PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Tejera Segura, Beatriz; Rua-Figueroa, Iñigo; Pego-Reigosa, Jose Maria; del Campo, Victor; Wincup, Chris; Isenberg, David; Rahman, Anisur

VERSION 1 – REVIEW

REVIEWER	Gustavo Guimarães Moreira Balbi Department of Rheumatology, Federal University of Juiz de Fora, Brazil
REVIEW RETURNED	03-Feb-2019

GENERAL COMMENTS	Sirs, The authors provided very insightful considerations regarding infections in SLE patients. It is widely known that infections are one of the main concerns in the treatment and follow-up of SLE patients, and one can assume that the use of validated scores to predict its risk might impact outcomes in this specific population. SLESIS is a new score developed to predict the risk of infection in SLE, derived from a Spanish cohort. The objetive of this study is to validate the use of the new SLESIS in a large British cohort. Even though the paper is well written and brings new relevant information, there are some issues that need to be clarified before it is ready to be published. 1) Although already briefly stated in the Patients and Methods section, SLESIS calculation should be more extensively described in Page 8, line 12, in order to make it easier for readers to understand it. Please include the reference to Table 1 in the appropriate site in this paragraph. 2) I would suggest adding to the ROC curve graphics (Figures 1 and 2) the sensitivity/specificity of the different selected cut-offs and also the AUC. 3) In Page 18, lines 16 and 17, the authors say "This reinforces the idea that repeated measurement of SLESIS may be a helpful clinical assessment tool". I agree that a higher SLESIS right before an episode of severe infection (vs. at diagnosis) may SUGGEST that SLESIS might be useful for clinical assessment during follow-up. Nevertheless, before we can draw this conclusion, SLESIS should be prospectively calculated multiple times during follow-up

	in order to asses its variation over time and see if its peak (vs. lower values during follow-up) is really associated with a higher probability of severe infection. As I consider this one of the most relevant points of discussion in this topic, I would like to invite the authors to provide a more in-depth discussion on this regard. 4) In Page 20, line 16, the authors "...suggest that patients with high SLESIS (>3.5) at any point could be followed-up with a higher index of suspicion for infections and lower threshold for using antibiotics". Although this may be an obvious extrapolation of the data, the authors cannot conclude that the early use of antibiotics in patients with high SLESIS will impact outcomes and, therefore, this treatment strategies cannot be suggested, based solely on the results published in this paper. Just like my comment in number 3, this is also a very relevant point of discussion and should be developed. 5) There is one last point I was intrigued about. In Table 2, it is stated that in the control (non infection) group 29 patients had renal disease and 12 had CNS disease. Considering that either all CNS patients also had renal manifestations or none of CNS patients had renal manifestations, there would be 29-41 patients with a potentially more severe subset of manifestations. Nonetheless, only 6 patients (14-20% of those patients) received corticosteroids equivalent to ≥10 mg of prednisone. Why did this happen? Which were the renal and CNS manifestations in those patients, how were they defined? Finally, I would like to congratulate the authors for the great work. Best regards,

REVIEWER	Alessandra Bortoluzzi Section of Rheumatology, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliera-Universitaria di Ferrara, Via Aldo Moro 8, 44124, Cona (FE), Italy
REVIEW RETURNED	12-Feb-2019

GENERAL COMMENTS	This is a retrospective study based on two large cohorts of SLE patients from tertiary referral centers in Spain and UK. The main aim of the study was to derive a risk score for serious infections (the SLESIS score) from the Spanish cohort and to retrospectively validate it in a large independent UK SLE cohort. The authors acknowledge that the retrospective nature of the study warrants further studies with prospective design, however, they suggest that patients with high SLESIS (>3.5) at any time point could be followed-up with a higher index of suspicion for infection, lower threshold for using antibiotics and higher access to vaccination programs. This is good practical information from this study in order to improve SLE patients care and survival. I have a list of comments. - Abstract: I suggest mentioning also in this section how severe infections are defined. - Introduction: authors enlisted several different objectives for this study, I suggest distinguishing primary aim of the study from the secondary ones. - Materials and methods/results: The authors developed SLESIS using data from the RELESSER cohort, and after analyzing a time repeated-events Cox regression model. They included items with HR superior to 1 in that model. Could the authors perform secondary analysis investigating whether disease duration

	influence infection rates and regarding cumulative glucocorticoid dosage, adjusted for disease duration? They performed analysis matching infectious SLE patients and not-infectious ones according to disease duration, so they clearly recognize that disease duration is relevant in occurrence of infections ("Development of chronic damage over time, as well as cumulative use of corticosteroids and immunosuppressive drugs could contribute to these changes in SLESIS related to increased infection risk"). - Materials and Methods: "We identified 98 patients who had suffered at least one severe infection and compared their medical records with those of 111 randomly selected patients with SLE who had never suffered from severe infections". Were these patients matched for age and sex? In the results section the authors declared "these two groups did not differ in age, sex or ethnicity". - Why did the author choose 111 SLE patients as controls? Which was the rule for choosing 111 pts? - At page 9 the authors say they calculated the SLESIS for each of the 209 patients with infections (I think this is a mistake). - Results: in table 2 (Descriptive data) Could the authors provide a cut-off for neutropenia and lymphopenia? Additional information regarding gamma-globulins levels, for example, as well as for SLEDAI-2K, SLICC/ACR Damage score (SDI) and smoking habits at diagnosis could be useful discussing the results reported in Table 3 (Comparison between patients who died for severe infections and those who did not).

VERSION 1 – AUTHOR RESPONSE

COMMENTS FROM REVIEWER 1

We are grateful to the reviewer for commenting that the paper contains insightful considerations, is well-written and brings new relevant information. With respect to the clarifications that were requested, we have made the following revisions.

Comment 1)
Although already briefly stated in the Patients and Methods section, SLESIS calculation should be more extensively described in Page 8, line 12, in order to make it easier for readers to understand it. Please include the reference to Table 1 in the appropriate site in this paragraph.
Response
We have now included an extended description of how SLESIS is calculated on pages 7-9, referring to Table 1 and including two example calculations.

Comment 2) I would suggest adding to the ROC curve graphics (Figures 1 and 2) the sensitivity/specificity of the different selected cut-offs and also the AUC.

Response
We have added horizontal and vertical lines to the ROC graphs for each of the cut-off points that we mention on page 16, and the AUC is also stated on each graph.

Comment 3) In Page 18, lines 16 and 17, the authors say "This reinforces the idea that repeated measurement of SLESIS may be a helpful clinical assessment tool". I agree that a higher SLESIS right before an episode of severe infection (vs. at diagnosis) may SUGGEST that SLESIS might be useful for clinical assessment during follow-up. Nevertheless, before we can draw this conclusion, SLESIS should be prospectively calculated multiple times during follow-up in order to assess its variation over time and see if its peak (vs. lower values during follow-up) is really associated with a higher probability of severe infection. As I consider this one of the most relevant points of discussion in this topic, I would like to invite the authors to provide a more in-depth discussion on this regard.

Response
We have included the following text on Page 19 paragraph 2.
Some variables of SLESIS, will never change over time, such as age at diagnosis, ethnicity and gender, whereas others, such as number of previous severe infections, Katz index and current dose of corticosteroids could change and may thus contribute to changes in SLESIS. One strategy could be to re-calculate SLESIS annually and after every severe infection and hospitalisation. In this way, a prospective study could be carried out to calculate SLESIS multiple times during follow-up in order to assess its variation over time and see if its peak (vs. lower values during follow-up) is really associated with a higher probability of severe infection.

Comment 4) In Page 20, line 16, the authors "...suggest that patients with high SLESIS (>3.5) at any point could be followed-up with a higher index of suspicion for infections and lower threshold for using antibiotics". Although this may be an obvious extrapolation of the data, the authors cannot conclude that the early use of antibiotics in patients with high SLESIS will impact outcomes and, therefore, this treatment strategies cannot be suggested, based solely on the results published in this paper. Just like my comment in number 3, this is also a very relevant point of discussion and should be developed.

Response
We agree, and we have included this wording on page 21, paragraph 2.

Comment 5) There is one last point I was intrigued about. In Table 2, it is stated that in the control (non infection) group 29 patients had renal disease and 12 had CNS disease. Considering that either all CNS patients also had renal manifestations or none of CNS patients had renal manifestations, there would be 29-41 patients with a potentially more severe subset of manifestations. Nonetheless, only 6 patients (14-20% of those patients) received corticosteroids equivalent to ≥10 mg of prednisone. Why did this happen? Which were the renal and CNS manifestations in those patients, how were they defined?

Response
Thank you for pointing out this discrepancy, which had escaped our notice. We have now corrected this table. The term CNS disease has been corrected to neuropsychiatric disease because some patients had peripheral neuropathy or seizures that did not always require high dose corticosteroids. In fact, most of the patients with renal disease (20/24) did receive high dose corticosteroids at some point during follow-up but some did not as they were treated by the rituxilup protocol that uses rituximab and mycophenolate without corticosteroids.

COMMENTS FROM REVIEWER 2
Comment 1) Abstract: I suggest mentioning also in this section how severe infections are defined.
Response
We have defined severe infections in the abstract.

Comment 2) Introduction: authors enlisted several different objectives for this study, I suggest distinguishing primary aim of the study from the secondary ones.
The overarching primary objective of the study was to validate SLESIS in an independent cohort from the one in which it was developed. This has now been specified in the introduction (bottom of page 6).

Comment 3) Materials and methods/results: The authors developed SLESIS using data from the RELESSER cohort, and after analyzing a time repeated-events Cox regression model. They included items with HR superior to 1 in that model. Could the authors perform secondary analysis investigating whether disease duration influence infection rates and regarding cumulative glucocorticoid dosage, adjusted for disease duration? They performed analysis matching infectious SLE patients and not-infectious ones according to disease duration, so they clearly recognize that disease duration is relevant in occurrence of infections ("Development of chronic damage over time, as well as cumulative use of corticosteroids and immunosuppressive drugs could contribute to these changes in SLESIS related to increased infection risk").
Response
In fact, the analysis of effect of disease duration has already been done. In the original study of Rua-Figuera et al (ref 17) from which SLESIS was developed, many different variables were tested in the bivariate analysis that proved not to be associated with severe infection and were thus not included in the final multivariable analysis. Disease duration was one of those factors. Data on cumulative glucocorticoid dosage is not available.

Comment 4) Materials and Methods: "We identified 98 patients who had suffered at least one severe infection and compared their medical records with those of 111 randomly selected patients with SLE who had never suffered from severe infections". Were these patients matched for age and sex? In the results section the authors declared "these two groups did not differ in age, sex or ethnicity".
Why did the author choose 111 SLE patients as controls? Which was the rule for choosing 111 pts?

Response
Male gender and age at diagnosis are two variables included in SLESIS, so we did not match cases and controls for age and gender because that would have meant that we could not detect any effect of these factors when comparing SLESIS between the infection and non-infection group. However, even without deliberate matching there were no significant differences between the groups in terms of age and gender.
Regarding the figure of 111 patients, we took advice from a statistician who is a co-author of the paper (VdC). Based on a nested case-control design within a cohort of 699 patients of whom 98 had severe infection, a sample size of 111 was suggested for the non-infection control group.

Comment 5. At page 9 the authors say they calculated the SLESIS for each of the 209 patients with infections (I think this is a mistake).

Response
This was a misprint. Thank you for pointing it out. We have corrected it and the text now reads "We calculated the SLESIS for each of the 209 patients at the time of diagnosis. For each of the 98 patients with infection we also calculated SLESIS for the clinical assessment carried out at the last consultation prior to the infection."

Comment 6) Results: in table 2 (Descriptive data) Could the authors provide a cut-off for neutropenia and lymphopenia? Additional information regarding gamma-globulins levels, for example, as well as for SLEDAI-2K, SLICC/ACR Damage score (SDI) and smoking habits at diagnosis could be useful discussing the results reported in Table 3 (Comparison between patients who died for severe infections and those who did not).

Response
Table 2 now shows the cut offs for neutropaenia (less than 2 x 109/l) and lymphopaenia (less than 1 x 109/l). Unfortunately, we do not have data regarding immunoglobulin levels, SLEDAI-2K and SDI at time of diagnosis. SLEDAI and SDI were recorded in the original paper (Rua-Figueroa et al, ref 17) from which SLESIS was developed and were included in multi-variable analysis but were found not to be associated with risk of severe infection.

VERSION 2 – REVIEW

REVIEWER	Gustavo Balbi Department of Rheumatology, Federal University of Juiz de Fora, Brazil
REVIEW RETURNED	11-Mar-2019

GENERAL COMMENTS	Dear authors, All queries have been issued. Comments: - The paper is well written; - It contains a relevant question; - Methods are appropriate for the investigation; - Results are clearly stated, as well as the study limitations; - Conclusion is supported by the presented data. Therefore, the paper is suitable for publication. Congratulations for the great work. Best regards,

REVIEWER	Alessandra Bortoluzzi University of Ferrara, Department of Medical Sciences, Italy
REVIEW RETURNED	27-Mar-2019

GENERAL COMMENTS	The Authors properly addressed all the comments. No further changes are required.