Systemic Lupus Erythematosus in a Multiethnic Cohort (LUMINA): XXIX. Elevation of Erythrocyte Sedimentation Rate Is Associated with Disease Activity and Damage Accrual

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ABSTRACT. ***Objective.*** To determine if different categories of erythrocyte sedimentation rate (ESR) elevation are associated with disease activity and/or damage in systemic lupus erythematosus (SLE).

Methods. We studied 2317 study visits in 553 SLE patients (≥ 4 American College of Rheumatology criteria, ≤ 5 years' disease duration at enrollment) from a multiethnic (Hispanic, African American, and Caucasian) longitudinal study of outcome. A study visit was done every 6 months for the first year and annually thereafter. Erythrocyte sedimentation rate (ESR) was measured using the Westergren method; results were expressed in 4 categories: < 25 (normal), 25–50 (mild elevation), 51–75 (moderate elevation), and > 75 (marked elevation) mm/h. Anti-dsDNA antibodies were measured at enrollment with the *Crithidia luciliae* assay. Disease activity was assessed with the Systemic Lupus Activity Measure (SLAM) and the Physician's Global Assessment (PGA). Because ESR is one of the measures evaluated in the SLAM, it was excluded from the total SLAM score. Disease damage was assessed with the Systemic Lupus International Collaborating Clinics damage index (SDI). The relationship between the SLAM (total and PGA) and SDI scores (at baseline and for all visits) and anti-dsDNA antibodies (at enrollment) with ESR was examined by univariable and generalized estimating equation (GEE) regression analyses. Ethnicity, age, and sex were entered in all regression models.

Results. The cohort consisted of 89.7% women with mean age 36.8 (SD 12.6) years and disease duration 4.6 (SD 3.2) years. GEE analyses showed that increasing levels of ESR and anti-dsDNA antibody positivity were independently associated with SLAM and PGA scores, at enrollment and for all visits. Overall, the associations of ESR with SLAM and PGA scores were stronger than for the presence of anti-dsDNA antibodies. At baseline, there was no relationship of ESR elevation or anti-dsDNA positivity with SDI scores. However, when all visits were studied, moderate and marked elevations of ESR were independently associated with SDI scores.

Conclusion. Mild, moderate, and marked ESR elevations are strongly associated with disease activity in SLE. Moderate and marked ESR elevations are also associated with damage accrual. These associations are stronger than those for the presence of anti-dsDNA antibodies. Our data suggest that ESR could be used to assess disease activity and predict organ/system damage in a relatively rapid and inexpensive manner in SLE. (J Rheumatol 2005;32:2150–5)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS ERYTHROCYTE SEDIMENTATION RATE
CLINICAL OUTCOME DISEASE ACTIVITY DISEASE DAMAGE

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Erythrocyte sedimentation rate (ESR) is used as a screening test to identify patients with inflammatory conditions[1]. The Westergren method is the procedure of choice to measure ESR as recommended by the International Council (previously Committee) for Standardization in Haematology in 1977[2]. It is a useful marker to monitor disease activity of rheumatic conditions such as rheumatoid arthritis and has great value in the diagnosis and followup of patients with temporal arteritis and polymyalgia rheumatica[3-5].

Although ESR elevation is common in patients with systemic lupus erythematosus (SLE), its clinical relevance is still uncertain[6]. ESR is infrequently used in the evaluation and followup of patients with lupus[7]. Indeed, most US rheumatologists prefer to use anti-dsDNA antibodies and/or complement C3 level to monitor SLE activity than other laboratory tests, ESR included[7]. Some studies suggest that ESR correlates with SLE activity, but the selection of patients and activity indices in these studies vary widely, and most importantly, they were not designed specifically to address this relationship[8-11].

To evaluate the clinical value of ESR in lupus we studied a large multiethnic cohort of patients participating in the LUMINA study (Lupus in Minority Populations: Nature versus Nurture) to investigate whether different categories of ESR elevation are related with disease activity and damage accrual. LUMINA is a longitudinal study of SLE to determine the relative contributions of immunogenetic, clinical, sociodemographic, and psychosocial factors to the course and outcome of lupus in 3 ethnic populations: Hispanics, African Americans, and Caucasians[12-14].

MATERIALS AND METHODS

Study population. The eligibility and enrollment of patients, patients' evaluation and followup, and data collection into LUMINA have been described[12-14]. Briefly, patients that meet at least 4 of the 11 American College of Rheumatology (ACR) criteria for the classification of SLE[15], have disease duration of ≤ 5 years at enrollment, have defined ethnicity (4 grandparents of the same ethnic background), and that are resident in the catchment area of the participating centers (University of Alabama at Birmingham, Birmingham, Alabama; University of Texas Health Science Center at Houston, Houston, Texas; and University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico) are eligible to participate. The Institutional Review Board of each participating center approved the LUMINA study, and written informed consent was obtained from each subject according to the Declaration of Helsinki.

Prior to enrollment, all previously available medical records are reviewed to confirm the patient's eligibility and to gather socioeconomic-demographic and relevant clinical data from the time of diagnosis to enrollment. Time of diagnosis is defined as the time at which a patient meets 4 ACR criteria for SLE. Disease duration is defined as the interval between time of diagnosis and time of last visit. A study visit is done every 6 months for the first year and annually thereafter. Each study visit consists of an interview, a standard physical examination, laboratory tests, completion of questionnaires to gather information of socioeconomic-demographic, psychological and behavioral variables, and chart reviews to obtain clinical information for the interval.

Variables. The LUMINA database consists of variables from the following domains: socioeconomic-demographic, clinical, and immunologic-immunogenetic. Selected variables from these domains were examined as follows. Socioeconomic-demographic variables included age, sex, and ethnicity (same as that of the 4 grandparents) and immunologic manifestations were assessed as defined in the ACR criteria for the classification of SLE[15]. Cumulative clinical features were recorded at last visit. Anti-dsDNA antibodies were measured at initial visit with the *Crithidia luciliae* assay. ESR was measured by Westergren method; results were expressed in 4 categories: < 25 (normal), 25–50 (mild elevation), 51–75 (moderate elevation), and > 75 (marked elevation) mm/h, according to the Systemic Lupus Activity Measure (SLAM)[16,17]. Disease activity was assessed with the SLAM. The SLAM is a physician-rated instrument that assesses symptoms and objective findings in 9 organ systems and 7 laboratory items, present during the preceding month and attributable to SLE. Possible scores with this instrument vary from 0 to 74. Because ESR is one of the measures evaluated in the SLAM, it was excluded from the total SLAM score. Quantification of disease activity was also assessed by the Physician's Global Assessment (PGA), a 10 cm visual analog scale where 0 represents "completely inactive" and 10 "greatest disease activity possible." Disease damage was assessed with the Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI)[18]. The SDI documents the cumulative and irreversible damage irrespective of its cause in 12 different organ systems. To be scored, each manifestation must be present for at least 6 months, unless otherwise noted. Possible scores with this instrument vary from 0 to 49.

Statistical analyses. Descriptive analyses were performed to determine the demographic and cumulative clinical manifestations at last visit. The mean SLAM, PGA, and SDI scores in different categories of ESR elevation and anti-dsDNA antibody positivity or negativity were calculated at baseline and for all visits. Multivariable regression models by generalized estimating equation (GEE) were examined next; this approach was used to maximize the utilization of data available for all patients. The dependent variables were the SLAM, PGA, and SDI scores. In each case 2 models were examined, one at baseline and the other including all study visits; age, sex, and ethnicity were entered in all models. In the analyses for all visits, the ESR corresponded to the same visit being examined. The level of significance in these regressions was ≤ 0.05. Data were analyzed using the SAS statistical package (SAS Institute, Cary, NC, USA).

RESULTS

The study population consisted of 553 SLE patients representing a total of 2317 visits. Table 1 shows selected demographic variables and cumulative clinical manifestations at last visit. The cohort had a mean age of 36.8 (12.6) years and a disease duration of 4.6 (3.2) years. The female to male ratio was 8.7:1. Hispanics represented 35.5% (19.0% Hispanics from Texas, 16.5% Hispanics from Puerto Rico), African Americans 36.2%, and Caucasians 28.4% of the study population. The most common ACR clinical and laboratory manifestations were antinuclear antibody positivity (96.8%), arthritis (76.8%), immunologic disorders (67.8%), and hematologic abnormalities (67.2%), followed by photosensitivity (51.6%), malar rash (49.5%), oral ulcers (42.9%), and serositis (42.0%). Renal involvement was seen in 30.8% of patients and neurologic disorder in 9.1%. Discoid lupus was infrequent, overall (12.1%).

ESR elevation was common in our cohort. At baseline, 29.6%, 12.7%, and 8.6% had mild, moderate, and marked elevation of ESR, respectively. When all study visits were studied, 39% had at least mild elevation of ESR, whereas 9.0% had moderate elevation and 6.1% had marked elevation during their disease course.

Table 1. Demographic and cumulative clinical features of the LUMINA cohort (n = 553).

Feature	
Age, mean yrs (SD)	36.8 (12.6)
Sex, % women	89.7
Disease duration, mean yrs (SD)	4.6 (3.2)
Ethnicity, %	
Hispanic from Texas	19.0
Hispanic from Puerto Rico	16.5
African American	36.2
Caucasian	28.4
Clinical manifestations*, %	
Malar rash	49.5
Discoid rash	12.1
Photosensitivity	51.6
Oral ulcers	42.9
Arthritis	76.8
Serositis	42.0
Neurologic disorder	9.1
Renal disorder	30.8
Hematologic disorder	67.2
Immunologic disorder	67.8
ANA positivity	96.8

ACR classification criteria[15]. ANA: antinuclear antibody.

Univariable analysis. Mild, moderate, and marked elevations of ESR were associated with higher SLAM (excluding the ESR component of the SLAM) and PGA scores at baseline, as well as for all visits. Anti-dsDNA antibody positivity was also associated with SLAM and PGA scores. Similar findings were noted for the SDI scores. These data are depicted in Table 2.

Multivariable analysis. As noted in Table 3, on GEE analyses, mild, moderate, and marked elevations of ESR were independently associated with higher SLAM scores, both at baseline and for all visits. Anti-dsDNA antibody positivity was also associated with SLAM scores, although marginally at enrollment. Similarly, ESR elevation was associated with disease activity as measured by PGA; at enrollment, mild and marked elevations of ESR were associated with higher PGA scores. For all study visits, all categories of ESR elevation were strongly associated with higher PGA scores. Anti-dsDNA positivity was associated with higher PGA scores at baseline and for all visits. These data are depicted in Table 3.

Table 3 also shows the GEE analyses for the association between ESR and the SDI. At baseline, ESR elevation (any category) was not associated with the SDI. Similarly, no association was found with anti-dsDNA positivity. However, when all study visits were evaluated, moderate and marked elevations of ESR (ESR > 50 mm/h) were independently associated with higher SDI scores, whereas no association was found with anti-dsDNA positivity.

DISCUSSION

Our data show a strong association of increasing levels of ESR with SLE disease activity, as measured by the SLAM and PGA. These findings were observed early in the disease course as well as over time. These associations were even stronger than those observed for the elevation of anti-dsDNA antibodies. In addition, a strong association was observed between moderate and marked elevations of ESR

Table 2. Disease activity and disease damage in different categories of sedimentation rate and of anti-dsDNA antibody reactivity.

Variable	SLAM Score, mean (SD)	p	PGA Score, mean (SD)	p	SDI Score, mean (SD)	p
At baseline						
ESR (mm/hr)						
< 25	6.5 (4.5)	< 0.001	1.7 (1.7)	< 0.001	0.8 (1.3)	< 0.001
25–50	8.5 (4.6)		2.4 (1.8)		1.0 (1.3)	
51–75	9.6 (5.5)		2.5 (1.8)		1.3 (1.9)	
> 75	11.3 (6.2)		3.8 (2.6)		1.4 (1.8)	
Anti-dsDNA						
Negative	7.3 (4.7)	0.013	1.9 (1.8)	< 0.001	0.9 (1.3)	0.035
Positive	9.4 (5.2)		3.0 (2.1)		1.3 (1.8)	
All visits						
ESR (mm/hr)						
< 25	6.3 (3.9)	< 0.001	1.7 (1.7)	< 0.001	1.1 (1.6)	< 0.001
25–50	7.8 (4.2)		2.3 (1.8)		1.4 (1.7)	
51–75	10.0 (5.2)		2.8 (2.0)		2.0 (2.2)	
> 75	11.1 (5.4)		3.6 (2.4)		2.1 (2.3)	
Anti-dsDNA						
Negative	6.3 (3.9)	< 0.001	1.7 (1.7)	< 0.001	1.1 (1.6)	< 0.001
Positive	8.8 (4.8)		2.6 (2.0)		1.6 (2.0)	

SLAM: Systemic Lupus Activity Measure (ESR score excluded from total SLAM score). PGA: Physician's Global Assessment. SDI: Systemic Lupus International Collaborating Clinics Damage Index.

Table 3. Variables independently associated with SLAM, PGA, and SDI scores by generalized estimating equation (GEE) regression analyses*.

	SLAM		PGA		SDI	
	Parameter Estimate	p	Parameter Estimate	p	Parameter Estimate	p
At baseline						
ESR 25–50	1.887	< 0.001	0.673	< 0.001	0.232	0.123
ESR 51–75	2.370	0.004	0.419	0.138	0.415	0.117
ESR > 75	4.431	< 0.001	1.731	< 0.001	0.327	0.323
Anti-dsDNA+	0.986	0.056	0.680	0.001	0.223	0.206
All visits						
ESR 25–50	1.078	< 0.001	0.540	< 0.001	0.223	0.112
ESR 51–75	3.192	< 0.001	1.012	< 0.001	0.725	0.007
ESR > 75	4.046	< 0.001	1.623	< 0.001	0.817	0.002
Anti-dsDNA+	1.137	< 0.001	0.346	0.006	0.092	0.533

SLAM: Systemic Lupus Activity Measure (ESR score excluded from total SLAM score). PGA: Physician's Global Assessment. SDI: Systemic Lupus International Collaborating Clinics Damage Index. * Adjusted for age, sex, and ethnicity.

and damage accrual. No association was found between the presence of anti-dsDNA antibodies and the SDI.

The association between elevated ESR and disease activity has been reported in other studies[8-11]. However, the aim of those studies had been to evaluate inflammatory markers other than ESR, and their relationship with SLE activity. ESR was used as a control marker of inflammation. For example, in a study that showed that serum neopterin, $ß_2$-microglobulin, and soluble tumor necrosis factor-α (TNF-α) and interleukin 2 receptors were associated with disease activity, it was found that ESR correlated strongly with disease activity[8]. In another study that evaluated the association of plasma concentrations of terminal complement complex (SC5b-9) with disease activity, it was found that a significant elevation of ESR was present in SLE patients with moderate/severe activity compared to those without active disease or mild disease activity[9]. Similarly, in a study in which serum thrombomodulin was shown to be associated with ESR, a moderate correlation between ESR and SLAM was observed[10]. Finally, ESR was found to correlate positively with disease activity in a study in which serum level of oxidant/antioxidant status of patients with SLE was examined[11]. In contrast, other studies are ambiguous regarding the relationship between ESR and disease activity[19]. Mirzayan and colleagues, for example, found that elevation of ESR did not predict an increase of SLE Disease Activity Index[19]. On the other hand, they noted that elevation of ESR predicted lupus flares. Similarly, Chang, *et al* found no significant association between ESR and physician-reported improvement[20]. However, they found that SLE patients that perceived improvement of their condition were more likely to have lower ESR.

ESR is related not only to disease activity but also to other biomarkers in lupus[21-25]. For example, ESR elevation has been found to be associated with serologic markers that correlate with disease activity such as anti-dsDNA antibodies, TNF-α, soluble receptors of TNF-α, and serum concentrations of intercellular adhesion molecule-1[21-23]. In addition, the presence of serum antiendothelial cell antibodies, a proposed marker for active lupus nephritis, has been associated with elevated ESR in SLE patients[24]. Further, the presence of rheumatoid factor (RF) in SLE, particularly of the IgA class, is related to increased ESR[25]. In the latter study, RF was associated with the presence of sicca symptoms, anti-SSA and anti-SSB antibodies, and hypergammaglobulinemia.

The association of elevated ESR with damage accrual is noteworthy. To our knowledge this relationship has not been reported before. This association, however, was expected for several reasons. As shown above, ESR is strongly associated with disease activity and is related to several biomarkers that are relevant in the immunopathogenesis of SLE. Of interest is that disease activity is an important predictor of damage accrual[26]. Thus, variables that correlate strongly with disease activity such as moderate to marked elevations of ESR are also likely to be associated with disease damage.

Several mechanisms might explain the increment of ESR in lupus patients, specifically hyperfibrogenemia and hypergammaglobulinemia, which are common abnormalities in SLE[27,28]. Fibrinogen and gammaglobulins have a high affinity for the erythrocyte membrane glycoproteins and form bridges between red blood cells (RBC)[29]. These phenomena cause RBC to aggregate and sediment more rapidly. Other molecules that increase RBC aggregation, such as cholesterol, triglycerides, and C-reactive protein, also could have a role in elevating ESR in lupus patients[29]. Another potential mechanism, particularly in patients with renal disease and significant proteinuria, is hypoalbuminemia. Albumin repels the negatively charged molecules on RBC, thus inhibiting their aggregation[30]. Therefore, decreased albumin will facilitate the aggregation and settlement of RBC.

The clinical use of ESR in SLE, however, has some limitations, since ESR can be altered in other medical conditions[31-33]. Infections, a common cause of morbidity and mortality in SLE, are commonly associated with increased ESR[31]. Similarly, malignancy, endstage renal disease, and other autoimmune diseases usually present with elevated ESR[31-33]. Increased ESR is also seen in pregnancy, particularly in the second half of pregnancy[34]. Thus, in these circumstances, more specific tests to assess disease activity (anti-dsDNA antibodies, complement C3 and C4) are preferable.

Our study also has some limitations. First, we used a categorical rather than a continuous scale for ESR determinations. Second, ESR was not adjusted for hematocrit level. Third, we did not determine anti-dsDNA antibodies for all visits as we did for ESR, nor did we use different categories of anti-dsDNA antibody elevations. Fourth, we did not ascertain other coexistent conditions that might be associated with increased ESR, for example, infections, malignancy, and pregnancy. However, these conditions were uncommon at the time of the study visits. Finally, we used the SLAM without ESR (SLAM-noESR) to measure disease activity. Although the SLAM-noESR is not a validated tool, we preferred to use it since we wanted to show that ESR is associated with higher disease activity even when excluding the ESR from the SLAM. On the other hand, if we include the ESR, the associations would be much stronger; but technically, a variable cannot be both a dependent and an independent variable.

Despite these limitations, our results have important clinical implications. First, our study suggests that ESR, especially when significantly elevated (> 50 mm/h), is helpful in monitoring disease activity and predicting damage in SLE. Second, ESR offers the advantage of speed and low cost compared to the usual serologic tests used to determine disease activity in SLE. Third, in this study, when the ESR was omitted from the SLAM, an apparent strong association with activity was observed, which suggests that ESR can be considered in the assessment of disease activity in lupus; notably, only the SLAM among all available instruments uses categories of ESR elevation[16,17].

Thus, ESR has significant clinical usefulness in SLE — our data suggest that it should be used more frequently in the evaluation and management of patients with lupus.

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