EXTENDED REPORT

Systemic lupus erythematosus in a multiethnic cohort: LUMINA XXXV. Predictive factors of high disease activity over time

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Aim: To ascertain the predictive factors of high levels of disease activity in systemic lupus erythematosus (SLE).

Patients and methods: Patients with SLE (American College of Radiology criteria), aged ⩾16 years, with disease duration ⩽5 years and of Hispanic (Texas and Puerto Rico), African American and Caucasian ethnicities, were included. The outcome was high disease activity at any time (Systemic Lupus Activity Measure—Revised >10). A basic multivariable model (including age, sex, ethnicity, health insurance, social support, abnormal illness-related behaviours, helplessness and prior disease activity) was first examined. Additional models were built by including other variables.

Results: 554 patients (100 Hispanics from Texas, 94 Hispanics from Puerto Rico, 199 African Americans, 161 Caucasians) and 2366 visits were analysed; 47% of the patients and 29% of the visits met the definition of high disease activity (more common among African Americans (72.0%) and Hispanics from Texas (71.3%) than among Caucasians (43.9%) and Hispanics from Puerto Rico (31.9%)). Variables found to predict high levels of disease activity were Hispanic (from Texas) and African American ethnicities, lack of health insurance, helplessness, abnormal illness-related behaviours and poor social support; age was negatively associated with high levels of disease activity. African admixture and anti-double-stranded DNA antibodies also predicted high levels of disease activity, as did prior disease activity. None of the human leucocyte antigen variables were retained in the models.

Conclusions: Socioeconomic–demographic (age, ethnicity, health insurance), behavioural and psychological variables are important mediators of high levels of disease activity in SLE during its course. Interventions aimed at modifiable factors may improve the outcomes of SLE.

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterised by different patterns of disease activity throughout its natural course.[1] Active disease, regardless of the organ system specifically affected at each point in time, reflects the presence of an ongoing inflammatory process and has been shown to be predictive of damage accrual[2–7] and mortality.[8–10] We previously described the factors associated with disease activity early in the disease course in patients from the Lupus in minorities: nature versus nurture (LUMINA) cohort.[11 12] Ethnicity (non-Caucasian), genetic (*C4A*3*, absence of *HLA-DRB1*0301* and the presence of *HLA-DRB1*01* and *HLA-DQB1*0301*) and non-genetic factors (socioeconomic, psychological and behavioural variables) were found to be associated with disease activity[11 12] in these analyses. By contrast, Karlson *et al*[13] found psychosocial factors, but not ethnicity, to be associated with disease activity. Like our earlier analyses, Karlson *et al*'s study was based on cross-sectional rather than on longitudinal data.

Disentangling the individual contribution of ethnic, genetic, socioeconomic–demographic, behavioural and psychological factors to the course of a disease such as SLE may be very difficult for several reasons. Firstly, ethnicity encompasses social, cultural, economic and genetic features that are tightly associated[14 15]; yet, there is a high degree of variability within people from the same ethnicity,[16–18] even when requiring all four grandparents to be of the same ethnic background. Secondly, some of the different socioeconomic–demographic, psychological and behavioural variables are highly correlated.[19] Finally, the temporal relationship between possible predictive factors and the outcome of interest may not be easy to ascertain, making it hard to establish causation.

In this study, we examined the factors predictive of disease activity in patients from the LUMINA cohort. Moreover, we included a measure of genetic admixture to adjust for ancestry within and between ethnic groups, and other genetic markers previously identified as relevant to the examination of the outcome.

PATIENTS AND METHODS

Patients

The LUMINA cohort was constituted as a collaborative study aimed at determining factors predictive of outcome among patients with SLE from different ethnic groups (Hispanics from Texas, primarily of Mexican or Central American ancestry, and from the Island of Puerto Rico, African Americans and Caucasians), geographical locations (Texas, Alabama and Puerto Rico) and institutions (the University of Alabama at Birmingham (Division of Clinical Immunology and Rheumatology), the University of Texas Health Science Center at Houston (Division of Rheumatology) and the

Abbreviations: AIM, ancestry informative marker; CODIS, Combined DNA Index System; dsDNA, double-stranded DNA; GEE, generalized estimating equation; SLAM-R, Systemic Lupus Activity Measure—Revised; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

University of Puerto Rico (Division of Rheumatology)).[19 20] The study was reviewed and approved by the Institutional Review Boards of these institutions, and written informed consent was obtained from each participant in accordance with the Declaration of Helsinki. Patients with SLE meeting four or more revised and updated criteria of the American College of Rheumatology for the classification of SLE,[21 22] with disease duration $\leqslant$5 years, age $\geqslant$16 years, defined ethnicity (four grandparents of the same ethnic background) and residing in the geographical catchment areas of the participating institutions, were eligible for this study. Detailed information about patient recruitment has been previously published.[19] Patients are seen at recruitment or at T0, at 6 and 12 months (T0.5 and T1, respectively, herein) and yearly thereafter (T2, T3, etc to TL, for the last visit available). All study visits consist of a review of all available medical records, interviews and questionnaires, physical examination and phlebotomy.

Variables

Our database includes variables from the following domains: socioeconomic–demographic, clinical, immunological, genetical, and psychological and behavioural. Only the variables included in these analyses will be described in detail.

Time of disease onset (TD) was defined as the time at which patients met the revised and updated American College of Rheumatology criteria for the classification of SLE.[21 22] Disease onset was considered to be acute if accrual of criteria evolved in 4 weeks or less, and insidious if otherwise. Disease duration was recorded as the interval between TD and T0. Follow-up time was defined as the interval between T0 and TL and total disease duration as the sum of disease duration (TD−T0) and follow-up time (T0−TL) or TD−TL. Disease activity was ascertained at TD and T0, and subsequently using the Systemic Lupus Activity Measure—Revised (SLAM-R).[23] For this study, high disease activity was defined as a SLAM-R score $>$10.[24] With the exception of TD, in which disease activity was ascertained using all available medical records, disease activity (SLAM-R) was assessed during regularly scheduled study visits. Of note, disease flares do not prompt these visits; rather they occur concomitantly or independently of regularly scheduled clinic visits. Socioeconomic–demographic variables include age, sex, ethnicity, education, occupation, marital status, health insurance and income (poverty was assessed on the basis of income and the number of household habitants as per guidelines from the US Federal Government).[25]

Antinuclear antibody testing was performed on Hep-2 cells by indirect immunofluorescence and anti-double-stranded DNA (dsDNA) testing was performed using *Crithidia luciliae* as a substrate (Antibodies Inc., Davis, California, USA). Anti-Smith (Sm), U1-ribonucleoprotein, Ro (Sjogren's syndrome A), and La (Sjogren's syndrome A) antibodies were assessed by immunodiffusion (Inova Diagnostics, San Diego, California, USA). Antiphospholipid antibodies were determined by enzyme-linked immunosorbent assay (Louisville Diagnostics, Louisville, Kentucky, USA) and the lupus anticoagulant by the staclot test (Diagnostico Stago, Asnieressur, France).[19]

Psychological and behavioural variables include social support (assessed by the Interpersonal Support Evaluation List (ISEL)),[26] coping with illness or illness-related behaviours (assessed by the Illness Behaviour Questionnaire (IBQ))[27] and helplessness (ascertained by the rheumatology attitude illness).[28]

Genotyping for *HLA-DRB1**, *HLA-DQB1** and *HLA-DQA1** and for mannose-binding lectin polymorphisms was carried out in previously extracted and stored genomic DNA.[29] For estimation of admixture proportions, 13 ancestry informative markers (AIMs) from Combined DNA Index System (CODIS), previously used for the study of populations with African, Caucasian or European and Amerindian (or native to the American continent) ancestry, were investigated in previously extracted and stored genomic DNA.[30] Admixture proportions were estimated by using existing software (ADMIXMAP, DNAPrint genomics, Inc. Sarasota, Florida, USA), analytical techniques[31 32] and AIMs data with high levels of discrimination between parental populations (CODIS).[30]

Statistical analyses

Disease activity, defined as a SLAM-R score $>$10 at any study visit after T0, was the outcome of interest. To account for the longitudinal nature of the study, generalised estimating equations (GEE) were used to calculate the association between a study visit with high disease activity and variables from the different domains. Follow-up time in the cohort ranged from 0 (for all new recruits into the cohort) to 11 years for the early recruitments, with a mean of 3.5 years. Patients with only one visit could not be included, whereas the others contributed with a variable number of visits to the analyses. GEE accounts for the different number of observations for each patient. Odds ratio (OR) and 95% confidence interval (CI) are used as the primary measure of association in GEE. A basic model including selected variables, significant in the univariable analyses ($p \leqslant 0.10$) or considered to be clinically relevant from the socioeconomic–demographic, clinical, psychological and behavioural domains, was first built. For these analyses, we used baseline data or the most recent available information before the visit. All candidate variables were included in this model. The variable that made the least contribution (by the likelihood ratio test) was omitted and the model was re-run. This process was continued until only variables with $p \leqslant 0.10$ were left in the model. Then, the omitted variables were individually added back into this basic model to see if their contribution changed. Variables retained in this basic model constituted the platform on which alternative models were built by adding other variables. All models were examined twice, including and excluding prior SLAM-R score as a covariate. We reasoned that since disease activity early in the course of the disease has been found to be associated with some genetic markers (vide supra), we needed to exclude prior disease activity as a predictor if we wanted to determine the role of genetic factors in disease activity later in the course of the disease. All analyses were performed using SAS, V.8.0 (SAS Institute, Coty, North Carolina, USA).

RESULTS

Descriptive and univariable analyses

Five hundred and fifty four patients (100 Hispanics from Texas, 94 Hispanics from Puerto Rico, 199 African Americans and 161 Caucasians) contributed 2366 visits to the analyses. Approximately 90% of the patients were women, whose mean age and disease duration (SD) at T0 were 36.8 (12.5) years and 17.4 (16.1) months, respectively. Approximately 47% of all patients and 29% of all visits met the high disease activity criteria. This occurred more frequently among African Americans (72.0%) and Hispanics from Texas (71.3%) than among Caucasians (43.9%) and Hispanics from Puerto Pico (31.9%). These differences were highly significant ($p<0.0001$). Tables 1 and 2 depict the salient data from the univariable results. Ethnicity (other than Hispanic from Puerto Rico), prior high disease activity (as per SLAM-R), anti-dsDNA and anti-Ro (Sjogren's syndrome A) antibodies, African but not Amerindian genetic admixture and several socioeconomic and psychological and behavioural variables (eg, lack of health insurance, poverty, poor social support and

Table 1 Socioeconomic–demographic and clinical factors associated with high disease activity* (univariable analyses)

Variable	OR	95% CI	p Value†
Age	0.976	0.965 to 0.986	0.0070
Sex (female)	0.858	0.520 to 1.415	
Ethnicity‡			
Hispanic from Texas	3.041	1.838 to 5.029	<0.0001
African American	2.968	1.888 to 4.665	<0.0001
Caucasian	1.361	0.815 to 2.270	
Marital status (single/divorced)	1.317	0.987 to 1.756	0.0606
Poverty§	1.590	1.168 to 2.165	0.0033
Education	0.928	0.885 to 0.972	0.0021
Lack of health insurance	2.169	1.549 to 3.036	<0.0001
Abnormal illness-related behaviours	1.063	1.045 to 1.080	<0.0001
Poor social support	1.189	1.112 to 1.272	<0.0001
Helplessness	1.044	1.025 to 1.062	<0.0001
Prior SLAM-R score	5.992	4.751 to 7.555	<0.0001

SLAM-R, Systemic Lupus Activity Measure—Revised.
*Defined as an SLAM-R score >10 at any given visit. †p values <0.10 are shown. ‡Hispanics from Puerto Rico form the reference group. §As defined by the US Federal government.

abnormal illness-related behaviours) were significantly associated with high disease activity, whereas age was negatively associated. Of the genetic markers examined, *HLA-DRB1*0301* and *HLA-DQB1*0201* (which are in linkage disequilibrium with *HLA-DRB1*0301*) were found to be predictive of the outcome of interest.

Multivariable analyses

Basic model

Table 3 shows the results of the final multivariable basic model. In this model, ethnicity (Hispanic from Texas, Mexican ancestry and African American; OR = 1.793, 95% CI 1.094 to 2.938, p = 0.0204 and OR = 2.310, 95% CI 1.507 to 3.540, p = 0.0001, respectively), and some socioeconomic and psychological and behavioural variables such as lack of health insurance (OR = 1.609, 95% CI 1.167 to 2.205, p = 0.0031), helplessness (OR = 1.016; 95% CI 0.998 to 1.034, p = 0.0829), abnormal illness-related behaviours (OR = 1.035; 95% CI 1.017 to 1.052, p<0.0001) and poor social support (OR = 1.065, 95% CI 1.000 to 1.205, p = 0.0481) were associated with high disease activity, whereas age was negatively associated (OR = 0.986; 95% CI 1.094 to 2.938). Prior high disease activity was also a strong predictor of high disease activity at the subsequent visit (OR = 4.556; 95% CI 3.601 to 5.764, p<0.0001). When prior high disease activity (previous SLAM-R score) was removed from the model, the results remained essentially unchanged (table 3).

Alternative models

When immunological, human leucocyte antigen or genetic admixture variables were added to the basic model, the results were consistent with the models presented in table 3. African admixture and anti-dsDNA antibodies were also predictive of high disease activity. African admixture, however, explained minimal additional variability over ethnicity, regardless of the inclusion or exclusion of prior disease activity in the model (data not shown).

DISCUSSION

SLE is a heterogeneous systemic disease, in which genetic and non-genetic factors are implicated in the aetiology as well as in the course and outcome of the disease. In a relatively simple paradigm, disease activity in lupus leads to the accrual of damage, which in turn predicts early mortality. Disease activity may, however, directly affect the mortality, as we and others have shown.[8–10] Thus, identifying the factors that may predict high levels of disease activity has practical implications. Factors associated with high disease activity during the course of the disease, as captured during yearly study visits in patients from a multiethnic lupus cohort (LUMINA), using longitudinal analytical strategies, have now been identified. In contrast with our earlier analyses in which some genetic markers (such as the absence of *HLA-DRB1* 0301*) were found to be associated with higher levels of disease activity at disease onset,[12] we have now found that, in addition to African American and Hispanic (from Texas)

Table 2 Immunological and genetic factors associated with disease activity* (univariable analyses)

Variable	OR	95% CI	p Value†
Anti-Ro (SSA) antibodies‡	1.576	1.123 to 2.211	0.0084
Anti-La (SSB) antibodies‡	0.677	0.334 to 1.385	
Anti-DNA antibodies‡	2.248	1.638 to 3.085	<0.0001
Admixture§			
African	1.800	1.176 to 2.753	0.0067
Amerindian	1.394	0.859 to 2.261	
*HLA-DRB1 *08*	1.054	0.734 to 1.515	
*HLA-DRB1 *1503*	1.394	0.976 to 1.987	0.0674
*HLA-DRB1 *0301*	0.625	0.442 to 0.886	0.0080
*HLA-DQB1 *0501*	0.822	0.614 to 1.100	
*HLA-DQB1 *0201*	0.627	0.442 to 0.889	0.0087
*HLA-DQB1 *0602*	1.116	0.828 to 1.506	
MBL null genotype	1.398	0.697 to 2.800	

*Defined as a Systemic Lupus Activity Measure—Revised score >10 in any given study visit. †p values ⩽0.10 are shown. ‡Measured at baseline. §Caucasians or Europeans form the reference group. MBL, mannose-binding lectin.

Table 3 Predictors of disease activity in systemic lupus erythematosus (basic model)

Variable	OR	95% CI	p Value†
Including prior SLAM-R			
Age	0.986	0.976 to 0.995	0.0046
Ethnicity			
Hispanic (from Texas)	1.793	1.094 to 2.938	0.0204
African American	2.310	1.507 to 3.540	0.0001
Lack of health insurance	1.609	1.167 to 2.205	0.0031
Helplessness	1.016	0.998 to 1.034	0.0829
Abnormal illness-related behaviours	1.035	1.017 to 1.052	<0.0001
Poor social support	1.065	1.000 to 1.205	0.0481
Prior high SLAM-R	4.556	3.601 to 5.764	<0.0001
Excluding prior SLAM-R			
Age	0.982	0.971 to 0.993	0.0024
Ethnicity			
Hispanic (from Texas)	1.949	1.099 to 3.453	0.0222
African American	2.722	1.678 to 4.413	<0.0001
Lack of health insurance	1.901	1.276 to 2.830	0.0016
Helplessness	1.021	1.001 to 1.041	0.0349
Abnormal illness-related behaviours	1.049	1.029 to 1.068	<0.0001
Poor social support	1.189	1.112 to 1.272	0.0266

SLAM-R, Systemic Lupus Activity Measure—Revised.
*Defined as a SLAM-R score >10. †Only variables with p value <0.10 are shown.

ethnicities, high disease activity during the course of the disease is consistently and independently associated with several socioeconomic–demographic, psychological and behavioural features, such as lack of health insurance, abnormal illness-related behaviours and poor social support, and is negatively associated with age, regardless of the model examined.

Interestingly, high levels of disease activity occur variably during the course of the disease. This may probably have been the case among African Americans and Hispanics from Texas than among Caucasians and Hispanics from Puerto Rico. Given that the study visits were not necessarily linked to clinic visits, higher disease activity among African Americans and Hispanics from Texas probably may not be related to delays in seeking medical care among those patients or to the fact that study visits were purposely conducted when patients presented to the clinic acutely ill or to the fact that they are treated less aggressively with glucocorticoids and immunosuppressants. Although we have collected data on compliance with study visits and clinic visits among our patients,[33] we have not collected data on drug adherence, and thus we could not include this construct in our models. The discrepancy in findings between the Hispanics from Texas and those from Puerto Rico are consistent with other features that distinguish these two Hispanic subgroups. In fact, we have reported the disease characteristics among these two subgroups, including differences in involvement of serious organ systems and also in disease activity at diagnosis and at enrolment in the cohort and in damage accrual at enrolment and over time, among others.[34] Moreover, these two Hispanic subgroups have distinct socioeconomic and genetic characteristics. Hence, finding that the Hispanics from Puerto Rico are less likely to exhibit high levels of disease activity at any one time during the course of the disease than the Hispanics from Texas was not unexpected.[34 35] We also found that high levels of disease activity predict subsequent high levels of disease activity, which has important implications in the outcome of SLE in terms of damage accrual and mortality.[2 7–10]

The remarkable consistency in identifying socioeconomic–demographic, psychosocial and behavioural variables in all models examined indicates how crucial these variables are in modulating the course of the disease. Some of these factors can only be modified through changes made at the societal level—for example, health insurance, whereas others such as abnormal illness-related behaviours or social support may be amenable to targeted interventions using methods already available from the social sciences.[36–40] Such interventions may favourably affect disease activity and also the final outcome of the disease.[3–8] Although in some cases we were unable to use baseline data in our analyses, we found that these features tend to be quite stable during the duration of the disease and thus we feel comfortable in having used them and in the results presented.

The immunological variable identified as being independently associated with high levels of disease activity was the presence of anti-dsDNA antibodies. These antibodies have been generally associated with disease activity[41 42] and with lupus nephritis,[42–44] but not concomitantly with flares, because as immune complexes are deposited in tissues their circulating levels decrease.[45 46] Thus, it is not surprising that we found these antibodies to be associated with high disease activity, particularly considering that they were obtained at T0 and not at the preceding visit. This is even more remarkable given that these antibodies were assayed using *C luciliae* as a substrate in our study rather than by the Farr assay, which has been shown to be superior in predicting disease exacerbations.[47–49] We, on the other hand, failed to identify any specific genetic marker independently associated with high disease activity (the exception was African admixture)—for example, we had expected to observe some contribution from Amerindian admixture given the differences in their proportions in the two Hispanic subgroups, but this was not the case. As noted before, genetic factors, including admixture, may have a strong effect on disease activity early in the disease course, but their influence may decline over time when environmental factors may become more important. Environment, defined here in its broadest sense, indicates exposure to exogenous physical or chemical agents and also the socioeconomic context in which patients experience their disease.[50]

Our study is not without some limitations. Firstly, we did not measure disease activity adequately in our patients, as we used the SLAM-R, which includes some subjective parameters that may or may not truly reflect lupus disease activity,[51] owing to which our results may lack validity. Although we agree with the fact that the SLAM-R is an imperfect measure of disease activity, all other available instruments are also imperfect. Similar to the SLAM-R, all other available instruments require judgement from the physician using them as to whether a manifestation is due to lupus activity.[23] Studies comparing the SLAM-R with the

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the instrument most commonly used in North America to measure lupus disease activity, however, have shown that both have adequate clinimetric properties.[52] Moreover, the SLAM-R has been found to better detect clinically important change in disease activity than the SLEDAI,[53 54] and by including such subjective variables it reflects what matters to patients the most and so should not be easily disregarded.[53 55–57] Furthermore, in a comparative study of the SLEDAI and the SLAM-R, a correlation of 0.873 ($p<0.001$) was found between these two instruments when they were applied to 80 patients with lupus attending our clinics.[24] In addition, the SLAM-R performed as well as other available instruments when used to ascertain treatment response in a recently published study conducted under the auspices of the ACR and performed in collaboration with the Systemic Lupus International Collaborating Clinics (SLICC) group.[58] In that study, a SLAM score of 6 was found to be indicative of disease activity. We chose a score of 10, on the basis of the distribution of the scores for patients otherwise considered to have moderate or marked disease activity as per the doctor's global assessment of disease activity[12] rather than a lower score.[59] Also, an instrument that assesses disease activity by organ system (such as the British Isles Lupus Assessment Group Index) may have been more appropriate for our analyses.[60] Unfortunately, we did not collect the clinical information necessary to score the BILAG in our patients. There is no precedent for scoring the SLAM-R by organ systems or domains, and thus the data generated using such an approach may lack validity.

Secondly, given that patients in our cohort had only yearly visits, these visits are not frequent enough to clearly depict disease activity during the course of the disease and we may have entirely missed episodes of high disease activity occurring more than 1 month before the study visit. Although in each study visit available medical records were reviewed, these data were not reflected in an interim SLAM-R score, as this had not been part of the LUMINA protocol when it was first developed. We have, however, not attempted to reconstruct the entire picture in terms of disease activity during the course of the disease (ie, area under the curve) as others have done,[61] but rather have attempted to identify those factors that may have a significant effect on the probability that high levels of disease activity will occur at any time during the course of the disease. We acknowledge the fact that we may have missed some periods of high disease activity. Thus, the data generated apply to all visits in which high disease activity was present, but probably also to other times in which high levels of disease activity, as defined, occurred. Finally, it should be noted that for patients recently recruited into the cohort, the data could be interpreted to represent early disease. These analyses, however, differ considerably from our previous cross-sectional analyses,[12] as they go well beyond the data at entry into the cohort for most patients. This is probably the main reason why we have not been able to support the role of genetic factors in the current analyses, and they may probably exert their greater effect earlier in the disease course.

We are also aware that these models fail to comprehensively explain disease activity in SLE. As noted before, sorting out the factors influencing disease activity in SLE is a complicated matter. For once, some of these factors are tightly correlated with each other, whereas the instruments used may either fail to examine a given socioeconomic–demographic or behavioural and psychological construct, or may be redundant in other cases. Moreover, in genetics, a role for stochastic events, such as gene rearrangements and somatic mutations among others, could be considered and other unidentified genes not associated with admixture, and not examined, may also be operative in influencing disease activity. Also, the admixture proportions used in the analyses were estimated from a relatively limited number of AIMs from CODIS.[30 32 62] The emphasis here is on estimation rather than on measurement, given that the computational methods used lack precision.[31 32] As technology to examine AIMs becomes less expensive and analytical techniques become more refined, a larger number of AIMs can be examined, admixture proportions can be estimated more precisely and the role of ancestral genes in disease activity in SLE can be determined more convincingly. Nevertheless, this study is the first to examine the relative contribution of most of the potential factors influencing the presence of high disease activity in patients with SLE.

In summary, we studied the factors associated with high levels of disease activity at any time during the course of the disease in a multiethnic lupus cohort. Disease activity was not found to be influenced by genetic factors, in contrast with that observed at disease onset.[11] African American and Hispanic (from Texas) ethnicities, lack of health insurance, poor social support and abnormal illness-related behaviours were consistently associated with high levels of disease activity regardless of the model examined, whereas age was negatively associated. Anti-dsDNA antibodies also seem to be important. African admixture, albeit retained in the model, failed to explain significantly more variability than ethnicity per se. Given the effect of persistent disease activity on the ultimate outcome of SLE, interventions aimed at factors amenable to modification appear to be quite relevant if the outcome of lupus is to be improved.

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ECHO

More endoscopists improve outcome for upper GI cancer

Please visit the *Quality and Safety in Health Care* website [www.qshc.com] for a link to the full text of this article.

More endoscopists may be the answer to better outcomes for upper gastrointestinal (GI) cancer, as recent improvement seems to owe more to the introduction of nurse endoscopists than the UK government's two week wait scheme for a specialist consultation, according to doctors in one cancer unit.

True enough, the odds of curative resection increased significantly (odds ratio 1.48) in their unit in the two years after the scheme was introduced compared with the two years before, and curative resections for early (stage 1 and 2) cancers rose from 47 to 58. But only two patients (5%) of 38 diagnosed with the cancer out of 623 referred under the scheme had early stage disease compared with 56 (27%) outside it. Furthermore, just over a third of patients with early stage cancer had symptoms consistent with the referral criteria in the scheme, but only two of them were referred under it.

When the scheme was implemented at Norfolk and Norwich University Hospital, in September 2000, it coincided with appointment of two full time nurse endoscopists, which reduced routine waiting times for endoscopy—and probably accounted for the improvement.

Under the scheme guidelines for urgent referrals for upper GI cancer were issued to general practitioners to ensure timely specialist evaluation. Detecting the cancer early is key to curative treatment, but symptoms can be unreliable. This may be why reducing times for routine endoscopy may be the best option.

The UK government has been under pressure to improve its poor record on upper GI cancer outcome in western Europe.

▲ Spahos T, *et al*. *Postgraduate Medical Journal* 2005;**81**:723–730.