODS

Derivation of adjusted mean. Letting X be the variable or index observed at each visit to be summarized over a period of time covering multiple visits, X_i is then the value for the ith visit. The time interval covers a total of n visits.

One approach to summarizing X over the n visits would be to evaluate the arithmetic mean of all available observations. This approach assumes that the time interval between all visits is the same. In reality, this is not necessarily the case. Because the AM includes in its evaluation the time interval between visits, the contribution of X_i to the overall mean is larger

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or smaller if the time interval between visits is larger or smaller:
Adjusted mean of X = (1)

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

where t_i = time interval between visit i and visit i – 1

In simpler terms, to evaluate AM we: (1) Calculate the area under the curve between each 2 visits, that is, the length of time between 2 visits multiplied by the average of the two X values; (2) add up all the calculated areas; and (3) divide the result by the total length of the time period.

The AM of X has the same unit as X and is interpreted in the same way. By definition, if only 1 or 2 visits are present or if all visits are equally spaced, the AM of X is equal to the mean of X.

Application to a disease activity index. University of Toronto Clinic. Patients with SLE have been followed prospectively at the University of Toronto Lupus Clinic since 1970[4]. By April 30, 2002, a total of 1037 patients had been registered. Clinical and laboratory information is collected according to a standard protocol at regular intervals (3 to 6 months between visits) and stored on a computer database. All patients are assessed by the directors of the clinic (MBU or DDG) or by a clinical fellow trained by them.

Disease activity index. Each patient undergoes a complete history and physical examination according to a standard protocol. The protocol includes basic demographic data, organ-specific disease-related symptoms, physical findings, and laboratory evaluations. The SLEDAI (original and revised SLEDAI-2K) evaluates disease activity at the time of the visit[5,6]. SLEDAI is a complex multifactorial index of 24 descriptors of disease activity in 9 organ systems. The maximum theoretical score is 105, but in practice, very few patients have scores greater than 45. The SLEDAI has been validated and has proven to be sensitive to change over time[7,8]. The modified SLEDAI-2K reflects persistent active disease in descriptors that had previously only applied in new or recurrent occurrences. These are proteinuria, rash, alopecia, and mucous membrane lesions. The lupus protocol, prospectively gathered since 1970, includes all individual variables necessary to calculate SLEDAI as well as SLEDAI-2K.

Adjusted mean of SLEDAI-2K. Disease activity in SLE patients as measured by SLEDAI-2K was used as an example of AM. A hallmark of SLE is the extreme variability of its expression, both between patients, but more importantly here, within individuals over time. The disease course may comprise periods of intense activity (flare), mild or moderate activity, or remission. A patient may remain in each of these periods for variable lengths of time. A descriptor of disease activity over time would have to be able to capture these multiple facets in summarizing a patient's profile over any time period.

Included in this study are patients from the University of Toronto Lupus Clinic with "regular" followup, defined as having been in the clinic for at least 3 visits and never having been away from the clinic for a period exceeding 18 consecutive months.

Use of AM of SLEDAI-2K in predicting mortality. In the cohort of 575 patients, 83 (14.4%) had died. Important risk factors for mortality in lupus are age at diagnosis and SLEDAI-2K at first visit[9]. We also analyzed sex as a potentially important factor. AM of SLEDAI-2K (AMS) was then included along with these risk factors in regression models to predict mortality.

Statistical analysis. Descriptive statistics and plots of the distribution of AMS were evaluated and presented. Descriptive statistics were also evaluated for each of the known risk factors for mortality, and comparisons regarding survival status were made using chi-square statistic and t test for categorical and continuous variables, respectively. Time-dependent covariate survival analysis was performed using the risk factors as well as AMS to determine their impact on survival[10]. In the first instance, the entire period of followup for the 575 patients was used. In a second look, the period was broken down into the first 5 years and 5+ years from time of first clinic visit. This was done to account for the known bimodal mortality pattern in SLE patients[11].

RESULTS

Derivation of AM. AM is derived and calculated as detailed in the Methods section.

Application of AMS. A total of 575 patients had had regular followup, i.e., at least 3 visits to the University of Toronto Lupus Clinic without being absent for more than 18 months between consecutive visits. Sixty-three percent of the time intervals between visits were of 3 months or less. Another 30% were of time intervals between 3 and 6 months. In total, only 0.8% of all visits included in the sample were greater than 1 year apart. AMS was evaluated for each patient and at each visit. The distribution of AMS at last visit (see Figure 1) has a mode on the lower values and a skewed tail at the right of the curve. Figure 2 represents 4 real patients with varying values of AMS: Patient 1 represents "average" values of AMS (5.5); patient 2, with a much shorter course, has extremely high AMS (21.3) (this patient died just over 1 year after diagnosis); patient 3 with very mild disease has AMS close to 0; and patient 4 with constant active disease has a high AMS (14.6). Also presented is their mean SLEDAI-2K.

In general AMS approximates mean SLEDAI-2K. For the entire group of 575 patients, the correlation coefficient between AMS and mean SLEDAI-2K is 0.98. Perhaps of greater significance is the absolute difference between AMS and mean SLEDAI-2K. In the cohort of 575 patients selected for this study, 490 (85.2%) patients had absolute differences between AMS and mean SLEDAI-2K within 1 unit of each other; another 72 (12.5%) had differences of between 1 to 2 units between the 2 measures; while the remaining 13 (2.3%) had differences greater than 2 units. Among patients not retained for this analysis (they did not meet criteria for regular followup described above), 63.9% had AMS and mean SLEDAI-2K less than 1 unit apart, 23.5% had differences between 1 and 2 units, and 12.6% had differences in excess of 2 units. As in any clinical setting, suggested visit frequency is not always adhered to by patients. The observed cases with very large differences between AMS and mean SLEDAI-2K were mostly found in patients with either large gaps of time between visits or more frequent visits when disease is very active and fewer visits in periods of relatively low activity or low visit frequency in periods of high activity and multiple visits with low activity. Thus patients with irregular intervals between visits demonstrate greater diversity between mean SLEDAI-2K and AMS. This indicates that AMS and mean SLEDAI-2K are different instruments even though they are strongly correlated.

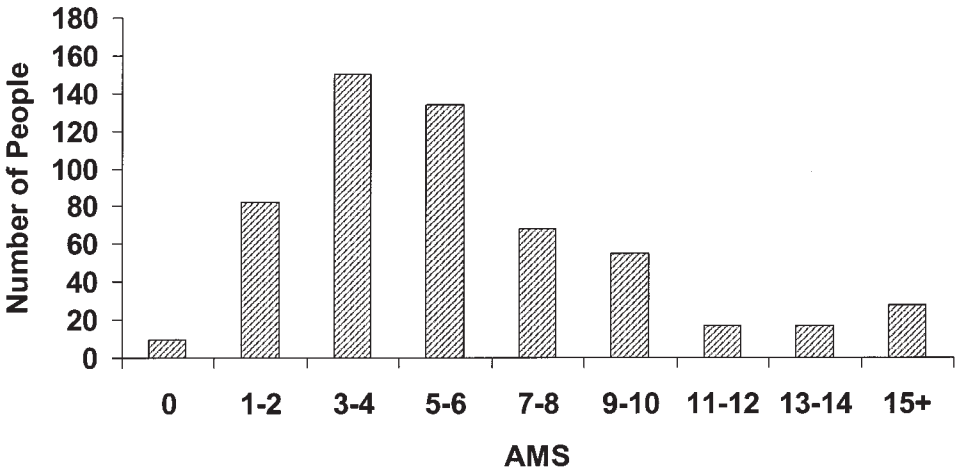
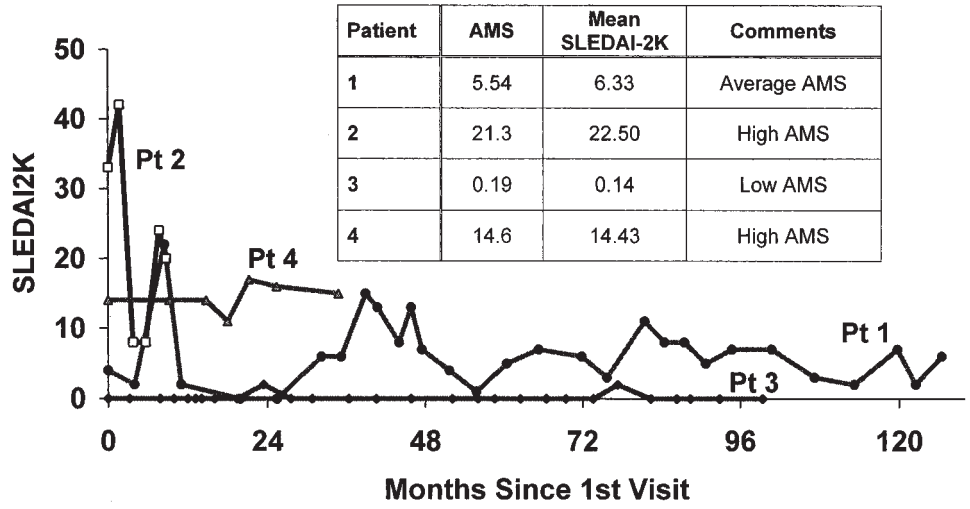


Figure 1. Distribution of adjusted mean SLEDAI-2K at last visit in 575 patients.



Patient	AMS	Mean SLEDAI-2K	Comments
1	5.54	6.33	Average AMS
2	21.3	22.50	High AMS
3	0.19	0.14	Low AMS
4	14.6	14.43	High AMS

Figure 2. SLEDAI-2K at each visit for 4 real patients.

Prediction of mortality. Table 1 shows the demographic distribution of the population assessed. The 54 men and 521 women were followed for an average of 23 visits. There were 83 deaths (14.4%) in the group. Table 2 shows comparisons between the variables by survival status. In this table AMS is shown by years since first clinic visit for varying length of followup. At one year after entry into the clinic, the mean AMS for those who died in that 1st year is 15.8, while the mean AMS for those alive at one year is 7.85. The next interval — covering the period from 1 to 3 years — shows that the mean AMS for patients who died in that time interval is 9.6 while it is 6.3 among those who survived past year 1. All other values on the figure are determined likewise. AMS tends to be higher — although not always statis-

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

Number of visits	23 ± 21 (3–111)
Time interval between visits, mo	4 ± 2 (.2–18)
Sex	
Female	521 (90.6)
Male	54 (9.4)
Survival status	
Alive	492 (85.6)
Dead	83 (14.4)
Age at diagnosis, yrs	32.9 ± 14.1 (5–83)
SLEDAI-2K at 1st clinic visit	10.2 ± 8.3 (0–55)
Disease duration at last clinic visit, yrs	10.6 ± 8.1 (0.3–48.9)
AMS at last visit	5.85 ± 3.90 (0–23.3)

AMS: adjusted mean of SLEDAI-2K.

Table 2. Comparison of alive and dead at folloup intervals.

	Alive	Dead	p
Female (%)	452 (91.9)	69 (83.1)	0.0116
Age at diagnosis, yrs	31.5 ± 12.8	41.3 ± 17.9	0.0001
SLEDAI-2K at 1st visit	9.8 ± 8.0	12.8 ± 9.6	0.0081
Disease duration, yrs	10.8 ± 8.2	9.0 ± 7.6	0.0634
AMS at end of Year 1	7.85 ± 5.48 (553)	15.78 ± 6.84 (8)	0.0001
AMS at end of Year 3*, mean ± SD (n)	6.28 ± 4.07 (490)	9.55 ± 4.55 (18)	0.0009
AMS at end of Year 7**, mean ± SD (n)	5.19 ± 2.84 (269)	7.79 ± 3.60 (12)	0.0024
AMS at end of Year 15†, mean ± SD (n)	4.67 ± 2.15 (121)	6.55 ± 2.30 (5)	0.0583
AMS at end of Year 20‴, mean ± SD (n)	4.59 ± 1.95 (84)	4.39 ± 2.21 (6)	0.8186

* For patients who survived past Year 1. ** For patients who survived past Year 5. † For patients who survived past Year 12. ‴ For patients who survived past Year 15. AMS: adjusted mean SLEDAI-2K.

tically significantly different — for patients who died than for those who survived up to 20 years. Past this point, the number of deaths is too small to be reliable.

In order to establish the true relationship between AMS and survival in this group of patients, a regression analysis was conducted. Since AMS changes over time and from visit to visit, time-dependent covariate survival analysis is the approach of choice[10]. Table 3 shows the results of such analysis. Age at diagnosis and SLEDAI-2K at presentation, being known risk factors, were included in the model along with sex and AMS. Age at diagnosis is statistically significant in the model with a hazard ratio (HR) of 1.05. Neither sex nor SLEDAI-2K at presentation was significant. AMS is significant, with HR 1.15.

A characteristic of SLE mortality is its known bimodal mortality pattern[11]. Urowitz, *et al*[12] showed that SLE patients either died early from causes related to SLE or its treatment, or died later from causes other than active SLE, especially accelerated atherosclerosis. In order to capture this bi-modal mortality, the period of followup was broken down into the first 5 years and in any year past 5. All 575 patients had visits in the first 5 years, with 41 deaths. Two hundred one patients had followup data past the 5 year point, with 42 deaths. This breakdown of the period of followup was included in the survival regression; results are presented in Table 4. Age at diagnosis, sex, and SLEDAI-2K at presentation were again included in the model along with AMS. As shown in Table 3, age at diagnosis is significant, with HR 1.05. As previously, sex and SLEDAI-2K at presentation are not significant. AMS either before or after the 5-year point is significant, with HR higher for the period after the 5-year mark.

DISCUSSION

In summarizing patients' experience over time, no clear direction is found in the literature. The only proposed approach has been that of plotting data over time and subjectively assigning clinical course patterns[1]. This would be very time-consuming with a large database — especially when evaluating multiple variables. Further, the approach remains subjective! Mathematical formulas that would reflect the average level of a factor over time would be preferable. The AM satisfies this demand. AM is likely to be very close to the mean in many situations, particularly if patients are followed at set intervals. AM more accurately accounts for the varying time intervals between visits that are common in the usual clinic setting. AM units are identical to those of the factor under study and do not require learning new units. As its greatest advantages, AM is: (1) easy to calculate, (2) not subjective, (3) easy to interpret, (4) is a continuous scale, and (5) is not limited to any specific time interval.

When using AM to describe disease activity over time in a SLE cohort, we found that AMS has a skewed distribution with a long right tail. Most patients have values in the lower ends of the distributions. Applying AMS to specific patients' experience, we find that AMS is able to transcribe the essence of disease activity over time. Patients with

Table 3. Time-dependent covariate survival analysis.

	Parameter Estimate ± SE	Hazard Ratio (95% Confidence Interval)	p
AMS	0.137 ± 0.025	1.15 (1.09, 1.20)	0.0001
Age at diagnosis	0.45 ± 0.007	1.05 (1.03, 1.06)	0.0001
Male	0.366 ± 0.302	1.44 (0.80, 2.60)	0.2254
SLEDAI-2K at presentation	0.003 ± 0.013	1.00 (0.98, 1.03)	0.7967

AMS: adjusted mean SLEDAI-2K.

Table 4. Time-dependent covariate survival analysis. The first 5 years are separated from the remaining years of followup.

	Parameter Estimate ± SE	Hazard Ratio (95% Confidence Interval)	p
AMS			
First 5 years	0.123 ± 0.027	1.13 (1.07, 1.19)	0.0001
5+ years	0.234 ± 0.057	1.26 (1.13, 1.41)	0.0001
Age at diagnosis	0.047 ± 0.007	1.05 (1.03, 1.06)	0.0001
Male	0.363 ± 0.300	1.44 (0.80, 2.59)	0.2265
SLEDAI-2K at presentation	0.004 ± 0.013	1.00 (0.98, 1.03)	0.7678

AMS: adjusted mean SLEDAI-2K.

high/low SLEDAI-2K scores do have higher/lower AMS. The continuous spectrum of AMS also allows comparisons between patients in terms of the magnitude of the difference between them.

Looking at the correlation coefficient, we see that the mean SLEDAI-2K is almost equal to AMS (r = 0.98). This reflects the consistency with which patients are seen in the University of Toronto Lupus Clinic since, when all visits are separated by identical time intervals, AMS is equal to the mean SLEDAI-2K. However, in most clinical settings, the time interval between visits is not equal. Also, scheduled appointments may not be adhered to by all patients. For example, some patients may come to the clinic more regularly in periods of active disease and return with less frequency in periods of lower activity. Others may come less frequently when disease is more active — possibly due to greater traveling distance to clinic — and return regularly when disease activity is less. Other patients may be absent from the clinic for large periods of time for various reasons, unrelated to disease activity, and then return for regular visits. In such situations AMS better reflects the lifetime activity than the simple mean of SLEDAI-2K.

As AMS is still in its infancy, it is difficult to establish what magnitude of change is clinically significant. For SLEDAI-2K, a change of > 3 units between 2 consecutive visits is considered a flare and of clinical importance[13]. In a study comparing AMS in the first 3 years of SLE between patients who developed coronary artery disease versus those who did not, it was found that AMS was statistically different in the 2 groups by a magnitude of 2.3[14]. In Table 2, we find statistical differences between survivors and non-survivors in AMS that are different by 2.5 or greater. It is probably fair to say that differences of at least 2 units in AMS may be important. It remains to be seen when and by how much AMS is associated to different outcomes.

In previous studies, because of the inability to summarize disease activity over time, only SLEDAI at presentation had been included in prediction models. All other risk factors were evaluated at a single time point (at diagnosis, at first visit, at event), or their presence was evaluated as "ever occurred from first visit up to the event."

The comparison of AMS between patients who died and those who survived needs to be approached with caution. If our aim were to simply describe the population, then presenting AMS at the last visit in each group would be appropriate. To predict mortality, it would be inaccurate to simply compare AMS at the last patient visit between survivors and non-survivors. The survivors possibly have had a greater number of clinic visits, which could, in turn, affect AMS — especially since it is known that SLEDAI at presentation tends to be high. The more visits a patient has, the more possibilities for the AMS to be lower compared to a patient with fewer visits. In order to remove this bias against non-survivors, AMS is evaluated at similar time intervals and then compared. This breakdown and ensuing series of t tests (Table 2) did not show consistent statistical significance in the difference in AMS between survivors and non-survivors beyond year 5. There is a trend for non-survivors to have higher AMS than survivors, but this approach falls short in its ability to detect statistical significance or to look at all the patients in a single analysis. This is achieved through the use of a time-dependent covariate survival regression. In that model, AMS was strongly associated with mortality along with age at diagnosis. When looking at the period of followup as first 5 years or after 5 years, the results are very consistent for AMS and age at diagnosis. Since the AMS includes the SLEDAI-2K at presentation, it may not be so surprising that SLEDAI-2K did not remain as an independent predictor for mortality.

Some limitations exist with this measure at this time. Currently, when large blocks of time with no visits are present, too much importance is given to that time interval in the evaluation of AM. As well, while some patients have consistently high or constantly low values, others tend to fluctuate up- or downward over time. Thus the "average" of the variable over the period may not be sufficient to capture the essence of the patient's experience. Some measure of this variability would be an additional important characterization of the pattern of change over time. The derivation of such a variability measure is currently under study. Nevertheless, we propose that AMS be incorporated into the description of lupus disease activity over time.

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