Is it primary neuropsychiatric systemic lupus erythematosus? Performance of existing attribution models using physician judgment as the gold standard

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Abstract

Objective

Models for the attribution of neuropsychiatric manifestations to systemic lupus erythematosus (NPSLE) that incorporate timing and type of manifestation, exclusion/confounding or favouring factors have been proposed. We tested their diagnostic performance against expert physician judgment.

Methods

SLE patients with neuropsychiatric manifestations were identified through retrospective chart review. Manifestations were classified according to physician judgment as attributed to SLE, not attributed or uncertain. Results were compared against the Systemic Lupus International Collaborating Clinics (SLICC) attribution models A and B, and one introduced by the Italian Study Group on NPSLE.

Results

191 patients experienced a total 242 neuropsychiatric manifestations, 136 of which were attributed to SLE according to physician. Both SLICC models showed high specificity (96.2% and 79.2% for model A and B, respectively) but low sensitivity (22.8% and 34.6%, respectively) against physician judgment. Exclusion of cases of headache, anxiety disorders, mild mood and cognitive disorders and polyneuropathy without electrophysiologic confirmation led to modest increases in sensitivity (27.7% and 42.0% for SLICC models A and B, respectively) and reductions in specificity (94.8% and 65.5%, respectively). The Italian Group model showed good accuracy in NPSLE attribution with an area under the curve of the receiver operating characteristics analysis of 0.862; values ≥7 showed the best combination of sensitivity and specificity (82.4% and 82.9%, respectively).

Conclusion

Attribution models can be useful in NPSLE diagnosis in routine clinical practice and their performance is superior in major neuropsychiatric manifestations. The Italian Study Group model is accurate, with values ≥7 showing the best combination of sensitivity and specificity.

Key words

neuropsychiatric systemic lupus erythematosus, diagnosis, attribution models

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Introduction

In systemic lupus erythematosus (SLE), attribution of neuropsychiatric manifestations to the disease *per se* (termed primary NPSLE), rather than to comorbidities or complications of therapy, still remains challenging, due to the wide heterogeneity of manifestations and the paucity of specific diagnostic tests (1). Brain magnetic resonance imaging (MRI) is neither sensitive nor specific for primary NPSLE. Nevertheless, prompt and accurate diagnosis of primary NPSLE is important for the initiation of immunosuppressive or other specific treatment, instead of simply symptomatic management.

The decision to attribute a neuropsychiatric manifestation to SLE relies largely on physician judgment (the current "gold standard"), based on clinical, laboratory and neuroimaging results, often involving consensus among various medical specialties (2). To this end, the 1999 American College of Rheumatology NPSLE nomenclature (3) has provided an extensive appendix of factors that have to be taken into account before labelling a patient as primary NPSLE (collectively termed "association" and "exclusion" factors). Traditionally, neuropsychiatric manifestations are divided into "major" and "minor", based on an older population-based study which showed that inclusion of headache, anxiety disorders, mild mood disorders, mild cognitive impairment (*i.e.* deficits in ≤3 of 8 cognitive domains) and polyneuropathy without electrophysiologic confirmation (collectively termed as minor manifestations) significantly reduced the specificity of the ACR nomenclature for primary NPSLE, due to the high frequency of these manifestations in the general population (4). This observation has generated a debate, whether these minor manifestations should be considered as *bona fide* neuropsychiatric involvement of lupus, or the term NPSLE should be reserved only for more severe manifestations (5).

To facilitate physicians, a number of different models for attribution of NPSLE have been proposed. The multicenter Systemic Lupus International Collaborating Clinics (SLICC) inception cohort was the first to introduce two attribution models of different stringency for patients with newly diagnosed SLE (6, 7). More recently, the Italian Study Group on NPSLE proposed an additional model, which was tested against clinical judgment (8). All these models take into account the following parameters: type of neuropsychiatric manifestation (*i.e.* major *vs.* minor (4)), timing of manifestation relative to SLE diagnosis and presence of non-SLE factors (as described in the ACR appendix). The Italian Group model also includes "favouring" factors for attribution SLE (see below in Methods for a detailed description of the 3 models).

We recently described our cohort of primary NPSLE cases in two European centres and compared diagnostic and treatment decisions to the European League against Rheumatism (EULAR) recommendations for NPSLE (9, 10). In that study, attribution of neuropsychiatric manifestations to SLE was based on physician judgment after an adequate follow-up. We herein attempted to test the existing attribution models proposed for NPSLE in our patient cohort of neuropsychiatric manifestations and compare them against clinical judgment.

Methods

Patients/Study population

Two national tertiary referral centres for patients with SLE, Heraklion, Greece and Cluj, Romania participated in the study. Both study centres are tertiary referral centres for possible NPSLE cases and patients with confirmed neuropsychiatric involvement were retrospectively identified by file review of all lupus cases over the last fifteen years (2001-2015). Patients had to fulfil at least four of the revised American College of Rheumatology (ACR) classification criteria for SLE (11) and to have regular follow-up in each centre.

Neuropsychiatric manifestations and attribution according to physician judgment

All neuropsychiatric manifestations were defined according to the ACR nomenclature and case definitions (3). For patients experiencing more than

one neuropsychiatric manifestation, each manifestation was registered individually.

For the purpose of this study, we included all primary NPSLE cases (physician attribution) from the two centres, as reported elsewhere (9). For comparison, we also scrutinised patient files from our SLE cohort to retrieve neuropsychiatric manifestations not attributed or with uncertain attribution to SLE as determined by physician judgment (secondary NPSLE). In the routine practice of the two centres, attribution of neuropsychiatric manifestations takes into account a number of parameters such as: the ACR "exclusion" and "association" factors mentioned above (*i.e*. their absence favours attribution to SLE), the age of patient, presence of risk factors for primary NPSLE [antiphospholipid antibodies (aPL), prior major neuropsychiatric manifestation and generalised disease activity), findings of brain imaging and other diagnostic procedures. For central nervous system manifestations in particular, the presence of atherosclerotic risk factors (hypertension, diabetes, smoking, dyslipidemia) is specifically sought. In challenging cases, a multidisciplinary approach is followed involving physicians from different disciplines (rheumatology, internal medicine, neurology, psychiatry, infectious diseases and neuroimaging), and attribution is ascertained after prospective follow-up of patients.

For each neuropsychiatric manifestation, we documented the following variables:

Timing: Neuropsychiatric manifestations that occurred either before, concurrently or after the diagnosis of SLE were documented. Manifestations occurring before SLE diagnosis had to be still present when the disease was diagnosed (see below).

Type: Manifestations were classified into major and minor, according to the definition by Ainiala *et al*. (4). Classification of mood disorders in major depression (major) or mild mood disorders (minor) was done after formal psychiatric assessment; classification of cognitive dysfunction in mild (minor) vs. moderate/severe (major) was done either with a formal neuropsychological assessment or with the Montreal Cognitive Assessment (MoCA) screening tool (12). When the latter was used, mild cognitive impairment was defined as a MoCA score 22-26, with scores <22 indicating moderate to severe cognitive impairment (12, 13).

Presence of "association", "exclusion" and "favouring" factors at the time of neuropsychiatric manifestation: For each manifestation, patient record was scrutinised for the presence or absence of any "association" or "exclusion" factor (as outlined in the ACR appendix (3)), as well as for potential SLE-favouring factors [see below, Parameters of the Italian Study Group model (8)].

Attribution models and diagnostic performance

We tested all neuropsychiatric manifestations (attributed and not attributed/uncertain) for their attribution to SLE, according to the three published attribution models (SLICC models A and B and Italian study group model)(6-8):

Criteria for attribution to SLE with SLICC model A (stringent): The SLICC cohort is an inception cohort for patients with newly diagnosed SLE; it attempts to capture SLE patients close to the diagnosis of the disease and has a narrow enrollment window (6 months before to 15 months following SLE diagnosis, for a total period of 21 months). In model A, only neuropsychiatric manifestations i) in which the onset has occurred within the enrolment window in the cohort, ii) have no "exclusion" or "association" factors (ACR glossary) and iii) are not one of the minor neuropsychiatric manifestations identified by Ainiala *et al*. (4) are attributed to SLE (6, 7).

Criteria for attribution with SLICC model B (less stringent): SLICC model B follows a more lenient approach and includes neuropsychiatric manifestations i) in which the onset is set within 10 years prior to SLE diagnosis and are still present during the enrolment window, ii) which have no ACR "exclusion" factors ("association" factors may be present) and iii) are not one of the minor neuropsychiatric manifestations (6, 7).

Parameters of the Italian Study Group model: This model provides a total score comprised of the sum of 4 individual scores based on the following parameters: timing of neuropsychiatric manifestation (before, after or concurrent with SLE diagnosis (score 0–3), type of manifestation (minor *vs*. major, score 0–3), presence of confounding factors (identical to the "association" factors of the ACR glossary (3)) and presence of "favouring" factors for each manifestation (derived by systematic literature review and expert opinion), for a total score of 0–10. These favouring factors are specified for each neuropsychiatric manifestation; nevertheless, high disease activity, presence of aPL and abnormal neuroimaging are considered favouring factors in all (or almost all) manifestations (8). In the original study, the single best cut-off score correlating with physician judgment was ≥6 (sensitivity 83%, specificity 71%).

Patient data were scrutinised for all of the aforementioned factors. For the Italian model, a total score for each manifestation was calculated. We then calculated sensitivity, specificity, positive and negative likelihood ratios of each model, using attribution by physician judgment as the gold standard (*i.e*. derivation of the "true positive" and "true negative" cases).

Statistical analysis

Data analyses were performed with IBM SPSS Statistics (v. 21.0, Chicago, Illinois). Descriptive statistics were undertaken for continuous variables and mean values/standard deviations (SD) were calculated. Chi-square or Fisher's exact test were used to compare categorical variables and student's *t*-test or Mann-Whitney was used to compare continuous variables.

For each model and across manifestations, sensitivity and specificity, using physician judgment as the gold standard, were calculated as follows:

Sensitivity = correctly attributed cases (by the model) / correctly attributed + falsely not attributed cases

Specificity = correctly not attributed cases (by the model) / correctly not attributed + falsely attributed cases.

To test the accuracy of the Italian attribution model as a diagnostic test for NPSLE (*i.e*. a quantitative test related to a binary outcome, attributed *vs*. not

attributed/uncertain as per physician judgment), we performed receiver operating characteristics (ROC) analysis and calculated the respective area under the curve (AUC). Binary logistic regression analysis was used to calculate the odds ratio (OR) of attribution by physician judgment, for every unit increase in the total score of the Italian model. Statistical significance for all comparisons was indicated as a two-sided $p<0.05$.

The study was approved by the Institutional Review Board. A consent form was not obtained due to the retrospective, observational nature of the study.

Results

A total of 242 neuropsychiatric manifestations, experienced by 191 patients, were included. According to physician judgment, 136 manifestations were attributed (primary NPSLE) and 96 were not attributed to SLE (secondary NPSLE); for 10 manifestations, attribution was considered uncertain. Types of manifestations for primary and secondary/uncertain NPSLE, with basic demographic characteristics are shown in Table I. Primary NPSLE consisted largely of major neuropsychiatric manifestations (n=112, 82.4%), most frequently cerebrovascular disease (CVD), cognitive disorder and seizure disorder. Similarly but to a lesser extent, major manifestations comprised the majority (n=61, 57.5%) of non-SLE attributed or uncertain manifestations, although the most frequent individual manifestations were headache, mood disorder and anxiety disorder. Only 2.2% (n=3) of SLE-attributed manifestations had their onset before the disease diagnosis, as compared to 35.8% of not attributed or uncertain manifestations (Table I). Regarding CVD, the majority of attributed cases were due to antiphospholipid syndrome (APS, 15/25, 60%). For the remaining 10 cases, attribution to SLE was based on the young age of patients [mean (SD) 41.2(11.3) years) and the presence of generalised disease activity at the time of the event [mean (SD) SLEDAI 14.4(8.3)], despite the fact that frank vasculitis within the CNS could not be established by brain MRI or MR angiography in any CVD case. On the contrary, CVD cases not attributed to SLE by treating physicians, occurred in an older age [mean (SD) 45.5(10.6) years) and were all negative for aPL and positive for at least one traditional risk factor for atherosclerosis (hypertension, diabetes mellitus, dyslipidaemia, smoking); atherosclerosis was considered to be the main underlying mechanism.

Performance of SLICC models A and B

Using the SLICC models, only a small proportion of the total 242 manifestations were attributed to SLE [35 manifestations (14.5%) with model A, 69 manifestations (28.5%) with model B]. Compared with physician judgment, both models showed high specificity (96.2% and 79.2% for model A and B, respectively), but poor sensitivity (Table II), suggesting that only a minority of neuropsychiatric manifestations considered as SLE-related by treating physicians would be captured by the SLICC models. Indeed, SLICC model A misclassified 77.2% (n=105) of attributed by the physician manifestations, with only 3.8% (n=4) of non attributed or uncertain events. SLICC model B misclassified 65.4% of attributed manifestations (n=89), with an additional 20.8% (n=22) of non-attributed/uncertain cases.

We next attempted to dissect the individual components of the SLICC models (*i.e.* type and timing of manifestation), in order to check their contribution to this low sensitivity. Removal of the type of manifestation component from the SLICC models led to moderate increments in sensitivity (27.2% and 39.0% for models A and B, respectively), with comparable reductions in specificity, especially in SLICC model B (95.3% and 69.8% for models A and B, respectively). In contrast, removal of the component of time from the SLICC models (manifestations occurring after the enrolment window are by definition excluded) led to significant increases in sensitivity (52.9% and 79.4%% for models A and B, respectively), albeit at the expense of specificity (84.0% and 57.5% for A and B, respectively); this indicated that, if timing was not taken into account, many more neuropsychiatric manifestations attributed to SLE by physician judgment would also be classified as primary NPSLE by the SLICC models.

Performance of the Italian Study Group model

We found a significant difference in mean total scores of the model between primary NPSLE cases and SLE-unrelated neuropsychiatric manifestations [mean (SD) score: 7.51 (1.7) *vs.* 4.71 (1.8) for related *vs.* unrelated manifestations, respectively, $p<0.001$]. Regression analysis showed that for every 1-point increase in the total score of the Italian model, the OR for attribution to SLE by the treating physician was 2.2 (95% CI, 1.8–2.7). When serial cut-offs were tested, values ≥7 showed the best combination of sensitivity and specificity (82.4% and 83.0%, respectively [Table II]). Using this cut-off value, 82.4% of related manifestations had a score of ≥7, as compared to 17.0% of manifestations unrelated to SLE, as per physician judgment ($p<0.001$). Expectedly, higher and lower total scores led to losses in sensitivity and specificity, respectively (Table II).

The AUC of the ROC curve for the Italian study group model was 0.862, indicating good accuracy as a test for NPSLE attribution (Fig. 1a). Contrary to the SLICC models, which exclude minor neuropsychiatric manifestations from the possibility to be attributed to SLE, the Italian Study Group model can be used to attribute both major and minor manifestations to underlying SLE. Notably, in our cohort, the performance of the model was greatly superior in major versus minor NPSLE events, as indicated in Figure 1b-c (AUC for major manifestations: 0.893 *vs.* 0.731 for minor neuropsychiatric manifestations). Similarly, when we compared minor *vs.* major manifestations, we found substantially different sensitivity rates, with less than 20% of minor manifestations attributed to SLE by the physician reaching a score of 7, as compared to 96.7% of major manifestations (Table II). By contrast, all not attributed/uncertain minor manifestations were correctly classified by the same score cut-off (specificity 100% for a total score of ≥7).

Table I. Types of neuropsychiatric manifestations and basic demographic characteristics.

	Primary NPSLE	Secondary NPSLE	*p*-value	Alternative diagnoses in cases of secondary NPSLE or uncertain attribution
Number of manifestations, n	136	106 96 not attributed 10 uncertain	(-)	
Mean (SD) age at SLE diagnosis, years	35.7 (14.0)	38.9 (11.6)	0.05	
Mean (SD) age at NPSLE, years	40.7 (12.5)	40.7 (13.6)	0.99	
Timing of manifestation, n (%)				
Before SLE diagnosis	3 (2.2)	38 (35.8)		
Concurrently with SLE diagnosis	38 (27.9)	6 (5.7)		
After SLE diagnosis	95 (69.9)	62 (58.5)	<0.0001	
aPL (+), n(%)	49 (36.6)	12 (11.3)	<0.001	
Mean (SD) SDI at the time of NPSLE	0.50 (0.84)	0.26 (0.56)[a]	0.03	
Type of manifestation, n				
Cerebrovascular disease	25	7		Carotid artery dissection (one case) - TIA in a smoker (one case - attribution uncertain) - Presence of traditional risk factors and absence of disease activity (remaining cases)
Cognitive disorder	17	7		Primary psychiatric disorder (three cases) - Coexisting emotional distress and fatigue (all cases)
Moderate/Severe	14	4		
Mild	3	3		
Seizure disorder	13	6		Occurrence prior to SLE diagnosis (all cases): alcohol abuse and head trauma (one case each) - indeterminate cause in the remaining
Mood disorder	12	27		Marked coexisting psychosocial stress (all cases)
Major depression	7	15		
Mild mood disorder	5	12		
Psychosis	11	4		Occurrence prior to SLE diagnosis (three cases) - Occurrence after SLE diagnosis and attribution to corticosteroid use and marked psychosocial stress (one case)
Cranial neuropathy	11	6		HZV infection (one case of VII and VIII neuropathy in the same patient) - occurrence prior to SLE diagnosis (remaining cases)
Headache	11	18		Initiation of episodes prior to SLE diagnosis and/or absence of disease activity (all cases)
Myelopathy	10	1		Coexisting neuromyelitis optica (diagnosed one year after SLE diagnosis)
Polyneuropathy	9	2		Thalidomide side-effect (one case) - No electrophysiologic confirmation and absence of disease activity (one case)
Anxiety disorder	5	11		Marked coexisting psychosocial stress (all cases)
Acute confusional state	3	-		-
Movement disorder	3	1		Parkinsonian syndrome diagnosed 9 years after SLE diagnosis (attribution uncertain)
Mononeuritis multiplex	2	-		-
Aseptic meningitis	2	1		Attributed to a possible viral meningitis
Autonomic disorder	1	-		-
Acute inflammatory demyelinating polyradiculopathy	1	1		Guillain-Barre syndrome diagnosed one year prior to SLE diagnosis (attribution uncertain)
Myasthenia	-	6		Occurrence prior to SLE diagnosis and attribution to a thymoma (all cases)
Demyelination	-	8		Coexisting multiple sclerosis (diagnostic criteria for MS fulfilled) [b]

SDI: SLICC Damage Index (24); aPL: Antiphospholipid antibodies; TIA: Transient ischemic attack, [a]Mean SDI accounts for manifestations occurring after the diagnosis of SLE. [b]All cases previously published in (27).

Table II. Sensitivity and specificity of different attribution models for NPSLE. In the Italian attribution model, a cut-off score ≥7 shows the best combination of sensitivity and specificity for all types of manifestations (82.4% and 82.9% respectively). In the original study, the best cut-off score was ≥ 6, with 83% sensitivity and 71% specificity).

Model	All manifestations (n=242)				Major manifestations (n=172)				Minor manifestations (n=70)			
	Sensitivity	Specificity	LR+	LR-	Sensitivity	Specificity	LR+	LR-	Sensitivity	Specificity	LR+	LR-
Italian model												
Score ≥ 8	57.4%	93.4%	8.7	0.5	69.6%	88.5%	6.0	0.3	NA[a]	NA[a]	NA	NA
Score ≥ 7	82.4%	82.9%	4.8	0.2	96.4%	70.5%	3.3	0.05	16.7%	100%	NA[c]	0.8
Score ≥ 6	87.5%	68.9%	2.8	0.2	99.1%	47.5%	1.9	0.02	33.3%	97.8%	15.1	0.7
SLICC model A	22.8%	96.2%	6.1	0.8	27.7%	92.7%	3.8	0.8	NA[b]	NA[b]	NA	NA
SLICC model B	34.6%	79.2%	1.7	0.8	42.0%	63.9%	1.2	0.9	NA[b]	NA[b]	NA	NA

For each model and across manifestations, sensitivity and specificity, using physician judgment as the gold standard, were calculated as follows: *Sensitivity:* correctly attributed cases (by the model) / correctly attributed + falsely not attributed cases; *Specificity:* correctly not attributed cases / correctly not attributed + falsely attributed cases; [a]Minor neuropsychiatric manifestations by definition cannot reach a total score of ≥8 in the Italian attribution model; [b]Minor neuropsychiatric manifestations are by definition excluded from attribution to SLE in both SLICC models; [c]Impossible to calculate positive likelihood ratio due to a specificity of 100% (denominator = 0); LR+: Positive likelihood ratio; LR-: Negative likelihood ratio; NA: Not applicable.

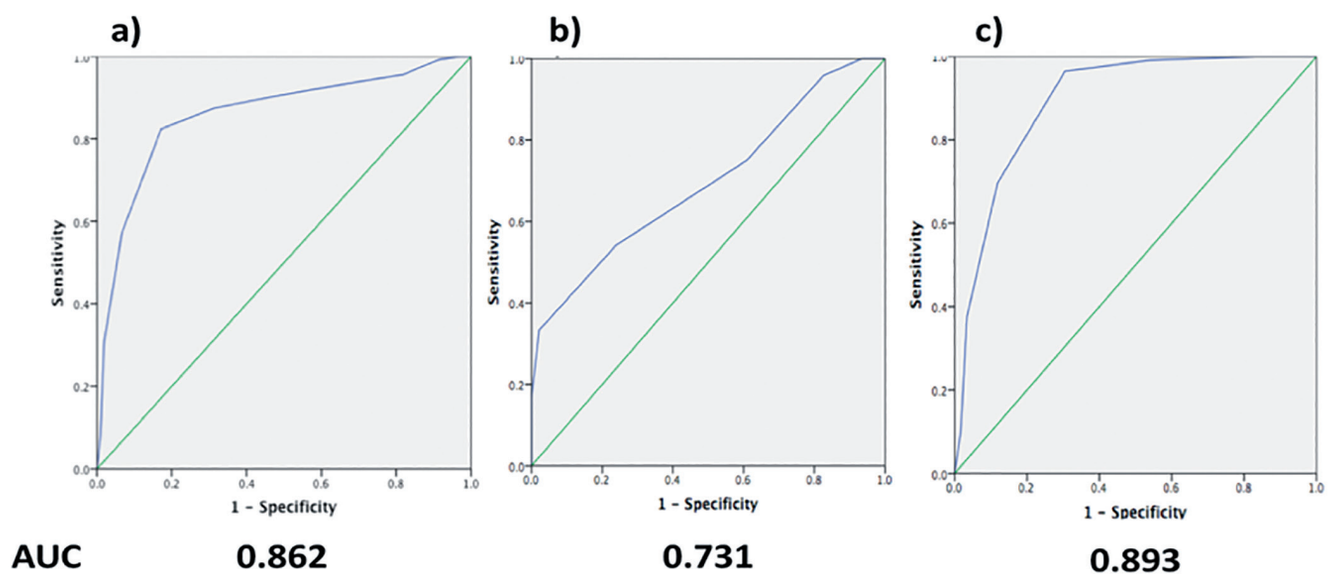

Fig. 1. Receiver operating characteristics (ROC) analysis of the performance of the Italian model related to physician judgment for **a)** all manifestations, **b)** minor manifestations and **c)** major manifestations. The area under the curve (AUC) represents the accuracy of the model, with a value approaching 1.0, indicating the best sensitivity and specificity. Note the strikingly different performance in the model between minor and major neuropsychiatric manifestations; major manifestations drive the overall high accuracy of the test.

Performance of individual manifestations in attribution models

Because NPSLE is extremely heterogeneous, we tested the diagnostic performance of the three models for individual manifestations with sufficient numbers of attributed and not attributed/uncertain manifestations in our cohort. As shown in Table III, the Italian Study Group model performed well in most manifestations with the exception of headache and mood disorders (low sensitivity) and a suboptimal specificity in CVD (see below). On the contrary, SLICC model A had very high specificity across all manifestations, but reached a sensitivity of >50% only in cases of psychosis.

The SLICC model A showed very low sensitivity for CVD, owing to the fact that it dismisses attribution to SLE in the presence of at least one "association factor" (*i.e.* one traditional risk factor for atherosclerosis). On the other hand, all CVD cases not attributed to SLE by physician judgment are also not attributed to SLE by SLICC model A, as illustrated in 100% specificity of the test. For the Italian model, all attributed CVD cases by the physician scored highly therein (sensitivity 100%); however ~ 4 in 10 cases not attributed by physician judgment would also be "captured" by the model (specificity 57%), potentially leading to "overattribution". SLICC model B performed in-between these two extremes.

Discussion

In this case-control study, we performed an independent validation of previously published attribution models for NPSLE. Ideally, the role of such attribution models would be to guide clinicians and centres with less experience in SLE care towards a correct attribution and management plan. In this regard, we found varying levels of sensitivity and speci-

Table III. Performance of individual neuropsychiatric manifestation in attribution models.

Manifestation	SLE-related (n)	SLE -unrelated or uncertain (n)	SLICC A		SLICC B		Italian score ≥7	
			Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
CVD	25	7	25.9%	100%	60.0%	71.4%	100%	57.1%
Cognitive disorder	18	6	0%	85.7%	11.8%	71.4%	81.4%	72.4%
Seizure disorder	13	6	30.8%	100%	38.5%	83.3%	100%	83.3%
Mood disorder	12	27	0%	100%	0%	84.0%	41.7%	88.5%
Psychosis	11	4	54.5%	100%	63.6%	100%	90.9%	100%
Cranial neuropathy	11	6	45.5%	83.3%	45.5%	50.0%	100%	100%
Headache	11	18	NA	NA	NA	NA	36.4%	100%
Anxiety disorder	5	11	NA	NA	NA	NA	0%	100%

For each model and across manifestations, sensitivity and specificity, using physician judgment as the gold standard, were calculated as follows: *Sensitivity:* correctly attributed cases (by the model) / correctly attributed + falsely not attributed cases; *Specificity:* correctly not attributed cases / correctly not attributed + falsely attributed cases; CVD: Cerebrovascular disease; NA: Not applicable.

ficity between the models, when compared with routine clinical judgment of physicians with experience in SLE. The quantitative model proposed by the Italian Study Group of NPSLE showed better correlation with our clinical decision than the SLICC models.

Using the SLICC models as "standard", only a small minority of neuropsychiatric manifestations could be attributed to SLE (14% with model A and 27% with model B); these rates are comparable to those of the original SLICC cohort (19% and 38%, respectively) (6). Interestingly, the SLICC researchers do not compare the models to "physician judgment" in their reports; rather, the models *per se* are considered the "gold standard" for attribution. This stringency serves to provide high specificity for both SLICC models, however, this is at the cost of low sensitivity.

Pertinent to the challenge of correct attribution is the fact that primary NPSLE lacks any hard and unequivocal diagnostic tests and consequently, judgment of an experienced physician still serves as the current "gold standard" (14). Accordingly, "correct" attribution may not be universally accepted, even between experts, since physician judgment is based on the subjectivity and expertise of the examiner, interpretation of brain imaging and other diagnostic tests, and performance of a multidisciplinary approach to patients (2). Indeed, in our cohorts, attribution of NPSLE cases was often done in such a multidisciplinary approach and was confirmed during follow-up visits.

While the incidence of a neuropsychiatric manifestation concurrently or near the diagnosis of SLE is universally weighed substantially in favour of primary NPSLE, manifestations occurring before or after disease diagnosis are differentially rated between the attribution models. The Italian Group model gives greater value to manifestations happening after the diagnosis of lupus, arguing that those happening before this time can hardly be related to the disease. On the contrary, based on the inception design of the cohort, both SLICC models preclude manifestations that have occurred after the enrolment window of 15 months following SLE diagnosis, while the lenient model B includes manifestations starting up to 10 years before diagnosis (15, 16). We believe that timing of a manifestation *per se* cannot provide a definite framework to guide attribution and should be taken into account in combination with other parameters.

The Italian Group model has introduced the additional feature of "SLE-favouring" factors, in parallel with the established "exclusion" and "association" factors of the ACR nomenclature and the SLICC models. This addendum is meaningful from a pathophysiological and clinical standpoint; in routine practice, physicians tend to take into account the presence of generalised disease activity, aPL or abnormal findings on brain imaging or other diagnostic procedures, in the attempt to accurately decide upon attribution (9). In terms of diagnostic reasoning, it is rational to balance such supporting factors for attribution to the disease against possible confounding factors. In this regard, the inclusion of generalised SLE disease activity as a universal favouring factor across all manifestations is appreciated, as NPSLE correlates with global disease activity (9, 17) and the latter has been recognised as a risk factor for neuropsychiatric involvement in lupus patients (10).

An important observation of our study is the contrasting performance of attribution models in major versus minor manifestations. The latter are by definition excluded from attribution to SLE in the SLICC models. Likewise, minor manifestations are not scored in the Italian Group model, and therefore can reach a maximum total score of 7. Consequently, less than 20% of minor manifestations deemed attributed to SLE by the treating physician reached the cut-off score of 7. This observation reinforces the notion that the current broad definition of NPSLE will inevitably lead to controversies regarding attribution and significance (18). Lupus experts continue to attribute some cases of headache, cognitive or mood disorder to SLE *per se* based on their clinical "gestalt" and expertise (19-21) and screening for the presence of such manifestations is recommended in routine clinical practice (22, 23). Although most often not directly related to underlying SLE, they can have profound impact on patients' quality of life, such that the adjective "minor" may serve as a misnomer (24, 25). On the other hand, encompassing

these common manifestations in an effort not to miss possible NPSLE cases has resulted in reduced specificity of attribution models. The question arising is whether NPSLE should continue to represent a generic term and a heterogeneous entity incorporating both mild and serious manifestations, or a more strictly defined condition limited to the more severe or lupus-specific neuropsychiatric manifestations (26). To this end, severe NPSLE cases should not be "missed" and it is reassuring that the latter perform fairly well in existing attribution models.

Our study has a number of limitations such as the retrospective retrieval of data, which cannot preclude occasional misclassifications regarding physician attribution. However, in everyday clinical practice of both study centres, the opinion of treating physicians is typically documented at the time of neuropsychiatric involvement and during follow-up. A second drawback is the inherent problem regarding subjectivity of the current "gold standard" for NPSLE, which may call into question the accuracy of our sensitivity and specificity results. Nevertheless, given the current limits in our understanding of NPSLE, the optimal means to avoid misclassifications in attribution is to regularly follow a multidisciplinary approach to SLE patients with suspected neuropsychiatric involvement, in combination with an extended follow-up. Several manifestations (such as aseptic meningitis, autonomic neuropathy, acute inflammatory demyelinating poly-radiculopathy or plexopathy) were under-represented or not represented at all in our cohorts; thus, the validity of attribution models could not be tested in these rare situations. For the study of the latter, multicentre studies with large number of neuropsychiatric manifestations would prove most valuable in the future. Finally, this study was performed in two tertiary centres with expertise in NPSLE. Should attribution models aim to facilitate physicians and centres with less experience in this challenging entity, further validation in such settings will be important.

In conclusion, we tested the applicability of different attribution models for NPSLE in an independent cohort of SLE patients with neuropsychiatric manifestations. Notwithstanding their limitations and differences, and until more robust data regarding NPSLE pathogenesis are available, such models may be helpful when encountering this demanding subset of patients.

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