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Development and validation of a score to predict the risk of severe infection in Systemic Lupus Erythematosus

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Keywords:	Systemic lupus erythematosus, severe infection, risk score

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Manuscripts

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3 **Development and validation of a score to predict the risk of severe infection in**
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5 **Systemic Lupus Erythematosus**
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39 **Running Head**
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42 A score to predict severe infection in SLE
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For peer review only

Abstract

Objective. Severe infections are a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Our objective was to use data from a large Spanish cohort to develop a risk score for severe infection in SLE, the SLE Severe Infection Score (SLESIS) and to validate SLESIS in a separate cohort of 699 British patients.

Methods. From the British cohort, we identified 98 patients with SLE who had suffered severe infections and 111 randomly selected patients with SLE who had never suffered severe infections. We retrospectively calculated SLESIS at diagnosis for all 209 patients at diagnosis. For the infection cases we also calculated SLESIS just prior to infection and compared it to SLESIS in 98 controls matched for disease duration. We carried out receiver operator characteristic (ROC) analysis to quantify predictive value of SLESIS for severe infection.

Results. Median SLESIS (IQR) at diagnosis was higher in the infection group than in the control group (4.27 (3.18) vs. 2.55 (3.79), $p=0.0008$). Median SLESIS prior to infection was higher than at diagnosis (6.64 vs. 4.27, $p<0.001$). In ROC analysis, predictive value of SLESIS just before the infection (Area Under Curve=0.79) was higher than that of SLESIS at diagnosis (AUC=0.63).

Conclusions. We validated the association of SLESIS with severe infection in an independent cohort. Calculation of SLESIS at each clinic visit may help in management of infection risk in patients with SLE. Prospective studies are needed to confirm these findings.

Strengths and limitations

- 1) Severe infection affected 1 in 7 of this cohort of 699 patients with SLE during the course of their disease. A quarter of these patients died during their admission with severe infection.
- 2) Treatment with high dose corticosteroids, previous infection and hospitalizations due to SLE were the most important risk factors associated with severe infection.
- 3) We developed an algorithm designed to predict the risk of severe infections in SLE patients which could be a useful tool in clinical practice.
- 4) We acknowledge several limitations: the retrospective design of the study, the different ethnicity in the Spanish and British population and the Katz Index as an item of the score.

Key Words

Systemic lupus erythematosus, severe infection, risk score.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that mainly presents in women aged between 30 and 50 years. Infection is a major cause of morbidity and mortality in patients with SLE, being responsible for 11-45% of hospitalizations as well as 20-55% of deaths, according to different studies¹⁻⁶.

There are immunological and genetic disorders that predispose to the development of infections in patients with SLE^{7,8}. Respiratory tract infections are the most common infections in these patients, and bacteremia the leading cause of mortality^{17,28}. Regarding the etiology, pathogenic bacteria are most frequently involved in the infection, followed by viruses and fungi^{9,10}.

There are several well-established risk factors for infection such as age at diagnosis, male sex, ethnicity and use of corticosteroids, among others; however, the independent contribution of each factor is not well understood¹¹⁻¹⁴. On the other hand, severe infections have been associated with decreased survival of patients with SLE, acting as an independent risk factor for mortality at 10 years after diagnosis^{2-4, 14}.

This information about the risk factors associated with infection in SLE has not yet been combined into tools to estimate the risk of severe infection in individual patients over time. The development of an algorithm for predicting the risk of severe infection could be very useful to monitor risk factors more closely in a weighted way. It could allow us to implement prophylactic measures such as vaccination in the highest risk

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3 patients and to consider early intervention such as antibiotic therapy in this group of
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5 patients with the ultimate goal of reducing morbidity and improving survival¹⁵⁻¹⁷. Similar
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7 scores to predict risk of severe infection have been developed and validated in patients
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9 with rheumatoid arthritis (RA) with encouraging results¹⁸.

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16 In a recent original study from Spanish Society of Rheumatology Lupus Registry
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18 (RELESSER), the authors studied 3,658 patients with SLE, of whom 705 (19.3%) had
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20 suffered one or more severe infections. A multivariable Cox regression model for
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22 repeated events (Andersen Gill) was used to define the impact of a range of
23
24 demographic and clinical variables on the risk of developing severe infection,
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26 expressed as Hazard Ratio (HR) of developing severe infection for patients with each
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28 associated factor, compared to those without that factor¹⁷. Seven factors had HR more
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30 than 1.
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39 In the study reported in the current paper these seven factors were used to generate
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41 a score – the Systemic Lupus Erythematosus Severe Infection Score (SLESIS),
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43 designed to predict the risk that a patient with lupus will develop a severe infection.
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45 We then validated SLESIS in an independent population of patients with SLE from
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47 London, UK.
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54 In the validation cohort, we aimed to answer three questions
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57 1) Does the SLESIS at the time of diagnosis predict future severe infection?
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3 2) In patients who suffer a severe infection, does the SLESIS change between
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5 diagnosis and the time of infection?
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8 3) Does the SLESIS just prior to an infection predict future severe infection?
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11 If 2) and 3) are true, it could support assessing SLESIS at every appointment rather
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13 than only at diagnosis.
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22 **Patients and Methods**

23 24 25 26 27 ***Development and definition of SLESIS***

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33 The SLESIS score was developed using data from the RELESSER (Spanish Society
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35 of Rheumatology Lupus Registry) cohort of 3,658 SLE patients who meet ≥ 4
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39 ACR classification criteria for SLE. The variables, definitions and methodological
40
41 characteristics of the RELESSER registry have previously been described in detail¹⁹
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50 In the RELESSER infection study, the following factors were found to be associated
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52 with increased risk of developing severe infection (defined as infection leading to
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54 hospitalization and/or death)¹⁷: age at diagnosis > 46 years (HR = 1.12); Latin
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56 American ethnicity (HR = 2.4); dose of corticosteroid ≥ 10 mg/day (HR = 1.33); male
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58 sex (HR = 1.49); previous hospitalizations for SLE (HR = 2.73); Katz Index²¹ of disease
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3 severity (HR = 1.40) and previous severe infection (HR = $n \times 2.40$ where n is the
4 number of severe infections) (Table 1).
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11 To calculate SLESIS for an individual patient at any time point the HR values for all
12 the applicable risk factors are added together.
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16 17 18 19 20 **Validation cohort** 21

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26 Validation was carried out in the lupus clinic at University College London Hospital
27 (UCLH). All patients fulfilled the 1997 revised criteria of the American College of
28 Rheumatology (ACR) for the classification of SLE²². The clinic has been running
29 continuously since 1979 and has records from 699 patients. Medical records of all the
30 patients were reviewed to identify those who had suffered severe infections. Severe
31 infection was defined as that leading to hospitalization and/or death. Isolation of the
32 causative agent was not required in every case, with final classification as an infection
33 being made using standard clinical criteria as in the previous RELESSER study¹⁷. Only
34 infections recorded during the follow-up period (i.e after the diagnosis of lupus) were
35 included as outcomes.
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53 We identified 98 patients who had suffered at least one severe infection and compared
54 their medical records with those of 111 randomly selected patients with SLE who had
55 never suffered from severe infections. By retrospective analysis of medical records,
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3 we obtained comprehensive information about demographic, clinical, serological and
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5 treatment factors in these two groups.
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11 We calculated the SLESIS for each of the 209 patients with infection at the time of
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13 diagnosis. For each of the 98 patients with infection we also calculated SLESIS for the
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15 clinical assessment carried out at the last consultation prior to the infection. For
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17 comparison, we calculated SLESIS in 98 controls matched for disease duration, as
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19 follows. For each infection case we selected one control case from the 111 who had
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21 never suffered severe infections. For the control we calculated the SLESIS at the time-
22
23 point after diagnosis corresponding to the duration after diagnosis when the matched
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25 case suffered severe infection.
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34 ***Statistical analysis***

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40 Demographic and clinical characteristics were compared between patients who
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42 developed severe infection and patients who did not, using a Pearson χ^2 for
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44 categorical variables or a Student's t-test for normally distributed continuous variables
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46 (data expressed as mean \pm standard deviation). For non-normally distributed
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48 variables, either a Mann-Whitney U test or a logarithmic transformation was
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50 performed, and data are expressed as median and interquartile range. Multivariable
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52 logistic regression analysis was performed to establish which factors were
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54 independently associated with severe infection.
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3 We compared SLESIS scores between case and control groups using the Mann-
4 Whitney U test. Receiver Operator Characteristics (ROC) analysis was used to define
5 the area under the curve (AUC) for SLESIS at diagnosis and SLESIS just prior to
6 infection. We also identified several possible cut-off scores for SLESIS with different
7 combinations of specificity and sensitivity for severe infection.
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18 The STATA for Windows statistical software package (v.13.1) was used for all
19 statistical analysis. Significance was defined as $p < 0.05$.
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27 ***Patients and/or public involvement***

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33 Patients and/or public were not involved in this study.
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Results

Table 2 shows a comparison of the 98 patients (14% of the total cohort of 699 patients) who developed severe infection and the control group of 111 patients who never suffered from severe infection. These two groups did not differ in age, sex or ethnicity.

Patients who developed severe infections after diagnosis of SLE were more likely to have suffered previous severe infections before diagnosis of SLE (Pearson $\chi^2 = 11.69$, $p=0.001$) or to have been hospitalized for SLE (Pearson $\chi^2 = 11.89$, $p=0.001$) compared to those patients who never had severe infections. In terms of SLE manifestations, skin and renal disease were more common in the infection group (Pearson $\chi^2 = 6.25$, $p=0.012$; Pearson $\chi^2 = 6.5$, $p=0.01$) whereas joint involvement was more frequent in the non-infection group (Pearson $\chi^2 = 11.21$, $p=0.001$).

Patients in the infection group were more likely to have been treated with high doses of corticosteroids or an immunosuppressant (IS). Whereas 55% of the infection group had ever been treated with corticosteroids at a dose ≥ 10 mg per day, this only happened in 5.4% of the non-infected group (Pearson $\chi^2 = 62.81$, $p = <0.001$). Significantly increased risk of infection was found for azathioprine (Pearson $\chi^2 = 5.89$, $P=0.015$) and cyclophosphamide (Pearson $\chi^2 = 8.26$, $p=0.004$) but not for mycophenolate or rituximab. Hydroxychloroquine had been taken by 77% of the non-infection group compared to 67% of the infection group with no significant difference between groups.

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6 Regarding laboratory data, only neutropenia, which was twice as common in the
7 infection group (34% vs. 17%), was significantly different between both groups
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9 (Pearson $\chi^2 = 7.63$, $p = 0.006$).
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17 After multivariable analysis adjusted for age, only previous infection (beta coefficient:
18 2.20, 95% CI: 0.77-3.62; $p = 0.003$), previous hospitalizations for SLE (beta coefficient:
19 1.12, 95% CI: 0.19-2.07; $p = 0.021$) and treatment with corticosteroids ≥ 10 mg/day,
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21 (beta coefficient: 3.39, 95% CI: 2.33 – 4.44; $p < 0.001$) remained statistically significant.
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30 ***Type of infection***

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36 The most common type of severe infection was respiratory tract infection (n=29; 29.6%
37 of all infections), followed by urinary tract infection (n=22, 22.4%) and gastrointestinal
38 infection (n=22, 22.4%). Less frequent were soft tissue infection (n=11, 11.2%) and
39 nervous system infections (n=4, 4.1%). Twelve (12.4%) of the patients developed
40 documented bacteraemia on blood culture and 15 (15.3%) had multiple organ
41 involvement.
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54 ***Mortality***

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3 About a quarter (26.5%) of the patients died during their admission for severe infection,
4 though this does not imply that death was always due to infection as many patients
5 had co-morbidities or active lupus as well. Having recorded this high proportion of
6 deaths, we analyzed the differences between the group of 26 patients who died during
7 their admission for infection and the 72 patients who survived. These results are
8 summarized in Table 3.
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21 Patients who did not die had more previous hospitalizations due to SLE, compared to
22 those who died (Pearson $\chi^2 = 33.71$, $p < 0.001$). In contrast, those who died were more
23 likely to have suffered from severe infections prior to the diagnosis of SLE (Pearson
24 $\chi^2 = 8.66$, $p = 0.003$).
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34 There were no statistically significant differences among the clinical manifestations of
35 SLE between these two groups.
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43 Regarding treatment, there were statistically significant differences for steroids at any
44 time (Pearson $\chi^2 = 8.19$, $p = 0.004$) and rituximab (Pearson $\chi^2 = 9.34$, $p = 0.002$).
45 However, for both these variables, patients who survived were more likely to have
46 taken these drugs than those who died. Importantly, we only considered use of drugs
47 in the period between diagnosis and first infection so survival from first infection would
48 not affect the proportion of patients recorded as taking any drug.
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3 Multiple organ involvement by infection was more common in deceased patients than
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5 in patients who survived (Pearson $\chi^2 = 20.5$, $p < 0.001$). Patients who died were more
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7 likely to have had positive anti-dsDNA compared to those who survived.
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14 After multivariable analysis adjusted for age, previous hospitalizations due to SLE,
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16 previous infection and the presence of multiple organ involvement remained
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18 statistically significant as factors differentiating patients who died from those who
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20 survived (Beta coefficient: -6.15, 95% CI: -9.57- -2.73; $p < 0.001$; beta coefficient: 3.55,
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22 95% CI: 0.47-6.63; $p = 0.024$ and Beta coefficient 3.51 95% CI: 0.9-6.12; $p = 0.008$).
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30 ***Analysis of SLESIS values over time***

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36 Median (IQR) SLESIS at diagnosis of SLE in patients with infection was 4.27 (3.18)
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38 which was significantly higher than in the control (no infection) group (Median 2.55,
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40 IQR 3.79 ($z = -3.34$; $p = 0.0008$)). Median (IQR) SLESIS just before the infection in the
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42 infection group was 6.64 (4.18) which was statistically higher than the median SLESIS
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44 at diagnosis in those patients ($z = -5.73$, $p < 0.001$) and also higher than median
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46 SLESIS in the duration-matched control group at a comparable time-point in their
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48 disease course (median 3.32, IQR 3.16, $z = -6.99$; $p < 0.001$). There were no significant
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50 differences between the first and second SLESIS values (i.e. diagnosis and
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52 comparable time-point to infection) for the matched controls.
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3 Figure 1 shows the ROC analysis for SLESIS at diagnosis. The area under the ROC
4 curve (AUC) was 0.6271 (SD 0.04; 95% CI: 0.56-0.70). We defined three possible cut-
5 offs to distinguish patients with and without severe infection. We selected the cut-offs
6 which had classified correctly the maximum percentage of the sample taking into
7 account sensitivity and specificity. A cut-off for SLESIS at diagnosis ≥ 3.18 identified
8 patients who would develop severe infection with sensitivity 77% and specificity 49%.
9 For SLESIS ≥ 3.46 , sensitivity was 66% and specificity 55%. For SLESIS ≥ 4.24 ,
10 sensitivity was 64% and specificity 60%.
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25 Figure 2 shows the ROC curve for SLESIS just prior to the infection. The AUC was
26 0.79 (SD 0.03 95% CI: 0.73-0.85), which was better than for SLESIS at diagnosis. We
27 selected three cut-offs: ≥ 3.67 identified patients who would develop severe infection
28 with sensitivity of 90% and specificity of 53%. Similar results were obtained using
29 ≥ 3.79 as a cut-off (sensitivity of 90%, specificity of 50%). For SLESIS ≥ 4.24 , sensitivity
30 was 86% and specificity 60%.
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43 **Discussion**

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47 In patients with SLE it has been reported that the prevalence of life-threatening
48 infections appears to be highest within the first five years after disease onset²³.
49 However, severe infection represents a threat throughout the course of the disease,
50 especially when these patients become older and develop more co-morbidities related
51 to age. Given the potential mortality in SLE patients due to such infections, it is
52 pertinent to pursue new options that allow us to predict which groups of patients will
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3 have higher risk of developing major infections. Our aim was to develop a risk score
4 (SLESIS) to aid in this purpose. This study fulfils the important task of testing the
5 properties of this SLESIS score in a cohort independent of the RELESSER^{19,20}
6 population in which it was developed. Our London cohort differs from the Spanish
7 cohort in terms of ethnicity but SLESIS still exhibits a valid and statistically significant
8 association with severe infection.
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21 During the last few years, there have been several publications aiming to develop
22 algorithms that could measure the risk of developing severe infections in patients with
23 other autoimmune diseases. Crowson²⁴ *et al* developed a score in order to detect
24 severe infection promptly in a cohort of 410 patients with RA. The score was designed
25 and validated to predict the 1-year risk of severe infection whereas SLESIS was
26 elaborated to predict the risk of severe infection ever. Zink¹⁸ *et al* built a score based
27 on the RABBIT (Rheumatoid Arthritis Observation of Biologic Therapy) cohort in order
28 to predict serious infection in patients on biologic treatment, with promising results.
29 However, the authors suggested that their risk score was valid only in Caucasian
30 populations in Western Europe. Beca²⁵ *et al* designed a risk calculator algorithm to
31 differentiate flares from infections in SLE patients with fever. The study encompassed
32 130 patients with SLE who presented with fever over a period of 13 years. ROC curve
33 analysis in both papers showed that both scores were able to predict infection with
34 AUC between 0.8 and 0.9. Nonetheless, both studies validated the algorithms in
35 similar cohorts in terms of ethnicity distribution compared to the original cohorts. In
36 contrast, we selected a validation cohort of patients in a different country, with a
37 different range of ethnicities. In the Spanish cohort, 93% of patients were Caucasian
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3 and fewer than 1% African/Caribbean. In London, 68% were Caucasian and 28%
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5 African/Caribbean, an ethnic group recognised as suffering more severe SLE.
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11 Patients with previous severe infection were predisposed to develop major infection
12 and were also more likely to die during admission for severe infection. Impaired
13 immune system functions in a sub-group of patients with SLE may contribute to
14 increase the infection risk in those patients. There are immunological and genetic
15 disorders that predispose to the development of infections in patients with SLE.
16 Furthermore, other clinical and treatment factors might play a crucial role in the
17 predisposition of patients with SLE to develop infection. For instance, the infection
18 group were more likely than the controls to have had previous hospitalisations for SLE.
19 These findings are comparable to other previous reports^{2, 26 - 28}. In contrast, in the
20 study of Ruiz-Irastorza *et al*, lung disease was the only clinical manifestation that was
21 considered a predictor of major infection after the multivariate analysis²⁹.
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41 In carrying out this project, we noted the fact that a quarter of the patients recorded as
42 suffering severe infections died during their admission for infection. To investigate this
43 mortality further, we carried out univariable and multivariable analysis of factors that
44 could potentially influence whether or not these patients died. Surprisingly, though
45 previous hospitalization due to SLE was a factor independently associated with
46 increased risk of severe infection it was also associated with increased chance of
47 surviving that severe infection, even after multivariable analysis. There is no obvious
48 explanation for this apparent paradox. Perhaps the threshold for starting antibiotics
49 was lower in such patients. We considered the possibility that deaths from severe
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3 infection had all occurred many years ago, during a period when more patients were
4 treated with high dose IS such as cyclophosphamide. However, this is not the case as
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8 12 patients died between 2000 and 2012 while the other 14 died before the year 2000.
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14 SLESIS was significantly higher just before the severe infection in comparison to the
15 value at the diagnosis of SLE. This reinforces the idea that repeated measurement of
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18 SLESIS may be a helpful clinical assessment tool. As lupus activity and treatment
19 change over time, it is predictable that SLESIS would change over time, but it was
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22 important to investigate whether this makes SLESIS at diagnosis a poorer predictor of
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25 infection. Development of chronic damage over time, as well as cumulative use of
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28 corticosteroids and immunosuppressive drugs could contribute to these changes in
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31 SLESIS related to increased infection risk. In line with other reports^{30 31}, we found that
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34 ever-use of corticosteroids ≥ 10 mg/day was associated with increased infection risk.
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37 In fact, more than 50% of patients of our cohort who suffered from severe infections
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40 had been treated with ≥ 10 mg/day of corticosteroids. Other immunosuppressive
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43 treatments have been associated with high risk of infections although results have
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46 been controversial among the different cohorts³¹. In our study, cyclophosphamide and
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49 azathioprine were associated with increased risk of severe infection in the univariate
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52 analysis but that significance was lost after the multivariable analysis.

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55 There was a trend with hydroxychloroquine (HCQ) which seemed to be the opposite
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58 direction to corticosteroids or immunosuppressants, since fewer patients in the study
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61 group than the control group had ever been treated with HCQ. This finding is in
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64 agreement with previous reports^{29 32} although in our study, it did not reach statistical

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3 significance. Ruiz-Irastorza²⁹ *et al.* found that patients taking antimalarials were 16
4 times less likely to suffer a major infection. Similarly, Sisó³² *et al.*, found a lower
5 frequency of infections among those previously treated with antimalarials in a
6 retrospective study. Bultink *et al.*, in a study designed to analyse the effect of the
7 deficiency of functional mannose-binding lectin, also found that treatment with HCQ
8 was associated with fewer severe infections although the authors attributed this
9 association to the presumed lesser severity of lupus patients who take HCQ³³.

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23 Overall, the AUC in our study were not as high as for previous scores developed for
24 RA^{18 24}. However, this is the first score that has been developed to predict severe
25 infections in SLE and may represent a first step in developing tools to do this
26 accurately. We acknowledge several limitations in our study. Firstly, the retrospective
27 design of the study. Secondly, the ethnicity item in SLESIS distinguishes only Latin
28 American ethnicity as a separate group, which was not helpful in the London
29 population. A modified SLESIS including HR for other ethnic groups would be more
30 widely applicable globally but could not have been derived from the RELESSER cohort
31 (too ethnically homogeneous) or the UCL cohort (too small). Thirdly, the Katz index
32 used by RELESSER is a simple and helpful measure of disease severity (not just
33 activity) but is not widely used in clinical practice. However, in the original RELESSER
34 study¹⁷, from which SLESIS was derived, SLICC/ACR/Damage Index (SDI), Katz
35 Index and SELENA-SLEDAI activity score were all measured and the Katz Index was
36 the only one statistically associated with severe infection. Notwithstanding these
37 limitations, we have shown that SLESIS at diagnosis was significantly higher in the
38 group of patients who later suffered severe infections than in the control group of SLE
39 patients who did not suffer severe infection.

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6 How might SLESIS be used in clinical practice? It is important to bear in mind that both
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8 sensitivity and specificity for severe infection were modest for SLESIS at diagnosis.
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10 For SLESIS just before the infection, sensitivity was high (90%) but specificity was low
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12 (54%). The low specificity means that SLESIS could not be used to decide upon use
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14 of management measures with a high risk of adverse effects. We would suggest that
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16 patients with high SLESIS (>3.5) at any point could be followed-up with a higher index
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18 of suspicion for infection and lower threshold for using antibiotics. SLESIS at
19
20 diagnosis, together with other factors, might also help in deciding which patients might
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22 benefit from vaccination against bacterial infections (e.g. pneumococcus) and
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24 considering benefit-risk balance of corticosteroids ($\geq 10\text{mg/day}$) and other
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26 immunosuppressants.
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In summary, despite the limitations, our study has demonstrated strong arguments to perform future prospective studies to assess if SLESIS, or an improved form of SLESIS, could be clinically useful in the early diagnosis and prevention of severe infections in patients with SLE.

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DATA AVAILABILITY STATEMENT

No additional data available.

CONTRIBUTORSHIP STATEMENT

AR and BTS designed the study. IRF, JMPR and VCP developed the SLESIS score and advised on design of the study. BTS, AR, CW and DI collected the data. BTS and VCP carried out the statistical analysis. BTS, JMPR, IRF, VCP, DI and AR all took part in interpreting the results and writing the final manuscript.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to disclose.

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Table 1 Variables incorporated into SLEIS

Variable	Beta Coefficient	Hazard ratio (HR) for severe infection	95% confidence interval
Age at diagnosis (>46 years old)	0.1163	1.12	1.07 – 1.18
Latin American ethnicity	0.427	2.40	2.29 – 2.5
Current dose of corticosteroids ≥ 10 mg/day)	0.2878	1.33	1.15 – 1.55
Sex=male	0.3692	1.49	1.22 – 1.81
Previous hospitalization for SLE	1.0049	2.73	2.22 – 3.35
Katz Index²¹	0.062	1.06	1.03 – 1.1
Each previous severe infection	0.8739	2.40	2.29 – 2.50

Footnote

These HR values were derived from the retrospective analysis of 3,658 Spanish patients described in reference 17.

Table 2. Descriptive data: SLE patients with infection vs without infection

	Study (infection) group (n=98)	Control (non infection) group (n=111)	P value
Gender, n (%)			
- Females	90 (92)	103 (93)	ns
- Males	8 (8)	8 (7)	
Median age at diagnosis of SLE (IQR), years	30.5 (27)	31 (18)	ns
Median age at time of infection (IQR), years	43 (25)	Not applicable	
Ethnicity, n (%)			
- Caucasian	48 (49)	72 (65)	ns
- Hispanics	3 (3)	2 (2)	
- Afro-Caribbean	28 (29)	20 (18)	
- Asian	7 (7)	6 (5)	
- Other	12 (12)	12 (11)	
Median length of follow-up (IQR), years	9.5 (14)	14 (9)	ns
Previous infection before SLE diagnosis, n (%)	16 (16)	3 (2)	0.001

1 2 3 4 5 6 7	Previous hospitalizations due to SLE n (%)	55 (56)	36 (32)	0.001
8 9 10 11 12	SLE main features (cumulative) n, (%)			
13	- Skin disease	76 (78)	67 (60)	0.012
14	- Joint disease	72 (74)	101 (91)	0.001
15	- Renal disease	42 (43)	29 (26)	0.011
16	- CNS disease	13 (13)	12 (11)	ns
17	- Serositis	19 (19)	33 (30)	ns
18 19 20 21 22 23 24	Previous drug treatment n (%)			
25	- Corticosteroids	89 (91)	43 (39)	<0.001
26	- Corticosteroids	54 (55)	6 (5)	< 0.001
27	(≥10mg per day at			
28	any time)			
29	- No	32 (33)	25 (23)	ns
30	Hydroxichloroquine			
31	- Azathioprine	47 (48)	35 (32)	0.015
32	- Mycophenolate	36 (35)	28 (25)	ns
33	- Cyclophosphamide	28 (29)	13 (13)	0.004
34	- Rituximab	26 (27)	25 (23)	ns
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	Laboratory data, n(%) at			

any time			
- Neutropenia	33 (34)	19 (17)	0.006
- Lymphopenia	76 (78)	73(66)	ns
- Anti-dsDNA +	67 (68)	66 (60)	ns
- Low C3	57 (58)	50 (45)	ns
Outcomes			
- Deaths	26 (27)	2 (2)	0.03
- Patients with >1 infection	18 (18)	0	

Table 3- Comparison of patients who died during admission for severe infection and those who survived

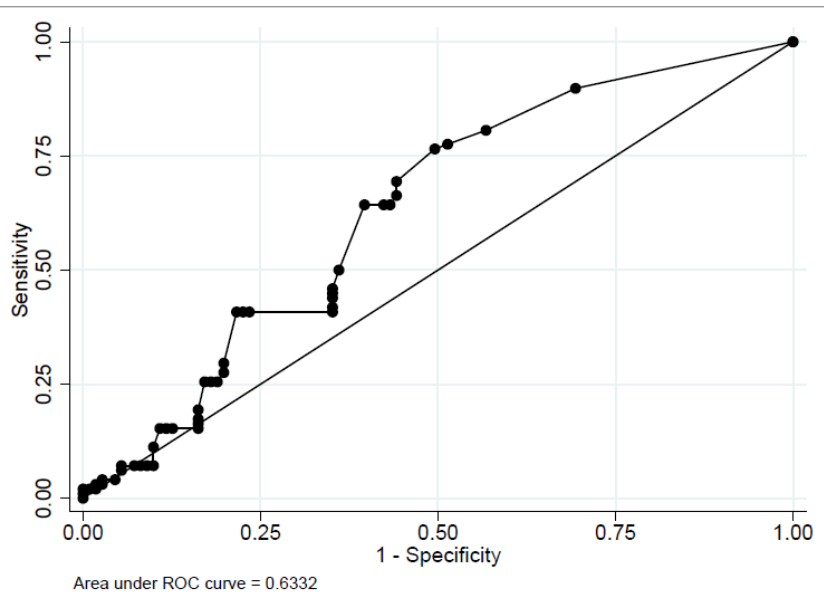
	Deceased Patients n=26 (26.5%)	Alive patients n=72 (73.5%)	P value
Mean age at diagnosis (SD)	33.8 (14.1)	31.2 (15.1)	ns
Mean age at infection (SD)	42.88 (16.7)	40.88 (16.7)	ns
Follow-up between diagnosis and first infection (years)	9.11 (7.04)	10.8 (10.3)	ns
Ethnicity n, (%)			
- Caucasian	16 (61.5)	31(43.1)	
- Hispanics	NA	3 (4.2)	
- Afro-Caribbean	8 (30.8)	20 (27.8)	ns
- Asian	2 (7.7)	4 (5.6)	
- Others	NA	12 (16.7)	
Gender (female), n (%)	25 (96)	65 (90)	ns
Previous hospitalizations, n (%)	2 (8)	53 (74)	<0.001

Previous severe infection before diagnosis of SLE, n (%)	9(35)	7(10)	0.003
Skin disease, n (%)	18 (69)	58 (81)	ns
Renal disease, n (%)	10 (39)	32 (44)	ns
Joint disease, n (%)	22 (85)	50 (69)	ns
CNS disease, n (%)	4 (15)	9 (13)	ns
Serositis, n (%)	7 (27)	12 (17)	ns
Corticosteroids per day at any time), n (%)	20 (77)	69 (96)	0.02
Corticosteroids \geq 10 mg/day at any time, n (%)	17 (65)	37 (51)	ns
Hydroxychloroquine, n (%)	20 (77)	46 (64)	ns
Rituximab , n (%)	1 (4)	25 (35)	0.002
Cyclophosphamide, n (%)	11 (42)	17 (24)	ns
Azathioprine, n (%)	14 (54)	33 (46)	ns
Mycophenolate, n (%)	10 (39)	26 (36)	ns
Splenectomy, n (%)	0	3 (4)	ns
Bacteraemia, n (%)	4 (15)	9 (13)	ns

Multiple organ involvement, n (%)	12 (46)	5 (7)	<0.001
Low complement, n (%)	11 (42)	46 (64)	ns
Neutropenia, n (%)	5 (19)	28 (39)	ns
Lymphopenia, n (%)	20 (77)	56 (78)	ns
a-dsDNA, n (%)	20 (77)	47 (65)	ns

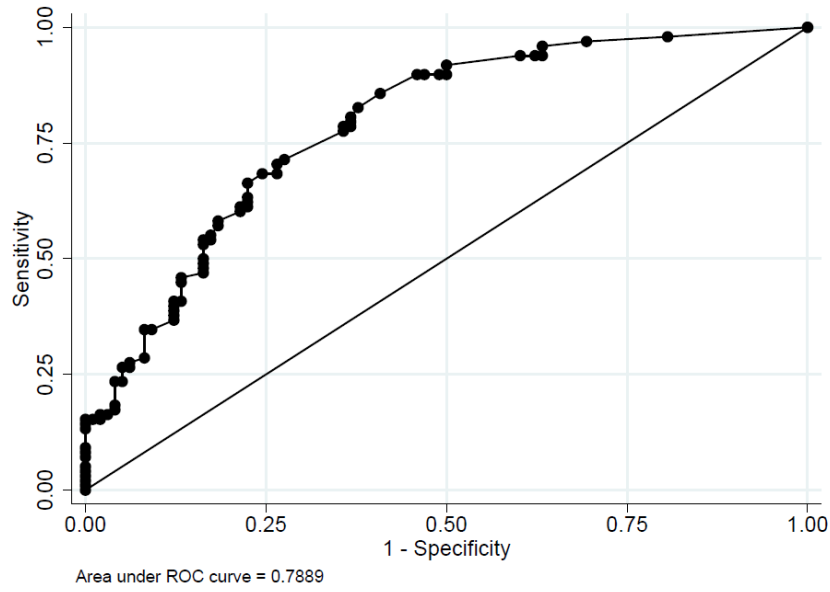
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Figure 1. ROC Curve analysis-SLESIS at diagnosis



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Figure 2- ROC Curve Analysis- SLEIS before infection



BMJ Open

Can we validate a clinical score to predict the risk of severe infection in patients with systemic lupus erythematosus? A longitudinal retrospective study in a British Cohort

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Infectious diseases
Keywords:	Systemic lupus erythematosus, severe infection, risk score

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3 **Can we validate a clinical score to predict the risk of severe infection in patients**
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6 **British Cohort**
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36 ⁵RELESSER Group (Spanish Rheumatology Society Lupus Registry)
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41 **Running Head**
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44 A score to predict severe infection in SLE
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Abstract

Objective. Severe infections are a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Our primary objective was to use data from a large Spanish cohort to develop a risk score for severe infection in SLE, the SLE Severe Infection Score (SLESIS) and to validate SLESIS in a separate cohort of 699 British patients.

Design and setting. Retrospective longitudinal study in a specialist tertiary care clinic in London UK.

Participants. Patients fulfilling international classification criteria for SLE (n=209). This included 98 patients who had suffered severe infections (defined as infection leading to hospitalization and/or death) and 111 randomly selected patients who had never suffered severe infections.

Outcomes. We retrospectively calculated SLESIS at diagnosis for all 209 patients. For the infection cases we also calculated SLESIS just prior to infection and compared it to SLESIS in 98 controls matched for disease duration. We carried out receiver operator characteristic (ROC) analysis to quantify predictive value of SLESIS for severe infection.

Results. Median SLESIS (IQR) at diagnosis was higher in the infection group than in the control group (4.27 (3.18) vs. 2.55 (3.79), $p=0.0008$). Median SLESIS prior to infection was higher than at diagnosis (6.64 vs. 4.27, $p<0.001$). In ROC analysis, predictive value of SLESIS just before the infection (Area Under Curve=0.79) was higher than that of SLESIS at diagnosis (AUC=0.63).

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3 Conclusions. We validated the association of SLESIS with severe infection in an
4 independent cohort. Calculation of SLESIS at each clinic visit may help in
5 management of infection risk in patients with SLE. Prospective studies are needed to
6 confirm these findings.
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16 **Strengths and limitations**

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19 1) We developed an algorithm (SLESIS) designed to predict the risk of severe
20 infections in SLE patients that could be a useful tool in clinical practice.
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- 23 2) SLESIS was developed using data from a Spanish lupus registry (RELESSER)
24 that includes almost 4000 SLE patients.
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- 27 3) We applied the algorithm in a British cohort of 699 patients with SLE in order to
28 validate it.
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- 31 4) The algorithm consists of seven variables that are all obtainable from
32 information obtained in routine clinical practice.
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- 35 5) We acknowledge several limitations: the retrospective design of the study, the
36 different ethnicity in the Spanish and British population and the Katz Index as
37 an item of the score.
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45 **Key Words**

46 Systemic lupus erythematosus, severe infection, risk score.
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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that mainly presents in women aged between 30 and 50 years. Infection is a major cause of morbidity and mortality in patients with SLE, being responsible for 11-45% of hospitalizations as well as 20-55% of deaths, according to different studies¹⁻⁶.

There are immunological and genetic disorders that predispose to the development of infections in patients with SLE^{7,8}. Respiratory tract infections are the most common infections in these patients, and bacteremia the leading cause of mortality. Regarding the etiology, pathogenic bacteria are most frequently involved in the infection, followed by viruses and fungi^{9,10}.

There are several well-established risk factors for infection such as age at diagnosis, male sex, ethnicity and use of corticosteroids, among others; however, the independent contribution of each factor is not well understood¹¹⁻¹⁴. On the other hand, severe infections have been associated with decreased survival of patients with SLE, acting as an independent risk factor for mortality at 10 years after diagnosis^{2-4, 14}.

This information about the risk factors associated with infection in SLE has not yet been combined into tools to estimate the risk of severe infection in individual patients over time. The development of an algorithm for predicting the risk of severe infection could be very useful to monitor risk factors more closely in a weighted way. It could allow us to implement prophylactic measures such as vaccination in the highest risk

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3 patients and to consider early intervention such as antibiotic therapy in this group of
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5 patients with the ultimate goal of reducing morbidity and improving survival¹⁵⁻¹⁷. Similar
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7 scores to predict risk of severe infection have been developed and validated in patients
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9 with rheumatoid arthritis (RA) with encouraging results¹⁸.

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16 In a recent original study from Spanish Society of Rheumatology Lupus Registry
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18 (RELESSER), the authors studied 3,658 patients with SLE, of whom 705 (19.3%) had
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20 suffered one or more severe infections. A multivariable Cox regression model for
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22 repeated events (Andersen Gill) was used to define the impact of a range of
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24 demographic and clinical variables on the risk of developing severe infection,
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26 expressed as Hazard Ratio (HR) of developing severe infection for patients with each
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28 associated factor, compared to those without that factor¹⁷. Seven factors had HR more
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30 than 1.
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39 In the study reported in the current paper these seven factors were used to generate
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41 a score – the Systemic Lupus Erythematosus Severe Infection Score (SLESIS),
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43 designed to predict the risk that a patient with lupus will develop a severe infection.
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49 The overarching primary objective of the current study was to validate SLESIS in an
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51 independent population of patients with SLE from London, UK.
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58 In the validation cohort, we aimed to answer three questions.
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3 1) Does the SLESIS at the time of diagnosis predict future severe infection?
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6 2) In patients who suffer a severe infection, does the SLESIS change between
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8 diagnosis and the time of infection?
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11 3) Does the SLESIS just prior to an infection predict future severe infection?
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15 If 2) and 3) are true, it could support assessing SLESIS at every appointment rather
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17 than only at diagnosis.
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20 21 22 23 24 25 **Patients and Methods** 26

27 28 29 30 ***Development and definition of SLESIS*** 31

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37 The SLESIS score was developed using data from the RELESSER (Spanish Society
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39 of Rheumatology Lupus Registry) cohort of 3,658 SLE patients who meet ≥ 4
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42 ACR classification criteria for SLE. The variables, definitions and methodological
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44 characteristics of the RELESSER registry have previously been described in detail¹⁹
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53 Table 1 shows the 7 factors that were found to be associated with increased risk of
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55 developing severe infection (defined as infection leading to hospitalization and/or
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3 death) in the RELESSER paper¹⁷ together with the Hazard Ratio (HR) for severe
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5 infection associated with each factor.
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11 There are four factors that are graded present or absent; age at diagnosis > 46 years
12 (HR = 1.12); Latin American ethnicity (HR = 2.4); dose of corticosteroid \geq 10 mg/day
13 (HR = 1.33); and male sex (HR = 1.49). For each of these factors, the contribution to
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15 SLEIS is either 0 (if absent) or 1xHR (if present).
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25 One factor (Katz Index²¹ of disease severity) is a continuous variable. The contribution
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27 of this factor is its absolute value x 1.06 (its HR).
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33 The other factors are previous hospitalizations for SLE (HR = 2.73) and previous
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35 severe infection (HR = 2.40). For these factors the contribution to SLEIS is the
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37 number of events x HR.
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44 Thus the SLEIS for a female Latin American patient, diagnosed at age 22, taking
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46 12mg prednisolone per day with Katz Index of 2, two previous hospitalisations for SLE
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48 and no previous severe infections would be calculated as follows.
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52 $(0 \times 1.12) + (1 \times 2.4) + (1 \times 1.33) + (1 \times 1.49) + (2 \times 1.06) + (2 \times 2.73) + (0 \times 2.40) = 11.31$.
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3 Conversely the SLESIS for a male Chinese patient, diagnosed at age 50, taking 5mg
4 prednisolone per day with Katz Index of 2, no previous hospitalisations for SLE and
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6 three previous severe infections would be calculated as follows.
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11 $(1 \times 1.12) + (0 \times 2.4) + (0 \times 1.33) + (0 \times 1.49) + (2 \times 1.06) + (0 \times 2.73) + (3 \times 2.40) = 10.44.$
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17 **Validation cohort**

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23 Validation was carried out in the lupus clinic at University College London Hospital
24 (UCLH). All patients fulfilled the 1997 revised criteria of the American College of
25 Rheumatology (ACR) for the classification of SLE²². The clinic has been running
26 continuously since 1979 and has records from 699 patients. Medical records of all the
27 patients were reviewed to identify those who had suffered severe infections. Severe
28 infection was defined as that leading to hospitalization and/or death. Isolation of the
29 causative agent was not required in every case, with final classification as an infection
30 being made using standard clinical criteria as in the previous RELESSER study¹⁷. Only
31 infections recorded during the follow-up period (i.e after the diagnosis of lupus) were
32 included as outcomes.
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50 We used a nested case-control design. We identified 98 patients who had suffered at
51 least one severe infection and compared their medical records with those of 111
52 randomly selected patients with SLE who had never suffered from severe infections.
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55 By retrospective analysis of medical records, we obtained comprehensive information
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60 about demographic, clinical, serological and treatment factors in these two groups.

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6 We calculated the SLESIS for each of the 209 patients at the time of diagnosis. For
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8 each of the 98 patients with infection we also calculated SLESIS for the clinical
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10 assessment carried out at the last consultation prior to the infection. For comparison,
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12 we calculated SLESIS in 98 controls matched for disease duration, as follows. For
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14 each infection case we selected one control case from the 111 who had never suffered
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16 severe infections. For the control we calculated the SLESIS at the time-point after
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18 diagnosis corresponding to the duration after diagnosis when the matched case
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20 suffered severe infection.
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28 ***Statistical analysis***

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35 Demographic and clinical characteristics were compared between patients who
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37 developed severe infection and patients who did not, using a Pearson χ^2 for
38
39 categorical variables or a Student's t-test for normally distributed continuous variables
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41 (data expressed as mean \pm standard deviation). For non-normally distributed
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43 variables, either a Mann-Whitney U test or a logarithmic transformation was
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45 performed, and data are expressed as median and interquartile range. Multivariable
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47 logistic regression analysis was performed to establish which factors were
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49 independently associated with severe infection.
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54 We compared SLESIS scores between case and control groups using the Mann-
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56 Whitney U test. Receiver Operator Characteristics (ROC) analysis was used to define
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58 the area under the curve (AUC) for SLESIS at diagnosis and SLESIS just prior to
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3 infection. We also identified several possible cut-off scores for SLEIS with different
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5 combinations of specificity and sensitivity for severe infection.
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11 The STATA for Windows statistical software package (v.13.1) was used for all
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13 statistical analysis. Significance was defined as $p < 0.05$.
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18 19 20 ***Patients and/or public involvement*** 21

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26 Patients and/or public were not involved in this study.
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Results

Table 2 shows a comparison of the 98 patients (14% of the total cohort of 699 patients) who developed severe infection and the control group of 111 patients who never suffered from severe infection. These two groups did not differ in age, sex or ethnicity.

Patients who developed severe infections after diagnosis of SLE were more likely to have suffered previous severe infections before diagnosis of SLE (Pearson $\chi^2 = 11.69$, $p=0.001$) or to have been hospitalized for SLE (Pearson $\chi^2 = 11.89$, $p=0.001$) compared to those patients who never had severe infections. In terms of SLE manifestations, skin and renal disease were more common in the infection group (Pearson $\chi^2 = 6.25$, $p=0.012$; Pearson $\chi^2 = 9.5$, $p=0.004$) whereas joint involvement was more frequent in the non-infection group (Pearson $\chi^2 = 11.21$, $p=0.001$).

Patients in the infection group were more likely to have been treated with high doses of corticosteroids or an immunosuppressant (IS). Whereas 55% of the infection group had ever been treated with corticosteroids at a dose ≥ 10 mg per day, this only happened in 22% of the non-infected group (Pearson $\chi^2 = 10.54$, $p = 0.009$). Significantly increased risk of infection was found for azathioprine (Pearson $\chi^2 = 5.89$, $P=0.015$) and cyclophosphamide (Pearson $\chi^2 = 8.26$, $p=0.004$) but not for mycophenolate or rituximab. Hydroxychloroquine had been taken by 77% of the non-infection group compared to 67% of the infection group with no significant difference between groups.

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6 Regarding laboratory data, only neutropenia, which was twice as common in the
7 infection group (34% vs. 17%), was significantly different between both groups
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9 (Pearson $\chi^2 = 7.63$, $p = 0.006$).
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17 After multivariable analysis adjusted for age, only previous infection (beta coefficient:
18 2.20, 95% CI: 0.77-3.62; $p = 0.003$), previous hospitalizations for SLE (beta coefficient:
19 1.12, 95% CI: 0.19-2.07; $p = 0.021$) and treatment with corticosteroids ≥ 10 mg/day,
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21 (beta coefficient: 3.39, 95% CI: 2.33 – 4.44; $p < 0.001$) remained statistically significant.
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30 ***Type of infection***

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36 The most common type of severe infection was respiratory tract infection ($n = 29$; 29.6%
37 of all infections), followed by urinary tract infection ($n = 22$, 22.4%) and gastrointestinal
38 infection ($n = 22$, 22.4%). Less frequent were soft tissue infection ($n = 11$, 11.2%) and
39 nervous system infections ($n = 4$, 4.1%). Twelve (12.4%) of the patients developed
40 documented bacteraemia on blood culture and 15 (15.3%) had multiple organ
41 involvement.
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54 ***Mortality***

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3 About a quarter (26.5%) of the patients died during their admission for severe infection,
4 though this does not imply that death was always due to infection as many patients
5 had co-morbidities or active lupus as well. Having recorded this high proportion of
6 deaths, we analyzed the differences between the group of 26 patients who died during
7 their admission for infection and the 72 patients who survived. These results are
8 summarized in Table 3.
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21 Patients who did not die had more previous hospitalizations due to SLE, compared to
22 those who died (Pearson $\chi^2 = 33.71$, $p < 0.001$). In contrast, those who died were more
23 likely to have suffered from severe infections prior to the diagnosis of SLE (Pearson
24 $\chi^2 = 8.66$, $p = 0.003$).
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34 There were no statistically significant differences among the clinical manifestations of
35 SLE between these two groups.
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43 Regarding treatment, there were statistically significant differences for steroids at any
44 time (Pearson $\chi^2 = 8.19$, $p = 0.004$) and rituximab (Pearson $\chi^2 = 9.34$, $p = 0.002$).
45 However, for both these variables, patients who survived were more likely to have
46 taken these drugs than those who died. Importantly, we only considered use of drugs
47 in the period between diagnosis and first infection so survival from first infection would
48 not affect the proportion of patients recorded as taking any drug.
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3 Multiple organ involvement by infection was more common in deceased patients than
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5 in patients who survived (Pearson $\chi^2 = 20.5$, $p < 0.001$). Patients who died were more
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7 likely to have had positive anti-dsDNA compared to those who survived.
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14 After multivariable analysis adjusted for age, previous hospitalizations due to SLE,
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16 previous infection and the presence of multiple organ involvement remained
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18 statistically significant as factors differentiating patients who died from those who
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20 survived (Beta coefficient: -6.15, 95% CI: -9.57- -2.73; $p < 0.001$; beta coefficient: 3.55,
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22 95% CI: 0.47-6.63; $p = 0.024$ and Beta coefficient 3.51 95% CI: 0.9-6.12; $p = 0.008$).
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26 27 28 29 ***Analysis of SLESIS values over time*** 30

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36 Median (IQR) SLESIS at diagnosis of SLE in patients with infection was 4.27 (3.18)
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38 which was significantly higher than in the control (no infection) group (Median 2.55,
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40 IQR 3.79 ($z = -3.34$; $p = 0.0008$). Median (IQR) SLESIS just before the infection in the
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42 infection group was 6.64 (4.18) which was statistically higher than the median SLESIS
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44 at diagnosis in those patients ($z = -5.73$, $p < 0.001$) and also higher than median
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46 SLESIS in the duration-matched control group at a comparable time-point in their
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48 disease course (median 3.32, IQR 3.16, $z = -6.99$; $p < 0.001$). There were no significant
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50 differences between the first and second SLESIS values (i.e. diagnosis and
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52 comparable time-point to infection) for the matched controls.
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3 Figure 1 shows the ROC analysis for SLESIS at diagnosis. The area under the ROC
4 curve (AUC) was 0.6332 (SD 0.04; 95% CI: 0.56-0.70). We defined three possible cut-
5 offs to distinguish patients with and without severe infection. We selected the cut-offs
6 which had classified correctly the maximum percentage of the sample taking into
7 account sensitivity and specificity. A cut-off for SLESIS at diagnosis ≥ 3.18 identified
8 patients who would develop severe infection with sensitivity 77% and specificity 51%.
9 For SLESIS ≥ 3.46 , sensitivity was 66% and specificity 55%. For SLESIS ≥ 4.24 ,
10 sensitivity was 64% and specificity 60%.
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26 Figure 2 shows the ROC curve for SLESIS just prior to the infection. The AUC was
27 0.79 (SD 0.03 95% CI: 0.73-0.85), which was better than for SLESIS at diagnosis. We
28 selected three cut-offs: ≥ 3.67 identified patients who would develop severe infection
29 with sensitivity of 90% and specificity of 43%. Similar results were obtained using
30 ≥ 3.79 as a cut-off (sensitivity of 88%, specificity of 50%). For SLESIS ≥ 4.24 , sensitivity
31 was 86% and specificity 60%.
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Discussion

In patients with SLE it has been reported that the prevalence of life-threatening infections appears to be highest within the first five years after disease onset²³. However, severe infection represents a threat throughout the course of the disease, especially when these patients become older and develop more co-morbidities related to age. Given the potential mortality in SLE patients due to such infections, it is pertinent to pursue new options that allow us to predict which groups of patients will

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3 have higher risk of developing major infections. Our aim was to develop a risk score
4 (SLESIS) to aid in this purpose. This study fulfils the important task of testing the
5 properties of this SLESIS score in a cohort independent of the RELESSER^{19,20}
6 population in which it was developed. Our London cohort differs from the Spanish
7 cohort in terms of ethnicity but SLESIS still exhibits a valid and statistically significant
8 association with severe infection.
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21 During the last few years, there have been several publications aiming to develop
22 algorithms that could measure the risk of developing severe infections in patients with
23 other autoimmune diseases. Crowson²⁴ *et al* developed a score in order to detect
24 severe infection promptly in a cohort of 410 patients with RA. The score was designed
25 and validated to predict the 1-year risk of severe infection whereas SLESIS was
26 elaborated to predict the risk of severe infection ever. Zink¹⁸ *et al* built a score based
27 on the RABBIT (Rheumatoid Arthritis Observation of Biologic Therapy) cohort in order
28 to predict serious infection in patients on biologic treatment, with promising results.
29 However, the authors suggested that their risk score was valid only in Caucasian
30 populations in Western Europe. Beca²⁵ *et al* designed a risk calculator algorithm to
31 differentiate flares from infections in SLE patients with fever. The study encompassed
32 130 patients with SLE who presented with fever over a period of 13 years. ROC curve
33 analysis in both papers showed that both scores were able to predict infection with
34 AUC between 0.8 and 0.9. Nonetheless, both studies validated the algorithms in
35 similar cohorts in terms of ethnicity distribution compared to the original cohorts. In
36 contrast, we selected a validation cohort of patients in a different country, with a
37 different range of ethnicities. In the Spanish cohort, 93% of patients were Caucasian
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3 and fewer than 1% African/Caribbean. In London, 68% were Caucasian and 28%
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5 African/Caribbean, an ethnic group recognised as suffering more severe SLE.
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11 Patients with previous severe infection were predisposed to develop major infection
12 and were also more likely to die during admission for severe infection. Impaired
13 immune system functions in a sub-group of patients with SLE may contribute to
14 increase the infection risk in those patients. There are immunological and genetic
15 disorders that predispose to the development of infections in patients with SLE.
16 Furthermore, other clinical and treatment factors might play a crucial role in the
17 predisposition of patients with SLE to develop infection. For instance, the infection
18 group were more likely than the controls to have had previous hospitalisations for SLE.
19 These findings are comparable to other previous reports^{2, 26 - 28}. In contrast, in the
20 study of Ruiz-Irastorza *et al*, lung disease was the only clinical manifestation that was
21 considered a predictor of major infection after the multivariate analysis²⁹.
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41 In carrying out this project, we noted the fact that a quarter of the patients recorded as
42 suffering severe infections died during their admission for infection. To investigate this
43 mortality further, we carried out univariable and multivariable analysis of factors that
44 could potentially influence whether or not these patients died. Surprisingly, though
45 previous hospitalization due to SLE was a factor independently associated with
46 increased risk of severe infection it was also associated with increased chance of
47 surviving that severe infection, even after multivariable analysis. There is no obvious
48 explanation for this apparent paradox. Perhaps the threshold for starting antibiotics
49 was lower in such patients. We considered the possibility that deaths from severe
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3 infection had all occurred many years ago, during a period when more patients were
4 treated with high dose IS such as cyclophosphamide. However, this is not the case as
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8 12 patients died between 2000 and 2012 while the other 14 died before the year 2000.
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14 SLESIS was significantly higher just before the severe infection in comparison to the
15 value at the diagnosis of SLE. This reinforces the idea that repeated measurement of
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18 SLESIS may be a helpful clinical assessment tool. As lupus activity and treatment
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21 change over time, it is predictable that SLESIS would change over time, but it was
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24 important to investigate whether this makes SLESIS at diagnosis a poorer predictor of
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27 infection. Development of chronic damage over time, as well as cumulative use of
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30 corticosteroids and immunosuppressive drugs could contribute to these changes in
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33 SLESIS related to increased infection risk. Some variables of SLESIS, will never
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36 change over time, such as age at diagnosis, ethnicity and gender, whereas others,
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39 such as number of previous severe infections, Katz index and current dose of
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42 corticosteroids could change and may thus contribute to changes in SLESIS. One
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45 strategy could be to re-calculate SLESIS annually and after every severe infection
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48 and hospitalisation. In this way, a prospective study could be carried out to calculate
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51 SLESIS multiple times during follow-up in order to assess its variation over time and
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54 see if its peak (vs. lower values during follow-up) is really associated with a higher
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57 probability of severe infection.
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3 risk of infections although results have been controversial among the different
4 cohorts³¹. In our study, cyclophosphamide and azathioprine were associated with
5 increased risk of severe infection in the univariate analysis but that significance was
6 lost after the multivariable analysis.
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16 There was a trend with hydroxychloroquine (HCQ) which seemed to be the opposite
17 direction to corticosteroids or immunosuppressants, since fewer patients in the study
18 group than the control group had ever been treated with HCQ. This finding is in
19 agreement with previous reports^{29 32} although in our study, it did not reach statistical
20 significance. Ruiz-Irastorza²⁹ *et al.* found that patients taking antimalarials were 16
21 times less likely to suffer a major infection. Similarly, Sisó³² *et al.*, found a lower
22 frequency of infections among those previously treated with antimalarials in a
23 retrospective study. Bultink *et al.*, in a study designed to analyse the effect of the
24 deficiency of functional mannose-binding lectin, also found that treatment with HCQ
25 was associated with fewer severe infections although the authors attributed this
26 association to the presumed lesser severity of lupus patients who take HCQ³³.
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46 Overall, the AUC in our study were not as high as for previous scores developed for
47 RA^{18 24}. However, this is the first score that has been developed to predict severe
48 infections in SLE and may represent a first step in developing tools to do this
49 accurately. We acknowledge several limitations in our study. Firstly, the retrospective
50 design of the study. Secondly, the ethnicity item in SLESIS distinguishes only Latin
51 American ethnicity as a separate group, which was not helpful in the London
52 population. A modified SLESIS including HR for other ethnic groups would be more
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3 widely applicable globally but could not have been derived from the RELESSER cohort
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5 (too ethnically homogeneous) or the UCL cohort (too small). Thirdly, the Katz index
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7 used by RELESSER is a simple and helpful measure of disease severity (not just
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9 activity) but is not widely used in clinical practice. However, in the original RELESSER
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11 study¹⁷, from which SLESIS was derived, SLICC/ACR/Damage Index (SDI), Katz
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13 Index and SELENA-SLEDAI activity score were all measured and the Katz Index was
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15 the only one statistically associated with severe infection. Notwithstanding these
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17 limitations, we have shown that SLESIS at diagnosis was significantly higher in the
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19 group of patients who later suffered severe infections than in the control group of SLE
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21 patients who did not suffer severe infection.
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30 How might SLESIS be used in clinical practice? It is important to bear in mind that both
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32 sensitivity and specificity for severe infection were modest for SLESIS at diagnosis.
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34 For SLESIS just before the infection, sensitivity was high (90%) but specificity was low
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36 (54%). The low specificity means that SLESIS could not be used to decide upon use
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38 of management measures with a high risk of adverse effects. We would suggest that
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40 patients with high SLESIS (>3.5) at any point could be followed-up with a higher index
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42 of suspicion for infection and lower threshold for using antibiotics. Although this may
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44 be an obvious extrapolation of the data, it is not possible to conclude that the early use
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46 of antibiotics in patients with high SLESIS will impact on the outcomes, and therefore,
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48 this strategy cannot be suggested based solely on the results of our work. SLESIS at
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50 diagnosis, together with other factors, might also help in deciding which patients might
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52 benefit from vaccination against bacterial infections (e.g. pneumococcus) and
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54 considering benefit-risk balance of corticosteroids (≥ 10 mg/day) and other
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56 immunosuppressants.
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6 In summary, despite the limitations, our study has demonstrated strong arguments to
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8 perform future prospective studies to assess if SLESIS, or an improved form of
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10 SLESIS, could be clinically useful in the early diagnosis and prevention of severe
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12 infections in patients with SLE.
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DATA AVAILABILITY STATEMENT

No additional data available.

CONTRIBUTORSHIP STATEMENT

AR and BTS designed the study. IRF, JMPR and VCP developed the SLESIS score and advised on design of the study. BTS, AR, CW and DI collected the data. BTS and VCP carried out the statistical analysis. BTS, JMPR, IRF, VCP, DI and AR all took part in interpreting the results and writing the final manuscript.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to disclose.

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Table 1 Variables incorporated into SLEIS

Variable	Beta Coefficient	Hazard ratio (HR) for severe infection	95% confidence interval
Age at diagnosis (>46 years old)	0.1163	1.12	1.07 – 1.18
Latin American ethnicity	0.427	2.40	2.29 – 2.5
Current dose of corticosteroids ≥ 10 mg/day)	0.2878	1.33	1.15 – 1.55
Sex=male	0.3692	1.49	1.22 – 1.81
Previous hospitalization for SLE	1.0049	2.73	2.22 – 3.35
Katz Index²¹	0.062	1.06	1.03 – 1.1
Each previous severe infection	0.8739	2.40	2.29 – 2.50

Footnote

These HR values were derived from the retrospective analysis of 3,658 Spanish patients described in reference 17.

Table 2. Descriptive data: SLE patients with infection vs without infection

	Study (infection) group (n=98)	Control (non infection) group (n=111)	P value
Gender, n (%)			
- Females	90 (92)	103 (93)	ns
- Males	8 (8)	8 (7)	
Median age at diagnosis of SLE (IQR), years	30.5 (27)	31 (18)	ns
Median age at time of infection (IQR), years	43 (25)	Not applicable	
Ethnicity, n (%)			
- Caucasian	48 (49)	72 (65)	ns
- Hispanics	3 (3)	2 (2)	
- Afro-Caribbean	28 (29)	20 (18)	
- Asian	7 (7)	6 (5)	
- Other	12 (12)	12 (11)	
Median length of follow-up (IQR), years	9.5 (14)	14 (9)	ns
Previous infection before SLE diagnosis, n (%)	16 (16)	3 (2)	0.001

1 2 3 4 5 6 7	Previous hospitalizations due to SLE n (%)	55 (56)	36 (32)	0.001
8 9 10 11 12	SLE main features (cumulative) n, (%)			
13	- Skin disease	76 (78)	67 (60)	0.012
14	- Joint disease	72 (74)	101 (91)	0.001
15	- Renal disease	42 (43)	24 (22)	0.004
16	- Neuropsychiatric	13 (13)	12 (11)	ns
17	disease			
18	- Serositis	19 (19)	33 (30)	ns
19				
20	Previous drug treatment n (%)			
21	Corticosteroids	89 (91)	43 (39)	<0.001
22	Corticosteroids (≥10mg per	54 (55)	25 (23)	0.009
23	day at any time)			
24	No Hydroxychloroquine	32 (33)	25 (23)	ns
25	Azathioprine	47 (48)	35 (32)	0.015
26	Mycophenolate	36 (35)	28 (25)	ns
27	Cyclophosphamide	28 (29)	13 (13)	0.004
28	Rituximab	26 (27)	25 (23)	ns
29				
30	Laboratory data, n(%) at			
31	any time			
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- Neutropenia	33 (34)	19 (17)	0.006
- Lymphopenia	76 (78)	73(66)	ns
- Anti-dsDNA +	67 (68)	66 (60)	ns
- Low C3	57 (58)	50 (45)	ns
Outcomes			
- Deaths	26 (27)	2 (2)	0.03
- Patients with >1 infection	18 (18)	0	

Table 3- Comparison of patients who died during admission for severe infection and those who survived

	Deceased Patients n=26 (26.5%)	Alive patients n=72 (73.5%)	P value
Mean age at diagnosis (SD)	33.8 (14.1)	31.2 (15.1)	ns
Mean age at infection (SD)	42.88 (16.7)	40.88 (16.7)	ns
Follow-up between diagnosis and first infection (years)	9.11 (7.04)	10.8 (10.3)	ns
Ethnicity n, (%)			
- Caucasian	16 (61.5)	31(43.1)	
- Hispanics	NA	3 (4.2)	
- Afro-Caribbean	8 (30.8)	20 (27.8)	ns
- Asian	2 (7.7)	4 (5.6)	
- Others	NA	12 (16.7)	
Gender (female), n (%)	25 (96)	65 (90)	ns
Previous hospitalizations, n (%)	2 (8)	53 (74)	<0.001

Previous severe infection before diagnosis of SLE, n (%)	9(35)	7(10)	0.003
Skin disease, n (%)	18 (69)	58 (81)	ns
Renal disease, n (%)	10 (39)	32 (44)	ns
Joint disease, n (%)	22 (85)	50 (69)	ns
Neuropsychiatric disease, n (%)	4 (15)	9 (13)	ns
Serositis, n (%)	7 (27)	12 (17)	ns
Corticosteroids per day at any time), n (%)	20 (77)	69 (96)	0.02
Corticosteroids \geq 10 mg/day at any time, n (%)	17 (65)	37 (51)	ns
Hydroxychloroquine, n (%)	20 (77)	46 (64)	ns
Rituximab , n (%)	1 (4)	25 (35)	0.002
Cyclophosphamide, n (%)	11 (42)	17 (24)	ns
Azathioprine, n (%)	14 (54)	33 (46)	ns
Mycophenolate, n (%)	10 (39)	26 (36)	ns
Splenectomy, n (%)	0	3 (4)	ns
Bacteraemia, n (%)	4 (15)	9 (13)	ns

Multiple organ involvement, n (%)	12 (46)	5 (7)	<0.001
Low complement, n (%)	11 (42)	46 (64)	ns
Neutropenia, n (%)	5 (19)	28 (39)	ns
Lymphopenia, n (%)	20 (77)	56 (78)	ns
a-dsDNA, n (%)	20 (77)	47 (65)	ns

Figure legends:

Figure 1. ROC Curve analysis-SLESIS at diagnosis

Figure 2. ROC Curve Analysis- SLESIS before infection

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Figure 1. ROC Curve analysis-SLESIS at diagnosis

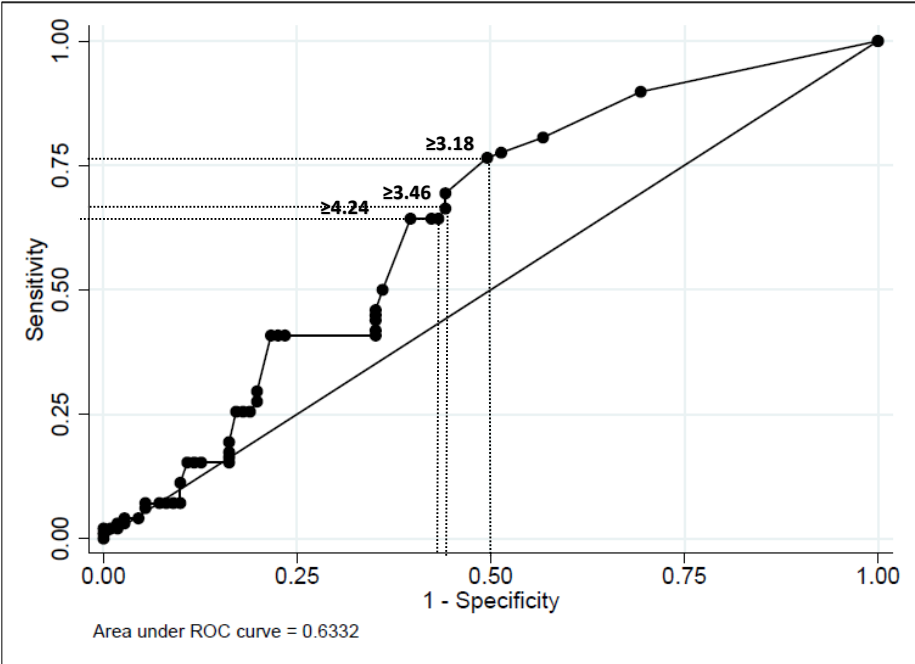
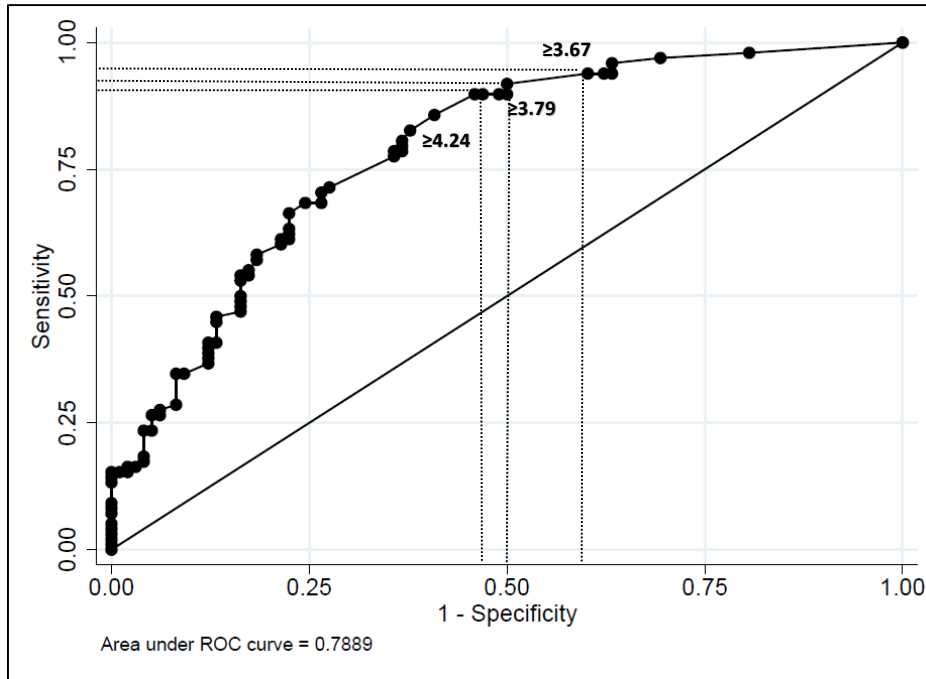


Figure 2- ROC Curve Analysis- SLEIS before infection



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