## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Validity of the Italian algorithm for the attribution of neuropsychiatric events in systemic lupus erythematosus: a retrospective multicenter international diagnostic cohort study. |
| **AUTHORS** | Bortoluzzi, Alessandra; Fanouriakis, Antonis; Appenzeller, Simone; Costallat, Lilian; Scirè, Carlo; Murphy, Elana; Bertsias, George; Hanly, John; Govoni, Marcello |

## VERSION 1 - REVIEW

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| **REVIEWER** | Savino Sciascia<br>Center of Research of Immunopathology and Rare Diseases, Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, S. Giovanni Bosco Hospital, Turin, Italy |
| **REVIEW RETURNED** | 18-Jan-2017 |

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| **GENERAL COMMENTS** | This is an interesting study aiming to validate the Italian algorithm of attribution of neuropsychiatric events to systemic lupus erythematosus in an external international cohort of patients with SLE.<br>Major comments:<br>-It would be very informative to show the diagnostic accuracy of the proposed algorithm when stratifying patients for the time (before, after or concurrent with SLE diagnosis) of the NP event. Indeed, knowing that a patient has been already diagnosed with SLE might represent a bias when attributing a neuropsychiatric events to systemic lupus erythematosus. Being the time of NP event one of the variables computed in the algorith, one could choose an arbitrary cut-off (e.g. more than 1 year before the diagnosis of SLE, within 1 year, more than 1 year after the diagnosis)<br>- In line with the previous comment, this reviewer would appreciate to see the diagnostic accuracy of the proposed algorithm when separating patients for ischemic Vs non-ischemic/inflammatory events (mainly for major NP episodes).<br>Minor comments<br>-Double check if the distribution of M/F is correctly stated in table 1.<br>-The retrospective design of this analysis should be clearly listed among the limitations of the study in the discussion.<br>-Abstract: it would be informative to read the total number of NP events rather than '' with at least one NP event. Similarly, a brief description of the distribution of the NP events should be provided (e.g. % Mood disorder, % headache, % cerebrovascular disease... ) |

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| **REVIEWER** | Jorge Sanchez-Guerrero<br>Director, Division of Rheumatology<br>Mount Sinai Hospital/University Health Network<br>Professor of Medicine |

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| | University of Toronto |
| **REVIEW RETURNED** | 29-Jan-2017 |

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| **GENERAL COMMENTS** | I reviewed with interest the study by Dr. Bortoluzzi et al. Their objective was to validate the Italian attribution algorithm in an international cohort of patients with SLE and NP events.<br>My major concern, as acknowledge by the authors, is the retrospective nature of the cohort. Patients were seen between 1982 and 2015, but the ACR NPSLE nomenclature was available until 1999; during this period, patients were assessed by different physicians, had diverse imaging studies and autoantibodies (APL antibodies became widely available in early 90s). Also, this is a selected cohort, since the frequency of major NP syndromes is very different from the SLICC inception cohort. Ideally, this exercise should be done in new patients.<br>Although the authors present a quantitative score to attribute the syndromes to lupus, in general it is not so different of what has been used in the SLICC cohort.<br>Except CVD and seizures, all other major NP syndromes have a very low or null frequency including acute confusional state and psychosis which are among the most challenging for attribution in clinical practice.<br>It is important to include in the manuscript the number of patients coming from each participating Centre.<br>The list of confounding and favouring factors must be included in the manuscript as they are key in the estimation of the score.<br>Authors should mention what characteristics of lupus are important in the attribution, particularly what is the role of extra NP lupus activity in the attribution? |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer #1: Reviewer Name: Savino Sciascia
Institution and Country: Center of Research of Immunopathology and Rare Diseases, Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, S. Giovanni Bosco Hospital, Turin, Italy
This is an interesting study aiming to validate the Italian algorithm of attribution of neuropsychiatric events to systemic lupus erythematosus in an external international cohort of patients with SLE.
Major comments:
1) It would be very informative to show the diagnostic accuracy of the proposed algorithm when stratifying patients for the time (before, after or concurrent with SLE diagnosis) of the NP event. Indeed, knowing that a patient has been already diagnosed with SLE might represent a bias when attributing a neuropsychiatric events to systemic lupus erythematosus. Being the time of NP event one of the variables computed in the algorithm, one could choose an arbitrary cut-off (e.g. more than 1 year before the diagnosis of SLE, within 1 year, more than 1 year after the diagnosis)

We thank the reviewer for the comments concerning the paper.

For the first question, in our preliminary work we have categorized the onset time of each NP event in three subheadings, taking into account the time of appearance of the NP picture with respect to the onset time of SLE: before (>6 months), concomitant (within 6 months) or after. In this study, we have adopted the same criterion.
We had better clarify this time interval in method section.

The diagnostic accuracy of the proposed algorithm stratifying events with respect to time is as follows

(added to the results)
- before: 51 events AUC 0.68 (0.12 – 1.00)
- concomitant: 64 events AUC 0.78 (0.64 – 0.92)
- after: 128 events AUC 0.85 (0.64 – 0.92)
p value 0.59

2) In line with the previous comment, this reviewer would appreciate to see the diagnostic accuracy of the proposed algorithm when separating patients for ischemic Vs non-ischemic/inflammatory events (mainly for major NP episodes).

We thank the reviewer for the suggestion. Now we have added the analysis of diagnostic accuracy for ischemic vs. non-ischemic/inflammatory events in Table 4.

Minor comments

1)Double check if the distribution of M/F is correctly stated in Table 1. We thank the reviewer. We have modified the table 1 and checked and the data.

2)The retrospective design of this analysis should be clearly listed among the limitations of the study in the discussion.
Added in the discussion.

3) Abstract: it would be informative to read the total number of NP events rather than " with at least one NP event.
Similarly, a brief description of the distribution of the NP events should be provided (e.g. % Mood disorder, % headache, % cerebrovascular disease...

As suggested by the reviewer, we have modified Table 1 entitled “Distribution of NP events in the international cohort” adding the details related to first, subsequent and all events observed; the corresponding results section has been modified stratifying descriptive and accuracy results by first and subsequent NP events. Results have been now briefly included in the text (additional data and analysis are now reported in detail, in supplementary material: supplementaryS3, Table S3) and accordingly, the discussion was revised slightly.
For reasons of space, we have synthesized this data in the abstract.

Reviewer #2: Reviewer: 2
Reviewer Name: Jorge Sanchez-Guerrero
Institution and Country: Director, Division of Rheumatology, Mount Sinai Hospital/University Health Network, Professor of Medicine, University of Toronto
I reviewed with interest the study by Dr. Bortoluzzi et al. Their objective was to validate the Italian attribution algorithm in an international cohort of patients with SLE and NP events.

1) My major concern, as acknowledge by the authors, is the retrospective nature of the cohort. Patients were seen between 1982 and 2015, but the ACR NPSLE nomenclature was available until 1999; during this period, patients were assessed by different physicians, had diverse imaging studies and autoantibodies (APL antibodies became widely available in the early 90s). Also, this is a selected cohort, since the frequency of major NP syndromes is very different from the SLICC inception cohort. Ideally, this exercise should be done in new patients.

We thank the reviewer for the comments concerning the paper that gave us the opportunity to clarify the limits of the study in the discussion.
Since the study is retrospective in its nature, we can assume that the attribution algorithm has been

applied retrospectively, but uniformly. However, we further analyzed the study data by following the reviewer's suggestion to test the performance of the attribution algorithm for the events diagnosed after 1999. From a total of 243 events, 206 were observed after 1999. For these the attribution algorithm has this performance, comparable to the pooled analysis:
AUC 0.88 (0.83-0.93, 95 % CI).

2) Although the authors present a quantitative score to attribute the syndromes to lupus, in general, it is not so different from what has been used in the SLICC cohort.

We thank the reviewer for the comment that gives us the opportunity to better explain the peculiarity of our model. In comparison with the model used in SLICC cohort, our attribution algorithm - although clearly inspired to (as already acknowledged in our previous paper)- presents at least three significant differences:
1. it can be applied to all NP events listed in the ACR nomenclature and case definition, including minor events (that is not the case for the SLICC models);
2. the structure of the model is based on four different items, each of them scored with specific weights;
3. the model enhances and includes a list of further factors (favoring factors) not included in previous studies and that, in our opinion, can effectively support the decision process.

3) Except CVD and seizures, all other major NP syndromes have a very low or null frequency including acute confusional state and psychosis, which are among the most challenging for attribution in clinical practice.
This is a good point. There are, of course, some limits for the correct attribution of the most rare events and this is declared in discussion. For psychosis the AUC obtained from our 11 cases observed was 0.98 (95% CI, 0.97-1.00).

4) It is important to include in the manuscript the number of patients coming from each participating Centre.
Added in the results section.

5) The list of confounding and favouring factors must be included in the manuscript as they are key in the estimation of the score.
As suggested by the reviewer we have included the lists of confounding and favoring factors in the supplementary materials (SupplementaryS1 and S2).

6) Authors should mention what characteristics of lupus are important in the attribution, particularly what is the role of extra NP lupus activity in the attribution?
This is a very good point. In agreement with this consideration, we have included the disease activity among favoring factors (see the attached supplementary material: SupplementaryS1) already in the original attribution model.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Savino Sciascia<br>Center of Research of Immunopathology and Rare Diseases, Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, S. Giovanni Bosco Hospital, Turin, Italy |
| **REVIEW RETURNED** | 25-Mar-2017 |

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| **GENERAL COMMENTS** | The Authors properly addressed the comments from this Reviewer. No further changes are required. |

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| **REVIEWER** | Jorge Sanchez-Guerrero<br>Mount Sinai Hospital/University Health Network<br>Toronto, ON. Canada |
| **REVIEW RETURNED** | 28-Mar-2017 |

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| **GENERAL COMMENTS** | No further comments |