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SLESIS-R: an improved score for prediction of serious infection in patients with systemic lupus erythematosus based on the RELESSER prospective cohort

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ABSTRACT

Objective To develop an improved score for prediction of severe infection in patients with systemic lupus erythematosus (SLE), namely, the SLE Severe Infection Score-Revised (SLESIS-R) and to validate it in a large multicentre lupus cohort.

Methods We used data from the prospective phase of RELESSER (RELESSER-PROS), the SLE register of the Spanish Society of Rheumatology. A multivariable logistic model was constructed taking into account the variables already forming the SLESIS score, plus all other potential predictors identified in a literature review. Performance was analysed using the C-statistic and the area under the receiver operating characteristic curve (AUROC). Internal validation was carried out using a 100-sample bootstrapping procedure. ORs were transformed into score items, and the AUROC was used to determine performance.

Results A total of 1459 patients who had completed 1 year of follow-up were included in the development cohort (mean age, 49±13 years; 90% women). Twenty-five (1.7%) had experienced ≥1 severe infection. According to the adjusted multivariate model, severe infection could be predicted from four variables: age (years) ≥60, previous SLE-related hospitalisation, previous serious infection and glucocorticoid dose. A score was built from the best model, taking values from 0 to 17. The AUROC was 0.861 (0.777–0.946). The cut-off chosen was ≥6, which exhibited an accuracy of 85.9% and a positive likelihood ratio of 5.48.

Conclusions SLESIS-R is an accurate and feasible instrument for predicting infections in patients with SLE. SLESIS-R could help to make informed decisions on the use of immunosuppressants and the implementation of preventive measures.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Severe infection is frequent in patients with systemic lupus erythematosus, and, while several risk factors have been identified, no clinically useful risk score has been developed to date.

WHAT THIS STUDY ADDS

⇒ The authors developed and internally validated an accurate and feasible score for the prediction of serious infection in clinical practice.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The score could help clinicians to make informed decisions on the use of immunosuppressants and the implementation of preventive measures.

INTRODUCTION

Patients with systemic lupus erythematosus (SLE) are at increased risk of severe infections that vary with the severity of the disease, use of immunosuppressants (including glucocorticoids), comorbidities and organ damage.[1–7] Moreover, infection remains a leading contributor to mortality in patients with SLE.[5 8–10]

Properly estimating the risk of infection in patients with SLE is paramount if we are to balance immunosuppression and implement preventive measures. Unfortunately, very few predictive models of severe infection in patients with SLE have been published to date. One systematic literature review showed that most of those published were from retrospective cohorts and were subjected to methodological limitations and a high risk of bias.[11] No evidence-based, widely validated, and suitable score for predicting severe infection in patients with SLE has been developed for use in daily clinical practice. Conversely, scores for predicting major infection have been successfully developed for other systemic immune-mediated rheumatic diseases, such as rheumatoid arthritis.[12]

Our group attempted to develop a tool for the prediction of severe infections in SLE. The SLE Severe Infection Score (SLESIS) was developed using data gathered from the retrospective cross-sectional phase of the Spanish Rheumatology Society Systemic Lupus Erythematosus Registry (RELESSER-TRANS)[13] and validated in an external cohort, the University College London Hospital SLE cohort, which was also based on retrospective-longitudinal data. The original SLESIS incorporated seven predictors, including the Katz severity index (KSI).[14] However, the performance of SLESIS was only moderate, with an area under the receiver operating characteristic curve (AUROC) of 0.63 (95% CI 0.56 to 0.70) at diagnosis and of 0.79 (95% CI 0.73 to 0.85) at the time of infection.

In the current study, we aimed to improve the ability of SLESIS to predict the risk of infection by reformulating the constituent variables and adding new markers, if appropriate, based on higher quality data from the prospective phase of the RELESSER register (namely, RELESSER-PROS). We also wished to improve the feasibility of our index by avoiding, if possible, inclusion of the KSI, which is cumbersome to calculate and has a limited degree of validation. Furthermore, we performed an internal validation of the resulting index.

PATIENTS AND METHODS

Design and participants

The data for this study were gathered from the RELESSER-PROS register, a multicentre prospective cohort of patients with SLE involving 39 Spanish hospitals. The RELESSER cohort comprises patients who meet ≥4 American College of Rheumatology (ACR) classification criteria for SLE, are under active follow-up, and have been recruited from the cross-sectional stage of the register (RELESSER-TRANS). Only patients with sufficient information regarding serious infection were included in the analysis. The general characteristics of the RELESSER register have been reported elsewhere.[15] The baseline visits of RELESSER-PROS took place between 2014 and 2023, and the patients are under active yearly follow-up.

Data collection and variable definitions

Potential predictors were extracted from data collected at the baseline visit (visit 1) and comprise demographic data and clinical characteristics, disease activity (Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Activity Index (SELENA-SLEDAI)) at baseline, severity (KSI), organ damage (Systemic Lupus International Collaborating Clinics (SLICC)-ACR/Damage Index) (SDI), comorbidities (Charlson comorbidity index), previous hospital admission for SLE, previous serious infections (any time after diagnosis of SLE), laboratory data (serum creatinine, lymphopenia <1000/mm^3, hypocomplementemia) and treatments received (antimalarials, immunosuppressants, rituximab, glucocorticoids and prednisone dose (or equivalent) (ie, dose at visit 1, and maximum prednisone dose during the observation period). In order to avoid overfitting of the model, which would have led to performance overestimation, an effort was made to reduce the number of candidate predictors based on our previous studies and a thorough review of the literature.

The dependent variable was the occurrence of a serious infection (ie, one leading to hospitalisation or death) during the first year of follow-up.

Statistical analysis

Descriptive data were expressed as measures of central tendency and dispersion in the case of quantitative variables and as frequency tables and percentages in the case of qualitative variables. A total of 362 out of 1821 patients were excluded owing to missing data regarding serious infection. A bivariate analysis comparing included patients ('valid case') and excluded patients was carried out. Although the excluded group was characterised by a higher Charlson index, lower percentage of antimalarials and more frequent use of mycophenolate, the percentages for previous infection differed significantly between the groups (99 (5.5%) vs 11 (3.1%), p=0.027), with the analysis favouring the 'valid' group (ie, more previous infection in the 'valid' group) (see online supplemental table 1 for the complete set of results).

A baseline comparison of patients in terms of severe infection during the first year of follow-up was performed using the *t* test or the Mann-Whitney test (continuous data) and the χ^2 test with a Fisher exact test (categorical data).

Bivariate logistic regression was used to analyse the predictive effect of baseline variables on the development of severe infection in the first year of follow-up. A predictive model was built based on multivariate logistic regression models and included all the predictors reaching a p value <0.25 in the bivariate analysis (saturated model), with successive elimination of variables without discriminatory power. When multiple options were available for adjustment (eg, adjust for proportion

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with any glucocorticoid or proportion with a glucocorticoid dosage threshold), we based our decisions on exploratory regression analyses. The most parsimonious model with the lowest Akaike and Bayesian information criteria (AIC and BIC) values was chosen as the final model. The performance of the final model was evaluated based on discrimination and calibration parameters.

In order to seek a more realistic estimate of performance, the model was internally validated using bootstrapping techniques, which were based on all the data used in the development of the model and enabled more robust equations to be obtained. The *Transparent Reporting of multivariable prediction model for Individual Prognosis of Diagnosis*[16] statement was followed for this publication (see online supplemental material).

Each predictor in the final adjusted model was transformed into a specific score item based on its corresponding logistic regression coefficient. The OR of each predictor was rounded up to the nearest integer for simplification. The sum of these values yielded the Systemic Lupus Erythematosus Severe Infection Score-Revised (SLESIS-R), whose performance was calculated using the AUROC. Finally, the cut-off point with the best validity parameters (sensitivity, specificity, likelihood ratio) was chosen.

The analysis was performed using STATA V.18 (STATA V.2023, Stata Statistical Software, Release V.18.0. College Station, Texas: Stata Corp LLC).

RESULTS

A total of 1459 patients who had completed visit 2 (1 year of follow-up) or had had infections or died during the study period were included in the analysis. The mean (±SD) age was 49±13 years, 90% of patients were women and 94% were Caucasian. The mean disease duration was 14.2±8.8 years.

The clinical characteristics, laboratory findings, comorbidities and treatments are shown in table 1. At baseline, the mean SLEDAI was low (2.7±3.8).

The frequency of cancer and diabetes was low in both cases and controls (table 1).

Up to 6% had had a prior major infection, that is, before entering the study, and 25% had been hospitalised with SLE. Twenty-five (1.7%) had experienced at least one serious infection in the first year of follow-up. A total of 13 patients (0.91%) died, 2 due to serious infection. Nine patients (0.49%) were admitted to the ICU; in 2 cases, admission was because of infection.

The results of the univariate analysis are shown in table 2. Patients with infection were older (OR=1.04; p=0.006), with more damage accrual (OR=1.29; p<0.0001) and comorbidity (OR=1.34; p<0.0001), including a higher frequency of chronic kidney disease (OR=3.82; p=0.004). The predictors that most increased the probability of serious infection in the following year were previous serious infection (OR=14.78; p<0.0001), previous hospitalisation (OR=15.50; p<0.0001) and cyclophosphamide (OR=12.38; p<0.002) or glucocorticoid dose ≥30 mg/day (OR=7.47; p=0.004) (table 2).

Predictive model building

The potential predictors with p≤0.25 that were entered into the multivariate logistic regression model were age, Charlson comorbidity index, chronic kidney disease, SDI, KSI, SLE-related hospitalisation, previous serious infection, treatments such as antimalarials, cyclophosphamide, mycophenolate as well as the maximum dose of glucocorticoids used during the observation period of ≥30 mg prednisone/day (or equivalent). In order to simplify construction of the index, we made the variable age dichotomous, namely, <60 years or ≥60 years.

Starting from a saturated model (all predictors with a bivariate p value of p≤0.250), we selectively eliminated variables without discriminatory power. A parallel stepwise procedure revealed no differences with the successive elimination approach. Eventually, the most parsimonious model, that is, that with the lowest AIC and BIC values, was chosen. According to our final adjusted multivariate model, the occurrence of a serious infection in the following year in SLE can be predicted from four variables: age ≥60 years (β=1.80; OR=6.06; p=0.002), previous admission for SLE (β=1.92; OR=6.84; p=0.007), previous infection (β=1.81; OR=6.09; p=0.002) and having received a maximum dose of glucocorticoids ≥30 mg (β=2.19; OR=8.93; p=0.010) (table 3). The KSI was eventually excluded from the model. Our model exhibited adequate performance, with 97.8% correct classification. The discrimination parameters revealed an AUROC of 0.874 (0.777–0.974), with adequate calibration (Hosmer-Lemeshow, p=0.932).

Internal validation

The model was internally validated using a bootstrapping procedure, taking up to 100 samples with replacement and adjustment for overfitting of the model using a heuristic shrinkage factor. The ORs and ß-coefficients of the adjusted model are provided in the online supplemental table 2. This model revealed appropriate discrimination parameters, with a C statistic of 0.810 (0.715–0.893).

The robustness of each predictor, measured as the number of times that it is included in the 100 bootstrap samples, is displayed in the online supplemental table 3.

SLESIS-R index design

Up to 11 mathematical transformations of the final model were performed to create the index; of these, 6 were based on coefficients and 5 on the ORs of the model adjusted for overfitting (online supplemental table 4). This approach yielded 11 possible indices (online supplemental tables 5 and 6). No significant differences were observed between the 11 ROC curves obtained with these indices (online supplemental figure 1). Consequently, the OR-based transformation (avoiding the effect of the constant) with the

Table 1 Sample description and group comparisons

Potential predictors	Total N=1459	Serious infection Absent N=1434	Serious infection Present N=25	P value*
Sociodemographic variables				
Age (visit 1)	49.1±13.5	48.9±13.3	56.6±18.2	**0.030**
Female sex	1315 (90.4%)	1292 (90.4%)	23 (92.0%)	1.000
Ethnicity				
Caucasian	1327 (93.8%)	1304 (93.9%)	23 (92.0%)	0.407
Latin-American	64 (4.5%)	63 (4.5%)	1 (4.0%)	
Other	23 (1.6%)	22 (1.6%)	1 (4.0%)	
Smoking				
Never	652 (48.9%)	641 (49.0%)	11 (45.8%)	0.065
Ever or current smoker	680 (51.1%)	667 (51.0%)	13 (54.2%)	
Clinical features and comorbidities				
Charlson comorbidity index	2.5±1.8	2.5±1.8	3.9±2.7	**0.004**
Diabetes	50 (3.5%)	48 (3.4%)	2 (8.3%)	0.200
Malignancy	40 (2.8%)	39 (2.7%)	1 (4.2%)	0.493
Chronic kidney disease	148 (10.6%)	141 (10.3%)	7 (30.4%)	**0.002**
SLE activity (SLEDAI)	2.7±3.8	2.7±3.8	3.2±5.7	0.918
Damage (SDI)	1.4±1.8	1.4±1.8	2.8±2.2	0.0005
Katz severity index	4.4±2.0	4.4±1.9	5.7±1.8	**0.0004**
SLE-related hospitalisation	354 (25.4%)	334 (24.4%)	20 (83.3%)	**<0.0001**
Previous serious infection	88 (6.1%)	77 (5.4%)	11 (45.8%)	**<0.0001**
Laboratory results				
Creatinine	1.03±1.82	1.03±1.83	1.15±0.71	0.468
Lymphopenia (<1000/mm^3)	272 (18.8%)	266 (18.7%)	6 (25.0%)	0.436
Hypocomplementemia	540 (37.5%)	531 (37.5%)	9 (37.5%)	1.000
Treatments				
Maximum GC dose				**0.044**
≤5 mg	526 (67.1%)	518 (67.6%)	8 (44.4%)	
>5 mg and<10 mg	116 (14.8%)	112 (14.6%)	4 (22.2%)	
≥10 mg and<30 mg	100 (12.8%)	97 (12.7%)	3 (16.7%)	
≥30 mg	29 (3.7%)	26 (3.4%)	3 (16.7%)	
Methylprednisolone pulse	13 (1.7%)	13 (1.7%)	–	
Antimalarials	802 (55.0%)	791 (55.2%)	11 (44.0%)	0.266
Cyclophosphamide	12 (0.8%)	10 (0.7%)	2 (8.0%)	**0.017**
Mycophenolate	114 (7.8%)	109 (7.6%)	5 (20.0%)	**0.022**
Rituximab	45 (3.1%)	44 (3.1%)	1 (4.0%)	0.546
Other (MTX or azathioprine)	215 (14.7%)	212 (14.8%)	3 (12.0%)	1.000

*P values for absent versus present comparisons. Statistically significant variables are highlighted in bold.
GC, glucocorticoid; MTX, methotrexate; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLE, systemic lupus erythematosus; SLEDAI, SLE Activity Index.

best performance (higher AUROC), corresponding to number nine and consisting of rounding the OR of each predictor, was finally chosen.

The final SLESIS-R is shown in table 4. The score is based on values ranging from 0 to 17. The ROC curve of the SLESIS-R is displayed in figure 1. The resulting AUROC was 0.861 (0.777–0.946). The validity parameters are displayed in table 5. According to these parameters, a score ≥6 was chosen as the best cut-off point, exhibiting a sensitivity of 76% and specificity of

Table 2 Univariate analysis

Potential predictors	OR (95%CI)	P value
Age	1.04 (1.01 to 1.07)	**0.006**
Female	1.22 (0.28 to 5.23)	0.789
Latin American origin	0.90 (0.12 to 6.77)	0.918
Current smoking	1.45 (0.56 to 3.78)	0.446
Charlson comorbidity index	1.34 (1.15 to 1.56)	**<0.0001**
Diabetes	0.33 (0.53 to 6.44)	0.333
Malignancy	1.28 (0.21 to 7.67)	0.788
Chronic kidney disease	3.82 (1.54 to 9.44)	**0.004**
Disease activity (SELENA-SLEDAI)	1.03 (0.94 to 1.13)	0.559
Organ damage (SDI)	1.29 (1.13 to 1.48)	**<0.0001**
Katz severity index	1.33 (1.12 to 1.58)	**0.001**
SLE-related hospitalisation	15.50 (5.26 to 45.69)	**<0.0001**
Previous serious infection	14.78 (6.41 to 34.1)	**<0.0001**
Creatinine	1.02 (0.88 to 1.19)	0.756
Lymphopenia (any time)	1.45 (0.57 to 3.68)	0.439
Hypocomplementemia	1.00 (0.43 to 2.30)	1.000
Maximum GC dose over the period (prednisone)	–	–
≤5 mg	1	NA
>5 mg and<10 mg	2.31 (0.68 to 7.81)	0.177
≥10 mg and<30 mg	2.00 (0.52 to 7.68)	0.311
≥30 mg	7.47 (1.87 to 29.82)	**0.004**
Antimalarials	0.64 (0.29 to 1.42)	0.270
Cyclophosphamide	12.38 (2.57 to 59.70)	**0.002**
Mycophenolate	3.04 (1.12 to 8.25)	**0.029**
Rituximab	1.32 (0.17 to 9.95	0.790
Methotrexate or azathioprine	0.79 (0.23 to 2.65)	0.698

Variables associated with serious infection.
Statistically significant variables are highlighted in bold.
GC, glucocorticoid; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Activity Index; SLE, systemic lupus erythematosus.

Table 3 Adjusted final multivariate predictive model

Predictor	OR (95%CI)	P value
Age	1.03 (1.00 to 1.06)	0.040
Previous SLE-related hospitalisation	3.81 (1.33 to 10.97)	0.013
Previous serious infection	3.72 (1.58 to 8.77)	0.003
Having received a GC dose≥30 mg/d	4.45 (1.34 to 14.76)	0.015

GC, glucocorticoid; SLE, systemic lupus erythematosus.

Table 4 SLESIS-R index calculator

Predictor	Score
Age (years)≥60	4
Previous SLE-related hospitalisation	4
Previous serious infection	4
GC doses	
>5 mg and<10 mg	2
≥10 mg and<30 mg	2
≥30 mg	5

GC, glucocorticoids; SLE, systemic lupus erythematosus; SLESIS-R, Systemic Lupus Erythematosus Infection Score-Revised.

86.6%, with an accuracy of 85.9% and positive likelihood ratio of 5.48.

DISCUSSION

Based on data from a large, prospective multicentre cohort, we developed and internally validated an improved version of SLESIS, namely SLESIS-R, a score that is able to predict the risk of severe infection in patients with SLE during the following year. The performance of SLESIS-R was very favourable, notably improving on the previous version of the score in terms of the AUROC (0.861 (95% CI 0.777 to 0.946) vs 0.790 (95% CI 0.730 to 0.850)). The SLESIS-R also improved feasibility, given the greater simplicity of the new version and the exclusion of the KSI. This latest version includes only four clinical parameters, namely, age, previous SLE-related hospitalisation, previous severe infection and glucocorticoid dose ≥30 mg/day, all of which are readily available in the patient's clinical records. The four parameters found are consistent with most previous studies regarding major infection-associated factors, which identify mostly age, glucocorticoid dose and previous serious infection as the best predictors of severe infection in SLE.[1 2 4 6 7 11 17] In addition, the prospective nature of the data used to develop SLESIS-R, with a better-defined temporal framework, increases the reliability of the results.

Because of its simplicity and the fact that it is based on clinical parameters and not laboratory results, SLESIS-R could become a useful instrument for predicting infection in both daily clinical practice and observational studies and even in clinical trials in Caucasians. In fact, the use of numerical probabilities is to be preferred not only for decision-making but also in teaching materials and in communication between physicians.[18] We think that our score improves prediction of the risk of infection, facilitating an informed decision-making process and supporting more careful implementation of preventive measures. Thus, in the case of a patient with an increased risk of serious infection, namely, a SLESIS-R score >6, this information should be considered when selecting therapy and for overall patient management (ie, taking

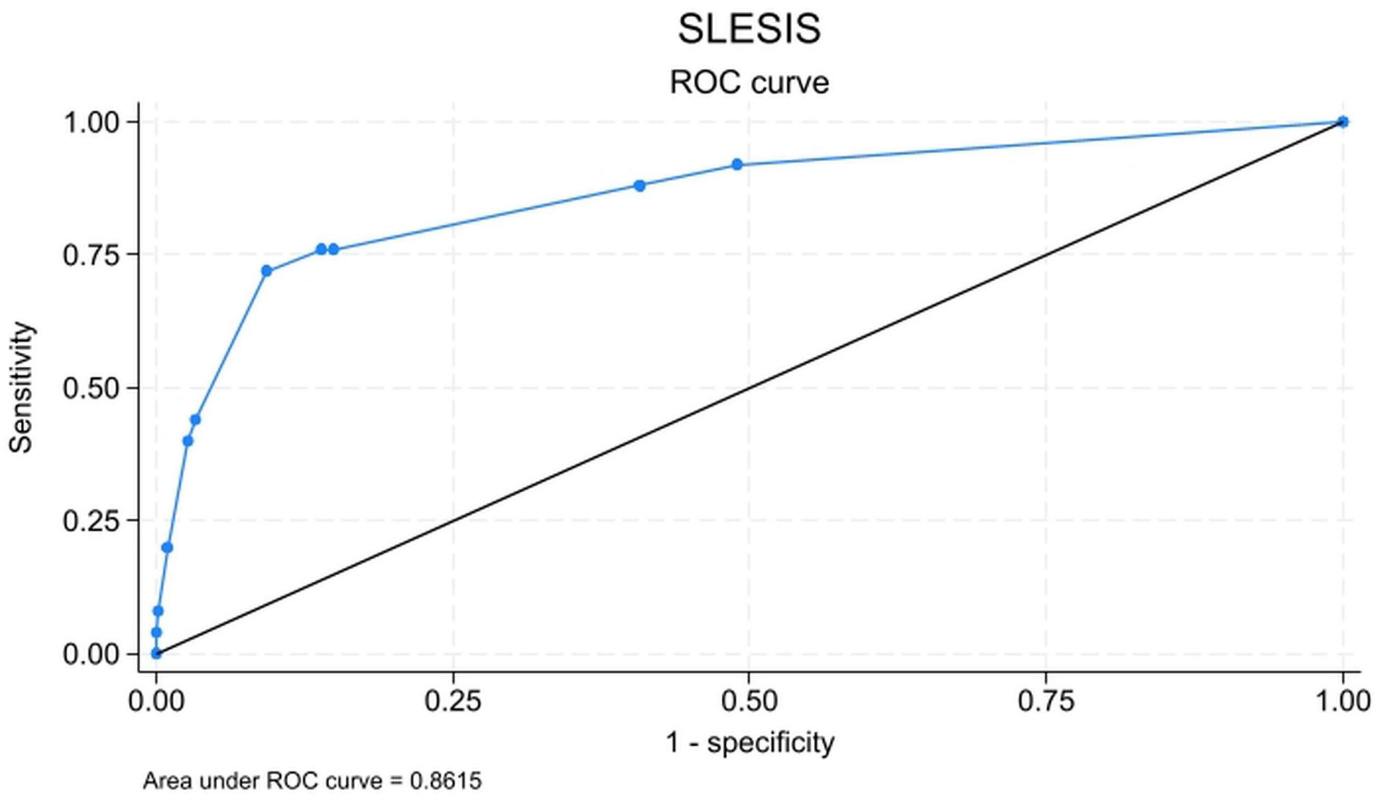

Figure 1 ROC curve for the SLESIS-R index. ROC, receiver operating characteristic curve; SLE, systemic lupus erythematosus; SLESIS-R, SLE Severe Infection Score-Revised.

extreme precautions to avoid serious infections, such as vaccinations, hygiene, smoking cessation, etc). Similarly, seeking early medical care in the case of fever would also be appropriate. Additionally, we should perhaps choose therapies with a reduced risk of infection or opt for more aggressive' tapering of glucocorticoids.

Several previous studies have attempted to develop predictive models of infection in patients with SLE. All of them are discussed below and were based, in contrast to our study, on retrospective data analysis (with the exception of Torres-Ruiz *et al*[19]) and single-centre SLE cohorts.

The first formal attempt to develop a predictive model and rigorously test its performance was that of Yuhara *et al*,[17] which was carried out in an Asian single-centre cohort. In contrast to SLESIS, the model of Yuhara *et al* was developed for inpatients

Table 5 SLESIS-R—validity parameters

Cut-off point	Sensitivity	Specificity	Properly classified	Likelihood ratio
≥ 0	100%	–	1.71%	1.00
≥ 2	92.0%	51.0%	51.7%	1.88
≥ 4	88.0%	59.3%	59.8%	2.16
≥ 5	76.0%	85.1%	84.9%	5.09
≥ 6	**76.0%**	**86.1%**	**85.9%**	**5.48**
≥ 8	72.0%	90.7%	90.4%	7.76
≥ 9	44.0%	96.7%	95.8%	13.42
≥ 10	40.0%	97.3%	96.4%	15.09
≥ 12	20.0%	99.1%	97.7%	22.06
≥ 13	8.0%	99.9%	98.3%	57.36
≥ 17	4.0%	100%	98.4%	
>17	–	100%	98.3%	

The optimal cut-off point is highlighted in bold.
SLESIS-R, Systemic Lupus Erythematosus Severe Infection Score-Revised.

with SLE. The independent predictors of infection, all of which were available at admission, were decreased serum albumin, increased serum creatinine and prednisolone ≥60 mg/day without methylprednisolone pulse therapy. Internal validation of the model yielded a valuable AUROC for cross-validation (0.846, CI not provided). However, it is difficult to generalise these results to an SLE outpatient population.

Torres-Ruiz *et al*[19] built a predictive score based on prospective clinical data and immunological-laboratory tests, the 'systemic lupus erythematosus infection predictive index'. The performance of the models, measured as the AUROC, was at most 0.75 (95% CI 0.56 to 0.85). However, a very low number of patients with SLE (ie, a total of 55 cases) were included in that study, and only 26% of the recorded infections were serious. Additionally, several of the immunological tests proposed are not widely available or standardised, thus limiting the feasibility of the index.

Restrepo-Escobar *et al*[20] developed a model for predicting bacterial infection in Latin-American patients with SLE, although, again, this model was limited to nosocomial infections and was, therefore, unable to predict serious infection in outpatients with more stable disease in terms of activity. Furthermore, no score was derived from the data obtained in the analysis.

Finally, Wang *et al*[21] conducted a study to evaluate the risk of major infection in an Asian SLE cohort and developed a prediction model that incorporated the following variables: SLEDAI >10, lymphocyte count $<0.8\times10^9$ /L and serum creatinine >104 µmol/L. The authors identified patients at low risk of major infection (3%–5%) and patients at high risk of major infection (37%–39%) within the first 4 months in newly diagnosed SLE. Up to 69 infections were recorded in 494 patients (14%) in the first year of the disease, an incidence that is substantially higher than in our cohort. That discrepancy could be explained by ethnic differences (Caucasian vs Asian population) or by selection bias. Moreover, and in contrast to our design, the cohort studied by Wang *et al* was an inception cohort, with a higher level of baseline activity. This predictive model has not been validated to date.

Our study is subject to a series of limitations. First, the number of major infections was relatively low in the cohort, thus potentially compromising the stability of the models. Moreover, the patients included were predominantly Caucasian. Furthermore, given the low grade of disease activity in the cohort, the risk of infection associated with disease activity could be underestimated. Consequently, a more extensive and external validation process is required in order to test the performance of the SLESIS-R in external cohorts, ideally with a more severely ill patients, a higher number of serious infections and more ethnic diversity.

CONCLUSIONS

1. SLESIS-R is an accurate instrument for predicting serious infections SLE and proved feasible for daily clinical practice.
2. SLESIS-R is simple and easy to calculate. It could help clinicians to make informed decisions on the use of immunosuppressive or biological therapy in patients with SLE and, therefore, to implement preventive measures.

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