Title: The BILAG-2004 index is associated with development of new damage in SLE

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Abstract

Objective:

To determine if BILAG-2004 index is associated the development of damage in a cohort of SLE patients. Mortality and development of damage were examined.

Methods:

This was a multi-centre longitudinal study. Patients were recruited within 12 months of achieving 4th ACR classification criterion for SLE. Data were collected on disease activity, damage, SLE-specific drug exposure, cardiovascular risk factors, antiphospholipid syndrome status and death at every visit. This study ran from 1st January 2005 to 31st December 2017. Descriptive statistics were used to analyse mortality and development of new damage. Poisson regression was used to examine potential explanatory variables for development of new damage.

Results:

273 SLE patients were recruited with total follow up of 1767 patient-years (median 73.4 months). There were 6348 assessments with disease activity scores available for analysis. During follow-up, 13 deaths and 114 new damage items (in 83 patients) occurred. The incidence rate for development of damage was higher in the first 3 years before stabilising at a lower rate. Overall rate for damage accrual was 61.1 per 1000 person-years (95% CI:50.6, 73.8). Analysis showed that active disease scores according to BILAG-2004 index (systems scores of A or B, counts of systems with A and BILAG-2004 numerical score) were associated with development of new damage. Low disease activity (LDA) states (BILAG-2004 LDA and BILAG Systems Tally (BST) persistent LDA) were inversely associated with development of damage.

Conclusions:

BILAG-2004 index is associated with new damage. BILAG-2004 LDA and BST persistent LDA can be considered as treatment targets.

Keywords: BILAG-2004; SLE; Disease activity; Damage; Mortality

Introduction

The BILAG-2004 index (BILAG-2004) is now widely used for assessment of disease activity of systemic lupus erythematosus (SLE) in clinical research studies and also in routine practice (especially for patients being considered for biologics in the United Kingdom). It has undergone validation with regards to inter-rater reliability, construct/criterion validity and sensitivity to change (responsiveness) (1–4). However, the association between disease activity measured by BILAG-2004 and the development of new damage and/or mortality has not been demonstrated previously.

Mortality is an important outcome measure that has been used to inform the management of SLE patients. There has been significant improvement in the survival of SLE patients with modern management. Hence it is necessary to complement the mortality statistic with an index that measures damage in the form of Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI) (5). Although there have been various studies analysing damage and/or mortality (6–16) in SLE patients, there is limited data on the relationship of disease activity to the development of damage and mortality in an inception cohort recruited very soon after diagnosis and none using BILAG-2004 index.

This study was designed primarily to assess the predictive characteristics of the BILAG-2004 index by determining if disease activity, as assessed using the BILAG-2004 index, is associated with development of subsequent damage and mortality. As this was an inception cohort recruiting patients within 1 year of diagnosis, we have also reported summary measures of the development of damage and mortality in this cohort.

Methods

This was a prospective multi-centre longitudinal cohort study involving 13 secondary care centres (hospitals) across the United Kingdom. This study received multi-centre research ethical approval from Hull and East Riding Research Ethics Committee and the local research ethics committee of all participating centres. Written informed consent was obtained from all patients and the study was carried out in accordance with the Helsinki Declaration.

Patients and Data Collection

SLE patients who satisfied the 1997 revised ACR criteria for classification of SLE were recruited if they were within 12 months of achieving the fourth criterion (17). Data were collected at baseline and every follow-up on disease activity (BILAG-2004 (1–4) or BILAG2004-Pregnancy index (18) when pregnant), SDI (5) and drug exposure. These assessments (baseline and follow-up) were predominantly outpatient clinic visits but also included inpatient and day case assessments when patients were admitted into hospital. The interval between assessments (data collection) was not fixed as the frequency of assessments was determined by the treating physician based on clinical need. The drugs of interest were those used to treat SLE disease activity (SLE-specific drugs) including antimalarials, glucocorticoids, immunosuppressives (methotrexate, azathioprine, mycophenolate mofetil or mycophenolic acid, tacrolimus, ciclosporin, leflunomide and cyclophosphamide), biologics (rituximab mainly) and intravenous immunoglobulins. Drug exposure between visits was determined at each visit and was assessed from two perspectives: since last assessment and since recruitment. The collection on drug exposure includes intravenous, intramuscular, intra-articular and intra-lesional administration. Where there were different formulations in the same group of drugs, the information was converted to equivalent of one common denominator such as prednisolone for glucocorticoids and mycophenolate mofetil for

mycophenolic acid. Information on cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes mellitus and smoking), antiphospholipid syndrome status (19) were also collected regularly during follow-up (as Yes/No response). Current smoker was defined as those who had smoked within the past 1 month. Any death that occurred was collected from medical records. There was censoring of data if the interval between follow-up visits was more than 18 months. Similarly, only deaths within 18 months of the last follow-up assessment were included in the analysis. This study ran from 1st January 2005 until 31st December 2017. A schematic flow diagram of the assessments and data collection is summarised in Supplementary Material Figure 1.

Explanatory Variables

BILAG2004-Pregnancy index (18) has very similar structure and scoring system to the BILAG-2004 index. Therefore, both are considered equivalent with regards to disease activity for the purpose of this analysis and will be referred to as a single index (BILAG-2004). Disease activity using BILAG-2004 was represented in several ways in the analysis:

1. BILAG-2004 system scores

2. BILAG-2004 system tally (BST) which was only available from the second assessment onwards (20)

3. BILAG-2004 numerical scoring (21)

4. Counts of system with Grade A or B which is the number of systems with a Grade A or B score per assessment

5. Low disease activity (LDA) states

Four LDA states were defined as follows:

1. BILAG-2004 LDA when all 9 systems had scores of C, D or E on assessment (no Grade A or B system score).

2. BST persistent LDA, when there was persistent score of C, D or E (which defines a system with minimal or no activity) in all 9 systems between two consecutive visits (equivalent to two consecutive visits with BILAG-2004 LDA).

3. BILAG-2004 remission when all 9 systems had score of D or E on assessment.

4. BILAG-2004 persistent remission when there was persistent score of D or E in all 9 systems between 2 consecutive visits (equivalent to 2 consecutive visits with BILAG-2004 remission).

For the exposure to SLE-specific drugs, exposure was defined as whether the patient was ever exposed to the drug since last assessment or since recruitment into the study.

Statistical Analysis

All statistical analyses were performed using Stata for Windows version 8.2 (Stata Corporation, Texas) and R statistical software version 4.0.2 (22). Descriptive statistics were used in the analysis of mortality and development of damage. As there were very few deaths within this cohort during follow-up, analysis on the potential explanatory variables for death was not performed.

Poisson regression (with patient level random effects modelled by a gamma distribution) was used for the longitudinal analysis on explanatory variables related to exposures prior to the development of new damage with count of new damage items developing between two assessments being the outcome variable and the logarithm of the time between visits included as an offset variable. Models were fitted using STATA package

xtpoisson. The explanatory variables used in the analysis were based on information available from the assessments prior to development of the new damage which included demographics, disease activity (according to BILAG-2004), SDI, cardiovascular risk factors, antiphospholipid syndrome (APS) status (19) and exposure to SLE-specific drugs. Categories of variables were added incrementally to the models after initial examination of the categories separately. As this study was primarily to determine if the BILAG-2004 index scores were associated with development of damage, disease activity variables using BILAG-2004 were included in the reported models. Results were reported as rate ratios (RR) with 95% confidence intervals (CI) and p values were provided. Poisson regression was expected to be highly efficient even in the presence of modest overdispersion (23). However, some sensitivity analyses to examine the potential effect of overdispersion were done based on the R packages *glmer* and *glmer.nb* for random effects Poisson and negative binomial regression respectively.

For discussion purposes, a simple two-state multi-state model was fitted to examine transitions from BILAG-2004 LDA to active disease and vice-versa. Transition rates were assumed to be constant and transitions were assumed to take place in continuous time. Maximum likelihood estimation based on the R package *msm* was used which accounted for states being observed only at the time of visits.

Results

A total of 273 patients were recruited into the study with a total follow-up of 1767 patient-years. The demographics of this inception cohort are summarised in Table 1. The patients were predominantly female (91.2%), 59% White British/European, with mean age at recruitment of 38.5 years, SDI of 0 at recruitment in 97.8% and median follow-up was 73.4

months. There were 36 (13.1%) patients who were lost to follow-up during the study (mostly because they moved away).

There were 6348 assessments with disease activity scores available for analysis. Systems with active disease scores (Grade A or B) were mainly mucocutaneous, musculoskeletal, cardiorespiratory and renal (summarised in Supplementary Material Table A). Of these, 284 assessments had at least a system with Grade A (severe) activity occurring in 95 patients (92.6% had only 1 system with Grade A, range: 1 to 3) while 1454 assessments had at least a system with Grade B (moderate) activity in 232 patients (81.6% had only 1 system with Grade B, range: 1 to 5) (summarised in Supplementary Material Table B). BILAG-2004 LDA was achieved in 74.2% of assessments (from 270 patients) and was never achieved in 3 (1.1 %) patients, while BILAG-2004 remission was achieved in 27.9% of assessments (from 226 patients) and was never achieved in 47 (17.2%) patients.

There were 6335 observations with BST as one observation was derived from the BILAG-2004 scores of 2 consecutive visits. Of these, 64.0% observations were in BST persistent LDA. There was no observation with BILAG-2004 persistent remission (BILAG-2004 remission at two consecutive visits).

There were only 13 deaths (4.8%) in this cohort (summarised in Table 2), mostly due to cancer or infection but, with 31% due to unknown cause, further analysis of risk factors for death in this cohort was not pursued.

Development of New Damage

There were 114 new items of damage that developed in 83 (30.4%) patients during the study period. No new item of damage was recorded on the first assessment but 6 patients did have damage by the time they were recruited into this cohort. The most common systems

affected by new damage were musculoskeletal (18.4%), neuropsychiatric (15.8%), ophthalmic (15.8%), renal (12.3%) and malignancy (10.5%). The majority of increases in SDI were one but 2 patients had an increase of 2 points and 2 patients had an increase by 3 points at a time.

The incidence rate for development of new damage over the period of follow-up and by age group are summarised in Tables 3 and 4. The overall rate for damage accrual in this cohort was 61.1 per 1000 person-years (95% CI: 50.6, 73.8). As shown in table 3, the development of new damage is higher in the first 3 years before stabilising to a lower rate subsequently.

Explanatory Variables for New Damage

Initial analysis using random effects Poisson regression was performed on the following categories of variables separately to determine which variables were to be included in the models examining the relationship between disease activity and damage: demographic variables, cardiovascular and APS risk factors and exposure to SLE-specific drugs (Supplementary Material Tables C to F). We did not find disease duration and prior SDI to be significantly associated with development of damage when both were included in the model (Supplementary Table C). However, prior SDI and disease duration were highly correlated and, when included in a model including the other demographic variables separately, both were negatively associated with development of damage (with estimated RRs of 0.47(CI: 0.30, 0.73) and 0.90 (CI: 0.84, 0.97) respectively). For subsequent modelling, only disease duration was included. Neither the cardiovascular risk factors nor antiphospholipid syndrome status were associated with the development of new damage (Supplementary Table D). With regards to exposure to SLE-specific drugs (Supplementary Table E for drugs since last

assessment and Table F for drugs since recruitment), we only found hydroxychloroquine (since recruitment) to be inversely associated while corticosteroids (since last assessment) and cyclophosphamide (since last assessment and since recruitment) were significantly associated (positively) with the development of new damage.

Based on the results of this initial analysis, we decided to include the following variables in subsequent models: demographic variables (disease duration, age at diagnosis and ethnicity), exposure to SLE-specific drugs (exposure to hydroxychloroquine since recruitment, exposure to corticosteroids since last assessment, exposure to cyclophosphamide since last assessment and exposure to cyclophosphamide since recruitment) and disease activity. Although disease duration was not statistically associated with development of damage on initial examination, the decision to include this variable in the models was based on existing literature on the development of damage in SLE (6,11,24).

The next step was the addition of variables related to disease activity to models including demographic variables (disease duration, age at diagnosis and ethnicity). Active disease (BILAG-2004 A and/or B scores) in Mucocutaneous, Neuropsychiatric, Cardiorespiratory, Renal and Haematological systems were significantly associated with development of damage (Supplementary Material Table G). When other BILAG-2004 variables were used in place of BILAG-2004 active system scores, counts of systems with Grade A score and BILAG-2004 numerical score were associated with damage while low disease activity states and the count of systems with BST minimal disease were negatively associated with damage (Supplementary Material Table H).

Illustrative sensitivity analyses were done by fitting Poisson and negative binomial models, the latter allowing for overdispersion in the Poisson model, for the model involving counts of BILAG A and B systems and for the model involving BST persistent LDA reported

in Supplementary Material Table H. Only minor increases of 3.2% and 3.8% were seen in estimated standard errors for the significant effects of A systems and BST persistent LDA respectively using a negative binomial model (data not shown).

The final step was to additionally include exposure to SLE-specific drugs in the model containing demographic variables and disease activity (Tables 5 and 6). In general, the estimated RRs associated with BILAG-2004 variables were slightly smaller after adjustment for treatment but with the exception of BST persistent LDA and BILAG-2004 remission which became marginally non-significant, these variables remained significantly associated with development of damage.

Discussion

This study has demonstrated that disease activity scores according to the BILAG-2004 index are associated with the development of subsequent new damage. From our analysis, Grade A score (severe disease activity) was highly associated with development of new damage and the risk increased with an increase in the number of systems with a Grade A score. Conversely, a low disease activity state was negatively associated with development of damage. Therefore, a rapid resolution of severe disease activity and maintenance of low disease activity state in the treatment of patients with SLE are important goals. In this study, adjustment for treatment had limited effect on the observed association between BILAG-2004 measures of disease activity. Nevertheless, resolution of severe disease activity should be achieved with the judicious use of corticosteroids and cyclophosphamide as they have been shown to be associated with development of damage in this study and others as well (6,9–11,14,24,25), highlighting the need for new and more effective therapies with less risk of inducing damage.

We have defined 4 low disease activity states using the BILAG-2004 index scores which should be suitable as treatment targets: BILAG-2004 LDA, BILAG-2004 remission, BST persistent LDA and BILAG-2004 persistent remission. The two definitions for clinical remission are in accordance with the framework of DORIS (26) but do not include immunological results or therapy. However, the data from this cohort indicate that BILAG-2004 remission and particularly BILAG-2004 persistent remission (with only BILAG-2004 D and E scores at two consecutive visits) may not be realistic treatment targets for trials given their less common occurrence than the low disease activity states that include BILAG-2004 C, D and E scores. This is probably due to the ability of BILAG-2004 index to capture minor disease activity scoring C that occurs commonly such as diffuse alopecia, mouth ulcers, inflammatory arthralgia/myalgia, leucopaenia and lymphopaenia. Nevertheless, with improvement in therapeutic options, we would anticipate the occurrence of persistent remission becoming more common. Hence, aiming for complete clinical remission in the treatment of SLE (especially as a secondary outcome in clinical trials) remains a viable option. Assessment of the whole spectrum of disease activity including low disease activity states as defined using the BILAG-2004 index is easy to implement in clinical studies as they require only one index to be completed (the BILAG-2004 index) without the need for physician's global assessment which can be inconsistently recorded by different observers (27) but is required in LLDAS (28) and SLEDAI-based definition of remission (29). The development of Easy-BILAG as a simplified tool for recording BILAG-2004 index would further facilitate implementation of BILAG-2004 index in clinical studies (30).

Although not the primary purpose of this paper, we did further analysis of BILAG-2004 LDA in this cohort using a two-state (LDA and active disease states) model. It showed that if a patient developed active disease state, the patient will remain in active disease state for an estimated average of 0.18 years. If the patient enters the LDA state, they will remain in

this state for an estimated average of 0.77 years. Over a 5-year period, our analysis suggested that a patient would be estimated to spend on average 1.03 years in active disease state and 3.94 years in LDA. Hence, there is room to improve the management of SLE patients so as to lengthen the time in low disease activity states which is the hope with new therapies. Further studies are required to confirm the value of these BILAG-defined LDA states as treatment targets but the strength of our observations is that this data is based on assessments of the patients at every visit throughout the study.

It is of interest that the mortality in this inception cohort is low. In addition, the development of new damage (61.1 per 1000 person-years) is much lower when compared to the analysis of the Birmingham cohort (93.0 per 1000 person-years) (6) or the Hopkins Lupus cohort (130 per 1000 persons-years) (8). This is most likely due to recent improvement in management as the Birmingham and Hopkins cohorts were from an earlier time period. As compared to the earlier cohorts, there had been increased usage of rituximab and mycophenolate mofetil with more judicious use of corticosteroids and cyclophosphamide which could in part explain the slower rate of damage accrual in our cohort.

In conclusion, we have shown in a prospective inception cohort study that high disease activity measured by the BILAG-2004 index is associated with an increased risk of damage accrual, whereas low disease activity states are negatively associated with damage making them suitable treatment targets.

Key Messages:

1) High disease activity according to the BILAG-2004 index is associated with subsequent damage.

2) BILAG-2004 LDA and BST persistent LDA are potential treatment targets for SLE

3) BILAG-2004 remission is relatively less common and BILAG-2004 persistent remission was not observed

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MK is an employee of Glaxo-Smith Kline and hold stocks and shares in the company.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Tables

Table 1. Demographics of inception cohort of SLE patients (N=273)

Patient Characteristics	
Female gender	249 (91.2%)
Ethnic group	
White British/European	162 (59.3%)
African-Caribbean	47 (17.2%)
South Asian	47 (17.2%)
Others	17 (6.2%)
Mean age at recruitment (baseline), years (SD)	38.5 (14.8)
SDI at recruitment (baseline)	
0	267 (97.8%)
1	6 (2.2%)
Duration of follow-up, months	
Mean (SD)	79.1 (42.5)
Median	73.4
Range	1.8 – 153.8
Prevalence of risk factors during follow-up (cumulative)	
Hypertension	63 (23.1%)

Hypercholesterolaemia	97 (35.5%)
Diabetes Mellitus	15 (5.5%)
Smoker or Ex-smoker	120 (44.0%)
Antiphospholipid syndrome	19 (7%)

Table 2. Mortality in this inception cohort (n=13)

Characteristics	
Female sex	10 (76.9%)
Ethnic group	
White British/European	11 (84.6%)
South Asian	2 (15.4%)
African-Caribbean	0
Mean age, years (SD)	62.6 (15.8)
Mean disease duration at death, years (SD)	3.0 (1.8)
Cause of death	
Infection	3 (23.1%)
Ischaemic heart disease	1 (7.7%)
Cancer	5 (38.5%)
Unknown	4 (30.8%)

Table 3. Incidence rate for development of new damage over period of follow-up at 3 yearly intervals

Period of follow-up (year)	Person-years at risk	Number of new damage events	Incidence rate, per 1000 person-years (95% CI)
0 – 3	753.4	60	79.6 (61.8, 102.6)
3 – 6	534.0	31	58.1 (40.8, 82.6)
6 – 9	321.2	12	37.4 (21.2, 35.8)
9 – 12	152.5	5	32.8 (13.6, 78.7)
> 12	5.9	0	-

Table 4. Incidence rate for development of new damage by age group

Age group	Number of new damage events	Incidence rate, per 1000 person-years (95% CI)
20 - 29	14	32.9 (19.5, 55.6)
30 - 39	24	53.1 (35.6, 79.2)
40 - 49	25	57.7 (39.0, 85.4)
50 - 59	16	62.3 (38.2, 101.7)
60 – 69	18	141.8 (89.3, 225.0)
70 - 79	11	265.0 (146.7, 478.5)

Table 5. Poisson regression analysis with demographic variables, exposure to SLE specific drugs and BILAG-2004 active system scores of A or B as explanatory variables for development of new damage (significant association in bold).

Variable	RR (95% CI)	p value
Disease duration	0.93 (0.86, 1.00)	0.055
Age at diagnosis	**1.06 (1.04, 1.73)**	**<0.001**
Ethnicity		
South Asian	**2.05 (1.15, 3.65)**	**0.014**
Afro-Caribbean	1.29 (0.74, 2.24)	0.369
Others	1.27 (0.44, 3.66)	0.662
Exposure to SLE-specific drugs		
HCQ (since recruitment)	0.81 (0.48, 1.36)	0.433
Steroids (since last assessment)	**1.77 (1.10, 2.86)**	**0.018**
Cyclophosphamide (since last assessment)	2.33 (0.98, 5.53)	0.055
Cyclophosphamide (since recruitment)	**1.94 (1.14, 3.32)**	**0.015**
Disease activity		
Constitutional A	0	1.000
Constitutional B	0	1.000
Mucocutaneous A	3.13 (0.71, 13.72)	0.130
Mucocutaneous B	**2.10 (1.21, 3.62)**	**0.008**
Neuropsychiatric A	**5.35 (1.56, 18.32)**	**0.008**
Neuropsychiatric B	3.66 (0.86, 15.64)	0.080
Musculoskeletal A	0	1.000

Musculoskeletal B	0.92 (0.42, 2.02)	0.834
Cardiorespiratory A	2.25 (0.26, 19.38)	0.459
Cardiorespiratory B	0	1.000
GIT A	0	1.000
GIT B	0	1.000
Ophthalmological A	0	1.000
Ophthalmological B	0	1.000
Renal A	**4.55 (1.67, 12.39)**	**0.003**
Renal B	1.07 (0.41, 2.80)	0.882
Haematological A	0	1.000
Haematological B	**3.59 (1.04, 12.43)**	**0.044**

Table 6. Summary table of Poisson regression analysis with BILAG-2004 variables as explanatory variables for development of new damage with adjustment for demographic variables and exposure to SLE-specific drugs (significant association in bold).

BILAG-2004 variables	RR (95% CI)	p value
Counts of systems with A	**1.90 (1.05, 3.45)**	**0.035**
Counts of systems with B	1.22 (0.87, 1.72)	0.256
BILAG-2004 numerical score	**1.04 (1.00, 1.07)**	**0.027**
BILAG-2004 LDA	**0.63 (0.41, 0.99)**	**0.044**
BILAG-2004 remission	0.67 (0.42, 1.06)	0.085
Counts of systems with BST minimal disease	**0.75 (0.58, 0.96)**	**0.022**
BST persistent LDA	0.68 (0.45, 1.04)	0.074